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Interview with P Jeffrey Conn

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How did you become involved in the field of neuroscience?

My interest in neuroscience started when I was young. My first encounter of a major brain disorder was watching as a close friend developed schizophrenia and seeing the dramatic change following his first psychotic break. He never really recovered from that, as is often the case with schizophrenia. That experience when I was a teenager had a major impact. From that, and other experiences, I developed an interest in therapy for people with major brain disorders. I started by looking at the field from a clinical perspective and in college I majored in psychology with a plan of going into clinical psychology. In the course of that I really became convinced, through taking some neuroscience courses and some psychology courses, that the approaches that had the most promise were more neuroscience oriented.

After college I went to graduate school for a single year in psychology. From that I decided that really I wanted to be more fully on the neuroscience side, so I switched programs to a pharmacology program with a neuropharmacology focus. I abandoned my plans to pursue a career as a clinical psychologist and focused on building a research career as a neuroscientist, but maintained my strong therapeutic interest. I think that the origin of my interest in neuroscience has stayed with me and I am still focused on the same goals of impacting human health, but more from a research angle.

Can you update us on some of your research group's current work?

We are engaged in a broad range of activities that touch upon multiple brain disorders. We are large group – The Vanderbilt Center for Neuroscience Drug Discovery (VCNDD; TN, USA) that I direct, comprises approximately 100 scientists and there are several principal investigators and faculty members that head different groups within the center. We all focus on the same issues and work together as a team – it is a really close-knit, team-oriented way of doing research. The 100 scientists are all working together as one huge laboratory, with principal investigators over major groups. We span a large gamut of research and we have

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major efforts in Parkinson's disease, schizophrenia, Alzheimer's disease and several other major brain disorders, as well as childhood developmental disorders. We come at each of these from a multidisciplinary approach that includes a lot of basic neuroscience and neurophysiology. We tend to think of normal and pathological brain function in terms of brain circuits that may be disrupted in a given disorder. As we understand the pathological changes that may contribute to a disorder, we work to manipulate those circuits with pharmacological agents. This requires a combination of cellular neurobiology, electrophysiology, behavior, *in vivo* imaging, and a major focus on medicinal chemistry and drug disposition. We integrate efforts from this broad range of fields, going from chemistry, to cellular biology, to molecular biology, to behavior, as well as using imaging and *in vivo* biomarkers, and then ultimately translating to clinical studies. I should point out that we are not a clinical group, so the clinical studies are carried out by partners that we are in collaboration with who take the drug candidates that we develop on to clinical studies.

Do you feel that the Center's approach to drug discovery is quite unique in that it is so multidisciplinary?

I certainly think that it is unique. However, there is an increasing number of academic drug-discovery groups, each of which is developing their own complementary models. Really, I guess that the core of what we do is drug discovery, but it is drug discovery that is also unique relative to what I see in most industry settings. In our academic environment, we can place high priority on the highest level basic science and fully integrate this into the drug-discovery process. Because of this, everything we do in drug discovery is tightly inter-meshed with major investments in basic science. I have never seen an industry setting where this is possible. Industry drug discovery is unparalleled in terms of the infrastructure and tremendous expertise required to take a target and develop a drug candidate that can then advance that on towards clinical studies. However, when I worked in industry, it could be frustrating as there were so many basic science questions that we could not afford the time or the resources to address, but that could be critical to the drug-discovery process. What is unique in our academic setting is to be able to pursue drug discovery using the best practices that have been established in industry but to integrate this with the level and commitment to basic science that is typical of academic environments. The basic science critically informs our drug-discovery efforts and all of major basic science in a way that could not be achieved without dedicated funding for the basic science efforts from NIH and other traditional funding agencies.

There are a lot of academic groups that are now building similar efforts, so hopefully over the next 10 years we will likely see an increasing impact of this kind of work.

Having worked in industry yourself, at Merck and Co., do you find that because industry is so results-driven it sometimes fails to grasp the bigger picture and critical aspects of research are ignored?

