MOVING TOWARD PERSONALIZED CANCER THERAPY

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Introduction

Recent years have seen great increases in our understanding of the mechanisms of cancer. This improved understanding is beginning to be translated into therapies that are directed specifically at the molecular drivers of the disease. Such molecular-targeted therapies are often more effective and less toxic than the non-specific therapies that were developed when our knowledge of cancer biology was limited. Recent advances in technology are facilitating very large-scale study of cancer genome structure and function. It seems very likely that such study will suggest new cancer mechanisms that can be targeted by novel treatment strategies, and that, in the not-too-distant future, it will be commonplace to determine the unique characteristics of an individual's cancer and choose specific mechanism-based treatment based on this information. One anticipates that such therapy will be more effective than most current approaches.

Chronic Myelogenous Leukemia (CML) as the exemplar of molecular-targeted cancer therapy

CML is a malignancy of hematopoietic stem cells that results in excessive production of mature myeloid cells.[1-3] With time the disease inevitably transforms from a relatively indolent phase into a highly aggressive blast phase which results in marrow failure and death within a few weeks. Previous treatment for CML was limited to non-specific anti-proliferative chemotherapy, which did not prolong survival, or to allogeneic stem cell transplantation, which, although potentially curative, was complicated by a high rate of treatment-related morbidity and mortality.

It was known since 1960 that CML is a genetic disease, characterized by an abnormal chromosome called the Philadelphia chromosome.[4] In 1973 it was reported that the Philadelphia chromosome resulted from a reciprocal translocation of genetic material between chromosomes 9 and 22—t(9;22).[5] In 1985 the molecular genetics of t(9;22) were described: the abl oncogene, which normally resides on chromosome 9, is translocated to the BCR gene on chromosome 22, creating a fusion gene, BCR-ABL, that combines elements from both the BCR and ABL gene.[6, 7] The fusion gene gives rise to a fusion protein, BCR-ABL, that displays excessive tyrosine kinase activity. Additional studies showed that BCR-ABL transformed cells and induced leukemia in transgenic animals by phosphorylating various substrates, leading to excessive proliferation and impaired apoptosis.[8-10]

Thus genetic and functional studies had shown that BCR-ABL, a tyrosine kinase, is the key driver of the disease, and investigators, in particular Brian Druker, worked to develop inhibitors of BCR-ABL. One drug was found to selectively and potently inhibit ABL kinase activity by competitively inhibiting ATP binding in the ATP binding pocket.[11] This drug inhibited growth of CML cell lines, primary CML cells and CML in animals. The drug was formulated for oral use (eventually called imatinb—trade name Gleevec) and entered clinical trials.[12]

In the first phase I clinical trials nearly all the patients responded rapidly to the drug, normalizing their blood counts within 4 weeks.[13, 14] Imatinib soon entered definitive comparative trials and was shown to be markedly superior to the previous standard treatment.[15] 98% of CML patients treated in chronic phase have a complete hematologic response, 87% have complete normalization of their cytogenetics (with suppression of CML cells normal hematopoiesis is established). Remissions are durable with 93% of patients being free of disease progression at 5 years.[16] Side effects typically are relatively mild, limited to mild fluid retention, skin rash, arthralgias and myalgias. Imatinib was FDA-approved in 2001 and is the standard of care for newly-diagnosed CML patients. (See Figure 1.)

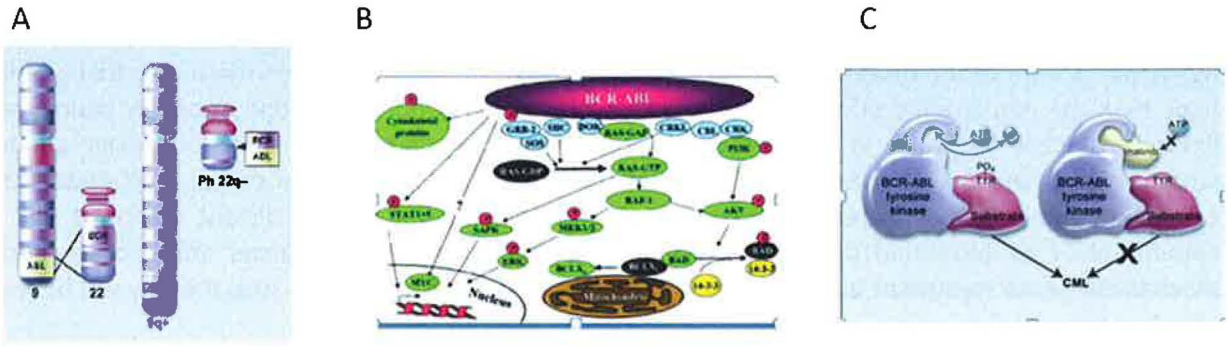

Figure 1. From genetics to biology to rational therapy: CML as the examplar of molecular targeted therapy. A. The t(9;22) of CML translocates ABL from chromosome 9 to BCR of chromosome 22, to create a fusion gene, BCR-ABL. B. BCR-ABL encodes a fusion protein that acts as an overactive tyrosine kinase, leading to activation of pathways that cause excessive proliferation and impaired apoptosis. C. Imatinib binds in the ATP binding pocket of BCR-ABL, inhibiting the enzyme's kinase activity and thus shutting down CML pathways. From Druker[1].

