Analgesic R&D

There is a considerable need for novel analgesics that are more effective or safer than existing drugs. Richard Silverman highlights some of the research that led to the discovery of a novel analgesic drug, while Bob Rappaport discusses his role in the regulation of analgesic drug products.

Richard B. Silverman, Ph.D., John Evans Professor of Chemistry, Northwestern University, Evanston, Illinois, USA.

Although many valuable pharmacological tools have been discovered in academia, it is rare for such compounds to make it all the way to becoming a drug. Richard Silverman, the John Evans Professor of Chemistry at Northwestern University, USA, has the distinction of having discovered such a compound, the drug pregabalin (Pfizer). Pregabalin is approved for the treatment of neuropathic pain, epilepsy, fibromyalgia and, in Europe, for generalized anxiety disorder.

Inspired by exposure to the explosive power of chemistry sets as a child, Silverman decided to pursue studies in chemistry. Following a Ph.D. in organic chemistry at Harvard, USA, and postdoctoral research on enzyme inactivation at Brandeis University, USA, he joined Northwestern in 1976 as an assistant professor of chemistry. At the time, the job climate for his area of organic chemistry was very limited in the US, with only six possible places to apply, but Silverman has never regretted his choice: "[Northwestern] has been a fantastic place to do science and to teach. I don't know of a more collegial and stimulating environment to spend your career."

There, he began research on GABA (γ-aminobutyric acid) metabolism in the early 1980s, initially focusing on designing and studying the mechanism of GABA aminotransferase (GABA-AT) inactivators that could increase levels of GABA in the brain for the treatment of epilepsy. It was imperative that these compounds did not inhibit L-glutamic acid decarboxylase (GAD) too, an enzyme that converts L-glutamate into GABA. So, in 1989, Ryszard Andruszkiewicz, a scholar visiting Silverman's group, was asked to synthesize a series of compounds that could potentially bind to GABA-AT but not to GAD. "A surprise came when we found that the compounds we were studying activated GAD, which I thought might be a potential new mechanism for increasing GABA levels in the brain," says Silverman.

Tests in animals indicated promising anticonvulsant activity, and Parke–Davis (now Pfizer) pursued the clinical development of the best compound — pregabalin — which was granted regulatory approval in 2004.

There was still one surprise to come though: it has now been shown that the drug's therapeutic activity is related to its binding to a specific calcium-channel subunit, rather than any direct effect on the GABA system.

Now the John Evans Professor of Chemistry, Silverman balances two chemistry courses each year with his research, as well as serving on journal editorial boards and on the scientific advisory board of two companies. He finds teaching and being involved with research students most fulfilling, particularly when students test his research ideas. "It's rewarding when the ideas work," he says. Fitting all this in uses what Silverman feels is the most important lesson he has learnt — time management — to also ensure he always got home for dinner with the family during the week. "I could have gotten a few more publications if I skipped the family interactions, but it wouldn't have been worth it."

For academic researchers working on projects that have the potential to lead to drugs Silverman advises a tenacious approach. "Continue to hypothesize and to test hypotheses with controlled experiments, then search for rational explanations for unusual observations. If all else fails, maybe you can just get lucky!"

Bob Rappaport, M.D., Director of the Division of Anesthesia, Analgesia and Rheumatology Products in the Center for Drug Evaluation and Research at the FDA, Rockville, Maryland, USA.

When Bob Rappaport joined the FDA division that evaluates analgesic drug products, he discovered that the field was decades behind most other drug development areas. Since then he has worked with numerous talented physicians and scientists inside the FDA, as well as from academic institutions and the pharmaceutical industry, with the aim of advancing the field.

"We have had to reassess the entire paradigm for analgesic drug development from the appropriate animal models to the clinical trials — not to mention the development of risk-mitigation strategies to address the significant toxicities and high abuse potential associated with many of these products," says Rappaport.

Analgesia has been an interest of Rappaport's since he attended the George Washington University School of Medicine and Health Sciences, USA, where he first witnessed the inadequacy of the available drugs to manage pain. Following further clinical training and a position as an assistant professor of neurology at George Washington University Hospital, he joined the FDA in 1994 as a primary reviewer of neurology drugs. However, he soon wanted a broader perspective on the regulatory process and a better understanding of drug development. "When I was offered the opportunity to move to the division that reviewed analgesic drugs as a Clinical Team Leader, I immediately accepted," he says.

Currently, as Director of this Division, Rappaport leads a large team whose responsibility it is to oversee the investigation, development, approval, continued safety and safe use of drug products to treat pain, rheumatological disorders and addiction, as well as drug products used in the setting of clinical anaesthesia. "Our decisions are ultimately based on a risk-to-benefit analysis that must consider the value of a drug to patients and public health, the adverse effects of the drug and the specific needs of the patient population targeted for use of the product," he says.

It is the risk–benefit analysis that Rappaport finds most challenging, particularly for opioid analgesic products. He explains: "I have struggled for 10 years to find the right balance for these products; one that would maintain availability for legitimate patients while reducing their misuse and abuse. We have made incremental advances but remain far from achieving that balance."

Given this challenge, Rappaport's reward is knowing that what his team does has a profound impact on the public. Keeping this in mind also helps Rappaport when he is faced with the challenges associated with regulating new products. "If I strongly believe in something, whether it's the correct way to analyse the results of a clinical trial or the best way to lead a group of people to a successful project outcome, I can overcome the obstacles… not because I'm smarter or more powerful, but because I have maintained a logical approach and put people first."

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