ENCODED LIBRARY TECHNOLOGIES IN DRUG DISCOVERY

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Johannes Ottl is Director at the Novartis Institutes of BioMedical Research (NIBR) heading the Chemical Genetics group in Basel. Current focus of his research includes the investigation of novel innovative pharmaceutical drug discovery approaches and the identification of lead finding starting points with DNA-encoded small molecules libraries (DEL) as well as encoded peptide libraries in the Chemical Biology and Therapeutics department. He received his Ph.D. in Bioorganic Chemistry at the Max Planck Institute of Biochemistry in Martinsried in 1998 and his Chemistry diploma at the Ludwig Maximilians Universitaet in Munich in 1995. After his PhD he worked as PostDoc at Novartis Pharmaceutical Research in Basel on radio-tag encoded combinatorial library synthesis. In 2000 he started his pharmaceutical industry career in various multidisciplinary drug discovery assignments focusing on highly miniaturized fully automated confocal microscopy based screening, lead finding, biophysics, and collaborations with BioTech partners around encoded library technologies.

What are the key benefits of encoded library technologies in drug discovery?

I think the concept is very intuitive and concise. Those technologies offer a relatively low entry barrier for small companies or academic labs to step into drug discovery. Establishing compound collections for classical screening requires significant logistics efforts, resources, and costs. Encoded library technologies facilitate that. This is also attractive for big pharma: they simplify access to a broader or denser chemical space for lead finding at comparably low resource cost. And: chemical space not yet available can be accessed easier as well. Generally speaking, the operational principle of encoded library technologies is a flow chart or process workflow which you can copy and re-apply for different projects. In addition, it is particularly attractive because you can follow multiple hypotheses in parallel with comparably low investment, resources and timeframe.

Are there any key innovations within that area that have helped you?

Every company tries to adapt the area for a better fit to individual needs. DEL became a very hot technology area in the last couple of years and I believe most people are trying to tackle similar things. For example there are many developments in terms of DEL-applicable chemistry. The nature of DNA is not well compatible with some typical medicinal chemistry reactions. They can harm the DNA or are not working under DNA-compatible conditions. The development of such chemistry is really an area of innovation. On the biology side, developments towards more physiological or functionally relevant targets and their screening is another big innovation area, and there are a lot of facets to that.

Would you say that these innovations have solved the main challenges that you face in your work? What are the main challenges?

There are many statements on how important or game changing encoded library technologies would overall be for drug discovery. I am not so over-enthusiastic about this. My background is a big pharma company, and I went through various stages of drug discovery applications and technology developments. For me, encoded library technologies augment, and are a sweet spot for many target classes. Particularly for those at early stage, where you need to form or prove the hypotheses. However, encoded library technologies do not replace certain other drug discovery technologies, for example classical screening, etc. We do less of that in favor of encoded library screening, but I would not say that encoded library technologies are replacing. For small companies, as I said, this entry-level aid is very attractive, and for such companies - in my opinion - it can be the only branch of drug discovery. However, what is indeed game changing for us: gaining relatively quick access to probe certain hypotheses on a target level, as well as getting a fast entry into novel or broadened chemical space we do not yet have in our compound archive.

What are the future steps for your company?

There are areas where the technology is not so suitable. The main gap is: such screening is performed for affinity and you do not per se have a functional or activity readout. Achieving such functional phenotypical readout with the technology in my view would be a game-changing step. There are a couple of publications around that, and I would say there are several groups who work towards that direction. This is one of the key future development areas I can see for others and us.

Would you consider partnering with the people working in that direction?

We did internalize both of our technologies by partnering with biotech companies. We first explored the feasibility and impact in collaborations and then performed a full technology transfer for internalization. Partnering and scientific exchange is fundamental to be successful. In conferences like this one, we exchange with others and get new insights. We also regularly talk to others in the field, for example with our colleagues are a little bit upstream the Rhine, and exchange on the non-proprietary aspects of the technology and experiences. Of course, everybody has proprietary targets, projects, and libraries, sometimes technology-flavors. However, we do definitely exchange and partner because this is the nature of scientific innovation.

What would you say are the top three takeaways from your presentation?

Number one: we are quite unique having both encoded technologies (DNA-Encoded Libraries and the Peptide Discovery Platform) in one fully integrated setup. To my knowledge, we are the only organization who has established that for low molecular weight and peptidic chemical space. Second: the encoded technology field has evolved to a matured stage. More or less every bigger pharma company today is applying it in collaborations or in-house. Third: it would be game changing if we can achieve phenotypic or functional activity screening with the technologies. However, that's a big step.

What do you aim to gain from attending events such as this one?

I aim to get a broad overview, as well as hearing about evolving new areas. Networking is also important; within but also outside of the conference sessions. For instance, in the afternoon session, there were three or four presentations from companies active in our field, or presenting posters. Talking to them, discussing their data and technology status in a more relaxed environment outside of the usual company setting is great. Interacting on a one-on-one basis is crucial; and listening to the questions people are asking. This event is attractive because it is quite central within Europe. For US-Americans, this might look different. However, for Europe, it's a very attractive event and location to go; easy to reach for most companies in one or two hours flight or a train ride.

What do you think the future of the discovery will be?

A future of drug discovery would be to further facilitate the entry barrier to answering therapeutic questions. For example: in screening and in medicinal chemistry, I believe the biggest potential would be to make full use of all the data around, i.e. deep learning and machine learning,. We have huge data sets, yet we barely make best use of them. We should combine and leverage them within the different networks. There are a number of computational science presentations in this conference going in this direction. Of course, we as well have people engaged in this field, but this is still a truly evolving field. I see a big future there.