AN AUDIENCE WITH…

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Roche

Although several large pharmaceutical companies have reduced their involvement in research and development for central nervous system (CNS) disorders in recent years, Roche is among those that have remained strongly committed to the field. Speaking with **Alexandra Flemming**, Luca Santarelli, Senior Vice President and Head of Neuroscience Research and Early Development at Roche, discusses why and highlights areas where progress seems most promising.

What are the unique challenges of CNS drug discovery?

There are many, but among the most important is the fact that the molecular understanding of disease mechanisms for brain disorders has not progressed as far as in other fields, such as cancer. However, we think that neuroscience is now where oncology was about 15 years ago, at the brink of a revolution that will allow a deep understanding of brain function and a true comprehension of disease mechanisms.

Are there aspects of cancer research that have informed Roche's approach to CNS drug discovery?

Absolutely. What we have learned from cancer is that you can get more efficacy and less toxicity if you target the disease biology directly. This shift was made possible in cancer in the 1990s thanks to the discovery of the molecular pathways that lead to tumour formation. I think we're doing the same in neuroscience now by focusing on those conditions where we have a better understanding of disease biology: for example, in schizophrenia, where we are starting to appreciate the role of glutamate in negative symptoms; in Alzheimer's disease, where we learned that the misfolded proteins amyloid and tau have a significant role in inducing neuronal degeneration; and more recently in neurodevelopmental disorders, especially in conditions like fragile X syndrome, where we have a genetic mutation to start from and map our way back into the molecular pathophysiology, and to potential ways to intervene.

How do you increase the probability of developing a successful CNS drug?

The first thing is to target conditions where there is a high unmet medical need — those with no approved drugs, no highly effective drugs or where the drugs are not safe enough — but you also have to focus on those diseases that are most tractable because the mechanism is better understood. That's not enough though; you also have to increase your ability to target patients who are more likely to respond to a given treatment, ideally based on molecular biomarkers that predict response. Basically, we are focusing on areas where it is possible to target a specific disease mechanism in the most relevant patients, identified with appropriate companion diagnostics.

How far along are you with applying such diagnostic tools?

Where we are most advanced is Alzheimer's disease, because by using molecular diagnostics we can detect the disease before it progresses to dementia. We are taking this approach for our Phase II/III SCarlet RoAD programme, which is testing our monoclonal antibody gantenerumab in patients with prodromal Alzheimer's disease — an earlier disease stage that precedes clinically diagnosed dementia by 3–4 years. We can identify these patients by performing a test on cerebral spinal fluid to measure amyloid levels.

In partnership with Seaside Therapeutics, we also have a Phase III trial in fragile X syndrome, the most common genetic cause of autism, caused by the lack of a protein called FMRP. In this case, disease severity depends on levels of residual FMRP, and so we are measuring FMRP to adapt the treatment to maximize benefit and minimize side effects.

What is your view on the recent failed Phase III trials for antibodies for Alzheimer's disease?

Although the trials did not meet their primary end points, the efficacy data we have seen have made us more optimistic that approaches that reduce brain amyloid early in the disease can potentially result in clinical benefit, as was the case in some of the studies. This is very important, because we already knew from genetics that excessive amyloid production can result in early-onset Alzheimer's disease. In addition, the recent data confirmed our suspicion that the disease needs to be approached earlier. In our view, antibodies have great therapeutic potential but they should be applied at a stage of the disease when benefits can be achieved. This is our approach with the gantenerumab programme that we started in 2010. Finally, the available data also confirm a long-held belief that there is a high rate of misdiagnosis in Alzheimer's disease, with up to 25% of patients not having amyloid by PET imaging. This is a huge problem if your drug targets amyloid, but fortunately we think that implementing the molecular diagnostic test in our programme will reduce that rate considerably.

What are the opportunities and challenges for autism spectrum disorders?

Autism research is an exciting area, as genetic research in the past 5 years or so has brought us greater knowledge regarding the main molecular changes that underlie autism, namely alteration of synaptic structure and function. Right now, one of the greatest challenges in autism drug research has to do with the ability to understand the disease at a molecular level and define common pathophysiological alterations that can benefit from a given therapeutic intervention. Indeed, we know that there are more than 400 genes that are risk factors for autism and that combinations of multiple genetic alterations can contribute to the disease in different individuals. In addition, the symptoms can be very heterogeneous, and do not necessarily represent a good way to classify the disease and guide treatment choices. This is why we have focused our research on identifying and targeting those alterations that define the disease at a synaptic or circuit level.

To help do this, we want to learn more about basic disease processes, and here we have been involved in various alliances and collaborations in different ways. One example is a public–private partnership known as

EU-AIMS, which has been set up as part of the Innovative Medicines Initiative in Europe. In this case, the focus is understanding disease biology, biomarkers and clinical end points that could help develop new therapeutics for autism spectrum disorders. We also have partnerships with individual collaborators. For example, we have a collaboration with Harvard University where we are developing ways to generate induced pluripotent stem cells from skin cells of patients with autism. We plan to differentiate them into neurons to create an *in vitro* brain tissue model, where we can perform biological investigations that were not previously possible. This is a way to understand more about the disease biology directly from patients, which can enable us to find new drugs and also to identify the type of autism they have.

Where do you see the biggest breakthroughs in the next few years from your perspective?
I am very excited by the Alzheimer's disease programme with gantenerumab, which targets a disease stage that nobody has tested before with a monoclonal antibody.

I am also excited by our ongoing Phase III programme with bitopertin in schizophrenia that should read out in 2014. This programme targets a set of symptoms in schizophrenia not addressed by current therapies, namely negative and residual positive symptoms. Negative symptoms include poor communication, lack of speech, lack of pleasure, lack of volition and social withdrawal, which lead to significant disability and reduced functioning. We previously obtained positive data on negative symptoms in a Phase II trial that was communicated at the 2010 annual meeting of the American College of Neuropsychopharmacology. Bitopertin is a glycine reuptake inhibitor that modulates glutamatergic transmission by increasing synaptic levels of glycine — a co-agonist of glutamate at the *N*-methyl-D-aspartate (NMDA) receptor. For many years, glutamatergic transmission has been considered to be altered in schizophrenia, and there is evidence suggesting that this deficiency could be improved through NMDA receptor activation. What bitopertin does is to positively modulate NMDA receptor activation. We have also identified a potential biomarker for response to bitopertin, a molecule called complement factor H-related protein 1 (CFHR1), and we are working on validating this initial finding in the Phase III trial programme. Bitopertin might be the first effective treatment for negative symptoms based on a novel mechanism in more than 60 years of schizophrenia pharmacology, and so it is a very exciting programme.

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