

What's next in translational medicine?

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A B S T R A C T

Translational medicine is the integrated application of innovative pharmacology tools, biomarkers, clinical methods, clinical technologies and study designs to improve disease understanding, confidence in human drug targets and increase confidence in drug candidates, understand the therapeutic index in humans, enhance cost-effective decision making in exploratory development and increase phase II success. Translational research is one of the most important activities of translational medicine as it supports predictions about probable drug activities across species and is especially important when compounds with unprecedented drug targets are brought to humans for the first time. Translational research has the potential to deliver many practical benefits for patients and justify the extensive investments placed by the private and public sector in biomedical research. Translational research encompasses a complexity of scientific, financial, ethical, regulatory, legislative and practical hurdles that need to be addressed at several levels to make the process efficient. Several have resisted the idea of supporting translational research because of its high costs and the fear that it may re-direct funds from other biomedical disciplines. Resistance also comes from those more familiar with traditional clinical research methods. In this review, we argue that translational research should be seen as enabled by ongoing efforts in basic and clinical research and not competing with them. Translational research provides the knowledge necessary to draw important conclusions from clinical testing regarding disease and the viability of novel drug mechanisms. Advancing translational research requires education and new sources of funding. This could be achieved through public and congressional education by a joint coalition of patients' advocacy groups, academia, drug regulatory agencies and industry.

TRANSLATIONAL RESEARCH CATALYSES OLD SUBSTRATES

We have previously summarized the fundamental concepts that define translational research as a discipline [1] (Table 1). It should be recognized that none of the goals encompassed by this definition are unique to translational research, since medical sciences have thrived in the past on the same premises under the umbrella of definitions such as pre-clinical research, clinical research,

disease-targeted research, evidence-based research, etc. As biomedical research has become more complex, specialized and fragmented, the interests and necessary skills of laboratory researchers have diverged from those of clinical researchers, and the success of the clinician scientist, the individual with a foot in both camps, has become more challenging. This has opened up the demand for researchers with a different skill set, expertise in translational research. Thus the need to bridge this gap called upon several stakeholders to join forces under

Key words: clinical research, drug target, translational medicine, translational research.

Abbreviations: FDA, Food and Drug Administration; LTB₄, leukotriene B₄; NCE, new chemical entity; NIH, National Institutes of Health.

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Table 1 Goals and areas defining translational researchAdapted from Mankoff, S. P., Brander, C., Ferrone, S. and Marincola, F. M. (2004), *J. Transl. Med.* **2**, 14, published by BioMed Central Ltd.**Goals**

The establishment of guidelines for drug development of for the identification and validation of clinically relevant biomarkers.

Experimental non-human and non-clinical studies conducted with the intent of developing principles for discovery or new therapeutic strategies.

Clinical investigations which provide the biological foundation for the development of improved therapies.

Any clinical trial initiated in accordance with the above goals.

Basic science studies which define the biological effects of therapeutics in humans.

a unifying concept aimed at identifying ways to better translate basic biomedical achievements into practical benefit. Some feel that the term 'translational research' has been invented to re-direct funds and resources from other disciplines without providing any true conceptual novelty. Indeed, translational research is not claiming originality in all areas covered by biomedical research. Translational researchers may not invent new clinical technologies or make the important new discoveries about disease, but they will be able to apply these in a new kind of clinical research that tests hypotheses derived from knowledge gained in the laboratory and from animal models and use biomarkers that can be applied in the laboratory and across species. The traditional goals of biomedical research function as a substrate for the catalytic activity of translational research that, like an enzyme, is aimed at enhancing the efficiency rather than modifying the process. The secret to this catalytic reaction rests in the ability to integrate disciplines of increasing complexity by allowing a dialogue among the stakeholders, by identifying the hurdles that hamper this interaction and propose creative solutions.

Animal models are an important source of information about the pharmacology of compounds and the relationship of novel drug targets to downstream outcomes (efficacy and safety). There are very few animal disease models that universally predict efficacy of drugs in humans regardless of the drug's mechanism of action. However, there are many disease models that have been found to predict efficacy of drugs with precedented mechanisms. Arthritis models are a good example. Rat adjuvant arthritis and carrageen-induced inflammation models are very good predictors of the response of humans with rheumatoid arthritis to cyclo-oxygenase inhibitors [NSAIDs (non-steroidal anti-inflammatory drugs)] and can be used to predict efficacious human doses of these drugs. However, these models also respond to mechanisms that have no efficacy in rheumatoid arthritis, such as LTB₄ (leukotriene B₄) receptor antagonists. Nevertheless, these models are good pharmacology models for LTB₄ receptor antagonists, just not a useful disease model. They can be used to determine the amount of LTB₄ antagonism that is needed to result in downstream outcomes, and this information can be translated to humans using biomarkers of LTB₄

receptor blockade. Likewise, rodent tumour xenograft models are used to measure the activity of compounds for cancer, but activity in these models for many mechanisms does not predict efficacy in humans with cancer. Again, they are useful in determining the amount of activity a drug must have to translate into downstream outcomes. Thus animal models are valuable because they are good pharmacology models. We can use them to determine whether a novel mechanism of action will translate into downstream outcomes and translate biomarkers from these animal models to humans to measure the pharmacology in man. They become predictive of disease efficacy in humans only for specific drug mechanisms once efficacy in humans is confirmed.

