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Translational semantics and infrastructure: another search for the emperor's new clothes?

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The successful transition of drug-like new chemical entities from discovery to clinical trials coupled with real-time feedback from the latter represents a key element for success in drug discovery. Now designated as T1 translational medicine, this process has, similar to other recent solutions to improve productivity, been hyped as a novel discipline, despite the fact that many of its component activities have existed in the pharmacological sciences for many decades. Instead of proselytizing translational medicine, the priority is to improve the quality of the science and decision-making processes involved in advancing compounds to ensure that what is translated has value.

For nearly a century, biomedical research, focusing on understanding the etiology of human diseases, has contributed immeasurably to improving human health [1,2]. Beneficial outcomes include the discovery of insulin (1921), penicillin (1929), polio and other vaccines (1950), various antibiotics, antiasthmatic, psychotropic and antihypertensive drugs (developed during the 1950s–1970s), antiviral therapies (1980s) and, more recently, monoclonal antibodies and kinase inhibitors for treating cancer, inflammatory and autoimmune diseases. However, there remains an urgent need for improved treatment options for a variety of human disease states.

Although there has been an unprecedented growth in scientific knowledge that has been accompanied with enormous research investments in academia, federal research laboratories and the pharmaceutical and/or biotechnology industries, which reached US$150 billion in 2010 [3], new drug introductions over the past decade have stagnated [4,5]. Indeed, the 5% success rate of compounds entering clinical trials [3] continues to impact the successful development of new and improved therapeutics, especially for chronic diseases, such as diabetes and Alzheimer's disease (AD), that require lifelong treatment and for which the incidence is growing exponentially such that they have the potential to bankrupt healthcare systems worldwide in the absence of effective treatment options.

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A recent increase in drug approvals by the US Food and Drug Administration (FDA), with 35 new, innovative and 'many groundbreaking' medicines approved to date during fiscal 2011 (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM278358.pdf), more than a 50% increase over the number accepted in 2010 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM242695.pdf), has been heralded [6] as a 'refill…[ing of]…parched pipelines', a 'payoff from a research reorientation…[undertaken]…several years ago'. This view is not shared by seasoned industry observers (http://johnlamattina.wordpress.com/2011/07/12/pharma-rd-productivity-have-they-suddenly-gotten-smarter/, http://blogs.forbes.com/matthewherper/2011/07/18/the-truth-about-2011s-new-drug-approvals/), who question whether these increases are indicative of getting the R&D model 'right', instead ascribing the numbers to increased business development activity and licensing of late-stage development compounds, and 'clearer FDA guidance'. Although news of the increase in drug approvals is welcome, it should be viewed in the context of the proverb, 'a swallow doth not a summer make' as drug approvals over the past 6 years have averaged 22 per year as compared to 36 per year in the previous 9 years (Fig. 1) (http://johnlamattina.wordpress.com/2011/07/12/pharma-rd-productivity-have-they-suddenly-gotten-smarter/, http://blogs.forbes.com/matthewherper/2011/07/18/the-truth-about-2011s-new-drug-approvals/, http://www.oliverwyman.com/4638.htm).

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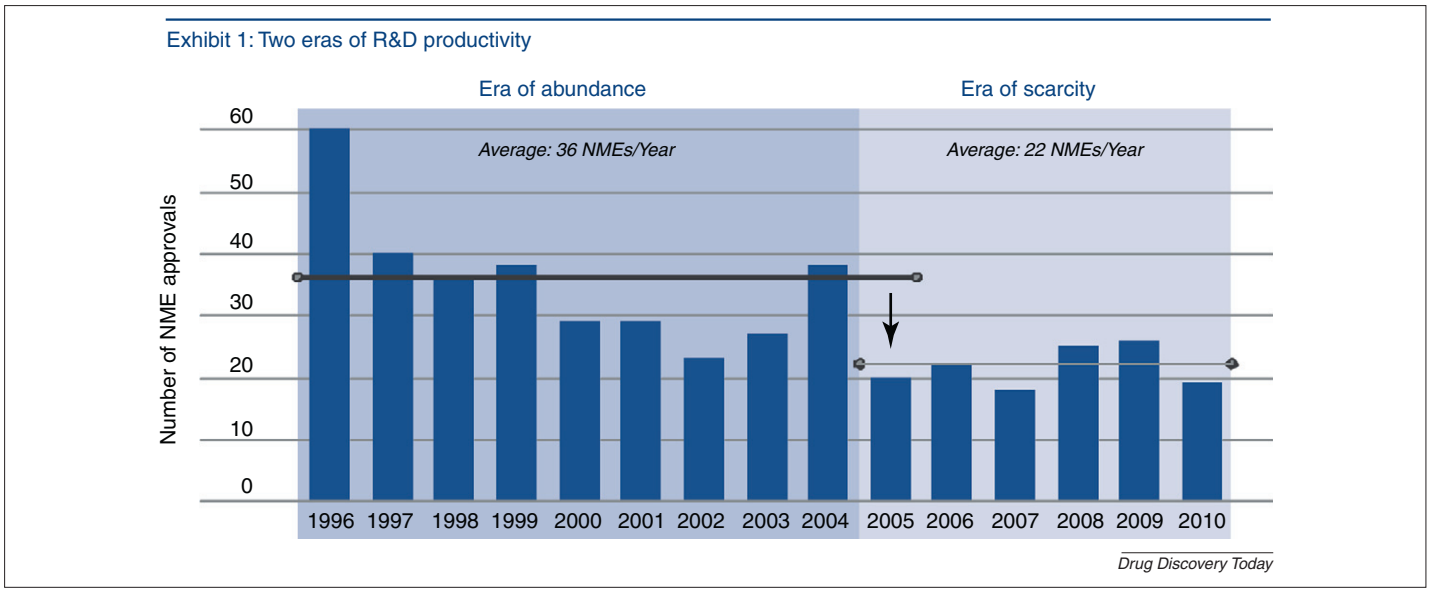

