From Bench to Bedside: Does Preclinical Practice in Translational Oncology Need Some Rebuilding?

Andrea Bertotti and Livio Trusolino

Correspondence to: Andrea Bertotti, MD, PhD, Laboratory of Molecular Pharmacology, Institute for Cancer Research and Treatment (IRCC), SP142, km 3.95, 10060 Candiolo, Torino, Italy (e-mail: andrea.bertotti@ircc.it).

After years of enormous research efforts for the systematic cataloguing of genetic alterations with causative function in cancer, the goal of “personalized medicine” in clinical oncology is now potentially in reach (1). With the overall aim to characterize more than 25,000 genomes from the 50 more relevant cancer types, major international endeavors are ongoing to provide a complete inventory of oncogenic mutations (2). When combined with the massive capacity of modern pharmaceutical companies to screen for inhibitors that target “druggable” mutant gene products, this undertaking will offer unprecedented opportunities to treat cancer through “precision” approaches whereby therapeutic decisions are informed by the genomic makeup of each tumor in each patient.

Nevertheless, the ultimate clinical implementation of personalized medicine in oncology is still a major challenge. Indeed, the categorization of molecularly circumscribed tumor subpopulations featuring specific genetic lesions, the validation of such lesions as therapeutic targets, and the definition of biomarkers for accurate prediction of sensitivity to rational treatments face technical, logistic, and ethical limitations in patients. If cancer therapies must be tailored around small, genetically defined patient subgroups, the efforts essential to identify, recruit, and treat a number of patients great enough to validate the therapeutic relevance of new targets must be massive and may hardly justify high-risk drug development strategies. Highly reliable preclinical models for discrimination between “actionable” therapeutic opportunities and those with weak clinical transferability are thus urgently needed to improve the bench-to-bedside pipeline as a means to systematically increase the success rate of rationally based clinical trials.

Further pointing to this criticality, the comprehensive and informed review by Lieu and colleagues in this issue of the Journal (3) depicts a different scenario, in which bedside-to-bench approaches have been clearly dominating the drug development scene in the last decade. Most of the genetic biomarkers that are currently used to predict drug efficacy in patients have been originally identified by retrospective clinical studies, and only subsequently mechanistically validated using preclinical models. There are many prototypic examples of this, ranging from the observation that patients with EGFR-mutant or ALK-translocated lung cancer respond to blockade of the corresponding targets, to the demonstration that mutations in the KRAS gene correlate with lack of benefit from anti-EGFR antibodies in colorectal cancer (3).

By robustly validating previously identified biomarkers of response and resistance to drugs, a number of studies—both in cell lines (4,5) and patient-derived xenografts (6)—have demonstrated the potential of preclinical models as tools to generate clinically relevant predictions. However, the fact that these approaches have infrequently translated into reliable instruments for definition of successful trial designs reinforces the notion that preclinical methodology should be renewed and adapted to meet the current needs of translational research. This in turn could reinstate preclinical research to play a central role in defining priorities and strategies for the clinical development of drug candidates, hopefully contributing to overcoming the actual hitches in the field.