DEFINITION

The question of how to define translational research remains unresolved and controversial. This is partly due to the fact that different stakeholders look at distinct aspects of this issue. For academia, translational research represents a general desire to test novel ideas generated from basic investigation with the hope of turning them into useful clinical applications. For academic purposes, translational research also responds to the need of identifying novel scientific hypotheses relevant to human pathology through direct observation of humans and their diseases [2]. For people more directly involved in clinical practice (physicians, clinical laboratory professionals and patients), translational research responds to the need to accelerate the capture of benefits of research, closing the gap between 'what we know and what we practise' [3]. This means the transfer of diagnostic and therapeutic advances proven effective in large well-conducted trials to daily medical practice [4]. For the commercial sector, translational research refers more to a process aimed at expediting the development of known entities particularly in early phases and/or identifying ways to make early go/no go decisions when the cost of product development is still relatively contained. These concepts are not mutually exclusive and can overlap, although naturally there are often differences in priorities between translational researchers with different goals and different definitions of success.

In spite of these practical differences, a generalized definition of translational research could be proposed that should unify the expectations of all involved including the ultimate beneficiaries: the patients. We, therefore, propose a simplified definition of translational research as follows: translational research (or translational medicine) represents a discipline that increases the efficiency of determining the relevance of novel discoveries in the biological sciences to human disease and helps clinical researchers identify, through direct human observation, alternative hypotheses relevant to human disease. A further goal is to accelerate the rational transfer of new insights and knowledge into clinical practice for improving patients' outcomes and public health [5]. To be successful, translational researchers need to identify scientific, financial, ethical, regulatory, legislative and operational hurdles and provide creative solutions to facilitate this process.

OBSTACLES TO TRANSLATIONAL RESEARCH: COST, COST, COST

Some of the obstacles faced by translational research include: lack of sufficient funding, high cost and slow results, inadequate samples, conflict of interest, regulatory burdens, right to privacy, fragmented infrastructure, shortage of qualified investigators, inadequate rewarding, shortage of willing participants, incompatible databases, and lack of congressional and public support. This topic has been extensively discussed in the literature [1,6–23] and, therefore, in this review, we will focus on the high cost of translational research, particularly in the bench-to-bedside direction in the case of drug development. Indeed, in this situation, the complexity of translational research in human subjects is overwhelming: production and validation of products of consistent safety, potency and quality, the necessity to keep elaborate documentation of treatments to safeguard patient safety while protecting the right to privacy, the ancillary needs associated with the care of patients with severe conditions and the cost of validating translatable biomarkers renders this discipline uniquely expensive. In addition, only a minuscule proportion of compounds tested in early phase clinical experimentation (phase I/II trials) prove commercially profitable and the time required to evaluate therapeutic benefit of an NCE (new chemical entity) with a novel mechanism of action is the order of a decade in most cases. Thus the high cost of testing potential new medicines is associated with the feeble likelihood of profitable returns increasing the risk/benefit ratio and dampening the interest to sponsor intellectually stimulating ideas. This applies particularly to the public sector as academics and their institutions are generally less equipped to deal with intellectual property practices, regulatory processes for preliminary approvals and the

extensive proof-of-principle and safety studies associated with them. This may result in early dismissal of a promising new drug target or NCE due to lack of sufficient funding from the public sector and limited interest on the commercial side because of insufficient intellectual property protection. It may be unrealistic to expect non-commercial sources to sustain this level of experimentation when cost is an order of magnitude higher than that obtainable through federal or other non-private sources. The best solution to this problem may be the promotion of academia–industry partnerships. Thus, at the financial level, translational research in academia is not resourced to a level comparable with the commercial sector and is predominantly limited by insufficient funding. For industry, translational research offers a potential business solution to expensive attrition. Although resources available for drug discovery and development in industry are much greater than in academia, industry-wide only approx. 2% of novel drug targets survive to a commercial proof-of-concept. Indeed, only one in five compounds entering phase II will survive and enter phase III. In industry, investing large resources in compounds that are likely to fail is the main rationale for investing in translational research. The successful conduct of translational research, enabled further by advances in clinical and biomarker technologies and recent regulatory changes, such as the Exploratory IND (Investigational New Drug) Studies in the U.S., allows for the creation of early go/no go decision criteria based on biomarker responses in humans and knowledge translated from the preclinical phase of development. Industry therefore has a large financial incentive to invest in translational research conducted by translational medicine groups, whereas academia lacks this incentive. This differentiates the hurdles of academia compared with those faced by industry in which the amount of resources available is larger, especially for large pharmaceutical companies and the big financial hurdle revolves around the excessive attrition and high fully absorbed costs required for product development. Therefore, for purposes of discussion, we argue that lack of funding for translational research pertains primarily to the academic exercise, whereas excessive costs pertain more to industry.