I do not think that they are more results-driven than we are. I think that we are extremely results-driven – we work on tight timelines with clear milestones. A lot of our funding

comes from industry and we have to hit many strict milestones. Our goal is always to get new molecules into development and so we are very results-driven, just as you see in industry.

I think the difference is that in industry there is a false efficiency, in which there is an effort to drive science by process rather than allowing data to drive day-to-day decisions. Ironically, this decreases efficiency because it removes the ability to respond quickly to new data or insights and makes it difficult to make the best decisions on a day-to-day basis. I think most major companies are starting to recognize that science cannot operate in a purely process-driven manner and are trying to operate in a different way. You see a lot of processes in place that can prevent scientists from following data that could ultimately be critical for the success of the program. When I was in an industry setting (and I think that this is even more the case today because you have the fiscal constraints), we would often see unique, surprising activities of our molecules that we thought could be critical to a drug candidate that could make it all the way to development. However, to keep a program on track, we almost had to put blinders on and just focus on getting to a clinical candidate. That requires ignoring a lot of the subtleties of the biology and the unique properties of different molecules with a hope that all the subtle differences would not be critical to whether or not the molecule is going to be successful in the clinic. Just by the processes that are often in place in large companies you are forced to work in this streamlined mode instead of following the data, and of course from an industry perspective I can understand this because you cannot endlessly follow rabbit trails and follow data that is not leading to a drug candidate. I understand the temptation to put rigid processes in place, but I do not think that it fits well with science. You have to approach science and any project or program with a level of humility; you have to accept that you do not understand all the details fully, the neuroscience and the biology, and you have to try and learn as you go and shift your plans when needed. So, in our setting we integrate that neuroscience very closely with drug discovery. This often requires dedicated chemistry and biology investments to understand molecules that we know will never be advanced as drug candidates. That is what is difficult in an industry setting but fits well with the basic science mission of academic institutions. I can point to multiple examples where we see different behavior of closely related molecules and subtle effects on signaling pathways in which molecules behave differently. Instead of just ignoring that we have the luxury of being able to invest the time in determining whether some of those differences are important. What we often find is that they are critically important for understanding the properties of a molecule that are needed to advance a drug candidate.

Are there any areas of your research that you are currently engaged in that you are particularly enthused about?

Yes, there are some areas of our research that we are really excited about currently. I am very excited about some of the new potential treatments that we are working on for the treatment of schizophrenia. I think schizophrenia is one of the most challenging areas in neuroscience; and neuroscience is one of the most challenging areas to develop new therapeutic approaches. One area of schizophrenia that I am especially excited about right

now is our focus on muscarinic acetylcholine receptors. One reason I am excited is that this is a direction that is based upon very strong clinical data sets coming from programs that were focused on Alzheimer's disease. Drug candidates from these earlier programs were taken into development and found to have antipsychotic efficacy in Alzheimer's disease patients. Based on those clinical trials the drug candidates were run in schizophrenia patients and displayed really robust efficacy, with positive and negative symptoms and some cognition improvement. This provides strong clinical validation for targeting muscarinic receptors for treatment of Alzheimer's disease and schizophrenia. However, problems with those earlier compounds stopped them from being advanced all the way to the market. We have been building on those earlier clinical findings and have developed ways to address this. Problems with the earlier programs came in developing high selectivity for specific muscarinic receptor subtypes. We have developed novel approaches to target these receptors that gave us very high selectivity for individual muscarinic receptor subtypes. In animal models these highly selective compounds had the efficacy demonstrated by the clinical compounds. Because of the strong clinical data set that this is being built on, we are more confident that efficacy can be achieved. Thus, by solving the major problems that were inherent of those earlier programs, this gives us a lot of optimism that if we can get these new compounds all the way to clinical testing in schizophrenia patients we will have a very strong chance of success.

The muscarinic programs is something I am particularly excited about right now – we have just partnered with AstraZeneca over one of those programs and that is doing really well.

