VIEWPOINT

Drug zone

BY **MICHAEL EHLERS**

26 OCTOBER 2012

Drug discovery for psychiatric diseases has been on a sterile and unproductive path, argues **Steven Hyman** in a perspective published 10 October in *Science Translational Medicine*. Hyman, director of the Stanley Center for Psychiatric Research at the Broad Institute in Cambridge, Massachusetts, issues a powerful call to arms for drug developers and provides some suggestions for how “to get back on a productive path of drug discovery.”

I agree with a number of Hyman’s points, especially regarding the models we use for drug development. He is spot on in his comments about traditional rodent models of psychiatric disorders. The newer generation of mice with mutated or deleted genes mimics genetic findings in humans. But these are models of specific pathways and not diseases, and should never be considered more than that. It is time to cease anthropomorphizing where unjustified.

Also powerful is Hyman’s recognition that human neurobiological measurements must be the foundation for dissecting the pathophysiology of human disease. There is a strong case for models using rodents and other preclinical species in which the underlying circuits are evolutionarily conserved (i.e., the more subcortical, the better). But if one is focused on higher cortical functions and behavior, one should tread with caution in claiming relevance to human psychiatric disease.

We have entered the era of human induced pluripotent stem (iPS) cells, which can be made

from adult human fibroblasts and converted into many different kinds of cells. With this amazing new technology, recognized justifiably by the Nobel Prize in Physiology or Medicine this year, the question becomes how to develop valid cell-based models for complex human disease.

Tempered optimism:

Despite the promise, optimism for iPS cell models must be tempered, particularly in psychiatry. Cell models may work well when analyzing problems that strike at the level of the cell, such as abnormal electrical activity of brain cells in **epilepsy** or misfolded protein accumulation in cystic fibrosis. But for many disorders, crucial deficits may be most visible in cells acting together to form a circuit. Most psychiatric diseases fall well into this latter category, and it's not yet clear how well iPS cells can be used to model neural circuits.

An unexpanded nuance within Hyman's article is the assumption that psychiatric disease represents a large market. By any measure of disease prevalence and socioeconomic impact, this is unquestionably the case. But, in the controlled global markets of health care and drug reimbursement, can we take this for a given?

A market is not just the number of affected individuals and thus potential ultimate 'consumers,' but also the payers who, for better or for worse, provide the direct economic valuation of the size of market. To be rather blunt, are we willing to pay for new psychiatric drugs in an era in which each new drug costs nearly $2,000,000,000 to bring to market (yes, the number of zeros is correct), and many new drugs are either not reimbursed or not included on formulary?

If so, this will require a change in cost-benefit calculation by payers and providers. For most payers, the bar is (and arguably should be) high to justify paying prices that recover investment when there are plenty of 'adequate' generics on the market (e.g., risperidone for schizophrenia, fluoexitine for depression).

In other areas, such as autism, we have no drugs whatsoever to treat the core features of the disease or most of the associated symptoms. Although a big scientific challenge, the absence of therapeutics in autism creates a space where unmet medical need and pharmaceutical company commercial interests may justifiably cohabitate.

What are the next steps, and what is the impact on autism research?

Recent history tells us that diagnosis and patient stratification based on underlying biological features of the disease will be critical for progress. Much of current research is focused on single genetic changes, but we must identify specific pathways and their association with quantifiable features of autism-related deficits. And as more compounds

reach **clinical testing**, it is essential that quantifiable, biologically **rational measurements** help to drive the regulatory path to therapeutics approval wherever possible.

Despite a dearth of new drugs in psychiatry in recent years, with a concerted effort to define genetic and signaling pathways, enable human biology, categorize disease in a quantifiable manner, take acceptable risk and advocate for the medical need, we have the potential to see a new golden era of psychiatric drug discovery, including autism drugs, over the next decade.

Michael Ehlers *is chief scientific officer of neuroscience at Pfizer.*