Cell biology: A key driver of therapeutic innovation

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All processes associated with cellular function are likely to contribute to disease. Particularly in the cancer field, most major therapeutic innovations have originated from the elucidation of basic molecular mechanisms by academic researchers. Recent breakthroughs in molecularly targeted drug discovery have made it clear that it is the depth with which a biological process is understood that empowers its translation. We propose that early, more strategic, support of cutting-edge academic research by industry may be more effective for translational purposes than the current model of a late selection of community-evolved projects.

The translation of insights obtained in scholarly, academic research into practical clinical use is not a trivial issue and cannot be left to itself to follow some sort of Darwinian selection principle (McClain, 2010). Rather, the development of a drug and new therapeutic approaches requires a concerted, well-organized effort. Yet, the process that takes ideas from basic research observations to medical practice is, unfortunately, long and inefficient (Fitzgerald, 2005). There are several discrete steps from the laboratory discovery to clinical application that include proof-of-concept studies in cellular and animal models, optimization of compounds or biologicals, evaluation of toxicity, bioavailability, and many more. Experience has shown that it is mostly the interface between these different steps that does not always work smoothly, as people with different skills and cultural backgrounds pass on the projects, often over an entire decade. During the same period, a given pharmaceutical company is likely to experience a change in leadership several times. At the same time, drug discovery is subject to "fashions" that focus on a particular pathway or drug design strategy, or target specific classes of proteins. Thus, the latest discoveries in academia, the aforementioned career cycles, and the progress of a particular project are not necessarily in synchrony. As a result, the feedback to the community of cell biologists by the drug discovery experts may cause uncertainties, mistrust, and confusion.

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Abbreviation used in this paper: CML, chronic myelogenous leukemia.

From a systems cell biologist point of view, all biological processes occurring in a cell or in an organism contribute to cellular homeostasis and therefore can act as disease modulators. It follows that all processes are worth being interrogated with modulating agents—be they drugs or biologicals—at the experimental level. Many cellular processes, such as the cell cycle, apoptosis, secretion, synaptic transmission, and epigenetic regulation are established pharmacological targets now, but have been unfashionable niches, neglected by the pharmaceutical industry for a long time. Likewise, there may be many other areas of cell biology, such as membrane biology, vesicular trafficking, intrinsically disordered proteins, chromosome segregation, and cell trans-differentiation that may garner mainstream attention by the industry soon.

There is hardly a cell biologist that works on a process or protein that has no "translational value." On the contrary, rather than following some trendy area of recent successful medical application, pursuing a neglected area of cell biology and biochemistry with rigor and persistence, to the point of becoming a world expert, appears to promise a good chance of long-term translational impact. It is the depth with which a certain biological process is understood that empowers its translation. It is not the convention derived by the history of drug discovery, such as if a target is considered druggable or not. For example, drugs targeting "allosteric" pockets of regulation, far away from the well-studied ortho-(proper) steric pockets are a current craze but were considered intractable until recently. Thus, every true expert in a particular process should have the peace of mind to explore as deep as necessary their process of interest, but then should be motivated to try "pharmacological interference" with tools of chemical biology or protein engineering. Being an expert on the biochemistry and biology of the process will allow the investigator to interpret and evaluate the consequence of the intervention wisely and to propose whether a particular "translational" avenue is worth exploring or not. This will eventually form the basis for the assays that, in partnership with the pharmaceutical/biotech industry, can lead to the discovery of new drugs and treatments (Fig. 1).

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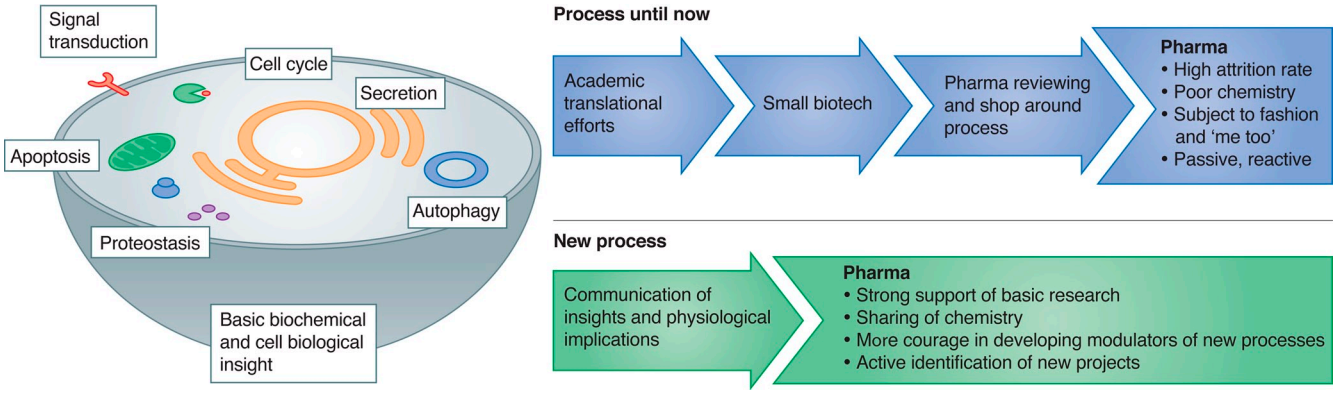

