An expanding role for cell biologists in drug discovery and pharmacology

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ABSTRACT **The profound challenges facing clinicians, who must prescribe drugs in the face of dramatic variability in response, and the pharmaceutical industry, which must develop new drugs despite ever-rising costs, represent opportunities for cell biologists interested in rethinking the conceptual basis of pharmacology and drug discovery. Much better understanding is required of the quantitative behaviors of networks targeted by drugs in cells, tissues, and organisms. Cell biologists interested in these topics should learn more about the basic structure of drug development campaigns and hone their quantitative and programming skills. A world of conceptual challenges and engaging industry–academic collaborations awaits, all with the promise of delivering real benefit to patients and strained healthcare systems.**

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Four decades of molecular and cellular biology has fundamentally improved our understanding of human disease, but this undeniable revolution has had less impact than hoped on human health, particularly in the area of discovery and use of therapeutic drugs. The missing link between basic science and useful therapeutics is the quantitative, multifactorial understanding of networks that operate within and between cells and of the changes that drugs induce in these networks (Berger and Iyengar, 2009). Contributing to this understanding of drugs and network dynamics represents a significant opportunity for cell biologists interested in careers in industry and for academic scientists seeking industrial collaborations. Success in such "translational" research is not simply a matter of applying known concepts to practical problems; interesting new ideas and science are required (Loscalzo and Barabasi, 2011). Fifty years ago, pharmacology and pathophysiology provided cell biologists with many fundamental research problems, and there is every reason to believe this will also be true in the future.

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Insufficient understanding of pathological and therapeutic mechanisms at a cellular level has contributed to the growing difficulty of bringing new drugs to market. Even when drugs win approval, it is rare that we can predict which patients will benefit from them. As a result, patients have too few treatment options, many serious illnesses remain difficult to treat, and the cost of new medicines is too high (often at the limit of what healthcare systems can support). High-throughput "-omic" approaches have been hailed as a means to understand disease and develop new drugs, but an outstanding opportunity exists for fundamental contributions from cell biologists. A central feature of cell biology is its emphasis on applying diverse conceptual and analytical approaches to biological processes

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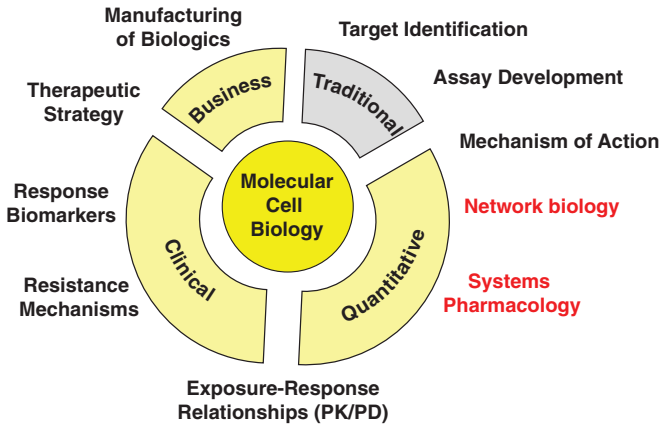

FIGURE 1: Traditional and emerging roles for cell biologists in drug development and pharmacology. Traditionally, cell biologists have worked on the earliest phases of drug discovery, during the identification and validation of targets. However, by expanding their horizons and adding new skills, cell biologists can become well-suited to other roles later in development, roles in which the stakes are higher and sophisticated understanding of the underlying biology less common. Some of these fields are traditional (e.g., pharmacokinetics and pharmacodynamics [PK/PD]; black) and others are newly emerging (e.g., systems pharmacology; red).

that are inherently multifactorial. This is in contrast to "-omic" approaches, in which the focus is usually on one type of data collected in volume (gene sequences being one example).