Another area that I am excited about is the metabotropic glutamate receptor (mGluR) research that we are working on in partnership with Johnson and Johnson. This has been a really challenging area and serves as a good example of where the approach we take is critical. There is an adverse effect liability with the mGluR5 modulators that we noticed early in the program. Early on, we focused a lot of effort on subtle differences of effects of these molecules on signaling by the receptor and that gave us a path forward towards the development of molecules that may avoid the adverse effect liability seen with some mGluR5 modulators. I think that really illustrates the effectiveness of the academic drug-discovery approach where we are taking the time to do the more basic work upfront. I think that for schizophrenia research, targeting mGluR5 is more of a high-risk approach in that we do not have the same clinical data set and will have to ensure that we understand what is required to avoid adverse effects. With the muscarinic programs I have a high level of confidence that if we can get good, safe, strong candidates then there is a good chance of efficacy. For mGluR5-positive allosteric modulators, I think that it is a more speculative hypothesis and a different set of challenges, but I am excited to see both programs move forward.

And then outside of schizophrenia, there are other areas that we excited about as well, including our Parkinson's efforts that were supported by Michael J Fox Foundation and are now partnered with Bristol-Myers Squibb, as well as earlier-stage efforts focused on major depression and childhood developmental disorders.

Do you notice strong similarities between the cellular and molecular mechanisms responsible for causing schizophrenia and other neurological and psychiatric disorders?

Yes, we do notice some overlap, but I would not say that the similarities are at the molecular and cellular level but at the systems level. That is where the similarities to me are most striking. Although it is early days, I think that we may start seeing similarities at the genetic susceptibility level. If you consider Alzheimer's disease and schizophrenia: Alzheimer's disease is a neurodegenerative disease involving massive loss of neurons. There is pathology that is observed at molecular and cellular level that is not observed with schizophrenia, so the molecular and cellular similarities are not as dramatic as what I think ends up being the case at a more systems and circuit level. We really focus more on circuit level biology in terms of thinking of the way that different diseases impact brain circuits and how that is involved in the pathology. Alzheimer's disease is a good example where the muscarinic acetylcholine approach, which I mentioned earlier, came about as a result of a lot of evidence in the 1980s and early 1990s that cholinergic systems were disrupted first in Alzheimer's disease leading to efforts to develop agonists. When Eli Lilly took one of their muscarinic receptor agonists into Phase III trials for Alzheimer's disease what they found was that in Alzheimer's patients these compounds had an effect on what one would view as the more psychotic symptoms of Alzheimer's patients, such as hallucinations, delusions and paranoia symptoms, which are very similar to what you see in schizophrenia patients. From that, they ran a trial in schizophrenia patients and they found efficacy with positive and negative symptoms and also an improvement in cognitive function. Based on that, we have really been focusing on some system level disruptions that we think are common to Alzheimer's disease and schizophrenia. Some of the programs focused on new approaches to treatment of these symptoms include plans for clinical testing in Alzheimer's patients as well as schizophrenia patients because of this clear overlap.

Another area of overlap is the disruptions in cognition that you see in schizophrenia, Huntington's, Alzheimer's and Parkinson's diseases. I would never claim that the cognitive disturbances in each of these diseases are identical, but it is interesting that there are significant overlaps. For example, prefrontal cortical function is disrupted in schizophrenia and other neurodegenerative disorders so we have spent a lot of time thinking about how to improve activation of the prefrontal cortex in the context of different cognitive learning tasks that we think could have relevance to both neurodegenerative disorders and schizophrenia.

As Director of the VCNDD what is your vision for the center?

The mission at the center is to take new advances in basic neuroscience that we think have implications for novel therapeutic approaches and put enough investment in those to de-risk them so that companies can invest. We really see our major role as de-risking novel approaches by doing the work that can really make a convincing case for whether a project warrants further investment and should be pursued. That mission came from my time in industry, where I was charged with choosing the directions that the team should take in

