Am J Transl Res 2011;3(5):422-433
www.ajtr.org /ISSN:1943-8141/AJTR1107005

Review Article

Translational research: current status, challenges and future strategies

Dale Yu

Hoffmann-La Roche Inc. 340 Kingsland Street, Nutley, New Jersey 07110-1199, USA.

Received July 26, 2011; accepted August 29, 2011; Epub September 12, 2011; Published October 31, 2011

Abstract: Advances in translational research are expected to mitigate the recent drought in new drug development. Despite significant progress recently made in biological sciences, the results are decidedly mixed with significant breakthrough in some disease areas while extensive work remains to be completed in other areas. This review article provides a general survey of the current landscape of translational research so as to identify progress and areas of needs and the associated strategy. While significant advances in the development of translational tools have been made in all fronts, the availability of predictive preclinical models remains critical for the success of translational research. This is directly correlated with the success of translational research as illustrated by the recent approval of targeted drug therapies. By the same logic, unexpected side effects can also be explained by laboratory findings, thus completing the translational cycle. Because of this reason, further collaboration between preclinical and clinical scientists is essential. Non-scientific issues have important influence on the future of this endeavor cannot be underestimated either. Nonetheless, with definitive commitment of private industry and public resources, the future of translational research is promising.

Keywords: Translational medicine, review, policy, government regulation, cancer, cardiovascular disease, renal disease, HIV/AIDS, skin disease, tools

Introduction

Advances in translational research are expected to facilitate the development of safe and efficacious drug therapies in the 21st century. Despite significant progress recently made in biological sciences, the results are decidedly mixed. Continuing on this journey, a review of successes and hurdles could help identify the areas of needs and strategies. This article is intended to review the general landscape of translational research from the perspectives of strategy, processes, tools, actual successes, unrealized goals, and challenges. While this summary is not intended to be comprehensive, a survey does illustrate significant progress in drug therapies in some disease areas. This author hopes that this article could generate additional interest in the translational research community and promote further inter-discipline collaboration that results in improved patient care.

Traditional translational research processes

Preclinical investigation

In the first step of discovering new drug therapies, in vitro model systems of cell and tissue preparations are frequently used to elucidate the etiology/pathogenesis of disease states based on which the hypotheses for possible therapies are developed. Experiments are then conducted to examine novel therapeutic strategies that might interfere with these pathologic processes. This is followed by examining potential drug effects in more complex systems including animal disease models. The closer the animal model resembles the pathophysiology of the human disease, the more likely is the model predictive of the human response to an intervention. Unfortunately, many diseases have no good animal models and safety and efficacy can only be properly assessed in patients with the target disease. This underscores the uncertainty of the predictive value of animal data [1, 2].

Clinical investigation

Initial human experimentation, also referred to as Phase I or human pharmacology testing, is usually performed in healthy volunteers [3]. If the accumulated safety and laboratory data support further human investigations, Phase II or therapeutic exploratory testing (proof of con-

cept study) is conducted in the target disease patient population to provide a further assessment of safety as well as potential efficacy across a range of doses. The vast majority of compounds tested in Phase I and II studies fail to progress to Phase III testing because of safety concerns, lack of efficacy, or both. These problems, although discouraging, are to be expected. What is more disconcerting are the number of agents that are well tolerated, but fail to provide efficacy in clinical trials despite compelling laboratory efficacy evidence [2]. An incomplete understanding of the disease states and the impact of treatment modalities is frequently the cause of this type of failures.

Private industry and government initiatives

Recognizing the challenge, the pharmaceutical industry has recently been focusing on translational research actively. The academic medical research community has similarly embraced this paradigm largely through the motivation of National Institute of Health (NIH) via its Roadmap initiative. The NIH concludes that barriers between clinical and basic research, along with increased complexities in conducting clinical research, are making it more difficult to translate new knowledge to the clinic - and back again to the bench. In collaboration with the academics and research community, the NIH launched the Clinical and Translational Science Awards (CTSA) Consortium in 2006 with the plan of linking approximately 60 institutions to energize the discipline of clinical and translational sciences. The primary goal of the CTSA Programs is to assist institutions to forge an integrative academic home for Clinical and Translational Science. By consolidating resources, this consortium hopes to promote multi- and inter-disciplinary clinical and translational research so that new knowledge and techniques will become more readily available to patient care. Operationally, the members of the CTSA consortium are to attract basic, translational and clinical investigators, community clinicians, clinical practices, networks, professional societies, and industry together to form new professional interactions, programs, and research projects. These new institutional arrangements, coupled with innovative advanced academic degree programs, are to foster the new discipline of Clinical and Translational Science that will be broader and deeper than the classical and separate domains of translational research and clinical investigation [4]. As this is a fairly new initiative, the impact may not be immediately apparent until decades later.

Available tools

Currently, translational biology, predictive toxicology, in vitro–in vivo extrapolation, quantitative pharmacology, biomarkers, and surrogate endpoints are the translational research tools that are commonly used in the scientific community. A summary of these different approaches is provided in the following sections.

Translational biology

The microarray technology is enabling scientists to simultaneously investigate the expression of thousands of genes. Basic scientists and clinical investigators appreciate the great potential of this technology, not only for gaining new insights into cell biology and ultimately for developing a more biologically sound and clinically useful classification, but also for improving the management of a myriad of different diseases, with cancer being one of the important focuses. Other important technology platforms are available to analyze genetic and epigenetic changes in DNA, microRNAs, proteins and functional proteins. Ultimately, the use of all these platforms should help develop a much more comprehensive picture of the biology of diseases, as well as the variability in responses between patients [5].

