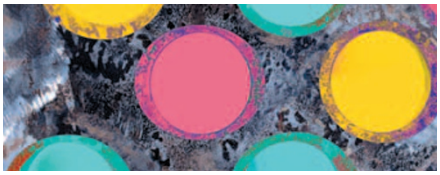
Assay development



High-throughput screening is a core technology in drug discovery. This month, we feature two people who have been in the field since its inception: one developing assays at a pharmaceutical company and one from a company developing the technologies involved.

Thomas D. Meek, Ph.D.
Vice President, Biological Reagents and Assay Development, GlaxoSmithKline, Collegeville, Pennsylvania, USA

Tom Meek's interest in chemistry and biochemistry may be traced back to the arrival of James Bond and *The Man From U.N.C.L.E.* in the early 1960s. With the 10-year old Meek setting out to recreate the poisonous gases favoured by such secret agents in a makeshift basement laboratory in his parents' house, his family was soon distinguished as the only one in its neighbourhood that would bond on the front lawn coughing following another successful production of chlorine gas.

This early curiosity about the effects of chemicals led to Meek completing a degree in chemistry a decade later at the University of Virginia, USA. During these studies, he developed a more directed interest in how small molecules are recognized by enzymes, and how enzymes generate their remarkable catalytic power. "In 1975, I talked myself into pursuing enzymes as targets for drug discovery as a career goal, while I was trying to convince a classmate of mine that the pursuit of a graduate degree in chemistry could do the world some good, by making drugs and so forth," recalls Meek. "I wonder if Stuart Schreiber remembers the conversation we had then!"

Meek then pursued this interest and his Ph.D. in organic chemistry in the laboratory of Joseph Villafranca at Penn State University, USA, in which he completed detailed pre-steady-state and steady-state kinetic analysis of the glutamine synthetase of *Escherichia coli*. He also synthesized and characterized amino-acid analogue inhibitors of this enzyme, which further strengthened his ambition to pursue a career involving the identification of enzyme inhibitors as potential drugs.

The early 1980s was a good time to be interested in this topic. Encouraged by the success of angiotensin-converting enzyme inhibitors for the treatment of hypertension, pharmaceutical companies were then seeking enzymologists. Meek took a position at the SmithKline and French laboratories in Philadelphia, USA, under Brian Metcalf, where he was given the opportunity to set up an enzymology laboratory. "There, I was involved in the development of specific, rationally designed inhibitors of HIV protease in the late 1980s, comprising perhaps the the earliest work demonstrating their potential as anti-AIDS therapies," says Meek. "Back then very few people thought that an inhibitor of this newly discovered aspartic protease had a chance of becoming an orally bioavailable drug, but nearly two decades later, these are important therapeutic agents."

Since then, Meek has held numerous other positions at GlaxoSmithKline, and is currently the Vice President of Biological Reagents and Assay Development, a multinational department that produces cell lines, purified proteins and their attending assays to feed GSK's pipeline. "A consistent theme though has been the adaptation of assay methodology and technology to compound screening and profiling, which has its origins in 'quantitative biochemistry' such as the field of enzymology", says Meek. "While there have been many times that I have been concerned about the sustainability of drug discovery based on enzyme inhibition, advances such as the characterization of the human genome have provided new targets highly susceptible to this approach. This also indicates that the principles of quantitative biochemistry in which I was trained 30 years ago remain valuable today in newer areas such as high-throughput screening, so I would hope that students continue to find these areas of scientific interest as a basis for their careers."

Gérard Mathis, Ph.D.
Director of Research and Development, Cisbio International, Bagnols/Cèze, France

Since his childhood, Mathis has always wanted to be an inventor. "Finding new, unexplored fields of investigation and creating something new from them has always been of particular interest. In fact, no matter what the field is, it's the hands-on aspect that interests me the most," Mathis says.

Following this goal has led Mathis to spend two decades at the life-sciences firm Cisbio International — where he is now Director of R&D — working on technologies that are widely used in drug discovery and development. For example, Mathis and his team pioneered time-resolved fluorescence resonance energy transfer (TR-FRET), which led to the development of homogeneous immunodiagnostic tests. "One of the most exciting aspects of my career so far has been developing an interest in fluorescence techniques and reagents, and then recognizing the potential they represent and developing a novel technology as a result," says Mathis. "Continuing to explore ways to develop this technology, such as applying it to the emerging area of molecular screening in the pharmaceutical industry was both challenging and very rewarding."

Mathis began his professional career as a researcher investigating the use of fluorocarbon microemulsions as oxygen carriers and blood substitutes with France's National Scientific Research Center, the CNRS, after a Ph.D. in organic chemistry engineering and an M.Sc. in physical chemistry at the University of Nancy I, France. He then joined France's Atomic Energy Center as a senior researcher and research manager for a division that later became Cisbio, focusing on homogeneous methods for immunoanalysis using long-lived rare-earth cryptates. Understanding the photophysical processes involved and developing homogeneous methods that adapted FRET to the unusual properties of cryptates ultimately led to the marketing of TR-FRET technologies such as Cisbio's HTRF (homogeneous time-resolved fluorescence) platform.

Researching and developing new fluorescent rare-earth cryptates was the area of a fruitful long-term collaboration with Nobel Prize winner Professor Jean-Marie Lehn, and the value of collaboration is one that Mathis emphasizes. "I've learned the utmost importance of having qualified colleagues who contribute to successful high-technology projects or technology transfers," says Mathis. "I was fortunate to establish collaborations with renowned scientists and research institutions, and with R&D teams such as Cisbio's, whose knowledge and ability to combine chemistry, biophysics and biology disciplines were key in making these endeavours successful."

The strength of such collaborations, together with the strength of conviction for R&D activity arising from a passion for the field are what Mathis considers to be the most important lessons he has learned. "Over the years, I was able to satiate my passion for invention by exploring new fields of research and seeing projects to fruition," says Mathis. "And at the same time, the challenges of cultivating R&D initiatives, implementing them, discovering new technologies and making them work from a business perspective have all fuelled this passion."

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