# CONTEXT-SELECTIVE SUPPORT OF THE AKT/mTOR REGULATORY AXIS BY TANK-BINDING KINASE 1 (TBK1)

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## DEDICATION

In Loving Memory of my brother, Adam Conoly Cooper (May 9, 1990 – September 7, 1995)

&

My grandmother, Elizabeth Jane Cooper (July 16, 1923 – October 24, 2008)

~ Soli Deo Gloria ~

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"If I have seen a little further it is by standing on the shoulders of Giants." – Sir Isaac Newton

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# CONTEXT-SELECTIVE SUPPORT OF THE AKT/mTOR REGULATORY AXIS BY TANK-BINDING KINASE 1 (TBK1)

by

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Oncogenic mutation of Ras or Ras effector signaling characterizes roughly thirty percent of all cancers. Persistent obstacles to the treatment of these diseases by direct Ras inhibition prompt alternative strategies aimed at leveraging signaling networks downstream of Ras. Tank-Binding Kinase 1 (TBK1) is downstream of the RalGEF/RalB arm of Ras effector signaling and supports Ras-driven oncogenic transformation via direct regulation of AKT. While TBK1 has been nominated as a therapeutic target, the field lacks knowledge of the mechanisms whereby TBK1 inhibitors mediate lethality and of the preferential context(s) for their application. We therefore leveraged toxicity profiles for TBK1 inhibitors in 100 NSCLC cell lines and identified robust correlation between TBK1 inhibitors and a cadre of mTOR direct and upstream regulatory network signaling inhibitors. This observation, along with orthogonal phosphoproteomics data, suggested an intersection exists between TBK1 and mTOR regulation and mechanistic target space. We identified that TBK1 is required for AKT/mTOR activation during the nutrient starved-to-fed state transition. Furthermore, we established that TBK1 physically intersects with the AKT/mTOR regulatory axis signaling at multiple nodes and can follow permissive and instructive mechanistic routes to regulate mTORC1 activation in response to nutrients. In parallel, we utilized a bioinformatics approach to identify that "Ras-mutant/mesenchymal" status serves as a molecular indicator of TBK1 inhibitor sensitivity in NSCLC. Concordantly, signaling through the AKT/mTOR regulatory axis was acutely attenuated by TBK1 inhibition in Rasmutant/mesenchymal but remained unresponsive in Ras-mutant/epithelial NSCLC, indicating TBK1-resistant NSCLC may have uncoupled AKT/mTOR signaling from substantive TBK1 regulation. We furthermore demonstrated that TBK1 inhibition synergizes with Transforming Growth Factor-beta (TGF-beta)-mediated induction of the epithelial-to-mesenchymal transition (EMT) to reduce cancer cell viability. Together, these observations suggest that TBK1 supports pro-survival signaling downstream of Ras and EMT/TGF-beta signaling through the AKT/mTOR regulatory axis. Our findings, therefore, reveal novel mechanistic contributions of TBK1 in the regulation of AKT/mTOR signaling, and also nominate Ras-mutant/mesenchymal NSCLC as the preferential context for therapeutic interventions targeting TBK1.

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## **PRIOR PUBLICATIONS**

Thomas, J.C., **Cooper, J.M**., Clayton, N.S., Wang, C., White, M.A., Abell, C., Owen, D., and Mott, H.R. 2016. Inhibition of Ral GTPases Using a Stapled Peptide Approach. *Journal of Biological Chemistry*, 291(35): 18310-25

**Cooper, J.M**., Bodemann, B. O., and White, M. A. 2013. The RalGEF/Ral Pathway: Evaluating an Intervention Opportunity for Ras Cancers. *The Enzymes* 34: 137-157

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## LIST OF ABBREVIATIONS

- AKT V-Akt Murine Thymoma Viral Oncogene Homolog 1
- AUC Area-Under-the-Curve
- DMEM Dulbecco's Modified Eagle Medium
- EAA Essential Amino Acid Solution
- EBSS Earle's Balanced Salt Solution
- ECL Enhanced Chemiluminescence
- ED50 Median Effective Dose
- EMT Epithelial-to-Mesenchymal Transition
- EN Elastic Net
- FBS Fetal Bovine Serum
- FUSION Functional Signal Ontology
- GSK3-beta Glycogen Synthase Kinase 3 Beta
- HRP-Horseradish Peroxidase
- IB Immunoblot
- IKKe Inhibitor Of Kappa Light Polypeptide Gene Enhancer In B-Cells, Kinase Epsilon
- IP Immunoprecipitation/Immunoprecipitate
- KRAS Kirsten Rat Sarcoma Viral Oncogene Homolog
- KS Kolmogorov-Smirnov
- LKB1 Liver Kinase B1 (aka Serine/threonine kinase 11 (STK11))
- MAP2K1 (aka. MEK) Mitogen-Activated Protein Kinase Kinase 1
- MEFs Mouse Embryonic Fibroblast

- mTOR Mammalian Target of Rapamycin
- mTORC1 or 2 mTOR Complex 1 or 2
- NSCLC Non-Small Cell Lung Cancer
- PI3K Phosphatidylinositol-4,5-Bisphosphate 3-Kinase
- PIK3CA Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
- PRAS40 Proline-Rich Akt Substrate Of 40 kDa
- PVDF Polyvinylidene Difluoride
- qPCR Quantitative Real-Time PCR
- RAG Ras-related GTP binding
- RAPTOR Regulatory-Associated Protein Of mTOR
- RPMI Roswell Park Memorial Institute
- RT Room Temperature
- s6 Ribosomal Protein S6
- S6K-p70 S6 Kinase
- SNAI1 Snail Family Zinc Finger 1 (aka SNAIL)
- TBK1 Tank-Binding Kinase 1
- TBST Tris-Buffered Saline W/Tween
- TGFB1 Transforming Growth Factor Beta 1 (aka TGF-beta)
- TGFBR2 Transforming Growth Factor Beta Receptor 2
- TSC1 Tuberous Sclerosis Complex 1
- TSC2 Tuberous Sclerosis Complex 2
- WB-Western Blot
- ZEB Zinc finger E-box-binding homeobox

#### **CHAPTER ONE**

# INFILTRATING THE CITADEL THROUGH THE POSTERN GATE: RAL DOWNSTREAM EFFECTOR SIGNALING AS A COMPELLING INROAD IN THE EFFORT TO DEFEAT RAS-DOMINATED CANCERS.

# **Overview of RalGEF/Ral Protein Signaling and Therapeutic Intervention Strategies** *Oncogenic Ras Signaling: Targeting Troubles Prompt Alternative Approaches*

Roughly 30% of cancers worldwide harbor oncogenic mutations in Ras and Ras signaling network member genes. The common participation of oncogenic Ras proteins in many of the most lethal of human cancers has spurred persistent and intensive efforts to identify pharmacological agents that perturb oncogenic Ras specific activity (Baines et al., 2011; Lu et al., 2016; H. Singh et al., 2015; Y. Wang et al., 2013), and for good reason. For certain cancer subtypes such as Non-Small Cell Lung Cancer adenocarcinomas, Ras and Ras effector genes comprise over 40% of identified driver mutations (32% from mutations in KRAS and the remaining 8% from HRAS, NRAS, MAP2K1 and BRAF mutations) (Cancer Genome Atlas Research Network, 2014). The American Cancer Society estimates 2016 will see approximately 220,000 new cases of cancers of the lung and bronchus in the United States alone ("Cancer Facts & Figures 2016 | American Cancer Society," n.d.). Given additional estimates that upwards of 80% of all lung cancers are NSCLC and that within that subdivision adenocarcinomas represent 40% of cases, potentially 20,000 patients this year may be diagnosed with KRAS-mutant NSCLC - highlighting the urgent need for potent and selective treatments of this disease ("Detailed Guide," n.d.). The majority of the following introductory section to Ras and inroads into its

targeting in cancer was originally published in 2013 (Cooper et al., 2013) with Dr. Brian O. Bodemann and Dr. Michael A. White. It provides helpful context for understanding the need for new Ras therapies and identifies creative inroads for novel treatment strategies in the pursuit of Ras-dominated cancer eradication.

Given the frequency of representation of oncogenic Ras expression in human tumors; the numerous demonstrations of required participation of the oncogene in disease initiation; and the ease of detecting the mutant allele in patient samples; agents that directly inactivate the oncogenic protein present themselves as the most compelling opportunity for effective therapy. However, successful invention of such agents has proven to be an indomitable task to date. Here, suffice it to say that intervention strategies directed against the biochemical and cell biological consequences of oncogenic Ras activity rather than against Ras itself has become an important "next best" opportunity. Leveraging this opportunity requires rigorous mechanistic annotation of the key regulatory events engaged by oncogenic Ras that drive tumor initiation and progression together with the isolation of molecular nodes within this regulatory framework that are pharmaceutically addressable.

The current state of the art strongly indicates that oncogenic Ras mobilizes three primary direct effector pathways: the Raf/mitogen-activated protein kinase (MAPK) cascade, the phosphoinositide 3-kinase (PI3K) dependent phosphoinositide second messenger pathway, and the Ral guanine nucleotide exchange factor (RalGEF)/Ral GTPases cascade (Figure 1) (Baines et al., 2011; Camonis and White, 2005). Of these three, the Raf/MAPK and PI3K pathways have been established as bona fide targets in cancer and are associated with successful development of antineoplastic drugs that have shown success in the clinic as single agents and in combination (Britten, 2013). However, pervasive context-specific limitations in the spectrum of sensitive

tumors together with rapid development of resistance to PI3K and Raf inhibitors has forced consideration of additional intervention points within the oncogenic Ras regulatory network (Britten, 2013). A relatively untapped opportunity may lie within the RalGEF/Ral pathway. Below, we will discuss how the study of this pathway and the effects of its inhibition has provided additional insights into the biology of Ras signaling, the role of RalGEF activation in oncogenesis, and a rationale for pursuing components of the RalGEF/Ral regulatory network as intervention targets in cancer.

#### **RalGEF/Ral Pathway Overview**

#### **RalGEFs**

The Ral guanine nucleotide exchange factors (RalGEFs) are a group of enzymes that share the capacity to directly and specifically catalyze GDP/GTP exchange on the Ras-like small G-proteins RalA and RalB, thus promoting their active signaling state (Figure 2). This activity derives from a "CDC25 homology" domain, which by structural analogy to Ras/RasGEF mechanism of action, directly and transiently reduces the affinity of RalA/B for guanyl nucleotide, thus favoring loading with the vastly more abundant GTP in cells (Vigil et al., 2010). Outside of the CDC25-like exchange domains, RalGEFs possess structural features that determine selective coupling to diverse cellular signaling environments. As such they can be parsed into two main families based on the presence of a Ras-association (RA) domain that directly couples Ras activation to Ral activation (RalGDS, RGL1, RGL2/RLF, and RGL3 (Colicelli, 2004; Linnemann et al., 2002; Vigil et al., 2010; Wolthuis, 1997)); or the presence of a pleckstrin homology (PH) domain that presumably enables engagement of RalA/B signaling through Ras-independent mechanisms that remain to be fully described (RalGPS1A/B and RalGPS2) (Bodemann and White, 2008; Rebhun et al., 2000).

As elaborated in detail in later sections, much of the contribution of RalGEF activity to tumorigenesis is likely accounted for by their direct role in RalA/B activation. However, distinct RalA/B-independent activities have been characterized. For example, catalytically-dead RalGDS can enable phosphoinositide-dependent kinase-1 (PDK1) interaction with and activation of AKT during growth factor signaling (Marchlik et al., 2010). In addition, macrophage migration in response to chemoattractants is facilitated by  $\beta$ -arrestin-dependent RalGDS relocalization to the plasma membrane to mediate actin cytoskeletal re-organization (Bhattacharya et al., 2002). Though likely of relevance in normal tissue development and homeostasis, the respective contribution of these activities to Ras-mediated transformation is an open question.

#### Ral GTPases and Their Effectors

Reminiscent of H-, K- and N-Ras, RalA and RalB are 82% identical at the amino acid sequence level, with discriminatory sequences concentrated in a carboxy-terminal "hypervariable" domain (Chien and White, 2003; Colicelli, 2004; Shipitsin and Feig, 2004). They are ubiquitously expressed and indiscriminately activated by oncogenic Ras, but can be selectively engaged by adaptive regulatory signals. The mechanistic basis of the later is unclear but likely involves a combination of distinct subcellular localization features together with dynamic and selective post-translational modifications including phosphorylation, ubiquitination, and perhaps acetylation (Martin et al., 2012; Neyraud et al., 2012; Wu et al., 2005; Yang et al., 2012).

GTP-loaded Ral proteins adopt a physical conformation that enables direct interaction and consequent functional mobilization of three distinct effector pathways described to date. These include RLIP76/RALPB1, ZONAB, and the exocyst (Bodemann and White, 2008). Ral signaling through Ral-interacting protein of 76 kD (RLIP76, also known as RalA-binding protein 1 or RALBP1), regulates clathrin-mediated endocytosis through direct interactions between RLIP76 and the AP2 clathrin adaptor complex at the plasma membrane (Jullien-Flores et al., 2000). The Ral-RLIP76 effector arm also appears to participate in the modulation of cell cycle progression by cytoplasmic sequestration of the cyclin-dependent kinase inhibitor, p27, (Kfir et al., 2005; Tazat et al., 2013; Vigil et al., 2010). ZO-1-associated nucleic acid-binding protein (ZONAB) is a Y-box transcription factor that directly represses mitogen-stimulated gene expression programs. Interaction with Ral-GTP constrains ZONAB to the plasma membrane to facilitate derepression of immediate early gene promoters and responsiveness of cell-cycle progression to mitogen stimulation (Frankel et al., 2005). Finally, the exocyst is a heterooctameric protein complex that participates in vesicular trafficking, dynamic membrane assembly, and the organization and activation of adaptive signaling cascades (Moskalenko et al., 2002; Rossé et al., 2006). Activated Ral proteins directly engage the exocyst through two different subunits, Sec5 and Exo84 (Moskalenko, 2003; Moskalenko et al., 2002). These physical interactions collectively mobilize exocyst complex assembly for selective engagement of the full hetero-octameric complex as well as distinct subcomplexes in response to appropriate regulatory signals (Figure 3). Ral-dependent exocyst holocomplex assembly is required for appropriate organization of polarized plasma membrane domains and for selective signal dependent secretory events (Guo et al., 2000; He and Guo, 2009; Moskalenko et al., 2002; "The Exocyst Complex in Polarized Exocytosis A2 -," 2004). On the other hand, a distinct RalB/Exo84 subcomplex promotes productive interaction of the UNC-51-like kinase 1 (ULK1) and the Beclin1-VPS34 complex to induce autophagy (Bodemann et al., 2011). In addition, a

distinct RalB/Sec5 subcomplex promotes activation of TANK-binding kinase 1 (TBK1) to help engage the host defense response (Chien et al., 2006).

Mechanisms that control signal-dependent discrimination of Ral/effector pairs are a subject of active investigation and likely involve context-dependent modulation of effector concentrations, subcellular localization, and binding affinities. Absolute concentrations of RLIP76 can be dynamically regulated by the cMYB transcription factor and its coactivator p300 (Sehrawat et al., 2013), and multiple splice forms have been detected which produce proteins both with and without Ral-GTP binding domains (Fillatre et al., 2012). Relative concentrations of Ral and Ral effectors can be modulated by collateral signals controlling Ral localization. For example, phosphorylation of RalA at Ser194 by Aurora Kinase A (Aurora A) results in localization of RalA to mitochondria during mitosis, where it interacts with RLIP76 to mediate mitochondrial fission and distribution of mitochondria to daughter cells (Kashatus et al., 2011). In addition, Protein Kinase C alpha (PKCa) phosphorylation of RalB at Serine 198 results in an increase of GTP-bound RalB and the preferential localization of RalB to endomembranes to support vesicular trafficking events (Martin et al., 2012). Finally, evidence that binding affinities can be modulated by post-translational modification of Ral effectors comes from the observation that Protein Kinase C phosphorylation of Sec5 at Serine 89 is required for physical release of RalA from the exocyst at the culmination of exocytosis (Chen et al., 2011a).

In anticipation of consideration of the evidence for Ral pathway participation in oncogenic transformation, it is worth noting that a number of regulatory events supported by Ral GTPases remain to be assigned to specific effector relationships. For example, RalGEF activation of RalA, in response to reactive oxygen species, results in c-Jun N-terminal kinase (JNK)-dependent phosphorylation and activation of the Forkhead transcription factor 4 (FOXO4) (Essers et al., 2004; van den Berg et al., 2013). In addition, RalB can support oncogenic Ras activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and consequent accumulation of Cyclin D (Henry et al., 2000). Active Ral has also been shown to positively regulate the Signal transducer and activator of transcription 3 (STAT3) transcription factor in a Src-dependent manner (Goi et al., 2000). Of note, this pathway results in direct activation of RalGDS expression in a feedback activation loop, perturbation of which may promote cardiac hypertrophy (Kawai et al., 2003; Rifki et al., 2013; Senga et al., 2001). *RalGAPs* 

Opposing the effects of the RalGEFs on RalA and RalB proteins are the Ral GTPaseactivating proteins, or RalGAPs. RalGAPs are functionally homologous to the tuberous sclerosis tumor suppressor complex (TSC), which catalyzes the conversion of GTP to GDP in another Ras-family member, Rheb. Both RalGAPa1 and RalGAPa2 are components of heterodimeric enzymes, with each complex composed of one of the two catalytic alpha subunits ( $\alpha$ 1 or  $\alpha$ 2) and one common beta subunit (Shirakawa et al., 2009). Currently, the most-clearly described mechanism for RalGAP regulation occurs through insulin-induced phosphorylation of RalGAP $\alpha$ 2 by AKT, which inactivates the GAP leading to an increase of GTP-bound RalA (Chen et al., 2011b). One of the primary consequences of this regulatory event is the promotion of exocyst-mediated glucose transporter 4 (GLUT4) relocalization to the plasma membrane in response to insulin. This relationship reveals a co-regulatory connection between PI3K and RalGEF/Ral pathway members for glucose utilization. Additionally, Ral GTPase-activating proteins (RalGAPs) have been shown to inhibit mTORC1 activity through modulation of RalB activity. (Martin et al., 2014) This report also confirmed that RalB exists in a Sec-5/exocystdependent complex with mTORC1 – similar to observations previously made by (Bodemann et

al., 2011) – and suggest RalGAPs negatively regulate AKT/mTORC1 signaling in a possible feedback relationship with AKT-mediated GAP inhibition described above. Further definition of the mechanisms of RalGAP regulation will likely reveal additional integration of RalGEF/Ral pathway activation with adaptive cell signaling events.

#### **RalGEF/Ral Signaling and Cancer: A Rationale for Pathway Inhibition**

Subsequent to the discovery of the RalGEF/Ral pathway as an effector arm of oncogenic Ras, more than 1000 studies have elaborated the contribution of this pathway to pathological regulatory events that support evasion of normal cell and tissue growth and survival restraints. Corruption of the RalA/B regulatory network has been directly implicated in cancer cell survival, proliferation, invasion and metastasis. This literature continues to grow, and current knowledge has been extensively reviewed (e.g. (Bodemann and White, 2008; Neel et al., 2011). Below, this section highlights representative observations that incriminate the RalGEF/Ral pathway as a bona fide antineoplastic target.

#### Evidence from Tumor Cell Models.

Ras effector mutants selectively uncoupled from Raf kinases and PI3Ks (RasE37G), RalGEFs and PI3Ks (RasT35S), or RalGEFs and Raf kinases (RasY40C) (Figure 1) have been broadly employed in gain-of-function studies to estimate the relative contributions of RalGEF, Raf, and PI3K activation to oncogenic Ras-induced tumorigenic transformation (Camonis and White, 2005; Joneson et al., 1996; White et al., 1995). Evaluation of these variants in telomeraseimmortalized human cell models, derived from normal tissues, revealed remarkable contextselective requirements for Ras effector pathway activation (Hamad et al., 2002). In mammary epithelial cells, the combined effects of all three effector arms were required to support xenograft tumor formation (Rangarajan et al., 2004). However, RalGEF activation together with Raf activation or PI3K activation was sufficient to transform human fibroblasts or human kidney epithelia respectively (Rangarajan et al., 2004). Inferred, is a unanimous dependence on Ral pathway activation for oncogenic Ras-induced tumorigenic transformation. Selective activation of the Ral GTPases by Ras was also shown to be sufficient to promote bone metastasis in a prostate cancer xenograft model (Yin et al., 2007); to mimic defective myeloid differentiation characteristic of hyperactive Ras signaling in acute myeloid leukemia (AML) (Omidvar et al., 2006); and to mediate Raf/MAPK-independent inhibition of skeletal muscle differentiation by Ras (Ramocki et al., 1998).

Loss-of-function studies have also revealed wholesale participation of RalA and RalB signaling in the maintenance of tumorigenic phenotypes. RNAi-mediated evaluation of the distinct contributions of RalA and RalB to cancer cell viability revealed that RalA expression was necessary for anchorage-independent proliferation of transformed cells, while RalB expression was necessary for cancer cell survival (Chien and White, 2003). The relevance of these phenomena to tumorigenicity was established with xenograft models of pancreas cancer with the observation that Ral signaling is required for tumor metastasis (Lim et al., 2006). Subsequent studies have iterated similar observations in other disease models together with directly implicating the Ral effector proteins RLIP76, Sec5, and Exo84 (Issaq et al., 2010; Lim et al., 2005; Martin et al., 2011; Mishra et al., 2010; Oxford et al., 2007; Zipfel et al., 2010). *Evidence from Genetically Engineered Mouse Models* 

Some of the most compelling evidence supporting the RalGEF/Ral pathway as an intervention target comes from studies perturbing pathway activation in mouse models of cancer. An elegant "multi-hit" transgenic model employed stochastic expression of Ras effector mutants in lung epithelia to query the relative requirements of Raf, RalGEF and PI3K pathway activation in support of oncogenic K-Ras-induced lung adenocarcinoma (Musteanu et al., 2012). This strategy employed a transgene carrying each of the three effector mutants in an inverted orientation with respect to their promoters and flanked by heterotypic FRT sites. Following Creinduction of randomized expression of the effector-selective Ras mutants from the transgene in the lung, self-selected tumors were isolated to determine the frequency of co-occurrence of Ras effector mutant expression within the tumors. While each possible combination was recovered, the vast majority (over 85% of examined lesions) expressed all three effector mutants, indicating a required collaborative role for RalGEF pathway activation in this model.

Mice with whole-animal homozygous deletion of RalGDS are viable, and outside of minor defects in stress adaptation (Rifki et al., 2013), are overtly normal. Importantly, carcinogen induced skin papilloma formation and progression were markedly delayed in RalGDS knock-out mice as compared to wild-type littermates (González-García et al., 2005). Tumor histology displayed enhanced apoptosis of neoplastic cells in these mutant mice, indicating a role for RalGDS in support of tumor cell survival in this model. These observations suggest agents that impair RalGDS function may have tumoricidal activity and yet be well tolerated in normal tissues.

Genetic ablation of RalA or RalB is well borne in the laboratory mouse, however compound deletion of RalA and RalB is embryonic lethal (Peschard et al., 2012). This indicates that, as expected, some level of signaling through the Ral regulatory network is a developmental necessity. When conditional alleles were tested in a mouse model of oncogenic K-Ras induced lung cancer, compound inactivation of RalA and RalB (but not individual inactivation of RalA or RalB) in oncogenic K-ras expressing lung epithelia significantly reduced tumor burden (Peschard et al., 2012). This is exciting in that it clearly demonstrates that K-ras lung tumors are addicted to Ral signaling, however additional work is required to determine if post-mitotic lung epithelia are robust to Ral pathway inactivation.

#### Evidence from Clinical Correlates

In contrast to Raf kinases and PI3Ks, high frequency recurrent mutations in RalGEFs in particular, or components of the Ral G-protein regulatory network in general, have not been detected in human tumors. Low frequency, non-recurrent alterations, have been observed in RalGEFs, RalA/B, and exocyst subunits across multiple disease settings, though the extent to which these are driver versus passenger mutations remains to be investigated (Bodemann and White, 2008). On the other hand, elevated accumulation of "active" GTP-loaded RalA and RalB protein has been detected in cell lines and tissue specimens from pancreas, colon, melanoma, bladder and malignant peripheral nerve sheath tumors relative to corresponding normal tissues (Bodempudi et al., 2009; Lim et al., 2006; Martin et al., 2011; S. C. Smith et al., 2007; Zipfel et al., 2010). This activity does not always correlate with the presence of oncogenic Ras mutations. For example, aberrant activation of RalA has been detected in a panel of human melanoma cell lines, independent of the mutational status of the commonly mutated melanoma genes *BRAF* or *NRAS* (Zipfel et al., 2010), revealing the potential for the new classification of some melanoma patents as "Ral-A positive".

A directed effort to detect clinical correlations, reporting elevated Ral signaling in human malignancies, leveraged genomic expression profiling. A transcriptional signature composed of 39 RalA and RalB-responsive genes was used to query corresponding expression signatures derived from human tumors with associated outcome data (S. C. Smith et al., 2012). Tumors with a high Ral signature score were associated with poor patient prognosis for both bladder and prostate cancer. Conversely, squamous cell carcinomas with a high Ral expression signature were associated with better patient prognosis, consistent with reports that Ral proteins can have a tumor suppressive role in the skin (Sowalsky et al., 2011; 2010). The later observation provides a cautionary note for the importance of establishing the appropriate disease contexts that will be responsive to anti-Ral intervention strategies.

#### Modes of RalGEF/Ral Pathway Inhibition

#### Inhibiting Ral Prenylation

All evidence to date indicates that RalGEF/Ral pathway activation and function requires localization of Ral G-proteins to cell membranes. Plasma membrane and endomembrane targeting is a consequence of RalA/B protein carboxyl-terminal prenylation by geranylgeranyltransferases. An expanding cadre of geranylgeranyltransferase inhibitors (GGTI) have been developed that exhibit promising antineoplastic activity in preclinical models (Berndt et al., 2011). For example, the dihydropyrrole ring derivative, P61A6, effectively blunted tumor cell proliferation in culture and xenograft models of non small cell lung cancer (Zimonjic et al., 2013). While GGTIs have pleiotropic consequences on the geranylgeranyl "proteome", a number have been shown to directly inhibit membrane localization and activity of Ral g-proteins, and there is evidence that perturbation of RalA/B signaling can account for GGTI antineoplastic activity in at least some contexts. This comes from the observation that artificially bypassing Ral pathway sensitivity to GGTIs, by engineering carboxy-terminal farnesylation moieties on RalA and RalB, was sufficient to rescue GGTI inhibition of pancreas cancer cell survival and anchorage-independent growth (Falsetti et al., 2007). These observations suggest that Raladdicted tumors could become addressable with a drug targeting geranylgeranyltransferases.

#### Inhibiting RalGEF/Ral Pathway Phosphorylation

Ostensibly, integration points between protein kinase activity and Ral pathway activation could represent fit targets for chemical intervention given the extensive development of kinase inhibitors as drugs over the past decade. As described above, multiple protein kinases are suspected to directly modulate accumulation and function of "active" GTP-loaded RalA and RalB proteins (Figure 4). Direct phosphorylation of RalB by Protein Kinase C (PKC) appears to be required for growth and metastatic capacity of bladder cancer cells (H. Wang et al., 2010). Similarly, there is evidence that direct phosphorylation of RalA at Serine 194 by Aurora Kinase A (Aurora A) promotes RalA activation and anchorage-independent growth (Wu et al., 2005). Cyclin-Dependent Kinase 5 (CDK5) has also been nominated as a key regulator of Ral pathway signaling, as shRNA-mediated depletion of CDK5 resulted in reduced RalA and RalB activity and reduced colony formation in pancreatic cancer cell lines (Feldmann et al., 2010). The specific CDK5 substrate responsible for this phenotype remains unknown; however this inhibition was partially rescued by overexpression of the RalGEF, Rgl2, suggesting the shRNAmediated perturbation was at the level of Ral protein activation (Feldmann et al., 2010). Finally, AKT inhibition is likely to restrain Ral pathway activation in some contexts given its direct role in suppression of RalGAP2 activity (Chen et al., 2011b).

A challenge for effective mobilization of kinase inhibitors against Ral-addicted tumors is the diversity of substrates serviced by PKC, Aurora A, AKT and CDK5. These kinases have been broadly implicated in human disease, and chemical inhibitors have broad consequences in both normal and diseased tissues. As such, clinical effectiveness as a consequence of collateral activity on Ral pathway activation will likely be difficult to assign. An exception could be selective inhibition of PKCα. This kinase impacts multiple points in the RalB/Sec5 pathway (Chen et al., 2011a; Martin et al., 2012) which may enhance the therapeutic index of PKC isozyme-preferential inhibitors (Mochly-Rosen et al., 2012), particularly if an effective molecular response indicator was developed that predicts addiction to RalB/Sec5 pathway activity.

#### Inhibiting Ral/Ral-Effector Binding

Lessons from Ras suggest that direct and specific inhibition of the protein-protein interaction interface between a G-protein and its effector is unlikely to be accomplished using reagents with reasonable pharmacological properties. The conundrum is the large and simple feature space characteristic of interaction motifs that form antiparallel  $\beta$ -sheets. Following the structural paradigm of Ras/Raf, Ras/PI3K, and Ras/RalGEF interactions, co-crystals indicate that the Ral-binding domains of Sec5 and Exo84 associate with the RalA/B effector loop through anti parallel beta strands (Fukai et al., 2003; Jin et al., 2005; n.d.). This iterates the dilemma thwarting strategies to directly target oncogenic Ras. A notable exception is the Ral-binding domain of RLIP76. This 54 amino acid motif interacts directly with the RalA/B effector loop in a manner that occludes all other effector interactions and which is sufficient to block Ral pathway activation in cells (Chien et al., 2006; Fenwick et al., 2010; Moskalenko et al., 2002). However, unlike Sec5 and Exo84, the RLIP76 Ral binding domain folds into an  $\alpha$ -helical coiled-coil. NMR studies have mapped residues 393-436 within the coil as responsible for direct interaction with the RalA/B effector loop (Fenwick et al., 2010). This presents a compelling opportunity to leverage stapled peptide technology for development of an intervention agent that directly prevents endogenous activated RalA and RalB proteins from engaging their cognate effectors. Structurally constrained short helical peptides are at the forefront of protein mimics with

pharmacological properties, and have shown promising results in a variety of preclinical models of cancer using agents that directly target NOTCH and BCL2 family members (Azzarito et al., 2013; Moellering et al., 2009; Walensky et al., 2004). It is anticipated that progress in those arenas may directly inform stapled peptide-based strategies for Ral pathway intervention.

