Where is the Future of Drug Discovery for Cancer?

With both small molecules and biologics succeeding in trials and in the clinic, the scope of drug discovery in cancer is changing. We asked a group of researchers to share their visions for how to identify new targets and how to approach taming them.

Cancer Metabolism Games

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We have known for a long time that cancer cells adopt metabolic states that fit their growth impetus and reflect their relinquishing of tissue homeostasis, yet the degree and variety of ways by which metabolic networks are rewired in tumors continues to surprise us. What has received less attention is the interplay between the metabolism of tumors and other cells in the microenvironment. Metabolism is not cell-autonomous; instead, it reflects an obligatory dialog between tumor cells and the surrounding tissue. We are increasingly appreciating that immune cells are also profoundly affected by metabolism, including nutrient, metal, and oxygen levels. These insights highlight a potential innovative therapeutic target: the integrated metabolic space of tumor, stromal, and immune cells, where cells must compete for nutrients or enter mutually advantageous dependencies. An opportunity now exists to alter nutrient traffic to draw in and activate the right immune cell types and to disadvantage cancer cells. But how to attempt this? The solute carrier and ABC membrane transporters are responsible for influx and efflux of nutrients and metabolites. These transporters are differentially expressed in different cell types and respond to environmental supply and internal demand. They are also exquisitely druggable. By targeting transporters, perhaps in combination, we may be able to subtly and safely turn the tables in the cancer metabolism game in favor of immune cell well-being and cancer cell starvation for the re-establishment of healthy tissue homeostasis.

Designer Proteins as Cancer Therapeutics

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Monoclonal antibodies dominate the modern pharmaceutical industry. These agents have achieved clinical success, led by recent excitement about arming them with chemotherapeutic agents for targeted drug delivery or interactions with the immune system. Despite these advances, challenges in the field remain, including how to best tackle tumor and patient heterogeneity, rapid drug resistance, and issues with effective tumor penetration and delivery across the blood-brain barrier.

Advances in our understanding of disease pathophysiology and the development of rational and combinatorial technologies for creating protein-based biologics are spawning drug candidates with improved therapeutic and safety profiles. We now have “multi-specific” proteins that target and modulate several key biochemical pathways and “multi-epitopic” proteins that bind different locations of the same target for improved efficacy. Researchers are also exploring peptides and so-called “alternative scaffolds” that are modular like antibodies, but evoke potential benefits such as enhanced tumor penetration. Along with these elegant approaches come development, manufacturing, or regulatory hurdles, but also new opportunities for impactful cancer treatments.

Clinical trials are increasingly combining targeted therapies or coupling them with more traditional modalities such as chemotherapy or radiation to address multiple facets of cancer. While these approaches bring increased costs and questions about toxicity, they are proving highly effective and are poised to offer new standards of care.

Growing the Drug Target Space

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Greater than 20% of industrial cancer drug development programs focus on just eight proteins—sadly ironic in this post-genomic era, when ~20,000 possible proteins are known. While many potential drug targets are enzymes, it is clear that non-enzymatic proteins also play key roles in cancer biology. Currently, these structural and regulatory classes of proteins appear “undruggable,” since they lack a catalytic site for small-molecule inhibition. This unsuitability is especially applicable to transcription factors, which regulate gene expression via protein complex formation. Given these challenges, how can one make these proteins pharmaceutically vulnerable? RNAi and CRISPR offer some hope via preventing oncogene expression. However, their clinical potential has not been fully realized due to challenges with cost, delivery, and off-target effects. Clearly, new approaches are needed to identify modulators of protein expression (and thereby, function). Ideally, these approaches should be small molecule based, should possess favorable pharmaceutical properties, and should have the potential to target all proteins, irrespective of protein class.

