Translational science: what is it and why is it so important?

'The translational sciences are those areas of the basic sciences that enable the transition from Petri dish to people'

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US Democratic Presidential candidate, Senator Joseph Lieberman, recently announced his plan to establish an 'American Center for Cures', with an annual funding of US$15 billion (http://www.dmdoptions.com/gov_1222.html). Lieberman's bold proposal to create a center that is funded at a level nearly comparable to NIH, is the most visible acknowledgment, to date, of the persistent inability to convert progress in basic research into new treatments and cures for cancer and chronic disease. The proposal for an 'American Center for Cures' implicitly questions the 50-year old assumption that cures for cancer and chronic disease will spontaneously emerge from progress in pure science. Indeed, cures for humans diseases have not materialized, thus far, from a research enterprise that invests disproportionately in studies in worms, fruit flies, and cultured cells in Petri dishes, without a parallel investment in research enabling the translation of fundamental knowledge into disease cures. For example, it is now 15 years since the identification of the gene that causes cystic fibrosis (CF), yet this discovery has had relatively little impact on the suffering of CF patients.

The demand for disease cures is naturally increased in the genomics era of drug development and there has been a spectacular expansion in the discovery sciences over the past ten years, culminating in the sequencing of the human genome. However, this progress is not being translated into disease cures, as a result of the chronic under-development of the translational sciences – those areas of the basic sciences that enable the transition from Petri dish to people. The model of the translational sciences is drug targeting; drugs encounter targeting problems in people that do not exist in Petri dishes. The drug-targeting sciences originate from transport biology, as opposed to classical drug delivery and controlled release, which arise from the materials sciences. The materials sciences provide formulation solutions and alternative modes of drug administration, but do not provide solutions to human transport barriers. Although there is significant worldwide investment in drug delivery, there is little concerted effort in the drug-targeting sciences. The acceptance of the idea that we need to invest in the translational sciences, such as targeting biology, stems from the recognition that there is a real problem in translating progress in the discovery sciences into disease cures.

Failure of the discovery sciences to produce disease cures

Gene therapy

More than 6000 patients have been enrolled in gene therapy trials over the past 15 years with little, if any, success; the viral vectors that work so well in Petri dishes have failed in humans. Gene therapy has the potential to be the most potent and safest form of medical therapy ever created, but the current scientific model is not allowing this to happen. Gene therapy will be effective when the gene delivery problems are solved, but gene delivery is a translational science that is chronically under-developed. We can discover genes, but we cannot deliver them.

Brain disease

Despite the 1990s being the 'decade of the brain', the majority of chronic brain disorders remain untreated and the mainstay of neurotherapeutics is still the relatively ineffective lipid-soluble small molecule. Large molecule drugs, such as the neurotrophins, have the potential to treat brain disease with favorable safety profiles, but the neurotrophins uniformly failed as neurotherapeutics in clinical trials in the 1990s because they do not cross the blood–brain barrier following subcutaneous administration. In a recent trial of glial-derived neurotrophic factor (GDNF) for Parkinsons disease, GDNF was administered

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via craniotomy and intracerebroventricular (ICV) infusion [1]. Any activity of GDNF administered by the ICV route was obscured by the adverse events associated with such an invasive route of drug delivery to the brain. The ICV route is a form of craniotomy-based drug delivery to the brain, which is invasive, expensive and relatively ineffective, but is the only alternative available to brain drug developers. However, brain drug delivery is a translational science that remains a marginal activity at academic and industrial neuroscience centers. We can discover brain drugs, but we cannot deliver them.