Humanized mice overcomes the ethical and technical constraints of studying human biology in vivo that would otherwise not be possible [6]. This genetically engineered mouse model has been applied to the study of pancreatic cancer, brain tumors, leukemia, prostate cancer programmed cell death mechanisms, and rational chemotherapy [7].

Predictive toxicology

Liver and the cardiovascular system often give rise to safety related drug attrition. The highest incidence of concordance between animal and human toxicities is commonly observed for the cardiovascular, gastrointestinal, and hematological effects of drugs. The isolated, paced Langendorff-perfused female rabbit heart model provides detailed information on the overall profile of drug-induced electrophysiological ef-

fects and allows drugs to be classified based on their action potential morphology and conduction properties [8]. Dog telemetry is the standard in vivo study used to assess cardiovascular liability. These animal studies are often required to support human testing and registration.

The liver is the first point of contact of a drug following oral absorption, and drug-related idiosyncratic toxicity is still one of the major causes of acute liver failure cases in human. High concordance of drug-induced human hepatotoxicity with in vitro cytotoxicity has been reported via the high content screening technology in man [9].

In vitro–in vivo extrapolation

Computer program like Simcyp® links in vitro and early human study data by predicting the systemic drug exposure in humans. This facilitates the "go–no go" decisions in drug discovery and development [10]. Systems biology computer simulation tools like CellDesigner, COPASI and VirtualCell, are used to facilitate translational research in genomics, proteomics and systems biology [11].

Pharmacokinetic-pharmacodynamic (PK-PD) modeling and simulation

PK-PD links drug concentration to a temporal biological effect profile over time. Translating these measurements from animals to man is the key to successfully reducing attrition in drug development. Animal and human PK-PD experiments are conducted to predict efficacy or side effects [10]. Thoughtful planning and quantitatively based decision making have increased the chance of successful drug treatment, and when failure occurs the root cause is more readily understood [12].

Biomarkers

Biomarkers can be used for diagnosis, prognosis, selection of patient therapy, and for providing insights in disease mechanism and progression [13]. The enormous biological variability among individual patients, as well as the huge dynamic range of biomarker concentrations present the main challenges to deduce diagnostic patterns that are unique to specific disease states [14]. To determine if a biomarker can offer prognostic-predictive or predictive clinical utility, a prospective or retrospective exploratory analyses of clinical study data could be performed. This could be followed by a validation step in a well designed randomized controlled clinical trials [15].

Recent clinical successes and setbacks in translational research

Important progress has been made recently in therapeutic area like oncology as a result of successful translational research. On the other hand, limitations and hurdles that require extensive research are also quite clear in disease like Alzheimer's, nicotine dependence, and neural repair due to a lack of predictive animal model. In other cases, new translational technology tool like functioning MRI and a better understanding of the mechanisms of pathogenesis are now available which could set the foundation for future breakthrough.

Oncology

DNA repair

Exaggerated environmental exposures of polyvinyl compounds, sunlight, nicotine, diet, polycyclic aromatic hydrocarbons, alkyl amines, arsenic, and chromium could induce DNA damage that may not be adequately repaired and could represent an early step in the pathogenesis of disease. Among the familial diseases, defective DNA repair pathways have been reported in xeroderma pigmentosum (XP), hereditary nonpolyposis colon cancer, and hereditary breast cancer, among others [16]. Topical application of the T4 DNA glycosylase repair enzyme in liposomes reduced the 1-year appearance of skin tumors in XP patients which led to the FDA approval of Dimericine®, a "DNA repair drug" for XP and severe skin-burn patients [17].

Monoclonal antibody treatment

The approval of bevacizumab (Avastin®) and trastuzumab (Herceptin®) by the FDA and the European Community also represents a recent successful example of translational research. Bevacizumab and trastuzumab are monoclonal antibodies that bind specifically to proteins critical to cancer cell growth and are examples of targeted therapy. Trastuzumab targets human epidermal growth factor receptors highly expressed in up to 25% of metastatic breast can-

cers [18]. It reduced tumor progression and prolonged survival in those patients with human epidermal growth factor R2 positive metastatic cancer [19]. Bevacizumab targets vascular endothelial growth factor and blocks the binding of this potent, pro-angiogenic factor to tumor vasculature, thereby inhibiting tumor blood supply and growth. When used in patients with metastatic colorectal cancers, bevacizumab inhibited tumor growth and improved survival [20, 21]. The discovery, sequencing, and cloning of the human epidermal growth factor receptor back in 1985 was a critical first step [22]. Subsequent advances in molecular biology, in particular proteomics, led to the synthesis of human antihuman epidermal growth factor antibodies for use in clinical trials. Successful transition through phase II and III trials resulted in its approval for human use in 2000 [18, 23].

Targeted gene therapy

Advances in antisense methods targeting genes involved in cell proliferation, angiogenesis, and apoptosis could interfere with cancerous growth. For example, gefitinib (Iressa®) inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including those associated with the epidermal growth factor receptor (EGFR-TK). EGFR is expressed on the cell surface of many normal cells and cancer cells and a subset of patients that possess activating mutations in the EGFR was most responsive to geftinib [24, 25].

Continuous technological advances in genomics, proteomics, genetics, and epigenetics are continuing to provide new insights into oncogenic pathways, DNA repair, stem cells, metabolism, and the tumor microenvironment. This is augmented by advances in animal and quantitative models of cancer which leads to novel approaches to cancer prevention, therapy, and progress in individualizing cancer treatment [26].