Expanding molecular-targeted therapy to other cancers

In addition to inhibiting ABL kinase activity, imatinib also inhibits the tyrosine kinases KIT and PDGFR alpha and beta. Diseases characterized by activating mutations of these kinases have responded extremely well to imatinib. Chronic leukemias with PDGFR alpha or beta rearrangements have shown complete, durable remission.[17, 18] Advanced and inoperable gastrointestinal stromal tumors (GIST) have responded remarkably well to imatinib;[19, 20] since the introduction of this drug to GIST therapy median survival has increased from about 18 months to 5 years. Marked responses in other solid tumors have been seen as well including mucosal melanomas (c-kit mutations)[21, 22] and dermatofibrosarcoma protuberans (PDGFβ mutations).[23]

Based on the clinical success (and financial success—imatinib is a $3.9 billion/year drug for Novartis), many additional agents targeting kinases and other cancer proteins in many cancer types have been developed.[24-29] With few exceptions, when it can be demonstrated that a malignancy is driven by a mutant or overexpressed kinase, then pharmacologic inhibition of that kinase has been successful in the clinic. (See Table 1.)

Resistance to molecular-targeted agents

Resistance to molecular-targeted therapy was first observed in imatinib-treated patients soon after the drug entered clinical testing. Conceptually, imatinib resistance could occur either because the drug is no longer binding to and inhibiting the target, or because the disease has evolved and is now being driven by mechanisms which do not depend on BCR-ABL.[30] Early studies of imatinib-resistance showed that BCR-ABL targets were being phosphorylated in imatinib-resistant cells, suggesting that the disease process was still BCR-ABL-dependent; additional study showed that BCR-ABL was either amplified or mutated in the kinase region so that imatinib could no longer bind in the ATP-binding pocket.[31, 32]

These studies led to rational design of second-generation inhibitors that could bind to most of the mutant forms of ABL kinase; in addition these drugs were more potent against the non-mutant form of

Table 1. Selected molecular targeted therapies.

Disease	Gene	Drug
Chronic myelogenous leukemia	BCR-ABL	Imatinib
Acute lymphoblastic leukemia	BCR-ABL	Imatinib
Gastrointestinal stromal tumor	KIT	Imatinib
Cchronic eosinophilic leukemia	PDGFRA	Imatinib
Chronic myelomonocytic leukemia with t(5;_)	PDGFRB	Imatinib
Myeloproliferative Disorder	JAK-2	JAK-2 inhibitors
Dermatofibrosarcoma Protuberans	PDGFRB	Imatinib
Mucosal Melanoma	KIT	Imatinib
Non-small cell lung cancer	EGFR ALK	Erlotinib Gefitinib PF-02341066
Breast Cancer	HER-2	Herceptin
Kidney Cancer	VEGFR2, PDGFRB mTOR	Sorafinib, Sunitinib Temsirolimus
Medulloblastoma	Hedgehog	GOC-0449
Melanoma	BRAF	PLX4032
Colon Cancer (and others)	VEGF	Bevacizumab

the ABL kinase.[33, 34] These second-generation drugs, dasatinib and nilotinib, have shown high rates of durable responses in patients with clinical imatinib resistance and are FDA-approved for use in this setting.[35, 36] Recent studies of the second generation drugs compared to imatinib as initial treatment of CML have demonstrated modest superiority of the new drugs.[37, 38] However, the second generation drugs do not have significant activity against a particular, common ABL kinase mutation, T315I;[31] this so-called gatekeeper mutation creates steric hindrance which inhibits the second generation drugs as well as imatinib from binding, and patients with this mutation are clinically resistant to all three drugs. However, third-generation drugs appear to be effective against the T315I mutation[39] and clinical trials are showing promise in patients with this mutation. One imagines that in the future patients with newly diagnosed CML will be treated with a combination of a second-generation drug and a drug which inhibits the T315I mutation.

The lessons learned from study of imatinib-resistance have proved instructive for other molecular-targeted therapies. The same principles have applied, with observation of kinase mutations that impair

drug-binding, gatekeeper mutations, development of second generation drugs, and recognition of non-kinase dependent resistance mechanisms.[24, 40-42]

Lessons from molecular-targeted therapy with kinase inhibitors

The success of imatinib in CML demonstrated the promise of molecular targeted therapy. The clear lesson was that definition of a cancer in terms of its genetic alterations and oncogenic mechanisms could lead to highly effective, rational treatment. Moreover, although resistance could be anticipated it could also be carefully studied and strategies for its management could be developed, again, rationally.

