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Genomics and the History of Precision Oncology

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Introduction

The use of molecular characterization of an individual patient's tumor in routine oncologic practice began only 20 years ago. In that short time, it has enhanced the specificity and efficacy of cancer therapy.[1] Molecular selection criteria, both genomic and protein-based, have now been used to support the first histology-independent FDA approvals of anticancer agents.[2–7] This paradigmatic shift in oncologic practice has been accompanied by discontinuation of nonspecific cytotoxic anticancer agent development.[8]

The use of precision medicine principles in cancer therapy[9] depends upon measurement of biologic characteristics in a tumor that suggest the potential value of a specific molecularly-targeted treatment. This shift away from nonspecific mechanisms of tumor cell killing has occurred because of improvements in biomarker discovery and validation, and the availability of instrumentation capable of previously-inconceivable levels of diagnostic throughput. Precision oncology has also advanced because of innovations in clinical trial design.[10–12]

While precision oncology has changed both the landscape of treatment options for patients with cancer and the fabric of clinical and translational research, cytotoxic agents remain the backbone of therapy for the majority of cancers, and targeted agents rarely provide durable responses. Moreover, innovative clinical trial designs to evaluate novel targets remain in the early stages of development, engendering numerous operational challenges[11] and modest clinical benefit to date.[12,13] This paper examines the history of precision oncology, including

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milestone developments in therapeutics, translational science, and clinical trial design over the last 20 years.

Several case studies illustrate the benefits and limitations of the “one gene, one drug, one disease” paradigm. While clinical responses may be common and dramatic, they are rarely lasting. Moreover, this model does not apply to the majority of neoplastic diseases. These case studies also illustrate the ways in which targeted therapies have unexpected effects, and frequently transform the natural history of disease. The identification and targeting of molecular aberrations requires sufficiently efficient and accurate technologies, many of which have become more sensitive and comprehensive over the last ten years. Finally, master protocols have been developed to provide a coordinated framework for evaluation of multiple therapeutic approaches in one or more molecularly-defined tumor types, with the goal of improving the efficiency of the cancer clinical trials process. Such studies can be designed to provide sufficient information to support an application for new drug approval by the FDA, or, more frequently, to identify biomarker-selected drugs that can be more effectively predicted to be successful in the setting of a subsequent, definitive randomized study.

The “Magic Bullet” Paradigm in Precision Oncology, 2000-2010

Most retellings of the beginnings of precision oncology focus on the development of a series of drugs, each of which was intended to treat a single tumor type with a single molecular aberration. Each were heralded by physicians and by the lay public as near-miracles of science. While these developments were critical to the development of precision oncology, they were often unpredictable and uniformly never sudden. We discuss them here not as a means of uncritically listing a series of successes, but as a window into the promises and limitations of precision oncology more broadly.

In the late 1980s, Dennis Slamon and his colleagues at the University of California, Los Angeles demonstrated that one quarter of breast cancers could be characterized by amplification or overexpression of human epidermal growth factor-2 (HER2), a tyrosine kinase receptor which activates multiple signal transduction pathways to regulate cell growth.[14,15] Moreover, patients harboring such tumors had a poorer prognosis than those who did not.[14,15] Simultaneously, multiple investigators determined that HER2 overexpression induced tumorigenesis, making the protein a desirable therapeutic target.[16–18] A humanized HER2 antibody, engineered at Genentech in 1992,[19] was quickly introduced into multiple phase I and phase II clinical trials, the latter of which focused on enrolling only patients with increased HER2 expression by immunohistochemistry.[20] However, the definition of increased HER2 expression was inconsistent; one trial enrolled patients with >25% membrane staining, a second enrolled those whose tumors had “light to strong” IHC staining, and a third used the now-standard 2+/3+ nomenclature to refer to weak or complete tumor cell membrane staining in >10% of cells.[20]