The role of cell biology in unraveling disease mechanisms is well established, but the value of cell biology in drug development is less well appreciated. Cell and molecular biologists currently play a role during the earliest preclinical stages of drug development in the identification and evaluation of potential drug targets (Figure 1). However, it is increasingly apparent that existing procedures for qualifying targets are inadequate, and this manifests itself as frequent and expensive late-stage failures of efficacy (typically during phase II and III clinical studies (Paul *et al.*, 2010). To overcome this problem, we require a much better understanding of the functions of target proteins within the context of cellular networks in normal and diseased cells, both in culture and in the organism ("network biology"). Opportunities exist for cell biologists to help define optimal therapeutic strategies (e.g., aiding in the choice between using a recombinant antibody or small molecule) and to ascertain exposure/response relationships in tissues. Cell biologists also have an important role to play in understanding acquired resistance. A lack of durable responses is the bane of many recently approved targeted drugs. Finally, in diseases such as cancer, we have many plausible targets (the Akt kinase, for example), but it is not clear how to inhibit the target without causing excessive toxicity. It is also unclear why only a subset of patients responds to even the most potent and selective inhibitors. In our opinion, many drugs fail because cell biology is ignored during the later stages of drug development, when selecting indications and drug combinations and determining dosing schedules are the key tasks.

Cell biology also has an important role to play in discerning the precise mechanisms of action of existing drugs; it is a remarkable fact that we understand very few drug responses in mechanistic detail. This is as true of the latest generations of targeted therapeutics (many of which aim for selective inhibition of disease-specific mutants) as for older drugs that constitute the mainstay of standard-of-care therapy. The challenge lies less in the interaction between a drug and its intended target than in the consequences of target inhibition for cellular phenotype. This is particularly true when we consider genetic variation from one patient to the next and from one cell to the next within a single patient (particularly with diseases such as cancer). Cellular responses to the microtubule inhibitor and anticancer drug Taxol are an excellent example. Despite being an "old-fashioned" cytotoxic drug, Taxol and its various derivatives are a mainstay of contemporary cancer care, and more patients have probably benefited from taxanes than from all the targeted anticancer drugs combined (Ni Chonghaile *et al.*, 2011). Understanding responses to taxanes at a cellular level has also been central to understanding the biology of the spindle assembly checkpoint and mitosis in general. Over the past two decades, checkpoint pathways have been identified and studied in many organisms, and we now understand in detail how processes such as mitotic catastrophe cause cell death (Mitchison, 2012). Remarkably, however, the factors that determine whether a cell lives or dies when exposed to Taxol differ dramatically between cultured cells and xenografted tumors (never mind real human tumors); progress through mitosis is always required in culture, but apparently not in the mouse (Orth *et al.*, 2011). Understanding this difference represents a fascinating problem in cell biology likely to reveal how cell-autonomous processes, such as mitosis, interact with factors from the local environment in controlling cell fate. Such understanding could also have a real and immediate impact on cancer care.

Over the past decade, the success of classical antimitotic chemotherapeutics, such as Taxol, has given rise to efforts to develop other antimitotic agents. For example, drugs that target spindle motors promised to combine the therapeutic antimitotic effects of Taxol, while minimizing neuropathy (motors such as Eg5 are not expressed in neurons [Huszar *et al.*, 2009]). Despite a massive effort by multiple companies, these drugs have proven disappointing in the clinic, as have many drugs that target mitotic kinases. It is now clear that inhibiting mitosis in cancer cells simply does not have the effects we have assumed for the past 50 years, and those antimitotic drugs that do work must do something fundamentally *more*. Working this out is likely to advance our understanding of the complexities of cell division in humans and animals. However, given the time pressures in industry, there is little opportunity to pursue "failed" drugs, and academic cell biologists have largely ignored problems such as the mechanisms of cell killing by antimitotic agents in real tumors. We must adopt a more holistic and physiological perspective in which we admit that detailed mechanistic understanding is required not only in model organisms and HeLa cells, but also in myriad normal and diseased tissues that have low mitotic index, unusual forms of endo-replication, and complex interactions with neighboring cells. New programs sponsored by the National Center for Advancing Translational Sciences promise to provide some support for this type of research (Allison, 2012).

More generally, while we all recognize that the "one gene–one disease" paradigm is insufficient for understanding human disease and for selecting patients who will respond to therapy, an effective alternative remains to be developed. Even when the multiplicity of factors involved in a particular disease can be discerned, this understanding does not necessarily reveal how to develop a treatment or cure. For therapy, we must elucidate not only the nature of the initial insult (e.g., a cancer-causing mutation) but also the operation of biological networks that attempt to compensate for the insult (to reestablish homeostasis) and variation in network properties from one individual to the next. It is also important that we identify and understand factors that determine the concentrations and biodistribution of drugs in patients with diverse genotypes. This, in turn, requires a multiscale, network-based approach involving systemic and quantitative study of biological processes at the cellular, tissue, and organismal levels and

of the effects of drugs on these processes—precisely the areas in which cell biology has much to contribute.