Following this strategy, in collaboration with the laboratories of Drs. Helen Mott and Darerca Owen at the University of Cambridge, I performed biochemical and cell biology experiments to validate that a stapled-peptide mimic of RLIP a-helical coiled coil domain inhibits RalB/effector binding and attenuates autophagic flux in cells. The full results from this collaboration can be found in our recent paper by (Thomas et al., 2016). Endogenous RalB immunoprecipitation experiments revealed that 24 hour pretreatment with SP1 (high affinity RalB-specific stapled peptide) markedly attenuated RalB engagement with Sec5 (Figure 5A, asterisk), where as SP6 (low affinity RalB stapled peptide control) elicited a slight decrease in Sec5 association. I did not observe strong association of RLIP76 under un-treated conditions, so it was difficult to assess the level to which SP1 could specifically perturb RalB/RLIP76 interactions. However, to address the functional consequence of SP1 treatment on RalBdependent signaling, I harnessed the requirement of RalB signaling via the exocyst (Exo84 in particular) in the promotion of autophagosome formation and maturation during cell nutrient deprivation (Figure 5B). We decided to utilize starvation induced autophagic clearance of autophagosomal adaptor protein microtubule-associated protein 1A/1B-light chain 3 (LC3). Upon nutrient depletion by Earle's Balanced Salt Solution (EBSS), LC3 is recruited to and subsequently degraded by mature autophagolysosomes (Figure 5C). 24-hour pretreatment with SP1 but not control SP6 was potently inhibited clearance of LC3 under starvation-induced clearance (EBSS) and above nutrient replete basal autophagy conditions (DMEM-serum free)

(Figure 5D). I furthermore validated that that SP1 was not indiscriminately inhibiting autophagy, as it did not perturb starvation-induced activation and nuclear localization of GFP-TFEB, a RalB-independent process (Figure 5E). My work in collaboration with *Thomas, et al.* shows the effective application of stapled-peptide based strategies in the inhibition of Ral GTPases. As this intervention was rationally designed to target the highly specific G-protein-effector binding interface, it will potentially escape the off-target effects that continue to limit the development of potent, yet selective, small molecules inhibitors.

#### Inhibiting Ral Downstream Effector Signaling

Accumulating evidence indicates Ral signaling may lie at the nexus of coordinated modulation of cell growth versus metabolic self-renewal and thus may offer a target to disrupt that balance in metabolically deranged tumors. In particular, RalGEF/Ral signaling, through activation of Phospholipase D (PLD) and Sec5 exocyst subcomplexes, supports amino-acid and growth factor induced activation of the pro-growth mammalian target of rapamycin complex 1 (mTORC1) (Bodemann et al., 2011; Maehama et al., 2008; Ou et al., 2011; L. Xu et al., 2011). In contrast, nutrient deprivation engages a RalB-Exo84 signaling complex that induces autophagy, a process which is antagonistic to pro-growth signaling by mTORC1 (Bodemann et al., 2011). Intriguingly, RalGDS homozygous null mice, which are resistant to carcinogeninduced papillomas, also have reduced mTORC1 activation and reduced autophagic flux in the heart, which correlates with resistance to stress-induced cardiac hypertrophy (Rifki et al., 2013). These observations may foreshadow opportunities to exploit aberrant nutrient sensing mechanisms in cancer through tailored inhibition of Ral signaling. For example, uncoupling RalGEF/Ral from mTORC1 in K-Ras tumors could result in a mal-adaptive autophagic response with collateral consequences on sensitivity to drugs inhibiting autophagolysosome maturation.

The corruption of TBK1 activity by RalB signaling during oncogenic transformation also invites consideration of TBK1 itself as an antineoplastic target. The RalB-Sec5-TBK1 subcomplex can directly engage AKT and AKT-dependent mTORC1 to promote survival of tumor lines in culture and in mouse xenografts (Ou et al., 2011). This activity can deflect programed cell death that would otherwise engage in response to oncogenic stress (Chien and White, 2008). There are currently several potent TKB1-specific inhibitors, with distinct chemotypes, that show antineoplastic activity in cells and animals (Clark et al., 2011; Molina-Arcas et al., 2013; Newman et al., 2012; Ou et al., 2011). These observations formed the foundation of my dissertation work examining mechanistic consequences of TBK1 inhibition and discovery of biomarkers directing the context-specific application of TBK1-based therapy in the treatment of cancer.

#### Conclusion

At its most rudimentary level the RalGEF pathway is simply a GTPase cascade, whereby GTP-loading of Ras proteins instructs GTP-loading of Ral proteins. As such, one might forecast that efforts to target RalGEF signaling in cancer are destined for decoration with the same albatross that graced past efforts to target Ras itself (Coleridge, 1906). On the other hand, molecularly targeted drug development is a nascent science, growing in sophistication, such that the term "undruggable" is only transiently relevant. As described above, consideration of elements within the RalGEF signaling network as oncology targets is supported by clear indications of obligate contributions of these elements to tumor initiation and progression. In addition, several nodes within this network are pharmaceutically addressable with current intervention technologies (Figure 4). Through my collaboration with (Thomas et al., 2016), I

helped demonstrate the success with which rationally designed anti-RalB stapled peptides can disrupt RalB-effector interactions in cells and perturb RalB-regulated autophagy. Hopefully, our findings will spur additional advances in this field as our approach is applied in the inhibition of other currently "undruggable" protein-protein interactions.

On the other hand, many of the same elements that may form weaknesses in cancers' defenses are also centrally involved in critical developmental pathways, homeostasis of selfrenewing tissues, and post-developmental organ function. Successful prosecution of Ras- and RalGEF- pathway intervention in cancer will require careful evaluation of the on-target toxicities that may stem from disruption of cell polarity, organellar maturation, regulated secretion, and host defense signaling. In addition, it will require the co-development of molecular response indicators to serve as enrollment biomarkers for stratification of patients harboring disease that is responsive to pathway inhibition. This issue in particular is potently illustrated by the conundrum surrounding prediction of the appropriate disease setting where TBK1 inhibitors will work. Cancer cell models predict that TBK1-addiction is significantly correlated with the expression of oncogenic Ras (Barbie et al., 2009). However, accumulating evidence suggests the presence of an oncogenic Ras mutation is not sufficient to specify TBK1-addition (Muvaffak et al., 2014; Ou et al., 2011), and additional molecular response indicators will need to be developed to successfully test TBK1 as an oncology target (J.-Y. Kim et al., 2013a). It is to this end that I undertook the line of investigation described in the following chapter.

### Figure 1



#### Figure 1. Primary Ras Effector Pathways

(A) Oncogenic Ras activates three direct effector pathways: the Raf/mitogen-activated protein kinase (MAPK) cascade, the phosphoinositide 3-kinase (PI3K) dependent phosphoinositide second messenger pathway, and the Ral guanine nucleotide exchange factor (RalGEF)/Ral GTPases cascade. Effector-specific Ras12V mutants promoting one of the three direct Ras effector pathways are as follows: T35S: Raf/MAPK signaling, Y40C: PI3K signaling, and E37G: RalGEF signaling. Image from (Cooper et al., 2013) (Cartoon by Dr. Brian O. Bodemann)





#### **Figure 2. Modulators of Ral GTPases**

(A) The Ral guanine nucleotide exchange factors (RalGEFs) directly and specifically catalyze GDP/GTP exchange on RalA and RalB, thus promoting an active signaling state in response to diverse stimuli (Baines et al., 2011; Camonis and White, 2005). RalGEFs can be parsed into two main families based on the presence of a Ras-association (RA) domain (RalGDS, RGL1, RGL2/RLF, and RGL3 (Colicelli, 2004; Linnemann et al., 2002; Vigil et al., 2010; Wolthuis, 1997); or the presence of a pleckstrin homology (PH) domain (RalGPS1A/B and RalGPS2) (Bodemann and White, 2008; Rebhun et al., 2000). Opposing the effects of the RalGEFs on RalA and RalB proteins are dimeric Ral GTPase-activating protein complexes, RalGAP1 and RalGAP2. RalGAP2 activity is negatively regulated by AKT (Chen et al., 2011b). Image from (Cooper et al., 2013) (Cartoon by Dr. Brian O. Bodemann)


#### Figure 3. The Exocyst Is a Multi-Function Ral Effector Complex

(A) The exocyst is a hetero-octameric protein complex that participates in vesicular trafficking, dynamic membrane assembly, and the organization and activation of adaptive signaling cascades (Moskalenko et al., 2002; Rossé et al., 2006). Activated Ral proteins directly engage the exocyst through two subunits, Sec5 and Exo84 (Moskalenko, 2003). These physical interactions collectively mobilize exocyst complex assembly into the full hetero-octameric complex as well as distinct subcomplexes in response to appropriate regulatory signals. Inhibition of Ral/Exocyst signaling in cancer is likely to have pleotropic effects on other Ral/exocyst downstream functions in non-neoplastic tissue. Image from (Cooper et al., 2013) (Cartoon by Dr. Brian O. Bodemann)





### Figure 4. Intervention Opportunities within RalGEF/Ral Target Space

Image from (Cooper et al., 2013) (Cartoon by Dr. Brian O. Bodemann)

### Figure 5



**GFP-TFEB HeLa** 

# Figure 5. RalB Stapled Peptide SP1 disrupts RalB/Ral-effector binding and perturbs autophagic clearance of LC3 in cells

(A) HEK293T cells were treated for 24 h prior to endpoint with or without the stapled peptide indicated (at 100μM). All cells were starved in EBSS 90 min prior to endpoint. Endogenous RalB was immunoprecipitated with mouse anti-endogenous RalB antibody. Immunoblotting was conducted with primary antibodies against RalB (Rabbit anti-RalB), RLIP76 (Rabbit anti-RLIP76), and Sec5 (Mouse anti-Sec5). Asterisk (\*) marks band specific to Sec5 or RLIP76. Ab = mouse anti-RalB antibody alone. WCL = Whole Cell Lysate.

(B) Cartoon of the role of RalB/Exo84 in supporting autophagy.

(C) In HeLa cells stably expressing GFP-LC3, bright -LC3-positive puncta accumulate under high nutrient conditions (DMEM, left image). This signal is diminished under low nutrient conditions (EBSS, right image), as GFP-LC3 is degraded during RalB-dependent autophagy. Images provided by Ms. Chensu Wang (UTSW).

(D) SP1, but not SP6, specifically blocks RalB-dependent turnover of GFP-LC3 under nutrientrich (DMEM-H) and nutrient-deprived (EBSS) conditions. Columns represent fluorescenceintensity value ratios of GFP-LC3:Hoechst stain following 24-hour pretreatment with peptides in GFP-LC3 HeLa cells (n=4).

(E) Unlike their ability to perturb autophagic clearance of GFP-LC3 in (D), SP1 does not perturb starvation-induced activation and nuclear localization of GFP-TFEB, a RalB-independent process.

This figure was originally published in (Thomas et al., 2016).

### **CHAPTER TWO**

## CONTEXT-SELECTIVE SUPPORT OF THE AKT/mTOR REGULATORY AXIS BY TANK-BINDING KINASE 1 (TBK1)

### Cross-Examination of Small Molecule Inhibitor Screens in NSCLC Reveals the Intersection between TBK1 and AKT/mTOR Regulatory Axis Target Space

Given the need for new strategies to defeat Ras-dominated cancers and the potential opportunities of targeting Ral-pathway down stream effector, Tank-Binding Kinase 1 (TBK1), I began my work to answer two interrelated and fundamental questions: What are molecular indicators of TBK1 sensitivity in cancer and how do they reveal or reflect previously unknown mechanisms of TBK1 function in non-neoplastic cell homeostasis? In pursuit of these aims I employed two small molecule inhibitors of TBK1, BX795 and Compound II, that are known to potently and selectively inhibit TBK1 and its homolog, IKKe (Clark et al., 2009; Ou et al., 2011). We assayed the relative cell viability after treatment with either inhibitor via multipoint compound dose-response curves in 100 NSCLC cell lines with the assistance of the High-Throughput Screening (HTS) Core Facility at UT Southwestern. Both compounds exhibited a broad spectrum of sensitivity, spanning high nanomolar to mid-micromolar mean EC50 (Figures 6A-B, and Table 1). They also displayed significantly correlated patterns of sensitivity, as calculated by ED50 and area-under-the-curve (AUC) (Figures 6C-D). Additionally, celldoubling times did not correlate with sensitivity (Figures 6E-F), lending confidence that the significantly correlated potency of both molecules was not biased by rates of cell division.

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To generate mechanistic hypotheses for our observed selective sensitivity to TBK1 inhibitors, we chose to harness the power of orthogonal datasets that profiled sensitivity of NSCLC cells to compounds with diverse target space. With the generous assistance of Dr. Rachel Vaden, I examined how well sensitivity to our TBK1 inhibitors correlated with sensitivity to other compounds of known mechanism of action. We hypothesized that compound toxicity profiles that strongly correlated with TBK1 inhibitors would suggest they may disrupt the same or similar signaling networks. To this end, we first identified the intersection of NSCLC cell lines tested in our hands with those subjected to two independent, though not wholly mutually exclusive, small molecule screens conducted by separate research groups, (Garnett et al., 2012) and (Seashore-Ludlow et al., 2015). We then compared the sensitivity profiles of our TBK1 inhibitors to those of the small molecules tested in those studies. Of the compounds examined by Garnett et al., 131 displayed a measurable correlation with our NSCLC data, of which two of the most-positively correlating compounds targeted the AKT/mTORC1 pathway (Figures 6G-H). Comparison between our sensitivity profiles and those of compounds examined by Seashore-Ludlow, et. al. revealed a positive correlation between Compound II and GSK1059615, a PI3K/mTOR inhibitor (Rank 8 of 481) (Figure 6I). Interestingly, Momelotinib (aka. CYT387)(Zhu et al., 2014), another potent TBK1 inhibitor, was ranked 49 of 481 (Figure 6J). Concurrently, given previous evidence of TBK1's role in supporting KRAS-mediated oncogenic transformation (Barbie et al., 2009; Chien et al., 2006; Ou et al., 2011), we examined whether correlations within the KRAS-mutant subpopulation of NSCLC lines tested would return additional insights into possible mechanisms of TBK1 sensitivity. Temsirolimus, an analog of Rapamycin and potent mTORC1 inhibitor (Chiarini et al., 2014), exhibited positive correlation with our TBK1 inhibitors, which was markedly enhanced in the KRAS-mutant (MUT)

subpopulation (Figures 6K-M). Examination of the KRAS-mutant subpopulation also retuned an enriched correlation between GSK2636771, another PI3K/mTOR inhibitor, and Compound II (Figure 6N). These results suggest that cell lines sensitive to TBK1 inhibitors may also especially depend on signaling through the PI3K/AKT/mTORC1 pathway, because TBK1 plays a role in supporting signaling through PI3K, AKT, and/or mTORC1. Corroborating this idea, perturbation of TBK1 in NSCLC has been reported to perturb phosphorylation of multiple nodes in the AKT/mTORC1 signaling network (J.-Y. Kim et al., 2013b). These members include the Tuberous Sclerosis Complex 2 (TSC2), Regulatory-associated protein of mTOR (Raptor), proline-rich Akt substrate of 40 kDa (PRAS40), Ras-related GTP binding C and D (RagC, RagD) p70-S6 Kinase (S6K), and ribosomal protein S6 (S6) (Figure 6O). This observation, in tandem with our correlation analyses, prompted the question of whether TBK1 functions as a bona fide regulator of mTORC1 signaling.

# TBK1 is Required for AKT/mTORC1 Activation during the "Starved-to-Fed" State Transition

While overexpression of TBK1 was sufficient to elicit activating, auto-phosphorylation on mTOR (pS2481) in a TBK1 kinase activity-dependent manner (Figure 6P) in HEK293FT cells, we wanted to assess whether TBK1 was necessary for mTORC1 activation in cells. mTORC1 activity is attenuated by amino acid nutrient scarcity and potently activated by subsequent amino acid nutrient repletion resulting in a "starved-to-fed" state transition (Hara et al., 1998; Huang and Fingar, 2014; Jewell et al., 2013). These nutrient availability-governed signaling changes can be experimentally recapitulated by cell culture amino acid starvation, followed by re-feeding with free essential amino acids, which results in ablation and then sharp induction of

phosphorylation of mTORC1 substrates, such as p70 S6 Kinase (S6K) (pT389) (Figure 8A). We utilized this paradigm in mouse embryonic fibroblasts (MEFs) to discover that homozygous deletion of TBK1 resulted in a marked reduction in mTORC1's ability to phosphorylate S6K (Figure 7A). Loss of TBK1 also resulted in decreased phospho-AKT (pT308 and pS474) consistent with TBK1's function as a direct activator of AKT (Ou et al., 2011; Xie et al., 2011). I also observed decreased AKT-mediated phosphorylation of TSC2 (pT1462), but the phenotype was subtle at best when observed. While homozygous deletion of TBK1 in animals is embryonic lethal (Bonnard et al., 2000), mice harboring partial N-Terminal kinase domain deletions in TBK1 are viable (Marchlik et al., 2010). Lower levels of a catalytically inactive TBK1 transcript are still translated in both heterozygous  $(+/\Delta)$  or homozygous deletion  $(\Delta/\Delta)$  mice, but only  $(\Delta/\Delta)$ MEFs exhibited uncoupling of AKT and S6K phosphorylation from nutrient stimulation (Figure 7B). The decreased AKT/mTORC1 pathway phosphorylation seen in the absence of functional TBK1 remained sensitive to mTOR inhibitors Rapamycin and Torin 1 (Figures 8B-C), suggesting that TBK1 tunes mTORC1 activity, rather than turn it completely on or off. Transient depletion of TBK1 by siRNA in two developmental lineage-distinct cancer cell lines was also sufficient to blunt AKT and S6K phosphorylation in response to nutrient stimulation (Figures 7C-D). In addition to genetic perturbation of TBK1 function and abundance, I also observed that our TBK1 inhibitors were potently sufficient to disrupt mTORC1 activation. As BX795 has also been reported to inhibit PDK1 (the protein product of PDPK1) (Clark et al., 2009), I tested this compound in PDPK1 null (-/-) HCT116 cells and observed the potent perturbation of AKT and S6K phosphorylation upon nutrient re-addition. BX795, Compound II, and a experimental TBK1/IKKe inhibitor developed by Glaxo-Smith-Kline (GSK2292978A, aka GSK) (Richter et al., 2009) (Figure 8D) also displayed potent inhibition of S6K phosphorylation in immortalized

MEFs (Figure 7F). Together, these data indicate that TBK1 is required for the activation of AKT/mTORC1 signaling during the starved-to-fed state transition.

#### TBK1 Physically Engages the AKT/mTOR Regulatory Axis at Multiple Nodes

Concurrent to my discovery that TBK1 was required for AKT/mTORC1 activation in response to nutrient stimulation in cells, we also wanted to examine the degree of physical proximity of TBK1 to the key regulatory molecules governing this network. I collaborated with two colleagues in our laboratory to experimentally assess this question, Yi-Hung Ou, PhD and Mr. Aubhishek Zaman. They gathered the data contained in Figure 9 and their individual contributions are also noted in the figures. However, I completed the figure layout and formatting, as well as provided the following results summary and analysis. RNAi-mediated depletion of known TBK1 adaptors (e.g. AZI2, NEMO, AKT, Sec5, Sec8, etc.) (Figure 10) exhibited inhibition of nutrient-dependent mTORC1 signaling similar to depletion of TBK1 alone (Figures 7C-D), suggesting disruption of TBK1's interaction space may similarly affect TBK1-dependent functions in the regulation of mTORC1. Testing the interaction between TBK1 and mTOR directly, we observed that mTOR immunoprecipitates (IP) with endogenous TBK1. Furthermore, mTOR displayed increased association with TBK1 as well as increased activating phosphorylation (pS2448) in that TBK1 complex by nutrients in a time-dependent manner (Figure 9A). To examine the functional contributions of TBK1 to mTOR in the TBK1-mTOR complex, we overexpressed and immunoprecipitated WT or Kinase-Dead (KD) Mutant (K38M) TBK1. Intriguingly, while both TBK1-WT and TBK1-KD equivalently captured AKT/mTORC1 regulatory interactors (mTOR, Raptor, AKT, TSC2, Exo70), TBK1-KD was sufficient to prohibit nutrient-induced phosphorylation of AKT and mTOR, as well as basal mTOR

phosphorylation under starvation, in the TBK1 complex (Figure 9B). TBK1 association with mTORC1 was also independently identified in a TBK1 IP-mass spectrometry analysis, which returned mTORC1 definitive subunit, Raptor, and mTOR substrate, S6K, as top hits among specific TBK1 interactors (Figure 9C). Co-IP experiments also revealed a robust interaction between TBK1 and S6K, as well as a weak association between TBK1 and mTORC1 substrate and activator of autophagy, Unc-51 Like Autophagy Activating Kinase 1 (ULK1) (Figure 9D). Though TBK1 associated with mTORC1-regulating and -regulated kinases, we also probed to see whether TBK1 exhibited affinity for the Rag GTPases (RagA, RagB, RagC, or RagD) that also play a critical role in the activation of mTORC1 by amino acid nutrients (Sancak et al., 2008). This inquiry was also directed by the fact that depletion of TBK1 corresponded to an observed decrease of RagC and RagD phosphopeptide abundance in phosphoproteomics data from ((J.-Y. Kim et al., 2013b)) (see also Figure 6O and 11D). Intriguingly, IP of either TBK1 (Figure 9E) or the Rag GTPases (Figure 9F) revealed a strong preference of TBK1 for RagD, though a weak interaction is detectable between TBK1 and RagC. As the Rag proteins function in cells as heterodimers (A or B pairs with either C or D), we examined Rag GTPase heterodimer-TBK1 interactions, and discovered the preferential affinity of TBK1 for RagB/D heterodimers (Figure 9G). Additionally, we examined the extent to which TBK1 affinity for RagD was dependent on its differential nucleotide-bound states and observed a slight preference of TBK1 for either constitutively GDP-bound (S77L) or GTP-bound (Q121L) RagD mutants over WT RagD. (Figures 9H).

## TBK1 Follows Permissive and Instructive Mechanistic Routes to Regulate AKT/mTOR Signaling

Though TBK1 resides in AKT/mTORC1 regulatory network complexes and is required for mTORC1 activation by nutrients after starvation, we wanted to determine which input points of mTORC1 regulation are directly impacted by TBK1 activity. To assess this, we first sought to confirm whether TBK1's contribution to mTORC1 was dependent on AKT by testing BX795 and/or AKT allosteric inhibitor, MK2206 in PDPK1 -/- HCT116 cells (Figure 11A). Treatment with BX795 and MK2206, either alone or in combination, exhibited equivalent inhibition of S6K phosphorylation upon nutrient stimulation in support of the hypothesis that TBK1 regulation of mTORC1 is AKT-dependent. However, AKT positively regulates mTORC1 along multiple routes, the chief of these residing in the AKT-dependent inactivation of the Tuberous Sclerosis complex (TSC1/2) and its inhibition of mTORC1. We have observed that TSC2-/-, p53-/immortalized MEFs exhibit markedly higher phospho-S6K than their TSC2 WT p53-/immortalized counterparts, even in the starved state (Figure 11G). This is partially consistent with previous studies of the role of TSC1/2 in amino acid nutrient sensing by mTORC1, which reported low starved-state p-S6K (pT389) that was nevertheless sensitive to amino acid addition in a TSC2 -/- independent manner (Nobukuni et al., 2005; E. M. Smith et al., 2005). The experimental GSK TBK1 inhibitor potently ablated this activating phosphorylation in TSC2 -/-MEFs (Figures 11G), directing our attention to other paths of AKT input to mTORC1.

Apart from its role in removing mTORC1 repression by TSC1/2, AKT can also permissively modulate the complex's activity through phosphorylation of PRAS40 at threonine 246 (Haar et al., 2007; Sancak et al., 2007). This action promotes dissociation of PRAS40 from Raptor, which subsequently results in increased activation of mTORC1. We were able to confirm TBK1-dependent loss of PRAS40 phosphorylation by AKT upon TBK1 knockdown with siRNA (Figures 7C-D) and TBK1 inhibitor treatment in PDPK1 -/- HCT116 cells (Figure 11A) or immortalized MEFs (Figure 11G). We furthermore confirmed that loss of TBK1 activity in  $(\Delta/\Delta)$  MEFs corresponded to increased association of PRAS40 with Raptor, commensurate with a TBK1-dependent phosphorylation of PRAS40 by AKT (Figures 11B-C). This increased association was robustly maintained, even under detergent conditions (11C) reported as sufficient to disrupt mTOR/Raptor interactions (D.-H. Kim et al., 2002; L. Wang et al., 2008; 2006).

To uncover additional TBK1-dependent mechanisms of mTORC1 regulation, I again examined the phosphoproteomics data from (J.-Y. Kim et al., 2013b), and observed that TBK1 depletion corresponded to a roughly threefold reduction of S6K phosphopeptides corresponding to T421 and S424 (Figure 11D). Phosphorylation of S6K at T421 and S424 is reported to promote S6K activation and phosphorylation by mTORC1, through the disruption of C-terminal autoinhibitory domain repression of the kinase (Schalm and Blenis, 2002; (Magnuson et al., 2011). Though JNK and insulin-activated, proline-directed serine/threonine protein kinases are reported as kinases for this site (Mukhopadhyay, et. al 1992; (J. Zhang et al., 2013), it remains an open question as to what other kinases might also govern T421 and S424 phosphorylation. We found that nutrient stimulation induced phosphorylation at T421/S424, which was sensitive to TBK1 homozygous deletion in MEFs (Figure 11E) and to TBK1 inhibitors in both TSC2 WT and TSC2 -/- immortalized MEFs (Figure 11G). Given our data above showing a physical proximity between S6K and TBK1 (Figure 9D), we hypothesized that TBK1 might directly promote phosphorylation of S6K at T421/S424 in a TBK1/S6K complex, and observed that this occurs in a TBK1 kinase-dependent manner (Figure 11F). Together, these data reveal that TBK1, through its multi-nodal connections to mTORC1 signaling regulators (11H), can provide at least two specific mechanistic contributions to mTORC1 activation by amino acid nutrients. First,

TBK1 can permissively regulate mTORC1 activity through AKT-mediated phosphorylation of PRAS40. Secondly, TBK1 can promote phosphorylation of S6K C-terminal residues, commensurate with necessary conditions for maximum activation of S6K by mTORC1.

### **Ras-Class Mutant/Mesenchymal Status Indicates Sensitivity to TBK1 Inhibition in NSCLC**

These novel insights into TBK1's role in mTORC1 regulation show the usefulness of our strategy to harness the intersection between pan-institutional chemical screen data and our own TBK1 inhibitor sensitivity profiles to glean insights into the fundamental biology of our target of interest. Work by our lab and others have identified that TBK1 can form a synthetic lethality in KRAS-mutant lung cancer. Unfortunately, though not entirely unexpectedly, not all KRAS-mutant cancers are dependent on TBK1 expression or function for their survival (Barbie et al., 2009; Muvaffak et al., 2014; Ou et al., 2011). This points to the vital need for the identification of discrete molecular features to segregate the population of NSCLC patients that might benefit most from TBK1 inhibitors from those harboring potentially intrinsic resistance. To this end, I, relying on the tremendous computational skill and expertise of Ms. Elizabeth McMillan, employed several data analysis strategies to uncover a functional biomarker that revealed identifiable molecular differences between TBK1-sensitive and TBK1-resistant NSCLC cancer cell lines. First, we performed empirical cumulative distribution functions and Kolmogorov-Smirnov (KS) tests to identify a group of cell lines whose distribution is significantly more sensitive than all other cell lines not harboring a given molecular characteristic, in this case mutant for gene or genes "X", "Y", or "Z". This unbiased approach returned cell lines with mutations in any of a "Ras-Class" of Ras/Ras-effectors (KRAS, HRAS, NRAS, PIK3CA, BRAF) as significantly more sensitive than Ras-Class Wild-Type cell lines (Figure 12A) (See also Table

1 for NSCLC mutation annotations used for these analyses). This sensitivity distribution separation also remained intact if the molecular characteristic was more strictly defined by RAS/PIK3CA mutations (no BRAF) or even KRAS mutation alone (Figures 13A-B). While KRAS expression did negatively correlate with TBK1 sensitivity (Figure 13C), it was evident that further distinctions remained between TBK1-sensitivie and TBK1-resistant Ras-Class mutant lines. The uncoupling of Ras-Class mutation status from TBK1 sensitivity has been observed previously and posited as a reason to abandon TBK1 inhibitors as interventions in Rasdriven cancers (Vangamudi et al., 2014). However, since TBK1 inhibitors displayed clear differences in their ability to disrupt AKT/mTORC1 signaling in Ras-Class mutant sensitive vs. resistant NSCLC cell lines (Figure 12B), what is needed is identification of detectable, secondary molecular characteristics that help discriminate between these two classes. Previously, (A. Singh et al., 2009) have described distinct gene expression signatures distinguishing KRAS-dependent and KRAS-independent cancer lines, and we sought to determine whether TBK1 sensitivity represented a similar distinction. Among the most differentially expressed genes (top 5% or bottom 5%) between TBK1-sensitive and TBK1-resistant Ras-Cass Mutant NSCLC cell lines (Figures 12C-D), we observed significant (p-value = 2.3e-07) overlap between genes up regulated in their "KRAS-dependent" gene signature and our Ras-Class mutant/TBK1-resistant lines. We also observed significant (p-value = < 1.6e-16) overlap between genes up regulated in their "KRAS-independent" gene signature and in our Ras-Class mutant/TBK1-sensitve lines. This was intriguing because this indicated cells harboring this signature displayed relative insensitivity to shRNA-mediated KRAS depletion but acute sensitivity to TBK1 inhibitors. Interestingly, (A. Singh et al., 2009) also observed that the two classes of KRAS-dependent or KRAS-independent cancer lines additionally displayed distinct epithelial or mesenchymal

characteristics, respectively. This led us to hypothesize whether segregation of Ras-Class mutant NSCLC cell lines based on their TBK1 sensitivity could be described by expression of gene sets implicated in the epithelial-to-mesenchymal transition (EMT). This hypothesis was supported by S2N comparisons of mesenchymal state-associated genes (Shaul et al., 2014), which showed robust enrichment of this gene cadre (including pro-mesenchymal state transcription factors, *ZEB1* and *ZEB2*) in the Ras-class mutant/TBK1-sensitive cell lines (Figure 12E). We additionally observed a significant (p-value = < 1.6e-16) overlap between pro-epithelial state reporter genes from an independent EMT gene set (Byers et al., 2013) and the top 5% most highly expressed genes in Ras-Class mutant resistant vs. Ras-Class mutant sensitive lines (Figure 13D). Furthermore, these pro-epithelial state reporter genes display overall decreased expression in *KRAS*-mutant/TBK1 sensitive vs. *KRAS*-mutant/TBK1-resistant NSCLC lines (p-value = 3.464 e-14) (Figure 13E).

