

## A conversation with Dan Drucker

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### Conversations with Giants in Medicine

Dr. Dan Drucker, of the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, and the University of Toronto, is a diabetes treatment pioneer (Figure 1). Drucker's early work explored the biosynthesis, secretion, and action of glucagon, and he later went on to delineate the novel mechanisms of action of glucagon-like peptides (GLP) 1 and 2. His work on GLP-1 and -2 agonists as well as DPP-4 inhibitors provides the foundation for the largest spectrum of drugs for both gut disorders and type 2 diabetes. To see the full interview, including his early stumbles in the lab and his prediction that his next five to ten years in the lab will be very boring, see [www.jci.org/videos/cgms](http://www.jci.org/videos/cgms) JCI: Can you tell me a little bit about your parents and what you were like as a kid? Drucker: My parents were Holocaust survivors. They found each other in Israel after the war and moved to Montreal in 1953. I grew up in Montreal until I was about 13 years old, and my dad then got a job for the federal government, based in Ottawa. My dad was an engineer and an architect and a builder. My mom was trained as a dietitian and later transitioned to interior design. She did whatever she could to make a living. Maybe I was insecure and unable to extend [...]

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*JCI:* Can you tell me a little bit about your parents and what you were like as a kid?

Drucker: My parents were Holocaust survivors. They found each other in Israel after the war and moved to Montreal in 1953. I grew up in Montreal until I was about 13 years old, and my dad then got a job for the federal government, based in Ottawa.

My dad was an engineer and an architect and a builder. My mom was trained as a dietitian and later transitioned to interior design. She did whatever she could to make a living.

Maybe I was insecure and unable to extend myself in the humanities, but I just gravitated to science, and back in those days, one didn't have to be particularly well-rounded or highly educated to get into medical school. We had some entry-level programs where one could apply after two years of college, and that's what I did. Ultimately, I ended up at the University of Toronto. We had nobody in the family doing science or medicine, but I thought it was a cool way to apply science and help people, and it was a very secure profession. Maybe being the child of Holocaust survivors, and after my dad went bankrupt two or three times as a builder and developer, I thought medicine would be steady work.

*JCI:* What was it about endocrinology that intrigued you?



Figure 1. Dan Drucker.

Drucker: I was flipping through the elective catalog, and endocrinology caught my eye, all these cool diseases. There was a brand-new chair of endocrinology at the time, Gerard Burrow. He had a great personality, he loved teaching, he had a lab as well as a clinical practice, he was enthusiastic about everything. Burrow was a thyroid person, and in fact, I did some experiments with him looking at phosphorylation of thyroglobulin in ovine thyroid cells and culture. I thought it was cool and didn't really understand why I was given 5 millicuries of  $^{32}\text{P}$  and everyone else was hiding outside the door.

*JCI:* With an interest in the thyroid, what led you to going to work with the incretin biologist Joel Habener at Mass General?

Drucker: I interviewed at three great labs: Bruce Weintraub at the NIH, who had cloned TSH, the legendary Seymour Reichlin at Tufts University, who was an expert on thyroid hormone, and Joel Habener at Mass General had at that time a grant on glycoprotein hormone genes and TSH. All of these interviews were directed at thyroid training, and I accepted Habener's offer because he had the most experience in molecular biology, which at the time in the early 1980s, was the up-and-coming area to be in.

When I got to Habener's lab he said, "Bill Chin is spearheading the thyroid project, and he's going to the Brigham, so you'll just have to work on proglucagon." I probably said to myself, "What just happened?" But in those days, one did what one was told. There was no concept of questioning the professor. I really wanted to learn science and molecular biology, and the reality was it didn't really matter that much if I learned it in a thyroid or a glucagon system.

My first project was to express the proglucagon cDNAs in a bunch of cell lines from fibroblasts to pituitary cells to islet cells and ask if the cells had the machinery — what we now know as prohormone convertases — that allowed them to liberate the glucagon-like peptides. Obviously, the fibroblasts didn't, and the pituitary and the islet cells did. We could see that not only were GLP-1 and GLP-2 liberated, but there were multiple molecular forms of GLP-1. In parallel, I was to figure out what GLP-1 did: dumping GLP-1 on a whole bunch of cell lines and looking for bioactivity changes in gene expression, proliferation, cAMP formation. Through that work, we figured out that GLP-1 stimulated insulin secretion.

*JCI:* At what point did you decide to start looking for faculty positions on your own?

Drucker: It was always understood that I would go back to Toronto. Toronto is a wonderful environment for science; we only have one medical school, the University of Toronto, and that has meant that everyone's appointed to the same school, and we don't have a competitive internal set of issues. I had a wonderful collaborator — still do — in the Department of Physiology, Patricia Brubaker, who was also working on glucagon-like peptides. The funding climate was better then than it is now — paylines were probably 25% to 35%. I had to generate most of the initial data myself: one day in clinic and four days in the lab. It was pretty hectic, with a young family; I was jack of all trades, master of none, always feeling inadequate.

I had an amazing mentor named Lou Siminovitch, who was the founder of the Hospital for Sick Children's Research Institute; he founded the Lunenfeld. Siminovitch adopted me as one of his scientific sons and

would say to me, “Drucker, you have to make transgenic mice.” And then a few years later in 1993, he said, “Everyone’s making knock-out mice now. Knock out your favorite gene.” All of those experiments he suggested were fundamentally important for my career.

*JCI:* Through that time, you had a front row seat to watching GLP-1 become a therapeutic target.

