

An eye for the big picture



When the Boehringer Ingelheim Science Department was founded 100 years ago, future Nobel Prize winner Heinrich Wieland ensured that this was done in a future-oriented way. Today, the company's scientific activities are bundled in the Innovation Unit, which continues to embody the company's spirit of research. Although scientists such as Michael Mark do things quite differently now compared to Wieland's time, there are still lots of similarities.

Michael Mark noticed one thing straight away: “Everyone gave such a friendly welcome”, he says, looking back on his first day at Boehringer Ingelheim in Biberach, in Germany’s Upper Swabian region. The then 28-year-old pharmacology graduate joined the research department in 1985.

His feeling of belonging has remained to this day, Mark says. In other respects, a lot has happened since then. The company has grown enormously and Mark has participated in countless research projects, advancing to become Head of the Cardiometabolic Research Department within the Innovation Unit. He has never for one minute regretted choosing Boehringer Ingelheim. “The job appealed to me straight away – it was exactly what I wanted. Here, I was able to discover new mechanisms of action and develop new medicines – there’s nothing more appealing to a trained pharmacist.”

Today, Mark is responsible for the work of 80 researchers in Biberach as well as 40 people in Ridgefield, Connecticut, USA. He organises the various research projects internally and in partnership with collaboration partners, reviews ideas put forward by the working groups, withdraws staff from projects or increases their number if a substance is looking particularly promising. “At Boehringer Ingelheim, we are able to work on fundamental issues with the necessary foresight”, Mark says. “We get the time required and, above all, the responsibility.”

It is not least the spirit of Heinrich Wieland that has a lasting effect here. The company’s Science Department celebrated its centenary in 2017 and the great chemist and later Nobel Prize winner was there from the very beginning.

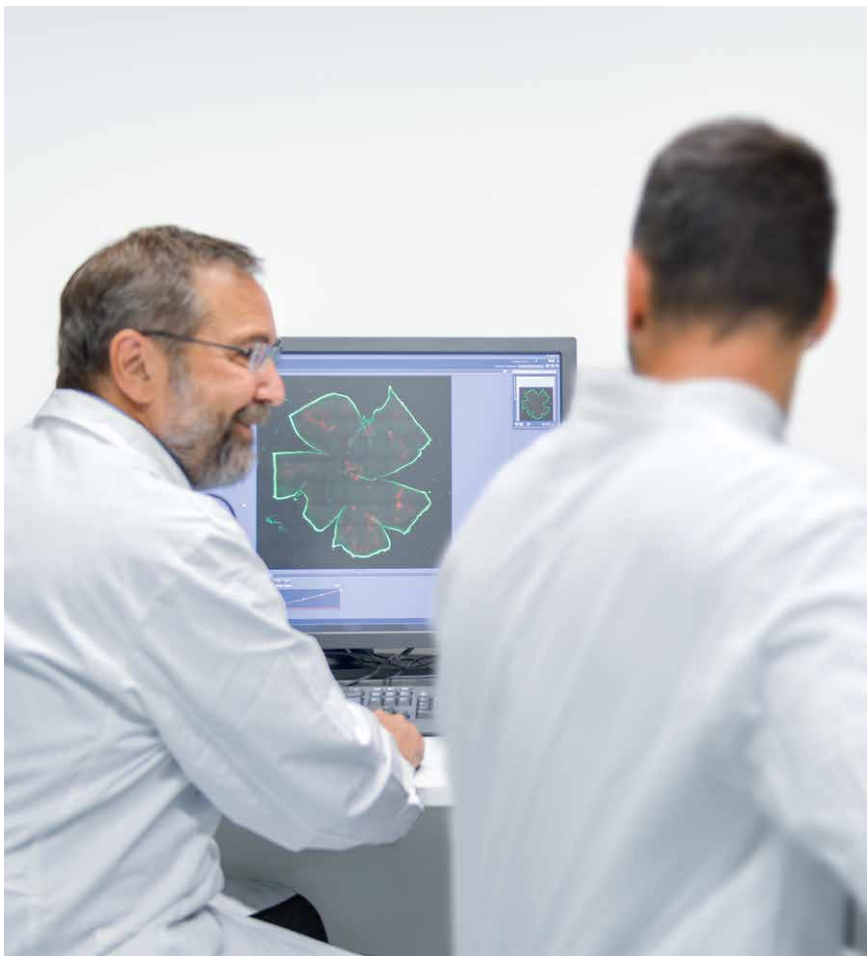
Heinrich Wieland (right)
in the laboratory.

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Born in 1877, Wieland was a cousin of Helene, the wife of company founder Albert Boehringer. From 1904 onwards, he advised Boehringer’s company on the development of new medicines. At the time, he was about the same age as Mark was when he started at Biberach.

A gifted chemist, Wieland pushed the boundaries of research into plant-based alkaloids. He developed the cardiovascular medicine CADECHOL® for Boehringer Ingelheim and later LOBELIN®, an emergency treatment for respiratory arrest and other shock conditions. He conducted regular basic research with his students and assistants at the University of Munich – to a degree that would hardly have been possible for the medicine developers at the Ingelheim-based company on their own.





Dr Michael Mark with his staff evaluating digital images from a fluorescence laser microscope.