Despite modest activity in a placebo-controlled phase 3 study (using the latter definition of HER2 positivity) trastuzumab (Herceptin®) was approved by the FDA in 1998.[21] Trastuzumab was hailed by the popular press as “ushering in a new era of cancer treatment

that attempts to target the very flawed genetic mechanisms that cause the disease."[22] The *Washington Post* described how one patient's impending death was dramatically reversed by Herceptin, which shrunk her liver metastases "to mere dots" and showed "how 20 years of basic cancer research are beginning to pay off for patients."[23] Yet the popular press also reminded readers that while trastuzumab appeared to be a wonder drug, it was not a cure.[22]

While trastuzumab did not dramatically improve outcomes as a single agent, it has become a critical, life-prolonging adjunct to chemotherapy in the metastatic,[24] neoadjuvant,[25] and adjuvant[26] settings. The identification of HER2 as a valuable therapeutic target spurred additional work resulting in the development of trastuzumab emtansine, a novel antibody-drug conjugate targeting HER2,[27] and pertuzumab, a monoclonal antibody binding a different epitope of HER2.[28] Perhaps most intriguingly, trastuzumab has changed the natural history of HER2-positive breast cancer. Whereas Slamon and colleagues initially identified HER2 overexpression as a poor prognostic marker, patients who are treated with HER2-directed therapies may no longer be at a survival disadvantage. Now, HER2 overexpression has become a predictive biomarker, indicative of a subset of patients likely to respond to HER2-directed therapy.

Three years after trastuzumab was approved by the FDA, another landmark drug was introduced: imatinib for the treatment of chronic myeloid leukemia (CML). The press similarly described the drug as a 'magic bullet', proclaiming that "the dream of a pill that can treat cancer with almost no side effects became a reality" and referring to targeted drugs as "smart bombs" that did not induce the collateral damage seen with cytotoxic chemotherapy.[29] Patients who had participated in clinical trials spread the news in online chat rooms before trial results had even been published.[30] This enthusiasm was understandable. The phase I study of imatinib, a small molecule inhibitor of the BCR-ABL tyrosine kinase, had identified no maximally tolerated dose (MTD), and 53 of 54 patients achieved a complete hematologic response;[31] based on these results as well as those of three phase II studies, imatinib was granted accelerated approval by the FDA in 2001. The 72 days required for FDA review was the fastest agency approval in the history of anticancer agent development.[32]

Despite the perception of a sudden breakthrough, the story of imatinib illustrates the lengthy research timeframe involved in identifying a molecular target and crafting a drug to engage it. While CML had been described as a disease entity in Germany and Scotland in 1845,[33] the majority of work done to identify the *BCR-ABL* fusion as the causative aberration in CML was performed between 1960 and 1990.[34] In 1960, Peter Nowell and David Hungerford described a "minute chromosome" present in the peripheral blood of 7 patients with what was then known as chronic granulocytic leukemia.[35] In the early 1970s, Caspersson *et al.* and O'Riordan *et al.* identified the abnormally small chromosome as number 22 using novel quinacrine mustard fluorescence techniques,[36,37] and Janet Rowley described its balanced translocation with the long arm of chromosome 9.[38] In the 1970s and 1980s, work with retroviruses was critical to the identification of multiple putative oncogenes; one of these was c-abl, the human cellular homologue of the Abelson murine leukemia virus, which was translocated from 9q to the breakpoint cluster region (BCR) of 22q- in patients with CML.[34] In the mid-1980s, Davis *et al.*[39] and Ben Neriah *et al.*[40]

discovered that the resulting chimeric mRNA transcript was itself a tyrosine kinase, and murine work published by Daley *et al.*[41] and Heisterkamp *et al.*[42] in 1990 identified the *BCR-ABL* translocation as necessary and sufficient to induce CML.

