Genome Biology

COMMENT

Bailing out

Gregory A Petsko*

My online dictionary defines "bail" as a verb meaning, among other things, to abandon a commitment, obligation, or responsibility. It's hard for governments, or public agencies, to bail on commitments that affect the lives of many people, because ultimately they are held accountable by those same people. It's not as hard for the private sector to bail, because most for-profit companies see themselves as responsible primarily to their shareholders, who represent a pretty small segment of the population. I've never understood why critics of public spending and advocates of the privatization of virtually everything don't understand that elementary distinction. Anti-government zealots constantly try to suck the public into a debate on how much more efficiently or cost-effectively the private sector can do things, while conveniently ignoring the fact that there are a great many important things it will simply not choose to do at all.

If we ever needed reminding of that fact, it should have come in this month's announcement by the European pharmaceutical company Merck Serano that it has decided that the experimental Parkinson's disease drug salfinamide won't be as strong a commercial drug as once thought. Consequently, the company, a unit of Germany's Merck KGaA, has handed back its rights to that drug to the small, Italy-based biotech company Newron Pharmaceuticals. Salfinamide, which is in late-stage development for use as an add-on to levodopa in treating the symptoms of Parkinson's disease, is Newron's lead drug. Merck Serono, which gained rights to the Parkinson's drug in 2006, stated that "safinamide has a more limited market potential than originally anticipated by the company". The drug maker plans to cut support of the Phase III program after April 2012, a decision expected to cost the company about €40 million.

Interestingly, the pharmaceutical company wasn't abandoning the drug because of safety or efficacy issues; it made the decision to shed the program as part of a review of its pipeline. Merck Serono is among a host of big pharmaceuticals that have chopped programs from their pipelines over the past year because of, among other things, limits on R&D spending in certain areas and the health-care systems of governments such as Germany's holding new drugs to higher standards before agreeing to pay for them. So Merck Serano's decision wouldn't be news were it not for the fact that prospective neurologic disease drugs have been hit particularly hard. Companies such as GlaxoSmithKline and Sanofi have been ordering large cutbacks, not only of clinical trials but also of early research and development efforts on drugs that target diseases of the central nervous system. The private sector, it seems, is bailing on CNS drugs.

It is doing so at a time when such drugs are about to be needed desperately. As birthrates in developed countries continue to fall (Italy's and Spain's are already below those needed to sustain their populations) while life expectancy in those same countries continues to increase (it has almost doubled since the mid-1800s), the number of people over the age of 65 is poised to skyrocket. In the US today, there are about 11.5 million people over the age of 80; by 2050, there will be 32 million - and half of them will have Alzheimer's or Parkinson's disease or some other form of dementia or fatal movement disorder because the risk of developing one of these diseases rises exponentially with age. Age-related neurologic disorders currently cost the US about $350 billion/yr. For comparison, the cost of cancer plus diabetes in the US is about $330 billion/yr. (Incidentally, the US government investment in biomedical research is only $320 billion. Over the past 120 years. Total.) By 2050, the financial burden of Alzheimer's disease alone in the US is expected to top $1 trillion annually (by comparison, the gross domestic product of the country is around $13 trillion today). The figures for other countries basically just scale according to their populations.

Given that the market for CNS drugs is rising rapidly, why would for-profit companies abandon the sector? To be fair, it's not hard to see how they could make such a decision, given the problems associated with bringing such drugs to market. In contrast to cancer, where recent advances in the genetic bases of many forms of the disease have led to the development of novel approaches to treatment, resulting in a number of new drug approvals, the causes of neurodegenerative diseases

*Correspondence: petsko@brandeis.edu
Rosenstiel Basic Medical Sciences Research Center, Brandeis University, Waltham, MA 02454-9110, USA

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remain murky and nearly all recent development efforts have either stalled or failed.

A dearth of good animal models for the major neurologic diseases has severely hindered research. Small mammals like rats and mice have relatively short lifespans, and efforts to mimic the age-dependent neurodegeneration of human diseases have been forced to overdrive the expression of pathological forms of normal proteins, often in conjunction with other damage-inducers such as oxidative stress. Consequently, nearly all such models fail to reproduce many of the histopathological and other features of the human disease, and many miss most of them. Efficacy in such models has proven to be virtually worthless as a predictor of efficacy in clinical trials.

Then there is the enormous problem of the clinical trials themselves. Amyotrophic lateral sclerosis (ALS) is a rapidly fatal disease (mean survival time post-diagnosis is only about 3 years), but the other major neurodegenerative illnesses are very slow to progress. People with Parkinson's typically survive for 20 years after they are diagnosed, and those with Alzheimer's can similarly live for decades. If delay of death is the endpoint for a clinical trial, such timeframes are unacceptable for any private company. Worse, the progression of these diseases is far from smooth. People who are afflicted with them often plateau in terms of symptoms for periods of time, making any short-term evaluation of a drug's effectiveness problematic. In addition, the absence of biomarkers that would allow early detection - or, even better, reliable estimation of the likelihood of developing the disease at all - means that delayed onset cannot be used as a clinical trial goal. These factors leave drug makers with no option but to enroll patients after symptoms have developed, when so much damage to the CNS (including massive inflammatory responses) has already occurred and could be impossible to reverse or halt. (For example, it is estimated that over 70% of the dopaminergic neurons in the substantia nigra pars compacta have already been lost by the time a person typically presents with symptoms of Parkinson's disease.) I would argue that there has not yet been a single clinical trial for Alzheimer's disease that has been designed in such a way as to give a reasonable chance of showing a therapeutic benefit.