FIGURE 1

New drug application (NDA) approvals from 1995 to 2011.
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Since the early 1990s, there have been many initiatives to potentially enhance productivity (e.g. combinatorial chemistry, high-throughput screening, genomics, systems biology, among others) all of which, in their original guises, have been treated as unequivocal solutions to fixing the problem. However, following a typical overenthusiastic acceptance that prioritized these approaches to the exclusion of all others, they proved to be naive hype. The question we address in this review is whether translational science, although attractive conceptually, represents yet another fad that is distracting attention from the real issues in improving drug discovery metrics, namely a decline in the quality of the underlying science and its interpretation.

The advent of translational medicine

As researchers in pharmaceutical companies and, more recently, the broader world of biomedical research, continue to debate the disconnect between R&D funding and drug approvals [6,7], the response of some 'key opinion leaders' to the axiom 'research proposes, development disposes', has been to focus on translational medicine (TM) [9–13] as yet another unequivocal solution [12]. The most recent manifestation is the establishment of the controversial National Center for Advancing Translational Sciences (NCATS). As a direct legacy of the National Institutes of Health (NIH) Roadmap of 2003, this latest initiative is intended to improve the shortfall in drug approvals with the assumption that federally funded scientists will, for reasons unknown, be able to solve the pipeline problem currently experienced by pharma companies. Because such concepts remain outside the sphere of competence and experience of the NIH (member institutes of the NIH have been conducting R&D to identify new drugs for several decades without tangible success), it is unclear whether such initiatives are more form than substance. This latter view is certainly reinforced by the absence of any long-term strategy for their funding [14]. The architect of the NIH Roadmap, now head of R&D at Sanofi and consequently exposed to the practical challenges of the real world of drug discovery, recently noted that there are 'no simple solutions' to the challenges of translational research and 'that such ''bench to bedside'' research is more difficult than...[I]...thought.' (http://blogs.wsj.com/health/2011/05/20/sanofis-zerhouni-on-translational-research-no-simple-solution/).

One outcome of the NIH Roadmap initiative (the NIH Common fund) in making TM a priority was the establishment of the Clinical and Translational Science Award (CTSA) program in 2006. It seems that almost every major academic medical research institute has created a translational department to compete for these (and other) awards, with CTSA funding for 60 such centers expected in 2012. Harvard is one of the latest to join the fray with its recently announced Initiative in Systems Pharmacology (ISP) (http://www.focushms.com/features/transforming-drug-development/) with a mission to 'improve[e] the quality of drug candidates as they enter the clinical testing and regulatory approval process' elaborating on yet another 'new discipline', that of Quantitative and Systems Pharmacology (QSP) (http://isp.hms.harvard.edu/wordpress/wp-content/uploads/2011/10/NIH-Systems-Pharma-Whitepaper-Sorger-et-al-2011.pdf). With 60 NIH-funded TM centers in addition to the clinical capabilities of most pharmaceutical companies and Clinical Research Organizations (CROs) that are being re-engineered along similar lines, the added need for NCATS is not abundantly clear (other than the important administrative task of overseeing and fostering interactions between the CTSA sites). A recent report from the Senate Appropriations Committee cited 'unnecessary uncertainty' that 'contributed to the impression that it [NCATS] was being rushed' when they cut the requested budget of the center from US$720 to US$580 million for 2012 (http://news.sciencemag.org/scienceinsider/2011/09/nih-chided-on-translational-center.html).

What is translational medicine?

The challenge of translation in biomedical research has been apparent for the better part of a century [15] and has led to numerous definitions that tend to differ in semantics and construct [16], many of which have been viewed as more fashionable than substantive in the way of structure and progress [17]. A broadly adopted definition of TM encompasses a two-part process [9,10], an essential component of which is the 'bidirectional flow' of information 'between patients and models' [16]. The initial phase, termed T1 [9], focuses on the translation of findings from basic preclinical science to human studies [e.g. new chemical entities (NCEs) and new targets] to human studies and clinical trials. Although inappropriately labeled 'bench to bedside', because the basic concept is a continual flux of information between clinicians and laboratory researchers, this is the area that has garnered most attention.

