Drugs from D2

Philip Seeman's discovery of the D2 Dopamine receptor transformed psychiatry. He's hoping his new company does, as well.

By Victoria Stern

As medical students at McGill University in Montreal in the late 1950s, Philip Seeman and his wife Mary took classes at a local hospital to see what schizophrenia looked like. “That’s what changed my life,” says Seeman. The patients were extremely difficult to manage. “I was shocked by the patient’s screaming and catatonia, along with the terrible stench of urine on the floor. It was unforgettable,” he recalls.

Several years later in the 1960s, the couple moved to New York City, where Mary Seeman oversaw a hospital ward of 100 patients with schizophrenia. These patients were markedly different from those suffering from schizophrenia in the previous decade: they were not screaming or catatonic. The couple soon discovered that, in just a few years, powerful antipsychotic drugs had arrived in the United States and Canada. Amazingly, these drugs, such as haloperidol and chlorpromazine, could subdue psychotic symptoms quite effectively, although doctors didn’t know why. Mary encouraged her husband, who was pursuing a PhD at Rockefeller University with George Palade (who later received the 1974 Nobel Prize in Physiology or Medicine for discovering ribosomes), to “do something useful” and search for the mechanism of these antipsychotic drugs.

“If there was such a thing as a brain target for antipsychotic drugs, then perhaps this target was abnormally overactive in psychosis,” Seeman surmised at the time. “And if I could find out where these drugs worked their magic, it might open the door to better treatments.” “Philip always had fantastic insight and wisdom into where the field should go,” notes Bertha Madras, a colleague of Seeman’s for over 30 years and currently a professor of psychobiology at Harvard Medical School.

Now a professor at the University of Toronto, Seeman spent the next 12 years searching for possible targets for antipsychotics. “Many people told me I was wasting my time because there were many types of antipsychotic drugs [so likely many different targets], but I felt there was probably one common target relating to them all,” he recalls.

In 1974, Seeman synthesized radioactive haloperidol and added it to the postmortem brain tissue samples of schizophrenic patients. He found that the schizophrenia tissues had about double the number of haloperidol binding sites, as compared to postmortem tissues of people who died of heart attacks or cancer. Because these receptor sites were sensitive to haloperidol, he called the sites “antipsychotic/ dopamine receptors.”

Seeman later dubbed the receptor the D2 dopamine receptor. There are a total of five different dopamine receptors (four of which were cloned by his lab group), but the D2 receptor is the primary target for all the antipsychotic drugs. To verify his findings, Seeman “looked at hundreds and hundreds of samples and repeated his experiments over and over to ensure his work was solid,” says Madras. Seeman showed that all antipsychotics, regardless of chemical type, blocked binding to the D2 receptor in direct correlation to dose. He published his results in 1975 in *PNAS*.

Seeman’s discovery transformed antipsychotic drug design. In the 30 years following his pivotal paper, antipsychotic drugs have become a multibillion dollar business with blockbusters like Eli Lilly’s olanzapine and Novartis’s clozapine. His findings also shed light on our understanding of how schizophrenia develops, since dopamine must play a major role.

In that time, Seeman continued to explore the D2 system. In addition to cloning dopamine receptors, Seeman and other labs determined how many receptors needed to be blocked in order to alleviate the psychotic signs and symptoms. They found that the delusions and hallucinations tended to disappear when about 70 percent of D2 receptors were blocked. In addition, patients with psychosis who were never treated with antipsychotic drugs had more D2 receptors than patients who received treatment (*Neuroimage*, 29:662–6, 2006).

In early 2000, Seeman's son Bob pushed him to go beyond his university research. "Bob thought it was a good idea to start a drug company to complement over 40 years' worth of findings," says Seeman. So in 2001, Seeman started Clera Inc., which focuses on the discovery and development of novel small-molecule therapies for schizophrenia, psychosis, and Parkinson's, which target the D2 receptor.

The company first opened its doors in the MaRS incubator in downtown Toronto, and soon graduated to an independent facility based in Toronto and Vancouver. Since its inception, Clera Inc. has received $9 million in grant funding as well as an additional $5 million from private research support from major hospitals and pharmaceutical companies. The company currently employs 10 people and is working on 5 to 6 clinical projects, including new antipsychotics and Parkinson's drugs as well as compounds that reduce side effects of the current drugs. To cut costs, Clera struck a deal with hospitals and pharmaceutical companies to develop these drugs.

In 2004, Clera Inc. received the Promising Early Stage Company of the Year award from BIOTECanada, a nonprofit association dedicated to building a biotech- based economy in Canada.

"Starting Clera was extremely important because Seeman has such a depth of knowledge," says Gabriela Novak, a cell biologist at University of Toronto who was a postdoc in Seeman's lab for years. "He has the uncanny ability to synthesize work in the field and translate it into practical ideas ripe for drug design."

Seeman is doing exactly that. While dividing his time between Clera and the lab at University of Toronto, he found that the D2 receptor appears to alternate between two states—a high-affinity and low-affinity state. In the past 5 years, Seeman has found that the proportion of D2 receptors in the high-affinity state is elevated in animals that are super-sensitive to dopamine. When too many high-affinity D2 receptors exist, it can lead to psychotic-like behavior in animals (*PNAS*, 102:3513–8, 2005). Currently, Seeman is designing the first drugs to specifically target the high-affinity D2 conformation.

Clera Inc. is also designing drugs to diminish side effects caused by anti-Parkinson and antipsychotic medications. Parkinson's patients take dopamine-like stimulants, such as L-DOPA, to improve their muscle control, but excess dopamine can often lead to psychotic side effects such as delusions and hallucinations. Seeman's drug, taken in tandem with a daily dose of L-DOPA, binds to D2 receptors just long enough to prevent hallucinations but not so long as to impair the therapeutic function of L-DOPA. The drug is now being tested in nonhuman primates before entering clinical trials.

"Philip always had fantastic insight and wisdom into where the field should go," says Bertha Madras at Harvard Medical School.

Seeman not only wants to come up with new drugs, he also wants to use the old ones in more effective ways. For instance, he decided to explore how long certain drugs sit in the D2 receptors in order to prevent over- or underdosing. He found that clozapine, for example, is loosely bound and comes off the D2 receptor 24 hours after a dose is administered. Because the drug is so loosely bound, it is necessary for a patient to receive a high dose of about 350 mg per day to retain the antipsychotic effects of the drug. Haloperidol, like clozapine, quickly enters the brain within an hour or so, but unlike clozapine, it remains attached for many days. To prevent overdosing and related side effects, Seeman recently published his belief that it may only be necessary to administer haloperidol every second day to maintain antipsychotic effects and to not overload the brain with D2 blockers.

"These findings show that we would want to treat patients every second or third day with haloperidol to avoid side effects, whereas we could give doses of clozapine everyday," says Seeman.

Although Seeman has transformed antipsychotic research, he does not feel like his work is near done. "There will always be answers I haven't figured out yet," he says. Still, he's well equipped to pursue those answers. "I have not met another person who understands and knows the dopamine system better," says Madras.