

An interview with P. Jeffrey Conn

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How did you come to be interested in pharmacology?

I became interested in severe brain disorders as a teenager. I watched a close friend experience a sudden-onset psychotic break, beginning the journey of a lifelong struggle with schizophrenia. Over time, I became increasingly aware of the struggles of other friends and family members with serious brain disorders. I wanted to understand and help individuals dealing with these devastating disorders, and I therefore entered college with the plan of becoming a clinical psychologist. In my first year as a psychology graduate student I took an introductory course in psychopharmacology and was immediately hooked. I became convinced that the best approach to helping patients suffering from severe brain disorders was to understand the neurobiology and pathophysiology underlying these disorders, and to use this understanding to guide discovery of new therapies. I decided to transition from psychology to pharmacology, and I therefore took courses to strengthen my background in chemistry and biology to allow me to enter a graduate program in pharmacology.

Why have you decided to focus primarily on neuronal signaling?

Virtually all drugs used for treatment of neurological and psychiatric disorders act by modulating neuronal signaling. Although there are many areas that are crucial for understanding drug action in the brain, the discovery of new treatment strategies must ultimately hinge on understanding the mechanisms by which changes in neuronal signaling alter specific brain circuits that are important for both normal brain processes and the pathophysiological changes that underlie different disease states. For me, it is crucial to incorporate all aspects of pharmacology into a balanced and highly integrated research effort. Thus, we also focus on areas other than neuronal signaling, including drug disposition, behavioral pharmacology, quantitative molecular pharmacology, and medicinal chemistry. However, our efforts in each of these areas are ultimately aimed at understanding and manipulating neuronal signaling in CNS circuits that are important for brain function and disease. Although new therapies can also emerge from less mechanistic approaches, I am convinced that the most important breakthroughs in the discovery of new therapeutic agents will emerge from a strong understanding of neuronal signaling.

Do you have a scientific hero?

There are so many individuals who have had a profound influence on my approach to science. I love studying

the history of science and the lives of the great scientists who paved the way to our current understanding. Individuals I admire most are those with a strong passion and perseverance in pushing the boundaries of our understanding; individuals who are not overly impressed with themselves but are intensely focused on a mission that they believe in. Also, I am inspired by scientists who are willing to think out of the box and take personal risks to accomplish these goals. There are many scientists, both historical and contemporary, who I could point to. However, if I were to name people who I have personally worked with and who have inspired me in this way, I would point to two very different individuals I worked with when I was at the Merck pharmaceutical company. The first is Ed Skolnick. Before moving to industry Ed was a world-class scientist and highly successful by every measure. At Merck he maintained a passion for advancing patient care and was committed to making decisions that were firmly grounded in science. As president of research for a large pharmaceutical company, he took the time to read the primary literature in every major area that was represented in the company. I received emails from him at all hours asking questions about specific papers in my field. This was not unique to me, and heads of research efforts in other therapeutic areas, from cancer to vaccines, had the same experience. What I appreciated most was that you could change his view on a topic or research area by articulating strong arguments that were grounded in research. However, he could see through poorly based arguments. Ultimately, his goal was, and continues to be, advancing patient care rather than building his own ego or status. The second is Robert Gould, who was the head of Merck's West Point, PA site when I was there. I do not know any individual in the world who understands virtually every aspect of pharmacology and drug discovery as well as Robert. His knowledge base in drug discovery is phenomenal and he has a strong grasp of quantitative aspects of molecular pharmacology, drug disposition, medicinal chemistry, issues that determine drug toxicity, and a range of issues that are crucial to the discovery and development of new therapeutic agents. As with Ed, he is an intellectual giant but also has a scientific humility that makes him comfortable with being challenged and willing to seek understanding of the things that he does not know. Again, his major passion is advancing science and patient care rather than protecting his ego or defending a predetermined scientific position. In my view, passion and strong intellect coupled with humility are crucial ingredients of the best science.

What stands out as a highlight accomplishment for you?