developing new strategies for treating different disorders, including schizophrenia. We relied on the academic community to create data sets for new approaches and what I would find is that the academic community would perform great basic science, but it would stop short of really providing the data needed to say a new approach would be viable for a new therapeutic strategy. It was hard to get the company to invest in these speculative ideas, and we at the company did not have the infrastructure to investigate a lot of the basic science needed to make a decision. Investigators at the universities did not have the infrastructure or expertise to start the early stages of drug discovery to see if these approaches were viable. So that is the primary mission at the center – target validation and de-risking. Now we focus almost exclusively on basic science and drug discovery. We partner with companies when we get to the point where we are ready to advance into development, and we will often partner with companies earlier than that during the discovery phase. My vision, looking forward to what I would like to see evolve is that we would advance some select programs into early clinical development. This is based on the understanding that the only true validation of a novel approach is clinical validation. Right now we focus a lot of efforts on opportunities where there is some clinical data set, such as the muscarinic receptors, but ultimately we need to provide that clinical validation of new approaches. We need to continue to do what we are doing now and work with companies when we advance into early development. However, for key programs, where the real need is to get novel molecules into humans for clinical proof-of-concept or proof-of-mechanism, I would like to see us begin to span the gap between discovery and clinical testing. This is a big gap and there are no readily available funding sources for investigational new-drug enabling studies (which are studies that the US FDA requires before you can start testing molecules in humans). If we can start working out ways to bridge that gap and raise the money for those studies between discovery and development then we could take really novel approaches and try to get them to the point where we have clinical proof-of-concept. That would dramatically increase the chances of a company investing in the project and going all the way to the market. Also, part of that goal is for us to create very high-quality clinical molecules where we have all the information to do a very well-controlled definitive clinical study and make those clinical compounds available to the academic clinical research community. That is a big goal and hard to achieve but we are just at the beginning stages of thinking about how to breach that discovery-to-clinical research gap.

Can you tell us about some of the VCNDD's most important achievement to date?

I think some of the most major achievements are the major programs where we have developed drug candidates that are now advancing in development in partnership with companies. Each one of those is a major achievement. However, I think the most important achievement is developing an academic drug-discovery center that is reliably delivering very high-quality development candidates to advance towards clinical testing. I have never seen an academic drug-discovery group really operate in a way that is reliable in systematically delivering new drug candidates and partnering with companies. I think that the Center's biggest achievement is to show that this is possible. When I moved to Vanderbilt many people told me that it would not be achievable. Honestly, I understood why they felt that

way and knew that it would be really challenging in this environment. However, while I was uncertain of whether this endeavor would be successful, I was convinced of the need. To build an integrated academic drug-discovery effort and to show that it can be done has been very rewarding. To do this in neuroscience, which is a challenging area, is critical for make a case for novel approaches that industry has an appetite for investing in. It is the big picture of what we have done that I see as the major achievement. Equally important is doing this in a way that the basic science is tightly integrated and informing the discovery, which builds on the traditional strengths of academic science. I believe that this is allowing us to create better clinical development candidates. Neuroscience drug discovery is high risk and we cannot predict whether any of our individual programs will reach the market. However, regardless of whether any individual programs ultimately succeed in reaching the market, my hope is that this conceptual advance in how we approach therapeutic discovery will have a broad impact.

Having worked at Merck and Co., prior to your move to Vanderbilt University, do you do feel that, in general, industry's role in advancing the development of novel therapies for schizophrenia is hindered by a lack of open collaboration among companies?

The answer is a definite yes. Clearly the lack of open collaboration hinders drug discovery in general, and certainly within neuroscience. Obviously, once you have proprietary molecules, a company has to protect its most valuable assets, which is its intellectual property, so I can understand that large companies would not collaborate with each other at that level. What I think is most striking is the secretive nature in which many companies in the past have operated in areas of nonproprietary basic science. I think some companies have come to realize that they have to change and that the model that they are building their R&D on is not the most effective. Company scientists need to be actively engaged in the broader scientific community and this requires them to be more aggressive in presenting and publishing their data, as well as actively engaging other scientists to discuss results and so on. Much of the work done in companies is not proprietary and this can be done without compromising the companies' assets. The benefit of being more plugged in to the broader scientific community far outweighs any risk that nonproprietary data presented will hurt the companies' competitive advantage. Although I think that more companies are putting more focus on collaboration, there is still the issue of companies being secretive about early ideas and research for which there is no reason to be secretive. We should not over estimate of the value of basic science data we may have, and should use it as a way to be at the forefront and actively engaged in the broader research community that shares our interests. If you are openly engaging with researchers in the field then you are going to get 100-times more information as there are so many people out there that are doing great science. I think that dialog and exchange across a large community is critical for science and in the past a lot of companies have been overly conservative in terms of sharing information. The more open you are with sharing your data, the more open others are in sharing theirs, and this can be done without compromising intellectual property. I think an understanding of that is starting

