

Exploratory clinical testing of neuroscience drugs

Dennis W. Choi

Published online 28 October 2002; doi:10.1038/nn930

Other articles in this special issue illustrate the remarkable promise of today's neuroscience for ameliorating the impact of nervous system diseases: a massive impact measurable in deaths, suffering, lost human potential and drained resources. At last we have the tools and understanding to begin to identify rational countermeasures against scourges that have long had names but not treatments. In just the past few years, the first drugs useful in the amelioration of stroke, multiple sclerosis, amyotrophic lateral sclerosis and Alzheimer's disease symptoms, as well as several new anticonvulsants, have been approved by U.S. and European regulatory agencies. New therapeutic strategies are emerging at a quickening pace, filling the research pipelines in biotechnology and pharmaceutical companies. In tantalizing view are drugs that may slow the progression of Alzheimer's or Parkinson's disease, reduce the brain's vulnerability to ischemic insults, alleviate depression, anxiety or pain refractory to current medications—and even help restore functions lost to spinal cord injury.

This ongoing revolution in the identification of novel therapeutic concepts is well matched to advances in the science of practical drug development. Medicinal chemists have learned how to hit identified molecular targets with precision and efficiency, drawing structural clues from crystal structures, molecular modeling and the high-throughput screening of compound libraries; resulting leads are filtered with the eye of experience and refined through combinatorial chemistry. Elaborate counterscreening ensures high levels of specificity, and candidate compounds are run through a gauntlet of assays designed to turn back those with potential for organ toxicity, carcinogenicity, teratogenicity, immunogenicity or interference with the metabolism of other drugs.

The author is at Merck Research Laboratories
WP42-212, 770 Summeytown Pike, West Point,
Pennsylvania 19486, USA
e-mail: dennis_choi@merck.com

Yet a problem is also looming: flow through this waxing pipeline of potential therapies narrows abruptly at the clinical interface, a stricture so far resistant to amelioration. Viewed across all therapeutic areas, research costs per successful new prescription drug now exceed 800 million US dollars, reflecting a stunning 250% rise in inflation-adjusted terms over the past decade, driven in large part by increases in the resources devoted to clinical testing (J.A. DiMasi, Tufts Center for the Study of Drug Development, unpublished data). Many years and hundreds of million dollars can be expended to bring a drug through human study, encompassing metabolic and safety measurements (Phase I), testing of efficacy (Phase II) and evaluation of overall risk–benefit relationships (Phase III). Even though clinical testing is initiated on only a highly selected subset of preclinical drug candidates, fewer than 1 of 5 such candidates typically makes it through to regulatory agency approval. And, daunting as these general statistics are, they are likely to underestimate the challenge of translating research advances into new treatments in the neurosciences, where the ability of preclinical bench work to predict efficacy in humans is more limited than in other therapeutic areas.

It is our brain that most distinguishes us from lower mammals, rendering the modeling of human neurological or psychiatric diseases in rodents, or even monkeys, predictably treacherous. One can model hypertension or cholesterol metabolism in rodents with reasonable fidelity. But do rodents anguish over the “unbearable lightness of being”¹? How analogous is the biology of a rodent that stops swimming in a Porsolt forced swim test, and a human who has yielded final hope, or veers from mania into the black depths of depression? It is clearly possible to use dopamine system perturbations to identify, iteratively, potential antipsychotic drugs that block dopamine receptors. But can one expect to capture enough of the essence of human schizophrenia or human judgment in laboratory animals

to use the models predictively in the identification of breakthrough treatments? Although efficacious anticonvulsants have been successfully developed based on effects in preclinical models, will it be possible to advance against refractory epilepsies without confronting circuitry specific to the human neocortex?

