PROC. N.S. INST. SCI. (2006)
Volume 43, Part 2, pp. 235-243

2005 NSIS Scientific Writing Award

RATIONAL DRUG DESIGN: A WINDOW INTO THE AMBITIOUS QUEST OF A NEUROLOGIST AND CHEMIST

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In the difficult world of drug discovery, two main courses of action are open: one is to screen extensive libraries of chemical compounds against hundreds of disease models; another is to acquire a detailed understanding of the molecules involved in a particular disease, and then rationally design compounds that can interact with or block those molecules. The first approach is favoured by large pharmaceutical companies, while the second is favoured by academics. This article illustrates the pursuit of this second approach by a Dalhousie University neurologist and chemist. Through interviews with this scientist and several of his colleagues, the article reveals the science of rational drug design, as well as some of the challenges and compromises involved in bringing discoveries to commercial stages.

Dans le monde difficile de la découverte de médicaments, il existe deux lignes de conduite principales : 1) analyser de vastes bibliothèques de composés chimiques à l'aide de centaines de modèles de maladies; 2) acquérir des connaissances détaillées sur les molécules en jeu lors d'une maladie donnée, puis concevoir de façon rationnelle des composés qui peuvent interagir avec ces molécules ou les bloquer. La première approche est la préférée des grandes entreprises pharmaceutiques, tandis que la seconde a la faveur du milieu universitaire. Cet article illustre un cas d'utilisation de la deuxième approche par un neurologue-chimiste de l'Université Dalhousie. Par le biais d'entrevues avec ce chercheur et plusieurs de ses collègues, cet article révèle la science derrière l'élaboration rationnelle de médicaments, ainsi que certains des défis qui se présentent et des compromis qui doivent être faits lors de la commercialisation des découvertes.

Among the small group of neurologists in Halifax, 'peculiar' can be taken as a compliment. So when lead neurologist Allen Purdy says his colleague Don Weaver is probably one of the most peculiar neurologists he's known, his voice is tinged with pride and awe. "You have to understand," Purdy explained. "He thinks in terms of molecular structures. I'm sure he dreams in terms of molecular structures. He sees things differently."

It's not just any molecular structure that dances around in Don Weaver's head at night. It's a breakthrough drug that prevents epileptic seizures, or reverses the memory loss of Alzheimer's disease. This drug may already exist in the files on his hard drive, or in one of the small vials in his labora-

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tory. The quest to find it and bring it to the people who need it will not be easy, but it will certainly be interesting.

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Today, in front of about a hundred first year science students, Don Weaver picks up a piece of chalk and turns to the blackboard. He is in his late 40s, but seems younger, with intense eyes, a small frame, and mostly brown hair, just slightly balding.

Weaver is a professor of neurology and chemistry at Dalhousie University in Halifax. He sees patients in the neurology division on Mondays and runs a drug design laboratory in the chemistry department the rest of the week. He can also, on occasion, be found in various other locations debating with philosophers, psychologists and even venture capitalists about the nature of the brain and the opportunities to design drugs for it.

Weaver steps back from the black board to evaluate his chalk drawing. It looks like the front of a house with two enormous tennis rackets coming out of the roof.

"I hope you appreciate how painful writing really is for a physician", he says. He explains that the tennis house is supposed to represent a drug called dilantin, and he's given it to many patients with epilepsy. He draws a dotted line around the right side of the house and indicates that's the part that prevents seizures. He then draws another dotted line around the bottom of the house. "This is the part that causes your gums to grow down over your teeth," he says. "I get hate mail from dentists."

Weaver explains that it would be a fairly simple chemical procedure to remove the part of the drug that causes gum growth, while leaving that part that prevents seizures. Years ago, he brought this idea to a big pharmaceutical company. "Their attitude was 'Don't let the door hit you too hard on the way out, but please leave'," he says. The executives explained that it would cost so much money to put that new drug through clinical trials that they could never make their money back with sales. They might be able to make money with a blockbuster, but not from an old drug with different side effects.