Neurology

Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent form of dementia and the number of cases is expected to increase exponentially worldwide. To date, three identified highly penetrant genes (AbetaPP, PSEN1, and PSEN2) can explain only a small number of AD cases with a Mendelian transmission pattern. Many genes have been analyzed for association with non-Mendelian AD, but the only consistently replicated finding is apolipoprotein E (APOE). At the present, the possibilities for prevention, early detection, and treatment of the disease are limited and APOE genotyping is not considered useful for screening, presymptomatic testing, or clinical diagnosis of non-Mendelian AD. Most research on genome-based applications in AD is still in the first phase of the translational research which means that extensive work is still needed before a new treatment modality is feasible [27].

Migraine and pain

During episodes of migraine attack and pain, functional brain imaging is now used to study activity within the brain as a translational technology. Specifically, the brain patterns of activation alongside responses to thermal and mechanical stimuli are evaluated and compared between healthy individuals and patients [28, 29]. Therefore, functional MRI can be used preclinically to define functional pain pathways and activation signatures for therapeutically useful drug therapies. This tool can highlight pathways that may be sensitive to pharmacological or behavioral therapeutic intervention within the brain during pain [30].

Nicotine dependence

Dependence on psychoactive substances including illicit drugs, alcohol or nicotine continues to exact a heavy burden on the health and welfare of users and on society. A major obstacle to the development of medications for nicotine dependence is that the current animal and human laboratory models have limited predictive clinical validity. Despite common underlying CNS circuitry, drug effects might manifest in different behaviors in animals and humans. Looking to the future, using imaging to develop profiles of neural activation corresponding to particular dimensions of dependence — might be helpful in determining behavioral model validity and in medication development [31].

Insomnia

Insomnia is a common and disabling complaint for which there is a need for improved treat-

ments. Caffeine administration is a simple and effective model of the difficulty in initiating sleep in both rats and humans. Interestingly, it's stimulatory effects are sensitive to sleep-promoting agents including zolpidem (Ambien®) and trazodone (Desyrel®) which have different mechanisms of action. Collectively, these data provide a potentially predictive translational model of onset-to- insomnia. The model could provide a quick and simple way to evaluate the likelihood of success of a new treatment [32].

Neural repair

Clinicians seeking interventions for neural repair in patients with paralysis and other impairment have traditionally extrapolated the results of cell culture and rodent experiments into the framework of a preclinical study. The various rodent models of repair for stroke and spinal cord injury still lack information that identifies key considerations of the disease. These included the lesion of etiology, volume and location that reflects the human disease; examine changes induced by injury and by repair procedures both near and remote from the lesion; and etc [33]. Similar to AD, extensive research work is still needed in pursuing neural repair.

Anesthesia

Even though anesthetic care during a surgical intervention is remarkably safe, further advances is needed to address clinical problems in the risky perioperative period. Paraplegia is a complication that occurs in 3%–16% of thoracic and thoraco-abdominal aneurysm repair which could be associated with an increase in mortality and a reduction in the quality of life [34-36]. Recent translational research work discovered that the μ and δ opioid receptor agonists facilitate the release of the excitatory neurotransmitter, glutamate, which triggers excitotoxic cell death via stimulation of N-methyl d-aspartate receptors on inhibitory interneurons in the ventral horn of the spinal cord, thereby causing spastic paraparesis [37]. This is a good example how the feedback of clinical findings led to laboratory research that could offer a treatment solution in the future.

Focal cortical dysplasia

Cortical dysplasia (CD) are the pathological substrates in a large percentage of patients with pharmaco-resistant epilepsy who may be amenable to surgical treatment. Although genetic models that clearly mimic human malformations are still limited, some models seem to reproduce some rare dysplastic pathologies. Difficulties encountered in the studying of such models are the determination of how mutations in diverse sets of genes ultimately lead to alterations in brain excitability [38]. Other animal models were not able to establish an association between pathology and electrophysiology findings.

Further research is needed to determine how transformation of various models of "dormant" pathology into an active (spontaneous) epileptic pathologies. These studies should reproduce some of the features that are characteristic of the natural history of some forms of human pathology and would ultimately lead to the identification of some of the cellular mechanisms of epileptogenesis and the future design of "preventative" interventions [39].

Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a clinically severe and fatal neurodegenerative disease characterized by a loss of both upper and lower motor neurons, resulting in progressive muscle loss and paralysis. While the exact cause of neuronal death in ALS remains unknown, multiple molecular defects were theorized to trigger motor neuron cell death. These pathophysiological mechanisms include oxidative stress, mitochondrial impairment, protein aggregation, glutamate cytotoxicity, transcription dysfunction, inflammation, and apoptotic cell death. An important advance in clinical trials in ALS patients has been the introduction of genetic mouse models of ALS [40, 41]. The phenotypes of ALS transgenic rodent models appeared to highly correlate with human neurological disease by providing parallel pathophysiological targets that are also present in ALS patients which may validate the known CNS drug targets in a therapeutically relevant manner.

While drug trials in mice confirm therapeutic direction, a more definitive understanding of the molecular events leading to motor neuron death in ALS still remains to be elucidated. Specific neuroprotective strategies targeted at identified molecular mechanisms have the potential to dramatically delay the onset and slow the pro-

gression of ALS. As such, compounds like creatinine, Coenzyme Q10, histones, riluzole, rasagiline, minocyclin and etc. could emerge as relatively safe therapeutics for the treatment of ALS. As the drug agents and their analogs described here are already available for human use, combine neuroprotective therapies may reach greatest efficacy due to the multiple levels of molecular pathology and treatment [42].