Additional caution is signaled by recent failures of therapeutic translation in settings where the fidelity of rodent models might *a priori* have been expected to be above average. Studies of primary pain pathways in rodents clearly implicated substance P neurotransmission and neurokinin (NK)-1 receptors; yet NK-1 antagonists failed to show antinociceptive activity in humans². N-methyl-D-aspartate (NMDA) receptor antagonist drugs, which handily reduce infarction after focal ischemia in rodents and cats, have failed to improve outcome after human stroke in several clinical trials³. The pathophysiology of acute brain infarction is relatively well understood and conserved across mammals: if it defies accurate modeling in lower animals, what are the prospects for modeling Alzheimer's disease or Huntington's disease? A quick perusal of the literature yields myriad proposed approaches for altering the course of Alzheimer's disease: inhibitors of β -amyloid formation, deposition, aggregation and cytotoxicity; growth factors; tau phosphorylation inhibitors; anti-inflammatory drugs; downstream inhibitors of excitotoxicity or apoptosis; cellular replacements, and so on. Only a small fraction of these promising ideas can possibly undergo adequately powered full clinical testing, each ultimately involving hundreds or thousands of patients and years of work, yet it is unclear that preclinical experiments can provide a rational basis for culling the pack.

The best way to refine target selection at present may be to utilize the only powerful model system for human nervous system diseases available today—humans—prioritizing the rapid, efficient, yet safe exploration of early candidate approaches in both normal volunteers and

people with targeted diseases. In the past, it was not uncommon for neuroactive drugs with a plausible mechanism of action to be 'lobbed over the wall' into standardized clinical development; some years and many dollars later, clinical scientists returned with an answer regarding efficacy in humans, all too often negative. However, new methodologies have begun to permit the detection of intermediate molecular, biochemical and physiological consequences of drug action within the intact, functioning human nervous system. Positron emission tomography (PET), in combination with appropriately designed emitter ligands, is now regularly used to measure the fraction of a target brain receptor occupied by a given compound, reducing the guesswork involved in the selection of drug dosage for Phase II testing. Functional imaging with PET and magnetic resonance imaging (MRI), alone or in combination with electrophysiological monitoring, and biochemical detection thresholds in blood and CSF that in some cases approach single molecules, routinely permit pharmacodynamic assessments and may ultimately prove useful in establishing drug efficacy (see below). To gain maximal advantage from these measurements, changes may be needed in development protocols to enhance flexibility and feedback to discovery scientists. The attainable goal should be to provide a seamless transition from bench to bedside, such that the process of drug discovery and concept refinement continues during clinical testing.

Although only rigorous clinical trials—adequately powered, randomized, blinded and controlled, and enrolling a representative patient population—can provide definitive evidence of drug efficacy in the field, smaller exploratory efforts lacking one or several of these key attributes may be useful in testing mechanistic hypotheses or prioritizing approaches. Despite design-induced uncertainties in result interpretation, these exploratory efforts may still provide enough of a directional signal to be helpful in improving the odds that a drug brought forward into full clinical testing will indeed work, especially if the threshold for detecting drug efficacy is intentionally set high to reduce false positives. Furthermore, in exploratory studies, enrollment can be selective—for example, people not being treated with other medications, or who have a specific symptom subset—thus reducing the variables that might obscure a therapeutic signal. In the best case, one may be able to utilize an 'n of 1' design, in which each

subject or patient serves as his/her own control. This favorable structure will be more easily achieved in testing reversible, symptomatic treatments (such as agents aimed at reducing pain, inhibiting movement disorders or enhancing cognition) than with treatments aimed at inducing permanent state changes (such as neuroprotective agents), but even the latter may become tractable with sufficient delineation of disease natural history and the identification of accessible biomarkers quantitatively correlated to disease state.