Despite these opportunities, several factors stand in the way of a greater role for cell biologists in drug discovery and development. The first is an unfamiliar vocabulary. We are repeatedly amazed by postdocs who have decided they want to pursue a career in biotechnology or the pharmaceutical industry but who have not spent the time to learn the basics of the drug discovery process from preclinical development to phased clinical trials. Anyone interested in an industrial career should stay abreast of the lively and interesting debates about the best ways to structure and evaluate trials (Kelloff and Sigman, 2012). An industrial career usually requires writing more but shorter reports than an academic career, and familiarity with the language of drug discovery makes report writing much easier. A career in industry also benefits from knowledge of the diverse scientific, medical, and business factors that determine success in a drug development campaign. At the same time, it is important to note that some key drug discovery concepts, such as "target identification" or "target qualification," are widely used but elusive. They imply that the key task is identifying (or cloning) a specific target protein and then screening for agonists and antagonists. As mentioned above, the current challenge increasingly involves understanding targets in the context of biological networks, homeostatic processes, and pathophysiological mechanisms (Wang *et al.*, 2012). This implies a more nuanced and holistic approach to understanding the ways the targets and drugs interact (Chene, 2012).

Many cell biologists in industry find themselves involved in the development or evaluation of assays, particularly for high-throughput screening. Evaluating such screens requires basic understanding of statistics and the trade-offs between false-positive and false-negative results (Atkinson and Lalonde, 2007). If high-content screening by imaging is involved, then it is necessary to develop and apply machine vision approaches. Unfortunately, many cell biologists are insufficiently trained in basic statistics, and they have poor programming skills. In our experience, this can be a significant impediment to employment in industry that can be overcome by taking courses in probability and statistics and by gaining practical experience with MatLab or languages such as Python and R. Particularly in biotech, learning the rudiments of intellectual property law can also be a real asset, since it makes it easier to spot patentable inventions.

Even the largest drug companies have come to doubt their ability to pursue development projects all the way from target identification to drug approval. It is widely believed that more frequent and effective collaborations between industry and academe are part of the solution (Rubin and Gilliland, 2012). This obviously represents a significant opportunity for academic cell biologists. However, the days in which companies were willing to shower academic institutions with generous and unrestricted financial support are long gone. It is now necessary to develop research programs that revolve around concrete goals and deliverables. In our experience, this can be an exciting process for academics accustomed to the conservatism of federal grants, since industry is often willing to pursue ideas that are risky and innovative. Moreover, we have rarely found the perceived difference between applied and basic research to be a significant issue. However, very different expectations over the duration of projects are a major challenge. Industry typically works on 12- to 18-month time lines and academe on a schedule that is at least twice as long. In our experience, even the most effective industry–academic projects tend to underdeliver over the first 18 months, and then only prove their worth in subsequent years. Industry must be more sensitive to the fact that starting a new project in an academic setting means recruiting a new student or postdoc and that there is no way for such an individual to be trained and to succeed with only 18 months of support. However, academics must learn to accommodate the real need for industrial partners to reevaluate projects after approximately 18 months. In our opinion, academics could speed up the initial stages of a project and industry should slow down. We have personally witnessed many industrial projects that were discontinued without reaching a firm conclusion, only to result in an exciting opportunity being missed or to leave open questions that impede progress many years later. A frank discussion of these issues is essential at the outset of any collaborative project.

Despite obvious challenges, we envision an expanding role for cell biologists in drug discovery that extends beyond their traditional involvement in early-stage target identification. Significant opportunities exist in better qualifying potential targets and in identifying the role of target proteins in cellular function and pathophysiology. Better understanding of targets in the context of cellular and tissue networks should make it possible to design better therapeutics based on optimizing selectivity, affinity, and type of molecule. Cell biologists can also become more involved in clinical development of new and standard-of-care drugs, particularly with respect to identifying indications, developing diagnostics, and stratifying populations. In this case, learning more about the clinical phases of drug development is valuable. In our personal experience, the most effective approaches are those that involve quantitative analysis and combine experimentation and modeling. This often goes under the name "systems biology" but can easily be viewed as a natural evolution of cell biology in the face of ever-larger data sets and more complex cellular mechanisms. Thus, if we had a single piece of advice for cell biologists interested in pharmacology or drug discovery, it is to acquire or hone skills in statistics, bioinformatics, programming, and applied mathematics in general.

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