Translational science: past, present, and future

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The concept of translational science is at least 15 years old. However, in its most recent incarnation, it represents the identification of a funding category designed to encourage academic participation in a critical stage of the drug discovery and product development process. It is hoped that this will make the process both shorter and more efficient. In this review, the author first considers the historical development of the pharmaceutical R&D process. The place of translational science in the process, the scientific techniques involved, and aspects of the business environment necessary for its success are then considered. Translational science does not displace preclinical development. Both concepts are relevant to the paramount importance of successfully and expeditiously bridging the gap between preclinical science and clinical testing, "from bench to bedside." Translational science is particularly likely to stimulate biomarker research in the universities and related business community and will probably give a modest boost to early clinical testing and commercialization of discoveries within the academic setting. Whether there will be a consequent improvement in the quality and efficiency of the overall process remains to be seen.

INTRODUCTION

From time to time there is a paradigm shift in the way in which new drug products are invented and in the underlying science on which the inventions are based. The advent of translational science (sometimes called translational research or medicine) is one of those paradigm shifts. At its core is the identification of a funding category for making public money available to facilitate the movement of an idea from bench to bedside.

Seemingly for decades, there has been criticism of the drug discovery and development process, as practiced by the biotechnology and pharmaceutical industries, as too slow and too inefficient. These are obviously related issues—the current conventional wisdom is that up to 15 years are needed to take an original idea to first product introduction, that approximately one billion dollars of expenditure will be involved, and that only one in every 5000–10,000 compounds synthesized will become products. There is a general idea that a time of seven years and a success rate more like 1 in 250 compounds is feasible. Unfortunately, the changes in the process evolve over many years, albeit with the occasional signal event causing a specific, instant change. Measurement of the impact of change is difficult—basically, the changes in the process are followed by further changes before their impact can be measured.

The process of discovery of new drugs and their full evaluation in the patients for whom they are designed involves at least five crucial extrapolations: (*i*) from physicochemical properties to biology (structure-activity relationships); (*ii*) from in vitro to in vivo (within animal species and within humans); (*iii*) from animals to healthy human volunteers (phase I—human safety and pharmacological proof of concept studies); (*iv*) from single doses to multiple doses; and (*v*) from healthy volunteers to patients (including pathology and drug interaction considerations).

Of these, the extrapolation from animals to humans is probably the most significant (1). This step is now viewed as a critical component of a broader area of interest, termed translational science, which potentially embraces four of the five extrapolations listed above, excluding only structure-activity relationships.

Historical Considerations

The term translational science can be traced back to the early 1990s in the literature describing biology-based attempts to find new drugs for cancer (2–7). It has since found its way into the literature concerned with cardiology, stroke, psychiatry, pathology, and other areas of medicine (8–14). It has been the subject of multiple catch phrases, such as "bridging the chasm," "walking the bridge," "lost in translation," "bridging the gap," and most prominently "from bench to bedside" (3,8,9,15,16). The literature has been, obviously, concerned with the science, but has found its way into ethics, finances and commercial viability, informatics, artificial adaptive systems, and electronic health records (17–24). Questions have been raised about whether it is new and what exactly it is (5,22,23,25). The reality is that in its current manifestation, it is new jargon for an eminently fundable area of medical science identified as

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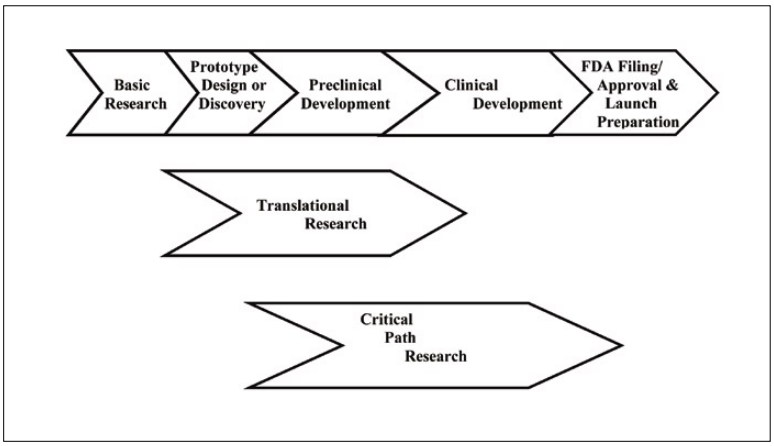

Figure 1. Translational science as defined by the Food and Drug Administration (FDA).

