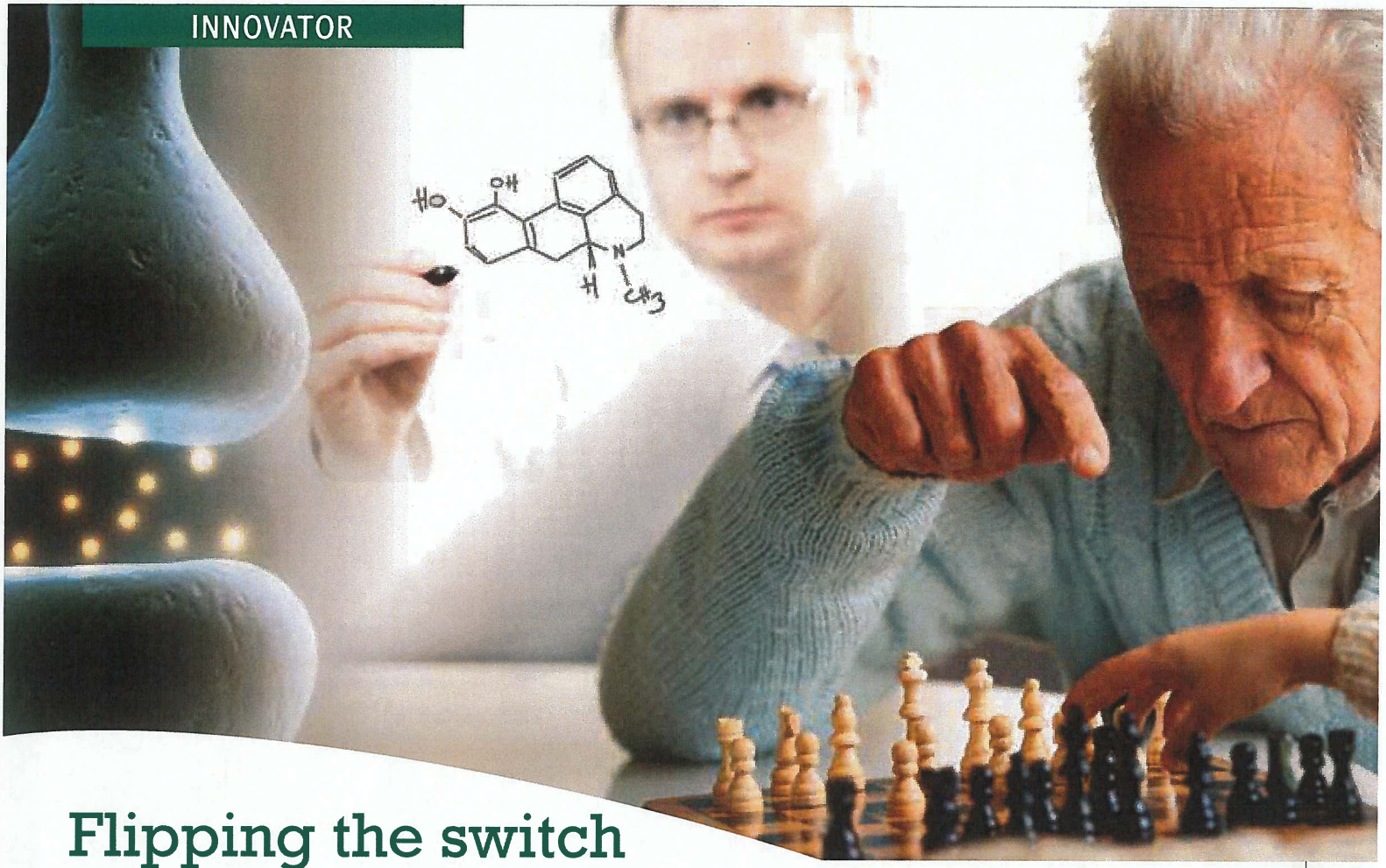


Flipping the switch in Parkinson's patients

FROM "OFF" TO "ON"

Anthony Giovinazzo, CEO and President of Cynapsus Therapeutics Inc.

Parkinson's disease, it affects more than one million people in the U.S. and approximately six million globally, with both figures expected to double in the next 15 years due to the effect of the aging Baby Boomer Generation. And for many sufferers of this chronic and progressive neurodegenerative disease, the loss of motor activity is just half of the struggle that they are burdened with. It's estimated that one quarter to one half of all people with Parkinson's disease also experience what are called "freezing" or "off" episodes. These episodes can occur between one and several times a day and last anywhere between 30 and 120 minutes per episode.