Industrial drug development

The number of new molecular entities (NMEs) presented to the FDA (http://www.fda.gov) in 2002 was half that seen in 1999 (the substantial investment by the pharmaceutical industry in genomics, proteomics and HTS notwithstanding) [2]. Before the advent of receptor-based rational drug design, drugs were discovered by a 'trial and error' approach that relied on animal testing. The use of early animal testing enabled the selection of drugs that bound receptors and that easily traversed biological membrane barriers. The types of drugs discovered in the HTS era have higher molecular weights and higher hydrogen bonding than traditional drugs, both of which cause problems in drug transport across biological membranes. Drug companies invest in drug discovery, but not targeting, with the primary emphasis on the cloning of drug receptors to facilitate new drug discovery. However, the industry pays little attention to the cloning of new endogenous transporters that could aid drug transport to the receptor. Why discover drugs if you cannot deliver them?

Genomics-driven discovery sciences

Drug development in the 20th century was a chemistry-driven process that relied on a 'trial and error' approach and enabled small-molecule drug discovery. Small molecules worked both *in vitro* and *in vivo* because those selected were the molecules that could easily traverse biological membranes *in vivo*. Drug development in the 21st century is a genomics- or biology-driven process that relies on receptor-based rational drug design, which enables the discovery of large-molecule drugs, including recombinant proteins, gene medicines, antisense, RNA interference and monoclonal antibodies. These large-molecule drugs have a level of potency and specificity that is generally not achieved with conventional small molecules; they promise better therapeutics, and even disease cures. However, the limiting problem of transport of these large-molecule drugs effectively terminates future drug development.

Large-molecule drugs encounter severe targeting problems in humans

Unlike cultured cells, humans have a complex vascular system of arteries, veins and microvasculature. There are >100 billion capillaries perfusing most organs, and all molecules reaching the target cells must first traverse the walls of these capillaries. Most large-molecule drugs do not effectively achieve this, but the impact of the capillary barrier in the drug development process is not well understood and is frequently ignored in drug development. The 'investigational new drug' applications (INDs) filed in the 1990s for the use of neurotrophins in chronic brain disease were prepared nearly entirely on the basis of cell culture findings of discovery scientists who paid little, if any, attention to the transport problems that would be encountered in migration from the bloodstream into the brain.

Translational sciences

The drug development process must be expanded beyond the discovery sciences, to include the targeting sciences as a translational science and as an equal partner. Targeting science can be used to re-formulate small- or large-molecule drugs and genes into medicines that cross the membrane transport barriers *in vivo* and are effectively distributed to the target sites. In addition to providing solutions for transportation *in vivo*, the targeting sciences focus on pharmacokinetics, metabolic stability and other problems that are absent in cell culture, but which enable the translation of the drug and gene discovery sciences into treatments and cures in humans.

Common origins of the discovery and translational sciences

The discovery and translational sciences have common origins, meaning that the translational sciences should not be equated with clinical science, applied science or technology-driven science. Translational sciences use the same tools as the discovery sciences, and incorporate the following:

- endothelial genomics or proteomics to drive the discovery of novel endogenous transporters or genes controlling microvascular permeability;
- the molecular and cell biology of endothelial transcytosis;
- the molecular cloning of endogenous transporters as conduits for small-molecule drug delivery, or novel endogenous receptors for large-molecule drug delivery;
- the genetic engineering of bifunctional fusion proteins that target two different receptors: one receptor to mediate transport and one receptor to mediate drug action;
- the fundamental physiology of capillary transport of gene medicines or monoclonal antibodies;

- the molecular and cellular biology of cellular crosstalk between parenchymal cells and the neighboring capillary endothelial cells.

Chronic under-development of the targeting sciences

The above examples of targeting science are rarely addressed by the discovery sciences in either academia or industry; <5% of the drug development effort is devoted to targeting. Current models can be modified to integrate the targeting sciences fully with the discovery sciences. Alternatively, the door is open to new models of how academic research can be funded, where the primary emphasis is placed on disease cures, rather than on molecular mechanisms. Industry will continue to see a decline in approvable NMEs despite the investment in the discovery sciences. If targeting science is funded to the same extent as discovery science, then cures for disease will be developed and there will be no need for a fragmentation between the bodies that fund research in the basic sciences and those that fund research in disease cures.

References

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