The second part, T2, lies outside the scope of this review and involves the translation of new knowledge regarding disease causality and treatment (new drugs) into clinical practice and healthcare decision-making [9], the successful implementation of which can enhance the adoption of 'best practices' within the community [18].

The *Journal of Translational Medicine*, in defining its mandate in 2004, acknowledged the T1 and T2 hurdles to the successful development and utilization of drugs and added a third: that '...the available standard therapies for most common diseases are less efficacious than they are believed by the public to be and significant funds are allocated to maintain this ''placebo'' effect through standard care' [19], which no doubt has been part of the drive towards comparative effectiveness research (CER) [18,20]. This initiative has been rather puzzling in practice because, on the one hand, its use led to the controversial conclusion that second-generation antipsychotics were no different in their efficacy to first-generation ones that are now generic [21]. On the other hand, the initiative led to the 2010 FDA approval of iloperidone, a second-generation compound of questionable merit (http://www.thestreet.com/story/10997122/1/vandas-fanapt-falls-flat.html).

Another T1 definition from the American Society of Pharmacology and Experimental (ASPET) is 'to develop methods and systems to integrate molecular, cellular, tissue, organ and clinical information so that the response to experimental therapeutics in model disease systems and patients is fully understood' (http://www.aspet.org/ISTCP/Home/), accurately describing the 150-year-old discipline of pharmacology (Table 1) ([22], http://isp.hms.harvard.edu/wordpress/wp-content/uploads/2011/10/NIH-Systems-Pharma-Whitepaper-Sorger-et-al-2011.pdf). Indeed, it has been argued that because T1 and T2 lack any inherent meaning, these terms should be replaced, with 'preclinical research' substituting for T1 [23], thereby almost completing the nomenclature circle. It is perhaps not surprising that one of the earliest and more successful CTSA sites for TM was formed at the University of Pennsylvania by Garret FitzGerald, a thoughtful investigator steeped in both basic and clinical pharmacology whose own definition of TM is 'moving basic research findings into clinical application' [24].

Although TM has been described as a 'discipline', replete with its own academic centers, funding initiatives, journals and symposia, to 'create...excitement and enhance...visibility' [25], it might be more valuable to regard it as an 'approach', analogous to the view of systems biology espoused by Kohl and Noble [26]. The lack of any generally accepted definition for TM could be regarded as advantageous as it avoids the imposition of artificial uniformity. Accordingly, despite the apparent opportunity for innovation, there are few, if any, practical precedents to provide universally applicable guidelines despite attempts to do so [12].

Recent successful drug approvals, such as those of the kinase inhibitors, vemurafenib and ruxolitinib, which argue against a narrow, bureaucratic focus on 'process' to the exclusion of situational flexibility (and emerging data), have merit. Thus, it is unlikely that the preclinical and/or clinical interface for advancing a compound into and through its clinical hurdles, its translational path, can be reduced to a 'one size fits all' paradigm [12] because it still fails to address the real-world challenges of linking preclinical research to the clinical setting [27], many of which are highlighted in this article. Immediate victims of any rigidified T1 approach that ignores the crucial human element (from innovation, to bias, to indifference, to mediocrity, to fraud) will be creativity and serendipity. The human factor is a conspicuous omission in the list of initiatives to 'reengineer...translational science' [12] that are long on optimism and short on practical experience. In summary, this is a near-perfect example of pretense-of-knowledge and/or wisdom syndrome that highlights a disconnection within biomedical research [28].

The difficulties in predicting drug efficacy from preclinical models have been of concern for more than two decades, and pharma has enabled various approaches in an attempt to overcome this problem. These include the formation of specific research-based clinical groups; for example, the clinical venture system at Abbott that, for a time, was adept in expediting the movement of compounds from bench to clinic; and the clinical biology unit at Ciba-Geigy during the 1980s, which was charged with small proof-of-concept studies, but was too small to move adroitly and tackle many issues; to the current trend to form smaller, semi-autonomous research units with responsibility from drug discovery through Phase II proof-of-concept studies in discrete therapeutic areas. All these models have sought to improve translational success, with limited identifiable achievements to date. So the premise, that new drugs are not being delivered effectively to treat patients in need, is valid; however, is the new focus exclusively on TM both myopic and naive?

Can everything be translated?

A major consideration in TM is whether everything emerging preclinically as novel and important has use in the improvement of human health. Furthermore, as discussed below, is everything accurate, reproducible and 'fraud free'?