What is an "off" episode? It's a period of time during which Parkinson's symptoms re-emerge despite taking standard-of-care Parkinson's drugs. These episodes are relatively common in patients who use Levodopa (L-dopa), the gold standard-of-care for the disease. The episodes begin when during treatment L-dopa enters the bloodstream too slowly, or the dose is insufficient. While there is a rescue therapy available to patients via a drug called apomorphine, it too has its own set of complications. Specifically, its mode of delivery, injection, is both inconvenient and painful. It also can produce negative reactions, including irritation at the injection site.

Enter Canadian biotech company Cynapsus Therapeutics Inc., whose lead product APL-130277 may soon prove a viable alternative for the delivery of apomorphine.

Cynapsus CEO and President Anthony Giovinazzo explains, "What we are developing is an under-the-tongue thin-film strip system, similar to a Listerine® Breath strip, that a Parkinson's patient can easily retrieve, place under their tongue and is fast acting when an 'off' episode is starting, thus eliminating the requirement for injections."

With the administration of injectable apomorphine being cumbersome and painful, Giovinazzo believes his strip will allow for more widespread adoption of this effective

drug. The drug, apomorphine (which is not a narcotic or scheduled drug) has been approved in the U.S. for 10 years and in Europe for 20 years. Its rapid and unique efficacy has been known for a long time.

The strip, which dissolves in about one to two minutes, delivers the drug into the bloodstream in a similar time interval and concentration as an injectable dose, making it a more convenient and tolerable alternative. Moreover, as a sublingually delivered drug, Giovinazzo says it has the potential of treating a much larger group of Parkinson's patients.

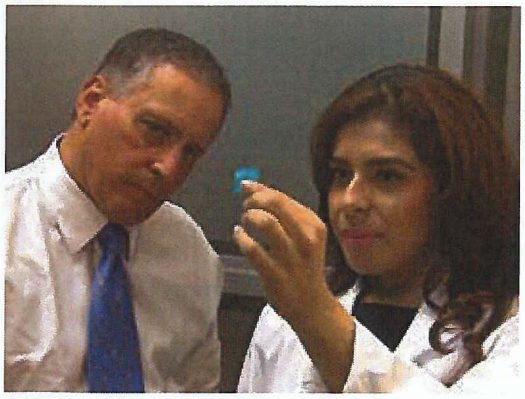
"Essentially, we're delivering the same drug unaltered but through an improved mode of delivery."

He adds that over the last 15 years, some 10 or more companies have tried to reformulate apomorphine in other ways, such as drops inside the nasal cavity, pumps, patches, pulmonary inhalers and suppositories, but all failed for two reasons.

"Firstly, they could not get enough of the drug into the bloodstream fast enough, and secondly they did not deal with the irritating nature of the drug," says Giovinazzo. "The choice to use a sublingual strip allows us to address both challenges."

Cynapsus acquired the rights to APL-130277 when it purchased Adagio Pharmaceuticals in 2011, but Giovinazzo's ties to the technology stretch further than that. He was a co-inventor of the original intellectual property.

For Giovinazzo and his two other initial co-inventors (they had worked for him in two other CNS companies, Cervelo Pharmaceuticals Inc. and Cita NeuroPharma Inc.) who each had had several years of experience in Parkinson's related drug development, the unmet medical need was obvious. Together, they had met several neurologist experts over the past five years, all of whom said that if a more practical solution to the delivery of apomorphine could be found, many hundreds of thousands and possibly millions of patients would benefit.



The drug APL-130277

One of the co-inventors was an MD from Europe who had worked in Parkinson's for several years at Novartis, the other was an American Ph.D. in formulation chemistry with 25 years of pharma experience. The three of them spent some 18 months together (with the costs borne by Giovinazzo's lines of credit and mortgages on his home) looking at everything the other companies and researchers had tried.

The invention team compiled a list of chemistry and delivery issues that would need to be overcome. The result was a complex multivariate set of problems that if the result was going to be protectable by patents (which today it is) would require a unique solution.

"The three of us all came to the same conclusion, that a sublingual thin film strip system just might do the trick," Giovinazzo recalls. "That led to the filing of the initial broad patents which were held by our private holding company Adagio Pharmaceuticals Ltd."