Figure 1. **Streamlining the drug discovery process.** Schematic representation of the current way in which basic research makes its way to the pharmaceutical industry and our suggestions for improvements that would support and increase therapeutic innovation and its translation to the clinic.

Bcr-Abl inhibitors illustrate the power of academia in drug discovery

Some of the principles that we just discussed are illustrated in the history of the targeted cancer therapeutic imatinib and its second-generation successors for the treatment of chronic myelogenous leukemia (CML), B cell acute lymphoblastic leukemia (B-ALL), gastrointestinal stromal tumors (GIST), and a few other diseases (Capdeville et al., 2002; Heinrich, 2010; Hantschel et al., 2012). Milestones in the imatinib discovery include the identification of Bcr-Abl fusion tyrosine kinase as the gene product of the Philadelphia chromosome and as causative lesion of CML, development of mouse models to study the disease and action of drugs, the use of phosphotyrosine-specific antibodies to monitor the effects of small molecules on kinase activity, and the identification of an early lead compound to possess potent inhibitory activity against Abl (Fig. 2; Buchdunger et al., 1996; Druker et al., 1996; Rowley, 2008). Finally, it was the persistence of a group of committed clinicians to convince Ciba-Geigy (now Novartis) to provide sufficient amounts of imatinib to start a phase I and soon after a phase II clinical trial. Imatinib induced rapid and durable hematological and cytogenetic remission in most patients and has transformed CML from a dismal disease with poor survival to a chronic and well-manageable disease. Yet the first reports on clinical resistance to imatinib were published only a few months after the approval of imatinib for the treatment of CML (Fig. 2; Gorre et al., 2001). In the last 10 years, ∼100 mutations in the Bcr-Abl kinase domain have been identified that cause imatinib resistance. It was again the dedicated work of academic researchers and clinicians that uncovered additional molecular mechanisms of imatinib resistance in relapsed CML patients, including Bcr-Abl and Lyn overexpression, deletions and mutations in Bcr-Abl "regulatory" domains, expression changes in drug transporters, and many more (O'Hare et al., 2006). All of these insights triggered and guided the rapid development and approval of second-generation Bcr-Abl inhibitors nilotinib and dasatinib (Shah et al., 2004; Weisberg et al., 2006). In parallel, a large number of drugs or drug-like molecules targeting mutated Bcr-Abl directly, newly identified allosteric sites on Bcr-Abl, proximal Bcr-Abl signaling nodes (Lyn, PP2A, STAT5, Jak2, Grb2), or pro-survival/anti-apoptotic pathways were developed and tested in preclinical models and partly in clinical trials (Hantschel, 2012; Hantschel et al., 2012; O'Hare et al., 2012). Additionally, a whole new set of reagents and methods was developed to monitor efficacy and selectivity of new agents, e.g., comprehensive screens for resistance mutations, selectivity profiling using chemical proteomics, cocrystal structures, phosphoproteomics and transcriptomics profiles, and many more (von Bubnoff et al., 2005; Bantscheff et al., 2007; Rix and Superti-Furga, 2009). Likewise, basic insights into the biology of GIST, hypereosinophilic syndrome (HES), mastocytosis, and other diseases, its translation, and the rigid design of clinical trials expanded the spectrum of use of imatinib and its successors to other diseases (Heinrich et al., 2000).

The development of small-molecule kinase inhibitors for Bcr-Abl heralded a new era in drug discovery, showing for the first time that the pathological activation of a protein kinase can be specifically targeted, resulting in improved survival of patients (Druker, 2008). Additionally, we have seen steep progress in our understanding of Bcr-Abl biology over the past decade. We solved the puzzle of how the cognate cellular protein product of the proto-oncogene *ABL1* is kept in a state of low kinase activity and have a better understanding of why Bcr-Abl is constitutively active (Hantschel and Superti-Furga, 2004). Moreover, signaling pathways critical for the growth-promoting and anti-apoptotic activity of Bcr-Abl were identified (Van Etten, 2007). Thus, it has been the detailed molecular understanding of the Abl kinases and their biology built from intense collaborative research of dozens of academic research groups that has been essential for this rapid progress. The lessons learned from Bcr-Abl served as a paradigm for the ensuing targeting of EGFR, VEGFR, ALK, BRAF and other kinases in solid tumors.