We next sought to identify a biomarker that could report TBK1 sensitivity in the larger panel of TBK1i-treated NSCLC lines. To this end, we utilized an Elastic Net-based approach (Potts et al., 2015) to identify a minimal set of high-confidence gene expression indicators of TBK1 sensitivity. This analysis returned high *ZEB1* expression as a distinctive marker for TBK1-sensitive NSCLC (Figure 12F). Additionally, scatterplots of TBK1 sensitivity vs. EMT gene expression displayed significant anti-correlation with pro-mesenchymal genes, such as *ZEB1*, *ZEB2* and *SNA11*, and significant positive correlation with pro-epithelial gene, *CDH1* (Figure 12G). A full list of statistically significant correlations between TBK1 toxicity and gene expression of EMT markers and modulators of Ras and Ras effector signaling can be found in Table 2. Consistent with *ZEB1*'s role as a transcription factor that supports EMT by the suppression of pro-epithelial genes, we observed that expression of *ZEB1* target genes (Aigner et al., 2007) was significantly reduced (p-value = 0.0004275) in *KRAS*-mutant/TBK1 sensitive vs. *KRAS*-mutant/TBK1-resistant lines (Figure 13F)

### Modulation of Relative EMT Status is Sufficient to Alter Ras-Class Mutant NSCLC Sensitivity to TBK1 Inhibitors

These data suggest that toxicity to TBK1 inhibition is uniquely sensitive to the relative epithelial or mesenchymal state of Ras-Class mutant NSCLC lines. If this were the case, I hypothesized that TBK1-sensitivty would be increased or decreased through the induction of more mesenchymal or epithelial characteristics respectively. In this year, I first sought to reverse TBK1 sensitivity by leveraging the fact that the KRAS-mutant/LKB1-mutant genotype in NSCLC mirrors gene expression phenotypes of mesenchymal/claudin-low breast cancer (H. S. Kim et al., 2013). In this background, then, we induced epithelial characteristics by stable overexpression of wild-type LKB1 in HCC44 (KRAS-mutant/LKB1-mutant) cells. Stable LKB1-WT overexpression displayed, in an LKB1 kinase-dependent-manner, a shift in EMT marker protein expression (Figures 14A) commensurate with epithelialization, and a greater than two-fold reduction of sensitivity to both TBK1 inhibitors (Figures 14B-C). We concurrently sought to determine an appropriate means of promoting the mesenchymal state, thereby sensitizing resistant NSCLC lines to TBK1 inhibition. In this pursuit, I hypothesized that I could induce sensitivity to TBK1 inhibitors by testing them in a KRAS-mutant/LKB1-WT background (Calu6 cells), with and without shRNA-mediated LKB1 depletion to mimic LKB1 deletion-induced loss of function. While shLKB1 Calu6 cells displayed markedly increased sensitivity to both BX795 and Compound II (Figure 15B, Left), they displayed limited reduction in LKB1 total protein and no obvious induction of EMT marker protein expression (Figure 15B, Right). Further work is

required to tease out the obvious sensitization of Calu6 to TBK1 inhibitors by incomplete depletion of LKB1 protein from the changes seen in EMT marker expression (no detectable Ecadherin, and ZEB1 expression decrease that indicates shLKB1 represses ZEB1). I, however, decided to follow an alternative approach to test the effects on EMT induction on TBK1 inhibitor sensitively in NSCLC.

In pursuit of an additional rational strategy to induce EMT, we noted that Functional Signal Ontology (FUSION)-derived clustering of siRNA and miRNA effects on gene expression revealed Transforming Growth Factor-Beta (TGF-beta) Receptor 2 (TGFBR2) as the RNAi agent most closely associated with TBK1 siRNA (Figures 14D-E) (Potts et al., 2013). TGF-beta signaling is a potent inducer of EMT and can robustly support the survival and migration of cancer cells (Tiwari et al., 2012; J. Xu et al., 2009). Interestingly, expression of TGFBR2 (Figure 14F) and its ligand, TGFB1 (Figure 15A) negatively correlated with TBK1 sensitivity among all NSCLC lines (See also Table 2), suggesting TGF-beta signaling may play a greater role in those line. Furthermore, TBK1, RalBP1 (a canonical RalA/B effector), and TGFBR2 emerged from an array of >4000 shRNAs as among the targets most highly-correlating with BX795 sensitivity in NSCLC (Figure 14G) (Cowley et al., 2014). We therefore chose to employ TGF-beta-mediated EMT induction to test whether lung cancer lines could be sensitized to TBK1 inhibitors if pushed into a more mesenchymal state. Prolonged culture of KRAS-mutant A549 cells in media condition with recombinant TGF-beta protein (TGFB1) (2ng/mL) was sufficient to induce EMT protein expression changes as well as marked increase in sensitivity to both TBK1 compounds, which was reversible by prolonged re-culture of TGFB1-adapted cells in normal culture media (Figure 14H). This strategy failed, however, to induce sensitization in TBK1-resistant line H1573 (Figures 15D). This is partially explainable by the non-intact TGFB1 signaling seen as

TGFB1 treatment was uncoupled from the induction of SMAD2 phosphorylation (Figure 15C). Intriguingly, TBK1 inhibitor-resistant H2347 cells displayed intact, though muted, TGFB1/SMAD2 signaling, which helps explain the miniscule increase in chronic TGFB1 treatment-induced sensitization to either BX795 or Compound II (Figures 15D). In addition to enhancing TBK1 inhibitor reduction of cell proliferation, TGFB1 treatment also synergized with Compound II in the induction of apoptosis. This was seen as acute pretreatment with TGFB1 (10ng/mL) in A549 cells supported dose-dependent Compound II-induced caspase 3/7 activity, an indicator of apoptosis induction (Figure 14I). Compound II was unable to elicit increased caspase 3/7 activity in TGFB1-treated KRAS-mutant sensitive (HCC44 or A427) and KRASmutant resistant (H1573 or H2347) (Figure 15E). As HCC44 and A427 already displayed mesenchymal characteristics (Figure 15C), it is not surprising that TGFB1 treatment did not alter the level Compound II -mediated apoptosis in these lines. Conversely, as H1573 and H2347 were relatively non-responsive to TGFB1 at the level of SMAD2 phosphorylation, as mentioned above, it is not wholly unexpected that TGFB1 treatment was likewise ineffective at increasing Compound II-mediated apoptotic induction. This then suggests that if a cell line is sensitive to TGFB1 induction of EMT, then it can be sensitized to TBK1 inhibition. To examine whether TBK1 was required for TGFB1-induced EMT gene expression changes, we performed quantitative real-time PCR (qPCR) following TGFB1 stimulation in the presence or absence of Compound II. While the statistical significance was obscured by wide variation in one of the biological replicates, possibly due to a sample pipetting or mixing error, TGFB1 treatment displayed an overall decrease in CDH1 and overall increases in ZEB1, VIM, and SNAI1 expression (Figure 15F). In these experiments, SNAI1 displayed statistically significant induction by TGFB1, which was attenuated by Compound II in a dose-dependent manner (Figure 14J).

This suggests TBK1 may likewise be required for the TGFB1-mediated induction of EMT at the level of transcription of *SNAI1*, a key inducer of expression of other EMT genes such as *ZEB1*.





## Figure 6. Cross-Examination of Small Molecule Inhibitor Screens in NSCLC Reveals the Intersection between TBK1 and AKT/mTOR Regulatory Axis Target Space

(A-B) Sensitivity profiles of (A) BX795 and (B) Compound II in 100 NSCLC cell lines. Error bars represent standard deviation (SD) above the mean ED50 values of most-concordant replicates (n = 2). See also Table 1.

(C-D) Correlation scatterplots of (C) BX795 ED50 (Log<sub>10</sub>) vs. Compound II ED50 (Log<sub>10</sub>) and
(D) BX795 Area-Under-the-Curve (AUC) (Log<sub>10</sub>) vs. Compound II AUC (Log<sub>10</sub>).

(E-F) Correlations scatterplots of either (E) Log<sub>10</sub> BX795 ED50 or (F) Log<sub>10</sub> Compound II ED50
vs. cell line doubling time (reported as a ratio of Day 5:Day1 to Day3:Day1 growth rate ratios).
Cell line doubling time data were generously provided by Dr. Ralph DeBerardinis (UTSW).
(G-H) Correlations between TBK1 inhibitors and (Garnett et al., 2012) compounds among (black trend line) all or (cyan trend line) KRAS-mutant only NSCLC cell lines. (G) BX795 vs.
AKT1/2/3 inhibitor, A-443654, and (H) Compound II vs. mTOR inhibitor, JW-7-52-1 (Torin 1).
Insert: Pearson correlations among all (P(all) or KRAS-mutant only (P(mut)) lines tested. Box:
WT = KRAS wild-type cell lines (grey); MUT = KRAS mutant cell lines (cyan).
(I-J) Correlations between TBK1 inhibitor GSK1059615 or (J) JAK/TBK1/IKKe inhibitor,
Momelotinib (CYT387). Insert: Pearson correlations among all (P(all) or KRAS-mutant only NSCLC cell lines (I)
Compound II vs. PI3K/mTOR inhibitor GSK1059615 or (J) JAK/TBK1/IKKe inhibitor,
Momelotinib (CYT387). Insert: Pearson correlations among all (P(all) or KRAS-mutant only
(P(mut)) lines tested. WT = KRAS wild-type cell lines (grey); MUT = KRAS mutant cell lines (red).

(K-N) TBK1 inhibitors strongly correlate with mTORC1 inhibitor, Temsirolimus, in KRAS-mutant NSCLC lines. (K) Compound II or (L) BX795 vs. Temsirolimus (Garnett et al., 2012).
Correlation analyses and scatterplots in G-N were provided by Dr. Rachel Vaden (UTSW).
(M) BX795 vs. Temsirolimus (Seashore-Ludlow et al., 2015). Additionally, (N) PI3K inhibitor, GSK2636771, also strongly correlated with Compound II in KRAS-mutant NSCLC lines.
Correlation values and trend line listed as in G-J.

(O) Summary of decreased mTORC1 regulatory network member phospho-peptides upon shRNA-mediated depletion of TBK1 in A549, summarized from (J.-Y. Kim et al., 2013b).
(P) Transient overexpression of TBK1 elicits activating phosphorylation of mTOR (pS2481) in a kinase-dependent manner in HEK293FT cells. WT = Wild type, KD = Kinase Dead (K38M) Mutant. Data were provided by Dr. Yi-Hung Ou (Y-H Ou) (UTSW).

Figure 7



## Figure 7. TBK1 is Required for AKT/mTORC1 Activation during the "Starved-to-Fed" State Transition

(A) Immunoblot comparison of essential amino acid (EAA) nutrient-dependent mTORC1 activation in TBK1 wild-type (WT) and homozygous knock-out (-/-) MEFs.

(B) Immunoblot Comparison of nutrient-dependent mTORC1 activation in TBK1 N-Terminal

mutant Homozygous WT, Heterozygous Mutant (+/ $\Delta$ ), Homozygous Mutant ( $\Delta$ / $\Delta$ ) MEFs.

(C-D) 72-hour transfection of TBK1 or LONRF1 (non-specific control) siRNA pools blunts activation of AKT/mTORC1 signaling in (C) MNT1 (melanoma) or (D) HCT116 (colorectal) cancer cell lines.

(E) Treatment with BX795 in PDPK1 homozygous knock-out (-/-) HCT116 cells. DMSO or BX795 added after starvation, 30min before addition of any EAA.

(F) TBK1 Inhibitors in p53-/- immortalized MEFs. DMSO or 2μM Compound II, BX795 or GSK2292978A (GSK) was added after starvation, 30min before addition of any EAA. An expanded version of this panel can be found in Figure 11G.

Figure 8



## Figure 8. TBK1 is Required for AKT/mTORC1 Activation during the "Starved-to-Fed" State Transition, Related to Figure 7

(A) Immunoblot of starved- vs. fed-state effects on mTORC1-dependent phosphorylation of S6K at T389. Maximum dynamic range of mTORC1 activation was observed as cells were starved of nutrients in 1X EBSS for 3 hours. After hour 2 of EBSS starvation, cells were "primed" by addition of Glutamine (Gln, 1mM final concentration) and then maintained in EBSS/Gln for the remaining hour before the addition of free essential amino acids (EAA) for 20min. NS = no starvation or simulation (cells in culture media only).

(B-C) Attenuation of AKT/mTORC1 signaling in TBK1 Δ/Δ MEFs remains sensitive to mTOR inhibitors (S2.B) Torin 1 or (S2.C) Rapamycin. mTOR inhibitors added, at the concentrations listed, either 1 hour (Rapamycin) or 3 hours (Torin) prior to any stimulation with EAA.
(D) TBK1 inhibitor GSK2292978A inhibits mTORC1 activation by nutrients in HeLa cells, as read out by phospho-S6K (pT389) and phospho-S6 (pS235/236). (Data from Y-H Ou (UTSW))

#### Figure 9



WCL Y-H Ou

#### Figure 9. TBK1 Physically Engages the AKT/mTOR Regulatory Axis at Multiple Nodes

(A) Nutrient addition increased the physical association of mTOR with TBK1 in a timedependent manner. Endogenous TBK1 immunoprecipitation (IP) in 293T, followed by anti-TBK1, -mTOR, or -p-mTOR (pS2448) immunoblot.

(B) Overexpressed WT or Kinase-Dead (KD) mutant (K38M) myc-FLAG-TBK1 in HEK293T, followed by anti-FLAG IP and immunoblot for members of AKT/mTORC1 regulatory network. Cells were starved in EBSS (containing 10% serum) for 50min, followed by addition of EAA for the times listed.

(C) Summary of anti-3XFLAG-TBK1 IP-mass spectrometry "hits" including numbers of identified unique peptide sequences and percent total coverage of protein "hit". Hits were defined as spectra matches present in 3XFLAG-TBK1 IP and absent in 3XFLAG-Empty Vector IP.

(D) Co-overexpression of myc-TBK1 and HA-S6K or HA-ULK1, followed by Anti-HA IP to determine relative abundance of bound myc-TBK1 by immunoblot.

(E-F) Co-overexpression of FLAG-TBK1 with HA-GST-RagA, -RagB, -RagC, or –RagD in 293T, followed by (E) anti-FLAG IP and anti-HA immunoblot or (F) anti-HA IP and anti-FLAG immunoblot.

(G) Co-overexpression of myc-TBK1 with HA-GST-RagA or –RagB and FLAG-GST-RagC or –RagD in 293T, followed by anti-FLAG IP and anti-myc, -HA, or –FLAG immunoblot.
(H) Co-overexpression of FLAG-TBK1 and HA-GST-RagD-WT, -RagD-77L (GDP-bound

mutant), or –RagD-121L (GTP-bound mutant) followed by anti-HA IP and anti-FLAG and –HA immunoblot.

Aubhishek Zaman (UTSW) and Dr. Y-H Ou (UTSW) provided the data for Figure 9.





(A) Data summary for "mini-screen" of TBK1 adaptor protein effects on mTORC1 activation by EAA nutrients. Pooled siRNA were used to deplete LONRF1 (non-specific control); canonical TBK1 adaptors (e.g. TANK, AZI2, AKT1, etc.); the exocyst; and amino acid transporters. EAA starvation was performed for 3hours, followed by EAA were added for 0, 10, or 30min. activation of mTORC1 was assessed via immunoblot for by S6K-dependent phosphorylation of its substrate, ribosomal protein S6. siRNA pools for TBK1 adaptors were always tested alongside LONRF1, and relative phospho-S6/total S6 ratios were calculated using ImageJmeasured densitometry and normalized to LONRF1 + 30min EAA for each set. While only one representative LONRF1 is here listed, all columns represent mean values ( $n \ge to 2$ ) relative to the LONRF1 + 30min EAA time point tested alongside a given siRNA pool. Error bars represent standard deviation from the mean for a given sample (column). Two-tailed unpaired Student's t test was performed between LONRF1 + 10min EAA or LONRF1 + 30min EAA and the respective time points of the siRNA pools tested along side them in each experiment set. ns = non significant. \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001, \*\*\*P < 0.0001. Data were provided by Dr. Y-H Ou (UTSW).



(pT246) PRAS40 Total

TSC2 Total



50

# Figure 11. TBK1 Follows Permissive and Instructive Mechanistic Routes to Regulate AKT/mTOR Signaling

(A) Immunoblot of BX795 and allosteric AKT inhibitor MK2206 effects on AKT/mTORC1 activity in PDPK1 -/- HCT116 cells.

(B-C) Endogenous Raptor IPs show increased PRAS40-Raptor accumulation upon TBK1 loss of function in TBK1 (D/D) MEFs. Association was maintained under (B) CHAPS- or (C) NP-40-based cell lysis conditions.

(D) Summary of specific fold changes of AKT/mTORC1 regulatory network member phosphopeptides upon shRNA-mediated depletion of TBK1 in A549 cells (modified from (J.-Y. Kim et al., 2013b)) with assistance in phospho-site identification by curated information provided by PhosphoSitePlus.com, as downloaded on 10/30/14).

(E) Examination of S6K C-terminal auto-inhibitory domain phosphorylation at T421/S424 during starvation and EAA stimulation in TBK1 WT and TBK1 -/- MEFs.

(F) Overexpression of pRK5-myc-empty vector, pRK5-myc-FLAG-TBK1-WT, pR5K-myc-FLAG-TBK1-KD, or pR5K-HA-TBK1 in HEK293FT cells. Anti-FLAG IP was performed, followed by immunoblot with phospho- or total protein-specific antibody as listed. WCL = whole cell lysate

(G) TBK1 inhibitors modulate AKT/mTORC1 signaling in TSC2 WT or homozygous knockout
(-/-), p53 -/- immortalized MEFs. DMSO or 2µM of the listed TBK1 inhibitors were applied
30min before the addition of any EAA. A subsection of this immunoblot appears in Figure 7F.
(H) Schematic indicating points of TBK1 interaction and regulation of AKT/mTORC1
regulatory axis. Green arrows point toward nodes whose activity is promoted by TBK1, whereas grey lines indicate points of physical association.

Figure 12



# Figure 12. Ras-Class Mutant/Mesenchymal Status Indicates Sensitivity to TBK1 Inhibition in NSCLC

(A) Empirical Cumulative Distribution Function (ECDF) plot of BX795 AUC values in NSCLC
lines (Red = "Ras-Class" (*KRAS*, *NRAS*, *HRAS*, *PIK3CA*, or *BRAF*) mutant, Blue = "Ras-Class"
WT.

(B) AKT/mTORC1 signaling response to Compound II in TBK1-senstive vs. TBK1 resistant Ras-Class Mutant NSCLC. Melanoma cell lines included as positive controls for Compound II sensitivity (LOXIMVI) or resistance (MNT1) (Eskiocak, et. al. 2016, unpublished).

(C) Ras-Class Mutant Comparators. Binary indication of specific Ras-Class inclusion criteria is listed for each cell line below its BX795 ED50 value.

(D) Heatmap highlighting intersection between TBK1-sensitve and "KRAS-independent" gene expression signatures. Venn diagrams represent degree of overlap between similarly differentially expressed genes. Overlap p-value for genes up in "KRAS-Dependent/Epithelial" and BX795-Resistant = < 1.6e-16. Overlap p-value for genes up in "KRAS-Independent/Mesenchymal" and BX795-Sensitive = 2.3e-07. Only top or bottom 5% of differentially expression genes ranked by Signal-to-Noise Ratio (S2N) for TBK1-sensitive vs. TBK1-resistant lines (from 5C) were plotted. Scale indicates S2N value. Scale indicates S2N value.</li>

(E) Heatmap highlighting enrichment of mesenchymal state gene expression markers in BX795sensitive NSCLC lines. Only top or bottom 5% of differentially expression genes ranked by Signal-to-Noise Ratio (S2N) for TBK1-sensitive vs. TBK1-resistant lines (from 5C) were plotted. Scale indicates S2N value. (F) Elastic Net (EN) analysis returns *ZEB1* expression as indicator of BX795 Sensitivity. Prior to run of Elastic Net, all BX7945 AUC values above 400 were capped at 400 and listed here in  $Log_{10}$ . Biomarker gene expression scale (right) indicates  $Log_2$  Illumina Microarray values. Values on either side of gene expression profile represent EN-generated biomarker weight (*ZEB1* = -0.055) and bootstrap pass frequency (*ZEB1* = 0.5).

(G) Scatterplots of BX795 AUC (Log<sub>10</sub>) sensitivity values vs. Illumina mRNA Microarray gene expression values (Log<sub>2</sub>) of EMT Markers (*ZEB1*, *ZEB2*, *SNAI1*, *CDH1*) in NSCLC cell line panel, including Pearson correlation (r), R-squared value (R<sup>2</sup>) and p-value (P) for each gene. Bioinformatics analyses depicted in this figure (Panels A, C-F) were provided by Elizabeth McMillan (UTSW).





# Figure 13. Ras-Class Mutant/Mesenchymal Status Indicates Sensitivity to TBK1 Inhibition in NSCLC, Related to Figure 12

(A) Empirical Cumulative Distribution Function (ECDF) plot of BX795 AUC values in NSCLC lines. Red = "Ras-Class", no *BRAF* (*KRAS*, *NRAS*, *HRAS*, *PIK3CA*)-mutant, Blue = "Ras-Class, no *BRAF*"-WT.

(B) Empirical Cumulative Distribution Function (ECDF) plot of BX795 AUC values in NSCLC lines. Red = *KRAS*-mutant, Blue = *KRAS*-WT. ECDF plots in A and B were provided by Elizabeth McMillan (UTSW).

(C) Scatterplot of BX795 AUC ( $Log_{10}$ ) sensitivity values vs. mRNA gene expression values ( $Log_2$ ) of *KRAS* in NSCLC cell line panel, including Pearson correlation (r), R-squared value ( $R^2$ ) and p-value (P).

(D) Heatmap highlighting intersection between TBK1-sensitve and "Byers-EMT" gene expression signatures. Venn diagrams represent degree of overlap between similarly differentially expressed genes. Overlap p-value for genes up in "KRAS-Dependent/Epithelial" and BX795-Eesistant = < 1.6e-16. Overlap p-value for genes up in "Byers Mesenchymal" and BX795-Sensitive = 2.3e–07. Only top or bottom 5% of differentially expression genes ranked by Signal-to-Noise Ratio (S2N) for TBK1 sensitive vs. TBK1 resistant lines (from 5C) were plotted. This heatmap was provided by Elizabeth McMillan.

(E-F) Empirical Cumulative Distribution Function (ECDF) plot for Illumina mRNA Microarray gene expression values (Log<sub>2</sub>) of (E) epithelial gene markers (Byers et al., 2013)) or (F) *ZEB1* target genes(Aigner et al., 2007) in *KRAS*-mutant sensitive (red) vs. *KRAS*-mutant resistant (black) NSCLC cell lines. Cell lines in each group listed below each plot. KS-tests and ECDF plots were provided by Dr. JiMi Kim (UTSW).
Figure 14



# Figure 14. Modulation of Relative EMT Status is Sufficient to Alter Ras-Mutant NSCLC Sensitivity to TBK1 Inhibitors.

(A-C) LKB1-dependent induction of (A) epithelial characteristics decreases sensitivity to (B) BX795 and (C) Compound II in Ras-Class mutant NSCLC. HCC44 cell lines stably expressing pbabe-vector only, pbabe-LKB1-Wild Type (WT), or pbabe-LKB1-Kinase Dead (KD) were treated with TBK1 inhibitors for 96 hours. Points represent mean relative viability for each dose relative to DMSO-only wells (N = 3).

(D-E) Functional Signal Ontology (FUSION) analysis of siRNAs and miRNAs most closely mirroring siTBK1 effects on FUSION reporter gene expression (column labels) revealed Transforming Growth Factor-Beta Receptor 2 (TGFBR2) as the RNAi agent most closely associated with TBK1 siRNA. (D) Heatmap of TBK1/TGFBR2 FUSION sub-cluster. Scale indicates Log<sub>2</sub> expression of the 6 FUSION reporter genes (*BNIP3L*, *LOXL2*, *BNIP3*, *NDRG1*, *ACSL5*, and *ALDOC*). FUSION sub-cluster data accessed via FUSION website (https://qbrc2.swmed.edu/whitelab/fusion/index.php?url=/whitelab/fusion/fusion.php) (E) Scatterplot of all siRNAs and miRNAs as a function of their calculated cluster distances (Pearson Distance Sum and Euclidian Distance Sum) from siTBK1.

(F) Scatterplot of BX795 AUC (Log<sub>10</sub>) sensitivity values vs. Illumina mRNA Microarray gene expression values (Log<sub>2</sub>) of (C) *TGFBR2* in NSCLC cell line panel, including Pearson correlation (r), R-squared value (R<sup>2</sup>) and p-value (P).

(G) NSCLC toxicity profile correlation between BX795 ED50 and >4000 shRNAs v, ranked by Pearson correlation. Arrows indicate location of shRNAs against *TGFBR2*, *TBK1*, and *RalBP1*.
(H) Prolonged (>1-2 week) culture of A549 in TGFB1 (2ng/mL)-conditioned media induces mesenchymal characteristics (Right) and increased sensitivity to TBK1 inhibitors (Left). Re-

culture of TGFB1-treated A549 cells in normal media (for >1 week) reversed TBK1 inhibitor sensitization. Cells were cultured in normal media (-TGFb), normal media supplemented with 2ng/mL TGFB1 (+ TGFb), or normal media after TGFB1 adaptation (post TGFb). (I) Compound II synergizes with short term (24hr) TGFB1 (10ng/mL) treatment to enhance apoptosis in A549. Apoptosis induction readout by caspase 3/7 activity as measured by Caspase Glo. Statistical significance was calculated using One-Way ANOVA, with Tukey's multiple comparisons test, \*\*\* = P < 0.001, \*\*\*\* = P < 0.0001.

(J) Short-term (24 hour) pretreatment of Compound II inhibits TGFB1-induced induction of *SNAI1* expression. mRNA reported in Log<sub>2</sub> values normalized to *GAPDH* (data not shown). Statistical significance was calculated as in 14I, \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001

Figure 15



# Figure 15. Modulation of Relative EMT Status is Sufficient to Alter Ras-Class Mutant NSCLC Sensitivity to TBK1 Inhibitors, Related to Figure 14

(A) Scatterplot of BX795 AUC ( $Log_{10}$ ) sensitivity values vs. mRNA gene expression values ( $Log_2$ ) of *TGFB1* in NSCLC cell line panel. Insert includes Pearson correlation (r), R-squared value ( $R^2$ ) and p-value (P).

(B) (Left) Stable shRNA-mediated depletion of LKB1 in Calu6 corresponded to increased sensitivity to BX795 or Compound II. (Right) Immunoblot for LKB1, ACC, p-ACC (pS79) & ZEB1.

(C) Immunoblot of Ras-Class mutant/TBK1-senstive (HCC44 and A427) and Ras-Class Mutant/TBK1-Resistant (H1573 and H2347) cell lines' EMT status and response to acute TGFB1 treatment.

(D) Prolonged culture in TGFB1 (2ng/mL)-conditioned media did not sensitize (left) TBK1resistant H1573 or H2347 cell lines to BX795 or Compound II in Cell Titer Glo assays. Prolonged culture in TGFB1 (2ng/mL)-conditioned media did not alter SMAD2 phosphorylation (pS465/467) or expression of EMT markers, E-Cadherin or Vimentin, in H1573 cells; but did slightly increase vimentin and decrease E-Cadherin expression in H2347 cells. (E) Short-term (24 hour) pretreatment with TGFB1 (10ng/mL) does result in increased caspase 3/7 activity (as assayed by Caspase Glo) in cooperation with Compound II in TBK1senstive/mesenchymal cells (HCC44 and A427) or TBK1-resistant/epithelial (H1573 and H2347). Statistical significance was calculated as in 14I, ns = not significant, \*P < 0.05, \*\*P < 0.01, \*\*\*\* = P < 0.0001.

(F) Short-term (24 hour) pretreatment of Compound II does not inhibit TGFB-induced modulation of EMT marker mRNA expression. Gene expression for *CDH1, VIM,* and *ZEB1* 

reported in  $Log_2$  values normalized to *GAPDH* (data not shown). Statistical significance was calculated as in 14I, ns = not significant.