LACK OF SUFFICIENT FUNDING

As discussed above, lack of funding pertains mainly to academia. In 2003, approx. US\$ 94 billion was spent on biomedical research [21]. Contrary to common belief, the majority of the spending was sustained by the private sector with the inclusion of pharmaceutical companies, biotechnology start-ups and firms developing medical devices, which accounted for approx. 60% of the total research and development spending (approx.

US\$ 55 billion). Federal, state and other public agencies contributed less than 40%, with approx. 3% contributed by private non-for-profit enterprises. These proportions have remained constant for the last two decades. The NIH (National Institutes of Health) contributed the biggest proportion of public support for biomedical research (approx. 28% of the total spending); however, the NIH supports predominantly basic research, whereas the 58% contributed by industry more closely relates to translational research, because it seeks the development and testing of biomedical products. Thus the overwhelming amount of resources spent in support of translational research comes from the private sector, whereas only a small proportion (less than 1%, as discussed later) is contributed by the public sector [21]. Because the goals and priorities of industry are different from publicly funded academic discovery, the extensive private resources cannot compensate for the lack of public support for some types of translational research. For instance, population studies for the understanding of disease patterns that may identify novel relevant targets of therapy are not supported by the commercial sector, because the breath of this kind of research is too broad and the expected returns too slow [24]. In addition, even in the area of drug development, translational research for orphan diseases receives relatively little support from both the private and public sectors, because they do not affect a substantial portion of the population supporting the costs of research and because of the limited market for therapeutic products. Publicly sponsored academic research is generally more openly interested in innovation whereas, for financial reasons, the private sector is constrained to conservative choices efficiently narrowing research prospects to those likely to identify successful agents through proof-of-principle studies at the preclinical-to-clinical interface and/or early phase go/no go decisions. It is unclear how these discrepancies can be bridged, but the guiding principle should be that commercial and academic research are not competitors, they are interdependent and complementary and their interactions should be encouraged. This is especially true when one considers the educational mission of academic medical centres. Industry has an unmet need for researchers with the academic background and clinical training necessary to become skilled at translational research. Pharmaceutical companies have the incentive and the financial resources to do translational research, but often lack the human resources with the right skills. This represents one opportunity for the academic sector to benefit from investments in translational research if they can also be used to train translational research clinicians.

The NIH has recognized the need to improve the efficiency with which innovative thinking emerging from the basic sciences could be tested for its clinical applicability unburdened by excessive financial considerations.

The NIH Road Map represents a good example of this interest (<http://nihroadmap.nih.gov>). However, it should be recognized that this initiative has mainly a conceptual value, since the amount of resources allocated for it are minuscule compared with the overall NIH budget. For instance, in 2004, US\$ 28 million were allocated to support translational aspects of research through the Road Map, which represents a little more than 0.1% of the whole NIH budget. With a decreased NIH budget (-2% projected for the 2007 fiscal year adjusted for inflation [25]), it is unrealistic for the foreseeable future to expect that such allocation, predicated on voluntary yearly contributions from 27 NIH Institutes and Centres, will significantly increase [25]. It should be emphasized that incremental funding for translational research must be sought beyond the current NIH budget, because translational research should not compete with basic sciences which have been the foundation of American leadership in natural sciences. Besides, the interpretation of translational research results heavily depends upon novel scientific insights that can only be achieved by a bidirectional dialogue with bench scientists [2].

At present, there are no good options to improve the allocation of public resources to translational research. The following strategies could be considered: (i) optimize academia-industry partnership, where academia delivers trained researchers skilled in translational research and industry helps to sponsor those programmes; (ii) consider alternative sources; (iii) decrease the cost of clinical investigation by decreasing unnecessary burdens and increasing its effectiveness; and (iv) increase public support for biomedical research spending. We will discuss later the need to increase public support for biomedical research, as this pertains to broader aspects of translational research, and we will focus here on two solutions specifically addressing insufficient funding.