Perhaps an even more important lesson was the observation of responses to kinase inhibition in other, more genetically complex cancers. The concern about CML had been that it was seemingly a fairly simple disease genetically, marked only by the BCR-ABL fusion gene. However, other cancers were known to be far more complicated, with numerous mutations and likely several interlocking mechanisms cooperating to result in the cancer cells' characteristics. It was initially somewhat of a surprise to see these genetically complicated cancers respond so reliably to inhibition of just one mutant kinase. These observations, along with studies in model systems, led to the appreciation of the phenomenon of "*oncogene addiction*" wherein a single oncogene mutation—particularly if in a kinase—could drive the cancer's growth and survival, such that inhibition of this single abnormality could be expected to be lethal to the cancer.[43-45]

Appreciation of the significance of oncogene addiction and mutated kinases leads to the suggestion that any new kinase mutation discovered in a subset of cancers should lead to drug discovery programs aimed at inhibiting the new target; a high likelihood of success can be expected.[46] For example, the ALK gene (which codes for a tyrosine kinase) was discovered to be mutated in some cases of non-small cell lung cancer in 2007. Functional studies demonstrated its oncogenic role.[47] A drug already in development for another kinase was found to inhibit ALK and thus rapidly entered clinical trials in lung cancer patients with ALK mutations. Extremely promising clinical results had been observed in clinical testing by 2009-2010 and the drug is now already in comparative phase III testing.[26, 48] Although only 3-5% of non-small cell lung cancer patients have the mutation, lung cancer is a common disease and 3% equates to 5,000 new cases in the United States per year.

Broadening molecular targeted therapy

Despite these successes relatively few cancer patients are treated with molecular targeted therapy and the big question is whether molecular targeted therapy will be broadly applied or will remain confined to small niches.

Again, CML showed that a new paradigm could work: understanding of cancer biology was relatively limited when CML was becoming understood but enough was known to appreciate the potential importance of mutated kinases in driving some cancers; this knowledge of basic biology served as a foundation while the disease was defined genetically and functionally; these investigations of CML biology led to the definition of a rational target and effective targeted therapy.

One can suggest that the stage is set for building on the framework of the paradigm, on a very large scale. Certainly our fundamental understanding of biology has increased greatly, and recent, quite remarkable, advances in technology are sure to amplify our understanding of cancer at the genetic and functional levels. This will lead to new therapeutic strategies, and, one reasonably hopes, an expansion of successes in rational cancer therapy beyond those seen thus far. (See Figure 2.)

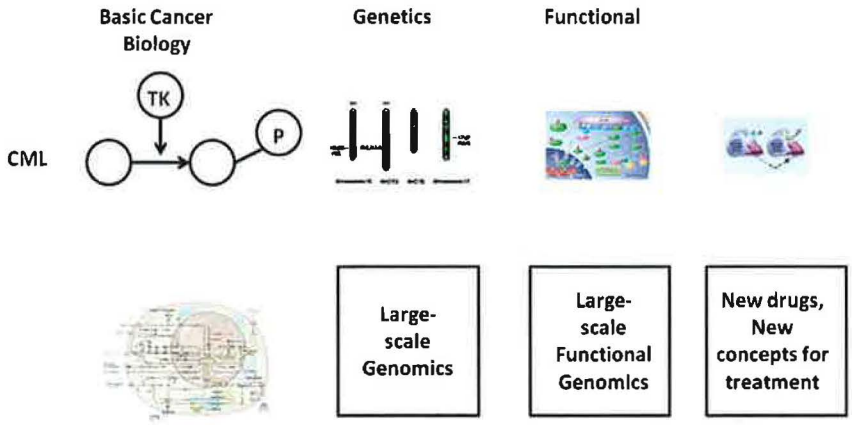

Figure 2. The CML success story broadened to other cancers. Understanding the key role of tyrosine kinases in some cancers served as the background for the successful CML treatment paradigm: genetics →function→molecular target and rational therapy. Understanding of basic cancer biology has advanced greatly since then and serves as the backdrop for current efforts in expanding the paradigm, using advanced technology for genetic and functional analysis.

Basic biology of cancer

The basic biology of cancer has come to be extremely well-understood.[45, 49, 50] What was once a complete black box is now understood to involve perturbation of a certain set of highly-regulated normal biological processes whose role is to control the growth and survival of normal cells.

Perturbation of these processes leads to: 1) self-sufficiency in growth signals; 2) insensitivity to anti-growth signals; 3) evasion of apoptosis; 4) limitless replicative potential; 5) sustained angiogenesis; 6) tissue invasion and metastasis.[49] These processes are well understood, both in broad terms at a conceptual level, and in detail at the level of individual pathways and pathway components. Although much remains to be learned, for example about how different pathways normally interact and overlap and about how these pathways are re-wired in cancer cells, we do have solid enough understanding to describe very coherently how a normal cell comes to behave like a cancer cell. (See Figure 3.)

Cancer cells contain several (typically 7-8 or so) mutations (or genes otherwise misexpressed, e.g. through amplification or deletion, epigenetic modification, or RNA interference) in different genes involved in the processes governing normal cells listed above. These mutations accumulate over several years, with each new mutation giving the cell a growth advantage over its neighbors until the cell finally displays frankly cancerous behavior. A mutated gene can promote cell growth either directly (e.g. an activating mutation in a growth pathway protein—an oncogene) or indirectly (e.g. an inactivating mutation in a protein that normally opposes growth—a tumor suppressor gene).