				BX795	Tota						Tota				KRAS					Log 10	og 10	og 10	02.10
Cell Line	Rank BX7 (AUC) AU	<u>95 Rank</u>	BX795 FD50	ED50			AUC (FI	ank C	DEO EI	D50 SD C		tank R	as Class Mutant	KRAS Mutant	Autant	PIK3CA Mutant	BRAF	<u>Nutant</u>	HRAS Mutant	BX795 B	X795 Cr	npd II C	II pdu
	   			BI	Rank	$\frac{1}{1}$		;   			Rank				Allele								
HCC15	1 309.	1	0.10	0.03	7	11	814.55	12	0.42	0.06	23	25	HCC15	HCC15 N/A		HCC15	HCC15	HCC15	HCC15	2.49	-1.00	2.50	-0.38
A427	2 313.	15 2	0.10	0.02	4	12 3	316.50	S	0.34	0.04	17	21	A427	A427 p.G.	12D	A427	A427	A427	A427	2.50	-0.98	2.50	-0.47
HCC44	3 322.	29	0.20	0.08	6	2 2	294.37	4	0.34	0.06	9	15	HCC44	HCC44 p.G	12C	HCC44	HCC44	HCC44	HCC44	2.51	-0.70	2.47	-0.47
H157	4 334.	302	0.22	0.07	12	71 3	373.19	80	2.09	0.29	139	151	H157	H157 p.G	12R	H157	H157	H157	H157	2.52	-0.66	2.57	0.32
H1 200	5 335		0T-0	61.0	1 u	2 10 7 2	17.610	202	1 86	0.0	C7	58	H1 200	H1 200 N/A		H1200	H1 200	H1 200	H1200	55.5 55.5	-0.76	00.2	-0.45
H1755	7 335.	99	0.21	0.03	14	, c , 0	10.14	2,00	0.37	0.05	16	30	H1755	H1755 N/A		H1755	H1755	H1755	H1755	2.53	-0.67	2.49	-0.43
H1703	8 335.	89	0.14	7.21	11	1 2	86.21		0.17	0.01	5	13	H1703	H1703 N/A		H1703	H1703	H1703	H1703	2.53	-0.85	2.46	-0.78
H1155	9 346.	13 9	0.31	0.0	18	- S	103.67	5	0.27	0.02		25	H1155	H1155 p.Q	61H	H1155	H1155	H1155	H1155	2.54	-0.51	2.48	-0.57
H2452	10 348.	52 15	1 0.39	0.07	23	48 3	151.45	49	1.29	0.26	97	120	H2452	H2452 N/A		H2452	H2452	H2452	H2452	2.54	-0.41	2.55	0.11
H838	11 348.	79 11	0.35	0.08	22	34 3	340.04	29	0.84	0.02	63	85	H838	H838 N/A		H838	H838	H838	H838	2.54	-0.46	2.53	-0.08
H1975	12 354.	13 1C	0.32	0.49	22	37 3	344.43	34	0.92	0.27	71	93	H1975	H1975 N/A		H1975	H1975	H1975	H1975	2.55	-0.50	2.54	-0.04
H1355	14 357.	60 15	3 0.44	0.33	32	33 3	339.28	20	0.59	0.04	53	85	H1355	H1355 p.G.	13C	H1355	H1355	H1355	H1355	2.55	-0.36	2.53	-0.23
H1734	16 359.	79 15	0.42	0.14	31	14	818.70	16	0.48	0.04	30	61	H1734	H1734 p.G.	13C	H1734	H1734	H1734	H1734	2.56	-0.38	2.50	-0.32
H2126	17 360.	94 24	t 0.58	0.04	41	38	344.65	56	1.62	0.17	94	135	H2126	H2126 N/A		H2126	H2126	H2126	H2126	2.56	-0.24	2.54	0.21
H2110	18 365.	35 14	t 0.39	0.08	32	72 3	875.70	20	2.37	0.21	142	174	H2110	H2110 N/A		H2110	H2110	H2110	H2110	2.56	-0.41	2.57	0.37
Hop62	19 366. 20 267	53 1( 7) 33	0.42	0.16	35	22 2	368.79	99	1.92	0.04	132	167	Hop62	Hop62 N/A	120	Hop62	Hop62	Hop62	Hop62	2.56	-0.37	2.57	0.28
H1792	21 268	.72 21 68 73			74	07 C7	05 A6	10	0.28	0.00	10	51	H1707	H1797 D.G.	120	H1707	H1702	H1707	H1707	75.5	CZ-0-	20.2	-0.42
Calu6	22 369.	07 19	0.45	0.21	41	78 3	84.57	68	5.01	2.43	167	208	Calu6	Calu6 p.0	61K	Calu6	Calu6	Calu6	Calu6	2.57	-0.35	2.58	0.70
DFCI024	23 370.	49 31	0.72	0.20	54	9	04.33	9	0.35	0.07	12	66	DFCI024	DFCI024 p.G	12C	DFCI024	DFCI024	DFCI024	DFCI024	2.57	-0.14	2.48	-0.45
HCC461	24 372.	11 21	0.56	0.11	45	67 3	168.92	57	1.63	0.38	124	169	HCC 461	HCC461 p.G.	12D	HCC461	HCC461	HCC461	HCC461	2.57	-0.25	2.57	0.21
H3255	25 373.	65 12	0.38	60.0	37	m m	100.67	7	0.36	0.11	10	47	H3255	H3255 N/A		H3255	H3255	H3255	H3255	2.57	-0.42	2.48	-0.44
H647	26 377.	30 35	0.87	0.09	61	10 3	313.30	25	0.76	0.15	35	96	H647	H647 p.G.	13D	H647	H647	H647	H647	2.58	-0.06	2.50	-0.12
HCC2108	27 383.	37 34	1 0.85	0.19	61	18 3	\$22.74	19	0.56	0.14	37	98	HCC2108	HCC2108 p.Q	61H	HCC2108	HCC2108	HCC2108	HCC2108	2.58	-0.07	2.51	-0.25
H2030	29 386.	63 32	0.82	0.24	61	30	37.45	35	0.94	0.04	65	126	H2030	H2030 p.G.	12C	H2030	H2030	H2030	H2030	2.59	-0.08	2.53	-0.03
HCC1195	30 386.	78 45	1.32	0.21	75	104 4	162.29	101	21.51	0.46	205	280	HCC1195	HCC1195 N/A		HCC1195	HCC1195	HCC1195	HCC1195	2.59	0.12	2.66	1.33
H460	32 387.	36	0.93	0.32	68	64 3	867.20	48	1.23	0.06	112	180	H460	H460 p.Q	61H	H460	H460	H460	H460	2.59	-0.03	2.56	0.09
H1650	33 390.	87 41	1.09	0.53	74	32 3	338.92	202	1.37	14.87	82	156	H1650	H1650 N/A		H1650	H1650	H1650	H1650	2.59	0.04	2.53	0.14
HZ009	34 394.	77 27	0.63	60.0	61	210	20.19	<u>8</u>	4.26	0.94	100	/77	H2009	H2009 p.G	12A	H2009	H2009	H2009	H2009	2.60	-0.20	2.59	0.63
HUCT93	35 397.	10	1 21	0.39	70	200	70.07	10	7 50	10.01	100	199	HUCLESS			HUC195	101E	HCC195		7 50	0T-0	10.2	0.30
11272	27 101	12 44	151	61.0	0/	- C6	1/060	10	7 55	0.21	156	007	CT6TU		120	CT6TU	CT6TU	CT6TU	CT 6T F	2.60	0.10	2 50	110
	104 00	16 13	+C-T	0.43	00	0 Z D 1	cn. / 01	22	12.0	17.0	000	110	0 30 1		777	C/CTL	C/CTU	C/CTL	0301	2 50	61.0	2 C J	0.41
H292	39 401.	19 50	1.54	0.39	50	36 3	141.98	27	0.82	0.03	63	152	H292	H292 N/A	-	H292	H292	H292	H292	2.60	0.19	2.53	-0.09
A549	40 401.	78 39	1.03	0.26	79	44 3	147.70	32	0.88	0.16	76	155	A549	A549 p.G.	12S	A549	A549	A549	A549	2.60	0.01	2.54	-0.06
H1993	41 403.	69 46	1.33	0.32	87	55 3	157.86	51	1.39	0.32	106	193	H1993	H1993 N/A		H1993	H1993	H1993	H1993	2.61	0.12	2.55	0.14
HCC515	42 404.	31 30	0.70	0.01	72	77 3	382.67	73	2.53	0.31	150	222	HCC515	HCC515 p.G.	13D	HCC515	HCC515	HCC515	HCC515	2.61	-0.15	2.58	0.40
H2122	43 405.	45 51	1.54	0.40	94	65 3	368.67	28	1.64	0.05	123	217	H2122	H2122 p.G	12C	H2122	H2122	H2122	H2122	2.61	0.19	2.57	0.21
Calu1	44 405	31 01	1 37	0.00	124 03	41 2	11.20	n 5	1.67	0.04	100	103	Calu1	Calu1 n.G.	120	Calu1	Calu1	Calu1	Calu1	10.2	00.0	2.40	00.0-
HCC2814	46 412.	17 58	1.98	1.02	104	91	197.76	97	15.00	10.13	188	292	HCC2814	HCC2814 N/A		HCC2814	HCC2814	HCC2814	HCC2814	2.62	0.30	2.60	1.18
HCC4006	47 412.	57 40	1.06	0.10	87	75 3	182.16	65	1.91	0:30	140	227	HCC4006	HCC4006 N/A		HCC4006	HCC4006	HCC4006	HCC4006	2.62	0.03	2.58	0.28
H2023	48 412.	97 52	1.61	0.24	100	52 3	\$55.04	53	1.41	0.04	105	205	H2023	H2023 N/A		H2023	H2023	H2023	H2023	2.62	0.21	2.55	0.15
H2087	49 412	97 35	0.99	0.17	87	58	861.43	2	2.84	0.12	135	222	H2087	H2087 N/A		H2087	H2087	H2087	H2087	2.62	0.00	2.56	0.45
HCC366	50 413.	21	0.63	0.15	9/	202	552.29	45	1.19	0.20	56	1/1	HCC366	HCC366 p.Q	61H	HCC366	HCC366	HCC366	HCC366	2.62	-0.20	2.55	0.08
H1568	51 415.	33 57	1.96	0.43	106	92 5	398.29	35	0.66	3.95	187	295	H1568	H1568 N/A		H1568	H1568	H1568	H1568	2.62	0.29	2.60	0.84
HCC1171	53 416	43 20	0.49	0.47	73	, r 192	12.209	64	1.87	02.0	120	193	HCC1121	HCC1171 N/A		HCC1171	HCC1171	HCC1171	HCC1171	2.02	-0.31	2.56	07.0-
H1944	54 417.	56 62	2.16	0.35	116	51 3	152.84	63	1.79	0.06	114	230	H1944	H1944 p.G	13D	H1944	H1944	H1944	H1944	2.62	0.33	2.55	0.25
H661	55 418.	09 73	3.12	0.41	128	47 3	150.99	40	0.99	0.66	87	215	H661	H661 N/A		H661	H661	H661	H661	2.62	0.49	2.55	0.00
HCC1438	56 420.	64 61	2.10	0.63	117	95 3	199.47	81	3.40	0.27	176	293	HCC1438	HCC1438 N/A		HCC1438	HCC1438	HCC1438	HCC1438	2.62	0.32	2.60	0.53
DFCI032	57 420.	99 47	1.34	0.11	104	42 3	347.20	43	1.09	0.10	85	189	DFCI032	DFCI032 N/A		DFCI032	DFC1032	DFCI032	DFC1032	2.62	0.13	2.54	0.04
H2073	58 421.	60 37	0.94	0.16	95	26 3	34.18	15	0.45	0.16	41	136	H2073	H2073 N/A		H2073	H2073	H2073	H2073	2.62	-0.03	2.52	-0.34
H322	59 422	10 67	2.68	0.40	126	69 3	\$70.99	46	1.20	0.19	115	241	H322	H322 N/A	+	H322	H322	H322	H322	2.63	0.43	2.57	0.08
HCC827	60 423.	55 55 37	3 1.64	0.35	113	21 3	325.31	17	0.51	0.05	38	151	HCC827	HCC827 N/A	+	HCC827	HCC827	HCC827	HCC827	2.63	0.22	2.51	-0.29
HCC364	62 425.	11 86	3.75	c/.0 0.87	148	57 3 57 3	10.39	47	1.23	0.19	104	252	HCC364	HCC364 N/A	+	HCC364	HCC364	HCC364	HCC364	2.63	0.57	2.56	0.09
HCC364	62 425.	11 86	3.75	0.87	148	57 3	160.39	47	1.23	0.19	104	252	HCC364	HCC364 N/A		되	C364	C364 HCC364	C364 HCC364 HCC364	C364 HCC364 HCC364 HCC364	C364 HCC364 HCC364 HCC364 2.63	C364 HCC364 HCC364 HCC364 2.63 0.57	C364 HCC364 HCC364 HCC364 2.63 0.57 2.56

# Table 1A (part 1)

				10570	I						1.1.1			26.01						101		6
Cell Line	Rank BX79	15 Rank	BX795	ED50	BX	Rank	Cmpd-II	Rank	II-pdw	Cmpd-II		verall R	as Class	KRAS Mutant	PIK3CA	BRAF	NRAS	HRAS	BX795 B)	<u>g 10 Log1</u> (795 Cmpc	I Cmpd	əl =
				8	Rank		AUL				Rank			Allele					AUC	DN AUG	LDN	
H2342	63 425.1	18 7.	3.35	3 1.65	140	89	395.36	6	5.55	0.55	179	319	H2342	H2342 N/A	H2342	H2342	H2342	H2342	2.63	0.53 2.	60 0.7	74
HCC4019	64 427.2	21 95	5.62	2 1.20	162	25	332.81	26	0.81	0.08	51	213	HCC4019	HCC4019 p.G12C	HCC4019	HCC4019	HCC4019	HCC4019	2.63	0.75 2.	52 -0.0	60
HCC4011	65 427.2	23 8;	3.77	7 0.79	152	63	367.15	52	1.40	0.01	115	267	HCC4011	HCC4011 N/A	HCC4011	HCC4011	HCC4011	HCC4011	2.63	0.58 2.	56 0.1	14
H2258	66 427.2	29 75	3.14	4 1.51	141	46	350.16	41	1.04	0.14	87	228	H2258	H2258 N/A	H2258	H2258	H2258	H2258	2.63	0.50 2.	54 0.0	8
Calu3	67 428.(	39 5f	1.94	4 0.65	123	20	324.59	24	0.71	0.05	4	167	Calu3	Calu3 N/A	Calu3	Calu3	Calu3	Calu3	2.63	0.29 2.	51 -0.1	15
1501H	68 429.8	202	1 3.0	0.3/	152	à r	12.145	2/5	3.05	0.33	100	318	L COLLA	A/N 1601H	1501H	TCOLH	TSOLD	TCOLO	2.03		0.4	2 Q
HZ250	-0 430.4	10	1.90	0.59	124	0/ 90	3/2.06	79	1./1	0.42	132	256	HZ250	HZ250 N/A	H2250	H2250	H2250	HZ250	2.63	0.28 2.	0.7	513
H2172	70 431.	33	3.52	2 0.16	148	100	421.62	66	18.73	2.08	199	347	H2172	HZ172 N/A	H2172	H2172	H2172	HZ172	2.63	0.55 2.	52 1.2	27
H1693	72 432.5	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	2.02	10.31	130	80	38/.U9	94	10.0 1.0 L	1.38	17/	307	H1693	H1693 N/A	H1693	H1693	H1693	H1693	2.64	0.31 2.	0.8	28
	12 432.1	10	0.0	6/.0	171	0000	16.260	00	40.0	20.00	1/4	670							2.04	-7 0C-0	0.0	5 6
HCC35	74 424.5	0 i	20.0	0.03	140	39	340.57	200	05.0	0.14	01	077	CKJJH		HCC30	CEJOH	10070	CCJJH	2.04	0.48	-0.0	70
HCC78	74 434.6	27	2.95	8 0.58	144	74	380.64	76	2.79	0.71	150	294	HCC78	HCC78 N/A	HCC78	HCC78	HCC78	HCC78	2.64	0.47 2.	58 0.4	45
H1573	75 435.7	75 74	3.37	2 0.60	151	76	382.32	71	2.38	0.10	147	298	H1573	H1573 p.G12A	H1573	H1573	H1573	H1573	2.64	0.53 2.	58 0.3	38
H2228	76 436.0	33 44	1.31	1 0.57	120	79	385.53	69	2.19	0.21	148	268	H2228	H2228 N/A	H2228	H2228	H2228	H2228	2.64	0.12 2.	59 0.3	34
H2347	77 436.2	22 6t	2.57	7 0.31	143	8	386.38	88	4.87	0.13	168	311	H2347	H2347 p.L19F	H2347	H2347	H2347	H2347	2.64	0.41 2.	59 0.6	69
H1869	78 439.5	31 6(	2.05	8 0.54	138	19	323.29	33	0.89	0.12	22	190	H1869	H1869 N/A	H1869	H1869	H1869	H1869	2.64	0.32 2.	51 -0.0	05
HCC4018	79 439.5	39 66	2.95	3 0.78	148	86	389.62	75	2.78	0.14	161	309	HCC4018	HCC4018 N/A	HCC4018	HCC4018	HCC4018	HCC4018	2.64	0.47 2.	59 0.4	4
HCC2279	80 440.0	30 00	9.45	3 1.42	172	49	351.89	44	1.13	0.13	93	265	HCC2279	HCC2279 N/A	HCC2279	HCC2279	HCC2279	HCC2279	2.64	0.65 2.	55 0.0	05
H650	81 440.4	12 85	9 4.1C	0.54	170	62	367.06	82	3.41	0.29	144	314	H650	H650 p.Q61L	H650	H650	H650	H650	2.64	0.61 2.	56 0.5	53
H520	82 441.7	71 90	4.11	1 0.58	172	29	335.33	13	0.43	0.16	42	214	H520	H520 N/A	H520	H520	H520	H520	2.65	0.61 2.	53 -0.3	37
H1648	83 442.3	31 85	3.85	5 18.85	171	43	347.55	37	0.97	0.08	8	251	H1648	H1648 N/A	H1648	H1648	H1648	H1648	2.65	0.59 2.	54 -0.0	5
HCC2935	84 442.4	46 71	. 3.01	1 0.95	155	45	349.40	42	1.05	0.50	87	242	HCC2935	HCC2935 N/A	HCC2935	HCC2935	HCC2935	HCC2935	2.65	0.48 2.	54 0.0	02
H125	85 443.2	21 75	3.54	4 0.94	164	98	410.27	103	30.40	7.17	201	365	H125	H125 N/A	H125	H125	H125	H125	2.65	0.55 2.	51 1.4	48
H1437	86 443.7	70 81	3.60	0.87	167	73	380.06	72	2.45	0.20	145	312	H1437	H1437 N/A	H1437	H1437	H1437	H1437	2.65	0.56 2.	58 0.3	39
H23	87 446.8	35 6:	3 2.2£	6 0.42	150	13	318.34	11	0.40	0.08	24	174	H23	H23 p.G12C	H23	H23	H23	H23	2.65	0.35 2.	50 -0.3	39
H1581	38 449.5	32 9:	3 4.65	5 0.55	181	102	449.08	100	21.34	0.08	202	383	H1581	H1581 N/A	H1581	H1581	H1581	H1581	2.65	0.67 2.	65 1.3	33
H1838	89 450.5	94 65	5 2.45	5 0.83	154	61	366.79	80	3.22	0.51	141	295	H1838	H1838 N/A	H1838	H1838	H1838	H1838	2.65	0.39 2.	56 0.5	51
H2052	90 455.2	23 100	5.83	3 0.58	190	35	340.24	39	0.97	0.05	74	264	H2052	H2052 N/A	H2052	H2052	H2052	H2052	2.66	0.77 2.	53 -0.0	5
H522	91 455.2	25 101	6.40	0.51	192	85	389.48	92	6.00	2.03	177	369	H522	H522 N/A	H522	H522	H522	H522	2.66	0.81 2.	59 0.7	78
H2086	92 460.2	26 9,	7 5.2£	5 1.10	189	96	407.54	84	3.90	0.28	180	369	H2086	H2086 N/A	H2086	H2086	H2086	H2086	2.66	0.72 2.	61 0.5	59
H1395	93 461.t	36 95	5.05	9 17.83	188	84	387.57	83	3.44	0.32	167	355	H1395	H1395 N/A	H1395	H1395	H1395	H1395	2.66	0.71 2.	59 0.5	54
HCC2450	94 461.7	77 94	4.90	1.01	188	97	408.55	102	24.09	22.36	199	387	HCC2450	HCC2450 N/A	HCC2450	HCC2450	HCC2450	HCC2450	2.66	0.69 2.	51 1.3	38
H1819	95 464.4	42 64	1 2.27	7 0.68	159	90	365.11	55	1.59	0.13	115	274	H1819	H1819 N/A	H1819	H1819	H1819	H1819	2.67	0.36 2.	56 0.2	20
H2887	96 464.5	92 95	5.77	7 0.64	195	94	398.76	91	5.80	0.89	185	380	H2887	H2887 p.G12V	H2887	H2887	H2887	H2887	2.67	0.76 2.	50 0.7	76
H920	97 466.1	12 10	9.10	0.00	200	101	425.47	96	13.33	3.32	197	397	H920	H920 N/A	H920	H920	H920	H920	2.67	0.96 2.	53 1.1	12
H820 HCC3051	98 400.	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	2.0.2	0.70	180 201	102	350.70	10	16 50	0.59	201	C07	H820 HCC2051	H820 N/A	H820 HCC2051	H820 HCC2051	H820 HCC3051	HCC2051	7 67	0.56 2.	0.2 0.2 55 1 2	2 57
H441	100 469.1	16 91	4.23	3 0.32	191	40	346.58	54	1.42	0.27	5 76	285	H441	H441 n.G12V	H441	H441	H441	H441	2.67	0.63 2.	54 0.1	12
H596	101 471.5	56 96	5.09	9 1.28	197	6	397.30	104	49.50	19.41	194	391	H596	H596 N/A	H596	H596	H596	H596	2.67	0.71 2.	60 1.6	69
EKVX	102 477.7	75 65	3 2.76	5 1.11	170	6	310.85	14	0.45	0.02	23	193	EKVX	EKVX N/A	EKVX	EKVX	EKVX	EKVX	2.68	0.44 2.	49 -0.3	34
H226	103 478.2	26 85	3.65	9 2.05	188	59	362.02	78	2.95	0.46	137	325	H226	H226 N/A	H226	H226	H226	H226	2.68	0.57 2.	56 0.4	47
H3122	104 501.7	71 102	1 11.67	7 3.58	208	66	412.28	93	6.51	0.14	192	400	H3122	H3122 N/A	H3122	H3122	H3122	H3122	2.70	1.07 2.	52 0.8	81
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56/TH	AN			AN N	AN	AN	330.02	AN S	0.00	0.04	AN S	AN	56/TH	H1/93 N/A	H1/93	101102	H1/93	56/TH	NA	NA C	T-0- Z0	קו
H2106			AN N	NAN	AN N	AN	388.93	A A	0.97	0.45	AN	AN	H2106	H2106 N/A	H2106	H2106	H2106	H2106	AN	NA 2.	0.0-	8 2
H1770	AN	AN NA	Z	NA	AN	AN	388.60	AN	2.63	0.29	NA	AN	H1770	H1770 N/A	H1770	H1770	H1770	H1770	AN	NA 2	59 0.4	42
H720	NA	IA N/	NAN	AN PA	NA	NA	381.93	NA	3.57	1.61	NA	NA	H720	H720 N/A	H720	H720	H720	H720	NA	NA 2.	58 0.5	55
HCC1359	NA NA	IA N/	N N P	A NA	NA	NA	373.01	NA	3.83	0.98	NA	NA	HCC1359	HCC1359 N/A	HCC1359	HCC1359	HCC1359	HCC1359	NA	NA 2.	57 0.5	58
696H	NA NA	IA N/	4N NA	A NA	AN	NA	407.15	NA	6.07	2.74	NA	NA	H969	H969 N/A	H969	H969	696H	H969	NA	NA 2.	61 0.7	78
H2444	AN		4N N	A	AN	AN	441.71	Υ Ν	26.73	26.19	AA	AN	H2444	H2444 p.G12V	H2444	H2444	H2444	H2444	AN	NA 2.	55 1.4	43
				0	0	ļ	10,000	,	i	2	ł	i.	ATO FOL O		Pro Por or	The form	-	ALC LOT OF	L L C	-		5
HBECIJKI	13 35/	53 76	0.4	0.13	200	Ì	92.125	2 5	10.0	10.0	<u>ନ</u> ୧	107	BEC13KI	HBECI3KI N/A	HBECT3KI	HBECI3KI		1BECLISKI	- CC.2	0.30	-0.2	10
HBEC34KT	78 386 5	30	0.64	1 0.10	192	53	340.30	77	1.68	0.18	113	1691	BECOUNT RFC34KT	HBECJUNI IN/A	HBEC30N1 HBEC34KT	HBECOUN I	HRECOUNT F	IBELOUNI HRFC34KT	65.5	-0.00 0.19 2	21 -U.2	2 10
HBEC3KT	15 359.3	33 25	0.62	2 0.15	4	28	334.75	38	0.97	0.05	99	106	HBEC3KT	HBEC3KT N/A	HBEC3KT	HBEC3KT	HBEC3KT	HBEC3KT	2.56	0.21 2.	52 -0.0	5

# Table 1A (part 2)

# Table 1B

Cell Line	BX795 ED50	BX795 ED50 SD	Cell Line	Cmpd-II ED50	Cmpd-II ED50 SD
HCC15	0.10	0.03	H1703	0.17	0.01
A427	0.10	0.02	H1155	0.27	0.02
H1703	0.14	7.21	H2882	0.27	0.04
H1299	0.17	0.14	A427	0.34	0.04
HCC44	0.20	0.08	DFCI024	0.35	0.07
H1755	0.21	0.03	H3255	0.36	0.11
H1155	0.31	0.09	H324	0.37	0.07
H1975	0.32	0.49	H1792	0.38	0.06
H838 H3255	0.35	0.08	H23 HCC15	0.40	0.08
H2452	0.39	0.07	H520	0.43	0.16
H2110	0.39	0.08	EKVX	0.45	0.02
H1734 Hop62	0.42	0.14	H2073 H1734	0.45	0.16
H1355	0.44	0.33	HCC827	0.51	0.05
Calu6	0.45	0.21	HCC2108	0.56	0.14
HCC461	0.49	0.42	Cal12T	0.59	0.04
HCC4017	0.56	0.11	H358	0.71	0.02
H1792	0.58	0.04	Calu3	0.71	0.05
HCC366	0.63	0.15	HCC4019	0.70	0.08
H2009	0.63	0.09	H292	0.82	0.03
HCC515	0.69	0.39	HCC4017	0.84	0.08
DFCI024	0.70	0.01	H1299	0.86	0.02
H2030	0.82	0.24	H2085	0.86	0.09
HCC2108	0.85	0.19	A549	0.88	0.16
H460	0.93	0.32	H1975	0.03	0.12
H2073	0.94	0.16	H2030	0.94	0.04
H2087	0.99	0.17	HCC95	0.96	0.14
HCC4006	1.05	0.20	H2052	0.97	0.05
H1650	1.09	0.53	H661	0.99	0.66
H1915	1.21	0.19	H2258	1.04	0.14
H2228	1.24	0.57	DFCI032	1.05	0.30
HCC1195	1.32	0.21	HCC2279	1.13	0.13
H1993	1.33	0.32	HCC366 H322	1.19	0.20
Calu1	1.37	0.20	HCC364	1.23	0.19
H1373	1.54	0.49	H460	1.23	0.06
H292 H2122	1.54	0.39	H2452 H1650	1.29	0.26
H2023	1.61	0.24	H1993	1.39	0.32
HCC827	1.64	0.35	HCC4011	1.40	0.01
H2250	1.69	0.16	H2023 H441	1.41	0.04
Calu3	1.94	0.65	H1819	1.59	0.13
H1568	1.96	0.43	H2126	1.62	0.17
H1693	2.02	0.31	H2122	1.63	0.38
H1869	2.08	0.54	Calu1	1.67	0.19
HCC1438	2.10	0.63	H820	1.69	0.59
H1944 H23	2.16	0.35	H2250 H1944	1.71	0.42
H1819	2.27	0.68	HCC1171	1.87	0.70
H1838	2.45	0.83	HCC4006	1.91	0.30
H322	2.68	0.40	HCC193	2.00	0.61
EKVX	2.76	1.11	H157	2.09	0.29
HCC4018	2.93	0.78	H2228 H2110	2.19	0.21
HCC2935	3.01	0.95	H1573	2.38	0.10
HCC95	3.03	0.83	H1437	2.45	0.20
H661 H2085	3.12	0.41	HCC515 H1373	2.53	0.31
H2258	3.14	1.51	HCC4018	2.78	0.14
H1573	3.37	0.60	HCC78	2.79	0.71
H2342 H2172	3.38	1.65	H2087 H226	2.84	0.12
H125	3.54	0.94	H1651	3.05	0.33
H2882	3.60	0.92	H1838	3.22	0.51
H1437 H820	3.60	0.87	HCC1438 H650	3.40	0.27
HCC122	3.66	0.79	H1395	3.44	0.32
H1651	3.67	0.37	H2086	3.90	0.28
HCC364	3.69	2.05	H2009 HCC122	4.26	26.08
HCC4011	3.77	0.79	H1915	4.50	0.45
H1648	3.85	18.85	H2347	4.87	0.13
H520	4.10	0.54	H2342	5.55	∠.43 0.55
H441	4.23	0.32	H2887	5.80	0.89
HCC2279	4.48	1.42	H522	6.00	2.03
HCC2450	4.90	1.01	H1693	6.61	1.38
H1395	5.09	17.83	H1568	6.94	3.95
H596 H2086	5.09	1.28	H920	13.33	3.32
HCC4019	5.62	1.20	HCC3051	16.59	0.60
H2887	5.77	0.64	H2172	18.73	2.08
H2052 H522	5.83 6.40	0.58	H1581 HCC1195	21.34 21.51	0.08
HCC3051	6.84	0.56	HCC2450	24.09	22.36
H920 H3122	9.10 11.67	0.90	H125 H596	30.40 49.50	7.17 19.41



# Table 1 – TBK1 Inhibitor Sensitivity in NSCLC

Source data of BX795 and Compound II toxicity profiles in NSCLC.

A) ED50 and AUC values for both compounds; available RAS class mutation status information; and growth rate ratios. Among cell lines tested with both compounds, Ranks were given from most sensitive (1) to most resistant (100). Total Ranks for each compound are sum of ED50 and AUC ranks for that compound (range 2-200). Overall ranks are sum of both ED50 and AUC ranks for both compounds (range 4-400).