Considering the paucity of therapeutic strategies, combined with a severe odds-against prospect when those strategies are eventually tried in people, it is no wonder that so many large pharmaceutical companies are abandoning programs aimed at neurologic disorders. Smaller biotech companies may stay in the game longer, but only the richest will be able to bring a drug to trials without the partnership of big pharma, and so many of them too, will probably soon look elsewhere for opportunities.

And while the private sector may have bailed, the public sector isn't exactly picking up the slack. Consider these US statistics (those for other countries are, sadly, not that different): 2008 federal spending on Alzheimer's research was $0.6 billion. 2008 federal spending on AIDS research was $2.6 billion, over four times higher. The number of new cases of Alzheimer's each year in the US is around 500,000 (the number is approximate because definitive diagnoses are only possible on autopsy). The number of new cases of HIV/AIDS each year in US is about 50,000. In other words, simply on a patient load basis, federal spending for biomedical research on Alzheimer's disease is out of whack by a factor of 40. (For other CNS disorders, divide the Alzheimer's figures by the ratio of the prevalence of Alzheimer's to their prevalence and you will be close to the research dollars available.) I am not arguing that spending on HIV/AIDS is too high, although it would seem prudent to examine the lowest-rated funded research projects in that field and ask if, say, $0.5-1 billion could be better spent on other priorities. But it is impossible to escape the conclusion that spending on CNS disease research is way too low.

What can be done to reverse this alarming trend of eschewing research into a set of diseases at precisely the time they are about to explode into a worldwide epidemic? Here is a set of six suggestions:

1) Clearly, government funding agencies need to reconsider their priorities and ask whether scarce resources are being allocated sensibly, given the likely number of cases of certain diseases in the near future and their likely cost to society. This rarely happens - actually, it may have never happened - and thanks to pressure from disease activists and politicians, it will not be easy to make it happen.

2) Funding for research on the causes, early diagnosis, treatment and prevention of neurodegenerative diseases needs to be increased at least four-fold, if one believes that the amount of federal funding for HIV/AIDS is largely responsible for the progress made in treating that disease.

3) Such research needs to focus not just on disease mechanisms and the development of potential therapeutics, but also on the development of biomarkers that would allow early diagnosis and serve as possible endpoints in clinical trials (encouragingly, this is already becoming a priority in some circles). It also needs to focus on the development of better animal models. I would argue that small animals are unlikely to provide what is needed here, and suggest that partnerships be forged with colleges of veterinary medicine and agricultural colleges to explore possible large animal models (sheep, for instance, develop prion disorders that closely resemble their human counterparts, suggesting that their CNS and lifespan might be suitable).

4) The entire area of clinical trial design for neurodegenerative diseases needs rethinking. The major stakeholders - the US Food and Drug Administration (which determines the validity of such trials and ultimately approves drugs for marketing), big pharmaceuticals, biotech companies, physicians, scientists, and disease-specific foundations - need to come together to devise trials that have a chance of providing meaningful data. My own suggestion would be to explore the use of rare surrogate diseases with similar underlying mechanisms but clear-cut clinical endpoints - such as multiple systems atrophy (MSA) and Gaucher disease for Parkinson's disease, and certain familial forms of Alzheimer's disease for the sporadic form - until such time as suitable biomarkers for the more widespread forms can be found.

5) Companies are right that CNS drugs are painfully difficult to create, and very difficult to win approval for. It might be time for governments to assume some of the risk, not by trying to develop drugs themselves - pharmaceutical development is no job for amateurs - but by underwriting some of the cost. A US fund of $2 billion/yr, made available by peer-reviewed competition to companies that have a promising clinical candidate and a sensible clinical trial design, might bring big pharma back into the sector or take some biotech drugs deep into trials without costly partnering.

6) Neither the private nor the public sector will give this area the attention it needs without pressure from the lay public. Taking a page from the HIV/AIDS activists' book, those afflicted with these disorders need to speak loudly, and with one voice. Up to now, each disease has existed largely in its own universe, with foundations and patient-oriented groups focused on their particular disorder. If we realize that many of these seemingly different diseases have similar underlying causes, often present together, and could in fact be a continuum whose seemingly distinct pathologies mask their interrelatedness, then progress in any one of them could legitimately be seen to be progress in many, if not all.

This last is my most important recommendation, because if it is not followed I don't think the other five will be implemented fast enough. I suggest that an umbrella organization is needed to coordinate advocacy efforts for all CNS disorders, much as FASEB and FEBS coordinate the disparate activities of societies for the life sciences in the US and Europe, respectively. Call it BRAIN - the Board on Research and Advocacy In Neurodegeneration - and let it bring together the various Alzheimer's, Parkinson's, ALS, stroke and other related foundations and organizations. Let it shout to the public and private sectors, in unmistakable terms, the message that we are facing a crisis as significant to the world as global warming, and that this is not the time to be bailing out.

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