

# Deciphering the Brain

*Elizabeth C. M. de Lange has dedicated her life to brain research to improve brain therapies.*

By Linda C. Brown

Elizabeth Cunera Maria de Lange, Ph.D., is head of the Target Site Equilibration Research Group of the Division of Pharmacology at the Leiden Academic Centre for Drug Research in the Netherlands. She is an active member of the American Association of Pharmaceutical Scientists (AAPS), and was designated as AAPS Fellow in 2013 for her research into preclinical approaches for predicting drug effects on the central nervous system (CNS). She shared some accomplishments that are of particular importance to her career:

## AAPS FELLOW

De Lange's designation as an AAPS Fellow means a lot, "It stands for having made sustained remarkable scholarly and research contributions to the pharmaceutical sciences. I am touched by the wonderful efforts and letters of my American colleagues, and I am very grateful for their recognition and support. For almost 25 years, I have been working on microdialysis, believing in the added value of direct experimental measurement of target site concentrations in mechanistic understanding of the dose-concentration-effect relationship and the resulting dose optimization."

"The gathering of multilevel CNS microdialysis and other sampling data from individual animals is highly complex and demanding, and advanced sample analysis is needed to analyze all small-sample-low-concentration samples," she says. "The road of model development for combining all these data is long and winding. This is not typically a high-frequency publishing approach, but this approach has led to two recent major successes in prediction of human brain concentrations and CNS-mediated effects. I am more than convinced that this will



considerably improve our insights for better CNS drugs and treatment."

"Apart from striving toward reduction of the use of animals and the fact that animal models of CNS diseases will never exactly reflect the disease conditions in humans, I am convinced that we will move forward considerably by systematic research on CNS drugs," she says. She compares it to the game Mastermind. "In this game you have to systematically and strategically vary the position and colors of the pins (variables) on different turns to decipher the code. Of course, the dose-effect relationship of CNS drugs includes many more variables, so it is much more complex. Because our brains do not have the capacity to integrate all these, we need to organize, condense, and store knowledge in mathematical frameworks."

## ANNUAL COURSES ON THE BLOOD-BRAIN BARRIER

With her Swedish colleague Margareta Hammarlund-Udenaes, Ph.D., from Uppsala University, de Lange presents annual courses

on the blood-brain barrier (BBB) in CNS drug development. "We just had our fourth annual course. It is a joy to lecture and discuss in-depth all issues that come with principles, transport kinetics, diseases, and methods to provide the insight in what factors or combination of factors impact CNS drug development. Without exception, the participants have rated these courses extremely high," de Lange says.

## HOPES FOR THE FUTURE

While de Lange wants to accomplish many things, one of her research-oriented goals is to contribute significantly to improving CNS disease treatment modalities by high-impact, predictive, CNS drug research. From a personal perspective, "I want to be a strong and wise person who can inspire others and likes to be inspired by others."

## LEADERSHIP PHILOSOPHY

"There are many types of leadership," de Lange says. "I believe a true leader is able to adequately switch between leadership types according to the needs of a situation. So, a flexible and dynamic leader is what I aim to be. I love interaction with my group, and I set my leadership mode according to the level of capability (actually, just a little bit higher) of an individual or the subgroup(s), and I strive to be stimulating. I have a clear opinion and love to be challenged with good arguments. This approach works well, provided that the team members are motivated and hardworking, which is usually the case. So I am blessed."

De Lange believes that good leaders should have a vision and a clear goal in mind, one they are contagiously passionate about. "A good leader should guide in a natural way and should care about and take care of the individuals of the group and the group as a whole," she says. "A good leader wants to

achieve a situation in which all group members win. I believe that this is very stimulating and inspirational.”

### LIFE'S LESSONS

De Lange's parents had a very positive view of humankind. “They were convinced that, in essence, everyone is good and wants to be good to others,” she says. “I have always been thankful for such a positive perspective. After finishing my education, I entered and approached the world with that viewpoint. However, things sometimes got mean out there. Some people indeed are good and aim for a win-win situation, while others think mostly about their own wins and might undertake holding you back. I have experienced both—stimulation and frustration. At a certain point, I decided I could not be defeated. Also, I promised to refrain from bad practices. I thought that if I, as a consequence, did not survive that way, it was not meant to be. (I am still around and doing well, so it *is* possible, luckily.) Interestingly, headwind has caused me to grow and made me more determined. In that sense, it has also helped me! I admire those who allow others to grow and be successful. They are the true diamonds of the world.”

### ACHIEVING SUCCESS

De Lange credits her “just do it” attitude for her accomplishments. Together with Hammarlund-Udenaes, she initiated a series of international symposia on microdialysis in drug research and development in 1998. She says, “It was a real adventure and turned out very well. We started a community of quantitative microdialysis researchers and friends that still exists.” She also believes that success comes from being determined, hardworking, and able to prioritize.

### GREATEST INFLUENCE

De Lange's parents influenced both her career choice and her outlook. They unconditionally supported her lifelong interest in science and encouraged her to pursue her own interests. “I have always been a very curious person—my main question was ‘why?’” she says. “I like to decipher and discover, and the brain has always fascinated

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me. This intriguing organ houses the steering of—and feedback on—all of our functions. It also makes us the way we are; it governs our personality. Sadly, quite a number of brain diseases change brain functioning so that the patient as well as his or her social environment may witness and have to deal with an alteration of the patient's personal identity and decline of abilities.” This combination led her to be dedicated to brain research and instilled a wish to improve brain therapies.

De Lange also credits several scientists who helped guide her career. She appreciates her colleagues at Leiden University—Douwe Breimer, Ph.D., and Meindert Danhof, Pharm.D., Ph.D.—and Hammarlund-Udenaes from Uppsala University, who have shared their inspiring scientific vision and support. Hammarlund-Udenaes was the one who introduced her to AAPS. She adds, “I would also like to mention my husband, whose strategic insights have been and are indispensable.”

### ADVICE FOR STUDENTS OR POSTDOCS

When advising students, De Lange refrains from giving direction, believing the choice on what career path to follow really depends on the individual. She'd rather say to a student: “I believe that your personal attitude will make the difference. Be brave, follow your heart and passion, remain faithful to yourself, and stick to your deepest convictions. Be good to yourself and others. Don't be afraid to fail; if you fail, just stand up and try again. Also realize that achieving goals takes

investment and focus. The higher the goal, the larger the investment, so you need to be willing to give up other things that you might like (so prioritize!). Your contribution is unique, and we need all kinds of people to make the world go round.”

### VOLUNTEERING WITH AAPS

“It is through AAPS that I have been able to experience leadership,” de Lange says, “from chairing the Microdialysis focus group to chairing the Pharmacokinetics, Pharmacodynamics, and Drug Metabolism section and now as Annual Meeting Program Committee chair for 2014. AAPS' turnover system makes it possible for all members to volunteer and to be recognized as potential valuable leaders. The turnover results in a continuously changing composition of teams, whereby the teams remain fresh. Because we are all different people with different skills, a multifaceted training in leadership like in AAPS is of high value; different leadership styles may blossom under different conditions. For me, in an environment totally different from my daily work, AAPS has provided opportunities to grow and helped me a lot.”

### THE JOURNEY SO FAR

“I am very grateful for what I have been able to achieve today,” de Lange says. “I have never thought in milestones, just on where I wish to go. And if you would ask me if I am heading where I wish to go, the answer is yes.”

*Linda C. Brown is the AAPS managing editor.*