The intricacy of the nervous system has limited the availability of such quantitative biomarkers in plasma or CSF, but imaging techniques are promising. Comparing perfusion-weighted and diffusion-weighted MRI scanning shortly after stroke onset may identify brain that is at risk for infarction, but potentially salvageable⁴, permitting powerful before- and after- neuroprotective treatment comparison (the latter assessed with MRI several days later). Such direct measures of tissue damage are likely to yield better signal-to-noise than clinical functional scales, as the functional impact of a given volume of infarction can vary from minimal to great, depending on location (orbital frontal lobe versus primary motor cortex, for example). The progression of chronic neurodegenerative diseases might also be accessible to imaging biomarkers, such as hippocampal atrophy or deposition of amyloid plaques in Alzheimer's disease, loss of presynaptic dopaminergic markers in Parkinson's disease, or decreased striatal glucose utilization in Huntington's disease. Specific patterns of regional brain activation, detected with fMRI or PET imaging, may provide an objective measure of depression or psychosis^{5,6}, although further study will be needed to establish that these methods can provide greater reliability than clinical examination. Some conditions may be amenable to electrophysiological endpoints: for example, quantitative electroencephalographic detection of discharges in epilepsy, or the use of evoked potentials to assess the integrity of spinal long tracts in settings such as multiple sclerosis or traumatic cord injury.

Introducing 'proof-of-concept' compounds into humans as soon as appropriate action and safety can be assured, rather than waiting for the refinement of characteristics needed in true drug candidates, may further facilitate early clinical exploration. For instance, a compound requiring frequent intravenous administration and interacting with commonly used med-

ications would likely lack viability as a drug candidate, but might still be utilized to test hypotheses in a small number of selected patients under controlled conditions, assuming, of course, informed consent and appropriate full ethical review. In addition, evolving capabilities in pharmacogenomics may permit the investigative use of compounds producing unacceptable side effects in certain individuals, e.g. those with atypical metabolic profiles, if those at risk for toxicity could be confidently excluded from the study population.

Besides improving target selection, a second goal should be to improve the power and efficiency of the Phase II and III clinical trials that rigorously test drug efficacy, as these consume the majority of the limiting resources now required for drug development. The performance of the nervous system is intrinsically complex and difficult to assess with conventional neurological or psychiatric examinations; factors often further confounding assessment are diagnostic uncertainty, disease heterogeneity and placebo effects, as well as fluctuations in attention, mood, fatigue and so forth. In addition, the accurate clinical assessment of the course of slowly progressive diseases can typically require following hundreds or thousands of affected individuals for many years. To accommodate these difficulties as well as inter-rater variability, many studies of putative neurological or psychiatric drugs have been accomplished with simplified rating scales, such as a 'clinician's global impression' index, either by themselves or incorporated into larger compilation scores. Not surprisingly, such scales are typically imprecise and insensitive, likely contributing substantially to a long history of failed trials involving CNS treatments ultimately established to be effective.

Whereas several strategies for improving the efficiency and power of Phase II / III clinical trials for neuroscience drugs have been discussed⁷, arguably the greatest impact would accrue from the deployment of disease state biomarkers as primary trial endpoints. Regulatory agencies are justifiably reluctant to base approval decisions upon such surrogate endpoints, as there is always risk that a treatment might favorably alter a surrogate endpoint but not correspondingly improve clinical outcome. But there is an equally real risk that excessive conservatism in regulatory requirements will deprive people of needed treatments. Surrogate endpoints, such as blood pressure in the testing of antihypertensives, or viral load and CD4

T-cell counts in the testing of antiretroviral agents, have been used extensively in past trials. Radiographic bone mineral density has been used to supplement the less tractable clinical endpoint, bone fractures, in the development of drugs capable of ameliorating osteoporosis, although the possibility that it may dissociate from clinical outcome is well recognized⁸. The ability of Betaseron, a human β -interferon analog developed by Chiron, to reduce MRI evidence of white matter demyelination was a secondary endpoint influential in supporting Food and Drug Administration (FDA) approval of the drug in 1993 for the treatment of relapsing-remitting multiple sclerosis.