Weaver has learned a lot about the pharmaceutical industry since then, and he's not giving up. In fact, he is currently spending $4.2 million in government grants to build the Cheminformatics Drug Discovery Laboratory in Halifax. He's also busy looking for investors for a private biotechnology company.

Today at Dalhousie he approaches the risky reality of drug design with a grim sense of humour. "Most drugs die on the way to the target," Weaver tells the students. "Or they make you die. Either way it's a negative patient outcome."

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Growing up in North Bay, Ontario, Don Weaver always said that if he couldn't be a hockey goalie, he wanted to do practical science. He turned out to be a terrible goalie so he went to medical school and became a doctor at the young age of 23. In 1980, Weaver started his neurology training at Queen's University in Kingston. He liked to joke that all the other doctors wished they were neurologists; but the truth was, he began to feel that all neurologists did was prescribe decades-old mediocre drugs with absolutely no idea how or why they worked. The epilepsy drugs in particular, had terrible side effects and often didn't work.

When Weaver looked into it, it turned out that every single epilepsy drug had been discovered completely by accident. One drug, phenobarbital, had been known for hundreds of years as a sedative until 1912 when a German doctor, fed up with his patients disturbing him at night, gave them this sedative and found that it stopped their seizures. Another drug, valproic acid, was discovered in the 1960s when a young French chemist dissolved his experimental epilepsy drug in a common laboratory solvent that turned out to be more potent than the compound he'd spent months synthesizing.

Although Weaver had always wanted to do practical science, in 1981 he began to suspect that the most practical thing he could do would be to quit his neurology training and try to make new drugs. He applied to chemistry departments across the country and most of them thought he was crazy, especially since he didn't have an undergraduate degree (he'd gone straight into Medicine after just two years of university). The only school that would accept him into a doctoral program was Queen's. As a result, Weaver has a PhD in chemistry without an undergraduate degree.

Weaver's first drug design strategy was to make small chemical changes to old epilepsy drugs, hoping that some of the new compounds would be better than the old ones. This was the most popular drug design strategy in the early 1980s. But as robotics technology became more sophisticated, the big pharmaceutical companies spent millions of dollars creating random libraries of chemical compounds. Then as today, their main strategy was to screen robotically these compounds against hundreds of disease models. "You've got six million molecules, so one of them has got to work," is how Weaver describes this approach. It can work, but only for disorders that can be modeled in a test tube. Epilepsy is not one of these.

In the mid 1980s, as biologists learned more about the molecular nature of disease, chemists, including Don Weaver, started dreaming of rational drug design. The goal was to figure out the molecular structure of proteins involved in diseases and then use computer models, theoretical chemistry and human intuition to design novel molecules that could interact with those proteins. A computer-designed drug could be tested and optimized using software, but eventually it would have to be constructed from chemicals in the laboratory and tested in the real world. Weaver describes this approach as elegant, attractive and cheap, but horrendously time-inefficient. He says pharmaceutical companies have largely abandoned it to academics while they screen robotically their random libraries.

Besides its elegance, rational drug design holds another lure for academics: it both requires and leads to an ever more intimate understanding of disease. In this way, designing drugs for epilepsy could be the exercise that leads to an understanding of what is probably the most mystifying structure in the universe: the human brain.

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Allen Purdy, a trim man with grey hair and glasses, peers at me across the large stack of papers that covers his desk in the neurology division of the Halifax Infirmary. In 1985, Purdy was a staff neurologist when Don Weaver arrived at Dalhousie to complete his neurology training after finishing his PhD in chemistry.

"When he was a resident," Purdy tells me, "he would think of molecular structures and how he could use quantum physics and other mathematical models to design drugs that would dock and produce effects... It's totally different from most discovery models for epileptic drugs."

Purdy remembers Weaver as 'peculiar', but also as 'bright' and 'funny'. "Every comment made about how good he is," says Purdy, "which is true, he is, is always balanced by either a laugh or a smile or a statement that makes you realize he's up to no good."