ALTERNATIVE SOURCES OF FUNDING

Optimize academia-industry partnership

As discussed above, the commercial sector has significant resources and incentives to translate emerging biological concepts into products at a scale beyond the capabilities of the public sector. The funding and, most importantly, the infrastructure necessary to move a drug through the initial proof-of-principle (preclinical testing followed by phase I/II trials) to the approval for marketability is huge, reaching approx. US\$ 1 billion. Thus there is no reason to utilize public funding for product development. Indeed, it may be almost impossible for academics to procure sufficient competitive grants to bring a drug or a test to the clinic in compliance with all the testing necessary to meet regulatory requirements. Seeking financial resources from industry by academic institutions beyond

those publicly provided through venture capital and educational programmes could generate financial and ethical conflicts of interest and may limit product development further [11]. Thus there are many reasons why academia in isolation should not focus on the type of translational research associated with drug development. Large biopharmaceutical companies are, instead, equipped with staff and resources to address and meet the administrative and regulatory requirements necessary to develop, test and bring a product to market. Few academic institutions are capable of providing a core infrastructure with appropriate and professional regulatory support. When they do, it is often limited and provided on a voluntary basis (i.e. institutional review boards). In addition, facilities necessary to meet the standards for clinical product preparation are not always available or compliant with changing regulatory requirements. Thus taxpayers' money should be saved for the continued enhancement of biological understanding relevant to human disease. However, participation in drug development by translational research experts in academia in partnership with the private sector is attractive to both sides. The cost of product development can be transferred to the private enterprise by providing incentives for academic and private partnership, while industry benefits from the translational research expertise of academia [11].

Based on this concept, the U.S. Federal Government recognized the need to facilitate academic–industry interactions. This need was based on the observation that the vast majority of patents claimed through U.S.-sponsored biomedical research did not translate into the development of commercial products (<http://www.csurf.org/eneews/bayhdole.403.html>). This limited the returns of the taxpayers' investment in biomedical research. In addition, lack of product development failed to stimulate industry and expand the job market in this country. Finally, Government and academic institutions primarily sponsored by public funds did not benefit from the indirect returns associated with patent licensing. The Patent and Trademark Law Amendments Act (also known as The Bayh–Dole Act) was, therefore, passed by Congress in 1980 to protect and encourage public–private partnerships emphasizing the need to transfer product development to the private sector. The Act regulates and allows joint resources to be dedicated to the research and development of potentially marketable products by ensuring fair financial returns to investors and taxpayers alike. Patenting and licensing under the Bayh–Dole Act thrived, with approx. 70% of active licenses in the life sciences resulting from Federal funding (<http://www.ucop.edu/ott/faculty/bayh.html>). Prior to Bayh–Dole, fewer than 250 patents were issued to universities per year. In the 2000 fiscal year, there were over 300 U.S. and Canadian institutions and universities engaged in technology transfer, and university

gross licensing revenues have continued to increase. In spite of this supportive legislation, the academia/industry partnership has room to grow considering that less than 10% of the total funding for university-based research is presently sponsored by industry, whereas the large majority of academic biomedical research is funded by Federal or State sources (<http://www.nsf.gov/nsb/documents/reports.htm>; see NSB-98-1). The concern of conflicts of interest has been partly responsible for limiting the partnership between academia and industry. Such conflicts cannot be denied and should be disclosed; however, regulatory measures could be implemented to limit potential conflicts through disclosure by the parties involved and mediation by third parties to ensure fairness of an otherwise useful process [11]. Indeed, in spite of potential conflicts among researchers, their institutions and corporate sponsors, successful co-operation can be achieved [26]. Questions about treatment selection biases, treatment toxicity disclosure etc. could be avoided by ensuring scientific integrity of trials. Public scrutiny should be allowed and facilitated by assigning key research activities, such as recruiting, consent and data analysis, to team members who have no financial stake in the results [11,27].

Another area for academic–industry collaboration is the education of experts in translational research. One example of this is the Clinical Investigator Training Program at Harvard and Massachusetts Institute of Technology sponsored by Pfizer and Merck (<http://www.hms.harvard.edu/gradprograms/citp.html>). In this example, industry experts help train fellows enrolled in the programme and contribute financial resources to pay fellows' salaries and for programme infrastructure. The fellows work on translational research projects under the mentorship of the Harvard and Massachusetts Institute of Technology faculty and receive a Masters degree in clinical research from Harvard after completing the 2-year classroom curriculum and their research projects. In this type of programme, industry is contributing directly to translational research activities and also training future independent researchers.

Private not-for-profit organizations

Private foundations, although representing a relatively minor component of the overall spending (3%), tend to support clinically relevant and disease-targeted research. There are approx. 1000 foundations that provide grants of least US\$ 10 000, representing important sources of funding [21]. Several foundations emphasize orphan or neglected diseases, such as the Bill & Melinda Gates Foundation (<http://www.gatesfoundation.org>), which is by far the largest contributor among the private foundations. Others allocate funds more broadly to translational research, such as the Burroughs Wellcome Fund (www.bwfund.org). Finally, the National Organization for Rare Disorders (<http://www.rarediseases.org>) is a

public/patient-driven organization which can provide information about disease-specific resources. Although these resources may be limited, they may have significant impact particularly in those cases where a good match between academic interest and the goals of the granting institution can be identified.

