



# Where will the (new) drugs for traumatic brain injury treatment be coming from?

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News: AstraZeneca closing its Neuroscience R&D. According to the news<sup>1</sup>: “Hit with sliding profits, a weak late-stage pipeline, and a troubling track record on clinical trials, AstraZeneca (AZN) has decided to trigger another round of layoffs, with 2,200 R&D staffers losing their jobs in this round. Part of a broader reorganization that will eliminate 7,300 jobs, AstraZeneca says that it is cutting way back on neuroscience, reducing the number of investigators it has in the field to a mere 40 or 50 in Boston and Cambridge, UK as it creates a new ‘virtual’ group which will collaborate with academic and industry partners around the world.”

While AZN was not heavily involved or even involved at all in R&D for TBI, the news is important and alerting since it further illustrates the trend that started last year or so. As the news continues: “AstraZeneca is joining a major exodus out of brain disorders, a tough field where scientists face extraordinarily high risks in the clinic and an imperfect understanding of many of the diseases. GlaxoSmithKline (GSK) and Sanofi (SNY) led the exit with Merck (MRK) cutting back as well. Alzheimer’s, Parkinson’s, and other conditions affect huge patient populations, raising the prospect that any pharmaceutical advances would swiftly be rewarded with blockbuster returns. Increasingly, though, the fear of high-profile clinical failures has won out over the search for big new drugs in the field, triggering deep worries among patient advocacy groups.”

There is a productivity crisis in pharmaceutical R&D in general (e.g., Pammolli et al., 2011). Among the main reasons, attrition rates across all categories have been increasing especially in Phase II and Phase III (the most costly) of clinical trials. Between 1990 and 2004, attrition rates in

Phase III has more than doubled across the board, from around 20% in 1990 to more than 50% in 2004. Pharmaceutical companies, like other businesses, have a primary responsibility toward their shareholders. (As it was posted at Intel, the number one semiconductor company: “We are in the business of making money”; Jackson, 1998). The combination of factors such as patent expirations, constrained health care budgets in virtually all developed countries coupled with increasingly stringent regulatory requirements and the skyrocketing costs of R&D have been forcing pharmaceuticals to cut their losses. Sadly, neuroscience R&D for reasons, some discussed above, is the logical and rational choice. So, what’s the new model for pharmaceutical R&D in neuroscience? As AZN has outlined it: “We have made an active choice to stay in neuroscience though we will work very differently to share cost, risk, and reward with partners in this especially challenging but important field of medical research,” says Martin Mackay, the company’s R&D chief. “The creation of a virtual neuroscience iMed will make us more agile scientifically and financially – we will be able to collaborate flexibly with the best scientific expertise, wherever it exists in the world.” In the absence of “brick and mortar” R&D at AZN (and at other pharmaceuticals), there will likely be only “virtual neuroscience” as AZN’s Mackay indicated. Likely, the model also means “virtual funding” for neuroscience R&D.

Based on available data, pharmaceutical R&D accounted for roughly 50% of funding sources for neuroscience research (in the US) between 1995 and 2005 (Dorsey et al., 2006). The figures are similar in the EU (and likely also in Japan and the Asia Pacific region). When pharmaceutical companies drastically cut back on neuroscience R&D and NIH (or similar EU and Japanese) organizations are not able to fill the gap, there can be a substantial,

50% deficit in neuroscience R&D funding. The unfortunate reality is TBI research has never received much support from the NIH or pharmaceutical companies. Funding for TBI research has been disproportional to the prevalence of the disease and also to its cumulative human and financial costs to societies.

Academic TBI research may have also contributed to the current crisis. Pharmaceutical companies have commonly based their own R&D efforts on data derived from academic research. When published results were not reproducible or were attainable only under specific circumstances they are useless for continuing the R&D process toward drug development. If the company was lucky, these were “early failures.” Many, too many promising “low hanging fruits” identified by academic TBI research turned out to be – just like in the real orchard – looking great but not ready for consumption.

In the light of the mass exodus of pharmaceuticals from neuroscience R&D, we are especially concerned about the future of R&D for TBI. Where will the new medications treating sufferers of TBI be coming from? Since pharmaceutical companies appear reluctant to invest money in R&D for drugs for Alzheimer’s and Parkinson’s Disease and multiple sclerosis claiming complexity, it seems unlikely that TBI, one of the most complex CNS disorders, would be prioritized.

