Perspective

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 response.

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.

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 ErB 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

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).

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Box 2: Predicting drug resistance to cancer drugs

Resistance to targeted therapies is commonly categorized as either primary (i.e. intrinsic) or secondary (i.e. acquired). Primary resistance indicates a direct lack of a treatment response, while acquired resistance is defined by disease progression following an initial response. Acquired resistance may be mediated by target modifications (e.g. secondary mutations or gene amplification of the target that will abrogate the inhibitory activity of the drug), “bypass signaling” resulting in reactivation of parallel and/or downstream signaling pathways, or histologic transformation. For EGFR TKIs, all of the above mechanisms of acquired resistance have been described clinically, including a secondary threonine-to-methionine substitution within the gatekeeper residue at position 790 (T790M), bypass signaling via amplification of the gene encoding the RTK MET to activate a parallel pathway, and phenotypic alterations either by an epithelial–mesenchymal transition, or even by a transformation from NSCLC to small-cell lung cancer (Sequist et al., 2012). Clinical studies of acquired resistance provide clear rationales on how to develop improved strategies to prevent or overcome resistance, guiding the development of next-generation inhibitors addressing secondary target mutations, or informing new combinations aimed at co-targeting of bypass tracks. Preclinical modeling of acquired resistance to targeted therapies also yields key insights into target modifications or bypass mechanisms providing the capacity to substitute for the driver oncogene and serves as a powerful starting point when searching for clinical resistance mechanisms. As a word of caution, only a subset of the preclinical resistance mechanisms are actually found in the clinical setting. For example, initial attempts to predict resistance mechanisms to BRAF inhibitors focused on generating mutations in the BRAF gatekeeper residue that is analogous to the clinically relevant residues in EGFR (T790M), BCR-ABL (T315I), and ALK (L1196M). Indeed, it turned out that although engineering of BRAF T529 gatekeeper mutations does confer vemurafenib resistance in vitro, these mutations have never been reported in tumor samples from BRAF inhibitor-resistant patients (Whittaker et al., 2010). Thus, in this case, the design of second-generation compounds based on the preclinical findings would have been premature.

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 antimitic 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 (Döhnner 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 muta-
tions that are harmless on their own, when
compounded can kill a cancer cell. Subse-
quent studies established that olaparib, a
potent PARP inhibitor, yielded notable clini-
cal 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
genomes, including several involved in cellular
processes not previously thought to be caus-
ally 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 “undrugga-
gable” oncoproteins; (iii) restore tumor
suppressor pathways; and (iv) identify
highly effective drug combinations.

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 target-
ing 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 thera-
pies. 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 clini-
cal trials. Since then, other top tier pharmaceutical companies have agreed on strategic collabora-
tions 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 investigat-
ing 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 combina-
tions 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.

“drug companies are now
increasingly teaming up to
clinically test targeted pathway
inhibitor combinations.”

Prioritizing the best possible targets
requires collaborative efforts at research
institutions and hospitals to establish
improved preclinical models, including
patient-derived xenografts, syngeneic
models, and genetically engineered mouse
data that better reflect the clinical situa-
tion (Toniatti et al, 2014). Furthermore, opti-
mized validation tools enabling effective and
versatile target knockdown, as well as
reduced off-target effects (Fellmann et al,
2013), complemented by suitable chemical
probes are most urgently needed to
systematically assess potential cancer driv-
ers. Importantly, strong cell biology and
cellular signaling expertise will continue to
prove crucial in exploring disease impact
and in developing concepts for new precision
drugs.

Overcoming technical hurdles to develop
therapeutics against traditionally “undrugga-
able” target classes remains a key issue. We
see a trend that academic groups are taking
up the challenge, supported by industry, to
tackle some of the major culprits of cancer
with innovative chemistry approaches.
These include protein–protein interaction
surfaces of highly validated targets, such as
KRAS, MYC, p53, and beta-catenin, perhaps
best illustrated by the recent report on KRAS
(G12C) lead compounds (Ostrem et al,
2013). Academic/industry collaborations
also feature prominently in current ambiti-
sions to broaden the scope of druggable
cancer-driving targets, with a focus on newly
emerging target classes involved in cancer
epigenetics, metabolism, splicing, and
protein homeostasis (Garraway & Lander,
2013). Based on precompetitive partnerships
with multiple drug companies, the Structural
Genomics Consortium is developing open-
access chemical probes to target proteins
that are involved in epigenetic signaling,
while the Dundee Consortium currently
focuses on components of the phosphoryla-
tion and ubiquitin systems (Mullard, 2011).

To fully exploit tumor suppressor path-
ways 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 collabora-
tive effort between academia and indus-
try 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 discov-
ery 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 treat-
ment of BRAF-mutated colorectal cancers
requires inhibition of both BRAF and EGFR
(Prahalad et al, 2012) has resulted in several
combination trials (Bernards, 2014). Again,
using a systematic approach, the combina-
tion of MEK and CDK4 inhibitors
was found effective in preclinical NRAS-
mutant melanoma models (Kwong et al,
2012), providing the basis for clinical combi-
nation trials (Johnson et al, 2014). Encour-
aged by such discoveries, drug companies
are now increasingly teaming up to clinically

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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.

References

patients (pts) with ovarian cancer and a BRCA1/2 mutation (BRCAm). *J Clin Oncol* 32: 5 (suppl; abstr TP5616).


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