After finishing his neurology training at Dalhousie in 1989, Weaver returned to Queen's for 12 years. While he was a professor there (in the chemistry and neurology departments), he also became the president of Epilepsy Canada, won a Financial Post 'Top 40 Under 40 Award' and helped found several drug design companies. One of these companies, Neurochem Inc. of Montreal, now has a drug for Alzheimer's in the last phase of clinical trials.

With Purdy's encouragement, Weaver came back to Halifax in 2001 and has been practicing his unique style of molecular neurology here ever since. This style has its advantages: once, Weaver accused a patient of not taking his seizure pills until he brought the pills to his chemistry laboratory and found they were ruined by the moisture in the bathroom cabinet. Another time, acting on a patient's hunch, he found that a chemical in black liquorice could act as a trigger for seizures. For Weaver, every neurological observation has a chemical explanation, and the insights gained from these connections supply the intuition needed for drug design.

Today in his crowded office, Purdy leans back in his chair and sips the Tim Horton's coffee his secretary brought in. He says Weaver has a desire to deconstruct the brain, but it's balanced by an awe of its complexity. "His balance is basically that he understands he's up against something more difficult and profound that just a bond between two molecules." Purdy says he's up against the greatest philosophical question of all time, which is trying to understand the brain. "Don has the kind of mind that likes to follow that road because there will be no end to it. The more he learns the more there will be to learn."

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Much of the legwork in this quest falls on Chris Barden, a young scientist designing drugs in Don Weaver's chemistry laboratory. There are five computers in Chris Barden's office but he tells me it's more like eight because one of them is so big it should count for at least three. He calls this big computer "the workhorse," as he flips off the front panel, revealing a dozen thin purple blocks he calls hard drives. In a lecture to the chemistry department, Barden later says his computer has two terabytes of memory, and it worked for several months straight on one of his projects.

Only two of Barden's computer screens are on right now. One displays what looks a little like a sprinkle doughnut rotating around in black space. Barden explains that thousands of these doughnuts are embedded in the membrane of every neuron in the brain. The hole in the middle of the doughnut is where a sort of electricity can flow into or out of the neuron.

The best scientific models of the brain say that thoughts and memories are somehow made up of the tiny electrical signals that pass from one neuron to another. The human brain has billions of neurons, and each neuron has many long fragile fingers that reach out to form trillions of connections. The sprinkle doughnut rotating on Chris Barden's computer screen is a model of one the electrical gates that controls the signals between neurons. Each sprinkle represents an atom and there are thousands of atoms, colour-coded like a rainbow on the black expanse of screen. The doughnut rotates around at different angles when Barden drags it with his mouse.

Epilepsy is a disorder characterized by an electrical short circuit in the brain. Instead of firing an electrical signal, and then waiting for a response, a rogue neuron will continue to fire over and over again; this chaos will spread to nearby neurons and eventually throughout the brain until the patient loses consciousness and possibly begins violent convulsions. In about a third of the cases, the seizures can be traced back to an earlier brain injury, but in most cases, no one knows what causes these short circuits. If the short circuit occurs in a part of the brain involved in vision, the patient may have hallucinations before a seizure. If it occurs in another part, the patient may hear voices, or recall a specific smell.

These doughnut shaped electrical gates may be the key to preventing a rogue neural firing from spreading throughout the brain. And with a click of his mouse, Barden can find the exact 3D location of any atom in the electrical gate. He can also figure out how strongly each atom is attracted to the one next to it. He even has a good idea which part of the molecule acts as a switch to open or close the gate. This, in particular, is a big help if your goal is to design a small molecule to prevent the spread of the electrical short circuit.

"Dr. Weaver provided a unique opportunity," says Barden, while rotating the doughnut around somewhat arbitrarily. "In this small circle of computational chemistry, there are probably only 30 jobs open worldwide. And really, what Don has here may be unique in the entire set-up of education

and further training in drug design." He's referring to the way his boss manages to combine the best from both academia and industry. They get public funding for research, but they also have every opportunity to commercialize their discoveries through industry. They have an open learning environment, but they work more toward patents than publications and as a result often can't discuss details of their research. They attend lectures by both chemists and lawyers.