Amortizing the cost of translational research through health care spending

Since a significant proportion of the cost associated with translational research revolves around the clinical care provided in support of the experimental treatment, it seems reasonable to suggest that such cost should be covered, at least in part, by reimbursement policies. To put things in perspective, it should be noted that health care spending in the US is projected to reach US\$ 3600 billion in 2006, representing approx. 15% of the gross domestic product [28], of which approx. two-thirds is used to treat chronic diseases such as cancer or cardiovascular pathologies for which there is no curative 'standard' therapy [29,30]. We proposed that funding for translational research could be partially linked to spending on medical care [15] for the support of institutionally approved clinical trials. Currently, many states have mandated insurance coverage for cancer clinical trials. This coverage should be extended to all disease states (<http://www.cancer.gov/clinicaltrials/learning/laws-about-clinical-trial-costs>). This could apply in those cases when standard treatments are clearly known not to offer a significantly greater chance for survival or improved quality of life [31]. Arguably, institutionally approved clinical trials are by definition judged by experts to be comparable and potentially better than standard care, otherwise they would not be allowed. Therefore these experimental trials offer the double opportunity to test novel therapies while giving hope to informed patients willing to receive unproven treatment over a recognized ineffective and toxic standard therapy. As patients' sophistication in researching and comparing the value of standard and experimental treatments relevant to their disease increases, this strategy would respond to the growing need to match the expectations of an informed public at the time of need. Therefore insurance coverage that would otherwise cover standard therapy should be redirected to clinical trials in all cases where the patient qualifies and chooses to participate. These funds should be designated only to costs associated with hospital stay, diagnostic tests and other components that are part of standard treatment. They should not be used to cover the cost of drug development and distribution, which should be covered by the sponsor. Therefore these policies may not significantly alter the overall spending in health care if these treatments are provided as alternatives to standard therapies which are often extremely costly. It could be argued that

regulatory approval could be expedited by agencies such as the FDA (Food and Drug Administration) basing judgment only on safety parameters and allowing patient-physician interactions to make treatment selection. These preliminary (intermediate) regulatory approvals would allow treatment coverage by insurance companies only for the medical care associated with the treatment at a ceiling comparable with standard care, therefore, disallowing extravagant expenses associated with complex novel strategies using a coverage system comparable with the Disease Related Groups principle (<http://www.ahrq.gov/data/hcup>). Obviously, changes of such a radical nature are conceivable only through strong pressure by the joint forces of patients' advocates, academia and industry underlining the need for such a coalition to be formed.

DECREASING THE COST OF TRANSLATIONAL RESEARCH BY INCREASING ITS EFFICIENCY

Another and important strategy to promote translational research is to decrease its costs. This can be achieved by optimizing the infrastructure (developing specialized departments, hiring trained personnel who can cover different tasks, stratifying patients by selecting those most likely to benefit from the studies, etc.). In addition, financial burdens should be lifted by modifying legislative and regulatory procedures. Regulatory agencies such as the FDA should accept creative solutions tailored to individual components to be tested, legislation should be passed to protect individual rights to privacy that could be achieved without extraordinary cost to the researchers, and research hospitals could be restructured according to translational research units that could more efficiently achieve the experimental goals through the integration of skills following an adhocacy model [32], as we proposed previously [15]. As we will discuss later, these changes are unlikely to occur unless powerful advocacy is organized to educate the public and Congress about the need to simplifying clinical testing. In addition, direct exchanges among stakeholders may help simplify the processes. For instance, policies protecting patients' privacy could be better designed if patients' advocates and researchers would sit at the same side of the table contributing synergistically to the joint goal of improving health care. In addition, medical practitioners should be educated in experimental practices and be involved in the debate to reach a consensus about the need for an unburdened delivery of medical care. A paradigm shift should be accepted whereby reactive medical interventions ('what is your chief complaint?') will progressively give way to a prospective approach based on risk assessment prior to the development of symptoms based on novel biological approaches. This preventive approach has the obvious advantages of cost reduction and the improvement

in patient prognosis, although it is punished by the present reimbursement system (pre-existing condition) [29,33,34]. The involvement of general practitioners in translational research will be key in educating patients of the advantages of such an approach, therefore, expediting regulatory practices based on a recognized need for a delivery of health care not dissociated from cutting edge biological concepts.