Still, many fundamental questions remain. The precise function of most of Bcr-Abl's phosphorylation sites is not known and its molecular structure has been deciphered only in part. Basic questions concerning the regulation of Bcr-Abl transcription, translation, and folding, including its critical interactions with chaperones, are only beginning to be revealed (Taipale et al., 2012). We only have a partial view of the Bcr-Abl signaling complex and signal transduction network, and regulation of its subcellular localization and nuclear–cytoplasmic partitioning is

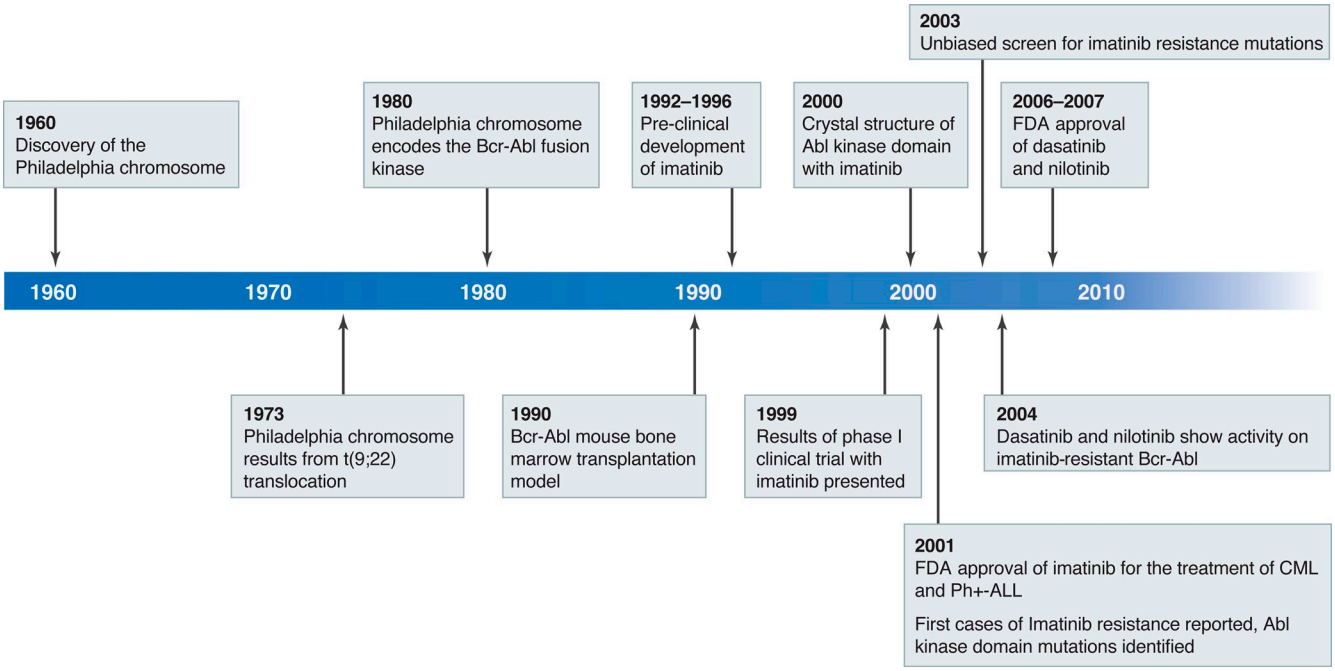

Figure 2. **Key events in the development of Bcr-Abl tyrosine kinase inhibitors.** A timeline that highlights some of the important breakthroughs that led to the development of Bcr-Abl tyrosine kinase inhibitors. Ph+-ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia.

still hazy. These many unknown molecular details may in part be the cause for the unclear mechanism of primary imatinib resistance. Also, the complex genetics and biology of the advanced disease stages of CML are not fully understood despite considerable efforts. Finally, CML is a prototypic stem cell disease, but the definition of CML stem cells and the factors governing their survival, self-renewal, and signaling are still heavily debated. Importantly, despite excellent improvements in overall survival of CML patients that was achieved over the past decade using tyrosine kinase inhibitors, CML is not curable. We believe that an even deeper understanding of Bcr-Abl biology and alternative "swim against the tide" approaches of targeting CML cells that go beyond simply generating new ATP-competitive inhibitors will be needed. These new approaches could include allosteric inhibitors, combinations of the growing arsenal of inhibitors, targeting kinases up- and downstream of Bcr-Abl, and targeting novel signaling nodes being identified in synthetic lethality screens and systems-type approaches.