Thus, by 1990, the *BCR-ABL* oncogene had been established as universally causative in CML; hence, the resulting tyrosine kinase was an attractive therapeutic target. Yet, general skepticism remained regarding the feasibility of inhibiting tyrosine kinases, with regard to the specificity, toxicity, and efficacy of doing so in heterogeneous cancers.[34] High throughput screens of chemical libraries identified the 2-phenylaminopyrimidines as promising inhibitors of BCR-ABL in the early 1990s, and by 1996 Brian Druker and colleagues had published in vitro and in vivo data demonstrating that one such agent - STI571, or imatinib - potently inhibited the BCR-ABL kinase and killed CML cells.[34] Five years later, STI571 had been approved by the FDA. While the development of imatinib had itself been brisk, the identification of BCR-ABL as a therapeutic target was an effort spanning more than three decades, an element of the imatinib story that is easy to overlook.[34]

The history of imatinib has been unusual in other ways, one of which is the durability of the responses produced by the drug. Resistance to therapy does develop and has spurred the introduction of second- and third-line agents. Still, patients with CML who are treated with BCR-ABL tyrosine kinase inhibitors can expect to live near-normal lifespans.[43] The introduction of these drugs, five of which are now FDA-approved, has altered the natural history of CML to the extent that the field is now exploring the potential of therapy discontinuation.[44]

While the importance of identifying a molecular target prior to developing a relevant therapy may appear obvious, in many prominent cases a target has been identified and refined during the course of drug development. For the epidermal growth factor receptor (EGFR), similar developments occurred in the development of EGFR-targeted agents in both lung and colorectal cancer. Initial work on EGFR, which was known to play an important role in modulating proliferative cell signaling, was based on its overexpression in multiple tumor types, including non-small cell lung cancer (NSCLC).[45] However, phase I trials of the EGFR tyrosine kinase inhibitor (TKI) gefitinib produced few clinical responses.[46–48] Two phase II studies of gefitinib in NSCLC were slightly more promising, with response rates of 9-19%.[49,50] However, a retrospective analysis of tumor specimens from these two trials found no relationship between EGFR expression (as determined by immunohistochemistry) and clinical response.[51] Based on the results of these trials, gefitinib was granted accelerated approval by the FDA in 2003.[52] However, review by the FDA also noted the negative, unpublished results of two phase III studies that failed to show clinical benefit of gefitinib in combination with chemotherapy in patients with advanced NSCLC.[52–54]

Several groups of investigators sought to characterize responders further by analyzing tumor specimens from patients entered on phase II studies as well as those treated during expanded access programs. They identified several subgroups of patients with higher response rates: Japanese patients (compared to non-Japanese patients),[50] women,[49,55] never smokers, [56,57] and patients with adenocarcinoma histologies.[55–57] Simultaneously, several groups of

investigators sequenced the *EGFR* gene in lung cancer specimens from patients who had been treated with gefitinib on clinical trials. They identified mutations in the *EGFR* tyrosine kinase domain in almost all tumors from patients who had responded, which were not present in nonresponders, establishing mutated *EGFR* - not overexpressed EGFR - as the molecular target for gefitinib.[57–59]

While EGFR-targeted therapies have become a success story in lung cancer, their evolving history is more representative of targeted therapies than that of imatinib, in that resistance to treatment is inevitable. Over the last ten years, studies have focused on the development of second and third generation EGFR inhibitors which specifically target mechanisms of resistance to first generation inhibitors such as the T790M mutation in exon 21 of *EGFR*.[60–64] Currently, the effort to characterize mechanisms of resistance to third generation inhibitors is ongoing with the aim of developing therapies that target these alterations or prevent their emergence.[65] Patients starting first-line osimertinib, a third-generation EGFR TKI, may respond for up to 22 months.[66] However, upon progression they are faced with the options of cytotoxic chemotherapy and immune checkpoint inhibitors, the latter of which have reduced efficacy in *EGFR* mutant NSCLC.[67–69]