to emerge and a lot more companies realize that we would all benefit from increased understanding of the complex biology that underlies the areas where we are all invested.

How do you think companies may be encouraged to share their knowledge of ‘basic’ science?

In a small way, I think we and other similar academic drug-discovery centers are encouraging it by doing it. We are developing a lot of proprietary compounds and carefully protecting our patents, but we are publishing very aggressively and presenting data sets that are key to our decision-making but are not proprietary in nature. In addition to drug leads, we are developing new tools that allow us to get at questions that are critical. By publishing and presenting data with these compounds at meetings, we engage in the dialog with a broad scientific community. I think that leading by example, being highly engaged in the research field, and talking about your data and your findings, including data that is related to drug-discovery programs, we can encourage companies to do the same. Really, I think all the things that we are talking about relate to the friction that comes at the interface of science and business where the cultures of the two are just fundamentally different. I think that science has to be a very open and communicative culture in order to be effective. I think we can acknowledge that we are all in competition, but we can do that in a way that is open and communicative. While our competitors will benefit, we benefit as well.

How do you anticipate the field of schizophrenia research and therapeutic development will progress in the next 5–10 years?

I think that in the next 5–10 years there will be more fundamentally new approaches, so moving away from dopamine- and other monoamine-based strategies. We have already seen that shift where most companies are focusing on areas other than those that have been traditional for the field. There will be a much greater focus on negative symptoms and cognitive disturbances, which have so far been very challenging and continue to be from a development perspective – how that will proceed I do not know, but I do think that there will be more emphasis on that than a continued focus on positive symptoms. More importantly, we will focus on improving our understanding of the biology and pathology of the disorder and on basing new therapies on that new understanding. I think that genetics will play a major role as we identify susceptibility genes. At this point I think we are at an early stage and it is too early to have any expectations of anything directly coming from genetic studies in schizophrenia. However, we are starting to understand that different susceptibility genes can influence the likelihood of an individual developing schizophrenia and this can help us begin to develop a better understanding that is based on human biology. Importantly, current treatments for schizophrenia came from insights from human studies. Observations of schizophrenia patients that were serendipitous led to new drugs. In recent years, we have departed from that clinical focus and have been in a period in which efforts for discovery of new drugs have been based primarily on preclinical studies. I think over the next 10 years, we will start to shift back to a focus on patients and developing new therapeutic approaches that are more grounded in insights from humans, and a better understanding of the biology and the underlying mechanisms of the disease. This will come

from genetics as well as other areas of clinical studies that inform new areas of drug discovery. Right now the animal models are very lacking and are all based on previous drugs so the development of different animal models that more faithfully recapitulate the pathology of the disorder is needed. We still have a long way to go but as we start developing animal models that perhaps have multiple mutations of different susceptibility genes that you might find in combination in a patient, hopefully that will help guide new therapies. Instead of bench-to-bedside research, we need to return to bedside-to-bench and then back to bedside research. I hope that we will see this shift in coming years.

I am very optimistic about where we are in neuroscience at the moment in terms of the increased understanding that we are developing. However, it comes at a challenging time with industry downsizing and academic research funding being very stressed. I do think that the opportunities that we have are tremendous. As we start to see successes come from those opportunities, that will naturally impact the investment in neuroscience therapeutics, both by industry and government. Hopefully we will see some of these new areas pay dividends over the next decade.

Why do you think that there is such a need for a more up-to-date animal model? Is it a case that, new targets have surfaced and the development of a more suitable animal model has been neglected?

