Key drivers of biomedical innovation in cancer drug discovery

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Discovery and translational research has led to the identification of a series of "cancer drivers"—genes that, when mutated or otherwise misregulated, can drive malignancy. An increasing number of drugs that directly target such drivers have demonstrated activity in clinical trials and are shaping a new landscape for molecularly targeted cancer therapies. Such therapies rely on molecular and genetic diagnostic tests to detect the presence of a biomarker that predicts drug discovery and development. In 2002, activating mutations in the gene encoding the serine/threonine kinase BRAF were identified by the Cancer Genome Project (Sanger Centre, UK) in a subset of human cancers, including about 50% of malignant melanomas (Davies et al, 2002). Less than 10 years later, the small-molecule kinase inhibitors vemurafenib and dabrafenib were approved for use in BRAF mutation-positive melanomas, as the front-runners in a competition between numerous companies engaged in cancer drug discovery (Bollag et al, 2012; Hauschild et al, 2012). As these compounds were made available to academic investigators (see Box 1), a broad range of studies emerged that investigated the mechanism of BRAF inhibition in BRAF-mutant tumors. Indeed, new insights, including on the activation of downstream pathway components such as MEK, have informed a recently approved targeted BRAF/MEK inhibitor combination of dabrafenib/trametinib (Flaherty et al, 2012).

In 2004, two Boston-based academic groups discovered EGFR mutations in NSCLC, one through a systematic kinome-directed sequencing approach (Paez et al, 2004), and the second thanks to a hypothesis-driven EGFR sequencing effort (Lynch et al, 2004). Both groups were able to link the presence of EGFR mutations with an outstanding sensitivity of mutation carriers to EGFR tyrosine kinase inhibitors (TKIs). This provided the basis for successful biomarker-guided clinical development of the two selective EGFR TKIs gefitinib and erlotinib, as well as the irreversible ErbB family blocker afatinib (Tartarone et al, 2014). About 60% of EGFR TKI-treated patients become resistant by developing the EGFR T790M mutation, and based on early clinical trials appear to respond well to next-generation mutant-selective/wild-type-sparing EGFR inhibitors such as AZD9291 and CO-1686 (Jänne et al, 2014; Sequist et al, 2014). Using a functional genomics approach, a Japanese team in 2007 discovered a chromosomal translocation resulting in an aberrant fusion gene that encodes a constitutively

Definition and translation of new therapeutic concepts

As exemplars of biomedical discoveries that have transformed the cancer treatment landscape, we will discuss recent therapeutic advances in malignant melanoma, non-small-cell lung cancer (NSCLC), acute myeloid leukemia (AML), and certain gynecological cancers.

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Box 1: Sharing of lead compounds with academia

Providing open access to “probe compounds” with attractive features such as potency, selectivity, cellular permeability, and ideally also suitable physicochemical properties to enable in vivo studies is an increasingly attractive concept for the pharmaceutical industry. Such probes are valued reagents in both fundamental and applied biological research and are key tools in drug discovery that allow preclinical target validation in both academic and industrial laboratories. Early sharing of lead compounds with academia may help the industry to prioritize between different therapeutic concepts, explore new disease links including patient selection strategies, inform effective combinatorial approaches, and gain insights into potential resistance mechanisms—highly valuable information that would fuel further translational research. Often, companies will not immediately publish the clinical candidate, but rather describe a closely related compound with very comparable features. Thus, sensitive structural data remain undisclosed, helping to mitigate perceived risks toward protection of intellectual property. For example, in the case of BRAF inhibitors, important new biological insight into the mechanisms of resistance and MAPK pathway activation was initially revealed with the BRAF inhibitor PLX4720 (Tsai et al, 2008), a compound closely related to PLX4032 (RG7204, vemurafenib) which was only later made available to the scientific community for preclinical studies, and subsequently became the first marketed BRAF inhibitor (Bollag et al, 2012).
active ALK kinase in a subset of NSCLCs (Soda et al., 2007). A mere 3 years later, dramatic clinical responses were reported in ALK-translocated NSCLC patients upon treatment with crizotinib (Kwak et al., 2010), followed by its approval in 2011. Even though this drug was developed initially as a MET kinase inhibitor and only later recognized to potently block ALK activity, these remarkable timelines to successful clinical translation and approval were only made possible through close academic/industry collaborations. As is the case with other targeted therapies for oncogene-addicted tumors, resistance to crizotinib is inevitable and is observed in less than a year (Camidge et al., 2012). Importantly, ceritinib, a second-generation ALK TKI approved by the FDA earlier this year, appears to be effective against many of the known resistance mechanisms that arise in patients exposed to crizotinib (Shaw et al., 2014). Over the past several years, multiple molecular mechanisms of resistance to targeted therapies have been discovered, resulting in the emergence of several common themes (see Box 2).