As the current dearth of new drugs attests [4,5], not everything can successfully transition from research to the clinic. The high attrition rates, 82% in Phase II proof-of-concept studies [29], even those that use surrogate endpoints purposely tailored towards showing compound efficacy with a lowered hurdle to success, never mind larger scale studies with endpoints suitable for approval, indicates a disconnect between preclinical and clinical observations. Thus, novel findings apparently related to the systems and targets involved in disease causality; the delineation of the efficacy, selectivity and safety of NCEs; and the predictive

TABLE 1

Translational science: key activities: basic and clinical pharmacology approaches

Translational scoring	Preclinical approaches	Clinical approaches
Target identification and validation	*In vitro:* Knockout/knock in recombinant cell lines; siRNA; Antibodies; Tool compounds; Functional sequelae (including mediator levels and biomarkers); Receptor and/or enzyme subtype, target activation state (constitutive versus dormant), agonist/antagonist, allosteric modulator and signal transduction analysis; Tissue receptor and/or enzyme selectivity *In vivo:* Knock out and/or knock in mouse and/or rat models; Comparison of wild-type versus transgenic models; Animal models recapitulating certain aspects of disease (e.g. SHR rat, NOD mouse, chronic pain, among others); Animal models of normal human behaviors (e.g. cognition); Orthotopic and syngeneic models of cancer growth; Tool compounds, competitive approaches and/or existing drug comparisons	*Unmet clinical need:* Genetic association (GWAS, SNPs, gene deletions, copy number variations (CNVs), microdeletions, among others); Epigenetic factors (DNA modifications; e.g. promoter CpG methylation, histone acetylation profiles) Mediator levels in body fluids Biomarkers [e.g. body temperature, blood pressure, lung function (FEV1), cholesterol, blood sugar/glycosylated hemoglobin, urine flow/content] Disease cohorts Size/frequency Odds ratio; genetic variability Key pathological features Accepted primary endpoints for clinical trials
Drug discovery, chemical/ pharmacological tractability	*Lead identification:* Target identification, expression and validation; HTS, parallel synthesis; Hit to lead chemistry; Modification of natural ligands; Initial safety liability assessment (e.g. HERG, Cyp interactions, Irwin test) *Lead optimization:* Species differences; Nuances of native versus recombinant target systems; Iterative assessment of druggability; Potency, efficacy, selectivity, safety; *In vitro* compound potency and/or efficacy translated to *in vivo* efficacy	Pharmacogenetics Disease diagnosis Objective classification Guidelines (e.g. EULAR, DSM IV, among others) Disease subclassification Concentration of 'responders' Early versus late disease stage, AD, PD, T1D
ADME/pharmacokinetics	Bioavailability Plasma/tissue levels when given by proposed clinical route of administration Quantitative whole-body autoradiography Duration of drug levels, dosing interval, repeat dosing Metabolic pathways Interaction with Cytochrome P450s Drug–drug interactions Metabolite activity Routes of elimination Radiolabelled compound profile	Plasma drug levels Oral bioavailability Tissue biopsies Compound elimination (in urine, feces) Trough compound levels, establishing dosing interval Phase 0 trials Phase I trials Healthy subjects Diseased population
Safety assessment	Toxicology On target effects (extension and/or exaggeration of pharmacology) Off target effects Pharmacological safety ICH 7 A and B safety guidelines renal, GI, CNS, CV, respiratory Two species safety/carcinogenicity studies	Impact of disease on daily life Safety profile Exaggerated pharmacology Off target effects Therapeutic index Efficacy-risk profile Comparison to existing/alternative medications

TABLE 1 (*Continued*)

Translational scoring	Preclinical approaches	Clinical approaches
Biomarkers for efficacy and safety prediction	***Development:*** Direct relationship to disease; relevant, easy to access Gene expression signals Proteomics Other 'omics'? *Validation:* Distinction of biomarker versus surrogate measure Biomarker leading to novel disease target Biomarker examples include blood pressure, plasma lipids (e.g. cholesterol), blood sugar, HIV, bacterial load, cellular pathology (tumor), FEV1, temperature and, ECG	Biomarker specificity (e.g. C-reactive protein) Postulated/known relationship to disease (cf. CSF Aβ levels) Defining patient sub-groups (guides selection for clinical trials)
Proof of principle, concept, mechanism	Target engagement in targeted tissue: MRI, among others Biomarker strategy Surrogate endpoint strategy	*Definition of specific drug characteristics for intended use of investigational compound to support regulatory filings* *Patient recruitment* Exclusion/inclusion criteria Inclusion using objective and accurate diagnostic criteria including validated biomarkers when available (e.g. hypertension and/or plasma cholesterol and lipids) *Biomarker strategy* Phase 0 Demonstrable in Phase 1? *Surrogate endpoint strategy* Phase 1 or early Phase 2
Clinical trial feedback	Formal, real-time interface for bidirectional information flow (e.g. 1990s Abbott Venture system) Clinical data informing preclinical research of: Human PK/PD; Need for alternative/back-up compounds; Properties required in next-generation drugs	Phases I–IV Phase IIa: proof-of-concept

relevance of biomarkers and animal model data to the human disease state, even when there is evidence for target engagement in humans, all frequently fail to enhance the success rate for new drug applications (NDAs). The question is why?