B) Source data and graphs for Figures 6A-B

# Table 2A

Gene Name	Pathway/Group	Gene Name	Pathway/Group	Gene Name	Pathway/Group
AXL	EMT/EMT-related	HRAS	Ras	FRAP1	mTOR Signaling
CDH1	EMT/EMT-related	KRAS	Ras	RPS6	mTOR Signaling
CDH10	EMT/EMT-related	NRAS	Ras	RPS6KA1	mTOR Signaling
CDH2	EMT/EMT-related	RALA	Ral/Ral Signaling	RPS6KA2	mTOR Signaling
CDH3	EMT/EMT-related	RALB	Ral/Ral Signaling	RPS6KA3	mTOR Signaling
CDH4	EMT/EMT-related	RALBP1	Ral/Ral Signaling	RPS6KA4	mTOR Signaling
CDH5	EMT/EMT-related	RALGAPA1	Ral/Ral Signaling	RPS6KA5	mTOR Signaling
CDH6	EMT/EMT-related	RALGAPA2	Ral/Ral Signaling	RPS6KA6	mTOR Signaling
CDH7	EMT/EMT-related	RALGAPB	Ral/Ral Signaling	RPS6KB1	mTOR Signaling
CDH8	EMT/EMT-related	RALGDS	Ral/Ral Signaling	RPS6KB2	mTOR Signaling
CDH9	EMT/EMT-related	RALGPS1	Ral/Ral Signaling	TSC1	mTOR Signaling
CLDN1	EMT/EMT-related	RGL2	Ral/Ral Signaling	TSC2	mTOR Signaling
CLDN10	EMT/EMT-related	RGL3	Ral/Ral Signaling	ULK1	mTOR Signaling
CLDN11	EMT/EMT-related	RGL4	Ral/Ral Signaling	ULK2	mTOR Signaling
CLDN12	EMT/EMT-related	EXOC1	Exocyst/Exocyst-related	ULK3	mTOR Signaling
CLDN14	EMT/EMT-related	EXOC2	Exocyst/Exocyst-related	LAMP1	Rag GTPases/Lysosome
CLDN15	EMT/EMT-related	EXOC3	Exocyst/Exocyst-related	LAMP2	Rag GTPases/Lysosome
CLDN16	EMT/EMT-related	EXOC3L2	Exocyst/Exocyst-related	LAMP3	Rag GTPases/Lysosome
CLDN17	EMT/EMT-related	EXOC4	Exocyst/Exocyst-related	RRAGA	Rag GTPases/Lysosome
CLDN18	EMT/EMT-related	EXOC5	Exocyst/Exocyst-related	RRAGB	Rag GTPases/Lysosome
CLDN2	EMT/EMT-related	EXOC6	Exocyst/Exocyst-related	RRAGC	Rag GTPases/Lysosome
CLDN20	EMT/EMT-related	EXOC7	Exocyst/Exocyst-related	RRAGD	Rag GTPases/Lysosome
CLDN22	EMT/EMT-related	IKBIP	TBK1/IKK Signaling	BRAF	Raf/MEK/ERK Signaling
CLDN23	EMT/EMT-related	ΙΚΒΚΑΡ	TBK1/IKK Signaling	MAP2K1	Raf/MEK/ERK Signaling
CLDN3	EMT/EMT-related	ІКВКВ	TBK1/IKK Signaling	MAP2K2	Raf/MEK/ERK Signaling
CLDN4	EMT/EMT-related	IKBKE	TBK1/IKK Signaling	MAP2K3	Raf/MEK/ERK Signaling
CLDN5	EMT/EMT-related	IKBKG	TBK1/IKK Signaling	MAP2K4	Raf/MEK/ERK Signaling
CLDN6	EMT/EMT-related	IRF3	TBK1/IKK Signaling	MAP2K5	Raf/MEK/ERK Signaling
CLDN7	EMI/EMI-related		IBK1/IKK Signaling	MAP2K6	Raf/MEK/ERK Signaling
CLDN8	EMI/EMI-related	TBK1	TBK1/IKKe Signaling	MAP2K7	Raf/MEK/ERK Signaling
CLDN9	EIVIT/EIVIT-related	I BKBP1	IBK1/IKKe Signaling		Rat/IVIEK/ERK Signaling
CLDNDI	EIVIT/EIVIT-related	AKT1C1	AKT Signaling		Rat/IVIEK/ERK Signaling
	ENT/ENT-related	AKIISI	AKT Signaling		Rdi/IVIEN/ERK Signaling
	ENT/ENT-related	AK12			Pof/MEK/ERK Signaling
SMAD1	EMT/EMT-related	GSK3A		MAD3K17	Raf/MEK/ERK Signaling
SMAD2	EMT/EMT-related	GSK3B GSK3A		MAD3K14	Raf/MEK/ERK Signaling
SMAD2	EMT/EMT-related		DI3K/DI3K-related Signaling	MAD3K3	Raf/MEK/ERK Signaling
SMAD4	EMT/EMT-related		PI3K/PI3K-related Signaling	MAP3K3	Raf/MEK/ERK Signaling
SMAD5	EMT/EMT-related	PIK3C2B	PI3K/PI3K-related Signaling	MAP3KA	Raf/MEK/ERK Signaling
SMADS	EMT/EMT-related	PIK3C2G	PI3K/PI3K-related Signaling	MAP3K5	Raf/MEK/ERK Signaling
SMAD7	EMT/EMT related	PIK3C3	PI3K/PI3K-related Signaling	MAP3K7	Raf/MEK/ERK Signaling
SMAD9	EMT/EMT-related	PIK3CA	PI3K/PI3K-related Signaling	MAP3K8	Raf/MEK/ERK Signaling
SNAI1	EMT/EMT-related	PIK3CB	PI3K/PI3K-related Signaling	MAP3K9	Raf/MEK/ERK Signaling
SNAI2	EMT/EMT-related	PIK3CD	PI3K/PI3K-related Signaling	MAP4K1	Raf/MEK/ERK Signaling
SNAI3	EMT/EMT-related	PIK3CG	PI3K/PI3K-related Signaling	MAP4K2	Raf/MEK/ERK Signaling
STK11	EMT/EMT-related	PIK3IP1	PI3K/PI3K-related Signaling	MAP4K3	Raf/MEK/ERK Signaling
TGFB1	EMT/EMT-related	PIK3R1	PI3K/PI3K-related Signaling	MAP4K4	Raf/MEK/ERK Signaling
TGFB1I1	EMT/EMT-related	PIK3R2	PI3K/PI3K-related Signaling	MAP4K5	Raf/MEK/ERK Signaling
TGFB2	EMT/EMT-related	PIK3R3	PI3K/PI3K-related Signaling	MAPK1	Raf/MEK/ERK Signaling
TGFB3	EMT/EMT-related	PIK3R4	PI3K/PI3K-related Signaling		
TGFBI	EMT/EMT-related	PIK3R4	PI3K/PI3K-related Signaling		
TGFBR1	EMT/EMT-related	PIK3R5	PI3K/PI3K-related Signaling		
TGFBR2	EMT/EMT-related	PIK3R5	PI3K/PI3K-related Signaling		
TGFBR3	EMT/EMT-related	PIK4CA	PI3K/PI3K-related Signaling		
TGFBRAP1	EMT/EMT-related	PTEN	PI3K/PI3K-related Signaling		
TWIST1	EMT/EMT-related				
TWIST2	EMT/EMT-related				
VIM	EMT/EMT-related				
ZEB1	EMT/EMT-related				
ZEB2	EMT/EMT-related				