Massive cancer genome surveys supported by public or private funding are now rapidly expanding the catalogue of genetic aberrations linked to a broad range of cancer types. The cancer genome landscape in AML (The Cancer Genome Atlas Research Network, 2013) has informed new precision oncology approaches beyond the use of kinase inhibitors. Thus, in addition to TKIs targeting FLT3, small-molecule inhibitors are being developed to address AML subtypes harboring oncogenic variants of the gene encoding isocitrate dehydrogenase (IDH) 2 (e.g. AG-221; Stein et al., 2014) and the mixed-lineage leukemia gene MLL1 (Dot1L inhibitor EPZ-5676; Daigle et al., 2013; ClinicalTrials.gov identifiers: NCT02141828, NCT01684150). In addition to the genome-based discoveries of “actionable” cancer genes, several examples of cancer-specific vulnerabilities are poised to yield new therapeutic advances and deserve discussion in this context. In AML, the gene encoding the bromodomain-containing protein 4 (BRD4) was identified by an epigenetically focused systematic in vivo RNAi screen at the Cold Spring Harbor Laboratory as highly essential for promoting proliferation and blocking differentiation. BRD-containing proteins function by binding acetylated lysines on histone residues and recruiting protein complexes, thereby regulating gene expression by modulating heterochromatin. When using a BRD4 inhibitor “probe compound” (for definition, see Box 1), discovered at the Dana-Farber Cancer Institute, anti-leukemic effects across genomically AML subtypes were precisely recapitulated and found to largely depend on blocking the oncogenic transcription factor MYC (Zuber et al., 2011). Several companies have rapidly initiated discovery programs, and clinical trials probing the utility of BRD4 inhibitors for the treatment of AML are underway (Papavassiliou & Papavassiliou, 2014).

Prioritizing the best possible targets requires collaborative efforts at research institutions and hospitals to establish improved preclinical models.

A particularly good example of the contribution of modern molecular cell biology toward new treatment paradigms in AML is the field of cell cycle regulators. Here, the detailed understanding of how mitotic kinases such as polo-like kinase (Plk) 1 orchestrate mitosis, built over the years in basic academic research, inspired the industry to consider Plk1 inhibition as a potential therapeutic cancer target. Several small-molecule inhibitors have been developed that have enabled cell biologists to advance our understanding of Plk1 biology, and helped collaborating industry partners to develop Plk1 inhibition as an attractive therapeutic concept based on very efficient tumor cell killing and—in contrast to microtubule-targeting antimitotic agents—specificity for proliferating versus non-proliferating cells (Steegmaier et al., 2007; Taylor & Peters, 2008). Importantly, recent clinical data in AML patients demonstrated that the Plk1 inhibitor volasertib combined with chemotherapy was associated with higher response rates and improved event-free survival than chemotherapy alone (Döhner et al., 2014).

Finally, turning to gynecological tumors, a breakthrough discovery by two groups in the UK showed that inhibitors of the DNA repair enzyme poly(ADP) ribose polymerase 1 (PARP1) preferentially killed cancer cells harboring defects in the homologous recombination (HR) repair tumor suppressor proteins BRCA1 or BRCA2 (Bryant et al., 2005; Farmer et al., 2005). When HR is defective, alternative DNA repair mechanisms are utilized that then become dependent on PARP1. Key to the success of these studies have been the insights into DNA repair pathways made in basic academic research, as well as the availability of exquisite PARP inhibitor probe compounds.
pioneered in industry. The discovery also delivered strong support to the concept of “synthetic lethality”, based on which mutations that are harmless on their own, when compounded can kill a cancer cell. Subsequent studies established that olaparib, a potent PARP inhibitor, yielded notable clinical activity in BRCA mutation carriers with breast and ovarian cancers (Fong et al, 2009), providing the basis for ongoing trials (Moore et al, 2014).

