The Translational Research Working Group Developmental Pathway for Anticancer Agents (Drugs or Biologics)

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Abstract

The Translational Research Working Group (TRWG) was created as a national initiative to evaluate the current status of the National Cancer Institute's investment in translational research and envision its future. The TRWG conceptualized translational research as a set of six developmental processes or pathways focused on various clinical goals. One of those pathways describes the development of agents—both small molecules and biologics—for the treatment and prevention of cancer. The Agents Developmental Pathway was conceived not as a comprehensive description of the corresponding real-world processes, but rather as a tool designed to facilitate movement of an agent through the translational process to the point where it can begin definitive clinical testing. This article presents the Agents Developmental Pathway and discusses key challenges associated with the processes described.

Agents (small molecule or biological compounds for the prevention or treatment of cancer) are some of the most familiar and important of anticancer interventions, and the process by which such agents are developed is considered a well-trodden path. However, by documenting the individual steps in the process and their relationships, the Agents Developmental Pathway created by the Translational Research Working Group (TRWG) reveals the intricacies of the process, and also the substantial number and nature of the challenges faced as a compound moves from the discovery benchtop to the clinic. An introduction and overview to the TRWG Developmental Pathways to Clinical Goals in general is found in Hawk et al. (1). In the sections that follow, we briefly describe key aspects of the Agents Developmental Pathway that present particular challenges or require improvement in design or implementation, so as to improve the efficiency of bringing new compounds to the clinic as drugs for human testing. The various steps of the Agents Developmental Pathway are depicted in Fig. 1.

Credentialed

The first decision diamond in the Agents Developmental Pathway, determining if a target has clinical potential, turns out to be far from straightforward (Fig. 1). This exercise, which has been termed target validation, asks the question: is the scientific basis for attributing clinical potential to the target convincing? Considering this crucial question is perhaps even more difficult in the age of targeted therapy, where variability in the experimental approaches used for target validation can have a larger effect than is seen with more traditional cytotoxic drugs.

The presence of the putative target in a tumor, even when the target is overexpressed or correlated with poor clinical outcomes, does not by itself predict that a drug directed against that target will be effective. Instructive in this regard is the contrast between the importance of the BCR-ABL tyrosine kinase (the product of a somatic genetic translocation between BCR and ABL genes) in chronic myeloid leukemia, and the epidermal growth factor receptor (EGFR) in non–small cell lung cancer and in colon cancer. Essentially all chronic myeloid leukemia cases express the BCR-ABL protein, which is pathognomonic of the diagnosis and drives progression of the malignancy (2–7). Inhibiting BCR-ABL with imatinib produces major clinical benefits for nearly all patients with chronic myeloid leukemia (8, 9). In contrast, whereas the great majority of non–small cell lung cancer and colon cancers express EGFR, its function is not necessarily required for the diseases to progress. Indeed, inhibiting EGFR with erlotinib or gefitinib in non–small cell lung cancer (10–17), or with cetuximab in colon cancer (18, 19), produces minimal benefits in unselected patients with these diseases. However, lung cancer patients with mutation or amplification of the EGFR gene are considerably more likely to respond to EGFR inhibitors.

In general, “agents” is defined to include targeted antibodies, wherever their mode of action is not primarily related to the immune system. The Immune Response Modifier Pathway addresses those modalities (cytokines, vaccines, etc.) whose primary mode of action is to modulate the immune system, especially those that involve the integration of multiple components such as antigens, delivery vehicles, and immune modulators.
In colon cancer, these alterations of the target are rare; activity of EGFR inhibitors seems more closely linked to overexpression of the EGFR ligands epiregulin and amphiregulin in tumor tissue (20). More importantly, if signal transduction pathways are activated downstream of EGFR—for example, in the case of \textit{K-ras} mutation—inhibition of EGFR does not seem to affect the tumor in a clinically meaningful way (20, 21).