At the start of the 20th century, in addition to pursuing their academic careers, young chemists usually worked as advisors to pharmaceutical companies in order to make a living as external lecturers. But Wieland was much better connected and integrated at Boehringer Ingelheim than most of his colleagues in the industry. He was thus a kind of founding father to today's researchers at the company – who also include Mark.

When he thinks of the great Heinrich Wieland today, Mark sometimes wishes he could engage in finding solutions with the same freedom and straightforward manner as was possible then. “Drug development is more complex now, involving many different disciplines. Regulations are of course necessary, not least to ensure patient safety”, says Mark. On the other hand, researchers today naturally have many more opportunities at their disposal. In his team, Mark works with scientists

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² jointly marketed with Eli Lilly and Company

from nine countries with differing education and expertise, including specialists in human medicine and molecular biology. He can employ gene analysis and modern microscopes, has access to all available scientific databases, and will probably even soon be able to simulate effects and side effects using software – as promised by the nascent discipline of systems biology. With regards to all research activities, Boehringer Ingelheim also builds on collaborations with external partners, universities as well as start-up companies (please see the guest contribution of Rui-Ping Xiao from Peking University on page 50).

Mark came to his current field of research thanks to his PhD supervisor. The well-known pharmacologist Hermann Ammon was working on diabetes research, so his young protégé – during and after his doctoral studies – worked on the mechanisms of insulin release. At Boehringer Ingelheim in Biberach, Mark directly linked in with these studies and initially focussed on glinides, the substance class that stimulates insulin secretion from the pancreas. From this emerged repaglinide, which was put on the market as Prandin¹ in 1997. After a protracted phase, during which Mark and his colleagues focussed on lipid metabolism and atherosclerosis, a new phase in diabetes research began in 1999. As one of the first projects, Mark initiated the search for DPP-4 inhibitors. These are substances that inhibit the breakdown of a specific hormone from the intestine, eventually lowering blood sugar. As a result of his work, the active substance linagliptin (TRAJENTA²) was launched in 2011 and is now one of the best-selling medicines in the Boehringer Ingelheim portfolio.

The next significant medicine in which Mark's work played a major role is the SGLT2 inhibitor called JARDIANCE³ with its active substance empagliflozin. Reading scientific articles in the late 1990s, it occurred to Mark that phlorizin, which was initially isolated from the root bark of apple trees, lowers blood sugar levels as it causes glucose to be excreted in the urine. While this mechanism had been known for a long time, Mark and his team were among the first to use this knowledge to develop a medicine to treat diabetes. They therefore applied knowledge about a rare genetic mutation, the carriers of which also excrete sugar in their urine. "We knew from these people that this mechanism has no apparent disadvantages. Accordingly, the SGLT2 inhibitors should be efficacious and well-tolerated long-term," says Mark. Although many experts were sceptical, the team was able to pursue the idea and JARDIANCE[®] is also a major success today.

For JARDIANCE[®], the diabetes researchers drew on a plant-based source material – one that Wieland would probably have been aware of. Wieland represented the last generation of Boehringer Ingelheim developers to work with natural active substances. His best student, Georg Scheuing, who headed the Science Department from 1926 onwards, guided the company to synthetic substances, which was a major step forwards. Mark and his colleagues approached the development of JARDIANCE[®] in a similar way to what Wieland did in his time. They had an idea of how a substance could work and pursued it until the application for diabetic patients. "In modern pharmaceutical research, we constantly ask ourselves which patients and which diseases need improved therapies. What applications are possible? And then we search for therapeutic approaches in full knowledge of the disease and with understanding of the fundamental biological mechanism, as well as with expertise in how to arrive at the suitable molecules."

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The fact that individual scientists, such as Wieland and his successor Georg Scheuing, developed entire medicines practically on their own would no longer be possible in today's world, Mark says. "The fields of research are simply too big and the individual topics too complex, making the specialist knowledge and expertise of many necessary." But Mark is convinced that even today we need "champions who believe in their idea and want to follow it through".

Currently, he and his colleagues are working on treatments for the complications of diabetes, addressing the damage that it causes to the eyes, kidneys and vascular system. Wherever possible, he also wants to investigate the root causes of diabetes development as well as what can be done to avoid this disease. Here, as with diseases of the liver – a further focus of cardiometabolic research – the lipid metabolism plays a major role and Boehringer Ingelheim is already one step ahead, Mark believes: "We have never looked at diabetes and glucose metabolism in isolation but always as being part of the body's entire metabolic events."

Something else has also remained fundamentally unchanged since the Wieland era. Boehringer Ingelheim has close ties with the scientific community, supports basic research and draws on these factors to attract talented people to work for the company. Mark calls it talent management – supporting promising young scientists, supervising them and preparing them for new tasks, or playing an active role in international research networks. So, in the final analysis, he is not all that different from Wieland, who regularly recommended some of his best students and promising scientists to Boehringer Ingelheim. And he was himself the PhD supervisor of Ernst Boehringer, younger son of the company's founder.

³ jointly marketed with Eli Lilly and Company



From his office in Biberach, Germany, Michael Mark is responsible for the work of 120 research colleagues.

For Boehringer Ingelheim Heinrich Wieland developed LOBELIN®, an emergency medication for respiratory arrest and other shock conditions.



Phlorizin, from which the SGLT2 inhibitor empagliflozin (JARDIANCE®) was derived, originally comes from the root bark of the apple tree. Today, the diabetes medicine JARDIANCE® is a great success.