"He has a curious sense of things," says Barden of Weaver. "He'll come into my office in the morning and say, 'Why is it that animals that are fed entirely on heavy water don't survive?' He had a rather provocative idea that water could act as a neurotransmitter. He'll be the first to say that his ideas may border on fantasy, but they lead to interesting discussions."

They also seem to lead, wherever Weaver goes, to new biotechnology companies. The latest one is called DeNovaMed, and its new headquarters are currently under construction on University Avenue in Halifax.

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On a sunny melting Friday afternoon in February, Chris McMaster squints out his window in Dalhousie's Atlantic Research Centre. He's trying to see if the construction crews across the street are making any progress on the Cheminformatics Drug Discovery Laboratory, the research facility that will also be the new headquarters of DeNovaMed. Scientists across the province and country will be able to use the laboratory's sophisticated computers and equipment to design drugs. Along with Don Weaver and David Byers, Chris McMaster is one of the founders of DeNovaMed.

We put our coats on and jaywalk across University Avenue, trying to avoid the slush. The new building fills prime space between the IWK Health Centre and a large five-story parking garage that was built recently beside the road. We walk into the Health Centre and up a couple of flights of stairs. Someone has wedged open the orange door that leads into the new laboratory, so McMaster eagerly offers me a tour.

The concrete floor is dusty and yellow insulation is still exposed, but there is already some demo office furniture in the corner by the door. Blinds are now drawn over the windows that cover two sides of the large room; one row of windows looks into the hospital lobby, while the other overlooks a roof, pierced by a blue glass pyramid-shaped sunlight. McMaster explains that eight drug design computers will be set up in front of these windows. He says they might convert one window into a door so they can have picnics on the roof.

While this is Don Weaver's fourth biotechnology company, it is a first for McMaster and Byers, both biochemists at Dalhousie University. McMaster explains that he and Byers came up with an idea for a new antibacterial drug several years ago, but they hadn't been able to do anything with that idea until Don Weaver arrived at Dalhousie in 2001.

"Here we had a perfect target, we thought, for an antibacterial," McMaster says of the initial idea, "and we could assay everything we needed to assay, but we didn't have a drug. Don was perfect for looking at protein structures, designing and synthesizing drugs in his laboratory. We set up a little marriage, got together and we showed him all the structures and all the data we had. People in Don's laboratory made twenty different compounds all based on an apparent structure, and we just hoped to death that they actually inhibited our enzyme and killed bacteria. And they did."

McMaster walks over to the row of windows that face the hospital lobby. He peeks behind the blind, and a woman in an office on the other side waves at us. He explains that although they are promoting DeNovaMed as an antibiotic company, Weaver's personal quest for neurologic drugs is also part of the plan.

"The venture capitalists don't want to fund the Alzheimer's and epilepsy projects," McMaster says, "because they're still too far removed from medicines that could actually be used to treat people, whereas the antibiotic projects are closer. We're actually at the point where it's just making drugs and testing them, with some drugs that already look promising." He says it's also helpful that antibiotics are usually taken only for a couple of weeks, so they don't require long-term clinical trials. With a neurologic drug that a patient might take for ten years, the cost of a clinical trial could easily be many times greater than for an antibiotic.

The DeNovaMed founders are hoping that Chris Barden will become the president of the new company, but nothing is official until they get some venture capital funding. Investors are wary because drug design is an extremely risky business.

"It's a big gamble," says McMaster, but he hopes the Cheminformatics Drug Discovery Laboratory will give them a head start.

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Cold February drizzle drips outside Don Weaver's window in the Dalhousie University Chemistry department. Two grey squeeze-toy brains sit on top of the computer monitor in his office. His mouse pad is a blue and pink cross section of brain. On the walls, anatomy posters mingle with Renoir prints and pictures of his two teenage boys.