Examples such as these underscore the complexity of biological processes and the challenges of rational targeting as a therapeutic strategy. The central challenge of target validation is to increase the predictive value of the fundamental knowledge about physiologic and pathophysiologic processes, thus improving the success rate and cost-effectiveness of drug development, while creating compounds with both adequate safety and efficacy (22). Obstacles to a successful drug target validation effort (and overall drug development process) include:

- Limitations in available animal models, including their fidelity to natural disease processes and their relevance to humans; problems can include species differences in target distribution, activity, and relevance to the disease process, as well as differences in response to the agent in question.
- No systematic assessment of the predictive utility of alternative models.
- Restrictive licensing of certain patented technologies related to genetically modified animals.
- Reliance on a narrow range of analytic and experimental tools for perturbing and characterizing animal models and human tissues.
- Insufficient understanding of pathophysiologic processes, particularly from an integrated systems biology perspective.
- The need for tools that can reliably model safety as well as efficacy, particularly for those effects on normal tissues that extend beyond rapidly proliferating cellular compartments; for example, cardiac and nerve tissue.
- Insufficient attention to quantitative as well as qualitative elements of pathophysiologic processes.
- Bias—in judging “ripeness” for translation—in favor of existing agent classes and familiar validation methods.
- The need for tools to screen large numbers of candidates that will prune those not worthy of more detailed and definitive validation and prioritize those that are.
- The need for greater attention to the methodologic quality, systematic analysis, and dissemination of negative results.
- Insufficient clarity and consensus on the character and quantity of evidence sufficient to justify investment in translation.

If target validation could be considered a critical but distinctive “enabling technology” in its own right, translational research may benefit from an initiative to define the status and limits of the technology in greater detail, set priorities for its improvement, and focus resources on the prioritized activities. Such an initiative should be implemented as a collaborative effort involving researchers from academia, government, and industry.

The quality of the evidence collected in support of the clinical potential of a target greatly informs the second and third decision diamonds in the Agents Developmental Pathway (Fig. 1), which ask whether the envisioned clinical need justifies the expense of drug discovery and development, and whether creating an agent to hit the target is technically feasible. All three questions (the first three decision diamonds in the Pathway) are considered in the “credentialing” of a target, and the answers need to be sufficiently robust to make a decision to proceed with further translational activities as outlined in the Pathway.
Supporting Tools

With an adequately credentialed molecular target—scientific validation, a critically unmet medical need, and a feasible strategy for drug design—the Agents Development Pathway next proceeds along parallel tracks aimed to produce the key components for an initial clinical trial: an agent, a pharmacodynamic assay for target inhibition, and a stratification test for identifying which patients are most likely to benefit from treatment (Fig. 1). Some of the supporting tools for drug discovery and development, including cell culture or animal models, reagents for target detection, and target function assessment, etc., are the legacy of target validation experiments; other such tools need to be established. As such, some of the limitations of current approaches to target validation define a compelling agenda for the development of additional research tools and resources. Closer interaction among discovery researchers is needed to move beyond the simple model of, first, identifying a target, and then, handing off a target for validation and translation. A more collaborative translational model would encourage and incentivize continual, bidirectional exchange of information and insights about the science underlying the biology of the target molecule and the pathways in which it is active. This section identifies some relevant issues and considerations, albeit in a nonsystematic way.

A critical step in the creation of a new agent is to verify that it decreases oncogenic activity. To do so, a model system or assay is needed for which the molecular target is responsible for the oncogenic phenotype (the fourth decision diamond in the Pathway; Fig. 1). This raises key questions: do the preclinical efficacy models—key supporting tools in the development process—fairly represent human tumor biology and predict drug effects in human cancer? Is the drug target present in the model tumor? Is it inhibited at drug concentrations that are achievable in humans? Are drug-sensitive and drug-resistant model tumors characterized in sufficient molecular detail to provide insight into the molecular features that might predict or explain drug effect in humans? If so, is it possible to derive predictive biomarkers in animal models that will be useful in the clinical assessment of a new agent?