Disconnects in the translational equation

As scientists active in TM focus on defining appropriate criteria [11] to improve decision-making and success at the preclinical and/or clinical interface, many of the basic paradigms in biomedical science that are key to these activities are being compromised. There is a failure to acknowledge the complexity of biology [27,30] to avoid confusing the simplistic, reductionist linearity of current approaches to biomedical research [13,26]. Added to this are significant concerns that the US research enterprise is now in crisis mode [31,32], coupled with a perception that the quality of scientific research has become 'low', approaching mediocrity (http://pipeline.corante.com/archives/2010/06/24/all_those_worthless_papers.php) with 'any paper, however bad, ...[get-]...published' owing to the pressures on peer review (http://www.guardian.co.uk/science/2011/sep/05/publish-perish-peer-review-science/print). The venture capitalist Bruce Booth has commented (http://lifescivc.com/2011/03/academic-bias-biotech-failures/) that at least 50% of published studies from academic laboratories could not be repeated in an industrial setting. The prestige of the investigator or the journal did not appear to impact these numbers. An analysis [33] by Bayer of their internal efforts to replicate published new drug target data indicated that 65% could not be reproduced to such an extent that projects had to be abandoned. A similar analysis of company-driven research programs and their reproducibility by independent third parties has not been performed, but it may not differ substantially since concerns of translation and robustness of data highlight several broad issues related to data generation, relevance, quality and transparency. These include:

(i) An over-reliance on animal models of diseases that are poorly validated in the manner they are applied. Such models are 'validated' either because they provide a phenotypic behavior in response to a 'gold standard' drug, or they represent some pathophysiological phenomenon thought to be associated with the human disease state. In the former situation, the models can only be relied upon with any assurance to identify NCEs with the same mechanism of action, whereas the latter often represents an oversimplification of the disease, where absolute belief in a mechanism often trumps any contrary data, however robust the latter. Examples of this include the T helper 2 (Th2)/eosinophil model of asthma [34], the Non-obese diabetic (NOD) mouse in diabetes [35] and the various animal models of stroke, that together, have led to over a 1000 failed compounds in the clinic [36]. Difficulties in interpreting results from animal models are far from new. However, they remain a key part of hypothesis testing

provided that newer data are integrated hierarchically and taken in context with other datasets to inform broadly the validity of the hypothesis being tested [37,38].

(ii) The intrinsic reductionism of molecular biology, where engineered cell lines bearing little resemblance to native systems (or the human species) are used to define disease pathophysiology where unique functions are ascribed for ubiquitous signaling pathways such as Nuclear factor κ B (NFκB) and Extracellular-signal-related kinase (ERK); the use of mRNA levels, particularly in the form of data-rich heat maps, as a surrogate for changes in functional protein expression; and a tendency to approach the target validation process without entertaining a null hypothesis approach (see below), let alone defining what precisely is being validated [39].

(iii) Ignoring the null hypothesis that states that no relationship exists between two measurable quantities. A null hypothesis data set demonstrating a statistically significant difference between two groups (control versus treated) can thus lead to the null hypothesis being refuted (e.g. the test compound is not producing its effect by chance). In testing a hypothesis, the null element can be undermined by designing experiments that introduce a significant bias in support of the hypothesis. It is therefore critical to use alternative approaches to assess any apparent association and to avoid the situation where biased studies supporting a hypothesis are merely repeated using the same flawed and/or biased experimental design that gave rise to the first data set, without actually challenging the result. The null hypothesis has fallen into disuse in current biomedical research through ignorance of its existence, neglect or because it is regarded as an inconvenience that unnecessarily complicates experimental design and is incompatible with subjective data interpretation.

(iv) Superficial and/or subjective experimentation encompassing a range of activities that lack rigor, transparency and objectivity. Among these issues are the use of single data points, or replications from a single experiment that are analyzed as separate experiments, and the failure to include an adequate quality control or even any controls. An example of the latter was the false-positives in a high-profile genome-wide association study (GWAS) profiling study of centenarians that resulted in retraction [40]. Retractions of scientific articles have increased by 44% since 2001, with the majority occurring in the fields of medicine and biology [41].

The inappropriate use or lack of statistical analysis adds further to subjective interpretation with *P* values greater than 0.05 being regarded as either a 'significant trend' or a bona fide change. The use of the Law of Mass Action has become increasingly discretionary [42] with the assessment of concentration and/or dose–response effects becoming increasingly rare, resulting in data that are qualitative rather than quantitative. Compounds are also frequently used to perturb biological systems at a single concentration, the high levels of which often negate the reported selectivity of the compound and, consequently, the utility for the data generated.

(v) The difference between one scientist's objectivity and another's subjectivity can often be resolved with data from appropriately designed experiments, ideally performed in a blinded manner, analogous to a clinical trial design. However, bias [43,44], subliminal or overt, often leads to conclusions that are inconsistent with the actual data or are based on data sets that are not representative and are rarely replicated. Significant bias in the literature has been repeatedly highlighted by Ioannidis, one example being reports relating brain volume abnormalities to central nervous system (CNS) disease states [45], where the number of positive associations was 'way too large to be true', being ascribed to outcomes reporting that involved selective analyses and/or a lack of reporting of negative data.