| of XY<br>Pairs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 93 ZEB1                                      | 93 KRAS<br>93 SNAI1                                                                               | 93 TGFB3                                         | 93 TGFB1                                        | 93 TGFBR2<br>93 VIM                                                                               | 93 AXL                                          | 93 PIK3R2                                    | 93 RALGAPB                                   | 93 PIK3R3                                    |                                               | 93 CLDN8                                | 93 CLDN8<br>93 IKBKB                                                              | 93 CLDN8<br>93 IKBKB<br>93 RRAGC                                                                                              | 93 CLDN8<br>93 CLDN8<br>93 IKBKB<br>93 RRAGC<br>93 CDH1<br>03 CDH1                                                                                                                             | 93 CLDN8<br>93 IKBKB<br>93 RRAGC<br>93 RPAGC<br>93 PIK3CA<br>93 EXOC3L2                                                                                                                                                                               | 93 CLDN8<br>93 IKBKB<br>93 RRAGC<br>93 RDA1<br>93 PIKAGC<br>93 EXOC3L2<br>93 PIK3IP1<br>93 PIK3IP1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 93 CLDN8<br>93 IKBKB<br>93 RRAGC<br>93 CDH1<br>93 PIK3CA<br>93 EX0C3L2<br>93 PIK3IP1<br>93 CLDN3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 93 CLDN8<br>93 IKBKB<br>93 RRAGC<br>93 RRAGC<br>93 CDH1<br>93 PIK3CA<br>93 PIK3CA<br>93 CLDN3<br>93 CLDN3<br>93 CLDN3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 93 CLDN3<br>93 IKBKB<br>93 IKBKB<br>93 RRAGC<br>93 RRAGC<br>93 PIK3P1<br>93 EXOC3L2<br>93 CLDN3<br>93 CLDN3<br>93 CLDN3<br>93 CLDN4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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| (two-<br>tailed)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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0.00355<br>0.02367<br>0.02286<br>0.02288<br>0.02244<br>0.02246<br>0.02748<br>0.00718<br>0.00718<br>0.00718<br>0.00718<br>0.00718<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0076<br>0.0077<br>0.0077<br>0.0077<br>0.0077<br>0.0077<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00778<br>0.00768<br>0.00768<br>0.00778<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.00768<br>0.0 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                                               | -0.5183 to -0.1594                           | -0.4787 to -0.1077<br>-0.4685 to -0.09460                                                         | -0.4290 to -0.04544                              | -0.4288 to -0.04520                             | -0.4054 to -0.01693<br>-0 3991 to -0 00936                                                        | -0.3920 to -0.000907                            | 0.0009382 to 0.392(                          | 0.007533 to 0.3975                           | 0.01207 to 0.4014                            |                                               | 0.01527 to 0.4040                       | 0.01527 to 0.4040<br>0.01839 to 0.4066                                            | 0.01527 to 0.4040<br>0.01839 to 0.4066<br>0.01855 to 0.4068                                                                   | 0.01527 to 0.4040<br>0.01839 to 0.4066<br>0.01855 to 0.4068<br>0.01855 to 0.4068<br>0.02306 to 0.4105          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| Comparison                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Log 10 BX LDN vs. ZEB1                       | Log 10 BX LDN vs. KRAS<br>Log 10 BX LDN vs. SNAI1                                                 | Log 10 BX LDN vs. TGFB3                          | Log 10 BX LDN vs. TGFB1                         | Log 10 BX LDN vs. TGFBR2                                                                          | Log 10 BX LDN vs. AXL                           | Log 10 BX LDN vs. PIK3R2                     | Log 10 BX LDN vs. RALGAPB                    | Log 10 BX LDN vs. PIK3R3                     |                                               | רחל וה בע רבוא אצ. כרבואס               | Log 10 BX LDN vs. IKBKB                                                           | LOG 10 BX LDN VS. CLUVO<br>Log 10 BX LDN VS. IKBKB                                                                            | LOG 10 BX LDN VS. IKBKB<br>LOG 10 BX LDN VS. IKBKB<br>LOG 10 BX LDN VS. RRAGC<br>LOG 10 BX LDN VS. CDH1<br>LOG 10 BX LDN VS. DH2                                                               | LOB OF A CDN VS. ICLNO<br>LOB 10 BX CDN VS. ICRKB<br>LOB 10 BX LDN VS. RRAGC<br>LOB 10 BX LDN VS. CDH1<br>LOB 10 BX LDN VS. EXOC3L2<br>LOB 10 BX LDN VS. EXOC3L2                                                                                      | Log 10 PC ALON W. ACMAN<br>Log 10 BX LDN W. IKBKB<br>Log 10 BX LDN W. RRAGC<br>Log 10 BX LDN W. PIK3GZA<br>Log 10 BX LDN W. FIK3GZA<br>Log 10 BX LDN W. FIK3G212<br>Log 10 BX LDN W. FIK31P1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Lug 10 BX LDN vs. REMAC<br>Lug 10 BX LDN vs. EXOC312<br>Lug 10 BX LDN vs. EXOC312<br>Lug 10 BX LDN vs. CLDN3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Log 10 BX LDN vs. CLDN vs. IKBKB<br>Log 10 BX LDN vs. IKBKB<br>Log 10 BX LDN vs. RFAGC<br>Log 10 BX LDN vs. CDH1<br>Log 10 BX LDN vs. EXOC3L2<br>Log 10 BX LDN vs. CLDN3<br>Log 10 BX LDN vs. CLDN3<br>Log 10 BX LDN vs. CLDN4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Log 10 BX LDN vs. CLDN vs. IKRAG<br>Log 10 BX LDN vs. IKRAGC<br>Log 10 BX LDN vs. RFAGC<br>Log 10 BX LDN vs. PK3CA<br>Log 10 BX LDN vs. PK3P1<br>Log 10 BX LDN vs. CLDN 3<br>Log 10 BX LDN vs. CLDN 3<br>Log 10 BX LDN vs. CLDN 4<br>Log 10 BX LDN vs. CSXR4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Log 10 BX LDN vs. CLDN vs. IRRAG<br>Log 10 BX LDN vs. IRRAGC<br>Log 10 BX LDN vs. RRAGC<br>Log 10 BX LDN vs. PIK3CA<br>Log 10 BX LDN vs. PIK3CA<br>Log 10 BX LDN vs. PIK3IP1<br>Log 10 BX LDN vs. CLDN4<br>Log 10 BX LDN vs. CLDN4<br>Log 10 BX LDN vs. CDH4<br>Log 10 BX LDN vs. CDH4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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IKRAB<br>Lug 10 BX LDN vs. RRAAC<br>Lug 10 BX LDN vs. RRAAC<br>Lug 10 BX LDN vs. RRAAC<br>Lug 10 BX LDN vs. PK31P1<br>Lug 10 BX LDN vs. PK31P1<br>Lug 10 BX LDN vs. CLDN4<br>Lug 10 BX LDN vs. GX73B<br>Lug 10 BX LDN vs. GX73B<br>Lug 10 BX LDN vs. GX73B<br>Lug 10 BX LDN vs. GX73<br>Lug 10 BX LDN vs. GX73<br>Lug 10 BX LDN vs. EXOC3<br>Lug 10 BX LDN vs. EXOC3<br>Lug 10 BX LDN vs. EXOC3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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GSC7<br>Lug 10 BX LDN vs. EXOC7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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CLDN4<br>Log 10 BX LDN vs. CLDN4<br>Log 10 BX LDN vs. CLDN4<br>Log 10 BX LDN vs. CDH3<br>Log 10 BX LDN vs. CDH3<br>Log 10 BX LDN vs. EXCC7<br>Log 10 Cmpd II LDN vs. EXCC7<br>Log 10 Cmpd II LDN vs. EXCC7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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GSR3B<br>Log 10 BX LDN vs. EXOC7<br>Log 10 BX LDN vs. EXOC7<br>Log 10 BX LDN vs. EXOC7<br>Log 10 Cmpd II LDN vs. RP4344,<br>Log 10 Cmpd II LDN vs. RP43444,<br>Log 10 Cmpd II LDN vs. RP43444,<br>Log 10 Cmpd II LDN vs. RP43444,<br>Log 10 Cmpd II LDN vs. RP4344,<br>Log 10 Cmpd II LDN vs. RP43444,<br>Log 10 Cmpd II LDN vs. RP43444,<br>Log 10 Cmpd II L                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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                                                                                | S6KB1<br>№3R3<br>AP3K1<br>RAGC<br>CLDN4<br>KOC3L2                                                                                                                                                                                                     | S6KB1<br>IK3R3<br>AP3K1<br>RAGC<br>LDN4<br>COC3L2<br>LDN8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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S6KB1<br>IK3R3<br>IK3R3<br>RAGC<br>LDN4<br>LDN4<br>LDN3<br>LDN3<br>LDN3<br>LDN3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | S6KB1<br>IKSR3<br>APSK1<br>RAGC<br>LDN4<br>LDN8<br>COC3L2<br>LDN8<br>LDN8<br>LDN8<br>LDN8<br>LDN8<br>LDN8<br>LDN8<br>LDN8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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S6KB1<br>PS4K1<br>PS4K1<br>PS4K1<br>PS4K1<br>PAGC<br>CD14<br>AGC<br>CD14<br>MMP1<br>PS4K1<br>PS4K1<br>PS4K1<br>PS4K1<br>COC7<br>COC7<br>PS4K4<br>ADD6<br>PA4K4<br>ADD6<br>PA4K4<br>ADD6<br>PA4K4<br>ADD6<br>PA4K4<br>ADD6<br>PA4K4<br>ADD6<br>PA4K4<br>ADD6<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K4<br>ADD7<br>PA4K44<br>ADD7<br>PA4K44<br>ADD7<br>PA4K44<br>ADD7<br>PA4K44<br>ADD7<br>PA4K7<br>ADD7<br>PA4K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>ADD7<br>PA7K7<br>ADD7<br>PA7K7<br>ADD7<br>ADD7<br>AD7<br>AD7<br>AD7<br>AD7<br>AD7<br>AD7<br>AD7                                                                                                                                                                                            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0.033 • 93<br>0.0224 • 93<br>0.0224 • 93<br>0.0224 • 93<br>0.0223 • 93<br>0.0145 • 93<br>0.0148 • 93<br>0.0148 • 93<br>0.0148 • 93<br>0.0148 • 93<br>0.0148 • 93<br>0.0109 • 93<br>0.0004 • 93<br>0.00000000000000000000000000000000000                                                                                              | 0.0033 • 93 F 0 0.0232 • 93 0.0232 • 93 0.02241 • 93 0.02241 • 93 0.02241 • 93 0.02252 • 93 7 0.01448 • 93 7 0.01448 • 93 7 0.01448 • 93 0.01448 • 93 0.01044 • 93 0.01044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 0.00044 • 93 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                                                                                                                                                                                                                                                                                                                                                                                                              | 0.033 • 93<br>0.0224 • 93<br>0.0241 • 93<br>0.0241 • 93<br>0.0241 • 93<br>0.0154 • 93<br>0.0154 • 93<br>0.0154 • 93<br>0.0154 • 93<br>0.0169 • 93<br>0.0109 • 93<br>0.0104 • 93<br>0.0106 • 93<br>0.0016 • 1 93<br>0.0001 • 1 93<br>0.0001 • 1 93<br>0.0002 • 1 93<br>0.0000 • 1 93<br>0.00000 • 1 93<br>0.0000000000 • 1 93<br>0.00000000000000000000000000000000000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.033 •• 93<br>0.0324 •• 93<br>0.0289 •• 93<br>0.0281 •• 93<br>0.0154 •• 93<br>0.0154 •• 93<br>0.0148 •• 93<br>0.0148 •• 93<br>0.0148 •• 93<br>0.0104 •• 93<br>0.004 •• 93<br>0.004 •• 93<br>0.004 •• 93<br>0.006 •• 93<br>0.006 •• 93<br>0.006 •• 93<br>0.0006 •• 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.033 • • • • • • • • • • • • • • • • • •                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Onose         Particle         Particle <t< td=""><td>0.0033         *         93         RP           0.0234         *         93         RH           0.0241         *         93         RH           0.0148         *         93         CI           0.0148         *         93         CI           0.0148         *         93         CI           0.0148         *         93         CI           0.0149         *         93         M           0.0142         *         93         M           0.0104         *         93         M           0.0004         *         93         M</td><td>Diama         Diama         <th< td=""><td>D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         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9           0.01246         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0104         9           0.0104         9           0.0104         9           0.0016         9           0.0016         9           0.0016         9           0.0017         9           0.0028         9           0.0028         9           0.0028         9           0.0028         9           0.00317         9           0.00328         9           0.00338         9<!--</td--><td>0.0233 • 933<br/>0.02241 • 933<br/>0.02241 • 933<br/>0.02241 • 933<br/>0.02253 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.0104 • 933<br/>0.0004 • 933<br/>0.0004 • 933<br/>0.0001 • 933<br/>0.0001 • 933<br/>0.0002 • 10<br/><b>Pvalue</b> • 933<br/>0.0002 • 10<br/><b>Pvalue</b> • 933<br/>0.0002 • 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10</td><td>0.033         0.033         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0154         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0021         93         93           0.00321         93         93           0.00321         93&lt;</td><td><math display="block">\begin{array}{cccccccccccccccccccccccccccccccccccc</math></td><td>0.0333         0.93           0.0324         93           0.02241         93           0.02241         93           0.02241         93           0.02241         93           0.0154         93           0.0154         93           0.0154         93           0.0154         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0044         93           0.0044         93           0.0044         93           0.0044         93           0.0016         93           0.0022         93           0.0023         93           0.0023         93           0.0023         93           0.0023         93           0.0032         93           0.0032         93           0.0032         93           0</td></td></th<></td></t<> | 0.0033         *         93         RP           0.0234         *         93         RH           0.0241         *         93         RH           0.0148         *         93         CI           0.0148         *         93         CI           0.0148         *         93         CI           0.0148         *         93         CI           0.0149         *         93         M           0.0142         *         93         M           0.0104         *         93         M           0.0004         *         93         M                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Diama         Diama <th< td=""><td>D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         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        0.0124         9           0.0124         9           0.0124         9           0.0104         9           0.0104         9           0.0104         9           0.0016         9           0.0016         9           0.0016         9           0.0017         9           0.0028         9           0.0028         9           0.0028         9           0.0028         9           0.00317         9           0.00328         9           0.00338         9<!--</td--><td>0.0233 • 933<br/>0.02241 • 933<br/>0.02241 • 933<br/>0.02241 • 933<br/>0.02253 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.0104 • 933<br/>0.0004 • 933<br/>0.0004 • 933<br/>0.0001 • 933<br/>0.0001 • 933<br/>0.0002 • 10<br/><b>Pvalue</b> • 933<br/>0.0002 • 10<br/><b>Pvalue</b> • 933<br/>0.0002 • 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10</td><td>0.033         0.033         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0154         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0021         93         93           0.00321         93         93           0.00321         93&lt;</td><td><math display="block">\begin{array}{cccccccccccccccccccccccccccccccccccc</math></td><td>0.0333         0.93           0.0324         93           0.02241         93           0.02241         93           0.02241         93           0.02241         93           0.0154         93           0.0154         93           0.0154         93           0.0154         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0044         93           0.0044         93           0.0044         93           0.0044         93           0.0016         93           0.0022         93           0.0023         93           0.0023         93           0.0023         93           0.0023         93           0.0032         93           0.0032         93           0.0032         93           0</td></td></th<> | D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D         D <thd< th=""> <thd< th=""> <thd< th=""> <thd< th=""></thd<></thd<></thd<></thd<>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.033         9           0.0324         9           0.02241         9           0.02241         9           0.02241         9           0.02241         9           0.02241         9           0.02241         9           0.02241         9           0.01244         9           0.01245         9           0.01246         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0124         9           0.0104         9           0.0104         9           0.0104         9           0.0016         9           0.0016         9           0.0016         9           0.0017         9           0.0028         9           0.0028         9           0.0028         9           0.0028         9           0.00317         9           0.00328         9           0.00338         9 </td <td>0.0233 • 933<br/>0.02241 • 933<br/>0.02241 • 933<br/>0.02241 • 933<br/>0.02253 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.01448 • 933<br/>0.0104 • 933<br/>0.0004 • 933<br/>0.0004 • 933<br/>0.0001 • 933<br/>0.0001 • 933<br/>0.0002 • 10<br/><b>Pvalue</b> • 933<br/>0.0002 • 10<br/><b>Pvalue</b> • 933<br/>0.0002 • 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10<br/>• 10</td> <td>0.033         0.033         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0224         93         93           0.0154         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0021         93         93           0.00321         93         93           0.00321         93&lt;</td> <td><math display="block">\begin{array}{cccccccccccccccccccccccccccccccccccc</math></td> <td>0.0333         0.93           0.0324         93           0.02241         93           0.02241         93           0.02241         93           0.02241         93           0.0154         93           0.0154         93           0.0154         93           0.0154         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0044         93           0.0044         93           0.0044         93           0.0044         93           0.0016         93           0.0022         93           0.0023         93           0.0023         93           0.0023         93           0.0023         93           0.0032         93           0.0032         93           0.0032         93           0</td> | 0.0233 • 933<br>0.02241 • 933<br>0.02241 • 933<br>0.02241 • 933<br>0.02253 • 933<br>0.01448 • 933<br>0.01448 • 933<br>0.01448 • 933<br>0.01448 • 933<br>0.0104 • 933<br>0.0004 • 933<br>0.0004 • 933<br>0.0001 • 933<br>0.0001 • 933<br>0.0002 • 10<br><b>Pvalue</b> • 933<br>0.0002 • 10<br><b>Pvalue</b> • 933<br>0.0002 • 10<br>• 10<br>• 10<br>• 10<br>• 10<br>• 10<br>• 10<br>• 10                                                                                                                                                                                                                          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         0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0148         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0016         93         93           0.0021         93         93           0.00321         93         93           0.00321         93<                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $\begin{array}{cccccccccccccccccccccccccccccccccccc$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0.0333         0.93           0.0324         93           0.02241         93           0.02241         93           0.02241         93           0.02241         93           0.0154         93           0.0154         93           0.0154         93           0.0154         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0164         93           0.0044         93           0.0044         93           0.0044         93           0.0044         93           0.0016         93           0.0022         93           0.0023         93           0.0023         93           0.0023         93           0.0023         93           0.0032         93           0.0032         93           0.0032         93           0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| squared tailed) summary Pe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.1538 0.0001 ***                            | 0.09954 0.0021 ** 9:<br>0.0832 0.005 ** 9:                                                        | 0.08026 0.0059 ** 93                             | 0.06121 0.0168 * 93                             | 0.06071 0.0173 * 93<br>0.05214 0.0277 * 83                                                        | 0.05136 0.0289 * 93                             | 0.0421 0.0485 * 93                           | 0.04454 0.0423 * 93                          | 0.04635 0.0382 * 93                          |                                               | 0.04899 0.033 * 93 RI                   | 0.04899 0.033 * 93 R<br>0.04931 0.0324 * 93 I                                     | 0.04899 0.033 * 93 RF<br>0.04931 0.0324 * 93 F<br>0.05142 0.0288 * 93 M                                                       | 0.04899 0.033 * 93 R <sup>1</sup><br>0.04931 0.0324 * 93 F<br>0.05142 0.0288 * 93 N<br>0.05463 0.0281 * 93 A                                                                                   | 0.014899 0.033 * 93 R<br>0.014891 0.0324 * 93 N<br>0.05413 0.0228 * 93 N<br>0.05473 0.0229 * 93 F<br>0.05678 0.0229 * 93 F                                                                                                                            | 0.04899 0.033 * 93 RN<br>0.04931 0.0324 * 93 FN<br>0.05142 0.0388 * 93 M<br>0.05463 0.0224 * 93 R<br>0.05646 0.02239 * 93 C<br>0.05646 0.02222 * 93 C                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.04899 0.033 * 93 R<br>0.04931 0.0324 93 M<br>0.05142 0.0288 * 93 M<br>0.05478 0.0229 * 93 F<br>0.05616 0.0229 * 93 F<br>0.0222 0.0154 * 93 F<br>0.062851 0.0148 * 93 F                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.04899 0.033 * 93 F<br>0.04931 0.0224 * 93<br>0.05432 0.0241 * 93<br>0.05443 0.0241 * 93<br>0.05478 0.0229 * 93<br>0.05676 0.0223 * 93<br>0.05651 0.0148 * 93<br>0.0552 0.0148 * 93<br>0.06735 0.0148 * 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.04899 0.033 * 93 F<br>0.04931 0.0324 * 93<br>0.05443 0.0241 * 93<br>0.05448 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M         M           0.1044         0.0016         93         M         M           0.1047         <                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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0.04893         0.0324         *         93         M           0.05142         0.0324         *         93         M           0.05478         0.0324         *         93         M           0.055478         0.03239         *         93         M           0.05557         0.0154         *         93         R           0.05556         0.0154         *         93         R           0.05557         0.0154         *         93         EX           0.05556         0.0148         *         93         C           0.05756         0.0148         *         93         C         C           0.05756         0.014         *         93         C         C           0.05756         0.014         *         93         C         C           0.058545         0.0144         *         93         C         C           0.1007         *         93         C         93         C         C           0.1007         *         93         M         93         C         C         C                                  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        93         MI           0.005442         0.00344         **         93         MI           0.005443         0.00241         **         93         RI           0.005443         0.00239         0.00239         93         RI           0.005871         0.00239         0.0148         **         93         RI           0.005872         0.0148         **         93         RI         0.0168         0.0168         0.0168         0.0168         0.0108         0.0109         93         RI         0.0108         0.0108         0.0109         93         MI         0.0108         0.0109         0.0108         0.0109         0.0109         0.0108         0.0109         0.0108         0.0108         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109         0.0109                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Q.04899         0.033         **         P3         RR           0.05442         0.033         **         93         RR           0.05442         0.0324         **         93         MI           0.05443         0.0241         **         93         MI           0.05443         0.0239         **         93         MI           0.05646         0.0239         **         93         RF           0.05651         0.0154         **         93         RI           0.05673         0.0154         **         93         RI           0.066735         0.0154         **         93         RI           0.066735         0.0148         **         93         RI           0.066735         0.0148         **         93         RI           0.066735         0.014         **         93         RI           0.1067         **         93         RI         CI                                                                                                                                                                                                                                                                                                                                                                                                                                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N           0.1040         0.0014         93         N           0.1040         0.0014         93         N           0.1040         0.0014         93         N           0.1040         0.0014         93         N <t< td=""><td>0.04899         0.0333         *         93           0.064311         0.0324         *         93           0.054312         0.0241         *         93           0.05478         0.0241         *         93           0.055416         0.0233         *         93           0.055416         0.0223         *         93           0.055416         0.0223         *         93           0.055416         0.0123         *         93           0.055312         0.0148         *         93           0.056312         0.0148         *         93           0.056312         0.0148         *         93           0.056313         0.0104         *         93           0.056313         0.0104         *         93           0.056313         0.0104         *         93           0.05845         0.0014         *         93           0.1047         0.0016         *         93           0.1047         0.0016         *         93           0.1049         *         *         93           0.1049         *         *         93</td><td>0.04895         0.033         **         93           0.05473         0.0288         **         93           0.05472         0.0288         **         93           0.05473         0.0288         **         93           0.055473         0.0223         **         93           0.056478         0.0223         **         93           0.056478         0.0223         **         93           0.056547         0.02223         **         93           0.056547         0.0222         **         93           0.056547         0.0124         **         93           0.066973         0.0124         **         93           0.066973         0.0104         **         93           0.066973         0.0104         **         93           0.10677        
0.0014         **         93           0.1077         0.0014         **         93           0.1076         0.0016         **         93           0.1077         0.0016         **         93           0.1078         0.0016         **         93           0.1074         0.0016         **         93<td>0.04999         0.033         **         93           0.06499         0.033         **         93           0.05442         0.0288         **         93           0.05643         0.0241         **         93           0.05645         0.0223         **         93           0.05645         0.0223         **         93           0.05646         0.0122         **         93           0.05647         0.0124         **         93           0.05651         0.0122         **         93           0.06673         0.0148         **         93           0.06673         0.0109         **         93           0.06673         0.0144         **         93           0.06735         0.0104         **         93           0.06735         0.0104         **         93           0.1047         0.0041         **         93           0.1047         0.0041         **         93           0.1043         0.0041         **         93           0.1044         0.0021         **         93           0.1044         0.0022         **         93</td><td>0.04899         0.033         **         93           0.056142         0.0288         9         93           0.056142         0.0288         93         93           0.056142         0.0288         93         93           0.05616         0.0222         93         93           0.056516         0.0222         93         93           0.056516         0.0222         93         93           0.056516         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0144         93         93           0.1047         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0002         93         93           0.1044         0.0002         93         93</td><td><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></td></td></t<> | 0.04899         0.0333         *         93           0.064311         0.0324         *         93           0.054312         0.0241         *         93           0.05478         0.0241         *         93           0.055416         0.0233         *         93           0.055416         0.0223         *         93           0.055416         0.0223         *         93           0.055416         0.0123         *         93           0.055312         0.0148         *         93           0.056312         0.0148         *         93           0.056312         0.0148         *         93           0.056313         0.0104         *         93           0.056313         0.0104         *         93           0.056313         0.0104         *         93           0.05845         0.0014         *         93           0.1047         0.0016         *         93           0.1047         0.0016         *         93           0.1049         *         *         93           0.1049         *         *         93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.04895         0.033         **         93           0.05473         0.0288         **         93           0.05472         0.0288         **         93           0.05473         0.0288         **         93           0.055473         0.0223         **         93           0.056478         0.0223         **         93           0.056478         0.0223         **         93           0.056547         0.02223         **         93           0.056547         0.0222         **         93           0.056547         0.0124         **         93           0.066973         0.0124         **         93           0.066973         0.0104         **         93           0.066973         0.0104         **         93           0.10677         0.0014         **         93           0.1077         0.0014         **         93           0.1076         0.0016         **         93           0.1077         0.0016         **         93           0.1078         0.0016         **         93           0.1074         0.0016         **         93 <td>0.04999         0.033         **         93           0.06499         0.033         **         93           0.05442         0.0288         **         93           0.05643         0.0241         **         93           0.05645         0.0223         **         93           0.05645         0.0223         **         93           0.05646         0.0122         **         93           0.05647         0.0124         **         93           0.05651         0.0122         **         93           0.06673         0.0148         **         93           0.06673         0.0109         **         93           0.06673         0.0144         **         93           0.06735         0.0104         **         93           0.06735         0.0104         **         93           0.1047         0.0041         **         93           0.1047         0.0041         **         93           0.1043         0.0041         **         93           0.1044         0.0021         **         93           0.1044         0.0022         **         93</td> <td>0.04899         0.033         **         93           0.056142         0.0288         9         93           0.056142         0.0288         93         93           0.056142         0.0288         93         93           0.05616         0.0222         93         93           0.056516         0.0222         93         93           0.056516         0.0222         93         93           0.056516         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0144         93         93           0.1047         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0002         93         93           0.1044         0.0002         93         93</td> <td><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></td> | 0.04999         0.033         **         93           0.06499         0.033         **         93           0.05442         0.0288         **         93           0.05643         0.0241         **         93           0.05645         0.0223         **         93           0.05645         0.0223         **         93           0.05646         0.0122         **         93           0.05647         0.0124         **         93           0.05651         0.0122         **         93           0.06673         0.0148         **         93           0.06673         0.0109         **         93           0.06673         0.0144         **         93           0.06735         0.0104         **         93           0.06735         0.0104         **         93           0.1047         0.0041         **         93           0.1047         0.0041         **         93           0.1043         0.0041         **         93           0.1044         0.0021         **         93           0.1044         0.0022         **       
 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.04899         0.033         **         93           0.056142         0.0288         9         93           0.056142         0.0288         93         93           0.056142         0.0288         93         93           0.05616         0.0222         93         93           0.056516         0.0222         93         93           0.056516         0.0222         93         93           0.056516         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0148         93         93           0.056517         0.0144         93         93           0.1047         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         0.0001         93         93           0.1044         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| interval squared tailed) summary Pa                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -0.5518 to -0.2049 0.1538 0.0001 ***         | -0.4879 to -0.1195 0.09954 0.0021  **    9:<br>-0.4648 to -0.09003 0.0832  0.005  **    9:        | -0.4604 to -0.08448 0.08026 0.0059 ** 93         | -0.4295 to -0.04601 0.06121 0.0168 * 93         | -0.4286 to -0.04494 0.06071 0.0173 * 93<br>-0.4129 to -0.02584 0.05214 0.0277 * 93                | -0.4113 to -0.02402 0.05136 0.0289 * 93         | 0.001551 to 0.3925 0.0421 0.0485 * 93        | 0.007660 to 0.3977 0.04454 0.0423 * 93       | 0.01212 to 0.4014 0.04635 0.0382 * 93        |                                               | 0.01846 to 0.4067 0.04899 0.033 * 93 RI | 0.01846 to 0.4067 0.04899 0.033 * 93 R<br>0.01922 to 0.4073 0.04931 0.0324 * 93 I | 0.01846 to 0.4067 0.04899 0.033 * 93 RF<br>0.01922 to 0.4073 0.04931 0.0324 * 93 F<br>0.02416 to 0.4115 0.05142 0.0288 * 93 M | 0.019846 to 14067 0.04889 0.033 * 93 R1<br>0.019845 to 0.407 0.04893 0.0324 * 93 N<br>0.02416 to 0.4115 0.05412 0.0288 * 93 N<br>0.03155 to 0.4176 0.05483 0.0241 * 93 F                       | 0.019846 to 1.067 0.04899 0.033 * 93 R<br>0.019845 to 0.407 0.04891 0.0324 * 93 N<br>0.024165 to 0.4115 0.05442 0.0288 * 93 N<br>0.021155 to 0.4176 0.05463 0.0241 * 93 F<br>0.03165 to 0.4204 0.05473 0.0239 * 93 F                                  | 0.019846 to 14.067 0.04899 0.033 * 93 RN<br>0.019845 to 0.407 0.04931 0.0324 * 93 F<br>0.02416 to 0.4115 0.05442 0.0288 * 93 M<br>0.03153 to 0.4176 0.05463 0.0241 * 93 R<br>0.03165 to 0.4176 0.05466 0.0239 * 93 C<br>0.04945 to 0.4323 0.055616 0.0222 * 93 E<br>0.04945 to 0.4323 0.06252 0.0154 * 93 C                                                                                                                                                                                                                                                                                                                                                                             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| 0.01846 to 1.4067 0.04899 0.033 * 93 F<br>0.01842 to 1.407 0.04899 0.032 * 93<br>0.02415 to 0.4175 0.05489 0.0241 * 93<br>0.02185 to 0.4176 0.05488 0.0241 * 93<br>0.03185 to 0.4278 0.05478 0.0239 * 93<br>0.03186 to 0.4276 0.05478 0.0239 * 93<br>0.03496 to 0.4236 0.05515 0.0154 * 93<br>0.06993 to 0.4335 0.06285 0.0154 * 93<br>0.05693 to 0.4335 0.06735 0.0148 * 93<br>0.05693 to 0.4400 0.06735 0.0148 * 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.01846 to 14.067 0.04899 0.033 * 93 F<br>0.019245 to 14.07 0.04899 0.032 * 93<br>0.02415 to 0.4175 0.04819 0.0224 * 93<br>0.02415 to 0.4176 0.05468 0.0241 * 93<br>0.03185 to 0.4176 0.05468 0.0241 * 93<br>0.03486 to 0.4176 0.05478 0.0239 * 93<br>0.03486 to 0.4204 0.05616 0.0222 * 93<br>0.03485 to 0.4323 0.06281 0.0146 * 93<br>0.05892 to 0.4320 0.06913 0.0148 * 93<br>0.05892 to 0.4420 0.06913 0.0109 * 93<br>0.025825 to 0.4429 0.06913 0.0109 * 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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93<br>0.03153 to .4176 0.05463 0.0241 * 93<br>0.03496 to .42204 0.05616 0.0229 * 93<br>0.04945 to 0.4323 0.06281 0.0148 * 93<br>0.06882 to .4423 0.06521 0.0148 * 93<br>0.06882 to .4429 0.06513 0.0148 * 93<br>0.06585 to .4429 0.06313 0.0148 * 93<br>0.06585 to .4429 0.06313 0.0104 * 93<br>0.06585 to .4429 0.06313 0.0104 * 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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93<br>0.03496 to 1.4203 0.05516 0.0144 * 93<br>0.03892 to 0.4400 0.06735 0.0144 * 93<br>0.05892 to 0.4400 0.06735 0.0124 * 93<br>0.05892 to 0.4400 0.06735 0.0124 * 93<br>0.05892 to 0.4400 0.06735 0.0124 * 93<br>0.05892 to 0.4409 0.06735 0.0104 * 93<br>0.05865 to 0.4429 0.06917 0.0104 * 93<br>0.05865 to 0.4429 0.06917 0.0104 * 93<br>0.05865 to 0.4430 0.06872 0.004 * 93<br>0.05966 to 0.4896 0.08875 0.004 * 93<br>0.02716 to 0.4937 0.1001 * 93<br>0.1271 * 0.4931 * 0.1001 * 93<br>0.1011 * 0.4931 * 0.1001 * 93<br>0.1271 * 0.4931 * 0.1001 * 93<br>0.1011 * 0.4931 * 0.1001 * 0.0011 * 93<br>0.1011 * 0.4931 * 0.1001 * 0.0011 * 93<br>0.1011 * 0.1011 * 0.0011 * 0.0011 * 93<br>0.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.01845 to 0.467         0.4893         0.033         *         93           0.01845 to 0.467         0.04931         0.033         *         93           0.03152 to 0.4175         0.05142         0.0324         *         93           0.03155 to 0.4176         0.05443         0.0234         *         93           0.03155 to 0.4176         0.05443         0.0234         *         93           0.03456 to 0.4176         0.05478         0.0234         93         93           0.03456 to 0.4220         0.05816         0.0222         93         93           0.03456 to 0.4223         0.0551         0.0143         93         93           0.03692 to 0.4230         0.06351         0.0143         93         93           0.03692 to 0.4429         0.06735         0.0143         93         93           0.03692 to 0.4429         0.06735         0.0142         93         93           0.036926 to 0.4429         0.06735         0.0142         93         93           0.036926 to 0.4429         0.06742         0.0042         93         93         93         93         93           0.03756 to 0.4429         0.0704         10042         100         93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0.01846 to 0.4067         0.04899         0.033         •         93           0.019245 to 0.4175         0.048191         0.0234         •         93           0.02415 to 0.4175         0.048191         0.0234         •         93           0.02155 to 0.4175         0.05463         0.0241         •         93           0.03155 to 0.4175         0.05463         0.0241         •         93           0.03155 to 0.4176         0.05463         0.0239         •         93           0.03155 to 0.4176         0.054618         0.0239         •         93           0.03155 to 0.4204         0.05616         0.0223         •         93           0.039895 to 0.4323         0.06351         0.0148         •         93           0.036925 to 0.4420         0.06951         0.0148         •         93           0.056956 to 0.4420         0.06951         0.0148         •         93           0.05696 to 0.4429         0.06961         0.0142         •         93           0.05696 to 0.4429         0.0697         0.0104         •         93           0.05756 to 0.4429         0.0697         0.0104         •         93           0.1771 to 0.4994         <                                                                                                                                                                                                                                                                        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     0.05478         0.0234         93         1           0.03155 to 0.4735         0.05478         0.0234         93         1           0.04965 to 0.4735         0.06873         0.0144         93         0           0.06035 to 0.4430         0.06735         0.0144         93         N           0.06435 to 0.4430         0.06875         0.0144         93         N           0.06435 to 0.4430         0.06845         0.0042         93         N           0.07244         0.08645         0.0042         93         N           0.07241 to 0.4894         0.107         0.0016         93         N           0.1214 to 0.5346         0.107         0.0016         93         N           0.1214 to 0.5346         0.107                                                                                                                                                                                                                                                                                               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Z<br>0.03565 to 0.4443 0.00637 0.0104 * 93 Z<br>0.03565 to 0.4443 0.00637 0.0014 * 93 Z<br>0.03756 to 0.4443 0.00637 0.0014 * 93 Z<br>0.03756 to 0.4443 0.00637 0.0014 * 93 Z<br>0.03756 to 0.4443 0.00016 * 93 Z<br>0.03756 to 0.4470 0.00019 * 93 Z<br>0.03756 to 0.4400 0.00016 * 93 Z<br>0.03756 to 0.4400 0.00019 * 93 Z<br>0.04400 0.00019 * 93 Z<br>0.00019 * 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.01845 to 0.4057         0.04895         0.0433         s         93         RP           0.019845 to 0.4175         0.04831         0.0324         93         R1           0.02416 to 0.4115         0.05443         0.02418         0.05443         0.02418         93         R1           0.03185 to 0.4115         0.05443         0.02418         0.05443         0.0233         93         R1           0.033185 to 0.4146         0.056478         0.05443         0.0233         93         R1           0.03345 to 0.4240         0.056478         0.056478         0.0233         93         C1           0.034965 to 0.4240         0.05637         0.0148         93         C1         93         C1           0.036925 to 0.4400         0.06755         0.0122         93         C1         93         M1           0.056926 to 0.4400         0.06913<0.0104                                                                                                 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                                                                                        | $ \begin{array}{c} 0.0184 \mbox{ io } 0.0035 & 0.033 & 0.0024 \mbox{ io } 0.00353 \mbox{ io } 0.04931 & 0.0241 & 0.933 & 0.0241 \mbox{ io } 0.03153 \mbox{ io } 0.05478 & 0.02473 & 0.02473 & 0.0243 & 0.930 \\ 0.03158 \mbox{ io } 0.4176 & 0.05478 & 0.0241 & 0.930 \\ 0.03496 \mbox{ io } 0.4202 & 0.05478 & 0.0223 & 0.930 \\ 0.03496 \mbox{ io } 0.4323 & 0.02522 & 0.0154 & 0.930 \\ 0.03495 \mbox{ io } 0.4323 & 0.02523 & 0.0124 & 0.930 \\ 0.03496 \mbox{ io } 0.4323 & 0.03551 & 0.0148 & 0.930 \\ 0.03592 \mbox{ io } 0.4420 & 0.06613 & 0.0122 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.06913 & 0.0104 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.06913 & 0.0104 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.06913 & 0.0104 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.06913 & 0.0104 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.06913 & 0.0104 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.06913 & 0.0104 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.00614 & 0.930 \\ 0.00256 \mbox{ io } 0.4420 & 0.00014 & 0.930 \\ 0.02756 \mbox{ io } 0.4420 & 0.00014 & 0.930 \\ 0.02756 \mbox{ io } 0.4420 & 0.00014 & 0.930 \\ 0.1217 \mbox{ io } 0.4420 & 0.00014 & 0.930 \\ 0.1217 \mbox{ io } 0.4420 & 0.00014 & 0.930 \\ 0.1217 \mbox{ io } 0.4420 & 0.00016 & 0.930 \\ 0.1217 \mbox{ io } 0.4232 & 0.0002 & 0.0001 & 0.930 \\ 0.1217 \mbox{ io } 0.4323 & 0.0002 & 0.00016 & 0.930 \\ 0.1217 \mbox{ io } 0.4323 & 0.0002 & 0.00016 & 0.930 \\ 0.1217 \mbox{ io } 0.4321 & 0.00016 & 0.930 \\ 0.1217 \mbox{ io } 0.00016 & 0.00016 & 0.930 \\ 0.1217 \mbox{ io } 0.00016 & 0.00016 & 0.930 \\ 0.1217 \mbox{ io } 0.00016 & 0.00016 & 0.930 \\ 0.00223 \mbox{ io } 0.00012 \mbox{ io } 0.00012 & 0.00016 & 0.930 \\ 0.00223 \mbox{ io } 0.0023 \mbox{ io } 0.00023 & 0.00023 & 0.00023 \\ 0.04311 \mbox{ io } 0.04371 & 0.00317 & 0.930 \\ 0.04311 \mbox{ io } 0.04371 & 0.0332 & 0.930 \\ 0.04311 \mbox{ io } 0.04371 & 0.0332 & 0.0032 & 0.00023 \\ 0.04311 \mbox{ io } 0.04312 & 0.0332 & 0.0032 & 0.930 \\ 0.04311 \mbox{ io } 0.04312 & 0.0332 & 0.0332 & 0.930 \\ 0.04311 \mbox{ io } 0.04311 & 0.03317 & 0.930 & 0.000010 & 0.930 \\ 0.04311 \mbox{ io } 0.04312 & 0.$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | $ \begin{array}{c} 0.01846 \text{ to} 0.4067  0.04899  0.033  \bullet  93 \\ 0.023165 \text{ to} 0.4176  0.05412  0.0228  \bullet  93 \\ 0.023185 \text{ to} 0.4176  0.05416  0.0224  \bullet  93 \\ 0.031955 \text{ to} 0.4176  0.05616  0.0223  \bullet  93 \\ 0.03496 \text{ to} 0.4203  0.05616  0.0222  \bullet  93 \\ 0.03496 \text{ to} 0.4230  0.05616  0.0222  \bullet  93 \\ 0.034955 \text{ to} 0.4233  0.056176  0.0523  \bullet  93 \\ 0.034955 \text{ to} 0.4233  0.056176  0.0123  \bullet  93 \\ 0.035955 \text{ to} 0.4433  0.056176  0.0123  \bullet  93 \\ 0.062565 \text{ to} 0.4423  0.06913  0.0103  \bullet  93 \\ 0.062565 \text{ to} 0.4423  0.06913  0.0103  \bullet  93 \\ 0.062565
\text{ to} 0.4423  0.06913  0.0103  \bullet  93 \\ 0.062565 \text{ to} 0.4423  0.06913  0.0103  \bullet  93 \\ 0.062756 \text{ to} 0.4423  0.06913  0.0103  \bullet  93 \\ 0.062756 \text{ to} 0.4423  0.06913  0.0104  \bullet  93 \\ 0.0756 \text{ to} 0.4230  0.09726  0.004  \bullet  93 \\ 0.0757 \text{ to} 0.4323  0.104  0.0103  \bullet  93 \\ 0.07124 \text{ to} 0.4834  0.1013  0.0002  \bullet  93 \\ 0.11274 \text{ to} 0.4834  0.1014  0.0016  \bullet  93 \\ 0.1274 \text{ to} 0.4334  0.104  0.0016  \bullet  93 \\ 0.1274 \text{ to} 0.4334  0.1032  0.0002  \bullet  93 \\ 0.1174 \text{ to} 0.4334  0.1033  0.0002  \bullet  93 \\ 0.1274 \text{ to} 0.4334  0.103  0.0002  \bullet  93 \\ 0.1374 \text{ to} 0.5346  0.103  0.0002  \bullet  93 \\ 0.1374 \text{ to} 0.5344  0.0216  \bullet  93 \\ 0.0002  \bullet  93 \\ 0.00016  \bullet  93 \\ 0.00016  \bullet  93 \\ 0.00016  \bullet  93 \\ 0.00016  \bullet  93 \\ 0.0002  \bullet  93 \\ 0.00016  \bullet  93 \\ 0.00016  0.0016  \bullet  93 \\ 0.00016  0.0016  \bullet  93 \\ 0.0002  \bullet  93 \\ 0.00016  \bullet  93 \\ 0.00016  0.0017  0.0019  \bullet  93 \\ 0.00016  \bullet  93 \\ 0.00016  0.0016  \bullet  93 \\ 0.0002  \bullet  93 \\ 0.0002  \bullet  93 \\ 0.00016  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017  0.0017 $                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | $ \begin{array}{c} 0.01846 \mbox{ to } 0.033 & 0.033 & 0.033 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.012 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.038 & 0.0013 & 0.038 & 0.0013 & 0.038 & 0.0013 & 0.038 & 0.0028 & 0.0002 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 0.0003 & 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                                                                   | $ \begin{array}{c} 0.01845 \mbox{ to } 0.4875 \mbox{ to } 0.0388 \mbox{ to } 0.0313 \mbox{ to } 0.0323 \mbox{ to } 0.0333 \mbox{ to } 0.0323 \mbox{ to } 0.0333 \mbox{ to } 0.0323 \mbox{ to } 0.0333 \mbox{ to } 0.0323 \mbox{ to } 0.00697 \mbox{ to } 0.0010 \mbox{ to } 0.00697 \mbox{ to } 0.0010 \mbox{ to } 0.00697 \mbox{ to } 0.0010 \mbox{ to } 0.00103  $                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| reation: 2010 continuence K (two- reative of the content of the co | -0.3922 -0.5518 to -0.2049 0.1538 0.0001 *** | -0.3155 -0.4879 to -0.1195 0.09954 0.0021 ** 9:<br>-0.2884 -0.4648 to -0.09003 0.0832 0.005 ** 9: | -0.2833 -0.4604 to -0.08448 0.08026 0.0059 ** 93 | -0.2474 -0.4295 to -0.04601 0.06121 0.0168 * 93 | -0.2464 -0.4286 to -0.04494 0.06071 0.0173 * 93<br>-0.2283 -0.4120to -0.02584 0.05214 0.0277 * 93 | -0.2266 -0.4113 to -0.02402 0.05136 0.0289 * 93 | 0.2052 0.001551 to 0.3925 0.0421 0.0485 * 93 | 0.211 0.007660 to 0.3977 0.04454 0.0423 * 93 | 0.2153 0.01212 to 0.4014 0.04635 0.0382 * 93 | 0.2213 0.01846 to 0.4067 0.04899 0.033 * 93 F |                                         | 0.2221 0.01922 to 0.4073 0.04931 0.0324 * 93 I                                    | 0.2221 0.01922 to 0.4073 0.04931 0.0324 * 93 F 0.2268 0.02416 to 0.4115 0.05142 0.0288 * 93 M                                 | 0.2221 0.01922t0.0.4073 0.04931 0.0324 * 93 F<br>0.2268 0.02416t0.0.4115 0.05443 0.0288 * 93 M<br>0.237 0.03158:0.0.416 0.05643 0.02241 * 93 F<br>0.231 0.04186.h.0.4178 0.05643 0.0224 * 93 F | 0.2221 0.01922 to 0.4073 0.04931 0.0324 * 93 1<br>0.2268 0.02416 to 0.415 0.05432 0.0288 * 93 N<br>0.2337 0.03153 to 0.4176 0.05433 0.0241 * 93 F<br>0.2337 0.03966 to 0.4178 0.05438 0.0223 * 93 F<br>0.234 0.03966 to 0.4242 0.055478 0.0223 * 93 E | 0.2221         0.01922 to 0.4073         0.04931         0.0324         *         93         F           0.2288         0.02416 to 0.4115         0.05433         0.02418         *         93         M           0.2288         0.037153 to 0.4115         0.05463         0.0241         *         93         M           0.2337         0.03153 to 0.4116         0.05463         0.0241         *         93         K           0.2337         0.03996 to 0.4178         0.05478         0.0241         *         93         K           0.237         0.03996 to 0.4204         0.05478         0.0239         *         93         C           0.226         0.04945 to 0.4323         0.05222         *         93         C         0.2506         0.04945 to 0.4323         0.05222         *         93         C | 0.2221         0.01922 [to 0.4073         0.04931         0.0324         •         93         1           0.2237         0.03145 [to 0.4176         0.05142         0.0288         93         N           0.22387         0.03145 [to 0.4176         0.05442         0.0288         93         N           0.2234         0.03145 [to 0.4178         0.05448         0.0241         93         F           0.224         0.03168 [to 0.4178         0.05616         0.0222         93         F           0.224         0.03168 [to 0.4178         0.05616         0.0222         93         F           0.2250         0.03996 [to 0.4232         0.05281         0.0222         93         F           0.2250         0.03698 [to 0.4235         0.05281         0.0144         93         F           0.2550         0.09693 [to 0.4235         0.05281         0.01464         93         F | 0.2221         0.01922 to 0.4073         0.04931         0.0224         *         93           0.2288         0.02416 to 0.4176         0.02486         *         93           0.2233         0.03218 to 0.4176         0.05486         0.02486         93           0.224         0.03486 to 0.4176         0.05478         0.0234         *         93           0.234         0.03486 to 0.4176         0.05478         0.0223         93         93           0.237         0.03486 to 0.4178         0.05478         0.0222         *         93           0.236         0.04461 to 0.4232         0.05510         0.0154         *         93           0.2560         0.04461 to 0.4335         0.05531         0.0144         *         93           0.25605         0.06903 to 0.4400         0.06735         0.0148         *         93           0.25565         0.05802 to 0.4400         0.06735         0.0142         *         93 | 0.2221 0.01922 10.04073 0.04931 0.0324 * 93<br>0.2268 0.003416 10.04176 0.05142 0.0288 * 93<br>0.2337 0.03161 10.04176 0.05463 0.0241 * 93<br>0.234 0.03166 10.04176 0.05463 0.0241 * 93<br>0.237 0.03496 10.04178 0.05616 0.0222 * 93<br>0.2560 0.034945 10.04232 0.05551 0.0154 * 93<br>0.2560 0.034945 10.04332 0.05551 0.0154 * 93<br>0.2560 0.03903 10.04335 0.05551 0.0148 * 93<br>0.2560 0.03603 10.04335 0.05551 0.0148 * 93<br>0.2569 0.052656 10.04490 0.06755 0.012 * 93<br>0.2669 0.036256 10.04490 0.06755 0.012 * 93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.2221         0.01922 to 0.4073         0.04931         0.0324         **         93           0.2288         0.021416         0.04135         0.0348         **         93           0.2324         0.03185 to 0.4176         0.05483         0.0328         **         93           0.2324         0.03185 to 0.4176         0.05483         0.0239         **         93           0.2324         0.03186 to 0.4178         0.05478         0.0239         **         93           0.2324         0.03186 to 0.4178         0.05478         0.0229         **         93           0.2324         0.03186 to 0.4178         0.05478         0.0229         **         93           0.2250         0.03995 to 0.44323         0.06522         0.0148         **         93           0.2555         0.05695 to 0.4429         0.66931         0.0148         **         93           0.25545         0.05825 to 0.4429         0.66931         0.0104         **         93           0.25645         0.06825 to 0.4429         0.69933         0.0104         **         93           0.25645         0.06826 to 0.4429         0.69933         0.0104         **         93           0.25645 <td< td=""><td>0.2221         0.01922 to 0.4073         0.04931         0.0228         0.02145         0.061475         0.06145         0.0728         93           0.2288         0.02155 to 0.4176         0.06463         0.0228         93         93           0.234         0.03185 to 0.4176         0.05463         0.0239         93           0.234         0.03185 to 0.4176         0.05463         0.0239         93           0.234         0.03186 to 0.4176         0.05282         0.0123         93           0.237         0.03496 to 0.4323         0.05282         0.0144         93           0.2550         0.09458 to 0.4323         0.05282         0.0148         93           0.2563         0.09458 to 0.4325         0.06236 to 0.1448         93           0.2564         0.04428 to 0.4443         0.06913         0.0104         93           0.2564         0.06426 to 0.4443         0.06913         0.0104         93           0.2645         0.06426 to 0.4443         0.06913         0.0104         93           0.2645         0.06426 to 0.4443         0.06912         0.0104         93           0.2645         0.074708         0.0704         93         93           0.2645</td><td>0.2221         0.01922 to 0.4073         0.04931         0.0224         *         93           0.2288         0.00135 to 0.4176         0.05435         0.02484         *         93           0.234         0.03136 to 0.4176         0.05435         0.02384         *         93           0.234         0.03145 to 0.4176         0.05453         0.0234         *         93           0.234         0.03496 to 0.4176         0.056478         0.0239         *         93           0.237         0.03496 to 0.4178         0.056478         0.0233         *         93           0.2256         0.04945 to 0.4323         0.05282         0.01524         *         93           0.2259         0.05935 to 0.4433         0.05835         0.0148         *         93           0.2259         0.05825 to 0.4429        
0.06735         0.0148         *         93           0.2264         0.06825 to 0.4423         0.06913         0.0109         *         93           0.2264         0.06825 to 0.4424         0.06913         0.0104         *         93           0.2264         0.07856 to .4400         0.08645         0.0042         *         93           0.2264         0.0786</td><td>0.2221         0.01922 to 0.4073         0.04931         0.0224         *         93           0.2288         0.02416 to 0.4176         0.05481         0.0288         *         93           0.2233         0.03416 to 0.4176         0.05481         0.0281         *         93           0.2234         0.03486 to 0.4176         0.05478         0.0281         *         93           0.2247         0.03486 to 0.4176         0.05478         0.0239         *         93           0.2250         0.04945 to 0.4273         0.05551         0.0144         *         93           0.25606         0.04945 to 0.4353         0.06531         0.0144         *         93           0.25605         0.03933 to 0.4400         0.06735         0.0144         *         93           0.25595         0.05655 to 0.4430         0.06735         0.0144         *         93         1           0.25645         0.036456 to 0.4430         0.06445         0.06442         0.0044         *         93         1           0.26944         0.0977         0.0094         *         93         1         033         1         103         103         1         103         1         103         10</td><td>0.2221         0.01922 to 0.4073         0.04931         0.0224         93           0.2288         0.023416 to 0.4176         0.07846         93           0.2234         0.03186 to 0.4176         0.03486         93           0.2234         0.03486 to 0.4176         0.03486         93           0.2246         0.03496 to 0.4176         0.03478         0.0244         93           0.2247         0.03496 to 0.4176         0.03478         0.0244         93           0.2247         0.03496 to 0.4204         0.064478         0.02478         93           0.22566         0.04945 to 0.4232         0.0148         93           0.22565         0.06995 to 0.4400         0.06735         0.0142         93           0.22565         0.06892 to 0.4400         0.06735         0.0122         93           0.22545         0.07826 to 0.4490         0.0104         93         93           0.2294         0.09807 to 0.4490         0.0104         93         93           0.2294         0.09806 to 0.4696         0.08645         0.0042         93           0.2294         0.09807 to 0.4493         0.0014         93         93           0.2294         0.09866 to 0.4696         0.0042</td><td>0.2221         0.01922 to 0.4073         0.04931         0.0324         93           0.2288         0.02416 to 0.4176         0.05432         0.02388         93           0.2234         0.03146 to 0.4176         0.05431         0.0248         93           0.2247         0.03146 to 0.4176         0.05431         0.93         93           0.2256         0.04346 to 0.4325         0.05831         0.0148         93           0.2566         0.04346 to 0.4325         0.06531         0.0148         93           0.2556         0.050351         0.0154         93         93           0.2556         0.050351         0.0148         93         93           0.2556         0.050351         0.0148         93         93           0.2556         0.056351         0.0148         93         93           0.2554         0.056561         0.04433         0.0014         93         93           0.2554         0.07443         0.03645         0.0042         93         93           0.2264         0.04433         0.0014         93         93         93         93           0.2264         0.045610         0.0077         0.0049         93         93<td>0.2221         0.01922         0.04973         0.04931         0.0228         93         1           0.2288         0.03153         0.04176         0.0543         0.028         93         1           0.2338         0.03153         0.04176         0.0543         0.028         93         93         1           0.234         0.03153         0.04176         0.0543         0.028         93         93         93           0.234         0.03153         0.04176         0.0543         0.028         93         93         93           0.237         0.03966         0.0435         0.0583         0.0154         93         93           0.255         0.03935         0.04335         0.0583         0.0164         93         93           0.2559         0.03956         0.04429         0.0673         0.0104         93         N           0.2544         0.09566         0.04429         0.0976         0.004         93         N           0.2544         0.09566         0.0443         0.0077         93         93         N           0.2544         0.09566         0.04429         0.0076         93         03173         0.1214100         93<td>0.2221         0.01922 to 0.4073         0.04931         0.0324         ***         93         P           0.2288         0.02416 to 0.4176         0.05436         0.0243         0.02436         93         M           0.2288         0.02416 to 0.4176         0.05436         0.0241         ************************************</td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td><math display="block"> \begin{array}{c ccccc} 0.01922 \ {\rm lo} 0.4073 &amp; 0.04931 &amp; 0.0324 &amp; {\rm ev} \\ 0.2288 &amp; 0.02416 \ {\rm lo} 0.01416 &amp; 0.05432 &amp; 0.0238 &amp; {\rm ev} \\ 0.2237 &amp; 0.03496 \ {\rm lo} 0.4176 &amp; 0.05432 &amp; 0.0238 &amp; {\rm ev} \\ 0.237 &amp; 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4248 &amp; 0.068616 &amp; 0.0152 &amp; {\rm ev} \\ 0.03695 \ {\rm lo} 0.4353 &amp; 0.06153 &amp; 0.0154 &amp; {\rm ev} \\ 0.2256 &amp; 0.069081 \ {\rm lo} 0.4353 &amp; 0.0154 &amp; {\rm ev} \\ 0.22645 &amp; 0.062856 \ {\rm lo} 0.4420 &amp; 0.06775 &amp; 0.0103 &amp; {\rm ev} \\ 0.22645 &amp; 0.067856 \ {\rm lo} 0.4420 &amp; 0.06755 &amp; 0.0172 &amp; {\rm ev} \\ 0.22645 &amp; 0.067656 \ {\rm lo} 0.4420 &amp; 0.06755 &amp; 0.0102 &amp; {\rm ev} \\ 0.22644 &amp; 0.067766 \ {\rm lo} 0.4426 &amp; 0.068645 &amp; 0.004 &amp; {\rm ev} \\ 0.22644 &amp; 0.067766 \ {\rm lo} 0.04864 &amp; 0.0016 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0104 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0104 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.004 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.004 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3324 &amp; 0.41916 \ {\rm lo} 0.0324 &amp; 0.0221 &amp; {\rm ev} \\ 0.3324 &amp; 0.41916 \ {\rm lo} 0.03324 &amp; 0.0224 &amp; {\rm lo} 0.321 &amp; {\rm ev} \\ 0.2354 &amp; 0.40116 \ {\rm lo} 0.0137 &amp; 0.0321 &amp; {\rm ev} \\ 0.2354 &amp; 0.04116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.05601 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.05601 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.0323 &amp; {\rm ev} \\ 0.2356 &amp; 0.04912 &amp; 0.0323 &amp; </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td></td></td></td<> | 0.2221         0.01922 to 0.4073         0.04931         0.0228         0.02145         0.061475         0.06145         0.0728         93           0.2288         0.02155 to 0.4176         0.06463         0.0228         93         93           0.234         0.03185 to 0.4176         0.05463         0.0239         93           0.234         0.03185 to 0.4176         0.05463         0.0239         93           0.234         0.03186 to 0.4176         0.05282         0.0123         93           0.237         0.03496 to 0.4323         0.05282         0.0144         93           0.2550         0.09458 to 0.4323         0.05282         0.0148         93           0.2563         0.09458 to 0.4325         0.06236 to 0.1448         93           0.2564         0.04428 to 0.4443         0.06913         0.0104         93           0.2564         0.06426 to 0.4443         0.06913         0.0104         93           0.2645         0.06426 to 0.4443         0.06913         0.0104         93           0.2645         0.06426 to 0.4443         0.06912         0.0104         93           0.2645         0.074708         0.0704         93         93           0.2645                                                                                                                  
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0.2221         0.01922 to 0.4073         0.04931         0.0224         *         93           0.2288         0.00135 to 0.4176         0.05435         0.02484         *         93           0.234         0.03136 to 0.4176         0.05435         0.02384         *         93           0.234         0.03145 to 0.4176         0.05453         0.0234         *         93           0.234         0.03496 to 0.4176         0.056478         0.0239         *         93           0.237         0.03496 to 0.4178         0.056478         0.0233         *         93           0.2256         0.04945 to 0.4323         0.05282         0.01524         *         93           0.2259         0.05935 to 0.4433         0.05835         0.0148         *         93           0.2259         0.05825 to 0.4429         0.06735         0.0148         *         93           0.2264         0.06825 to 0.4423         0.06913         0.0109         *         93           0.2264         0.06825 to 0.4424         0.06913         0.0104         *         93           0.2264         0.07856 to .4400         0.08645         0.0042         *         93           0.2264         0.0786                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0.2221         0.01922 to 0.4073         0.04931         0.0224         *         93           0.2288         0.02416 to 0.4176         0.05481         0.0288         *         93           0.2233         0.03416 to 0.4176         0.05481         0.0281         *         93           0.2234         0.03486 to 0.4176         0.05478         0.0281         *         93           0.2247         0.03486 to 0.4176         0.05478         0.0239         *         93           0.2250         0.04945 to 0.4273         0.05551         0.0144         *         93           0.25606         0.04945 to 0.4353         0.06531         0.0144         *         93           0.25605         0.03933 to 0.4400         0.06735         0.0144         *         93           0.25595         0.05655 to 0.4430         0.06735         0.0144         *         93         1           0.25645         0.036456 to 0.4430         0.06445         0.06442         0.0044         *         93         1           0.26944         0.0977         0.0094         *         93         1         033         1         103         103         1         103         1         103         10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.2221         0.01922 to 0.4073         0.04931         0.0224         93           0.2288         0.023416 to 0.4176         0.07846         93           0.2234         0.03186 to 0.4176         0.03486         93           0.2234         0.03486 to 0.4176         0.03486         93           0.2246         0.03496 to 0.4176         0.03478         0.0244         93           0.2247         0.03496 to 0.4176         0.03478         0.0244         93           0.2247         0.03496 to 0.4204         0.064478         0.02478         93           0.22566         0.04945 to 0.4232         0.0148         93           0.22565         0.06995 to 0.4400         0.06735         0.0142         93           0.22565         0.06892 to 0.4400         0.06735         0.0122         93           0.22545         0.07826 to 0.4490         0.0104         93         93           0.2294         0.09807 to 0.4490         0.0104         93         93           0.2294         0.09806 to 0.4696         0.08645         0.0042         93           0.2294         0.09807 to 0.4493         0.0014         93         93           0.2294         0.09866 to 0.4696         0.0042                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                   | 0.2221         0.01922 to 0.4073         0.04931         0.0324         93           0.2288         0.02416 to 0.4176         0.05432         0.02388         93           0.2234         0.03146 to 0.4176         0.05431         0.0248         93           0.2247         0.03146 to 0.4176         0.05431         0.93         93           0.2256         0.04346 to 0.4325         0.05831         0.0148         93           0.2566         0.04346 to 0.4325         0.06531         0.0148         93           0.2556         0.050351         0.0154         93         93           0.2556         0.050351         0.0148         93         93           0.2556         0.050351         0.0148         93         93           0.2556         0.056351         0.0148         93         93           0.2554         0.056561         0.04433         0.0014         93         93           0.2554         0.07443         0.03645         0.0042         93         93           0.2264         0.04433         0.0014         93         93         93         93           0.2264         0.045610         0.0077         0.0049         93         93 <td>0.2221         0.01922         0.04973         0.04931         0.0228         93         1           0.2288         0.03153         0.04176         0.0543         0.028         93         1           0.2338         0.03153         0.04176         0.0543         0.028         93         93         1           0.234         0.03153         0.04176         0.0543         0.028         93         93         93           0.234         0.03153         0.04176         0.0543         0.028         93         93         93           0.237         0.03966         0.0435         0.0583         0.0154         93         93           0.255         0.03935         0.04335         0.0583         0.0164         93         93           0.2559         0.03956         0.04429         0.0673         0.0104         93         N           0.2544         0.09566         0.04429         0.0976         0.004         93         N           0.2544         0.09566         0.0443         0.0077         93         93         N           0.2544         0.09566         0.04429         0.0076         93         03173         0.1214100         93<td>0.2221         0.01922 to 0.4073         0.04931         0.0324         ***         93         P           0.2288         0.02416 to 0.4176         0.05436         0.0243         0.02436         93         M           0.2288         0.02416 to 0.4176         0.05436         0.0241         ************************************</td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td><math display="block"> \begin{array}{c ccccc} 0.01922 \ {\rm lo} 0.4073 &amp; 0.04931 &amp; 0.0324 &amp; {\rm ev} \\ 0.2288 &amp; 0.02416 \ {\rm lo} 0.01416 &amp; 0.05432 &amp; 0.0238 &amp; {\rm ev} \\ 0.2237 &amp; 0.03496 \ {\rm lo} 0.4176 &amp; 0.05432 &amp; 0.0238 &amp; {\rm ev} \\ 0.237 &amp; 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4248 &amp; 0.068616 &amp; 0.0152 &amp; {\rm ev} \\ 0.03695 \ {\rm lo} 0.4353 &amp; 0.06153 &amp; 0.0154 &amp; {\rm ev} \\ 0.2256 &amp; 0.069081 \ {\rm lo} 0.4353 &amp; 0.0154 &amp; {\rm ev} \\ 0.22645 &amp; 0.062856 \ {\rm lo} 0.4420 &amp; 0.06775 &amp; 0.0103 &amp; {\rm ev} \\ 0.22645 &amp; 0.067856 \ {\rm lo} 0.4420 &amp; 0.06755 &amp; 0.0172 &amp; {\rm ev} \\ 0.22645 &amp; 0.067656 \ {\rm lo} 0.4420 &amp; 0.06755 &amp; 0.0102 &amp; {\rm ev} \\ 0.22644 &amp; 0.067766 \ {\rm lo} 0.4426 &amp; 0.068645 &amp; 0.004 &amp; {\rm ev} \\ 0.22644 &amp; 0.067766 \ {\rm lo} 0.04864 &amp; 0.0016 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0104 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0104 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.004 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.004 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3324 &amp; 0.41916 \ {\rm lo} 0.0324 &amp; 0.0221 &amp; {\rm ev} \\ 0.3324 &amp; 0.41916 \ {\rm lo} 0.03324 &amp; 0.0224 &amp; {\rm lo} 0.321 &amp; {\rm ev} \\ 0.2354 &amp; 0.40116 \ {\rm lo} 0.0137 &amp; 0.0321 &amp; {\rm ev} \\ 0.2354 &amp; 0.04116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.05601 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.05601 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.0323 &amp; {\rm ev} \\ 0.2356 &amp; 0.04912 &amp; 0.0323 &amp; </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td></td> | 0.2221         0.01922         0.04973         0.04931         0.0228         93         1           0.2288         0.03153         0.04176         0.0543         0.028         93         1           0.2338         0.03153         0.04176         0.0543         0.028         93         93         1           0.234         0.03153         0.04176         0.0543         0.028         93         93         93           0.234         0.03153         0.04176         0.0543         0.028         93         93         93           0.237         0.03966         0.0435         0.0583         0.0154         93         93           0.255         0.03935         0.04335         0.0583         0.0164         93         93           0.2559         0.03956         0.04429         0.0673         0.0104         93         N           0.2544         0.09566         0.04429         0.0976         0.004         93         N           0.2544         0.09566         0.0443         0.0077         93         93         N           0.2544         0.09566         0.04429         0.0076         93         03173         0.1214100         93 <td>0.2221         0.01922 to 0.4073         0.04931         0.0324         ***         93         P           0.2288         0.02416 to 0.4176         0.05436         0.0243         0.02436         93         M           0.2288         0.02416 to 0.4176         0.05436         0.0241         ************************************</td> <td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td> <td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td> <td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td> <td><math display="block"> \begin{array}{c ccccc} 0.01922 \ {\rm lo} 0.4073 &amp; 0.04931 &amp; 0.0324 &amp; {\rm ev} \\ 0.2288 &amp; 0.02416 \ {\rm lo} 0.01416 &amp; 0.05432 &amp; 0.0238 &amp; {\rm ev} \\ 0.2237 &amp; 0.03496 \ {\rm lo} 0.4176 &amp; 0.05432 &amp; 0.0238 &amp; {\rm ev} \\ 0.237 &amp; 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4178 &amp; 0.05478 &amp; 0.0239 &amp; {\rm ev} \\ 0.03496 \ {\rm lo} 0.4248 &amp; 0.068616 &amp; 0.0152 &amp; {\rm ev} \\ 0.03695 \ {\rm lo} 0.4353 &amp; 0.06153 &amp; 0.0154 &amp; {\rm ev} \\ 0.2256 &amp; 0.069081 \ {\rm lo} 0.4353 &amp; 0.0154 &amp; {\rm ev} \\ 0.22645 &amp; 0.062856 \ {\rm lo} 0.4420 &amp; 0.06775 &amp; 0.0103 &amp; {\rm ev} \\ 0.22645 &amp; 0.067856 \ {\rm lo} 0.4420 &amp; 0.06755 &amp; 0.0172 &amp; {\rm ev} \\ 0.22645 &amp; 0.067656 \ {\rm lo} 0.4420 &amp; 0.06755 &amp; 0.0102 &amp; {\rm ev} \\ 0.22644 &amp; 0.067766 \ {\rm lo} 0.4426 &amp; 0.068645 &amp; 0.004 &amp; {\rm ev} \\ 0.22644 &amp; 0.067766 \ {\rm lo} 0.04864 &amp; 0.0016 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0104 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0104 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.004 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.004 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3317 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3312 &amp; 0.1271 \ {\rm lo} 0.4337 &amp; 0.0016 &amp; {\rm ev} \\ 0.3324 &amp; 0.41916 \ {\rm lo} 0.0324 &amp; 0.0221 &amp; {\rm ev} \\
0.3324 &amp; 0.41916 \ {\rm lo} 0.03324 &amp; 0.0224 &amp; {\rm lo} 0.321 &amp; {\rm ev} \\ 0.2354 &amp; 0.40116 \ {\rm lo} 0.0137 &amp; 0.0321 &amp; {\rm ev} \\ 0.2354 &amp; 0.04116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.40116 \ {\rm lo} 0.0157 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.05601 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.05601 &amp; 0.0322 &amp; {\rm ev} \\ 0.2356 &amp; 0.049116 \ 0.05601 &amp; 0.0323 &amp; {\rm ev} \\ 0.2356 &amp; 0.04912 &amp; 0.0323 &amp; </math></td> <td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td> | 0.2221         0.01922 to 0.4073         0.04931         0.0324         ***         93         P           0.2288         0.02416 to 0.4176         0.05436         0.0243         0.02436         93         M           0.2288         0.02416 to 0.4176         0.05436         0.0241         ************************************                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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# Table 2B

