BRIGHTER FUTURES

FOR PATIENTS, RESEARCHERS, AND INVESTORS

COLLABORATION BETWEEN RESEARCHERS AND INDUSTRY WILL BRING NEW THERAPEUTICS TO MARKET AND STIMULATE FUTURE EXPLORATION OF BRAIN AND NERVOUS SYSTEM DISORDERS.

left to right Bill Gantz, Norbert Riedel, Joe Moskal

JOE MOSKAL REMEMBERS WHEN IT ALL BEGAN.

He was wearing jeans and sneakers working as a senior staff fellow at the National Institute of Mental Health's Intramural Research Program, developing molecules and monoclonal antibodies to use as probes to understand neural pathways of learning and memory.

After injecting the antibodies into an animal model, Moskal experienced a major breakthrough in his research. The animal models acted exactly as he predicted they would.

"I wanted to see if the antibody would stimulate learning and memory," Moskal said, "and it did. The injected animal learned twice as fast as the controls. This was a real, functioning mammal that was truly learning."

That was 1983. Over the next 30-plus years, that original spark of an idea became the focus of a research group headed by Moskal at Northwestern Engineering. It developed into a novel antidepressant with promising results, spawned a startup called Naurex Inc., and serves as a platform for even more promising pharmaceuticals. Now, at last, it stands at the brink of bringing relief to those who need it most.

THE WAY FORWARD

This past summer, Allergan, a large pharmaceutical company, acquired Naurex for a $560 million upfront payment, paving the way for the promising antidepressant programs to proceed into late-stage clinical trials and eventually enter the market. Under the terms of the all-cash transaction, there is potential for additional success-based research and development and commercial milestone payments.

The transaction caps decades of neuropharmaceutical development in the laboratory and seven years of business development by a team with many Northwestern Engineering connections. The transaction structure also results in a new spin-off company that will allow Moskal, distinguished research professor of biomedical engineering, and his colleagues to continue discovering and developing novel modulators of the NMDA receptor and innovating with that technology to discover new therapies for brain and nervous system disorders.

"We finished proving these molecules have dramatic potential through much of the early clinical work," Moskal says of the Naurex drug candidates acquired by Allergan, rapastinel and NRX-1074. "Now it's time to hand these important therapies to a capable party with the necessary large resources—and to focus on repeating this innovation with our proven team and technology."

A NEW PATH FOR TREATMENT

According to the National Institute of Mental Health, major depression is the second leading cause of disability in US adults, affecting as much as 10 percent of the population.

Rapastinel (previously called GLYX-13), Naurex's fast-acting drug candidate for major depression disorder, has shown unrivaled success in Phase I and II clinical trials: It takes effect within hours of a single dose, and one dose can last for one to two weeks without any serious side effects. Last year, the intravenous injectable drug received the highly coveted fast-track designation from the Food and Drug Administration, a classification given only to drugs that demonstrate superior effectiveness and safety.

With rapastinel now approaching Phase III clinical trials, the company's second antidepressant drug, NRX-1074, has shown similar success. It is now in Phase II clinical trials and will be available in an orally deliverable pill. Because they work differently from other antidepressants, rapastinel and NRX-1074 could provide much-needed therapeutic alternatives for the 30 to 40 percent of patients who are unresponsive to currently available medications.

Photograph by Chris Strong

"IT CAN BE A CHALLENGE TO TURN RESEARCH INTO A FULLY FUNCTIONING COMPANY. BUT WHAT'S WONDERFUL ABOUT JOE IS HIS CURIOSITY, WHICH EXTENDS NOT ONLY INTO SCIENCE BUT INTO BUSINESS AND HOW THINGS WORK COMMERCIALLY." **BILL GANTZ**

"Patients often go from one therapy to another to another," said Naurex president and CEO Norbert Riedel. "One treatment might work for a short time, but then they have to start all over. Meanwhile, they are burdened with all sorts of side effects that interfere with their quality of life."