It would be a tragedy if failure of imagination and energy in drug development or the regulatory endgame limited the potential of neuroscience to ameliorate the diseases weighing increasingly upon our society. We need to identify critical hurdles and seek paths forward that wisely balance the risks of commission and omission. The identification of surrogate endpoints useful in testing putative treatments for nervous system diseases requires integrating insights into disease biology with clinical insights and trial experience, and

should be a high-priority goal of the broad neuroscience community. Validating such metrics will be a particularly challenging task. Perhaps it would be possible for pharmaceutical companies to develop cooperative agreements to accomplish this, working under the prospective guidance of regulatory agencies. Standardizing surrogate endpoints and pooling treatment experiences across industry-wide studies of different therapeutic agents would permit faster and more stringent validation than any individual organization could perform, raising the standard for future studies and benefiting all. In the United States, NIH might have a central role in organizing and leading these efforts, a worthy mission that would leverage both the scientific leadership and intramural program resources of that august institution. NIH-sponsored workshops convening representatives from academia, industry and the FDA to plan the development of surrogate endpoints have been an effective mechanism in the past; an initiative along these lines has just been launched by Richard Hodes and Neil Buckholz at the National Institute on Aging in relation to treatments for Alzheimer's disease.

1. Kundera, M. *The Unbearable Lightness of Being* (HarperCollins, New York, 1984).
2. Hill, R. NK₁ (substance P) receptor antagonists – why are they not analgesic in humans? *Trends Pharmacol. Sci.* 21, 244–246 (2000).
3. Lee, J.M., Zipfel, G.J. & Choi, D.W. The changing landscape of ischaemic brain injury mechanisms. *Nature* 399, A7–A14 (1999).
4. Albers, G.W. Advances in intravenous thrombolytic therapy for treatment of acute stroke. *Neurol.* 57, S77–S81 (2001).
5. Curtis, V.A., Dixon, R.G., Morris, E.T., Bullmore, M.J., Williams, S.C.R., Sharma, T., Murray, R.M. & McGuire, P.K. Differential frontal activation in schizophrenia and bipolar illness during verbal fluency. *J. Affect. Dis.* 66, 111–121 (2001).
6. Drevets, W.C., Price, J.L., Barch, M.E., Reich, T., Todd, R.D. & Raichle, M.E. Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol. Biochem. Behav.* 71, 431–447 (2002).
7. Fillit, H.M., O'Connell, A.W., Brown, W.M., Altsteil, L.D., Anand, R., Collins, K., Ferris, S.H., Khachaturian, Z.S., Kinoshita, J., Van Eldik, L. & Dewey, C.F. Barriers to drug discovery and development for Alzheimer's disease. *Alzheimer Dis. Assoc. Disorders* 16, S1–S8 (2002).
8. Marcus, R., Wong, M., Heath, H. & Stock, J.L. Antiresorptive treatment of postmenopausal osteoporosis: comparison of study designs and outcomes in large clinical trials with fracture as an endpoint. *Endocr. Rev.* 23, 16–37 (2002).

Patenting basic research: myths and realities

Sheila R. Kirschenbaum

Published online 28 October 2002; doi:10.1038/nn932

Patents manage technology. They are a contract between an applicant and the government whereby, in return for a written disclosure of the technological invention, the United States Patent and Trademark Office (USPTO) gives the applicant the right to prevent the manufacture, use and sale of the invention by others for a limited period of time. This approach allows technology to evolve from basic research to real-world applications.

Although patents protect against unauthorized uses and promote further technological developments, some researchers are concerned that patenting does more harm than good. Patents, it is said, control technology, limiting its movement into and development by the commercial arena. Furthermore, patents allegedly interfere with collegial exchange of new information and ideas. Finally, neuroscience seems to be difficult to patent, which may exclude neuroscientists from sharing in patent-derived benefits. For academic scientists who conduct basic research, these are valid concerns. Here I briefly address these issues in an attempt to demystify the patent process and technology management.

Despite concerns that patent protection may limit the development of basic research into practical applications, in practice patents encourage the transition of technology to the marketplace. Research discoveries or inventions are rarely able to enter the marketplace in their laboratory form. Selling the invention as a product often requires further research, such as *in-vitro* and *in-vivo* preclinical studies, clinical studies and government-required regulatory studies. Because the measure of a scientist's success lies in publishing findings in peer-reviewed journals, companies are unable to keep the basic research technology underlying their product development

The author is Patent Counsel at the Office of Technology Management, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037, USA. e-mail: kirschenbaum@salk.edu