	Gene	RALA	SMAD4	TGFBR3	RRAGA	ZEB2	SMAD1	SERPINE2	EXOC2	TGFBR1	MAP3K7	CLDN4	EXOC3L2	PIK3AP1	<b>RALGAPA2</b>	BRAF	MAP3K11	CLDN3	CDH1	RALB	SMAD3	,	Gene	RALGAPA1	CLDN17	MAP3K15	FRAP1	PIK3R2	ULK2	PIK3AP1	<b>GSK3B</b>	CLDN4	RALB
Number	of XY Pairs	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	Number	of XY Pairs	29	29	29	29	29	29	29	29	29	29
P value	summary	:	;	\$	•	*	*	•	*	•	*	*	*	*	*	*	*	*	*	\$	**	P value	summary	*	*	•	*	*	*	*	*	*	•
P value	(two- tailed)	0.0058	0.0066	0.0093	0.0268	0.0289	0.0408	0.0428	0.0458	0.0463	0.0469	0.0335	0.0317	0.0247	0.0226	0.0195	0.0193	0.0186	0.0164	0.0072	0.0053	P value	tailed)	0.0103	0.017	0.0172	0.0228	0.0243	0.047	0.0467	0.041	0.0311	0.0258
œ	squared	0.2492	0.2431	0.2253	0.1688	0.1647	0.146	0.1434	0.1397	0.1391	0.1384	0.1567	0.1597	0.1734	0.1781	0.1861	0.1865	0.1885	0.1954	0.2384	0.2539	¥	squared	0.2197	0.1933	0.1926	0.1776	0.1742	0.1382	0.1387	0.1458	0.1608	0.1708
95% confidence	interval	-0.7318 to -0.1624	-0.7280 to -0.1544	-0.7165 to -0.1309	-0.6756 to -0.05223	-0.6724 to -0.04625	-0.6567 to -0.01820	-0.6544 to -0.01411	-0.6511 to -0.008428	-0.6505 to -0.007462	-0.6499 to -0.006370	0.03439 to 0.6658	0.03880 to 0.6683	0.05884 to 0.6792	0.06561 to 0.6829	0.07703 to 0.6889	0.07765 to 0.6893	0.08046 to 0.6908	0.09008 to 0.6958	0.1483 to 0.7250	0.1685 to 0.7347	95% confidence	interval	-0.7128 to -0.1234	-0.6943 to -0.08722	-0.6938 to -0.08623	-0.6825 to -0.06490	-0.6799 to -0.06004	-0.6498 to -0.006116	0.006781 to 0.6501	0.01781 to 0.6565	0.04046 to 0.6692	0.05516 to 0.6772
Pearson	E	-0.4992	-0.493	-0.4746	-0.4109	-0.4059	-0.3822	-0.3787	-0.3738	-0.3729	-0.372	0.3959	0.3996	0.4164	0.422	0.4314	0.4319	0.4342	0.442	0.4882	0.5039	Pearson	(I)	-0.4687	-0.4397	-0.4389	-0.4214	-0.4174	-0.3718	0.3724	0.3818	0.401	0.4133
	Comparison	Log 10 BX LDN vs. RALA	Log 10 BX LDN vs. SMAD4	Log 10 BX LDN vs. TGFBR3	Log 10 BX LDN vs. RRAGA	Log 10 BX LDN vs. ZEB2	Log 10 BX LDN vs. SMAD1	Log 10 BX LDN vs. SERPINE2	Log 10 BX LDN vs. EXOC2	Log 10 BX LDN vs. TGFBR1	Log 10 BX LDN vs. MAP3K7	Log 10 BX LDN vs. CLDN4	Log 10 BX LDN vs. EXOC3L2	Log 10 BX LDN vs. PIK3AP1	Log 10 BX LDN vs. RALGAPA2	Log 10 BX LDN vs. BRAF	Log 10 BX LDN vs. MAP3K11	Log 10 BX LDN vs. CLDN3	Log 10 BX LDN vs. CDH1	Log 10 BX LDN vs. RALB	Log 10 BX LDN vs. SMAD3		Comparison	Log10 Cmpd II LDN vs. RALGAPA1	Log10 Cmpd II LDN vs. CLDN17	Log10 Cmpd II LDN vs. MAP3K15	Log10 Cmpd II LDN vs. FRAP1	Log10 Cmpd II LDN vs. PIK3R2	Log10 Cmpd II LDN vs. ULK2	Log10 Cmpd II LDN vs. PIK3AP1	Log10 Cmpd II LDN vs. GSK3B	Log10 Cmpd II LDN vs. CLDN4	Log10 Cmpd II LDN vs. RALB
	Gene	RALA	ZEB2	SMAD4	RRAGA	CLDN5	TGFBR3	TGFBR1	MAP4K2	PIK3AP1	BRAF	RALGAPB	CLDN3	RALB	SMAD3	<b>RPS6KA6</b>	EXOC3L2	MAP3K11	CDH1				Gene	CLDN5	CLDND1	PIK3R2	EXOC2	CLDN17	MAP3K15	SMAD4	CDH5	ULK2	FRAP1
Number	of XY Pairs	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29	29			Number	of XY Pairs	29	29	29	29	29	29	29	29	29	29
P value	summary	*	\$	*	•	*	*	•	*	•	*	*	*	*	*	*	*	*	\$			P value	summary	*	*	•	*	*	*	*	*	*	•
P value	(two- tailed)	0.0053	0.0079	0.0133	0.0156	0.0319	0.0448	0.0491	0.0453	0.0451	0.0437	0.0436	0.0379	0.0265	0.0162	0.0143	0.0125	0.0084	0.007			P value	tailed)	0.0123	0.0212	0.0217	0.028	0.0317	0.0386	0.04	0.0413	0.0447	0.0471
œ	squared	0.254	0.2335	0.2065	0.1981	0.1594	0.1409	0.1359	0.1403	0.1405	0.1422	0.1424	0.15	0.1695	0.1958	0.2026	0.2097	0.2304	0.2401			¥	squared	0.2106	0.1814	0.1803	0.1665	0.1598	0.149	0.1471	0.1453	0.141	0.1382
95% confidence	interval	-0.7348 to -0.1686	-0.7219 to -0.1419	-0.7037 to -0.1054	-0.6978 to -0.09388	-0.6680 to -0.03840	-0.6522 to -0.01034	-0.6476 to -0.002460	0.009383 to 0.6516	0.009671 to 0.6518	0.01236 to 0.6533	0.01266 to 0.6535	0.02426 to 0.6601	0.05319 to 0.6762	0.09076 to 0.6961	0.1001 to 0.7010	0.1099 to 0.7060	0.1377 to 0.7198	0.1505 to 0.7261			95% confidence	interval	-0.7066 to -0.1111	-0.6854 to -0.07040	-0.6845 to -0.06875	-0.6738 to -0.04886	-0.6683 to -0.03891	-0.6593 to -0.02274	-0.6576 to -0.01981	-0.6560 to -0.01705	-0.6522 to -0.01044	-0.6497 to -0.006003
Pearson	(I	-0.504	-0.4833	-0.4544	-0.4451	-0.3993	-0.3754	-0.3686	0.3746	0.3748	0.3772	0.3774	0.3873	0.4117	0.4425	0.4501	0.458	0.48	0.49			Pearson	Ē	-0.4589	-0.4259	-0.4246	-0.4081	-0.3997	-0.386	-0.3835	-0.3812	-0.3755	-0.3717
	Comparison	Log10 BX AUC vs. RALA	Log10 BX AUC vs. ZEB2	Log10 BX AUC vs. SMAD4	Log10 BX AUC vs. RRAGA	Log10 BX AUC vs. CLDN5	Log10 BX AUC vs. TGFBR3	Log10 BX AUC vs. TGFBR1	Log10 BX AUC vs. MAP4K2	Log10 BX AUC vs. PIK3AP1	Log10 BX AUC vs. BRAF	Log10 BX AUC vs. RALGAPB	Log10 BX AUC vs. CLDN3	Log10 BX AUC vs. RALB	Log10 BX AUC vs. SMAD3	Log10 BX AUC vs. RPS6KA6	Log10 BX AUC vs. EXOC3L2	Log10 BX AUC vs. MAP3K11	Log10 BX AUC vs. CDH1				Comparison	Log10 Cmpd II AUC vs. CLDN5	Log10 Cmpd II AUC vs. CLDND1	Log10 Cmpd II AUC vs. PIK3R2	Log10 Cmpd II AUC vs. EXOC2	Log10 Cmpd II AUC vs. CLDN17	Log10 Cmpd II AUC vs. MAP3K15	Log10 Cmpd II AUC vs. SMAD4	Log10 Cmpd II AUC vs. CDH5	Log10 Cmpd II AUC vs. ULK2	Log10 Cmpd II AUC vs. FRAP1

# Table 2C

 In Krss Mutamt

 In Krss Mutamt

 Mscuc

 Nscuc

 Ash

 H23

 Calut

 H153

 Calut

 H155

 H630

 H157

 H2009

 H2366

 H2367

 H2364

 H2365

 H2364

 H2364

# Table 2 – TBK1 sensitivity vs. mRNA Expression in NSCLC

Summary of TBK1 inhibitor sensitivity, vs. mRNA expression values (Log<sub>2</sub>) (GSE32036)

A) Gene List picked by relevance to AKT signaling, EMT/EMT-related molecules,

Exocyst/Exocyst-related molecules, mTOR signaling, PI3K/PI3K-related signaling,

Raf/MEK/ERK signaling, Rag GTPases/lysosome, Ral/Ral signaling, Ras, and TBK1/IKKe signaling.

B) TBK1 inhibitors vs. mRNA (GSE32036) in all NSCLC cell lines tested with both compounds and for which mRNA expression data were available (93 lines)

C) TBK1 inhibitors vs. mRNA (GSE32036) in all KRAS-mutant NSCLC cell lines tested with both compounds and for which mRNA expression data were available (29 lines)

## **CHAPTER THREE**

#### DISCUSSION

The successful treatment of cancer hinges upon two key elements: knowing which mechanistic signaling network(s) to target therapeutically and in which context. Unfortunately, current investigations of TBK1 inhibitors as cancer interventions have lacked in both of these areas. While I am not the first one to suggest that inhibition of TBK1 is an attractive strategy in treatment of Ras signaling-controlled cancers (Barbie et al., 2009; Muvaffak et al., 2014; Ou et al., 2011), my work makes a substantive advance to the field in two primary ways. First, it reveals novel mechanistic roles of TBK1 in the AKT/mTOR regulatory axis; and second, it describes molecular indicators of selective sensitivity to TBK1 inhibitors in the context of Ras-dominated NSCLC.

Activation of the AKT/mTOR regulatory axis, as observed during nutrient stimulation, is acutely sensitive to TBK1 inhibition in murine fibroblasts, immortalized human epithelial cells, and cancer cell lines. Compound II treatment in TBK1-sensitive NSCLC cells compared to TBK1-resistant cells, this suggests TBK1's role in AKT/mTOR signaling contributes to survival of this NSCLC subpopulation. This is consistent with original characterization of Compound II which attenuated AKT phosphorylation in Compound II-sensitive but not resistant NSCLC (Ou et al., 2011). However, my work illustrates that TBK1 inhibition targets deeper within the AKT/mTOR axis to the level of PRAS40 and S6K regulation. This is an important finding, as it reminds the field that AKT is regulated by mechanisms other than the canonical AKT regulators such as PDPK1 and mTORC2. My work, in collaboration with Dr. Yi-Hung Ou and Mr. Aubhishek Zaman, also reveals that TBK1 physically engages the AKT/mTOR axis at multiple points, suggesting TBK1 and it adaptors may also regulate additional processes that govern AKT/mTOR signaling such as Rag GTPase function, mTOR localization, or nutrient sensing(Sancak et al., 2010). Preliminary immunofluorescence data suggest TBK1 loss of function can attenuate mTOR localization to lysosomes by nutrient addition, and quantification of these data is ongoing (data not shown). Additionally, my work characterizes a novel TBK1 kinase-dependent regulation of S6K C-terminal phosphorylation, linking TBK1 to direct support of S6K activation. Biochemical assays with recombinant protein suggested TBK1 can also directly phosphorylate S6K in vitro, (data not shown), but these preliminary results have been difficult recapitulate due to observed persistent phosphorylation of recombinant S6K even in the absence of TBK1. Pretreatment with lambda phosphatase was sufficient to reduce this phosphorylation, but not to a level where TBK1 mediated phospho-S6K p-T421/S424 was observed, and additional experiments with an alternative phosphatase-treatment strategy are planned. This newly discovered relationship between TBK1 and S6K may also play a role in S6K-dependent innate immune signaling through STING-TBK1-IRF3(F. Wang et al., 2016). These compelling mechanistic discoveries however are not sufficient if the end goal is the development of a clinical therapeutic, as knowing a compound's mechanism of action is only half the battle. One also needs to know the ideal context wherein the application of that compound might be most beneficial.

Current efforts are underway in the field to combine cancer biology approaches with cancer cell line "omic" data (genomics, proteomics, etc.) and biocomputing to discover biomarkers to deconvolve the Gordian knot of cancer heterogeneity (Vargas and Harris, 2016). I am very grateful to have undergone my research training in a laboratory on the leading edge of these efforts, as this has allowed me to collaborate with individuals like Ms. Elizabeth McMillan to identify molecular indicators of TBK1 sensitivity in NSCLC. These efforts returned high EMT gene expression (e.g. *ZEB1*, *ZEB2*, or *SNA11*) in addition to Ras-class-mutant (defined by mutant in *KRAS*, *NRAS*, *HRAS*, *PIK3CA*, or *BRAF*) or *KRAS*-mutant only status as indicative biomarkers for selective TBK1 sensitive in NSCLC cell lines. Testing the effect of relative EMT status modulation on TBK1 sensitivity in Ras-class mutant NSCLC cell lines was performed in two directions. Reconstitution of *KRAS*-mutant/*LKB1*-mutant cell line HCC44 with WT LKB1 induced epithelial protein expression and decreased sensitivity to BX795 and Compound II. Conversely, reversible induction of TGF-beta-driven EMT in A549 increased sensitivity to both TBK1 inhibitors in Cell Titer Glo and Caspase Glo assays. Additionally, inhibition of TBK1 by Compound II attenuated TGF-beta-driven induction of EMT transcription factor, *SNA11*.

A key question emerges from these results: do the biomarkers we identified simply indicate selective sensitivity of the cell lines (these cell lines are more sensitive than those cell lines, but by AKT/mTOR-independent mechanism "x"); or does it indicate the selective sensitivity of the pathway (the AKT/mTOR axis is selectively engaged or selectively essential within the sensitive population). My examination of the data lead me to hypothesize the latter, whereby *KRAS*-mutant/mesenchymal NSCLC cells are addicted to both EMT and Ras-class signaling, and therefore utilize TBK1 regulation of the AKT/mTOR axis to maintain both EMT and RAS signaling to promote cell survival and restrain apoptosis.

Previously unconnected observations support the hypothesis that TBK1 participates in both Rasdriven and EMT-driven engagement of AKT and mTOR signaling. TGF-beta is a master regulator of EMT and its signaling network makes multifaceted contributions to cancer cell survival. TGF-beta-mediated cancer cell dissemination has been shown to intersect with the RalGEF/RalB arm of Ras downstream signaling, as TGF-beta was shown to induce a RhoGEF GEF-H1-mediated cell dissemination that required RalB/exocyst (Sec5)-engagement (Biondini et al., 2015). Since RalB/Sec5 complexes can also contain TBK1 (Chien et al., 2006), this provides another potential contribution of TBK1 to TGF-beta-dependent EMT phenotypes in NSCLC. Interestingly, KRAS-driven signaling to TBK1 via RalB can also engage a CCL5/IL6 autocrine loop that promotes JAK/STAT3 activity that in turn supports TBK1/IKKe activity. This therefore potentially corresponds to a TBK1-dependent activation of pSTAT3. (Zhu et al., 2014). Intriguingly, IL-6 activation has also been reported to promote EMT via STAT3-mediated EMT gene upregulation (Bharti et al., 2016). This is compelling because TGF-beta signaling through SMAD3 has also been observed to synergize with Ras signaling to promote STAT3-mediated transcription of *SNAII*, a key transcription factor of EMT promoting genes. (Saitoh et al., 2016). While this report did not identify the mechanism whereby Ras signaling promotes STAT3 in EMT, it is very possible that TBK1 fills this role and as such could aid in the promotion of both TGF-beta and IL-6-medated EMT.