Both rapastinel and NRX-1074 work by targeting the brain's NMDA receptors, which are involved in learning and memory mechanisms. This is a markedly different approach from current, widely used antidepressants that instead increase serotonin levels.

While rapastinel and NRX-1074 are not the only drugs to target NMDA receptors, they are potentially the safest. None of the clinical trial subjects thus far have experienced serious adverse side effects related to the drugs. By contrast, other drugs on the market and in development that target these same NMDA receptors with a different mechanism of action can cause hallucinations, nausea, insomnia, and even psychotic episodes.

Moskal posits that, unlike most other NMDA receptor-targeted drugs, rapastinel and NRX-1074 do not block the receptor's ion channel, which may be the reason they don't have the same side effects. "Fundamentally, we have found the key to unlocking the way to modulate this receptor to restore normal brain function," he said.

MODEST BEGINNINGS

After those jeans-and-sneakers days at NIMH, Moskal joined Northwestern University in 1990 and founded the Falk Center for Molecular Therapeutics with the goal to translate discoveries into clinically useful compounds. There, he advanced his research with the successors to his early work with large monoclonal antibodies—smaller molecule derivatives that he suspected might get into the brain and have therapeutic potential. GLYX-13, now called rapastinel, was one of them.

With the goal of bringing his therapeutics to market, Moskal founded Naurex in late 2006 and started raising meaningful seed funding in 2008. It was the fourth company to grow out of his research, but the first to deliver on its hoped-for promise. He credits some of the success to Northwestern's supportive culture of innovation, which enabled him to work alongside students and world-class researchers while developing a business. Those who worked with him readily acknowledge that much of the success has come from Moskal's unflappable determination and resilience.

"If you're going to be in this business for 30 or 40 years, you're going to experience failure," he said. "For me, failure never felt like failure. It was just a different kind of data."

BUILDING THE RIGHT TEAM

In 2011, Naurex raised $18 million in financing, jumpstarting momentum for the company. That attracted the attention of Bill Gantz and Norbert Riedel, both veterans of the pharmaceutical industry and members of Northwestern Engineering's McCormick Advisory Council. At the time, Gantz was on the board of Adams Street Partners, a private equity firm that invested in Naurex. Riedel was the corporate vice president and chief science and innovation officer at Baxter International, where he developed Baxter Ventures in 2011 with a goal to invest in startups. One of the fund's first grants went to Naurex.

Convinced that Moskal and his team had discovered a breakthrough treatment for depression, Gantz and Riedel joined Naurex motivated also by their confidence in Moskal himself. Described by Riedel as "a bundle of energy," at age 65, Moskal, who talks fast and laughs easily, shows no signs of stopping.

"It can be a challenge to turn research into a fully functioning company," Gantz said. "But what's wonderful about Joe is his curiosity, which extends not only into science but into business and how things work commercially."

With the right team in place, Naurex became virtually unstoppable. Prior to the acquisition by Allergan, the company raised $163 million of venture funding and investments, with $80 million of the total coming from just one round of financing in November 2014.

AN EVEN BRIGHTER FUTURE

Moskal and his team are now poised to continue innovating in new disease areas with their spin-off company, Aptinyx Inc., which will move forward with the discovery engine and early-stage programs started at Naurex. For example, they have found that the NMDA receptor is involved not only in depression but in many other central nervous system disorders as well. Aptinyx will work to discover and develop other small molecules that modulate the same receptor to treat a wide array of debilitating diseases and disorders of the brain and nervous system, which Moskal says have few effective treatments and are "ripe" for his compounds.

"Joe's research has opened a whole universe of understanding brain conditions where the same master switch is either involved in the normal physiology of the brain or involved in helping trigger the disease," Riedel said. "If we now take a small molecule and administer it to models of many brain and nervous system conditions, we see striking therapeutic benefits in all instances."

AMANDA MORRIS

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JOSEPH MOSKAL

Distinguished Research Professor of Biomedical Engineering
Director of the Falk Center for Molecular Therapeutics