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Systems Biology in Drug Discovery

Eric J. Kunkel

The current drug discovery process is highly focused on discrete targets and simplified assays. With the target-based paradigm, certain development activities become easier (e.g. chemical optimization and mechanism-based toxicology), but there is also a significant downside. The single-target approach ignores the realization that many successful drugs have multiple targets (e.g. ibuprofen, Gleevec®) that only when inhibited in combination result in efficacy. The single target-based approach also limits the ability of researchers to identify innovative targets and/or mechanisms of action (including combination therapies) by limiting druggable space to recognized targets and modalities. The growing disparity between pharmaceutical R&D spending and the approval of new chemical entities means that the writing is on the wall: improvements in the drug discovery process are needed in order to improve the success rate for new chemical entities.

The solution is clearly a more integrated approach to understanding the mechanisms of disease processes, one that incorporates the complexity of cellular signaling pathways and cell-cell communication. Systems biology is such an approach. Systems biology aims to describe and to understand the operation of complex biological systems with the goal of developing predictive models of human disease. The most powerful systems biology approaches would ideally integrate information from (1) large datasets of gene, protein, and metabolite measurement ("omics" data), (2) complex cell- and tissue-level *in vitro* models of the disease process, and (3) *in silico* computer simulations that integrate information flow from the pathway to organism levels. Systems biology provides a framework for understanding biological processes and more rationally identifying points of intervention for therapeutics. While fully integrated models of human disease are still a distant goal, simplified systems biology efforts can (and are beginning to) have an enormous impact on both our understanding of disease and the success of the drug discovery process.

The oncology field will benefit greatly from a systems biology approach. Besides highly cytotoxic therapies that generally do not differentiate between cancerous and normal cells, the most successful approaches have involved multi-agent therapies that target several processes required for the cancer's survival. These multi-pronged treatment approaches clearly can work, but their discovery thus far has been mainly clinical; usually combinations of agents that were approved as monotherapies discovered using traditional approaches instead of rational discovery of compounds with complex mechanisms or several that could be used in combination. Thus, the ideal discovery process for oncology will involve a mixture of strategies linked together by their common systems biology-based approach.

The first strategy involves large-scale "omics" efforts to identify and reconstruct the disregulated networks inside cancer cells. It is very important that this work is carried out *in the context of our best approximation of their local environment* so that the resulting network is organized in the most relevant way. Of course, while some mechanisms of transformation may be shared between cancer types, many mechanisms may be cancer type-specific, requiring an extensive analysis of multiple cancer types (and patient diversity). The strategy will also likely require information on non-transformed cells from which the cancer develops in order to provide the network for normal cells so that more specific therapies can be hypothesized. Such efforts will dramatically accelerate hypothesis generation and provide information for cell-based screening and pathway modeling.

The second strategy builds on the knowledge of signaling pathways in normal and transformed cells, that is, using computer simulations to help identify the intervention points within these disregulated networks relative to normal cells for rational identification of multi-target or combination therapies. Modeling approaches are extremely valuable for many reasons, some of which include (1) the best combination of targets for a cancer cell may not be obvious due to pathway interactions, (2) *quantitative* changes in signaling through certain pathways, but not full inhibition, may be an important modality, and (3) pathway modeling may be able to identify parallel pathways that should be inhibited *a priori* to avoid drug resistance in the clinic.

The third, and arguably the most practical, strategy relies on the development and use of complex *in vitro* cell-based assays. Such assays provide an independent method for cancer drug discovery as well as a tool for integrating and validating the information from the "omics" and *in silico* modeling efforts. The important feature of these next-generation *in vitro* models is that they embrace the complexity of multiple aspects of cancer biology, including for instance, (1) assays incorporating interactions between cancer cells and the immune cells that would normally keep them in check, or (2) assays containing relevant environmental stimuli such as growth promoters and extracellular matrix components. Such assays should ideally cover as many aspects of the known cancer's biology as possible so that any compound or combination tested in the assays is interrogating the most relevant biology. Such complex assays can be used in a stand-alone manner for screening (a chemigenomics approach in a target/mechanism agnostic manner) to identify compounds that impact the correct biology since many thousands of targets or combinations of targets are present. Such assays can also be used as the source assays for the "omics" data and for validation of the pathway models, thus tying all three strategies together into a powerful discovery package. The approach is plausible, since at BioSeek, we have already developed such complex assays relevant to inflammation (BioMAP® assays) and used them to screen for and discover novel anti-inflammatory compounds in known chemical space.

In conclusion, cancer is a complex process that will require a complex systems biology-based approach to ultimately solve. Continued use and development of the three key strategies discussed here (and their eventual merger into a fully integrated whole) will provide an improved framework for cancer drug discovery.

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E. J. K. is with BioSeek, Inc., Burlingame, CA 94010 USA (phone: 650-231-1251; fax: 650-552-0725; e-mail: ekunkel@bioseekinc.com).