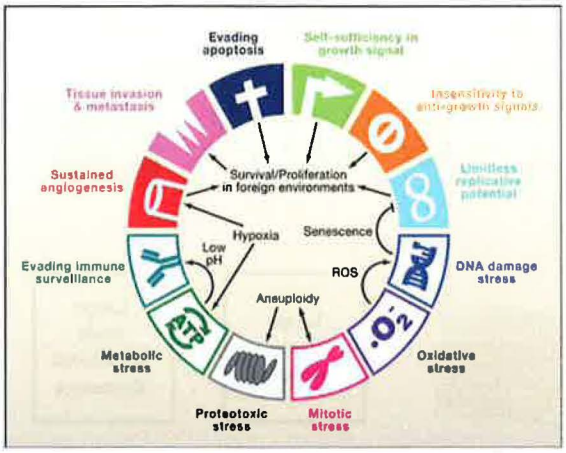

Figure 3. Hallmarks of Cancer. Cancer cells display perturbations in the six hallmark categories shown in the top half of the figure. In addition, certain stress phenotypes (bottom half) characterize cancer cells; effective stress relief pathways must be utilized by the cancer cells in order to remain viable. From Luo et al[50] and Hanahan and Weinberg[49].

Thus, a given cancer might have come to be cancerous by acquiring a specific set of activating and inactivating mutations in specific components of the key processes listed above while a different cancer might have come to be cancerous by acquiring a different set of activating and inactivating mutations in different components of the same processes. Thus, although the same basic processes are perturbed across different cancers, precisely how these processes are perturbed will differ from cancer to cancer.

An important concept that has come to be appreciated more recently has been called "*non-oncogene addiction*".[50] This concept notes that a cancer driven to great excesses of growth and proliferation—to the edge of its physiologic limits—is under great stress. To deal with the stress, the cancer cell activates numerous "stress-relief pathways". These stress-relief pathways typically are not activated directly by mutations; rather, the pathways are activated as a stress response to the more conventional oncogenic pathways. Nevertheless, to remain viable the cells becomes dependent on—"addicted to"—these non-oncogene stress relief pathways. Cancer-related can be grouped into the following categories: 1) DNA damage stress; 2) oxidative stress; 3) mitotic stress; 4) proteotoxic stress, and 5) metabolic stress.[50] (See Figure 3.)

Thus, our current understanding of cancer biology suggests many strategies to interfere with cancer mechanisms, from inhibiting various components of the more classical oncogenic pathways, to inhibiting the more recently appreciated stress-relief pathways, and indeed, many novel mechanism-based therapeutic strategies are under investigation. However, there is a strong sense that we are only at the tip of the iceberg, that we have a great deal more to learn, both about basic cancer biology mechanisms and about ways to subvert them. The challenge is being taken on from many different directions—in the next two sections I will discuss broadly some large-scale efforts in cancer genomics and functional genomics that are being facilitated by recent technologic advances.

Cancer genome sequencing

The first human genome was sequenced over ten years by an international multicenter collaboration at a cost of about $3 billion. Next generation sequencing using high-throughput, massively parallel techniques has allowed sequencing to be done much more quickly and much less expensively.[51] A whole genome now can be sequenced in a few days at a cost of about $50,000; focusing solely on exons (exome sequencing) comes at a cost of about $5,000. The technology is rapidly evolving and the cost is plummeting; the $1,000 genome is expected to be here in about 3 years. This increase in speed and decline in cost is leading to large-scale sequencing of human cancer genomes.[52-55]

Cancer genomes derived from next generation sequencing are compared to normal genomes from the patient (e.g. from a biopsy of normal skin) and to reference genomes, and the single nucleotide variants (SNVs) that are specific to the cancer cells are focused on—there are thousands of these per genome. Of these, the ones from coding regions are focused on (although it is appreciated that non-coding regions could be important too and so are set aside for later study). The coding SNVs are further winnowed down (silent mutations or mutations that would not be expected to change protein structure are set to the side) until SNVs are arrived at that are judged likely to be relevant. Annotated databases are consulted to identify the mutated genes of interest and their likely function. Genes of interest can be specifically sequenced in additional cases to determine if the mutation is recurrent, and thus especially likely to be important. Several dozen exomes, mostly from solid tumors, have been reported, and more recently about ten whole cancer genomes have been reported.[56-67] (See Figure 4.)

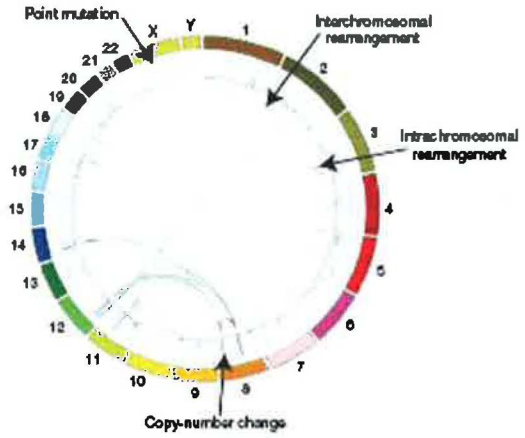

Figure 4. Circos diagram of a cancer genome. "Individual chromosomes are depicted on the outer circle followed by concentric tracks for point mutation, copy number and rearrangement data relative to mapping position in the genome. Arrows indicate examples of the various types of somatic mutation present in this cancer genome." From Stratton et al[52].