**Challenges in advancing new precision cancer therapies**

Recent surveys based on the sequencing of thousands of cancer genomes have yielded unprecedented insights into cancer genome landscapes (Vogelstein et al, 2013) and enabled the discovery of many new cancer genes, including several involved in cellular processes not previously thought to be causally linked to cancer (Garraway & Lander, 2013). In parallel, large-scale efforts, such as epigenomics, transcriptomics, proteomics, chemical genomics, and high-throughput functional screens have greatly increased our understanding of the underlying biology of cancer. While these transformative efforts continue to progress at a rapid pace, we perceive four key challenges going forward: how can we (i) prioritize the best possible targets; (ii) develop drugs against “undruggable” oncoproteins; (iii) restore tumor suppressor pathways; and (iv) identify highly effective drug combinations.

To fully exploit tumor suppressor pathways for genome-based therapies, we need to further intensify our efforts to find synthetic lethal drug targets akin to PARP. “Project Achilles” is an example of a collaborative effort between academia and industry partners to identify (tractable) molecular targets that address loss-of-function causing cancer mutations (Cheung et al, 2011). By using a large panel of well-characterized cancer cell lines or engineered isogenic cell lines that model the variability observed in patients in a defined genetic context, the goal is to systematically uncover genotype-dependent key cancer cell vulnerabilities.

Finally, a major challenge is the discovery and translation of highly effective drug combinations to further improve health outcomes in difficult-to-treat cancer types. Resistance (both primary and acquired) to current precision therapies is attributed to the genetic complexity and heterogeneity of tumors, clonal evolution, feedback loops in signaling pathways, and cellular plasticity which cumulatively result in a range of escape routes available to cancer cells. For example, the discovery that effective treatment of BRAF-mutated colorectal cancers requires inhibition of both BRAF and EGFR (Prahallad et al, 2012) has resulted in several combination trials (Bernards, 2014). Again, using a systematic approach, the combination of MEK and CDK4 inhibitors was found effective in preclinical NRAS-mutant melanoma models (Kwong et al, 2012), providing the basis for clinical combination trials (Johnson et al, 2014). Encouraged by such discoveries, drug companies are now increasingly teaming up to clinically

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**Box 3: Partnerships between companies to test drug combinations**

The combination of investigational cancer therapies into a single development program offers an attractive approach for generating more effective cancer treatments. This strategy allows the targeting of multiple cancer pathways, or addressing more than one key node in a single pathway to prevent or overcome intrinsic or acquired resistance (see Box 2). A single biomedical company rarely has adequate resources or the success rate to effectively target all major oncogenic pathways, their key nodes, and respective resistance mechanisms. To move forward efficiently, companies should collaborate rather than compete to be successful in developing highly effective combination therapies. Fortunately, we see a clear trend that such collaborative efforts are in fact happening. This started in 2009, with competitors AstraZeneca and Merck forming a partnership to evaluate a combination of AstraZeneca’s MEK inhibitor and Merck’s AKT inhibitor in multiple early-stage clinical trials. Since then, other top tier pharmaceutical companies have agreed on strategic collaborations to share drugs and development costs. Notable examples include partnerships between Merck KGaA and Sanofi on MEK and PI3K inhibitor combinations, as well as Roche and BMS on investigating Roche’s vemurafenib in combination with BMS’s ipilimumab, an immune-checkpoint inhibitor targeting cytotoxic T-lymphocyte activator-4 (CTLA-4), in patients with BRAF-mutated malignant melanoma. In the area of immune-checkpoint modulators, companies are teaming up for combinations centered around inhibitors of programmed cell death-1 (PD-1) combinations with other immunotherapies or with targeted therapies (Sheridan, 2014). We see it as very important for the entire drug development community to fully embrace and foster collaboration models to best advance investigational combination therapies for the benefit of cancer patients.
test targeted pathway inhibitor combinations (Box 3).

**A recipe for biomedical innovation**

Collectively, innovation leading to effective new cancer therapies is driven by the convergence of basic scientific discoveries, rapidly improving genomic analysis technologies, and increasingly precise biomarker-guided development strategies. As illustrated, breakthrough innovation can equally well emerge from academia and industry and can arise both from “data first”, large-scale efforts and from creative, “hypothesis first”, modern molecular cell biology studies, often in a complementary and mutually beneficial manner.

**Conflict of interest**

MAH has previously been compensated as a consultant and speaker for Roche and as a speaker for MSD and Amgen. NK is an employee of Boehringer Ingelheim.

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