Cardiovascuar disease

Toxicity resulting from drug treatments

Trastuzumab

Translational medicine has been used less frequently in the development of cardiovascular drugs or in predicting potential cardiovascular toxicity of non-cardiac agents. As described in the Oncology section, trastuzumab, a humanized monoclonal antibody acts against the proto-oncogene HER2, a receptor in the epidermal growth factor family that is amplified in many patients with breast cancers. When the HER2 gene was conditionally deleted in the mice heart, mice displayed no overt phenotype and survived to adulthood. However, the mice hearts showed morphologic and hemodymanic changes consistent with dilated cardiomyopathy and they were unable to tolerate the stress of increased load or administration of an anthracycline [43].

Trastuzumab's action against HER2 could now explain why it was associated with a 500% (4.1% versus 0.8%) relative increase in the incidence of left ventricular dysfunction in one study and a 6.6% absolute incidence of cardiac dysfunction in a second study in patients with early-stage breast cancer [44, 45]. Therefore, the challenge now is to translate the available basic science data into rationale use of this agent, particularly in that population of patients without metastatic disease [46].

COX-2 inhibitors

Another group of compounds that have been associated with unexpected cardiovascular toxicity are the inhibitors of prostaglandin (PG) endoperoxide synthases (cyclooxygenases) or COXs [47, 48]. COXs oxygenate arachidonic acid to form a wide array of products including a family of PGs and thrombaxane A2. These products have conflicting cellular effects as PGI2, PGE1, and PGD2 inhibit platelet aggregation by activating adenylyl cyclase, whereas thrombaxane A2 facilitates platelet aggregation and vasoconstriction; the role of these pathways in any tissue being mitigated by the presence and number of selective PG or thromboxane receptors [49]. There is experimental evidence that inhibition of the COX-2 gene is associated with increased cardiac [50] and pulmonary fibrosis [51], whereas deletion of one allele of COX-2 resulted in enhanced cardiac damage in mice with viral myocarditis [52]. Inhibition of COX-2-dependent pathways in the genetic mouse models also predisposes mice to an exaggerated response to thrombotic stimuli [53], increases blood pressure [54], facilitates an enhanced proliferative response to vascular injury [55], and accelerates atherogenesis [56]. Nonetheless, the effects of selective COX-2 inhibition can be modified by genetic background, gender, and disease state [57]. Thus, additional basic science data is needed to identify the genetic and phenotypic profile of patients that have a higher likelihood of developing an adverse response to the COX-2 inhibitors [49].

Restenosis

Numerous approaches to reduce the rates of restenosis were studied between 1988 and 2000 have been disappointing [58]. Regulating cell proliferation is essential to treating restenosis. Activation of regulatory enzyme sub-units known as cyclins can inhibit proliferation and without compensatory pathways exists, suitable drug therapy should be highly efficacious. For example, sirolimus indirectly elevates cyclin p27 concentrations which in turn inhibit the proliferation and migration of smooth muscle cells. A recent clinical trial result confirmed that sirolimus-eluting stents were able reduced restenosis in diabetic patients [59, 60].

In addition to drug therapy, regenerative biology and replacement therapy have been pursued together with the study of genomics and proteomics, embryo genesis, immunobiology, inflammation, thrombosis, public health, and health promotion [61]. However, the results of clinical trials in myocardial regeneration therapy have been relatively disappointing. Additional mechanistic laboratory studies are still needed on how the transplanted cells are transformed and what signaling pathways are modified. The

combined use of different cell types, cells in various stages of activation or differentiation, or both, might lead to improved myocardial regeneration [62].

Cardiomyopathy

Dilated cardiomyopathy (DCM) is the third cause of heart failure (HF) and is characterized by progressive ventricular dilation and functional impairment in the absence of coronary lesions and/or hypertension. An accurate large animal model of DCM is pacing-induced HF. It is obtained by continuous cardiac pacing at a frequency three- to fourfold higher than the spontaneous heart rate and is mostly applied to dogs, but also to pigs, sheep and monkeys. To date, this model is considered a gold standard in HF research. A wide variety of other animal models of HF is available to study DCM and to test innovative diagnostic procedures and therapeutic strategies. However, none of these animal models can entirely reproduce the human disease. Based on the analysis of a working group convened by the National Heart, Lung, and Blood Institute, testing promising interventions in large mammals and conscious preparations is recommended [63, 64].

Renal disease

Glomerular injury

In recent years, research into the role of complement in the immunopathogenesis of renal disease has broadened the understanding of the fragile balance between the protective and harmful functions of the complement system. Interventions into the complement system in various models of immune-mediated renal disease have resulted in both favorable and unfavorable effect and will help define the level of the complement cascade at which a therapeutic intervention will result in an optimal effect. The discovery of mutations of complement regulatory molecules has established a role of complement in the hamolytic uremic syndrome and membranoproliferative glomerulonephritis, and genotyping for mutations of the complement system are already moving from the research laboratory into clinical practice. These clinical discoveries have resulted in the creation of relevant animal models which may provide crucial information for the development of highly specific therapeutic agents. Research into the role of complement in proteinuria has facilitated the understanding of inflammation pathways which ultimately lead to renal failure irrespective of the underlying renal disease and is of major importance for the majority of renal patients. Complement science is expected to result in meaningful therapeutic advances in the near future [65].

Other diseases

HIV/AIDS

The new antiretrolviral, maraviroc, is a CCR5 fusion inhibitor. Based on the clinical experience to date, this agent looks promising as an option for treatment-experienced patients [66]. This agent blocks the binding between glycoproteins on the outer coat of HIV and receptors of these glycoproteins of CD4 cells. These results were later confirmed by the proof-of-concept studies in animals [67]. Depleting the latent reservoir of HIV is another attractive hypothesis based on which substantial research laboratory work is being conducted [68].