So how does the near future of R&D for TBI look today? Unfortunately, not bright. However, we believe that after surviving the current “strategic inflection point” (Grove, 1999) by adjusting, pharmaceutical companies will (re)discover the market for neuroscience including TBI drugs representing huge unmet needs. The similar “strategic inflection point” is likely reaching the academia, and TBI research in the academia also needs to adjust. We believe that this crisis brings about unique opportunities for the TBI

<sup>1</sup><http://www.fiercebiontech.com/story/astrazeneca-cutting-2200-rd-jobs-slashing-neuroscience-restructuring/2012-02-02>

community, funding and regulatory agencies, academia, pharmaceuticals, and biotech companies to change their models. Probably NIH and other funding agencies can make the largest impact in neuroscience and TBI R&D by fine-tuning their current models to finance TBI research. NIH already has a mechanism to fund small and also startup businesses, biotech companies, and others. At the expense of large center grants, these more agile entities and also small academic groups should receive more funding. These organizations would be more willing and more forced to “think outside of the box.” They will also be the natural partners – and small biotech companies are also natural targets for acquisitions – of big pharmaceuticals. Small biotech companies can provide innovative drug candidates, but a sustainable involvement of large experienced pharmaceutical companies is probably required in order to achieve a really effective development of new drugs. The large established companies have the resources to make the critical changes in ligands to refine receptor binding and to perform the clinical trials.

Regulatory agencies, including governments should create the framework for innovation and accumulating and retaining knowledge. Whichever country will establish easy, non-bureaucratic regulatory environment that is actively encouraging, nourishing, and supporting innovation, will attract neuroscience R&D (back). Remember the “iMed” concept by AZN? Pharmaceuticals are scouting for talent and opportunity globally.

Part of the new model adopted by pharmaceutical companies already includes collaborative alliances, shared precompetitive research (FitzGerald, 2010; Woodcock, 2010). Can these new models also be implemented in both experimental and clinical TBI research performed in the academia? Unless funding agencies, e.g., NIH will motivate (or enforce) sharing resources and information academic research will most certainly keep its current (fragmented) model. When however academia will have started to practice resource and data sharing (“open source”) it will be able to provide truly novel insights into pathological mechanisms that would be the targets for new drugs in TBI along with more useful models for preclinical trials.

Likely, after the current “creative destruction” the face of neuroscience R&D including TBI will however change. It will be

more translational and clinical. Academic and also industrial R&D in TBI can be far more productive through bringing clinical and experimental researchers together working in cooperative and correlated fashion (Agoston et al., 2012). Agreeably, we only have an incomplete understanding of the biology of CNS and its diseases, we do not have the ability to define and measure outcomes, we lack perfect biomarkers, etc. However, we have not been able even to figure out how to put the existing information together in order to generate new knowledge and to identify real gaps. It is astonishing how little available advanced information technology has been used in neuroscience and especially in TBI R&D. They transform our every day lives but when we enter the lab, the clinic, office, they mostly stay outside. Using the power of information technologies to generate new understanding and knowledge from existing but fragmented information in neuroscience is a challenge worst for Google’s “Solve for X” Project intended to tackle Big Problems<sup>2</sup>. Computer modeling connecting the physics and the biology of TBI can generate a completely new level of knowledge enabling among others a more efficient and ethical way of performing experiments and clinical studies. Information technology can also transform TBI research by creating advanced patient registers, databases for designing, and assessing clinical trials that will attract pharmaceuticals. One of the most effective ways to understand TBI, the disease, would probably be to perform a multicenter comparative effectiveness study. Using informatics tools, such a study can relatively quickly provide critical missing information about this complex disease. The value of such a study can be increased substantially by incorporating data from relevant experimental TBI studies using established criteria (Agoston et al., 2012). Large pharmaceutical companies present in many countries each with different models of healthcare and TBI treatment practices can play a major role in such studies by designing, coordinating (and also financing) such studies. In the US, the NIH has recognized the value of translational research and started to increase funding for it (Mullard, 2004).

<sup>2</sup><http://www.zdnet.com/blog/google/solve-for-x-google-gathers-top-minds-to-solve-everything/3569>

The Critical Path Institute (the fulfillment of the FDA Critical Path Initiative) since its inception in 2004 has been working hard to bring the major players—industry, academia, and regulatory agencies together in order to accelerate the development of safe drugs for various diseases (Woosley et al., 2010). (Unfortunately, TBI is not on the list.)

We believe pharmaceutical companies will come back to invest in R&D for neuroscience including TBI. They will do it when the conditions are right, the major stars are aligned; the regulatory agencies will have created the right conditions and funding agencies the innovative funding mechanism; the academic world will have learned to use the money more wisely and creatively; and will have implemented the “open source” model. When pharmaceutical companies will be back, they can expect very substantial returns on their investments. And after all, it is for the money they are in the business. Most importantly, TBI patients will also tremendously profit.

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