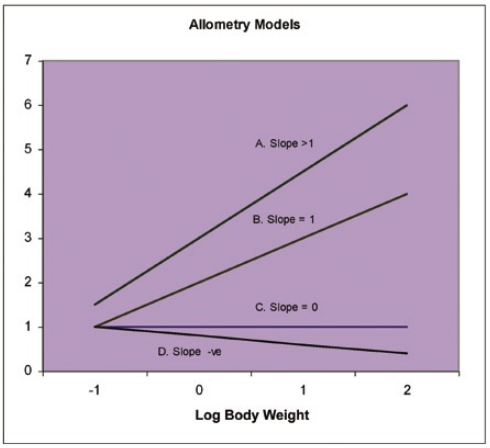

Figure 2. Model for allometric scaling.

Table 1. Examples of Allometric Relationships

Parameter	Constant
Heart rate	-0.28
Kel (rate constant of elimination)	-0.24
Drug half-life	0.24
Systemic clearance in vivo	0.70
Renal clearance of drugs	0.78
Apparent volume of distribution	0.95

important in the National Institutes of Health (NIH) Roadmap and comparable documents from the Food and Drug Administration (FDA) (26,27; see also www.fda.gov/oc/initiatives/criticalpath/whitepaper.html; downloaded 12/5/2006, Challenge and Opportunity on the Critical Path to New Medical Products; and nihroadmap.nih.gov/clinicalresearch/overview-translational.asp; downloaded 12/11/2007, NIH Roadmap for Medical Research). Philosophically, it seems to be connected with the movement into control by the academic community and partially in the public domain, of clinical research, work hitherto organized by the pharmaceutical industry, albeit using university hospital facilities. Academic units dedicated to translational research are cropping up rapidly in such places as New York City, Rochester (NY), Pittsburgh, Cincinnati, Atlanta, and California.

Translational research has been defined as the drug development phase in which preclinical and clinical applied research is conducted to aid dose and disease selection *with great financial impact* (author's emphasis). Its identification is intimately connected with the Critical Path Initiative of the FDA. In their desire to assist in the expeditious movement forward of the new drug discovery process, the FDA leadership has generated the diagram shown in Figure 1 to illustrate the prevailing view of which parts of the drug discovery and development process should be designated as components of translational science and of the critical path. This figure is redrawn from the FDA web site, and it shows the five standard sections of the drug discovery and development process (basic research to the final regulatory phase) and translational research as a phase from the beginning of prototype research to the end of the early part of clinical development (basically the end of phase II). The Critical Path as identified by NIH is from the beginning of preclinical development to the end of clinical trials. Thus, to relate this new jargon to older concepts, translational research is late discovery and preclinical development (preformulation, chemistry scale-up, safety studies, and phase I human pharmacology). The Critical Path reference is to preclinical and clinical development.

What is new about the identification of translational science? Historically, and by that is meant in the first half of the twentieth century, the organic chemists synthesized new drugs largely within existing families of chemicals. Thus, there was a time when the search for new drug products involved the synthesis of a new barbiturate, a new sulfonamide, or a new phenothiazine, or a little more recently, a new benzodiazepine. Approximately one-third of the classification of drugs was on the basis of chemical groups. There was considerable experience of these chemical series, and a new example could be expected to be a significant improvement on its predecessors within the context of a familiar risk-benefit combination. Big surprises were not expected from a new member of such a chemical class. The consequence was that brief exposure in animal safety studies was enough. Initial testing in human volunteers then proceeded cautiously.

