An audience with...

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How GLP-1 went from being a hard-to-handle hormone to a blockbuster success

Lotte Bjerre Knudsen, chief scientific advisor in research and early development at Novo Nordisk, discusses the past and future of GLP-1s and related anti-obesity drugs.

Wegovy is now a household name. If not for Novo Nordisk's Lotte Bjerre Knudsen, the GLP-1 drugs it represents might have been a footnote in drug development history.

Evidence started accumulating in the late 1980s that the GLP-1 hormone could be used to induce insulin secretion, hinting at a path to a new treatment for diabetes and attracting industry interest. Data quickly showed that GLP-1 had a role in obesity too, further raising the prospects for the hormone. But as drug developers struggled to overcome the peptide's minutes-long half-life or to figure out a small-molecule workaround, investments in the obesity applications evaporated. "They all ran away," recalls Knudsen, now chief scientific advisor in research and early development at Novo.

Novo had struggled with GLP-1 too, with little to show for it by the mid-1990s. Tasked with a last attempt at bringing the hormone to heel, Knudsen turned to a protein-engineering 'fatty acid acylation' strategy to extend the half-life of the hormone, inventing the once-daily GLP-1 analogue liraglutide. Thirty years later, Novo's next-generation once-weekly GLP-1 analogue semaglutide is a medical and commercial phenomenon, with sales of over US$18 billion last year in diabetes and obesity. Its success has revitalized the hunt for anti-obesity drugs.

Knudsen shared the Lasker prize with Harvard's Joel Habener and Svetlana Mojsov, now at the Rockefeller University, earlier this year for their contribution to this journey. For Knudsen, the importance of GLP-1 biology in obesity was never in doubt. "The interesting question is why we were the only ones who persevered here?"

Why did you decide to focus on fatty acid acylation to get to liraglutide?

We had a few ideas beforehand that didn't work out, and that goes into the thinking on why I actually ended up with this technology.

We'd already tried to just use a native GLP-1 peptide, but that gave patients skin reactions. We'd also tried to stabilize the backbone, but then DPP4 enzymes would still clear the peptide. After one year of work on this, we went from a molecule with a half-life of two minutes to a half-life of five minutes. Great. And we had tried small molecules [GLP-1 receptor agonists] too, but these didn't work at the time. So we had to come up with something else.

The theory behind our approach was that albumin [the most abundant protein in the blood plasma] can function as a transporter of all kinds of things — including fatty acids that are very poorly soluble in the blood. That physiological principle was already very well described at that time. So, we thought, let's take this principle and use that to engineer a longer-acting drug molecule by attaching a fatty acid to the peptide.

People had already started to work with this, both on peptide hormones and with larger proteins like insulin, so there were hints that it might work. It sounded like a possible way to extend the drug's half-life. But it was unproven whether it would work.

Another reason I picked this approach was that I could use my background to work on these molecules. I could have tried to harness GLP-1 by developing small-molecule DPP4 inhibitors, but I'm not an organic chemist. My training was in biotechnology, so I could see myself doing fatty acid acylation experiments.

How did these go?

We made about 200 compounds. It worked out pretty well.

We were really focused on using the native sequence for human GLP-1, because I was very focused on avoiding an antibody response. [Liraglutide has 97% homology with native GLP-1, with just one amino acid difference to make fatty acid acylation more practical.] That was a learning that I had taken from colleagues who worked with larger proteins, that small changes could drive antibody responses. Later on it turned out that this was absolutely true for the GLP-1 class too. Exenatide is still on the market but comes with neutralizing antibodies in a not-insignificant number of the patients. [Exenatide, a peptide with ~50% homology to GLP-1, is based on a protein from the venom of the Gila monster. It secured a first approval for the GLP-1 mimetic class in diabetes in 2005.] And Roche got all the way through to phase III with its taspoglutide but then never filed for approval because they had cases of anaphylactic shock with the drug. [Taspoglutide had 93% homology to native GLP-1, with 2 amino acid changes to improve its stability.]

What we learned is that our fatty acid acylated compounds come with really, really low levels of antibodies. It may be that the fatty acid acylation actually shields for antigenicity — which is something I cannot prove, but I think it's a good hypothesis.

Once you had a molecule in hand, what was the closest liraglutide came to getting terminated?

We had lots of small delays. The biggest delay we faced was just in learning how to produce the drug, how to scale it up and how to formulate it. And we had to do a phase II trial twice, because the dose we used was too low and we hadn't figured out how to titrate it yet. But I would still say the development time for liraglutide is not that bad. We formally sent the compound into clinical development in 1997 and our first approval in Europe was in 2009.

Several firms gave up on GLP-1 in that time. A case study showed how Pfizer and Metabio pulled back in the 1990s. Why was that?

There's a really good quote in that paper from a senior Pfizer leader that said there would never be another injectable therapy for diabetes other than insulin. We also worked with Pfizer

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in the early 1990s, trying to co-develop a formulation of native GLP-1. But I had not heard that quote before.