Corneal epithelial wound healing

Basic research on the mechanism of corneal epithelial wound healing has the potential to lead to the development of new modes of treatment for persistent corneal epithelial defects. Fibronectin is expressed at the site of corneal epithelial defects, serves as a provisional matrix for the migration of epithelial cells, and stimulates epithelial wound healing in vitro and in animal models. Eyedrops containing autologous plasma fibronectin are also effective for the treatment of persistent epithelial defects of the cornea in patients. Substance P and insulin-like growth factor-1 synergistically stimulate corneal epithelial wound healing in vitro and in animal models. Furthermore, the administration of eyedrops containing both a substance P-derived peptide (FGLM-amide) and insulin-like growth factor-1-derived peptide (SSSR) were effective in the treatment of persistent epithelial defects in individuals with neurotrophic keratopathy [69].

Surgical disease

Recent translational research in surgical diseases includes investigations in thyroid nodule diagnosis, treatment for gastrointestinal stromal

tumors (GIST) and colon cancer, aortic aneurysm treatment, mathematic models for kidney donor–recipient matching, and breast cancer treatment [70]. One of the earliest success stories of targeted molecular therapies in cancers arose among a subset of soft-tissue sarcomas referred to as GIST. These are rare tumors but comprise one of the common mesenchymal tumors of the gastrointestinal tract. In 2001, a patient with metastatic GIST tumor was successfully treated with imatinib (Gleevec®), a selective small-molecule inhibitor of the KIT (CD117) proto-oncogene [71]. The specific type of mutation in C-KIT determines the response to therapy to imatinib. Mutations in exon 11 of C-KIT were observed in approximately 70% of GIST cases and are associated with a response rate of 85%. However, patients with mutations in exon 9 of C-KIT was observed in about 17% of GIST which had a much lower response rates of only 45%. Patients with no mutations have no response. Unfortunately, most patients eventually develop resistance to imatinib with long-term therapy but, based on the success of this targeted therapy, other targeted therapies have since been developed. Sunitinib (Sutent®), a multi-target tyrosine kinase inhibitor, has now been developed and was approved by the Food and Drug Administration for use in patients who have an imatinib-resistant GIST or are intolerant to GIST [72].

Psoriasis

Psoriasis is perhaps unique for a disease that there is still no acceptable animal model despite many rounds of bi-directional translation research. The course of discovery that led to introduction of targeted biologics for psoriasis depended heavily on fundamental discoveries in basic science laboratories of immunological pathways. Subsequently, antibodies or fusion proteins to specific immune molecules have proved to be effective in models of inflammation or organ transplantation and 'humanized' molecules were created, but few were intended for psoriasis as the main indication.

Fortunately, the relevant pathways had been expressed in psoriasis lesions and many, but not all, of the intended therapeutics do have positive activity in patients with psoriasis. The currently approved biologic therapeutics mostly followed this pathway of discovery and implementation, while at the same time provide some new insights into disease biology. These therapeutics include T-cell blocker like efalizumab (Raptiva®) and tumor necrosis factor (TNF) alpha blocker like etanercept (Embrel®). While many of these new biologic therapies seem to have favorable safety profiles and may offer better long-term disease management than the older conventional agents, important information still remains to be gathered about the functional consequences of blocking specific immune molecules and pathways in humans. Future work should strive to learn more about the specific effects of new therapeutic agents on the human immune system [73].

Challenges and future strategies

So far, this review has described the current translational research strategy, process, and tangible results. While great challenges do exist, they have proven not to be insurmountable. Some challenges and mitigating strategies are summarized in the following sections.

Validation of clinically useful biomarkers

The discovery of clinically useful biomarkers is critical to the success of translational research but few such new tests have appeared to date [74]. In laboratory medicine, the transfer of promising research assays to daily laboratory practice could take years and involves many tedious and sequential steps. This difficulty is often related to methodological biases in animal experimentation and differences between animal and human pathophysiology. In addition, there is a serious concern regarding the reliability and reproducibility of results because of sample handling and pre-analytical variability. Therefore, the most feasible and standardized collection procedures should be established before results of a novel and promising diagnostic technique can be transferred to daily laboratory practice [75, 76].

Limitations of preclinical and clinical study results

The preclinical "proof-of-concept" study is a critical step of translational research. Data variability and bias in interpretation are the principal challenges in designing, conducting, and analyzing preclinical studies. To detect the consequences of an intervention, the effect size must overcome the inherent variability in the model.

Small studies are especially sensitive to the effects of missing data; the inclusion or exclusion of a single data point can alter the results and conclusions of a study. Thus, a prospective plan to deal with missing data and outliers is essential. Animal deaths and the handling of missing data along with outliers should be discussed with the study results, where applicable. Multiplicity in statistical testing is often an issue in preclinical studies that is inadequately addressed [77].

Clinically, the current approach of treating broad populations of patients using a singular approach is not well suited to the development of molecularly targeted drugs considering the inherent inter-subject variability in drug response. Although developing drugs with individual patient focus is immensely more complex, it should improve the success rate of development, as well as provide benefit to patients and ultimately to the economics of healthcare [78].

Non-scientific factors

Many non-scientific factors do have significant impact on translational research. The availability of funding, conflict of interest, regulatory burdens, right to privacy, fragmented infrastructure, shortage of qualified investigators and willing participants, incompatible databases, and lack of congressional and public support are important and real concerns. Optimized academia–industry partnership, where academia delivers trained researchers skilled in translational research and industry helps to sponsor those programs, consider alternative funding sources, reduce the cost of clinical investigation by decreasing unnecessary burdens, and increase public support for biomedical research spending could help alleviate some of these concerns [79]. As described before, both the private industry and the NIH initiatives could address these issues as well.