Weaver sits in a small swivel chair and tells me why he's spent most of his career trying to understand epilepsy: "I was totally fascinated by the fact that people with seizure disorders are sitting there, and you're having a conversation with them, then they're unconscious for two minutes, and then they blink their eyes and they're back. As a medical student and as a neurology resident, I went, 'They have a lot to teach us!' You know, we can learn a lot on how the brain works and all the rest of it from people who have seizure disorders. So I became fascinated by that. And as I mentioned in the chemistry lecture, I sort of like to look at trying to understand the combination of brain and mind and consciousness."

Weaver is referring to a lecture he gave on the Chemistry of Consciousness the previous fall at Dalhousie's Open House for students and the public. He explained that the deepest mystery of all, to him, was how a three-pound sac of grey mush could give us emotions, memories and a sense of self-awareness – a sense of being conscious.

Weaver used the opportunity of this special lecture to tell the stories of some of his most fascinating patients. They were hard to forget. There was the man who saw a giant fireball bowling toward his head before every seizure. When the fireball got too close, he would duck for cover and lose consciousness. The patient was an intelligent man, and he recognized the absurdity of a fireball coming at him in the middle of his living room or the grocery store or wherever he happened to be. But in the end, he could never face it. In the end it was always real. Another patient heard Barney Rubble say 'Hello neighbour... What are you up to today Fred?' before every seizure. During the lecture I wondered why these particular memories were always linked to the onset of a seizure. Could one damaged neuron, the neuron that remembered a specific episode of the Flintstones, be responsible? What does this tell us about our seemingly intangible memories?

"If we really want to figure out how the brain works," Weaver had said, "human illness provides us with experiments of nature."

Unfortunately, new epilepsy drugs can't be tested in human experiments of nature. The only real models for the disorder are rats, and it is very difficult to give a rat epilepsy. The current protocols involve either gruesome brain trauma or poisoning; and it is a fine line between giving a rat epilepsy and killing it. Unlike antibiotics, there is no good model in a test tube. Weaver says there are no pharmaceutical companies designing drugs for epilepsy today. The potential sales are just not worth the cost of development and testing.

I ask Weaver how the he ended up in a company designing antibiotics when the brain has been his passion for so long.

"This is a business move," he says, "because the biotech sector has been burned a lot lately, and they want something that has a faster payoff. And it's easier to develop antibiotics just because the biological testing is faster."

Weaver is realistic about his options. "We want to get molecules that make it to people that cure diseases," he says, "and whether one likes it or not, the only way to do that is within industry. No government develops drugs. No university has the commercial means to develop drugs. The World Health Organization does not develop drugs. I mean the only group out there that develops drugs, is industry. And I mean you can have all these philosophical debates about it and that's fine, but as it currently stands in 2005 the only group that's going to get a drug to people is industry."

Weaver does not seem bitter at the compromises he's had to make. His goal is to develop drugs to treat neurological disorders, and he will do whatever it takes to get there. He says one of the most difficult decisions he had to make was to leave Queen's University for Dalhousie in 2001. He explains that several neurologists had left Kingston, and his responsibilities

in the clinic kept increasing to the point that he was barely in the chemistry laboratory.

Upon hearing that Weaver was leaving, a long time patient from Kingston wrote: "I had just gotten to the point where I felt I had properly trained Dr. Weaver to the quirks of my condition. More important, I had grown accustomed to his sense of humour." He later adds: "Don's leaving is more important to me than just another doctor leaving the area. You see Dr. Weaver saved my life. He was more than a neurologist to me. He was my advocate when I needed it, my cheerleader when I felt I could no longer carry on this battle."

The patient, Tim Eichholz, later tells me "I wish everyone could see him as a neurologist, but his goal is to develop new drugs. If five years from now, he develops a drug that stops all seizures, I wouldn't be surprised."

In lectures to the public and his students, Weaver always explains it the same way, and he does so once again in his office. "The way I always word it," he says, "is a practicing physician can help people one at a time. But you make a drug that has widespread application and boy, you can touch a whole bunch of people."