Current experimental technologies used to validate targets in cell culture models or animal models typically involve cells or mice in which the expression of selected genes is ”knocked-out,” ”knocked-in,” or ”knocked-down” by genetic manipulation or exposure to small interfering RNA. These powerful experimental techniques provide valuable insights into physiologic and pathophysiologic mechanisms. Nonetheless, whether such models can recapitulate all the phenotypic attributes of human cancers, or anticipate the actions of targeted drugs, is not as clear. For example, it may be inappropriate to assume that a population of cells with a knocked-out receptor tyrosine kinase behaves in the same way as a comparable population in which the tyrosine kinase has been pharmacologically inhibited to a variable extent and for a limited time.

Tumor models vary in complexity, ranging from simple two-dimensional monolayer cell cultures through a variety of increasingly sophisticated three-dimensional culture systems, simple animal xenografts, and more complex genetic models of spontaneously arising tumors. Research continues to develop systems that capture essential aspects of the tumor microenvironment with greater realism, including the local immune response, the contributions of host non–tumor cells, soluble factors in the extracellular matrix, and other factors.

The increasing focus on antibodies and other targeted agents poses a systematic challenge to nonclinical modeling because it is more likely that such agents will evoke therapeutic and/or toxic effects that are species-specific. As a general matter, one must take into account potential species-specific differences in drug metabolism or, in the case of antibodies, whether immunogenicity issues confound the study of the drug in an animal model. An emerging issue is whether animal models can even predict some of the common toxicities of many targeted therapies. For example, most animal models are unable to assess such adverse effects as fatigue, hand-foot syndrome, neuropathy, or cardiac toxicity. Over the longer run, it is hoped that advances in systems biology and in silico modeling may facilitate an understanding of both therapeutic and toxic effects.

A key feature of the Agents Developmental Pathway is the parallel pursuit of critical biomarkers that can be used to assess whether a new agent is affecting the desired process/target (pharmacodynamic end point markers), to identify responders earlier than traditional radiographic measures (intermediate efficacy markers), or to identify patients that should or should not be enrolled in studies of specific agents (treatment stratification markers). These critical processes are captured in parallel flows in the Agents Developmental Pathway which converge at the time of clinical trials, permitting rapid and efficient assessment of whether the new agent hits the molecular target, and by doing so, affects the cancer in patients most likely to benefit from treatment (Fig. 1).

One subtlety is often overlooked in the development of molecular biomarker tools for drug discovery and development: assays that will support manufacturing, clinical research, or clinical practice must be reproducible outside of the original investigational setting. Developing such assays is an equally challenging process (see the discussion of the biospecimen-based assessment device pathway; ref. 23). Research on these auxiliary tools is essential to bring new agents efficiently to market and to realize their clinical benefit in real-world practice.

In addition, in order to anticipate which molecular subtypes of which cancers might best be treated in which patients, extensive studies are needed not only of animal models but of collections of human tumors to determine whether the target is present, whether the gene for it is mutated or amplified, whether any of these states correlate with clinical outcomes, and whether the target is, in fact, the control point for the relevant pathophysiologic pathway. This research, portrayed in the right-hand portion of the parallel flow diagrams in the Agents Development Pathway (Fig. 1), requires the availability of clinically annotated human tumor specimens from large numbers of patients with known clinical outcomes, preferably in a format amenable to large-scale screening efforts.
Selection and refinement of the appropriate targeted agent, through lead identification and optimization, is reflected in the Agents Developmental Pathway as an oval inside of a rectangle, intended to describe the recursive activities of chemical and structural biology, antibody and protein engineering, etc. (Fig. 1). An important feature of this activity in the Agents Developmental Pathway is the heterogeneity of the therapeutic entities; for example, small molecules, antibodies, cellular therapies, oligonucleotides, nanoparticles, and many others. Of the existing targeted anticancer drugs, the small molecules and antibodies present illustrative differences highlighting the varied challenges in agent development. Small molecules are generally easier to make, easier to modify, can in many cases be administered orally, and also may be readily developed to hit multiple targets, which might make them more effective yet also more toxic. Antibodies are typically more difficult and costly to make or modify; they require i.v. administration, reach extracellular targets only, and tend to be highly target-specific and therefore potentially less toxic.

