FRAGMENT-BASED DRUG DISCOVERY IN NEUROSCIENCE

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Dr Markus Schade has worked for over 18 years in the pharmaceutical industry. He started his career as a co-founder of the biotech company Combinature Biopharm AG. Next Markus worked for the global Pharma-CRO Evotec AG before he joined the BigPharma companies Pfizer and thereafter AstraZeneca in the UK. Since 2012 Markus does pre-clinical drug discovery with the pain specialist Grunenthal GmbH in Germany. He has specialized in the field of Fragment-based Drug Discovery (FBDD), where he has successfully led many projects and published several peer-reviewed articles and patents. Markus studied biochemistry at the University of Hannover, Germany, and the Massachusetts Institute of Technology, USA, and holds a Ph.D. in structural biology from the Free University Berlin, Germany. Presently he holds the position of a scientific director at Grunenthal.

What are the main advantages of fragment-based drug discovery in neuroscience?

The main advantage is it delivers low molecule-weight starting points for chemistry. That's a requirement for CNS exposure. With other technologies, the average molecular weight will already be at, or exceeding, what is allowed to passively permeate the blood-brain barrier.

Could you explain a bit more about your work with fragment-based drug discovery?

We apply FBDD in parallel to other small molecule discovery technologies and are virtually always successful in identifying novel starting points for synthetic chemistry, even for tough drug targets, such as protein-protein-interactions. That's a strong plus to begin with. If crystallography is enabled as well fragments can often be merged with chemical series from other sources to quickly arrive at novel and potent interventions.

What are the challenges that you face coming up with clinical molecules?

It includes getting sufficient exposure in the CNS, which can vary between rodent disease models and human patients. Often you can't predict, and there is some literature hypothesis on "leaky" blood-brain-barrier in rodent models, meaning that CNS exposure in such rodents could be substantially elevated as compared with human patients. Insufficient exposure in humans leads to insufficient efficacy, and a failed clinical trial. You're never entirely sure with regards to what is the reason for failure; insufficient exposure to the target tissue might be one, but of course, it could also be the mechanism of action not working in your patient group.

Have there been any recent innovations or technologies that have helped you to overcome or solve these challenges?

What is new in the industry, and quite interesting, is antisense-RNA and gene therapy, and you can intrathecally administer those. In the old days, daily or even weekly intrathecal administration wasn't really accepted and didn't sell very well, because it was hard on the patients. Nowadays, with those long duration of action RNA therapies, you only have to dose every two or three months, promising a much better patient compliance. You basically have a new window that opens up, and interventions for historically intractable CNS diseases can be designed .

What are the key priorities of the industry in this area?

We are specialized for moderate to severe pain medications. There, it is promising to focus on targets and mechanisms where we have robust human genetic validation data, rather than merely efficacy in rodents, which has often led to clinical failure. Human genetic data, especially from pain patients, provide us with a head start, where you're much closer to getting validation for analgesic efficacy but also some preliminary evidence for the safety in those patients.

Does that relate to the next steps of your company in this field?

We are investigating, among others, exactly those targets and trying to enrich our portfolio with the most promising new analgesics.

What would you say are the top three takeaways that you would hope delegates will take from your presentation?

Begin with a patient genetically-validated target. Use the smartest technologies, such as fragment-based discovery for small molecules, or siRNA or antibodies, or gene therapy interventions. Finally, try to go for druggable, feasible targets, don't embark on blue sky,hope and pray interventions; that's usually not giving a good return on your hard work and investment.

What do you hope to see in the future of fragment-based drug discovery in neuroscience?

The whole workflow could be a bit more automated. It could do with more integrated cheminformatic tools, better databases that will speed up and facilitate testing analogous chemicals, as well as smartly learning from prior art. Cryo-EM of CNS targets will certainly have a positive impact, too.

Would you like to see more talks on automation and new tools in neuroscience?

The cheminformatics field does get some good coverage, and machine learning and artificial intelligence is everywhere on the front pages; it just has to be intelligently implemented, and tools need to be user friendly for non-IT experts. But yes, every new tool is most welcomed and may help developing new medicines for the patients in need.