From studies thus far it appears that cancers—solid and hematologic—contain about 8-10 mutations that are driving the cancer—the so-called "driver mutations". Many more mutations are observed that are judged to be "passenger mutations"—random, inconsequential mutations that may have been present in the original pre-cancerous clone or may have been acquired by chance along the way as the cancer evolved.[52] Driver mutations mostly occur in well-defined cancer pathways but may occur in different components of a given pathway between different cases.[58] For example, two different cases of pancreatic cancer will have mutations in the TGF beta growth inhibitory pathway but one case will have

a mutation in a particular member of the pathway (e.g. SMAD4) while the other case may have a mutation in a different member of the pathway (e.g. BMPR2).

Certain well-known oncogenes and tumor suppressor genes have been observed to be mutated frequently whereas others have been observed less frequently, but often enough to deduce that they are important.[57] Some entirely new and clearly important cancer genes have been discovered by large-scale sequencing. For example, sequencing of glioblastomas revealed that more than 70% of cases had mutations of isocitrate dehydrogenase (IDH), a Krebs' cycle enzyme.[68] Subsequent studies in acute myelogenous leukemia likewise suggested that a high frequency of patients had mutated IDH-1 or 2 (the cytoplasmic or mitochondrial variants).[68] Mutated IDH converts isocitrate to 2-hydroxyglutarate instead of the normal metabolite, alpha-ketoglutarate.[69] 2-hydroxyglutarate appears to be an "oncometabolite" and the mechanism by which it contributes to cancer (again, apparently quite frequently) is under intense investigation.[70] Importantly, as mutant IDH is an enzyme it might be druggable, perhaps leading to a novel therapy for a great many patients.

Whole cancer genome sequencing is proceeding on a massive scale. Several large groups and consortia, in particular the International Cancer Genome Sequencing Project, aim to sequence at least 25,000 cancers—500 cancers from each of 50 different cancer types—over the next few years.[54] Each cancer will be fully analyzed in terms of DNA sequence, copy number alterations, and translocations; analyses of epigenetic modifications and RNA expression will be added soon.[71, 72]

Without question, large-scale sequencing of a large number of cancers will lead to important new insights into cancer, but a great deal of additional work will remain to be done. Most important will be analysis of the functional consequences of genomic alterations, in particular verifying the importance and mechanisms of presumed driver mutations.[52]

Functional cancer genomics

Functional analyses of genomic findings are ramping up at many centers and include high-throughput, massively-parallel gain-of-function assays and loss-of-function assays, compound library sensitivity assays, and systematic mouse modeling.[73-81] One particularly promising avenue of functional analysis involves screening for synthetic lethality.[82-84]

Synthetic lethal screens. Synthetic lethality is a concept originally described in yeast genetics: two genes are synthetic lethal to each other if mutation of one or the other is not lethal to the cell but mutation of both causes lethality. This principle has been adapted for study of cancer biology and therapeutics.[83] If a given gene is mutated in a cancer cell (but not a normal cell), then inhibition of a gene that is synthetic lethal to the mutated gene will, by definition, kill the cancer cell but not the normal cell. An example of successful application of the concept of synthetic lethality in clinical oncology involves the inhibition of the DNA repair enzyme, poly-adenosine diphosphate ribose polymerase (PARP) in patients with homozygous mutations of BRCA, which is also involved in DNA repair.[84-86] Cancer cells which lack BRCA can still repair DNA using PARP; such cells cannot repair DNA if PARP is inhibited and thus PARP inhibition is lethal to these cells. However, normal cells with intact BRCA can still repair DNA if PARP is inhibited. Thus PARP and BRCA are synthetic lethal to each other and PARP inhibition selectively kills cells with BRCA mutation. Clinically, PARP inhibitors have shown significant activity with minimal toxicity in breast and ovarian cancer patients with BRCA mutation.[87]

The concept of synthetic lethality holds great promise in cancer medicine and numerous groups have developed methods to screen for synthetic lethal interactions.[46, 88-90] For example, the oncogene RAS is mutated in a large percentage of cancer patients. Mutated RAS is locked in the on position and relentlessly signals the cell through the RAS-MAP kinase pathway to proliferate. It has been very difficult to develop a drug to inhibit RAS and investigators have begun to explore other ways to kill cells that are driven by RAS. One approach might be to take advantage of the concept of "non-oncogene" addiction discussed above.[50] Cells driven by RAS will be stressed and non-oncogenic pathways will be activated to relieve the stress. If these pathways or components of these pathways can be identified then their inhibition might kill RAS-driven cancer cells. Large-scale synthetic lethal screens using RNA interference (including genome-wide screens using high-throughput techniques) have been used to find genes in synthetic lethal relationship with mutant RAS.[88, 89] By inhibiting expression of up to all 20,000 genes, essentially one gene at a time, it is possible to identify genes which, when inhibited, cause death of mutant-RAS –driven cells but not normal cells. A variety of non-oncogenic stress relief pathways have been found to be in synthetic lethal relationship with mutant RAS, including pathways that brake apoptosis, limit mitotic stress, and limit proteotoxic stress. In particular two kinases from these stress-relief pathways were identified that are potentially druggable.[88, 89]

