

A conversation with Anindya Mukherjee, Direvo Industrial Biotechnology (Cologne)

“Fermentation Based Products Are Becoming Increasingly Popular”

Anindya Mukherjee, co-chief of Direvo Industrial Biotechnology, speaks about directed evolution and the challenges for an industrial biotech company to operate on a fully-owned basis.

Lab Times: Direvo Biotech's pharmaceutical unit was acquired by Bayer Schering, whereas its industrial unit was formed into a fully owned subsidiary named Direvo Industrial Biotechnology. Why?

Anindya Mukherjee: Once a technology platform has proven itself, pharma companies become interested in buying it for several reasons. Just one blockbuster drug from such a platform easily justifies the investment. Owning such a platform helps with optimising existing products. It also allows pharma companies to deny their competitor from having a similar product from the same platform. By acquiring the Direvo technology platform Bayer gained significant potential presence in antibody and therapeutic protease based drugs while denying the competitors similar access.

In industrial biotechnology, product development cycle times vary, but they are generally shorter than in pharma, and the probability of success can be far greater than in pharma. However, the market potential for individual products is not nearly as high as with therapeutics. Therefore companies are looking not so much for technolo-

gy platforms, but for products from startups and from companies with unique technology platforms. Given these differences, the business models of Direvo Biotech AG (pharma part) and Direvo Industrial Biotechnology GmbH, have been different.

Does Direvo IBT have any products on the market already?

Mukherjee: Yes, we have a product on the market but it is commercialised by Danisco, one of our partners. We developed a phytase for them and they have the exclusive rights to manufacture and market the product worldwide. Phytases are used in the animal feed industry as well as in grain processing and eventually for manufacturing bioethanol.

“We can improve many different attributes of an enzyme, for example its thermostability, its specific activity of enzymes, its inhibitor resistance, its binding characteristics, its catalytic activity, its pH and its storage/shelf life.”

What is Direvo IBT's business model?

Mukherjee: At Direvo IBT we have extended the Direvo platform to become a full service provider in industrial biotechnology product development. These services include discovery via access to natural strains/enzyme backbones, optimization of the gene or the strain enzyme and other fermentation products. We are capable of doing both GMO and non-GMO product development. Finally, we offer to develop a scalable process for manufacturing the product. This has allowed us expand our potential customer base significantly. We use all this capability to develop products for our customers which they could not do themselves.

The second part of our business model is to develop our own line of products such as industrial enzymes or other fermentation products in biorefineries and food and animal feed. Our goal here is to de-

velop products that could be licensed for manufacture and marketing by companies already present in these or related markets. Our customers include Danisco, Novozymes and Nestle.

Which product candidates are in advanced development and when will Direvo IBT bring them onto the market?

Mukherjee: We are focussing on several markets: Firstly industrial enzymes that break down biomass into fermentable sugars such as cellulases and hemicellulases. We've developed one cellulase and hemicellulase and I expect that we can offer them as products in spring of 2010. Our second focus is using the sugars you get from the hydrolysis of biomass to produce chemical intermediates. At the moment we cannot announce our candidate molecules. A third area is in functional foods where fermentation

based natural products are becoming increasingly popular as supplements or as nutraceuticals. Here we have a collaboration in place with one company to use our platform to further optimize the product and the economics and we expect to announce our own candidate molecule(s) by year end 2009.

When you develop a new product, the starting point is mostly a natural enzyme. Which of its attributes can be improved?

Mukherjee: We can improve many different attributes of an enzyme, for example its thermostability, so it can be used at higher temperatures or withstand high temperatures in processing. We have successfully improved specific activity of enzymes. Other attributes that we have been able to improve are inhibitor resistance, binding characteristics, catalytic activity, pH and storage/shelf life.



Who is ...?

Direvo Industrial Biotech

Founded in 2008 as a spin-off from Direvo Biotech (which was acquired by Bayer HealthCare), Direvo received exclusive access to the Direvo technology platform for all markets and applications outside the development of biopharmaceuticals. This platform combines confocal fluorimetry with fully automated ultra high throughput screening. Confocal fluorimetry is a laser-based fluorescence spectroscopy technique that can rapidly characterise single molecules in one femtoliter samples. The new company focuses on food, feed and biorefinery markets by discovering, developing and scaling up enzymes and strains, operating both independently and with partner companies such as Danisco/Genencor and Nestlé. Direvo raised €8 million from private investors. The company has 22 employees.

What is ...?

Directed Evolution

... uses natural selection to evolve proteins or RNA with properties not found in nature. First, the gene encoding the protein of interest is mutated and/or recombined at random by error-prone PCR and DNA shuffling to create a library of gene variants. Then the library is tested for the presence of mutants possessing the desired property. Lastly the variants identified are replicated over, enabling researchers to sequence "their" DNA in order to understand what mutations have occurred. Together, these steps are termed a "round" of directed evolution. Most experiments will perform more than one round, to diversify the best variants of the previous round in the next round to create a new library. The advantage of directed evolution is that one needs not understand the mechanism of the desired activity in order to improve it.

How are the variants of an enzyme produced?

Mukherjee: Primarily we use directed evolution by random mutagenesis. You can physically manipulate the genes without knowing exactly what the structure is. You apply pressure on these genes in the direction you would like them to evolve.

How many variants can you screen per day?

Mukherjee: We can screen up to 100,000 variants per day. In a primary screen we typically do something in the order of 60,000 to 100,000 variants depending on the parameters we're screening for. In a secondary screen for additional parameters we screen about 10,000 to 20,000 variants per day. This process is highly automated with little or no human intervention in order to improve throughput and to maximize quality.

What was the turnover of industrial products last year and what is Direvo IBT's estimated turnover this year?

Mukherjee: As a private company we don't publish these numbers. But it's possible to say that our business model has scheduled break-even in 2010 and in 2009 our revenues will be double that of 2008. Furthermore, in 2008 we were able to achieve all our company targets including financial targets that we had set in the beginning of the year.

Do you think that Direvo IBT will be dependent on further financing rounds by private investors?

Mukherjee: It's possible that we'll raise some additional money simply because we want to develop our own products and this will require additional capital. Our technology platform is so powerful that we believe that it makes sense to use the platform for more product development. At the moment we're concentrating on a dual business model, thus providing service and to develop our own products, but in the future we would like to do more own product development.

What's your long-term focus with Direvo IBT? Do you hope that in ten years or more Direvo IBT will still exist as a fully owned company or would you prefer a merger or sale?

Mukherjee: It's difficult to say what will happen in ten years but I can give you a five-year perspective. Provided that we

Direvo we expect that we will continue to develop and licence biotech based products in the future as an independent company.

I have the feeling that directed evolution is more prevalent in white biotechnology than in the red biotechnology. Do you have any idea why?

Mukherjee: Directed evolution is used both in red and white biotechnology, but is difficult to say where it is more prevalent. In food, directed evolution is not normally used. Here the traditional methods are more prevalent. Customers normally want to be sure that their food is natural and doesn't contain something that is gene manipulated. By contrast people have no problem with such methods in the red biotechnology or in white biotechnology such as in chemicals and biofuel production.

INTERVIEW:
THORSTEN BRAUN

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continue to develop products and can deliver them to our collaboration partners we want to make profit from 2010 on. But what is our strategy in the future? It can be said only in general terms. Such a platform as our one with all the capabilities that we've put together so far could be a tremendous growth engine in industrial biotechnology for a larger company that has a broad market presence in many different areas where such technology can be applied to develop a variety of products. However, even if this does not happen to