Address correspondence to: Dr. Dale Yu, Hoffmann-La Roche Inc. 340 Kingsland Street, Nutley, New Jersey 07110-1199 Tel: (949) 858-2280; E-mail: dale.yu@roche.com

References

[1] Kieburtz K, Olanow CW. Translational Experimental Therapeutics: The Translation of Laboratory-Based Discovery into Disease-Related Therapy. Mt Sinai J Med 2007; 74: 7–14.

[2] Hurko O, Ryan JL. Translational research in central nervous system drug discovery. NeuroRx 2005; 2: 671–82.

[3] Department of Health and Human Services, Food and Drug Administration. International conference on harmonisation: guidance on general considerations for clinical trials. Fed Regist 1997; 62: 66113–9.

[4] National Institutes of Health Translational Research Overview: http:// commonfund.nih.gov/ clinicalresearch/ overview-translational.aspx.

[5] Sotiriou C, Piccart MJ. Taking gene-expression profiling to the clinic: when will molecular signatures become relevant to patient care? Nature 2007; 7: 545-53.

[6] Shultz LD, Ishikawa F and Greiner DL. Humanized mice in translational biomedical research. Nature 2007; 7: 118-30.

[7] Abate-Shen C. A New Generation of Mouse Models of Cancer for Translational Research. Clin Cancer Res 2006; 12: 5274-6.

[8] Valentin JP, Hoffmann P, De Clerck F, Hammond TG and Hondeghem L. Review of the predictive value of the Langendorff heart model (Screenit system) in assessing the proarrhythmic potential of drugs. J Pharmacol Toxicol Methods 2004; 49: 171-81.

[9] O'Brien PJ, Irwin W, Diaz D, Howard-Cofield E, Krejsa C, Slaughter M, Gao B, Kaludercic N, Angeline A, Bernardi P, Brain P and Hougham C. High concordance of drug-induced human hepatotoxicity with in vitro cytotoxicity measured ina novel cell-based model using high content screening. Arch Toxicol 2006; 80: 580 –604.

[10] Jeffrey P, Karran E, Palmer A and Stemp G. Translational Sciences – Turning Drug Like Molecules into Medicine. Drug News Perspect 2006; 19: 659-63.

[11] Freedenberg M, Kaddi C, Quo CF, Wang MD and Coulter WH. Review of Systems Biology Simulation Tools for Translational Research. Proceedings of the 7th IEEE International Conference on Bioinformatics and Bioenginering 2007; 358-65.

[12] Powell R, Gobburu J. Pharmacometrics at FDA: Evolution and Impact on Decisions. Clin Pharmacol Ther 2007; 82: 97-102.

[13] Rai A. Biomarkers in translational research: focus on discovery, development, and translation of protein biomarkers to clinical immunoassays. Expert Rev Mol Diagn 2007; 7: 545-53.

[14] Schrattenholz A, Groebe K. What does it need to be a biomarker? Relationships between resolution, differential quantification and statistical validation of protein surrogate biomarkers. Electrophoresis 2007; 28: 1970–9.

[15] Wang SJ. Biomarker as a classifier in pharmacogenomics clinical trials: a tribute to 30th anniversary of PSI. Pharmaceut Statist 2007;