I think that historically investment in animal models has not received as much attention as other areas. However, we need a greater understanding of the human disease before we can start using that understanding to try to develop new animal models. Actually, as we develop an understanding from clinical studies I do think that the field is rapidly integrating that data into animal models. Examples would be some of the NMDA receptor antagonist work in demonstrating evidence that disruption of the NMDA receptor signaling can lead to schizophrenia-like syndrome in humans, which quickly led to introducing mutations that reduce NMDA receptor function in rodent models. The real gap is our lack of understanding of the human disease and it is only recently that we are starting to identify different susceptibility genes and as those genes have been identified, scientists have made those mutations and introduced them into mice. Those efforts have not been as fruitful as we had hoped. However, it is too early to be discouraged, and I think that it is too much to ask that a single susceptibility gene would lead to a syndrome in mice that recapitulates the human disease. Further understanding of the human disease through genetics, imaging and so on will be critical, and I think that that will stimulate a lot more animal model development. What we must understand is that we will never have a schizophrenic mouse or rodent that really recapitulates all the aspects of the disease that you see in humans. We have to understand what exactly we are trying to model and what those different models are useful for. I would say that we are really in a very similar place to most other neuroscience diseases areas. For Alzheimer's disease, we are light years ahead of schizophrenia in terms of understanding some of the genetics and pathology, and we have developed animal models based on that but they do not really recapitulate Alzheimer's disease faithfully. The same could be said for Parkinson's disease and for other brain disorders. This is forcing the field to really think about what we are trying to model. Different models may be more or less

useful for specific aspects of the disease. As we develop new understanding and better animal models, I do think that this will lead to new targets. In order for that to happen I think that there will most likely be a pause in launch of new drugs for treatment of schizophrenia. If we do not see as many monoamine antagonists moving into clinical development, those clinical development programs are not going to be immediately replaced by fundamentally new approaches at the drug candidate stage. This could lead to a decrease in the number of drug candidates that are progressing as the field catches up, but then as the field does catch up, my hope is that we will see a lot more targets and approaches begin to emerge.

What words of advice do you have for a young scientist envisioning a career in neuroscience?

I think that the major advice that I would have, and I give this advice daily to my trainees, is take a long view and do not look at the immediate short term. A lot of young scientists see the funding environment and where we are in the field and get really nervous. Time and time again, I have seen that these things cycle. This is the case in all career paths, not just in science. Just keep a long view and ask yourself if you are really passionate about neuroscience research. If so, follow that passion and give it everything you have. I think that is by far the best path to a highly successful neuroscience career. The anxiety that a lot of people have right now might decrease their willingness to just focus in and put all of their energy into that because they are trying to think about what their contingencies would be. The main thing is to follow your passion give it all you have. A really practical bit of advice for any graduate student is to do a postdoctorate and do it in the best laboratory you can find. I have been talking to a lot of students that are interested in alternative career paths, which I think are great, but for all of them, regardless of whether they want to go into scientific writing, law or any other area, I think after graduate school, if you can do the strongest postdoctorate possible, it will never limit your options after that, it will only give you more options.

Dr Conn is the Lee E Limbird Professor of Pharmacology at Vanderbilt University and Director of the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD). Dr Conn received a PhD in Pharmacology from Vanderbilt in 1986 and pursued postdoctoral studies at Yale University. He served as a professor of Pharmacology at Emory University from 1988 to 2000, before moving to Merck and Co. (PA, USA) as head of the Department of Neuroscience. Dr Conn moved to Vanderbilt University in 2003 where he is the founding director of the VCNDD, with a primary mission of facilitating translation of recent advances in basic science to novel therapeutics. The VCNDD consists of approximately 100 full-time scientists and has advanced novel molecules from four major programs as development candidates for clinical testing with industry partners. Dr Conn has served in editorial positions with multiple international journals and has served the scientific advisory boards of multiple foundations and companies. He has received numerous awards based on the impact of his basic and translational research. Dr Conn's current research is focused on development of novel treatment strategies for schizophrenia, Parkinson's disease and other serious brain disorders.

Interview conducted by Hannah Coaker, Assistant Commissioning Editor.