Interview with Gernot J. Abel from Novozymes.

- **by Stefani Pjaca and Benjamin Schwetz**

Present yourself and the work you are doing.

I'm not in R&D anymore, it's called R&T now - Research and Technology. Our organization has changed now, but the big picture is the same. I'm within protein assay chemistry and biotechnology research and my position is that I'm science manager and it's about developing analytic assays to detect biological solutions, benefits of biological solutions and to detect the products of NZ for tomorrow. It's targeting all the industries that we are working with - animal feed, human nutrition, washing laundry, bio energy and so on.
The other part is open innovation, so I'm working on the interface of R&D and business development where we have my colleagues in the business development team and business innovation. They get the R&D angle into that and we have been running projects like the "Biologi Garage" developing ethanol sensors. This is not something that business development could do usually, because they wouldn't get the biochemistry, biology site, so we are around this together. How can we work together with Biologi Garagen or with school pupils and that's what we call open innovation within biotech. It can be anything from being a mentor for Synbio start-ups. This week there is a venture startup, world cup for universities at the Copenhagen Business School and then I'll be in the judging committee for Mattech life science so it's kinda of a dual role.

How does Novozymes apply synthetic biology?

First of all, we have a discussion about what synthetic biology. I'm not sure if you know Synergy - it's kinda of a network for responsible innovation and they have a biotech or synbio track. It's a European funded project - it's called Synergy. It's the guys that I know, Karsten Boltz he's at the Karlsruhe Institute for Technology. We have been to workshops where we discuss synthetic biology. Synthetic biology is biotech 2.0. The coin synthetic biology is a subdiscipline of biology, but it's not more than that. It uses different tools, more advanced tools. Coming back to your question - how are we using it? We are trying to apply the newest tools in biotech whatever this can be. If they are available for us and no license and challenges. You probably know CRISPR-Cas. It's interesting and we can always use tools like these in research purposes. We have to make sure that we are not inferencing anybody. So we are using biotech and we are biotech company and we try to develop microorganisms and enzymes and giving biological solutions to the world. That's how we use biotech. The work is tangible - you don't make a PCR and then wait and weeks later you make the next PCR. Today you can kinda go for like a massive production and you can do things parallel. It's about tools and we look very much at assays. Assays are tools but they

are not part of synbio, partly you may say that assays are synbio because they are indicators.

How do you see iGEM (student innovation in general) within synthetic biology

Very valuable - I promoted very much internally and say that it is the World championship of biotech/synbio, because it gives you the bridge between application and learning. It's getting exposed to real world challenges, so accumulating knowledge and capturing knowledge and also engaging the knowledge that you have captured at an early stage of your career. It nice to have a platform where you can share it with other students so taking it out of your university context and have a good challenge and connecting good students who are going to make an impact. That's also great. iGEM for me is kinda turning science into impact. It's a building block to connecting what we have been doing with Biologi Garagen to citizen science because it's opening up lab protocols and cool tools for broader context in society.
I knew iGEM from when I joined the project with Biologi Garagen where we had this DIY biospace in Copenhagen and then I got aware of iGEM. I have been talking to iGEM students in synbio conference in London. I'm pretty aware of the concept and have been sitting together with Tom Knight, one of the founders of iGEM.

What does Novozymes value in a cell factory?

First of all, our products are either produced in a cell factory in huge fermentors and they are either microorganisms or enzymes producing secreted by host organisms to the growth media, which we then harvest separately, which then contains the enzymes, our products. Novozymes is about manufacturing. Our R&D research is important in developing but in the end of the day you have to deliver to the market place and be able to send enzymes and ship them to the customers. One question is if we can make these cell factories cheaper. It's a lot of plumbing and steel and it's a big investment to have all that running around. It has to be controlled, it needs to be clean, temperature control. You have to bring in all the nutrients. Cell factories is our heart and our production system so it's extremely important.
The nutrients are important and it's important to be flexible and be able to change according to what is available on the market. This sounds easier than it is. Manufacturing is about up-scaling and it's one of the challenges in synthetic biology. In the end you need to produce something with a robust quality which can be shipped. You don't change the processes from one day to another.

How relevant is substrate cost for Novozymes?

On the one site is the substrate but on the other site is the production. How many mg/L do you get out of your system. If you can make gain changes here to increase productivity, then it's pretty important. Cell factory is one thing, but you also need to harvest. You have to make a granulate from the enzyme you produce. You have to fix the enzyme to a particle in order to avoid any medical sensitization of people in contact with that so it does not lead to allergies. So it's not only production, it's a lot of wheels that are connected in the end.

What substrates are you currently using in production?

Sugars, starch. As cheap as possible. And also salts. Easy accessible carbohydrates and proteins also.

Are waste streams from other industry (e.g. glycerol, fats, mixtures of sugars) an option? Why/Why not?

DDGS the remaining of biofuels production. We are looking at any other kind of waste streams. In the end you need to have a robust production. You're not changing protocols easy because it might affect the "happiness" of your microbes, which then will affect your production (productivity down). You can't just have a reactor running and then figure out after five days that it didn't work. There might be a conservatism to take some new waste streams in. You also have to look at what effort you have to adapt. Our waste streams are sold as NovoGro which are sold to farmers across Zealand, so you also have to make sure that you don't get any problems out in the fields. I would assume that it takes a really long time to establish your straight production capabilities, but it doesn't mean that there isn't an openness to take in something new. The more well-characterized, the better.
So in general yes. As soon as you find a valuable application for one of the streams the prices will just go up.

The yeast Yarrowia lipolytica has been shown to grow fast on glycerol and fats. Would you consider switching production to this yeast, if our molecular toolbox for genome editing was up and running?

It sounds very greasy - thinking about that we help our customers to get rid of fatty acids with detergents, then I see a challenge that we actually add fat to our production. It's a challenge to clean it up afterwards. We don't necessarily have the same production of an molecule going on in the same reactor every time, so it has to be easy to clean.
I'm not saying that it IS a challenge, but it could be a challenge. If you cannot get the dirt out, then you need to use organic solvents and it might also have other consequences. But in general, I would say yes! There is a lot of available fat sources that could be used. But we

need to know the consequences. But what could be a real benefit? There are genes that are hard to express and you never know completely if it is due to transcription, translation, or secretion, so it might actually be an opportunity if you can prove that of those ten proteins we know that have failed from the literature then you take them and suddenly 50% of them can actually be expressed. That is a different setup.
It is hard to switch production setup - people have experience here. The more you can do with one single strain, the better. But if Yarrowia is excellent making more homogeneous proteins, then that would be a selling point. Get rid of your waste, so less waste and more value. If you can cut production costs to 10% down and use different waste streams, then cool! But still you have to build, there is a lot of capax in a big fermentor. But making you product a better one then it is a different story. For us it's more important that our enzymes can do their job. We keep trying to optimize our enzymes to perform better. That is where our focus is compared to changing our production host. But again said, if you can do some miracles than usually then it is a different story.

"iGEM is a great competition!"

What else would be needed to implement it on an industrial scale?

The costs are very important, what can you get out, what's your production economy. Is it GRAS?
Stability is important. Is the gene construct integrated, can you do multicopy strains? The more copies you can integrate, the better is your productivity. What kind of degrading activities do you have (proteases)? No antibiotic selection.
Is the system distressed? Secretion is also important. Safety. Characterization of your target - acylation, glycosylation, truncation - is your product okay? Storage testing. No aroma. Aroma is a show stopper.