An antibody might be a better strategy when investigators are certain of the target and its importance in cancer pathophysiology. If a target is less sharply specified, however, hitting multiple targets with a small molecule may increase the chances of success—in “targeted” therapy, a little promiscuity can be a good thing!

The spectrum of proteins that provide targets for traditional small molecules is relatively limited; protein targets must have binding pockets that drugs can bind, and in so doing, alter function. Antibodies expand the range of targets and newly emerging approaches modeled on small interfering RNA or small RNA molecules greatly expand the approach to nearly any protein. This approach is very helpful in the laboratory, but to date, clinical applicability faces the challenge of delivering the reagent to the target cells in a specific, efficient, and tolerable fashion.

Nonetheless, chemists are now able to generate large numbers of inhibitors even for traditional targets. As with targets, so with agents: new approaches are needed to identify lead candidates from among the vast number of possibilities. (Drugs can fail for many reasons: toxicity of the parent drug or a metabolite, lack of efficacy, drug-drug interactions, or pharmacokinetic considerations such as poor bioavailability, limited biodistribution, rapid clearance and others.) To produce effective drugs, we need to better understand and optimize the chemical and pharmaceutical properties of lead compounds.

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**Creation of Modality**

**Example of the Use of the Agents Developmental Pathway**

The development of bortezomib (marketed as Velcade) is an instructive example of the use of the Agents Developmental Pathway schema. Interest in the role of the proteasome, a complex of enzymes involved in degradation of misfolded proteins, in inflammatory processes and in carcinogenesis grew during the mid-1990s (24). In particular, the recognition that nuclear factor-κB, a proinflammatory transcription factor that can promote the survival of cancer cells, was activated via proteasomal degradation of its inhibitory binding partner IκB, provided a strong rationale for the discovery of small molecule proteasome inhibitors by investigators at ProScript, Inc. (25–30).

With these small molecule inhibitors, target validation studies were undertaken that revealed cell cycle arrest and apoptosis associated with inhibitor treatment in cancer cell lines, and IC50 concentrations for cancer cell growth arrest that correlated strongly with Ki concentrations for proteasome inhibition (31). These validation data, along with strategic decisions about the commercial promise of small molecule proteasome inhibitors, credentialed the target and embodied ProScript to proceed with the discovery and development of a proteasome inhibitor drug for cancer. To move forward with drug discovery and development, the ProScript group developed an *in vitro* fluorometric assay for proteasome inhibition, which served as a pharmacodynamic biomarker and supporting tool (one of the parallel tracks in the Agents Developmental Pathway) for the effectiveness of this class of drugs (32). Structure-activity/lead optimization activities (the oval within a rectangle in the Pathway) were assisted by the National Cancer Institute Developmental Therapeutics Program, featuring *in vitro* and animal model studies that identified one of these inhibitors, PS-341 (now termed bortezomib), as the best candidate agent from among the group of dipeptide boronic acid compounds that ProScript provided for testing (31).

In the ideal Agents Developmental Pathway, proteasome inhibitors should have reached the first human trials with: (a) an agent, e.g., bortezomib, that was formulated for human administration with appropriate toxicology, stability, and other requirements necessary for an Investigational New Drug application with the Food and Drug Administration, (b) a pharmacodynamic assay of drug inhibition of the proteasome that could be used in clinical trials, and (c) a...
tool for identifying which cancer patients would most likely benefit from proteasome inhibitor treatment. Unfortunately, there was no such treatment stratification tool developed. Instead, the issue of who should be treated with bortezomib was left to empiric preclinical and clinical development, a substantially less efficient strategy. ProScript pursued preclinical studies of PS-341 internally and with collaborators, enabling phase I clinical trials to be completed which established a tolerable human dose and schedule of administration for further clinical development (33). Of note, preclinical studies using myeloma cells and xenograft models had suggested that bortezomib might prove effective against human myeloma (34, 35). The acquisition of ProScript by Millennium Pharmaceuticals resulted in phase II trials in patients with multiple myeloma that ultimately led to approval of the drug by the Food and Drug Administration (36). The timeline of bortezomib development was less than 10 years from the development of proteasome inhibitors at ProScript (1994) to Food and Drug Administration approval (2003).