The decision to bring the technology to Cynapsus was personal, but it was also business driven in that it was urged by the company's investors.

"They essentially said if we're going to fund your company, we want the company to own all the rights going forward, so bringing the product in house was necessary," says Giovinazzo. "In doing so we substantially strengthened our hold on the product; we went from broad patents that claimed a whole area or field, to additional families of patents that are very specific to the formulations that we were developing."

It was a decision he hasn't regretted. The company has since examined APL-130277 in a number of prototypes, animal models and five clinical studies to date, with 110 subjects. Earlier studies confirmed its mechanical properties, dose proportionality and consistency of pharmacokinetics profile. The latest of which, CTH-105, is a Phase 2 trial (CTH-105) in Parkinson's patients that indicates the company is on the right track in achieving the goals of the technology.

Specifically, the multicenter open-label study assessed the drug in 16 patients with Parkinson's disease, and it was able to provide patients with a rapid improvement in motor function in as little as 10 minutes, lasting up to 90 minutes. In all, 14 of the 16 patients converted from "off" to "on" through the use of several different doses of APL-130277.

"I think this trial reinforced the market opportunity and our clinical and regulatory pathway for APL-130277," says Giovinazzo.

Likewise, the significant scientific milestone for the company was matched by an equally successful accomplishment on the financial side of the ledger in 2014. Namely, the company was successful with an oversubscribed financing of $25 million. Giovinazzo believes the successful financing is directly related to the interest shown by the clinical community in the merits of the technology and the small but highly effective team he has built.

That team is made up of an experienced Chief Medical Officer, Dr. Albert Agro, who Giovinazzo repatriated to Canada after several years of being in large pharma in the US and Europe; a Chief Scientific Officer & EVP Manufacturing, Dr. Thierry Bilbault, who left large pharma after 20 years of expertise in thin film development, manufacturing and some 50 + product launches; a Chief Financial Officer, Mr. Andrew Williams, with extensive experience in technology companies and capital management; a Senior Director, Clinical Development and Medical Affairs, Dr. Jordan Dubow, a US based movement disorder specialist neurologist who was at Abbvie helping develop Parkinson's related drug candidates; and a Director of Business Development, Mr. Nigel de Gruyther who is former pharmacist and sell side investment banking analyst.

In terms of the merits of the technology, APL-130277 was recognized as one of the "Top 10 Neurology Projects to Watch" by a joint selection committee. This award was based on an independent validation of the potential of APL-130277 by a group of independent U.S. CNS experts.

"They evaluated a number of companies in North America and determined that we were one of the top 10 that should be looked at by large pharma from a partnering or asset development perspective," Giovinazzo says. "Some of the rationale behind that was, there have been some validating transactions in the marketplace which have begun to corroborate the size of the potential market of 'off' episode [treatments] specifically."

In fact, the potential size of the worldwide market is likely in the range of $ 1 billion or more according to studies by the company, the Michael J. Fox Foundation for Parkinson's Research, investment banking analysts and others.

Moreover, it means a lot to have the largest not-for-profit foundation devoted to Parkinson's disease research in your corner. The Michael J. Fox Foundation for Parkinson's Research has expressed its faith in technology by providing two separate research grants to advance APL-130277 in clinical trials, one for USD$947,925 in 2012 and another for $500,000 awarded this past June. The process to apply for these grants included due diligence undertaken by scientists and medical

The Cynapsus Therapeutics Inc. team

practitioners who work inside the Michael J. Fox Foundation as well as an external review committee of world experts. In both instances, APL-130277 was deemed worthy.

In addition to the grants, the Foundation has also opened up its clinical trial database to Cynapsus, driving patients to the company's clinical sites—which was very helpful from a patient recruitment timeline point of view, says Giovinazzo.

"It's really a great partnership in that they've made a number of suggestions on what we do and how we do it, and they have been catalysts in helping us raise the money," he says. "As a funding mechanism, it's a great example of how not-for-profit organizations can effectively help industry move innovation forward. I think that having The Michael J. Fox Foundation Stamp of Approval was also significant in helping us leverage funds from the investor community."

Looking ahead, 2015 is a seminal year for the company as it embarks on completing its registration studies to enable a New Drug Application to the FDA in late 2016. The company believes that at a minimum the FDA (whom they will meet with in February) will require a bioavailability study in healthy volunteers, and efficacy and safety studies in Parkinson's patients. These studies are already in the works and are expected to be completed in 2015 through mid 2016.