In chronic disease states, such as diabetes [35,46], asthma [47] and AD [48,49], numerous NCEs and biologics that act robustly to improve outcomes via interactions with novel targets in disease-related preclinical models fail in clinical trials. This is probably because of a clinical diagnosis of these diseases occurring only when the disease is sufficiently advanced to preclude the efficacy of most of these treatment modalities, together with the result of an imprecise knowledge of disease causality and a lack of validated biomarkers. In Type 1 diabetes, modulating the immune system to prevent the destruction of pancreatic beta cells is a logical approach to prevent disease progression. However, by the time that overt symptoms are evident, 80% of the beta cells have been destroyed [46]. Similarly in AD, the initial pathology is thought to occur 10–20 years before the disease is typically diagnosed [49]. Despite these considerations, clinical failures in AD have morphed into a 'right target, wrong compound' focus, with the predominant research bias, the possibility of attenuating AD progression by removing and/or preventing formation of amyloid deposits [50], being apparently immune to reassessment despite late-stage clinical failures (γ-secretase inhibitors and amyloid antibodies such as AN1792 [48,50]) and an absence of convincing data to delineate whether amyloid deposits are causal or a protective response to the disease [51]. Such challenges to 'the primacy of Aβ in AD pathophysiology' [48], rather than leading to a reevaluation of the amyloid hypothesis have, instead, focused solely on the shortcomings in the NCEs selected for clinical evaluation. This contrasts with the process of deductive reasoning [52] wherein 'predictions...can be tested and the [hypothesis] rejected if these...are not shown to be correct' [53].

That flawed NCEs with questionable target selectivity and the lack of ability to engage their target in the brain at therapeutic levels [50] progressed to pivotal AD trials is an indictment of the compound selection process, and one that can be an immediate priority for rectification in any translational process. When compound selection lacks rigor and objectivity and is routinely influenced by other pressures (e.g. business decisions, personal ambition, financial incentives, among others [54]), then the translation process becomes a sham, wonderful on paper but flawed in practice.

(vi) Data selection and fraud are extensions of bias [55,56], further complicating T1-related activities. Whereas data reporting bias can occur by treating less than stellar data (e.g. that does not support the hypothesis under evaluation) as the product of failed experiments or the subjective ignoring of negative results, fraud, the outright fabrication of data is an infinitely more serious issue. Its incidence [41], and that of plagiarism, has either become more common in science or easier to detect. Well-publicized cases of fraud in recent years include the Korean cloning fraud, a fraudulent link between vaccination and autism [41], faked cancer biomarkers [57], and serial fraud in social psychology [58] and in clinical trials in pain [59] with the principle motivators being career pressure, laziness and ease of falsifying data (http://www.guardian.co.uk/science/2011/jul/28/scientific-fraud-regulation?INTCMP=SRCH, http://www.aaup.org/AAUP/pubsres/academe/2002/JF/Feat/good.htm).

(vii) The emergence of the scientist-entrepreneur and the intrusion of business into the scientific process [1,60–63] have tended to obfuscate boundaries and criteria in decision-making and led to concerns regarding objectivity. In the pharma business setting, the key role for a scientific authority figure has less to do with science and more to do with politics. In making the science simple, the scientist is tasked with using sound bites that relegate science to the superficiality of bullet points in a slide deck. Optimism is also obligatory, with the most mundane of data sets being described as 'innovative' and unrelentingly 'exciting'. In this context, the recruitment of a scientific advisory board (SAB) is often less about seeking an objective sounding board for the science and more about impressing investors and shareholders. An SAB can only reflect what it is told, and rarely (if ever) gets to review notebooks and raw data. Such situations lead to critical questions or key studies being postponed, with contrary data being routinely ignored [33,64], enabling programs to advance in a series of safe, small steps, the minimal innovation approach [3], to avoid failure. In the biotech setting, this can often lead to the creation of a body of sufficiently enticing information that facilitates a speedy and effective financial exit as the key goal, as contrasted to the development and advancement of an NCE to a NDA for marketing approval. Discovery science thus becomes relegated to a commodity that can be dealt with either by metrics (just add more people and stir, the critical mass mentality [1]) or outsourcing, where intellect, ingenuity, innovation and learning become sidelined, with the consequences of more than two decades of business-driven decisions only now being fully appreciated [1,54,61].

Disconnects in research objectivity and rigor lead to a breakdown in facilitating translational success, but these are not the only aspects in the evolution of the drug discovery process that have contributed to the dearth of new drugs. Searching for other reasons for the disconnect between funding and output in terms of NDAs has been a recurrent theme in the drug R&D literature over the past decade. Because it has been calculated that 50% of drugs in clinical development are discontinued for strategic reasons, rather than scientific concerns, it is appropriate to separate the issues accordingly, although there is significant overlap.