Basic research has steered the development of many targeted cancer drugs

Until today, about a dozen small-molecule kinase inhibitors are FDA approved, all of which have become or are on their way to becoming blockbuster drugs for the producing pharmaceutical companies (Mullard, 2012). We describe a few examples that illustrate the outstanding importance of academic research in the development of these powerful drugs. A similar success story as Bcr-Abl inhibitors can be told on the development of the "first-in-class" JAK2 kinase inhibitor ruxolitinib that was approved for the treatment of myelofibrosis at the end of the last year (Mesa et al., 2012). In 2005, four different academic groups identified the activating point mutation V617F in the cytoplasmic JAK2 kinase in patients with polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), and subsequently developed mouse models for this group of diseases (Baxter et al., 2005; James et al., 2005; Kralovics et al., 2005; Levine et al., 2005). This immediately triggered the start of JAK2 drug discovery programs in several companies and resulted in the development of JAK2 inhibitors and their clinical evaluation in the following six years (Tefferi, 2012). Detailed work on the genetic basis of PV, ET, and PMF along with identification of several additional mutations by a number of different academic groups pointed out very early possible limitations of JAK2 targeting in PV and ET (Kralovics, 2008), and this information will be critical to developing better therapies for these diseases.

For another hematological disease, diffuse large B cell lymphoma (DLBCL), classical work defined a distinct molecular subtype of DLBCL characterized by chronically activated B cell receptor signaling that depends on the activity of the Btk kinase (Alizadeh et al., 2000; Davis et al., 2010). Again, these insights from academic research put Btk in the limelight for the pharmaceutical industry. Several Btk kinase inhibitors are now in clinical trials for both B cell lymphomas and chronic lymphocytic leukemia (CLL), as well as for autoimmune and chronic inflammatory disorders (Sheridan, 2012).

Although these examples are among the shining success stories of translational cancer research, they also illustrate the problems in the whole process and the decoupling of academia and industry. In all of them, the basic research community identified limitations in the use of a particular drugs, be it the identification of mechanisms of resistance or why a drug will not be effective in certain patients. Are there ways to better integrate the translation process across academia and industry?

Measures and suggestions

Our first suggestion is that cell biologists need to embrace systems-level approaches given that our understanding of most drugs' true mechanism of action, i.e., at the systems level, is embarrassingly small. Chaperone inhibitors, proteasome inhibitors, and drugs targeting epigenetic regulators all work through a semi-pleiotropic effect that we desperately should learn to assess. But ultimately, most therapeutic agents will affect molecular machines and processes likely to be already familiar to the community. Also, the list of protein–protein interactions targeted successfully is growing, raising the hopes that innumerable targeting possibilities will arise for the knowledgeable cell biologist (Arkin and Wells, 2004; Oltersdorf et al., 2005; Filippakopoulos et al., 2010). We speculate that to overcome one of the limiting factors in translational efforts, it is important to lower the barriers for molecular cell biologists to attempt pharmacological (or biological entity-mediated) interference with the protein and process they best know and understand. Cultural resentments should be dismantled, making the cell biology community more comfortable in playing with chemistry. There is increasing evidence that academia is contributing to the discovery of first-in-class experimental chemical agents with new mechanisms (Cuatrecasas, 2006), often using phenotypic screens (Swinney and Anthony, 2011). The main area where the pharmaceutical industry indeed has tremendously valuable leadership that should be safeguarded is drug development, in particular medicinal chemistry, ADME (absorption-distribution-metabolism-excretion), toxicology, and pharmaceutical formulation.

In addition to academic research laboratories valuing their research as inherently feasible for translation, industry should be less passive and opportunistic and also less responsive to general trends in their choice of project portfolios (see Fig. 1). Instead of waiting for innovation to trickle through the translational funnel until it hits the industry radar, strategic support of key laboratories showing leadership in the elucidation of key biological processes or protein families should be considered. Early, high-quality support with tools for chemical biology types of approaches would go a long way in both streamlining the value chain and diversifying the opportunities. The biotech industry, in the current financial environment short of cash, is ill positioned to cover enough of the interesting biology and be the sole broker between academia and pharma.

To summarize, for a general improvement of translational rates, we propose that academia and industry should enter into both more transparent and closer alliances than is currently the case. Instead of rushing "me-too" type of projects according to ever-changing fashions, trust should be placed in those academic laboratories with deep expertise in fundamentally important areas of biology. Chances are good that through the early alliance, common campaigns will flourish that will couple modern molecular cell biology with the true translational impact it deserves.

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