I can also share some insight from Richard DiMarchi, who was head of research at Lilly at that point in time. He said earlier this year that he tried to get this project prioritized for obesity at Lilly, but was unsuccessful at the time. Svetlana Mojsov, who was one of my co-recipients for the Lasker, she was told so many times as well that these kind of molecules are not medicines. They're not drug-like molecules. I also got that pushback when I tried to first get our work on liraglutide into the *Journal of Medicinal Chemistry*. One of the reviewers asked: why are you doing this, this is not a drug-like molecule. And I wrote back: yes, it is. It's in phase I clinical development.

You started looking at the obesity applications early on, based on a finding that rats with GLP-1-producing tumours starved themselves to death. Tell me about that.

That was actually an important piece for us. That was back in the paper days, and we didn't travel then as much as we do today. And Ole Madsen, who made this finding, was working as an independent researcher in Hagedorn Research Institute, back then in the Novo family. I met with him, and heard about that work.

Stephen Bloom's paper in 1996 confirmed that finding, with a different methodology. Stephen Bloom's paper showed that GLP-1 controlled feeding when it was injected directly into the brain of rats, but I knew from Ole's studies that it actually could also potentially control feeding with peripheral administration.

We now know that GLP-1s drive weight loss via the brain. When did you figure that out?

That came later. Apart from actually coming up with these medicines, this is a piece of work that I'm really proud of because it has changed the view on how these medicines work.

In the beginning, we thought the effect of GLP-1 on obesity had something to do with peripheral fullness or effects on the stomach or something. But then we started to look more into the mechanisms, because we saw that there was so much stigma around the disease and these medicines and we were pretty convinced that we would need to explain the mechanism as well as we could if we wanted to get it approved for obesity.

We started to look more into how we could characterize uptake of GLP-1 into the brain, and found that liraglutide can access several parts of the brain. We characterized its effects on POMC neurons, for example, which are a well-established neuronal population with an effect on satiety. Plus it has effects in the hindbrain and in deeper brain regions.

That work was published in the *Journal of Clinical Investigation* in 2014, but we realized from around 2010 and onwards that GLP-1s had direct effects in the brain. And Randy Seeley, who is at the University of Michigan, showed in the same issue of *JCI* that when you knock out the GLP-1 receptor from the brain, you lose most of the effects on appetite. We now know that GLP-1 works on multiple GLP-1 receptors to orchestrate an overall reduction in energy intake.

These insights came after you discovered the longer-acting semaglutide, which has almost twice the weight-loss effect than does liraglutide. Semaglutide seems better at getting into the brain, which may contribute to its improved effect. Was that better brain access just a lucky turn of the cards?

Yes and no. There was a strategy for designing semaglutide, which was to make a molecule with a much-longer half-life, with optimized binding to albumin and with a better hydrophobicity profile than liraglutide. With liraglutide, there is a tiny amino acid spacer between the peptide and the fatty acid, whereas with semaglutide there is a whole extra molecule that was designed and put there to optimize the drug. [The team screened around 4,000 peptides before settling on the one that became semaglutide.] We knew that the physical and chemical properties of the drug were changed, we just didn't know exactly what that meant pharmacologically.

We didn't know that it would translate into more weight loss. So in that way, that was a really good surprise. And of course, I also have to say that the better brain uptake has only been shown in animals, because there really is no good way to do that in humans.

I think that we now have a very good understanding of the mechanism of action of these drugs on obesity. We have yet to see this understanding be used in drug design, but that could be the case now going forward.

These drugs are meant for chronic usage, but real-world data shows that only 30–50% of patients stay on them. What does that mean?

My take on that is that we just need a whole bunch more understanding of obesity as a serious, chronic disease. Some people still don't fully buy into the idea that obesity is as serious as diabetes, and there's still a lack of understanding in society that if people want to maintain the beneficial effects of GLP-1 on health, then these drugs have to be used as chronic treatments.

I think it's a general problem with many other serious chronic diseases, as well, where there's a lack of adherence.

What we really should be talking about with GLP-1 is all of the other benefits that they may offer, for the heart, the kidneys, the brain, the vasculature and there's possibly more. There needs to be a better understanding of that.

Many trials of GLP-1 receptor agonists are ongoing in many other indications. Which of these are you most excited about?

The next big ones for us in phase III trials are our MASH [ESSENCE] trial and our Alzheimer [EVOKE and EVOKE plus] trials, which could show something that has not already been shown. [Results in metabolic dysfunction-associated steatohepatitis (MASH) are due in 2024, and in Alzheimer disease in 2025.]

What are you excited about beyond GLP-1?

The amylin biology, which is also a hormone that has effects on the brain. I'm not sure whether we should call it a neurotransmitter in the same way as GLP-1, but it's definitely a hormone and it's a little bit the same story in that it has been around for a while.

Actually, pramlintide [an amylin analogue] has been marketed for a very long time for diabetes, but it turns out that you can actually get much better weight loss if you make a long-acting version of this peptide. And it is complementary to GLP-1 in its physiology: amylin is released from the pancreas, whereas GLP-1 is released from the intestine; they both work on the brain but on different neurons; and they have complementary effects, which might lead to higher weight loss.

We've seen some data with GIP [gastric inhibitory polypeptide], and there's some data coming with glucagon. Amylin is the next thing that will read out. [Novo expects first phase III data on CagriSema, a combination of the long-acting amylin analogue cagrilintide and semaglutide, on weight loss by the end of 2024].

Interviewed by Asher Mullard
Questions and answers have been edited for length and clarity.