"The bioavailability study will demonstrate that our strip is equivalent to a certain dose of the injection," he says. He adds that the company will also do an efficacy study of approximately 100 Parkinson's patients for somewhere between two and three months in active observation, and then we will do a safety study of about six to twelve months in length with about 100 to 150 Parkinson's patients.

"The purpose of that safety study is to demonstrate to the FDA that our film strip won't cause any greater irritation than the injection does and we're encouraged that it might in fact have lower irritation, because of the technical engineering that was built in to the strip to eliminate irritation—which is the real crux of [our] intellectual property *per se*."

Between the bioavailability study and the combined efficacy and safety study, Giovinazzo thinks Cynapsus is on the path for filing a new drug application sometime in late-2016.

The money we've raised from large sophisticated U.S. institutional investors in April of 2014, will provide the majority of the capital to reach that point."

He adds that company has also already spoken with the FDA, having done so three years ago, and is meeting them again this year in anticipation of filing an NDA by late 2016.

That said, Giovinazzo says the company may still explore the option of an exit via a licensing deal or sale to an interested third party. On that front, he is encouraged by the recent string of lucrative deals related to Parkinson's disease products. He cites two transactions in particular that bear watching as comparable for Cynapus: the purchase of Civitas Therapeutics and the worldwide rights to CVT-301, a Phase 3 treatment candidate for "off" episodes of Parkinson's disease by Acorda Therapeutics, Inc. for $525 million in cash; and Lundbeck's $658 million acquisition of Chelsea Therapeutics International, Ltd. and its Parkinson's disease-related blood pressure drop product, Northera.

"Both transactions set very serious comparable values. Like us, Civitas Therapeutics completed its Phase 2b study, issued their data and Acorda decided to pay $525 million cash up front to purchase them. In their case, they deliver levodopa and not apomorphine, and they deliver it through the lungs. They hope to deal with at least two of the four different types of 'off' episodes, whereas apomorphine deals with all four of them. On that basis, that $525 million implies a two-times value for Cynapsus. We believe that sets the floor and the global value of our company should be closer to a billion if APL130277 obtains FDA approval."

The other transaction saw Lundbeck, a very large specialty pharmaceutical company focused in CNS, acquiring American public company Chelsea for $530 million cash up front, and another $128 million in what's called contingent value rights for the company.

"They're also in the Parkinson's field in that their drug Northera deals with what's called blood pressure drop," says Giovinazzo. "This condition affects 10 to 15 per cent of all Parkinson's patients. This is significant in that the number of Parkinson's patients that drug helps, is about half the number of Parkinson's patients that apomorphine addresses. So again I believe we're looking at a two-time value proposition. Of course they had FDA approval for Northera, so the comparable would be in two to three years time."

In preparation for just such a scenario, Giovinazzo has already done his own due diligence to assess whether APL-130227, once approved, can gain a foothold in the market.

"We have been somewhat of an unusual small biopharma company in that over the last five years, regarding the APL project, we have undertaken a number of surveys by consultants of 775 neurologists in North America, Europe and several other major countries in the world. We've also interviewed and surveyed 14 of the largest payors in the U.S. and likewise we've had direct surveys and interviews of 37 Parkinson's patients in the U.S. The purpose of these surveys and interviews with the neurologists was to determine what they saw was the opportunity with APL-130277, and would they favour a sublingual strip of apomorphine over the injection. The payors we surveyed because we wanted to understand what the reimbursement issues might be, if any, and what their price elasticity relative to the injection would be. Lastly, our survey of patients was critical because we wanted to get firsthand knowledge of what their experiences had been with these off episodes. We wanted to know if they were important enough to treat, and would the availability of a strip as opposed to an injection make a difference to them."

As Giovinazzo explains, the business of biotech should go beyond just developing a drug. It's about gaining market intelligence and thinking bigger and beyond development.

"Through these surveys, we have to have raw data that is credible, that supports how we would penetrate the market; how we would approach doctors and payors and make sure we understand how to articulate that not just for our own purposes, but also to potential partners such that they understand the market."

In essence, he's already answered the question of who's going to pay how much for the drug, and has a firm grasp on the clinical value of the drug to the patient and the physician.

It's all shaping up for what could be a milestone year for Cynapsus in 2015 as the company embarks towards continued success in Phase 3 trials.

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