First, a consensus is needed to define unequivocally what should be deemed a successful endpoint at the preclinical level. If we agreed to raise the bar to more stringent criteria for the evaluation of treatment efficacy at the preclinical level, this would probably reduce the attrition of hypotheses during the clinical phases of experimentation. For example, as clearly stated by Lieu et al., there is growing evidence that predictions of drug sensitivity based on tumor regressions in vivo—especially when observed in patient-derived xenografts—are indeed more robust indicators of clinical transferability than those based on the more widely used criteria of tumor growth inhibition. However, although it is probably easy to reach a general agreement about these assumptions when targeting the cell-autonomous properties of cancer in vivo (mainly based on the concept of oncogene addiction), the situation is much less obvious when dealing with the tumor microenvironment. Within this context, the artifacts introduced by using nonhuman hosts are certainly more pronounced, and the definition of unquestionable, clinically relevant endpoints is not trivial. Even more complicated, the results of in vitro assays aiming at testing drug sensitivity in cancer cell lines can be barely correlated to direct measures of clinical efficacy. Thus, while remaining an invaluable resource for high-throughput screening approaches, hypothesis generation, and mechanistic investigation, cell lines should be considered mainly to be prioritization tools. In this view, cell line–based screens should be oriented at selecting promising options that deserve independent evaluation through in vivo approaches (ideally patient-derived xenograft based), which, albeit more laborious, are likely more interpretable in terms of translational implications. This will allow for the definition of clear-cut standards of preclinical activity, ideally based on objective endpoints that will demonstrate statistical correlation with clinical efficacy. In turn, consolidated preclinical knowledge will help rationalize risk assessment–based drug development policies for informed go/no-go decisions.
Second, efforts should be put at all levels to improve the preclinical representation of the complexity and heterogeneity of human cancer. One major requirement is to attain a large number of models. Because cancer is a highly heterogeneous disease, the only way to estimate the relevance and impact of a preclinical result is to gain an epidemiological contextualization of it. Indeed, to identify small subsets of rare or very rare variants, harbored by tiny patient subpopulations (which is very likely), population-scale studies (both in vitro and in vivo) are needed to guarantee the statistical power required to discriminate relevant correlations. Beside this, the experimental models per se should be refined to augment their intrinsic predictive proficiency. In vitro, promising results have been recently obtained in the setup of short- and long-term tissue cultures that better preserve the genetic and phenotypic features of cancer cells while maintaining the scalability typical of cell line studies (7). In vivo, host humanization approaches and complex models of genetically modified mice are paving the way for improved modeling of tumor–host interactions and for better prediction of activity when developing microenvironment-targeted drugs (8).

Third, but not less important, is the absolute need to leverage the informative potential of negative results. Historically, negative results have always been difficult to publish, leading to two harmful consequences: on one side, the widely diffuse habit of partial reporting, which introduces a highly distortive filter in the interpretation of an already very complex system; on the other, the impossibility to normalize the relevance and the consistency of new preclinical findings against the general level of experimental noise typical of biological systems. More open publishing policies, emphasizing the balancing role and the informative value of negative results (when obtained through robust methodologies), would certainly increase the overall reliability of preclinical studies.

Unfortunately, the current treatment for metastatic castration-resistant prostate cancer remains mostly palliative with little additional benefit. In this issue of the Journal, Wang and colleagues (1) present a landmark article that uncovers the Achilles heel of prostate cancer, which is cleverly disguised as the system L-type transporters (LATs). The LATs are amino acid exchangers that import the branched chain amino acids (such as leucine) in exchange for other intracellular amino acids (such as glutamine). The “Warburg effect” is a term often used to describe cancer cells that have an adapted metabolic profile. Such cancer cells have enhanced glucose uptake and even in the presence of oxygen, glucose is rapidly broken down by anaerobic metabolism. In a manner analogous to the dependency upon glucose in the Warburg effect, metastatic prostate cancer has an appetite for leucine. The research led by Dr. Jeff Holst reveals that metastatic castration-resistant prostate cancer cells are highly dependent on amino acid uptake through LATs for their growth and proliferation, as well as their malignant transformation (1). Discovery of this leucine hunger in metastatic prostate

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Affiliations of authors: Department of Oncology, University of Torino Medical School (AB, LT); Laboratory of Molecular Pharmacology, Institute for Cancer Research and Treatment (AB, LT), Candiolo, Torino, Italy.

Metastatic Castration-Resistant Prostate Cancer Hunger for Leucine

Andrew R. Tee

Correspondence to: Andrew R. Tee, B.Sc., PhD, Institute of Cancer and Genetics, Cardiff University, Heath Park, Cardiff, Wales, CF14 4XN, UK (e-mail: teea@cardiff.ac.uk).

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