Identifying and validating surrogate markers for early go/no go decisions

The rate at which potential therapeutic targets are identified by modern biotechnology has increased the competition in industry for resources to test the efficacy of multiple drugs and mechanisms for the treatment of the same condition. Many new drug candidates target reduction in the progression of chronic diseases that require long and expensive clinical trials. The biggest cost of bringing a new drug to market is incurred in late-phase clinical trials [33]. This makes the need for identification of relevant biomarkers that can predict treatment safety, efficacy and differentiation before investing in large clinical trials all the greater. For this reason, surrogate biomarkers that substitute for standard clinical end points, such as X-ray measurements of joint damage, functional status, survival, disease-free survival and/or symptom-free interval, are of increasing interest [35], therefore, dramatically shortening the time necessary for critical go/no go decisions in early phase development [33–35]. This is particularly relevant because the diseases that most impact U.S. health care spending are chronic and clinical benefit may take several years to decades to be judged in clinical terms [28,29]. Ultimately, the identification and validation of useful biomarkers will serve two purposes: (i) to allow researchers to make informed early decisions on the likelihood that a novel idea may turn into a useful and profitable product and, therefore, decrease the cost of late phase testing of an ineffective agent; and (ii) to be used as surrogate for treatment approval by regulatory agencies, therefore, decreasing the lag between product development and marketability. In addition to surrogate end points in phase II studies, biomarkers are also critical earlier in development if they can be used as pharmacodynamic end points that confirm the activity of compounds at safe doses and for PK/PD (pharmacokinetic/pharmacodynamic) modelling for dose and dose regimen selection. Failure to achieve efficacy in phase II with a compound that has its intended pharmacology can disprove the efficacy hypothesis for unprecedented drug targets.

Since biomarkers inform programme and compound go/no go decisions, and serve to help optimize biological dose in terms of safety and efficacy [7], criteria are needed to identify clinically useful markers, to assess the

best methodology for clinical evaluation and to establish criteria to appraise the incremental value offered over standard prognostic factors [36]. Single or combined biomarkers can also inform patient stratification by identifying probable responders to therapy [35], a goal exemplified by the National Cancer Institute-sponsored PACCT (Program for the Assessment of Clinical Cancer Tests) [37].

The biological relevance of a biomarker may be distinct from its clinical relevance. The goal of active-specific immunization against cancer is to expand the T-cell repertoire in favour of cancer-specific T-cells (a biological end point). In fact, active-specific immunization is one of the great success stories of the application of modern biotechnology to the identification of novel therapeutic targets [38]. The induction of cancer-specific T-cells detectable in the circulation may not in itself be sufficient to induce cancer regression (a therapeutic end point). Thus, although the treatment is perfectly effective for its intended purpose, additional steps are necessary to achieve the desired therapeutic goal [39]. This is a critical point because often the promise held by a therapeutic modality is standard to high (therapeutic end point), leading to premature dismissal by decreasing funding for further development rather than continuing its sponsorship with the purpose of identifying biological factors that may link a successful biological end point to therapeutic success [40].

Validation of relevant surrogated biomarkers suffers several hurdles, such as underpowered studies, heterogeneous practices in measurement methodology, sample collection and processing, and incompatible data management systems. All of these problems could be solved by refinement and standardization of assays, evaluation of biological variability, quality control procedures, clinical methods of measurement such as imaging methods, and re-organization of data collections [37]. The importance of identifying biomarkers is, therefore, critical and central to translational research because, ultimately, it may turn out to be the most effective way to reduce the cost of clinical experimentations while, most importantly, saving patients from ineffective and unnecessary treatments promptly redirecting them to treatments with higher likelihood of success.

Opportunities for target identification and for the study of therapeutic mechanisms in the clinic

Modern technology offers unprecedented opportunities in the clinical sciences [41]. High-throughput technologies enable researchers to study human disease in its globality, accounting for genetic variability of individual patients and the epigenetic instability of their diseases. Samples obtained through venipuncture, fine needle aspiration, cut needle biopsies and cytological

smears can be studied using DNA- and RNA-amplification techniques and high-sensitivity proteomic tools. Extensive analysis of an individual polymorphism could complement information related to the disease process at the genetic, functional and post-translational level. Genome-wide analysis is easy and requires only small samples for the preparation of genomic DNA. As these new frontiers in science emerge, a unified science curriculum that fully incorporates mathematics education and quantitative thinking has been proposed to prepare the 21st century scientists for the challenge of the study of systems biology [42].

Although it is relatively easy to analyse genomic DNA [43], collection of material for functional genomic studies requires more planning of the optimal time frame for sample collection (before, during or after treatment) and is limited by the amount of material realistically obtainable from patients. Analysis of tissues affected by the disease process and targeted by therapy is difficult because it requires repeated biopsies. Yet, less invasive methods, such as serial fine needle aspirates, can be used to predict response [44] or to study mechanisms of action [45] using high-fidelity RNA-amplification methods [46]. But such strategies are rarely employed. Transcriptional analysis should be complemented by documentation of epigenetic adaptations or genetic alterations. Comparative genome hybridization covers large genomic areas to detect deletion or amplification, while CpG island methylation arrays can investigate epigenetic regulation of gene expression if material for DNA extraction from affected tissues is saved during a clinical trial [47].