Optimal Management of the Translational Process

The Agents Developmental Pathway captures the range of activities needed to bring an innovative therapeutic concept to fruition as a specific agent that is ready for clinical trials. These different activities require a range of skills and experiences. Many kinds of team activities are required—for example, solving the structures of related proteins within a family; elucidating detailed mechanisms of action and toxicity; assessing structure/activity relationships across large, multidimensional families of agents; and developing and validating Good Manufacturing Practices in new assays and other supporting tools. Most of these team activities do not provide the incentives currently valued by researchers in academia, including opportunities for funding, publication, and promotion. Researchers in industry, working under a different set of expectations and incentives, generally have a low threshold for discarding candidates that carry excessive risks as a commercial investment.

Wholesale culture change is unlikely—in academia or in industry—and would risk neutralizing the virtues inherent in these respective cultures. At the same time, completing the path from discovery research to tangible agent entirely within a single organization or sector is not necessarily ideal, and unlikely to be feasible. More attention is needed to effectively choreograph the relationships between academia, government, and industry, so that each stage of the development process occurs in those settings—and with those inputs, ideas, skills and resources—that are most conducive to a successful and cost-effective outcome. Government could play an important role by adjusting policies and incentives that would promote such integration. Improving communication among all parties is key, to assure that needs and opportunities at each step along the Developmental Pathway are optimally matched to capabilities and resources. The goal is nothing less than to increase the pace and productivity of the nation’s overall translational effort.

New Frontiers in Agent Translational Research

Research continues to reveal the complexity of oncogenic pathways, including the complex feedback systems that regulate them, thus suggesting the potential value of rational combinations of targeted agents. This suggests a number of possible strategies: inhibiting multiple parallel paths simultaneously or sequentially and targeting a pathway at two or more levels by two or more different agents, which potentially reduces the risk that resistance will emerge via compensatory feedback loops. In principle, such combinations could involve agents that manifest little or no clinical effect individually, or which show an individual effect in some settings but not in others.

Developing novel combination regimens of targeted agents will likely require researchers to address issues such as sequence of drug administration, interval of drug administration, drug interactions, and tolerability of combination regimens. The effort to develop successful biomarkers may be aided by arrays of markers that capture the combination of attributes that identify those patients most likely to benefit from a targeted combination regimen. The field would benefit from more sophisticated ways of characterizing stable disease and tumor response rather than relying on two-dimensional anatomic imaging as defined by the Response Evaluation Criteria in Solid Tumors (37). Volumetric or functional imaging approaches may better reveal drug activity, particularly for targeted agents. As this new line of translational research emerges, it may be useful to adapt the Agents Developmental Pathway to include explicit parallel elements to capture the challenges of parallel development and integration of multiple components in a therapeutic modality. The Pathway is intended to be dynamic and adaptable to new strategies that improve the efficiency of moving drugs from the laboratory to the clinic.

Conclusion

Emerging insights into the molecular pathogenesis of human cancers have ushered in a new era of treatment that selectively targets the phenotypic consequences of somatic genome alterations. The discovery and development of molecularly targeted drugs has benefited from, and will continue to require, translational research strategies and methods. To better understand the processes by which anticancer drugs reach human clinical trials, a formal Agents Developmental Pathway has been constructed, starting with a molecular target and culminating in a phase I/II clinical trial. The Pathway captures key decision points, such as target validation and credentialing, and emphasizes the parallel development of specific agents and supporting tools needed to test new treatments efficiently in human studies. With the Agents Developmental Pathway as a general guide, translational researchers will be able to better traverse the complex terrain of drug development and, hopefully, improve the speed and efficiency of the process and the probability of success.

Disclosure of Potential Conflicts of Interest

T.M. Gilmer is an employee and stockholder of GlaxoSmithKline.
References


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