While resistance to targeted therapies may be due to so-called “on-target” molecular alterations, such as additional EGFR mutations, it often results from compensatory mechanisms, especially when a target is one member of a signaling pathway. This type of resistance proved an early stumbling block in the development of cetuximab, a competitive inhibitor of the extracellular domain of EGFR. Similar to gefinitib, cetuximab was studied in colon cancer based on the premise that EGFR was overexpressed in the majority of colorectal cancers, as well as promising preclinical data in colorectal cancer models.[70] The first phase III study of cetuximab, which studied it alone and in combination with irinotecan, utilized this rationale and required evidence of immunohistochemical expression of EGFR to enroll.[71] Seeking to better characterize cetuximab responders and nonresponders only a few years later, two French groups screened the tumors of clinical trial participants for mutations in *KRAS,* which was involved in EGFR downstream signaling. Not only did mutated *KRAS* predict for resistance to cetuximab, zero patients who responded to cetuximab had tumors with a *KRAS* mutation,[72–74] a finding confirmed in a larger retrospective study performed by an group from Australia and Canada.[75] Extended RAS testing is now recommended to demonstrate that a tumor is truly wildtype prior to treating a patient with cetuximab in order to predict primary resistance.[76]

It is now clear that downstream resistance accounts for a substantial proportion of acquired resistance to targeted therapies, a lesson learned in the development of BRAF inhibitors for patients with metastatic melanoma. Although the BRAF inhibitors vemurafenib and dabrafenib both improved progression free survival (PFS) in patients with untreated $BRAF^{V600E}$ mutated advanced melanoma compared to chemotherapy in two phase 3 studies, responses were short-lived, with a median PFS of just over 5 months for both drugs.[77,78] Additional pharmacodynamic studies performed on patient tumor specimens from these and other trials found that acquired resistance to BRAF inhibitors was frequently associated with up-regulation of signaling in the downstream MAPK pathway.[79–81] As a result, combinations of BRAF and MEK inhibitors were studied in multiple large phase 3 trials and

were found to improve both PFS and overall survival (OS) compared to the use of BRAF inhibitors alone;[82–85] these combinations now comprise the standard of care therapy for patients with *BRAF*-mutated melanoma. These cases clearly demonstrate both the promise and the limitations of the "magic bullet" model of precision oncology, and have more recently led to efforts to identify promising combinations of targeted therapies.[86]

The Promise and Limitations of "Tumor Profiling"

To detect molecular alterations that can be targeted, reliable, and efficient technology is required. The early work on trastuzumab was limited to immunohistochemical staining, whereas fluorescent in situ hybridization (FISH) is now a routine component of HER2 testing for tumor samples that demonstrate equivocal (2+) IHC staining; this combined approach has changed the definition of "HER2 positive" tumors.[87] In the 2000s and early 2010s, molecular alterations could be detected using either immunohistochemical evaluations of protein expression or PCR-based evaluations of mutational "hotspots," which could miss uncommon alterations. In 2019, a patient's tumor may undergo high throughput massively parallel DNA and RNA sequencing (often referred to as next generation sequencing, or NGS) over a matter of two or three weeks to identify potential therapeutic targets.[88,89] These analyses, which may examine several hundred genes or even comprise whole exome or whole genome sequencing, are regularly performed on the tumors of patients treated at tertiary cancer centers and in the community. The latter was made more accessible due to the recent announcement from the Centers for Medicare and Medicaid Services that Medicare will cover next-generation tumor profiling for patients with advanced cancer.[90]

Genomic and proteomic analyses now have the capacity to detect a variety of aberrations beyond point mutations, including insertion and deletion mutations (indels), copy number alterations, chromosomal rearrangements and gene fusions, DNA methylation patterns, transcript levels, and levels of protein expression.[89] Analysis of a patient's tumor is often paired with evaluation of matched normal cells, most often from a buccal swab or peripheral blood, to distinguish somatic aberrations found only in a tumor from germline abnormalities.[91] More recently, examinations of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) have been investigated as a means of dynamically and non-invasively assessing tumor burden as well as evaluating the changing genomic landscape of a tumor throughout a patient's treatment, with an eye to better understanding mechanisms of drug resistance.[92–94]