6: 283–96.
[16] Reinlib L. Report of the Working Group on Integrated Translational Research in DNA Repair. DNA Repair 2007; 6: 145–7.
[17] Wei Q, Wang LE, Sturgis EM and Mao L. Expression of nucleotide excision repair proteins in lymphocytes as a marker of susceptibility to squamous cell carcinomas of the head and neck. Cancer Epidemiol Biomarkers Prev 2005; 14: 1961–6.
[18] Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, Levin WJ, Stuart SG, Udove J, Ullrich A and Press MF. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989; 244: 707–12.
[19] Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, Wolter JM, Paton V, Shak S, Lieberman G and Slamon DJ. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999; 17: 2639–48
[20] Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S and Bergsland E. Phase II, randomized trial comparing bevacizumab plus florouracil (FU)/leucovrin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003; 21: 60–5.
[21] Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren BSE, Ferrara N, Fyfe G, Rogers B, Ross BSR and Kabbinavar F. Bevacizumab plus irinotecan, florouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335–42.
[22] Coussens L, Yang-Feng TL, Liao YC, Chen E, Gray A, McGrath J, Seeburg PH, Libermann TA, Schlessinger J, Francke U, Levinson A and Ullrich A. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with NEU oncogene. Science 1985; 230: 1132–9.
[23] Pegram MD, Lipton A, Hayes DF, Weber BL, Baselga JM, Tripathy D, Baly D, Baughman SA, Twaddell T, Glaspy JA and Slamon DJ. Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. J Clin Oncol 1998; 16: 2659–71.
[24] Kim R, Tanabe K, Emi M, Uchida Y and Toge T. Potential roles of anti sense therapy in the molecular targeting of genes involved in cancer (review). Int J Oncol 2004; 24: 5-17.
[25] Borkhardt A. Blocking oncogenes in malignant cells by RNA interference--new hope for a highly specific cancer treatment? Cancer Cell 2002; 2: 167-8.
[26] DeBusk L, Russell AJ, Imai K and Matrisian LM. In the Forefront of Basic and Translational Cancer Research: Seventh Joint Conference of the American Association for Cancer Research and the Japanese Cancer Association. Cancer Res 2007; 67: 10.
[27] Mihaescu R, Detmar SB, Cornel MC, van der Flier WM, Heutink P, Hol EM, Rikkert MG, van Duijn CM and Janssens AC. Translational research in genomics of Alzheimer's disease: a review of current practice and future perspectives. J Alzheimers Dis 2010; 20: 967-80.
[28] Borsook D, Becerra L. Pain Imaging: Future applications to integrative clinical and basic neurobiology. Adv Drug Deliv Rev 2003; 55: 967-86.
[29] Borsook D, Ploghaus A and Becerra L. Utilizing brain imaging for analgesic drug development. Curr Opin investig Drugs 2002; 3: 1342-7.
[30] Hargreaves R. New Migraine and Pain Research. Headache 2007; 47: S26-S43.
[31] Lerman C, LeSage MG, Perkins KA, O'Malley SS, Siegel SJ, Benowitz NL and Corrigall WA. Translational research in medication development for nicotine dependence. Nature Reviews Drug Discovery. 2007; 6: 746-62.
[32] Paterson LM, Wilson SJ, Nutt DJ, Hutson PH and Ivarsson M. A translational, caffeine-induced model of onset insomnia in rats and healthy volunteers. Psychopharmacology 2007; 191: 943–50.
[33] Dobkin BH. Curiosity and Cure: Translational Research Strategies for Neural Repair-Mediated Rehabilitation. Dev Neurobiol 2007; 67: 1133-47.
[34] Kakinohana M, Oshiro M, Saikawa S, Nakamura S, Higa T, Davison KJ, Marsala M and Sugahara K. Intravenous infusion of dexmedetomidine can prevent the degeneration of spinal ventral neurons induced by intrathecal morphine after a noninjurious interval of spinal cord ischemia in rats. Anesth Analg 2007; 105: 1086–93.
[35] Estrera AL, Miller CC 3rd, Huynh TT, Azizzadeh A, Porat EE, Vinnerkvist A, Ignacio C, Sheinbaum R and Safi HJ. Preoperative and operative predictors of delayed neurologic deficit following repair of thoracoabdominal aortic aneurysm. J Thorac Cardiovasc Surg 2003; 126: 1288 –94.
[36] Kakinohana M, Nakamura S, Fuchigami T, Davison KJ, Marsala M and Sugahara K. Mu and delta, but not kappa, opioid agonists induce spastic paraparesis after a short period of spinal cord ischaemia in rats. Br J Anaesth 2006; 96: 88–94.
[37] Kakinohana M, Kakinohana O, Jun JH, Marsala M, Davison KJ and Sugahara K. The activation of spinal N-methyl-daspartate receptors may contribute to degeneration of spinal mo-

tor neurons induced by neuraxial morphine after a noninjurious interval of spinal cord ischemia. Anesth Analg 2005; 100: 327–34.
[38] Sarkisian MR. Overview of the Current Animal Models for Human Seizure and Epileptic Disorders. Epilepsy Behaviour 2001; 2: 201–16.
[39] Najm IM, Tilelli CQ and Oghlakian R. Pathophysiological Mechanisms of Focal Cortical Dysplasia: A Critical Review of Human Tissue Studies and Animal Models. Epilepsia 2007; 48: 21–32.
[40] Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, Deng HX, Chen W, Zhai P, Sufit RL and Siddique T. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. Science 1994; 264: 1772-5.
[41] Bruijn LI, Becher MW, Lee MK, Anderson KL, Jenkins NA, Copeland NG, Sisodia SS, Rothstein JD, Borchelt DR, Price DL and Cleveland DW. ALS-linked SOD1 mutant G85R mediates damage to astrocytes and promotes rapidly progressive disease with SOD1-containing inclusions. Neuron 1997; 18: 327-38.
[42] Ryu H, Ferrante RJ. Translational Therapeutic Strategies in Amyotrophic Lateral Sclerosis. Mini Rev Med Chem 2007; 7: 141-50.
[43] Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, Peterson KL, Chen J, Kahn R, Condorelli G, Ross J Jr, Chien KR and Lee KF. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 2002; 8: 459–465.
[44] Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, Shannon RP, Swain SM, Brown A, Fehrenbacher L, Vogel VG, Seay TE, Rastogi P, Mamounas EP, Wolmark N and Bryant J. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005; 23: 7811–9.
[45] Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, Ingle JN, Rodeheffer RJ, Gersh BJ and Jaffe AS. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. J Clin Oncol 2004; 2: 3700–4.
[46] Feldman AM, Koch WJ and Force TL. Developing Strategies to Link Basic Cardiovascular Sciences with Clinical Drug Development: Another Opportunity for Translational Sciences. Clin Pharmacol Ther 2007; 81: 887-92.
[47] Topol EJ. Failing the public health – rofecoxib, Merck, and the FDA. New Engl J Med 2004; 351: 1707–9.
[48] FitzGerald GA. Coxibs and Cardiovascular Disease. New Engl J Med 2004; 351: 1709–11.
[49] Feldman AM, Koch WJ and Force TL. Developing Strategies to Link Basic Cardiovascular Sciences with Clinical Drug Development: Another Opportunity for Translational Sciences. Clin Pharmacol Ther 2007; 81: 887-92.
[50] Dinchuk JE, Car BD, Focht RJ, Johnston JJ, Jaffee BD, Covington MB, Contel NR, Eng VM, Collins RJ, Czerniak PM, and Trzaskos JM. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II. Nature 1995; 378: 406–409.
[51] Bonner JC, Rice AB, Ingram JL, Moomaw CR, Nyska A, Bradbury A, Sessoms AR, Chulada PC, Morgan DL, Zeldin DC and Langenbach R. Susceptibility of cyclooxygenase-2-deficient mice to pulmonary fibrogenesis. Am J Pathol 2002; 161: 459–70.
[52] Takahashi T, Zhu SJ, Sumino H, Saegusa S, Nakahashi T, Iwai K, Morimoto S and Kanda T. Inhibition of cyclooxygenase-2 enhances myocardial damage in a mouse model of viral myocarditis. Life Sci 2005; 78: 195–204.
[53] Kobayashi T, Tahara Y, Matsumoto M, Iguchi M, Sano H, Murayama T, Arai H, Oida H, Yurugi -Kobayashi T, Yamashita JK, Katagiri H, Majima M, Yokode M, Kita T and Narumiya S. Roles of thromboxane A(2) and prostacyclin in the development of atherosclerosis in apoE-deficient mice. J Clin Invest 2004; 114: 784–94.
[54] Francois H, Athirakul K, Howell D, Dash R, Mao L, Kim HS, Rockman HA, Fitzgerald GA, Koller BH and Coffman TM. Prostacyclin protects against elevated blood pressure and cardiac fibrosis. Cell Metab 2005; 2: 201–7.
[55] Cheng Y, Austin SC, Rocca B, Koller BH, Coffman TM, Grosser T, Lawson JA and FitzGerald GA. Role of prostacyclin in the cardiovascular response to thromboxane A2. Science 2002; 296: 539–41.
[56] Egan KM, Lawson JA, Fries S, Koller B, Rader DJ, Smyth EM and Fitzgerald GA. COX-2-derived prostacyclin confers atheroprotection on female mice. Science 2004; 306: 1954–7.
[57] Yang T, Huang Y, Ye W, Hansen P, Schnermann JB and Briggs JP. Influence of genetic background and gender on hypertension and renal failure in COX-2-deficient mice. Am J Physiol Renal Physiol 2005; 288: F1125–32.
[58] Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO and Smith SC Jr. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)—executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guide-