One emerging approach to target the “undruggable” proteome is the use of small molecule proteolysis targeting chimera (PROTACs) to induce the deliberate degradation of specific proteins by the ubiquitin/proteasome system. By co-opting the normal cellular quality control machinery responsible for removing unwanted proteins, all classes of proteins could be controlled using small molecules, greatly expanding the number of “druggable” protein targets.
The concept of the “druggable genome” has enumerated the human proteome’s potential to yield new medicines. “Drugging the undruggable” seeks to expand this target space and address the many proteins implicated as therapeutically relevant that fall outside the druggable genome, e.g., protein-protein interactions (PPIs). While the phrase, drugging the undruggable, is aspirational, it overstates the resilience of the original classification of druggability toward scientific progress. Rather, potential intervention points for small molecule ligands are either precedented or unprecedented. Indeed, over the last two decades, protein kinases have progressed from unprecedented to become a protein family with 28 FDA approvals. While precedent is retrospective, some attempts have also been made to prospectively analyze the “ligandability” of the proteome by structural and computational methods. These analyses deem unprecedented proteins as either easier (kinases in 1990) or more difficult (many PPIs today), but they suffer from an inability to anticipate induced-fit-binding modes. Given that our current understanding of druggability is strongly colored by history (“all experience is an arch wherethrough, Gleams that untraveled world, whose margin fades, Forever and forever when I move;” “Ulysses,” Alfred, Lord Tennyson) and limitations of computation, efficient experimental approaches are needed. Fortunately, unbiased assessments of druggability using the tools of chemical biology and quantitative proteomics are emerging. An experimentally determined druggable genome is within our grasp.

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Insofar as drug discovery is concerned, we are in the post-cancer-genome era, where we know the main driver oncogenes. Drugs targeting drivers of common cancers (B-Raf, PIK3CA, androgen receptor, estrogen receptor, Bcl-2, etc.) have been approved or are in late-stage clinical trials. What remain are some well-appreciated oncoproteins like K-Ras and c-Myc that are crucial in a range of tumors but lack obvious small molecule binding sites. These targets are “yet to be drugged” (YTBD), but that status may be fleeting. Recent success in discovery of lead compounds for one allele of K-Ras (G12C) might herald the emergence of additional drugs for other K-Ras alleles. The most important ingredient for drugging these kinds of targets is a long-term commitment by the community to better understand the key drivers biochemically, structurally, and functionally and to couple this understanding with creative chemical approaches to blocking the targets’ function. BCL-2 was considered undruggable until a decade’s worth of experimentation and application of fragment-based NMR screening altered and broadened our views of what drug-like molecules could look like. However, with major oncogenic drivers known, we need to ask if we’re out of good targets. I don’t think so. Components of “housekeeping” cellular machines are underappreciated targets, including those responsible for mRNA splicing and translation that are hijacked by cancer cells to selectively promote cancer formation. Our challenge is how to drug these cellular machines in a manner that blocks their cancer-specific functions.

The discovery of novel medicines is a daunting task, even more so when entering a new area of biology, as was the case when GSK started its early investment in epigenetics. Which of the epigenetic players that determine or interpret the histone code in response to environmental cues offer hope for therapeutic interventions? In order to tackle these questions, chemical biology combined with proteomics provided a vital toolbox. At the outset, a cellular screen for compounds modulating target gene expression led to biologically active small molecules, likely affecting epigenetic regulation. We used such compounds to isolate and identify by mass spectrometry a new target class, the BET bromodomain family of epigenetic regulators, that would be tractable for small molecule inhibition. But this was just the start: in order to understand function and full therapeutic potential, we characterized the mega-dalton protein complex surrounding BET proteins, using a combination of immuno-affinity and chemoproteomic approaches. The unexpected presence of BET proteins in distinct complexes closely associated with proteins that are commonly mutated or trans-located in certain leukemias pointed to therapeutic indications for BET inhibitors, which are now being tested clinically. Drug candidates targeting epigenetic regulators hold tremendous promise, but much of the biology of epigenetics and exciting therapeutic potential in indications beyond cancer is still to be discovered and is being aided by modern technologies on the flourishing interface between chemistry and biology.

“Drugging the Unprecedented”

Probing Epigenetics

Not Undruggable, but #YTBD