These advances have enabled the detection of low frequency alterations and have fostered the development of many new targeted therapies. However, complex challenges remain. Tumor profiling reports may list the molecular aberrations identified in a patient's tumor, but only a minority at best may be "targetable" with approved or experimental agents. Such reports may neglect to describe the allelic frequency of such aberrations or distinguish between driver mutations - those which induce tumorigenesis - and passenger mutations, which are not themselves pathogenic.[89,95,96] Moreover, tumor heterogeneity may limit the applicability of these findings.[97,98] As in the case of BRAF inhibition in metastatic melanoma, efforts to target tumor molecular aberrations have been hampered by the almost

universal development of on- or off-target resistance.[95] This has led to a recent focus on evaluating combinations of agents to delay the emergence of such resistance, for example by inhibiting a signaling pathway at more than one level.[82]

Novel Methods for Evaluating Targeted Therapies Using “Master Protocols”

While technologies like NGS have facilitated the detection of targetable molecular alterations, novel clinical trial designs - many of which are still in the early phases of development - have become critical to testing targeted agents. In the early 2010s, investigations of “exceptional responders” to targeted therapies were common.[99] In other instances, a patient’s response to a therapy that had been “matched” to a specific tumor alteration was compared to that patient’s response to a previous standard of care agent.[100] Many academic cancer centers developed molecular tumor boards in which a group of experts reviewed the molecular alterations in a patient’s tumor and recommended a matched FDA-approved therapy, an off-label standard therapy, or a clinical trial.[6,88] Such tumor boards are increasingly common in both the academic and community settings.

In efforts to evaluate the concept of precision oncology more broadly, several studies have attempted to assess whether “matched” therapy provides more clinical benefit than standard-of-care therapy. Multiple single-institution, observational studies have shown that it is feasible to match patients to both standard and investigational therapies, and that doing so may improve clinical outcomes. However, only a minority of patients could be assigned a matched therapy, and none of the trials were randomized.[101–105] SHIVA, the first randomized trial of precision oncology as an approach, randomized patients with multiple tumor histologies to receive either one of 11 molecularly targeted agents based on the presence or absence of aberrations in the hormone receptor, PI3K/AKT/mTOR, and RAF/MEK pathways or physician’s choice of standard therapy.[106] While no difference in PFS was observed, the study used only a limited range of targeted therapies and did not account for differing levels of evidence regarding the relevance of each patient’s pathway aberration.

Master protocols, which permit the testing of patients with multiple tumor histologies and/or tumor molecular aberrations, are both powerful and complex frameworks used to test a variety of hypotheses simultaneously. By grouping tumors by molecular alteration, they move oncology toward a less histology-based and more molecularly-based diagnostic and clinical framework.[13] Classically, master protocols have been described as falling into one of two categories: basket studies, which seek to treat patients across multiple histologies whose tumors share the same alteration, and umbrella studies, which assign patients with one tumor type to one of several therapies based on tumor profiling data.[13] While such studies may be used for FDA registration of a new agent, they are more often signal-finding trials intended to identify potentially interesting therapies worthy of further study in certain patient populations.

Basket studies play a critical role in promoting a histology-agnostic approach to treating cancer. Two phase II studies of pembrolizumab, an anti-programmed death 1 (PD-1) antibody, in patients with mismatch repair (MMR)-deficient tumors demonstrated its

efficacy across all MMR-deficient solid tumors[107,108], and led to the first tissue agnostic approval of a drug by the FDA in 2017.[109] The following year, a phase I/II basket study of larotrectinib in tumors with *TRK*-fusions led to the second such FDA approval in 2018.[110] Basket trials are not always unmitigated successes, however. A study of vemurafenib in patients with advanced $BRAF^{V600}$ mutated malignancies (exclusive of melanoma) found an overall response rate (ORR) of 42% of patients with NSCLC and 29% of those with anaplastic thyroid cancer,[111] leading to FDA approvals for dabrafenib in patients with V600E-mutated NSCLC[112] and anaplastic thyroid cancer.[113] However, few or no responses were observed in multiple other tumor types examined. Currently, multiple clinical trials are ongoing to evaluate the use of inhibitors of DNA damage repair (DDR) in tumors with a variety of DDR-deficient mutations; preliminary results are encouraging[114] but still evolving.[115]