Summary: Large scale cancer genomics and functional genomics

It is clear that these very large studies of cancer genomics and functional genomics will lead to a deeper understanding of cancer biology and will suggest new mechanism-based cancer therapies. For example, one can imagine that genomic studies will identify mutant kinases—both previously identified and new ones—that are driving cancers in "oncogene addiction" mechanisms and can thus serve as very effective targets for kinase inhibitors. In addition, one can imagine that many additional examples of non-oncogene addiction will be uncovered by synthetic lethal screens, suggesting novel treatments directed to stress relief pathways. In the end, one imagines thousands of different cancers distilled by combined genomic and functional genomic analysis into dozens (?) of cancer subtypes, each with its own molecular pathogenesis and potential Achilles' heels.

Moving toward personalized cancer therapy

Occasional patients are already being treated in a more or less ad-hoc way with personalized cancer therapy. For example we are currently managing a patient with a CML-like illness whose disease is characterized by a t(8;22) rather that the t(9;22) characteristic of CML. Further study of his leukemia has shown that his translocation involves the FGFR1 gene at chromosome 8p11 rather that the ABL gene of CML.[91] FGFR1 is a tyrosine kinase and, like, ABL, is activated by its fusion with BCR.[92] Thus we surmised that his disease should respond to FGFR1 inhibition and treated him with a commercially-available kinase inhibitor which inhibits FGFR1 among other kinases; he has had rapid and complete normalization of his blood counts. This case further illustrates the proposition that cancer patients with kinase mutations have a reasonably good chance of responding to inhibition of the offending kinase.

Thus one could suggest that it might be worthwhile systematically evaluating cancer patients for kinase mutations, especially if good therapeutic options are not otherwise available. Detecting a kinase mutation might lead to treatment with a relevant kinase inhibitor on a clinical trial, on a single-patient IND, or off label if the drug is commercially available. Several groups—academic, industrial, and venture start-ups—have set up molecular screening assays along these lines as beginning forays into personalized cancer medicine;[93, 94] several dozen potential cancer genes are screened for mutations with these assays; genes include, in addition to kinases, other known cancer genes which are being targeted

with agents available commercially or in clinical trials. As new promising cancer gene targets are discovered, they can be quickly added to the assays.

Functional assays are also being explored as a way of phenotyping individual cancers and suggesting potential therapies. For example, one group evaluates the tyrosine kinome in primary cells from leukemia patients not only by mutation analysis but also by RNA interference aimed at systematically inhibiting expression of each tyrosine kinase.[95] In this way, tyrosine kinases driving the disease can be identified as rational targets even if the kinase is not mutated; for example, mutation of an upstream molecule in a particular signaling pathway may activate a (non-mutated) tyrosine kinase which is more amenable to drug therapy than the (mutated) upstream molecule.

Such individualized cancer phenotyping will evolve over the next few years. At $1,000 per genome it would be feasible to analyze comprehensively the genomic characteristics of an individual's cancer. At the same time, one hopes, the large-scale genomic and functional studies currently underway will have defined cancer genome-types that are associated with certain functional characteristics and responses to certain targeted therapies. Comparing the individual patient's cancer genome to such a databank of cancer-genome types might then allow a choice of therapy that is best suited to the individual's cancer. (See Figure 5.)

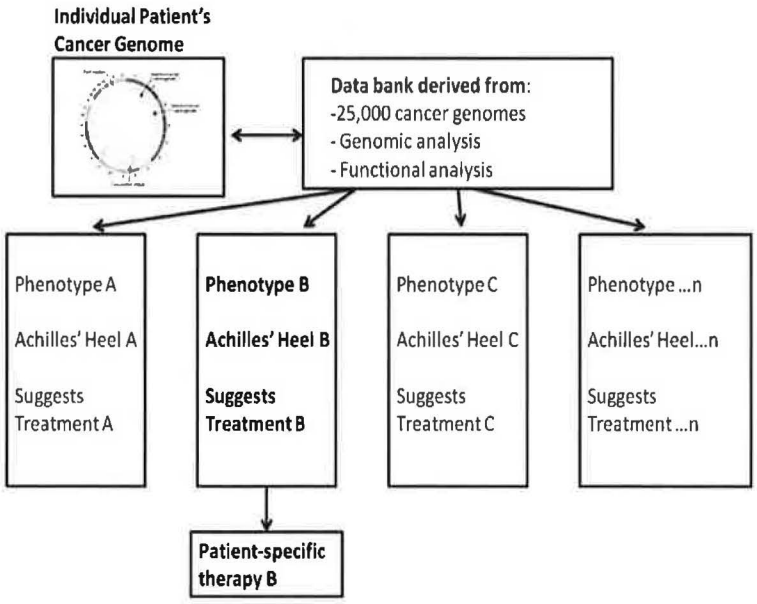

Figure 5. Future individualized cancer therapy? One can envision that current efforts in cancer investigation, especially large-scale efforts in cancer genomics and functional genomics, will lead to definition of many different molecular subtypes of cancer, each with its own particular Achilles' heel, suggesting its own particular targeted therapy. In-depth genetic analysis of an individual's tumor (made much less expensive as technology advances) will allow comparison of the patient's tumor with the data bank, allowing the patient's physician to choose the best therapy for the individual's cancer. In this example, a patient's cancer genome matches with a particular phenotype "B" suggesting particular therapy directed to that phenotype.