Protein analysis completes the picture, as protein function is modulated through post-translational changes and protein-protein interaction. For instance, the introduction of protein arrays dramatically expanded our understanding of alterations induced by the systemic administration of high-dose IL-2 (interleukin-2) to cancer patients [48]. Prospective collection of serum samples during therapy may help to identify patterns responsible for treatment toxicity and/or effectiveness. Application of standard practice for protein preservation using protease inhibitors and storage into appropriate aliquots are simple steps to ensure the usability of prospective collections.

High-throughput technologies have revolutionized the ability to understand human pathology by computing thousands of factors simultaneously, limiting the inherent barriers to controlling variables in human disease. However, samples collected retrospectively are often unusable for analysis, as RNA degrades quickly after tissues or fluids are removed from the organism. The opportunity to take specific steps to preserve the *ex vivo* profile is often lost unless researchers know early that the sample in question would be useful for a particular clinical study. Prospective collections are possible

but require full co-operation between scientists and clinicians. Good examples of broad-based efforts are starting to emerge [49]. Legislative and regulatory limitations, such as material transfer restrictions and HIPAA (Health Insurance Portability and Accountability Act), severely limit the utilization, interpretation and correlation of biological data with clinical data [33]. The unintended consequences of such legislation should be addressed rather than passively accepted by the scientific community.

Providing the appropriate infrastructure

The current organization in which academic research is performed is not suited to the efficient conduct of translational research, as different disciplines are separate from each other administratively, physically and culturally [15]. Thus the present academic system represents a 'professional bureaucracy' that relies on the standardization of skills [50], providing a common infrastructure to respond to unified needs, but does not promote interaction across disciplines. The need for such interaction in translational research is better met by a 'project structure' (termed an 'ad-hocracy') that draws upon the talents of experts representing different specialties to create smoothly functioning creative teams [50]. Translational research units should not be assembled according to similarity of scientific background, but around a mission-based goal. This congregation of talents can only be achieved by unifying not only goals on a voluntary basis through the commonly accepted concept of 'collaboration', but rather through a solid structure in which each team member belongs to the same unit at the physical and administrative level and, most importantly, is rewarded according to the same review process. This should increase the cost effectiveness of designing and running clinical trials from the primary conception, the pre-clinical and/or experimental proof-of-principle, the trial design, through the regulatory approval process, the clinical testing and data collection, management and analysis.

Rewarding translational researchers

Translation research requires different skills applied to a unified goal [11]. Translational researchers need special training in the complexity of novel technologies and they need to be sensitized to the complications of designing and conducting scientifically valid clinical trials while understanding the ethical limitations of research when dealing with human subjects. Considerations include the identification of informative control populations that are not denied appropriate treatment, understanding the demographics of a disease and the alternative therapies that may influence trial design, and understanding the ethical dilemma imposed by repeated sampling of lesions for research purposes. There are few dually trained clinician scientists because their training requires 3–5

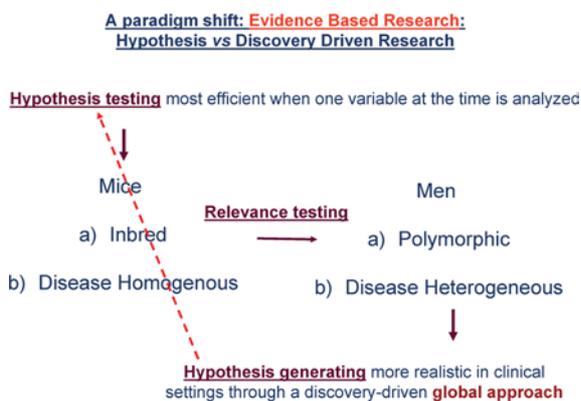


Figure 1 How hypothesis testing is irrelevant to translational research

Hypothesis testing has been utilized by scientists to verify the validity of a given hypothesis. The process involves minimization of the experimental variables (ideally to one) by homogenizing the experimental model through control of the genetic make up of test animals and standardization of their diseases. This strategy has proven extremely effective in the conduct of proof-of-principle studies to support or disqualify a given hypothesis. Unfortunately, this strategy is not intended and cannot identify novel hypothesis or predict their relevance to systems other than the one studied such as, in the present case, human pathology. This explains why when novel therapeutics are tested for their relevance in humans they almost infallibly fail. Novel technologies based on high-throughput genomic and proteomic assays allow an effective search for novel hypotheses relevant to human disease by taking a global view of the phenomena associated with a disease and its response to therapy. This approach turns the experimental heterogeneity associated with the uncontrollable genetic variability of humans and their diseases in its own favour, sorting common patterns necessary for the occurrence of a biological phenomenon from irrelevant ones. Hypotheses thus generated can then be taken back to the bench for testing according to standard experimental models. Unfortunately, this aspect of biomedical research has not received the appropriate recognition by the current biomedical establishment and this lack of appreciation represents one of the major hurdles faced by scientists interested in clinical sciences.

more years than the training of physicians in clinical practice and that of basic researchers [9,51,52]. In addition, medical school debts range around US\$ 100 000 and cannot be promptly repaid during the incremental years required for research training. As noted above, there are opportunities for industry–academic collaboration in this area with important benefits to both parties.