Umbrella trials have, to date, primarily served as exploratory signal-finding studies. They often operate using adaptive designs, wherein new arms may be added based on new evidence or removed based on lack of response, and patients may be assigned to a therapy based on an algorithm that utilizes evolving data to account for that patient's likelihood of response.[11] For example, the BATTLE studies assigned patients with advanced NSCLC to treatment arms based on molecular profiling of their tumors using real-time analyses of on-trial biopsies.[116,117]

The terms "basket trial" and "umbrella trial" are useful heuristics but may not adequately describe all large platform precision oncology trials.[118] A basket trial looking at patients whose tumors are DDR-deficient, for example, examines a group of functionally similar molecular alterations. The ongoing NCI-MATCH (Molecular Analysis for Therapy Choice) study uses on-study biopsies to assign patients with any histology to a broad range of therapies based on their tumor molecular alterations.[119] While neither is a strict umbrella or basket trial, these hybrid platform studies enable the evaluation of multiple histologies and multiple mutations or other alterations.[12]

Master protocols present numerous challenges. They are time-consuming, require significant coordination among multiple stakeholders, and can be costly.[13] Due to their complexity, master protocols provide a difficult format for sponsors hoping to achieve registration and create significant work for regulatory officials and institutional review boards faced with numerous amendments.[11] They are rarely randomized, making it difficult to draw conclusions about the efficacy of an agent.[118] Varying statistical designs may limit the ability of investigators to draw definitive conclusions. For example, some basket studies are designed as a series of Simon two-stage studies, treating each arm as a separate trial for statistical purposes and serving as a signal-finding study, whereas others allow aggregation of data from similar arms, which permits investigators to deem a therapy effective earlier.[120]

Despite these challenges, master protocols offer many opportunities for both patients and investigators. They enable patients with rare cancers to participate more readily in clinical trials and may lead to new therapeutic options. They efficiently group patients with multiple tumor types, are adaptable, and enable large collaborations.[11,13] They also can provide access to laboratories performing validated assessments of specific, treatment-defining

molecular alterations in patients' tumors. Once established, the infrastructure for these trials can speed the screening of new therapeutic agents across a wide range of both common and understudied malignancies. However, platform trials are still in a relatively early stage of development.

Summary

In conclusion, rapid improvements in a variety of molecular characterization technologies over the past two decades have directly supported the development of new systemic cancer therapies that can be selected to target specific pharmacological vulnerabilities in select patient populations across a wide range of human cancers. Molecular matching of drugs to specific targets for individual patients has substantively improved treatment for many hematological malignancies and solid tumors. Although this approach has become widespread only over the past 5-10 years, it has provided clinical benefits for many patients whose malignancies heretofore lacked effective therapy. Furthermore, in light of continuing improvements in our understanding of tumor biology and the tumor microenvironment, as well as remarkably efficient chemical biology and immunologic approaches now available for the development of therapeutics, further improvements in our ability to optimize cancer treatment based on the characteristics of an individual patient's tumor—the definition of precision oncology—are highly likely.

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Key points:

- The use of molecular tumor characteristics to select systemic therapy for individual patients has grown dramatically over the past 20 years
- The identification of tumoral DNA abnormalities using rapid gene sequencing techniques has underpinned the discovery of treatments for certain patients independent of disease histology
- Clinical trial designs using the ‘Master Protocol’ concept have facilitated the simultaneous evaluation of multiple new therapies based on matching drugs to specific genomic abnormalities

Synopsis

Progress toward the implementation of a molecular characterization paradigm in cancer drug development over the past 20 years, reviewed in this paper, has markedly enhanced our capability to select patients who are more likely to benefit from cancer therapy. Dramatic improvements in genomic and related diagnostic testing platforms have simultaneously permitted evaluation of the efficacy of treatment assignment based on pre-defined biologic features of an individual patient's tumor or germline using master protocols that may include many malignancies as well as their molecularly-characterized subsets. With this approach, a wide range of new targeted and immunologic treatment approaches have been defined for groups of patients who, heretofore, lacked effective therapeutic options.