I am extremely gratified by what we have accomplished in building world-class drug discovery in an academic setting and by seeing our work have an impact both in industry and in furthering basic science. In 2011, we advanced three programs to clinical candidate status and these are now advancing in Investigational New Drug (IND)-enabling studies in collaboration with partners in industry. A fourth program was licensed to a company that is now advancing the program independently. In each case, these are novel approaches to the treatment of some of the most devastating brain disorders. In the process we have generated tremendous interest in these novel targets in industry, and several companies have launched independent efforts. Also, I have been thrilled at how seamlessly we have been able to weave strong basic research into each of these programs. I am convinced that this commitment to basic research in the context of drug discovery is absolutely crucial for positioning programs to deliver the best drug candidates that act by innovative new mechanisms. Seeing our center mature and seeing other individuals increase their appreciation of the need for academic drug discovery is a highlight for me. A second would have to be the work that we have pursued in the discovery of novel approaches to the treatment of Parkinson's disease. This has been a long-term career focus and has encountered a number of barriers that have at times seemed insurmountable. We are finally at a point where we are advancing drug candidates with hopes for clinical testing in 2013. It is a tremendous personal highlight to see these ideas advance to this stage. Nothing could be more gratifying than to see this work have a real impact on patients suffering from this disease, and I hope that we are close to knowing whether this will be a reality.

Do you have any scientific regrets?

At a personal level, I must say that I do not have any real scientific regrets. I have been very fortunate and am extremely thankful for the opportunities I have had and the directions that our work has taken. As for all scientists, I have taken directions that have not been fruitful and others that have been more productive. However, that is the nature of science, and I have learned and benefitted from each of these experiences.

What do you think are the next big questions to be answered in the area of neuroscience drug discovery?

There are very many big questions to be answered. We are gaining an unprecedented understanding of many aspects of brain function that provide exciting opportunities. However, how these advances will translate into new therapies is not yet clear. We have all come to appreciate that the major diagnostic categories of brain disorders, such as major depression, schizophrenia, autism, and epilepsy, each represent a large number of separate diseases that share some common symptoms. A major question is whether we can develop an understanding of the genetic and biological underpinnings of these disorders in smaller better-defined patient populations and whether we can develop individual treatment strategies for each. I believe that this is absolutely crucial,

but the challenges of making this happen are enormous. At a basic science level, we have not really begun to develop this level of understanding for CNS disorders. Also, drug discovery is extremely expensive and high-risk, and current models for drug discovery and development do not lend themselves well to the challenges that advancing personalized medicine approaches as the opportunities emerge. I see tackling these issues at every level and establishing new models to de-risk neuroscience drug discovery as our greatest challenges in the coming years.

What are your thoughts on increasing collaborations between academia and the pharmaceutical industry in the search for new medicines?

I left industry to start a drug-discovery effort in an academic setting almost 10 years ago because I came to realize that the system we have established – with the traditional roles of academic and industrial scientists – has broken down. It simply does not lend itself well to the discovery and development of the most innovative new medicines. From my vantage point when I was in a pharmaceutical company, I was reliant on academic research to guide us in taking new directions in the treatment of human disease. We worked in a way that simply did not allow us the luxury of time required to support purely basic research or spend years understanding the complexities of a system that are essential for turning an idea into a treatment. On the academic side, I saw outstanding basic research that led to speculative ideas for new treatments, but these were rarely pursued at a level that would provide the datasets needed to justify launching a major drug-discovery effort in an industrial setting. I think it is crucial for academic scientists to be more committed to thinking critically about what would be required to develop a new therapy stemming from an idea that comes from their research. We should all pay close attention to the clinical literature and insist on performing the difficult studies needed to establish more rigorously the potential viability of a new approach. Collaborations between academic institutions and industry are absolutely crucial if we are to realize the promise of future therapies. However, we must enter these with a strong commitment to and understanding of the basic missions of the two institutions. A primary mission of a publically traded company must be to provide a return to its investors. In academic institutions, we must insist on maintaining a primary commitment to furthering science, basic knowledge, and patient care. Neither mission is inherently better than the other, but the two are fundamentally different. I could say volumes about how maintaining a commitment to our academic mission is crucial for academic drug discovery. If we respect and make decisions based on the different missions of the two institutions, we can work together to be much more effective in the discovery of new medicines than has been the case over recent decades.

What advice would you give to a young person today who is interested in pursuing a career in CNS drug discovery?

Try to keep your options open. We are in a period of tremendous change and transition in drug discovery, both

in industry and academia. I don't think anyone can fully predict what the pharmaceutical industry will look like in 10 years and it is too early to say whether academic drug discovery will have the impact that many of us hope for. If you are a graduate student, you should pursue the strongest possible academic postdoctoral placement. Focus on learning new skill sets that fit within drug-discovery

research, but insist on doing so in a context where you can publish high-impact papers. This will put you in the best position as a candidate for a job in either an industrial or academic setting in the future.

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