The thalidomide disaster in the 1960s was a salutary event. Novel chemical series were beginning to be tested, potentially for medical conditions for which there was no prior treatment. There was a new realization and provision of impetus for more predictive safety studies, and new toxicity tests were devised, durations of toxicity studies were defined, and quality maintenance systems (good laboratory practice; GLP) were put in place to ensure a higher standard of data capture and recording. However, in the 1970s and 1980s, the gap between research and development, between animals and humans, remained wide, and it was standard practice for research and development functions to be physi-

Figure 3. Critical factors in translational science.

cally, organizationally, and philosophically separate. The research scientists would invent a molecule, which met chemical and pharmacological criteria, and hand it to the development departments to investigate. Neither group was involved in the activities of the other. Associated with this was a high level of failure in GLP toxicology, pharmacokinetic studies in phase I, and often major difficulty in the pharmaceutical formulation and chemical scale-up processes.

Around 1990, concepts of preclinical development began to emerge. For the first time, preformulation (studies of physical and chemical properties relevant to pharmaceutical science), pharmacokinetics in the pharmacological test species, and experimental (pre-GLP) toxicology began to be incorporated into the drug discovery process. Additionally, there was new involvement in the process by the scale-up (process) chemists, the medical department, and even strategic marketing in the expectation that this would lead to "better" molecules being chosen for GLP toxicology and then for phase I. This was expected to reduce the attrition rate and the time for movement of molecules to the patient group for which they were designed.

Another major change in the process in recent years has been the atrophy, relatively speaking, of chemistry-based drug discovery and a parallel trend toward utilization of biological techniques as a substitute. This has been discussed in the *Wall Street Journal* (online.wsj.com/article_print/SB119430106055083082.html; downloaded 12/15/2007). The reader is encouraged to view the text "Periodic Table to DNA Cloning" with an excellent tabulated comparison of methods, tools used, pros and cons, major players, and currently available "big products." Two drugs, now in widespread use, with their origins in biological science, are tissue plasminogen activator (TPA) and trastuzumab. Two key scientific approaches to this brave new world are especially relevant—allometric scaling and biomarkers.

Allometric Scaling

This approach to interspecies relationships makes, at least in the version used in this context, the naive assumption that smaller animals are doing (biochemically and physiologically) more or less what humans do, only faster (1). So, their hearts are beating but more times per minute, etc. This is encapsulated in the equation $Y = aW^b$, in which Y is a pharmacokinetic or pharmacodynamic function (a "parameter"), W is body weight in kg, b is an allometric exponent, and a is an allometric coefficient. A logarithmic transformation of this equation yields: $\text{Log } Y = \log a + b \log W$, where a is the y-intercept and b is the slope of a log-log plot. The constants a and b can be determined from studies in rats, dogs, and marmosets, or obtained from tables of widely applicable estimates, and then the constants in humans for the parameter in question can be estimated.

In practice, we pay little or no attention to the constant a. The constant b, however, is the allometric exponent. Pharmacokineticists and pharmacologists seek straight-line relationships with slopes and intercepts. The general form of this equation tells us that the logarithm of our parameter, the characteristic of the population, relates to the logarithm of body weight in a linear function, with two constants characterizing the system—the slope here is positive, so the parameter increases with species body weight.

Figure 2 shows a selection of model relationships revealed by allometry. This figure shows four possible relationships between log of a parameter (arbitrary units) and log body weight (in kg). Line A is for a parameter that occurs faster or is larger in larger animals in excess of a linear relationship with weight. The possibility of a linear relationship is shown by line B. Line C is for a parameter that is the same in all species (e.g., number of eyes). Line D is for a parameter that occurs more slowly or is smaller in larger animals (e.g., heart rate). For examples, see Table 1, which shows some allometric relationships relevant to pharmacokinetics. Physiologically, the allometric exponents are approximately 0.3. For example, elephants have heart rates slower than ours, and rats have faster heart rates—in both cases out of proportion to the difference in weight.

We particularly use these exponents to predict the half-life of a new drug in humans based on animal data. We have to evaluate the relative significance of physical properties of drugs, physiological influences on their disposition, and biochemical influences on their elimination. This requires educated judgments and accurate predictions. The significance is that the process helps us choose the correct magnitude of doses in, and duration of, phase I studies, and the frequency of the measurement in the phase I study. The better the prediction, the safer, faster, and more economical is the study. As a rule of thumb, the half-life in the human will be in the range 3–12 times that in the rat, with a relatively low factor if elimination is mostly dependent on physical processes, and a relatively high factor if elimination is mostly dependent on metabolism in the liver.