lines for percutaneous transluminal coronary angioplasty); Society for Cardiac Angiography and Interventions. Circulation 2001; 103: 3019–41.
[59] Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL and Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349: 1315–23.
[60] Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ and Russell ME. A polymer-based, paclitaxeleluting stent in patients with coronary artery disease. N Engl J Med 2004; 350: 221–231.
[61] NHLBI SPARK Working Group [http://www.nhlbi.nih.gov/funding/fromdir/spark2web.htm].
[62] Yoon CH, Hur J, Park KW, Kim JH, Lee CS, Oh IY, Kim TY, Cho HJ, Kang HJ, Chae IH, Yang HK, Oh BH, Park YB and Kim HS. Synergistic neovascularization by mixed transplantation of early endothelial progenitor cells and late outgrowth endothelial cells: the role of angiogenic cytokines and matrix metalloproteinases. Circulation 2005; 112: 1618–1627.
[63] Recchia FA, Lionetti V. Animal Models of Dilated Cardiomyopathy for Translational Research. Veterinary Research Communications 2007; 31: 35–41.
[64] Bolli R, Becker L, Gross G, Mentzer R, Balshaw D and Lathrop DA. Myocardial protection at a crossroads. The need for translation into clinical therapy. Circulation Research 2004; 95: 125–134.
[65] Berger SP, Daha MR. Complement in glomerular injury. Semin Immunopathol 2007; 29: 375–384.
[66] Lalezari J, Goodrich J, DeJesus E and Lampiris H. Efficacy and safety of maraviroc plus optimized background treatment in viremicART-experienced patients infected with CCR-tropic HIV-1: 24-week results of a Phase 2b/3 study in the US and Canada. 14th Conferences on Retroviruses and Opportunistic Infections, 2007.
[67] Exploring the potentials of HIV microbicides. NCRR Reporter. Winter 2007; 31: 1. Available at www.ncr.nih.gov/newspub/Winter07rpt/director.asp.
[68] Valenti WM. Translational Research: Application to HIV/AIDS. AIDS Reader 2007; 17: 319-21.
[69] Nishida T. Translational research in corneal epithelial wound healing. Eye Contact stns 2010; 36: 300-4.
[70] Stojadinovic A, Ahuja N and Nazarianet SM. Translational Research in Surgical Disease. Arch Surg 2010; 145: 187-96.
[71] Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B and Demetri GD. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001; 344: 1052-6.
[72] Hueman MT, Schulick RD. Management of gastrointestinal stromal tumors. Surg Clin North Am 2008; 88: 599-614.
[73] Guttman-Yassky E, Krueger JG. Psoriasis: evolution of pathogenic concepts and new therapies through phases of translational research. British Journal of Dermatology 2007; 157: 1103–15.
[74] Lippi G, Plebani M and Guidi GC. The Paradox in Translational Medicine. Clinical Chemistry 2007; 53: 1553.
[75] Plebani M, Marincola FM. Research translation: a new frontier for clinical laboratories. Clin Chem Lab Med 2006; 44: 1303–12.
[76] Timms JF, Arslan-Low E, Gentry-Maharaj A, Luo Z, T'Jampens D, Podust VN, Ford J, Fung ET, Gammerman A, Jacobs I and Menon U. Preanalytic influence of sample handling on SELDI-TOF serum protein profiles. Clin Chem 2007; 53: 645–56.
[77] Unger EF. All Is Not Well in the World of Translational Research. J Am Coll Cardiol 2007; 50: 738-40.
[78] Simon R. Translational research in oncology: key bottlenecks and new paradigms. Expert Rev Mol Med 2010; 12: e32.
[79] Littman BH, Di Mario L, Plebani M and Marincola FM. What's next in translational medicine? Clin Sci (Lond) 2007; 112: 217-27.