Furthermore, TGF-beta integrates with AKT and mTOR at the level of Ras downstream effector PI3K, as both TGFBR1 and TGFBR2 promote this axis' activation via direct interaction. PI3K adaptor, p85, is constitutively bound to TGFBR2 and associates with TGFBR1 upon TGFB1 ligand-binding induced receptor dimerization, which leads to activation of PI3K and AKT/mTOR signaling (Lamouille and Derynck, 2007; Yi, 2005). There is, however, a fine balance in the regulatory environment of AKT and TGF-beta signaling, as AKT, in a phospho-independent manner, can bind to SMAD3 and prevent it's TGF-beta induced phosphorylation and nuclear translocation (Remy et al., 2004). This likely functions as a feedback mechanism to retrain uncontrolled engagement of particularly cytotoxic TGF-beta signaling by inhibiting SMAD3-induced apoptosis (Conery et al., 2004). This has been hypothesized to be an important

event in the early stages of cancer development that is subsequently overridden by other signaling events downstream of TGF-beta and other networks as cancer progression advances. The multifaceted intersections between TGF-beta and PI3K/AKT/mTOR signaling are helpfully and more comprehensively reviewed in (L. Zhang et al., 2013).

The link between AKT/mTOR signaling and TGF-beta mediated induction and support of EMT is further supported by the observation that RNAi-mediated depletion of AKT was sufficient to restrict TGF-beta-induced increased SNAII expression in murine mammillary epithelium (Lamouille et al., 2012). This was reminiscent of our finding that Compound II treatment attenuated TGF-beta induction of SNAII in A549 (Figure 14J), in which the compound is presumably also concurrently blocking AKT activation. Additional TBK1 inhibitor experiments, as well as RNAi- or CRISPR-mediated depletion of TBK1 and or AKT, will be needed to verify the hypothesized requirement of TBK1 in TGF-beta mediated induction of SNAI1 or other EMT-related genes. In additional support of this hypothesis, however, it is interesting to note that our lab has previously observed that TBK1 inhibition by Compound II attenuates not only phosphorylation of AKT, but also AKT phosphorylation of Glycogen Synthase Kinase 3 alpha/beta (GSK3-a/b) at S21/S9, respectively (Ou et al., 2011). Furthermore, overexpression of TBK1 was sufficient to induce GSK3-b phosphorylation by AKT in a TBK1 kinase-dependent manner. This is intriguing because phosphorylation of GSK3-b at S9 is a key event in support of EMT, as it inhibits GSK3-b-mediated phosphorylation and cytosolic sequestration of SNAIL (Zhou et al., 2004). TBK1 inhibition was recently reported to perturb radiation-induced EMT in A549, through repression of ZEB1 and activation of GSK-3b (Liu et al., 2014), suggesting TBK1 may function to maintain inhibition of GSK3-b to support EMT. Additionally, EMT-inducer upregulation of SNAI1 promotes expression of pro-EMT

transcription factor, *ZEB1*, the original biomarker returned by the elastic net, by suppressing miR-200-mediated destabilization of *ZEB1* mRNA (Dave et al., 2011). Compellingly, miR-200a resided proximally to *TBK1* and *TGFBR2* in FUSION-guided gene clustering (Potts et al., 2013). One observation in opposition to the hypothesized requirement of TBK1 for TGF-beta signaling noted that during antiviral innate immune engagement phosphorylation of IRF3 attenuates TGF-beta/SMAD3 functions (P. Xu et al., 2014). However, the degree to which this was due to direct regulation of IRF3 by TBK1 was not robustly examined; and the only TBK1-specific loss of function agent employed was BX795, which was used at a high dose potentially beginning to enter the range of off-target effect engagement ( $6\mu$ M). It may also be that the relative pro- or anti-TGF-beta effects of TBK1 are dependent on TBK1 location and adaptor engagement, which may be differentially regulated by viral stimulation of innate immunity or oncogenic induction of EMT.

Taken together, these observations suggest that TBK1 may play an essential contextspecific role in Ras-mutant/mesenchymal NSCLC, it supports engagement of AKT/mTOR signaling downstream of Ras and TGF-beta/EMT, while at the same time helping to sustain the EMT phenotype by supporting the expression and/or stability of pro-EMT transcription factors such as *SNA11* or *ZEB1*. However, while the *KRAS*-mutant/epithelial NSCLC subpopulation displayed resistance to TBK1 inhibitors, it is possible that this resistance is conferred through several potential mechanism, which all require further experimental exploration. As TBK1 inhibition did not perturb AKT/mTOR axis signaling in *KRAS*-mutant/epithelial NSCLC lines, it is possible that either the signaling from Ras and/or other upstream regulators through AKT/mTOR is so strong it overrides TBK1-induced pathway inhibition. This would suggest TBK1 regulation of Akt/mTOR may still be somewhat attenuated by TBK1 inhibitors in Rasclass mutant/epithelial lines, but another signaling pathway has compensated. Unpublished data from murine TBK1 loss of function experiments suggest loss of TBK1 can be compensated for by induction of PDK1 signaling to AKT/mTOR. Alternative, signaling from Ras itself may be higher in TBK1-resistant NSCLC and it would accordingly be informative to examine whether these cell lines exhibit higher Ras specific activity, as read out by higher Ras-GTP/Total Ras ratios, than KRAS-mutant mesenchymal cells. Alternatively, it is possible that these cell lines possess alternative signaling "wiring" which has uncoupled TBK1 from AKT/mTOR regulation altogether. One direct way to test this hypothesis would be to treat both *KRAS*-mutant/epithelial and *KRAS*-mutant mesenchymal lines with AKT inhibitors to see whether pathway could be perturbed equivalently in both subtypes. Even if AKT inhibition did not recapitulate the TBK1 inhibition effects on viability, these experiments would still aid in testing whether hitting the target (TBK1) or hitting the pathway (AKT/mTOR) is the crucial event conferring sensitivity or resistance to TBK1 inhibitors in the context of KRAS-mutant NSCLC.

In summary, my discoveries into role of TBK1 in the regulation of the AKT/mTOR regulatory axis reveal new mechanistic details about TBK1 function in homeostatic cell biology and describe molecular indicators for the cancer subtype context selectively sensitive to TBK1 inhibition. It is my greatest hope that this body of work will result in successful intervention strategies to help the thousands of NSCLC and other cancer patients urgently needing and counting on future advances in cancer therapy.

# **CHAPTER FOUR**

#### . MATERIALS AND METHODS

#### Cell Culture.

All 293T, 293FT, MNT1, LOXIMVI, HCT116, HeLa, and Mouse Embryonic Fibroblasts (MEF) cell lines were cultured in Dulbecco's Modified Eagle Medium (DMEM), containing 10% Fetal Bovine Serum (FBS) (Atlanta Biologicals) and 1% antibiotics (Penicillin/Streptomycin, Life-Technologies (15140-163) or Invitrogen (15140122). NSCLC lines, A549, HCC44, A427, H1573, H2347 were cultured in Roswell Park Memorial Institute (*RPMI*) 1640 Medium, containing 5% FBS and 1% antibiotics. TBK1 kinase domain homozygous Wild-Type (+/+), heterozygous mutant (+/ $\Delta$ ), and homozygous mutant ( $\Delta/\Delta$ ) were generated by 3T3 protocol (split 1:3 every three days until cells exited quiescent state or approx. 2-3 months) from mice described in (Marchlik et al., 2010), generously provided by Dr. Rolf Brekken (UTSW). TSC2 WT and TSC2 -/- MEFs were generously provided by Dr. James Brugarolas (UTSW). HCT116 PDPK1 WT and PDPK1 homozygous knockout (-/-) were kind gifts from Dr. Bert Vogelstein (Johns Hopkins University). HCC44 LKB1 series was generated by Dr. JiMi Kim (UTSW). siRNA reverse transfection was conducted for 72hr using RNAiMax (Invitrogen, 13778-150).

#### **Antibodies and Other Materials**

Most monoclonal antibodies (mAb) were purchased obtained from Cell Signaling Technologies (CST) (e.g. anti-AKT-pT308, 4056; anti-AKT-pS473, 4060, 3787; anti-Claudin-1, 13255; anti-E-Cadherin, 610181; anti-ERK1/2, 4695, anti-GAPDH, 5174; anti-PRAS40-pT246, 2997; anti-Raptor, 2280; anti-S6, 2217; anti-S6-pS235/236, 4858; anti-S6K, 2708; anti-S6KpT389, 9234; anti-S6K-pT421/pS424, 9204; anti-SMAD2-pS465/467); anti-Snail, 3879; anti-

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TBK1, 3504; anti-TBK1-pS172, 5483; anti-TSC2, 3635; anti-Vimentin, 5741). MEM Essential Amino Acid Solution (EAA) (M5550), Mouse anti-FLAG monoclonal antibody (F1804) and anti-FLAG antibody conjugated beads (A2220) were purchased from Sigma-Aldrich. Protein A/G beads (sc-2003), anti-HA monoclonal antibody (sc-7392), and anti-HA antibody conjugated beads (sc-7392ac) were purchased from Santa Cruz. cOmplete, Mini, EDTA-free Protease Inhibitor Cocktail Tablets (04693159001) was purchased from Roche. 5X Protein Reagent was purchased from Cytoskeleton Inc. (ADV01-A). BCA Protein Quantification Kit (23225) were purchased from Thermo Scientific. Pre-cast polyacrylamide gels (4-15%, 4561086; 4-20%, 456-4093) were purchased from Bio-Rad. MK-2206 (508726), Peirce Enhanced chemiluminescence substrate (ECL) (32106), SuperSignal West-Pico ECL, (34080), and SuperSignal West Femto ECL (PI-34096) were purchased from Thermo Fischer Scientific. Torin 1 was purchased from Tocris (4247). Rapamycin was purchased from LC Laboratories (R-5000). cDNA transfection reagent Fugene 6 (E2691) Cell Titer Glo (G7573), and Caspase-Glo (G8091/2/3 series) were purchased from Promega. LKB1 plasmids were purchased from Addgene (pBabe-FLAG-LKB1-WT, 8592; pBabe-FLAG-LKB1-KD (K78I), 8593). HA-TBK1 was generously provided by Dr. Xuetao Cao (Second Military Medical University, Shanghai, China) (Ahn et al., 2004). HA-S6K plasmid was generously provided by Dr. Kun-Liang Guan (University of California, San Diego). Source of Compound II and TBK1 plasmids (pRK5-myc-FLAG-TBK1-WT, pR5K-myc-FLAG-TBK1-K38M (KD) was (Ou et al., 2011).

#### **Ral-Stapled Peptide Immunoprecipitation Assays**

 $5 \times 10^{6}$  HEK293T cells were seeded 48 hr prior to endpoint into 10cm dishes (3 per condition) in DMEM supplemented with 10% FBS. Media was aspirated and fresh DMEM (with 10%FBS) with and without FAM-tagged SP1 or SP6 (at 100  $\mu$ M each) was added 24 hr prior to

endpoint. Media was then replaced with 1X EBSS (Earle's Balanced Salt Solution) 90 min prior to endpoint. At endpoint, cells were lysed in lysis buffer (20 mM Tris-HCl pH 7.4, 137 mM NaCl, 1 % Triton X-100, 0.5 % sodium deoxycholate, 10 % Glycerol, 10 mM MgCl<sub>2</sub>, 2 mM EGTA, 1 mM PMSF, 50 mM NaF, 1 mM Na<sub>3</sub>VO<sub>4</sub>, 80 mM β-glycerosphosphate plus EDTA-free protease inhibitor cocktail (Roche, 04693159001)). After 15 min lysis at 4°C, lysates were cleared at 20,000 g for 20 min at 4°C. Cell lysates were diluted with lysis buffer to prepare 120  $\mu$ L of Whole Cell Lysate (WCL) (4 $\mu$ g/ $\mu$ L) and 1400  $\mu$ L of IP Lysate (6  $\mu$ g/ $\mu$ L) for each condition. Endogenous RalB was immunoprecipitated by the addition of 30 µL of mouse anti-RalB antibody (a kind gift from Larry Feig, Tufts University) to IP lysates at 4 °C for 4h. Protein A/G agarose beads [Santa Cruz Biotechnology Inc., sc-2003)] were added for 1 hr at 4 °C to precipitate antibody-antigen complexes. Precipitated complexes were washed three times with lysis buffer for 5 min at 4°C. The samples were then separated via SDS-PAGE and transferred to PVDF membranes (Immobilon-P). Membranes were probed by immunoblotting with the following primary antibodies: rabbit anti-RalB (Cell Signaling Technology, cs-3523, lot 1) and mouse anti-Sec5 (a kind gift from Charles Yeaman, University of Iowa).

#### **GFP-LC3** turnover

72 hours prior to endpoint, 8 X  $10^3$  HeLa cells stably expressing GPF-LC3 were plated per well of glass bottomed 96-well plates. Cells were plated in 100mL of DMEM supplemented with 10% FBS and grown for 48 hours. 24 hours prior to endpoint, media was changed with 100mL fresh DMEM (w/ 10% FBS). DMSO and Peptides were added 24 or 12 hours prior to endpoint at final indicated concentrations (final concentration of DMSO per well was 1%). 4 hours prior to endpoint, cells were washed twice with PBS (w/ Ca2+ & Mg2+) and then fed with either 100mL of 1X Earle Balanced Salt Solution (EBSS) or Serum-Free (SF) DMEM as indicated. At endpoint, EBSS-treated cells were washed once and SF DMEM-treated cells twice with 1X PBS (w/ Ca2+ & Mg2+). Cells were then fixed in 4% PFA in 1X PBS (w/ Ca2+ & Mg2+) for 10min. Cells were then washed twice as before and then stained with 0.01% Hoechst in 1X PBS (w/ Ca2+ & Mg2+) for 20 min. Total fluorescence intensity for GFP and Hoechst was measured using the PheraStar FS plate-reader.

#### **GFP-TFEB** activation

5 X 10<sup>3</sup> HeLa cells stably expressing GFP-TFEB were plated in 500μL DMEM (w/ 10% FBS) per well of 8-Chamber Lab-Tek® II Chambered #1.5 German Coverglass slides and grown overnight. 24 hours prior to imaging, media was changed with 265μL fresh DMEM (w/ 10% FBS) and DMSO or Peptides at final concentrations indicated (final concentration of DMSO per well was 1%). 24 hours after peptide addition, live-cell images were acquired with an Andor Spinning Disc Confocal Microscope (oil immersion and 60X objective) under normal cell culture conditions (37 0C, 5% CO2). Initial images of fed-state cells were taken 24 hours after peptide addition. The media in each well was then changed with 265μL 1 X EBSS and subsequent images were taken at the times indicated above.

#### TBK1 Compound Screen/Cell Viability Dose-Response Curve (DRC).

TBK1 inhibitors BX795 and Compound II were tested across 100 NSCLC cell lines by the UTSW High-Throughput Screening (HTS) Core Facility, under the leadership of Dr. Bruce Posner. Briefly, cells were plated in 384-well cell culture plates and subsequently treated for 96 hours in the presence of DMSO or compound in 12-point, half-log doses ranging from 50µM to 50pm. Cell viability was assayed post-treatment via Cell-Titer Glo (Promega) and mean ED50 (median effective dose) and area-under-the-curve (AUC) were calculated from the two most concordant viability dose-response curves (DRC) replicates, normalized to the viability measured under the lowest compound dose. Full DRC results can be found in Table 1.

#### **Compound-Compound Correlations**

For Figures 6C-F, correlation plots and statistics were generated using GraphPad Prism 6. In remaining Figure 6 panels, correlation plots, linear regression best-fit lines, and statistics for these analyses were generated using R-studio. Correlations were calculated for Log<sub>10</sub>transformed BX795 or Compound II ED50s (Log<sub>10</sub>) vs. either ED50 (ln) (Garnett et al., 2012) or Area-Under-the-Curve (AUC) (Log<sub>10</sub>) (Seashore-Ludlow et al., 2015) values in overlapping sets of NSCLC lines. Pearson values represent correlation for given compound pair among either all (P(all)) or KRAS-mutant only (P(mut)) NSCLC lines.

#### **Essential Amino Acid (EAA) Nutrient Stimulation**

Cells were plated in 35mm or 6-well cell culture dishes in 2mL of cell culture media. The next day, cell culture media was aspirated and 2mL of 1X Earle's Balanced Salt Solution (EBSS) was added for 2 hours. 1 hour prior to the addition of MEM-Essential Amino Acids Solution (EAA) (Sigma Aldrich), L-glutamine (Gln) was added in EBSS to a final concentration per well of 1mM or 2mM. After 1 hour of Gln treatment, EAA was added to final well concentration of 1X for the times listed. All media were then aspirated, cells were washed once in cold 1X PBS (usually supplemented with phosphatase inhibitors NaF,  $\beta$ -glycerophosphate and sodium orthovanadate (Na<sub>3</sub>VO<sub>4</sub>)) and then lysed either in NP-40 buffer (50mM Tris HCl, 120mM NaCl, 0.5% NP40, 1mM EDTA, 1mM DTT), plus phosphatase inhibitors (NaF,  $\beta$ -glycerophosphate and sodium orthovanadate) and protease inhibitors tablet (Roche cOmplete Mini) or in 2% SDS buffer (50mM Tris pH 6.8, 2% SDS, 10% glycerol). Following lysis on ice at 4C, SDS lysates were heated at  $\geq$  95C for 5 min and then protein concentration was measured via Pierce BCA

assay. Protein concentration was equilibrated across experimental samples and Western Blot samples were prepared using 2X or 6X Sample buffer containing  $\beta$ -mercaptoethanol ( $\beta$ -me) and heated to  $\geq$  95C for 5 min. NP40 lysates were lysed (15min) and then spun down at 20,000g for 20min at 4C, and the protein concentration of the supernatant was quantified using Cytoskeleton Protein Reagent. 595nm absorbance of 300µL of 1x protein solution (10µL of protein lysate + 990µL 1x protein reagent) was measured via PheraStar FS plate-reader. Protein concentration was equilibrated across experimental samples and Western Blot samples were prepared using 6X Sample buffer (+ $\beta$ -me) and heated to  $\geq$  95C for 5 min.

#### **SDS-PAGE and Immunoblotting**

Equivalent amount (µg) of Western Blot lysates were loaded either in self-poured (6%, 8%, or 10%) or pre-cast (4%-20% or 4%-15%) (Bio-Rad) polyacrylamide gels. Gels were transferred to Polyvinylidene difluoride (PVDF) membranes using standard wet-tank transfer or BioRad TransBlot Turbo semi-dry transfer protocols. Membranes were blocked in 5% non-fat milk/Tris-buffered saline w/Tween (TBST) for 1 hour. Primary antibodies diluted in 5% non-fat milk/TBST or 5% Bovine Serum Albumin (BSA)/TBST (w/ 0.05% Sodium Azide) and incubated overnight at 4C. Primary antibody was saved for reuse and membranes were washed with TBST before HRP-linked secondary antibodies were added in 5% non-fat milk/TBST at Room Temperature (RT) for 1hr. Pierce enhanced chemiluminescence (ECL) was added and Horseradish Peroxidase (HRP)-catalyzed luminescence was captured on autoradiography film.

## **TBK1 Adaptor "Mini-screen"**

HeLa cells were plated and 16-18hr later transfected with pooled siRNA (Sigma) using RNAiMax (Invitrogen). Next day the media was replaced with fresh media. Three day post-transfection the cells were washed with EBSS once and then incubated with EBSS for 2hr

followed by incubation with EBSS plus 2mM glutamine for 1hr. The cells were stimulated with EAA and harvested at the indicated time points. Samples were separated by SDS-PAGE followed by immunoblot analysis using antibodies against total ribosomal S6 and phospho-S6. Pooled siRNA were used to deplete LONRF1 (non-specific control); canonical TBK1 adaptors (e.g. TANK, AZI2, NEMO, AKT1, etc.); the exocyst (e.g. Sec3, Sec5, Sec6, Sec8, etc.); and amino acid transporters (SLC7A5, SLC1A5, SLC3A2). siRNA oligo pools were generated from equal parts of 3 individual oligos/per gene from Sigma-Aldrich (stock concentration of each individual siRNA oligonucleotide sequence was 10µM). EAA starvation was performed for 3 hours, followed by 1X EAA addition for 0, 10, or 30 minutes. siRNA pools for mini-screen genes were always tested alongside a LONRF1 control siRNA pool. Relative phospho-S6/total S6 ratios were then calculated using ImageJ-measured densitometry and normalized to LONRF1 + 30min EAA for each set. Error bars represent standard deviation from the mean for a given sample (column). Two-tailed unpaired Student's t test was performed between LONRF1 + 10min EAA or LONRF1 + 30min EAA and the respective time points of the siRNA pools within each set. \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001, \*\*\*\*P < 0.0001.

#### **TBK1 IP-Mass-Spec**

*Cloning:* TBK1 was PCR amplified from FLAG-TBK1 vector using primers with an overhang 5' NOT1 and a 3' KPN1 site and cloned in N-terminal 3XFLAG pIRESpuro (Invitrogen) vector by dual restriction digestion of vector and insert with the aforementioned enzymes followed by ligation with T4 DNA ligase.

*Immunoprecipitation*:  $3X10^{6}$  293T cells were seeded in four 10cm dishes grown each in 10 ml 10% FBS DMEM. Next day, cells were transfected with either  $3\mp g$  of 3XFlag-TBK1 plasmid or 3XFlag-Empty using Fugene 6 (Promega) at a ratio of 3:1 (mL Fugene 6 to mg

DNA). 48 hours post-transfection, the cells were lysed in immunoprecipitation lysis buffer (20 mM Tris-HCl pH 7.4, 137mM NaCl, 1% Triton X-100, 0.5% sodium deoxycholate, 10mM MgCl2, 2mM EGTA) with protease and phosphatase inhibitors (Roche EDTA-free cOmplete ULTRA and PhosphoSTOP). Cells were lysed for 1 hour and cleared at 16,000 X g for 10 min at 4°C. 1500mg of lysate was brought to the concentration of 1.5mg/mL by diluting it with lysis buffer. The immunoprecipitation was carried out for 14 hours using 2.5mg of the antibodies: monoclonal anti-Flag M2 (Sigma) or mouse monoclonal anti-HA F-7 (Santa Cruz Biotechnology sc-7392). It was followed by 2-hour precipitation of antibody-antigen complexes using 90µl of Protein A/G-agarose beads (Santa Cruz Biotechnology). Subsequently, complexes were washed in lysis buffer 4 times for 1 min at 4°C and finally was eluted with 90µl 2X SDS sample buffer (BioRad, 161-0737) followed by boiling at 95°C for 12 min. Following Immunoprecipitation the sample was run on precast SDS-PAGE 4-20% gradient gel (Bio-Rad) and ran for 15mm length into the gel. Gel was washed with dH20, stained with colloidal coomassie for 1 hour to visualize and fix followed by another 30 min dH20 wash. For each sample, fixed immunoprecipitated proteins separated on the gel were excised as a single fragment with sterile scalpel, put on one Eppendorf tube and homogenized with a sterile needle. The samples were sent for mass spectrometry using Orbitrap Fusion Lumos<sup>TM</sup> using UTSW Proteomics core.

*MS/MS Data analysis:* LC-MS/MS data was generated and quantified by using spectral count based semi-quantitative label free quantification as reported in (Trudgian et al., 2011) The finalized dataset was further controlled for false positives using CRAPOME database (www.crapome.org.). High stringency inclusion criteria cutoffs for any protein identified in less than 5% of the studies in CRAPOME database, absent in 'tag-only' pull down and present in

specific pull down with at least 2 spectral counts identifies TBK1 as the top hit along with RPTOR and RPS6KB1 in top12 hits.

#### **Immunoprecipitations**

For immunoprecipitations (IPs) (Figure 9), whole cell extracts were prepared by lysing cells in IP lysis buffer (20 mM Tris HCl [pH 7.5], 10 mM MgCl2, 2 mM EGTA, 10% Glycerol, 137 mM NaCl, 1% Triton X-100, 0.5% Na Deoxycholate, 1 mM DTT) plus phosphatase and protease inhibitors (Roche). Lysates were incubated with anti-TBK1 rabbit monoclonal antibody (Cell Signaling, Cat #3504) and 30µL Protein A/G beads (Santa Cruz) overnight at 4C. Immunoprecipitates were washed three times in IP lysis buffer plus 1 mM PMSF then boiled in standard SDS sample buffer. Samples were separated by SDS-PAGE followed by western blot analysis. Co-immunoprecipitation (Co-IP) of overexpressed proteins from HEK293T cell lysates was performed with 30µL of anti-HA agarose beads (50% slurry, Sigma) or anti-FLAG M2 beads (50% slurry, Sigma).

For overexpression Co-IP in HEK293FT (fast-growing) cells (Figure 11F), plasmid cDNA was transfected via Fugene 6 (Promega) (3:1 µL Fugene 6/µg DNA) in serum-free Opti-MEM. 24 hours later the media was aspirated and fresh DMEM culture media was added 24 hr prior to endpoint. At endpoint (48 hours post-transfection), cells were lysed in lysis buffer (20 mM Tris-HCl pH 7.4, 137mM NaCl, 1% Triton X-100, 0.5% sodium deoxycholate, 10% Glycerol, 5mM MgCl<sub>2</sub>, 2mM EGTA with freshly added 1mM PMSF, 50mM NaF, 1mM NaVO4, 80mM beta-glycerosphosphate plus EDTA-free protease inhibitor cocktail (Roche). After 15-20 min rotating lysis at 4C, lysates were cleared at 20,000 g for 20 min at 4C. Cell lysate concentrations were assayed by Protein Assay Reagent (Cytoskeleton) and then equilibrated with lysis buffer. Lysates were diluted to achieve maximum equal IP sample concentration and to create Whole Cell Lysate (WCL) samples. 2µg mouse anti-FLAG antibody (Sigma) was added to each IP sample and antibody-lysate solution was rotated for 4 hours at 4C. Protein A/G agarose beads (Santa Cruz) were added for 1 hr at 4C to precipitate antibody-antigen complexes. Precipitated complexes were washed three times with lysis buffer for 5 min at 4C. The samples were then separated via SDS-PAGE, followed by immunoblotting.

#### **Endogenous Raptor IP**

3 plates of TBK1 +/+ or TBK1  $\Delta/\Delta$  MEFs per condition were plated and then 2 days later rinsed once in cold PBS and then lysed in 0.5% NP40- (50mM Tris HCl, 120mM NaCl, 0.5% NP40, 1mM EDTA, 1mM DTT) or 0.3% CHAPS-based lysis buffer (0.3% CHAPS, 50mM Tris HCl, 120mM NaCl, 1mM EDTA). Post lysis, protein concentration was equilibrated among samples and equal amounts of protein were added to anti-Raptor antibody-conjugated magnetic beads or anti-FLAG-IgG-conjugated magnetic beads and rotated at 4C for 2 hours. Beads were then washed 5 min (X3) with lysis buffer. Samples were boiled for 5 min in SDS sample buffer (+ $\beta$ -me) and then separated by SDS-PAGE, followed by immunoblotting.

#### S2N comparisons

S2N of differentially expressed mRNAs (Source data: GSE32036) in TBK1-sensitive vs. TBK1-resistant NSCLC lines was performed using the following formula: [(meanA - meanB) / (sdA + sdB)], where mean expression of mRNA "x" in cell line group B is subtracted from mean of mRNA "x" in cell line group A, and then divided by the sum of the standard deviations (sd) of "x" in groups A and B. This was then followed by a hypergeometric test (via "phyper" function in R-Studio) to determine significance of overlap between top and bottom 5% most differentially expressed mRNAs among the TBK1 treated lines and the genes comprising the EMT gene signatures.

#### **Elastic Net**

Elastic net biomarker identification was performed as in (Potts et al., 2015), using source mRNA expression data GSE32036 for BX795 AUC values (capped at AUC = 400) in NSCLC cell lines as listed.

#### **TBK1** Inhibitor vs. Gene Expression Correlations

TBK1 inhibitor sensitivity (ED50 or AUC) from NSCLC lines tested in the HTS core at UTSW were  $Log_{10}$ -transformed and plotted against  $Log_2$  mRNA expression (Source data: GSE32036) of Ras and Ras-effector network gene subset, as annotated in Table 2. Plots, linear regression best-fit lines, and statistical analyses were generated using GraphPad Prism 6. \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001, \*\*\*P < 0.001.

#### **EMT-modulation of TBK1 Sensitivity**

NSCLC cells were plated in 96-well cell culture plates and subsequently treated with DMSO or TBK1 inhibitors (BX795 or Compound II) for 96 hours. Cell viability was assayed post treatment via Cell-Titer Glo (Promega) (15µL per well). For TGFB1-treated cells, NSCLC lines were cultured in RPMI-5%FBS +antibiotics + 2ng/mL recombinant TGFB1 (Peprotech, 100-21) for 1-2 weeks. For "Post"-TGFb conditions, TGFB1-treated cells were re-cultured in TGFB1-free RPMI-5% +antibiotics media for greater than 1 week prior to compound treatment and viability assays.

#### Caspase 3/7 (Caspase Glo) Assay

For each cell line, 2000 cells were plated in 100 µL RPMI (0.5% FBS)/well in 96-well plates. Approximately 15 hours later, media was changed with serum-free RPMI or RPMI (+10 ng/mL recombinant TGFB1 [Peprotech]) for 24 hours. Compound was then added to the final

concentrations listed for 24 hours. At endpoint, 100 µL Caspase Glo (Promega) reagent was added and incubated for 30 min. Luminescence was then read via PheraStar FS plate-reader.

## Compound II inhibition of TGF-beta-dependent EMT gene expression

500,00 A549 cells were plated in 6-well dishes. The following day, 0.1% DMSO, 0.5 μM Compound II or 2 μM Compound II were added for 30 min, after which 10 ng/mL recombinant TGFB1 (Peprotech) was added for 24 hours. Cells were then washed with PBS and then collected into PBS and pelleted via bench top centrifuge. Pellet was lysed and RNA was collected via RNeasy Kit (Qiagen). mRNA was reverse transcribed into cDNA and relative abundance was measured by Taqman-qPCR probe set (Applied Bio-Science).

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