There is also a form of allometric scaling that permits the prediction of responses in vivo from in vitro data, and this is relevant to the field of biomarkers.

Biomarkers

Biomarkers are primarily designed to predict pharmacological responses across species (28–32). Anything that measures a physiological, biochemical, or pharmacological event is a biomarker. Thus, there are imaging biomarkers (e.g., positron emission tomography or PET) for studying the

disposition of drug molecules. For example, differences between healthy volunteers and patients in the brain distribution of certain drugs designed to be used in the treatment of Alzheimer's disease have been shown using PET, thus identifying the receptor areas for the drugs (33). Also, changes in endogenous macromolecules, which indicate pathological and pharmacological changes, observations such as blood pressure changes, and conventional blood chemistry qualify. Biomarkers permit assessment of both pathology and drug effects.

One of the most quoted examples is not new. Our knowledge of the blood-clotting cascade is highly developed, and the reactions involved can be studied both in vivo and in vitro, in animals and humans. Discovery of a new anticoagulant could involve studies in vitro, in animals and in humans with measurement of relevant biochemistry in vitro and in vivo, and of prothrombin time in animals and humans. Clotting time is used in modern medicine to assess the success of treatment with warfarin. However, all of the current excitement is around DNA-based gene sequence tests and proteomics, providing opportunities for the study of mechanism-based pharmacokinetic/pharmacodynamic (PK/PD) relationships—including simultaneous PK and PD events, the relationships between them, and the mechanisms that relate them.

Biomarkers permit the collection of data about the potential of a drug to successfully treat patient groups, to design clinical studies, to help in the identification of the best compound in a chemical series, to improve the objectivity of clinical trials, and to facilitate a step toward the goal of personalized medicine. Biomarkers also greatly enhance our potential to predict from in vitro studies which drug from among a group of candidates will give the best response in humans, greatly accelerating the movements of ideas "from bench to bedside."

One of the ways in which this may be facilitated is the use of large databases resulting from high-throughput screening in computer-facilitated studies of quantitative structure activity relationships (QSAR). For example, data can be collected from literally millions of compounds on such pharmacokinetics-related properties as metabolic stability, absorption, protein-xenobiotic interactions, and the Ames test. QSAR is studied using computer technologies relating the properties of molecules to topographical descriptors of the drug molecules. Hypotheses are generated, for example, for microsome-based metabolic prediction (systems absorption, distribution, metabolism, excretion, and toxicity or ADME/TOX), interactions between drugs and their receptors, and predicted human responses. Training groups and proposals for synthesis of molecules permit early triaging of compounds into useless, middle, and excellent compounds, permitting further iteration to lead rapidly to the best compound that can be proposed. Our fundamental need is for biomarker-based in vitro tests that scale to patients with, figuratively speaking, a slope of zero.

When all is said and done, PD and PK do not design the phase I study. The responsible physician must take into account all available information, and his or her primary concern has to be the safety of the subjects. Historically, phase I dosing has started with incredibly conservative exposure levels. The investigator will take note of all available data, checking on special situations, make compounds with other similar compounds, scrutinize toxicity data, etc., and if satisfied will probably choose a dose 1/100 or 1/40th of the lowest active dose in laboratory animals. He or she will then plan a strategy of exposure with increasing doses involving gradually enlarging increments. He or she will plan a blood-sampling scheme, which allows him or her to evaluate the half-life early in the investigation before the concentrations decline or later in the investigation (also) if the drug stays in the body a long time. Historically, the problem with this approach is that it moves slowly, and it is expensive with more exposures and blood samples than is desirable. Sometimes, the very small doses early on in this plan are effectively homeopathic and undetectable using analytical equipment.

Human Microdosing

Human microdosing is driven by developments in bioanalysis, which year by year provides us with new techniques to quantitate ever-lower concentrations of new drugs and the ability to do pharmacokinetic work at earlier stages in phase I. This has also been designated as phase zero (34).