What went wrong? The science

Aside from the viewpoint that existing therapeutics produce their effects at the 'easy targets' or 'low hanging fruit', and that newer targets are exponentially harder to 'drug' [65], three additional factors have contributed to the cost and/or success mismatch. The first is an overt focus on metrics [66], driven by computer-based technologies and used for: (i) data mining to predict relevant targets and compound efficacy; and (ii) designing, synthesizing and assessing the activity of compounds [67]. This has resulted in more compounds being synthesized and analyzed over the past decade than in the history of biomedical research. It has also tended to reduce drug discovery to an information management process, where a computer is more effective than a human in sorting, analyzing and interpreting the millions of data points. These technologies, although revolutionizing the process of drug discovery, have done little to establish a facile pathway to the holy grails of drug discovery, ingenuity and innovation, leading instead to diminution in intellectual oversight, reflection, inquisitiveness and logic, with quantity being stressed at the expense of quality [54,68,69]. The second is a reductionist focus, targeted at compound interactions with discrete molecular targets to the almost total exclusion of the more traditional (and historically successful) integrated pharmacological approach [22,30,68,70] that involves hierarchical tissue evaluation together with whole-animal approaches in the context of an appreciation of the serendipity afforded by phenotypic observation [22,54,70]. Indeed, during the decade 1999–2008, when most drug discovery efforts were target-driven, a greater number of approved NCEs (28 versus 17) were discovered by phenotypic screening compared with target-based approaches [70], an anathema to the established reductionist view of many scientists, research organizations and investors. There is even a school of thought that one reason why targeted compounds are less successful is because they are too specific, and that effective treatment requires nuanced effects at several sites that can only be identified by phenotypic approaches. A third contributor to the cost and/or success mismatch stems from naive expectations for the human genome map. The success in mapping the human genome led to the immediate prediction for the identification of novel, key targets to treat [71] and diagnose [79] disease. Now more than a decade on, the application of GWAS [72] has resulted in the identification of a large number of disease-related risk and causal genes in diseased populations (e.g. more than 120 associated with AD). Many of these would not have been predicted based on present knowledge of disease etiology and, consequently, have had minimal impact in informing existing research hypotheses, with dogma generally overriding the novel data. This has additionally led to the genomic misidentification of disease states that has had a major negative impact on the personalized medicine paradigm [79]. Clearly, predictions were overly optimistic [73] for the rapid identification of new, disease-associated targets that would become the basis of new generations of safer, more effective drugs, expectations that have not been met [3,74] and are thought unlikely to materialize for at least the next decade [28].

It has also become increasingly recognized that the majority of the genome comprised of noncoding, previously labeled 'junk DNA', actually contains key regulatory sequences that modify gene activity and function in a complex interplay [75]. This will necessitate repeating all GWAS to incorporate these previously

ignored regions questioning the contributions of GWAS to date. A similar comment might apply to the role of mitochondrial DNA [76]. Like the apocryphal story of the drunk searching for his car keys under the street lamp because the light is there, similarly, the search for disease-associated genes has looked only in discrete sites lit by limited understanding. The readiness to label that which is unknown as 'junk' is consistent with the frequent claims of 'redundancy' in cellular pathways/mediators, or the failure to recognize that drug targets in disease differ from those in normal tissues. This underscores the fact that the knowledge base in biology, especially as it relates to disease and its treatment, is complex and remains woefully incomplete [68].

What went wrong? The strategy

A total of 50% of drugs in clinical trials are discontinued for strategic reasons, which suggests a major disconnect between what is sought and what is actually required. Generally, issues such as cost–benefit determinations, comparative profiles with existing standard of care, marketing and regulatory concerns are typically not a focus until clinical development is underway. However, these can be a major hindrance to the success of any new drug and suppress truly novel, innovative therapies. In type 2 diabetes for example, the low cost and broad utility of metformin is a real impediment to the development and introduction of new, improved drugs that would have to be more expensive than generic metformin, although the field requires new treatment options and diabetes and obesity are at epidemic levels. In situations such as this it is not the lack of effective translation, but commercial realities that hamper innovation and success, part of the T2 equation.

Another strategic issues is the rush to embrace each and every new technological approach as the ultimate answer to providing universal treatments for all diseases (e.g. genes, peptides, proteins, antisense, siRNA, gene therapy, stem cells, TM, among others) often before basic questions of utility, delivery, stability, specificity and toxicity were considered let alone objectively addressed. For instance, fomivirsen, approved by the FDA in 1998 for the treatment of cytomegalovirus retinitis, remains the only marketed drug acting through an antisense mechanism and is administered by direct ocular injection to overcome the problems of delivery.

Although some of these technologies might, in time, have an important impact, - witness the unprecedented success of monoclonal antibodies,- for most, the return on investment will require long-term commitment and dedication. This contrasts with the support for RNAi. Less than 5 years after acquiring Sirna Therapeutics for US$1.1 billion, Merck decided to drop RNAi, as did Roche after purportedly spending US$500 million on the technology. Similarly, Novartis did not renew a 5-year, US$700M partnership with Alnylam, despite owning 13% of the company, whereas both Pfizer and Lilly have reduced or abolished their programs. Whether initial diligence on this early stage technology was lacking and, in retrospect, failed to justify the hundreds of millions of dollars expended, or this was regarded as a reasonable outlay to explore the potential of the technology, it seems an expensive strategy reminiscent of that in combinatorial chemistry during the 1980s.