Drucker: I had an inkling because my notebooks in Boston disappeared, and Joel told me they were filing a patent to potentially protect the idea that GLP-1 could be used to treat diabetes. I was pretty naive. Those were the early 1980s, so we didn’t really have the biotechnology industry that we do today; the technology transfer offices were either bolted on to the Vice President of Research or not in existence.

I was a bystander for that, but after seeing those first GLP-1 patents, once we cloned the *exendin4* gene, I knew it might be useful. Similarly, once we figured out the DPP-4 inhibitors had useful effects to lower glucose, that led to a dozen DPP-4 inhibitor patents. Once we identified the sequence of GLP-2, that led to about 18 patents for the use of GLP-2. I was really in the right place at the right time, to watch Joel and see how technology transfer worked.

*JCI:* Let’s talk a little bit more about DPP-4 inhibitors. The last I looked, the market share for these inhibitors is massive.

Drucker: This was a great story. I think the earliest description that DPP-4 cleaves GLP-1 and GIP was made by Rudolf Mentlein in Germany in 1993, and then very quickly thereafter by Tim Kieffer working with Pederson and McIntosh. Many, including in industry, jumped on this concept. I was a little bit late to the game, but I gave a talk at Tufts University in the early 90s and showed the sequence of these glucagon-like peptides and mentioned that they were degraded by DPP-4.

A scientist waited for me at the end of my lecture, named William Bachovchin, and he had been working on DPP-4 for years and had a company that was developing DPP-4 inhibitors for the treatment of cancer. He was fascinated by my glucose GLP-1 story and offered his inhibitors to test them. I’m not even certain we had a technology transfer agreement in place. That led to a dozen patents with Bachovchin to use DPP-4 inhibitors as a therapy for diabetes, and we weren’t the only ones. They

were all blended into a master patent bank that almost every company licensed when they developed their own DPP-4 inhibitors.

*JCI:* What about the GLP-2/teduglutide story — it was perhaps not quite so straightforward?

Drucker: We knew we needed to look at glucagon gene transcription in the gut. I made a transgenic mouse expressing SV40-T antigen under the control of the glucagon promoter, and lo and behold, I got intestinal tumors, and we used those tumors to isolate the GLUTag cell line.

We passaged the tumors in nude mice, and when we opened them up, the intestines were huge. I’m not talking 20% bigger, I’m talking two- to three-fold bigger. You didn’t need fancy math to see this biological effect, and there were examples of patients with glucagon-producing tumors with small bowel obstruction. You take out the tumor; the bowel abnormalities went away. We figured there was something the tumor was making that was promoting bowel growth and figured it was connected to glucagon, so we synthesized all of the glucagon-like peptides and injected them into mice.

I sent off about 30 FedExes to big pharma and some biotech companies to entice them to envision a treatment for inflammatory bowel disease or unhealed fistulas or short bowel syndrome. Very few responded other than a biotech in the Toronto suburbs, Allelix, who invited us to give a seminar. After the seminar, they gave us \$100,000. I don’t even think we signed a contract.

As I was getting ready to inject the peptides, Allelix made me aware of a Japanese patent filing — they had identified the glucagon-like peptide that promoted bowel growth: glicentin. I figured we could see, and if I confirmed that it’s glicentin, that’s fine.

It was true that glicentin was a bowel growth factor, but it turned out that GLP-2 was even more potent. The Japanese folks never studied GLP-2, and there was no real described biological activity of GLP-2 in the field whatsoever. This led to a series of GLP-2 patents, and we synthesized a hundred analogues of GLP-2, looked at the most robust ones, and Allelix was happy to support the work.

The European approval of Teduglutide [GLP-2 analog] for short bowel syndrome came first, which is unusual, because the FDA is usually faster. I was one of the experts that went to the FDA Advisory

Committee. I’ll never forget that day: I rode to the NIH in a taxi with a woman who was on Teduglutide, who had short bowel syndrome. She didn’t know who I was and kept saying, “If the FDA doesn’t approve this drug, me and my friends are all moving to Europe, because it’s approved there.” At that hearing, the company presented the data; the FDA advisors basically agreed with the assessment surrounding the efficacy and safety of Teduglutide. It was a huge buzz.

*JCI:* Has this aspect of your professional career, one that maybe you didn’t envision from the beginning, been satisfying?

Drucker: I’m always a clinician-scientist — the unmet needs of patients and the ability to make a clinical impact are huge. Seeing something go from discovery to patents to approval, it’s like winning a lottery. There aren’t that many people with short bowel syndrome that I meet in a supermarket, but I have met a lot of people taking the DPP-4 inhibitors.

I think there’s no question of the importance of being at the right place at the right time. Of course, one has to capitalize and do the experiments and follow through, and the patents were battles. I can tell you stories — we were sued by Merck, who were trying to overturn the patent portfolio, because Januvia was doing so well and the revenues were increasing. I was at the Prix Galien with Roger Perlmutter and Ken Frazier having drinks, and the thought to be a rabble-rouser came to me and I said, “Guys, what’s with the lawsuits, don’t you guys have enough success and enough financial sustainability?” But it’s just part of the business. Later I learned if no one’s suing you, you probably don’t have a lot that’s worthwhile out there. It’s just initially really terrifying to get sued; after a while, it just becomes part of the business.

*JCI:* If you could not have been a physician or a scientist, what other career might you have chosen?

Drucker: I thought about being a lawyer because I was told that I was argumentative. I like fixing things, although I’m not very good at it. I think accounting is cool. I’ve had tremendous exposure to the investment industry through interacting as a consultant to biotech or large pharma companies and think working as an investment analyst would be cool.

**Ushma Neill**