Table 2. Categories and Examples of Biomarkers in Various Stages of Development and Use

Type of Measurement	Example	Comments and Applications
Blood chemistry	Glucose, lipid profile	Detection of disease and monitoring of drug treatment.
In vitro biochemistry-based functional test	Clotting time/prothrombin time	Monitoring treatment with anticoagulants in patients; relationship to mechanisms in vitro in animals and humans clear.
Flow cytometry micronucleus assays	Micronucleus-based indicator of chromosomal damage	Assessing mutagenicity of investigative drugs in blood and/or bone marrow in animals and/or humans.
Gene expression	Soluble Kim-1 in blood	Kim-1 is kidney injury molecule, detectable in patients with acute tubular necrosis and in rats with toxicant-induced kidney damage.
Proteomics	Cardiac serum biomarkers	Blood proteins for identifying and analyzing cardiac disease and monitoring drug treatment.
Imaging	Positron emission tomography (PET)	Tissue concentrations of drugs and other molecules in vivo including validation and assessment of targets and drugs interacting with them.

Inactive doses are used (e.g., 100 µg or 1 µg/kg) and philosophically pharmacokinetic linearity is sought. This approach permits the use of exploratory investigational new drugs (INDs) and also the measurement of tissue levels. This can be preceded by single dose toxicity with recovery, rather than 14-day toxicity with autopsy. It is possible, because of the analytical techniques used (PET and accelerator mass spectrometry), to study intravenous (IV) and oral doses in the same subject in the same experiment. There are "administrative" advantages—reduction in animal use, earlier human exposure permitting expedited decision-making, less chemistry and manufacturing control (CMC) requirements, and easier pharmaceutical formulation. These all reduce the time and cost of initial human exposure assessments.

Dose Escalation in Phase I: Method of Whitehead

This is an exciting development in its infancy (35). One of the difficulties of the established approach to phase I is the multiple-step escalating dosage regimen. The need is to focus on the safe dose as early as possible in the process, in order to avoid unnecessary exposures. Whitehead has approached this using Bayesian statistics. The observations needed are of responses (whether or not a drug-induced event occurs) and these should preferably be for both desired and undesired events. Using the first set of data for calibration, the probability of a particular response occurring at a particular dose is calculated. That dose, rather than a dose chosen more arbitrarily, is chosen for the next step in the escalation. At its best, this process can lead to one inactive dose, two individual doses of the desired and undesired effects occurring in isolation, and one dose with both effects—a total of four doses in all, proving enough to characterize the system in preparation for ongoing work. Thus an accurate estimate is obtained of the therapeutic window.

Business Approach

The business side of translational science usually commences with a patent application. Unlike 30 years ago, scientists in research institutes and universities are now conditioned to proactively seek patent opportunities. This does not always "sit well" with many academics, who see themselves as serving societal interests by conducting public domain work. However, over the years, many opportunities for protecting intellectual rights have been squandered. For example, acetaminophen was first disclosed as a metabolite of another drug, in a scientific paper in a learned scientific journal, which greatly inhibited the ability of its sponsors to obtain useful patents. So the modern university has a vigorous department dedicated to promoting the idea of patenting, applying for patents, and outlicensing intellectual property in order to create private-source income for the university. Unfortunately, many universities now actually have too many patents, in that patent maintenance costs money, and an immense amount of time and effort has to go into the process of seeking licenses, investors, and companies with the resources, competence, and interest needed to successfully commercialize an idea.

The value of a patent varies over a very wide range. Factors affecting the value include the likely cost of commercialization, the product and income potential, the time needed for development of the product, and, from the side of the university, how much investment has gone into the discovery. In the end, an entrepreneur may obtain a license to develop a discovery for as little as $100,000 clear, or as much as many millions of dollars plus milestone payments and royalties on the product. Much depends on the negotiating skills of the parties themselves.

In many cases, an inventor will seek to form a company in order to commercialize the discovery. A typical structure for such a company will be a board of directors of three people, the inventor, a CEO with business experience, and a financial officer to handle the books. All will be part-time, perhaps pro bono, as the inventor will retain his or her academic position, the CEO will be a successful business person with a record of achievement, and the financial officer will have only modest amounts of work to do—after all, there is always a lack of money!