Another critical factor has been industry consolidation, the result of an incessant focus on short-term profitability to the exclusion of long-term value creation and stability, seemingly designed to subserve Wall Street interests [1,60,61] rather than patient and/or healthcare needs. An analysis from 1996 [8], which concluded that major pharmaceutical companies needed three NDAs per year per company to maintain reasonable growth yet were achieving NDA rates of approximately 0.25 per year per company, led to the conclusion that mergers and consolidation within the industry were inevitable to reach that target. Although multiple mergers have occurred during the subsequent 12 years, with only 25% of the pharmaceutical companies in existence in 1998 (42) remaining [62], this productivity goal has yet to be achieved and has been estimated to have resulted in the loss of over US$1 trillion in value in the period from 2000 to 2011 (http://www.pharmatimes.com/article/11-04-13/M_A_strategy_has_failed_miserably_-_Burrill.aspx). This failure has almost always been directed at the R&D organization despite post-merger integration issues and the resultant flux and instability in programs and staff.

A particular concern in this process is the inability to identify and foster innovation coupled with rampant risk aversion that results in 'bad risk' options in the drug R&D process [3]. Bad risk has been defined as superimposing the inherent risk in R&D with marginal innovation (itself an oxymoron), the latter reflecting a focus on existing targets, proven mechanisms of action and whatever the competitors are working on.

With the possible exceptions of Merck and Lilly, many pharmaceutical companies have now accelerated the externalization of much of their preclinical research activities, establishing new multimillion dollar academic research centers in Boston, San Diego and San Francisco, that are strangely reminiscent of the collaborations between Monsanto and Washington University, Shiseido and MGH–Harvard Medical School and Novartis and Scripps Research Institute (to name just a few) from the 1980s to 1990s, which were both expensive and had minimal impact on pharma pipelines.

Although the goals of academia to work with industry are no doubt well intended, these rarely align with those of pharma, nor should they [2]. Experience suggests that academic scientists are unlikely to understand and accept dictates as to what constitutes valid, valuable or proprietary research. Moreover, a lack of experience in the pharma translational process (http://blogs.wsj.com/health/2011/05/20/sanofis-zerhouni-on-translational-research-no-simple-solution/) coupled with a lack of knowledge and hands-on experience in development activities makes it difficult to understand how translational success will be improved by this strategy anymore than it was 20 years ago, although academia is viewed as a major source of innovation for the future [77].

Biotech has been a key source of multiple and useful ideas, and, importantly, is an obvious site to germinate academic discoveries and sift out those with real potential using criteria amenable to drug development. However, decreased funding of early-stage companies owing to the current economic environment has significantly impacted this important role, such that it is unclear where the next generation of drugs will come from. It is difficult to see pharma serving this function, despite its close, direct associations with academia, as it does not have sufficient 'bandwidth' to evaluate all opportunities after downsizing the R&D groups even when scientific input/oversight is sought.

Concluding remarks

The present state of productivity in pharma remains a serious problem, especially as the affordability of health care for the future

remains uncertain. As the general concept of TM continues to gain momentum, greater efforts will be required to vet adequately the ideas, processes, targets and compounds entering the T1 process. This will necessitate a more effective and transparent level of due diligence with independent replication of the data being used to advance targets and compounds rather than accepting these at face value ([33,64], http://lifescivc.com/2011/03/academic-bias-biotech-failures/).

TM represents yet one more example where efforts to improve the drug discovery process have been built on a collective amnesia of what is important in science, prompting the need to reinvent critical areas and disciplines as 'new' paths to enlightenment, when an update of what has worked would suffice. In the past, clinical pharmacology did provide a semblance of continuity between basic research and clinical development, but lack of support, appropriate training programs, interest at academic centers and sundry other reasons resulted in its decline [24]. In establishing TM as a new discipline [9,17], there is a major challenge in the context of its inherent political 'optics'. Thus, the reinvention of a perfectly serviceable and successful drug discovery paradigm (e.g. pharmacology [22], http://isp.hms.harvard.edu/wordpress/wp-content/uploads/2011/10/NIH-Systems-Pharma-Whitepaper-Sorger-et-al-2011.pdf, http://www.aspet.org/ISTCP/Home/) will require that proponents of the TM concept avoid the temptation to dissociate and eliminate direct references to the 'senior' discipline, for fear that the emperor's trendy new clothes of the 21st century [12] might in fact prove to be the same perfectly serviceable pair of Levis used in the previous century by successful drug hunters such as James Black, Paul Jansen, George Hitchens, Trudi Elion and David Jack, to discover drugs that are instrumental in helping contain health care costs while improving the quality and quantity of life for hundreds of millions of individuals worldwide.

Rather than creating a new science ripe for hype [12,78], current translational efforts would be better focused on reinvigorating and refocusing the scientific infrastructure in the biomedical sciences to ensure the inherent quality and validity of existing drug discovery research. In doing so, this will help reintroduce the 'logical, deductive, constructive, thoroughly prepared and pharmacologically oriented mind' similar to that of James Black [30], while concurrently, eliminating unnecessary business influence from the scientific decision-making process.

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