Bibliography

1. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. Blood 2008;112:4808-17.
2. Druker BJ. Perspectives on the development of imatinib and the future of cancer research. Nat Med 2009;15:1149-52.
3. Sawyers CL. Shifting paradigms: the seeds of oncogene addiction. Nat Med 2009;15:1158-61.
4. Nowell PC, Hungerford, D.A. A minute chromosome in human chronic granulocytic leukemia. Science 1960;132.
5. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-3.
6. Collins SJ, Kubonishi I, Miyoshi I, Groudine MT. Altered transcription of the c-abl oncogene in K-562 and other chronic myelogenous leukemia cells. Science 1984;225:72-4.
7. Gale RP, Canaani E. An 8-kilobase abl RNA transcript in chronic myelogenous leukemia. Proc Natl Acad Sci U S A 1984;81:5648-52.
8. Lugo TG, Pendergast AM, Muller AJ, Witte ON. Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. Science 1990;247:1079-82.
9. Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science 1990;247:824-30.
10. Heisterkamp N, Jenster G, ten Hoeve J, Zovich D, Pattengale PK, Groffen J. Acute leukaemia in bcr/abl transgenic mice. Nature 1990;344:251-3.
11. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2:561-6.
12. Druker BJ, Lydon NB. Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia. J Clin Invest 2000;105:3-7.
13. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031-7.
14. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
15. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
16. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408-17.
17. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med 2002;347:481-7.
18. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 2003;348:1201-14.
19. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
20. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127-34.

21. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24:4340-6.
22. Handolias D, Hamilton AL, Salemi R, et al. Clinical responses observed with imatinib or sorafenib in melanoma patients expressing mutations in KIT. Br J Cancer;102:1219-23.
23. Rubin BP, Schuetze SM, Eary JF, et al. Molecular targeting of platelet-derived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. J Clin Oncol 2002;20:3586-91.
24. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2005;352:786-92.
25. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med;362:2380-8.
26. Garber K. ALK, lung cancer, and personalized therapy: portent of the future? J Natl Cancer Inst;102:672-5.
27. Lacouture ME, McArthur, G.A., Chapman, P.B., Ribas, A., Flaherty, K.T., Lee, R.J., Nolop, K.B., Kim, K.B., Duvic, M., Sosman, J.A. PLX4032 (RG7204), a selective mutant RAF inhibitor: Clinical and histologic characteristics of therapy-associated cutaneous neoplasms in a phase I trial. Journal of Clinical Oncology 2010 (suppl; abstr 8592);28.
28. Brugarolas J. Renal-cell carcinoma--molecular pathways and therapies. N Engl J Med 2007;356:185-7.
29. Rudin CM, Hann CL, Laterra J, et al. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med 2009;361:1173-8.
30. Sawyers CL. Cancer treatment in the STI571 era: what will change? J Clin Oncol 2001;19:13S-6S.
31. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001;293:876-80.
32. Shah NP, Nicoll JM, Nagar B, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell 2002;2:117-25.
33. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005;7:129-41.
34. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004;305:399-401.
35. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med 2006;354:2531-41.
36. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 2006;354:2542-51.
37. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med;362:2260-70.
38. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med;362:2251-9.
39. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell 2009;16:401-12.
40. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039-43.
41. Massarelli E, Varella-Garcia M, Tang X, et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. Clin Cancer Res 2007;13:2890-6.

42. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764-74.
43. Weinstein IB. Cancer. Addiction to oncogenes--the Achilles heal of cancer. Science 2002;297:63-4.
44. Weinstein IB, Joe AK. Mechanisms of disease: Oncogene addiction--a rationale for molecular targeting in cancer therapy. Nat Clin Pract Oncol 2006;3:448-57.
45. Sharma SV, Settleman J. Oncogene addiction: setting the stage for molecularly targeted cancer therapy. Genes Dev 2007;21:3214-31.
46. Sawyers CL. Finding and drugging the vulnerabilities of RAS-dependent cancers. Cell 2009;137:796-8.
47. Soda M, Takada S, Takeuchi K, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A 2008;105:19893-7.
48. Bang Y, Kwak, E.L., Shaw, A.T., Camidge, D.R., Iafrate, A.J., Maki, R.G., Solomon, B.J., Ou, S.I., Salgia, R., Clark, J.W. Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC). Journal of Clinical Oncology 2010 (suppl; abstract 3);28.
49. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.
50. Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 2009;136:823-37.
51. Shendure J, Ji H. Next-generation DNA sequencing. Nat Biotechnol 2008;26:1135-45.
52. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature 2009;458:719-24.
53. Downing JR. Cancer genomes--continuing progress. N Engl J Med 2009;361:1111-2.
54. International network of cancer genome projects. Nature;464:993-8.
55. Ledford H. Big science: The cancer genome challenge. Nature;464:972-4.
56. Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. Nature 2007;446:153-8.
57. Wood LD, Parsons DW, Jones S, et al. The genomic landscapes of human breast and colorectal cancers. Science 2007;318:1108-13.
58. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 2008;321:1801-6.
59. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science 2008;321:1807-12.
60. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 2008;455:1061-8.
61. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature 2008;455:1069-75.
62. Maher CA, Kumar-Sinha C, Cao X, et al. Transcriptome sequencing to detect gene fusions in cancer. Nature 2009;458:97-101.
63. Ley TJ, Mardis ER, Ding L, et al. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. Nature 2008;456:66-72.
64. Mardis ER, Ph.D., Ding, L., Ph.D., Dooling, D.J., Ph.D., et al. Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome. New England Journal of Medicine 2009;361.
65. Ding L, Ellis MJ, Li S, et al. Genome remodelling in a basal-like breast cancer metastasis and xenograft. Nature;464:999-1005.
66. Pleasance ED, Stephens PJ, O'Meara S, et al. A small-cell lung cancer genome with complex signatures of tobacco exposure. Nature;463:184-90.
67. Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. Nature;463:191-6.

68. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765-73.
69. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462:739-44.
70. Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell;17:225-34.
71. Katsnelson A. Genomics goes beyond DNA sequence. Nature;465:145.
72. Payton JE, Grieselhuber NR, Chang LW, et al. High throughput digital quantification of mRNA abundance in primary human acute myeloid leukemia samples. J Clin Invest 2009;119:1714-26.
73. Chin L, Gray JW. Translating insights from the cancer genome into clinical practice. Nature 2008;452:553-63.
74. Hahn WC, Dunn IF, Kim SY, et al. Integrative genomic approaches to understanding cancer. Biochim Biophys Acta 2009;1790:478-84.
75. Moody SE, Boehm JS, Barbie DA, Hahn WC. Functional genomics and cancer drug target discovery. Curr Opin Mol Ther;12:284-93.
76. Lamb J. The Connectivity Map: a new tool for biomedical research. Nat Rev Cancer 2007;7:54-60.
77. Zender L, Lowe SW. Integrative oncogenomic approaches for accelerated cancer-gene discovery. Curr Opin Oncol 2008;20:72-6.
78. Ngo VN, Davis RE, Lamy L, et al. A loss-of-function RNA interference screen for molecular targets in cancer. Nature 2006;441:106-10.
79. Bric A, Miething C, Bialucha CU, et al. Functional identification of tumor-suppressor genes through an in vivo RNA interference screen in a mouse lymphoma model. Cancer Cell 2009;16:324-35.
80. Hahn CK, Berchuck JE, Ross KN, et al. Proteomic and genetic approaches identify Syk as an AML target. Cancer Cell 2009;16:281-94.
81. Boehm JS, Zhao JJ, Yao J, et al. Integrative genomic approaches identify IKBKE as a breast cancer oncogene. Cell 2007;129:1065-79.
82. Hartwell LH, Szankasi P, Roberts CJ, Murray AW, Friend SH. Integrating genetic approaches into the discovery of anticancer drugs. Science 1997;278:1064-8.
83. Kaelin WG, Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005;5:689-98.
84. Iglehart JD, Silver DP. Synthetic lethality--a new direction in cancer-drug development. N Engl J Med 2009;361:189-91.
85. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913-7.
86. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-21.
87. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123-34.
88. Scholl C, Frohling S, Dunn IF, et al. Synthetic lethal interaction between oncogenic KRAS dependency and STK33 suppression in human cancer cells. Cell 2009;137:821-34.
89. Luo J, Emanuele MJ, Li D, et al. A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. Cell 2009;137:835-48.
90. Li B, Gordon GM, Du CH, Xu J, Du W. Specific killing of Rb mutant cancer cells by inactivating TSC2. Cancer Cell;17:469-80.

91. Roumiantsev S, Krause DS, Neumann CA, et al. Distinct stem cell myeloproliferative/T lymphoma syndromes induced by ZNF198-FGFR1 and BCR-FGFR1 fusion genes from 8p11 translocations. Cancer Cell 2004;5:287-98.
92. Demiroglu A, Steer EJ, Heath C, et al. The t(8;22) in chronic myeloid leukemia fuses BCR to FGFR1: transforming activity and specific inhibition of FGFR1 fusion proteins. Blood 2001;98:3778-83.
93. MacConaill LE, Campbell CD, Kehoe SM, et al. Profiling critical cancer gene mutations in clinical tumor samples. PLoS One 2009;4:e7887.
94. Dias-Santagata D, Akhavanfard S, David SS, et al. Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine. EMBO Mol Med;2:146-58.
95. Tyner JW, Deininger MW, Loriaux MM, et al. RNAi screen for rapid therapeutic target identification in leukemia patients. Proc Natl Acad Sci U S A 2009;106:8695-700.