It is the CEO's job to raise money. There are obviously many sources of money, and they are usually hard to tap into. Companies in this stage are often described as in a "pre-seed" situation, referring to the fact that they do not even have the critical first $250,000 needed to pay for additional patenting, legal costs, travel for endless presentations in the search for the next stage of financial development, and perhaps one or two people in a laboratory dedicated to ongoing, scientific development of the discovery. Pre-seed workshops, at which inventors present their ideas (once patents have been applied for), and at which coaches help the inventors work on business plans, definition of roles for members of the team, slide presentations, ideas on sources of money, etc., are particularly valuable. They help greatly in preparing inventors for the work of the next stage of financing, once family and friends have been exhausted, tapping into angel networks, venture capitalists, and eventually, working with the lawyers for the big companies, which will be needed to finance product development.

So how does a good translational science program fit into this? The corporate relations experts in the university should undoubtedly be working with the inventors at the earliest possible moment. The leaders of the translational science effort need to be providing pre-seed expertise to their inventors, and they should be promoting cross exposure between the inventor community and the local business community, such as by arranging scientific presentations, seminars, symposia, etc., at which scientific work with commercial potential is put on show. The local community of patent lawyers, entrepreneurs, investors, and regulatory experts needs to be involved in this, for the benefit of the community and its individual businesses. It helps greatly to have a business incubation organization to catalyze this, as an incubator can provide office space, laboratory space, and advisory services on an economical

basis, through utilization of local expertise and resources to aid development of local start-up companies for the benefit of the local economy. One necessary skill, however, stands out as vital—project management.

Project Management Considerations

Johnstone (25) has emphasized the significance of three factors in success of translational medicine—good science, excellent project management, and excellent interpersonal skills, echoing the views expressed some years ago by this author in collaboration with Rodney Brown (36,37) (Figure 3). Project management comprises a whole collection of attitudes, methods, and techniques designed to ensure that stages in an evolving project occur expeditiously and avoid duplication and conflicts. It involves contributions from specialist project managers.

Project managers bring order to complex and turbulent tasks (projects) by, for example, assisting in the preparation of a target product profile, providing work breakdown structures, managing external liaisons, and providing structure to projects, especially in regard to dependencies and bottlenecks, identification of milestones, and other stage markers. Further, they provide templates for completion during the course of the project to ensure timely and accurate recording of data, they organize team meetings and keep records, and they organize team training. These activities are essential when working with a team of equal people from different disciplines who relate to each other in a horizontal hierarchy. This type of activity is foreign to the average university researcher but essential in translational science (35,36).

CONCLUSION

The reader might be excused for thinking that the preceding account merely documents the process, in its modern form of new drug discovery, giving it a fancy name (translational science) and a cute slogan (from bench to bedside). Unfortunately, the drug discovery process remains a slow and inefficient process. Formulation of the translational science concept, at the very least, is serving to focus our minds on how this process can be expedited and made more successful, by creating centers of excellence where basic and clinical scientists, government, academia, and industry, and entrepreneurs and investors can meet with a reasonable expectation of giving the process a kick-start into a more healthy future, putting into history some of the more archaic constraints documented by such authors as Cavalla (38) and Ostholm (39). The formal identification of translational science can be expected over the next 10 years or so to: (*i*) give a major boost to biomarker research in the universities; (*ii*) cause a modest transfer of early clinical testing work into academic control; (*iii*) create better opportunities for universities to commercialize their discoveries; and (*iv*) catalyze an increase in the efficiency and quality of the process and its products.

The scientific search should be for biomarkers that scale, figuratively speaking, with a slope of zero from in vitro to patients and for drugs that interact predictably with the systems highlighted by those biomarkers and that have predictable pharmacokinetic properties amenable to successful allometric scaling.

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COMPETING INTERESTS STATEMENT

The author declares no competing interests.

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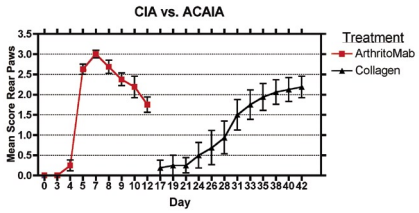

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