The incentive to perform clinical research is also limited. Basic science studies are often valued more than clinical research in the promotion scale, ultimately providing little incentive to chose a career in translational research. In particular, scientific achievement is judged more on the basis of basic experimental testing of hypotheses rather than on hypothesis-generating terms (Figure 1). This paradigm does not apply to translational efforts as, in most cases, hypotheses generated from experimental models do not apply to human disease, due to the biased selection of a model in which experimental

variance is minimized by limiting the genetic diversity of animals and their diseases. Bench-to-bedside efforts predominantly test the relevance to human pathology of hypotheses derived through experimentation and pre-clinical proof-of-principle. However, as experimental variance cannot be limited in human beings, such exercises often prove futile while novel hypotheses need to be generated through direct observation of human disease throughout their natural course or during therapy. However, hypothesis-generating studies are often and, unfortunately, classified as ‘descriptive’ and are not given the weight that they deserve in redefining the boundaries of biomedical research within the limits of human relevance [2]. This, in turn, discourages this line of research due to the difficulties encountered in publishing human-derived observations in high-impact journals. Finally, the present system of career advancement in science rewards the individual independent investigator, inadvertently discouraging team projects. This creates a conflict between the reward structure of academic institutions and the results that are actually expected of translational researchers [16]. Career structures need to be re-organized, credit for achievements should be shared among scientists and clinicians and, more grants should value teams of investigators. The NIH Road Map is attempting to foster this principle, but much still needs to be done to change the framework of rewarding systems in the academic environment.

Several initiatives are focusing on the development of scientific training programmes for clinicians [24,41,42,51,52]. The purpose of these initiatives is not to increase the number of individuals who are fully trained in multiple disciplines, but who know enough about the fields of others so that they can communicate effectively. Definitely more needs to be done in this regard.

INCREASING PUBLIC SUPPORT FOR BIOMEDICAL RESEARCH SPENDING: A PROPOSAL FOR AN ASSOCIATION FOR TRANSLATIONAL MEDICINE INCLUSIVE OF ACADEMIA, INDUSTRY AND PATIENTS’ ADVOCATES

In the discussion above, we summarized several of the key problems faced by translational medicine. Several of these problems cannot be readily solved without the participation and support of the public [18]. In many ways, it could be said that biomedical scientists themselves have been part of the problem by isolating themselves from public discourse. In addition, the biomedical community has not been effective in advocating the need for further investment in biomedical sciences. This resulted in a reshuffling by the current administration of funds for research and development to promote

physical sciences and engineering at the cost of biomedical research [53].

Public understanding and appreciation of biomedical sciences, and their intellectual, financial and practical potential, will be key to solving most of the problems discussed above. Surveys suggest that public attitudes and perceptions about health-related research are positive [54]; however, this optimism does not seem to translate into sufficient public pressure on legislators to significantly affect budgetary allocations [25].

On the occasion of the 2nd Annual Meeting for Translational Medicine (<http://www.healthtech.com/2006/ddd/index.asp>) held recently in Philadelphia on 28 February–1 March 2006, a proposal was made to form an Association for Translational Medicine inclusive of academia, industry and patients' advocacy groups. This suggestion was followed by enthusiastic positive feedback from individuals associated with all of these constituencies who understand the importance of representing the issues related to translational research from a unified viewpoint. Such an association would provide: (i) an open collaborative membership association and forum for translational research professionals, supporters and sponsors, including academic, industry, advocacy and government organizations, (ii) a virtual community encouraging translational research collaboration, dialogue and partnerships which will benefit all constituents, (iii) a process for organized focused advocacy, (iv) education for new investigators and seasoned researchers, (v) a process to enhance translational research and medicine by leveraging translational research innovations and scientific findings, (vi) a vehicle to promote and publicize member contributions to society by offering active support, (vii) guidelines for translational research standards, applications and implementation, and (viii) professional meetings and publications.

Although organizations exist that represent individual aspects of translational research, they often clash with each other. Discussion over divergent opinions and priorities should be facilitated internally among all the stakeholders to present a unified front to the public, legislators and regulatory agencies as we all share the ultimate goal of helping patients in the near future.

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