FMI History

The origins

It started with a position paper written in 1969 by Hubert Bloch, then Head of Pharmaceutical Research at Ciba AG. In this paper, Bloch argued that the pharmaceutical industry is dependent on innovation and should therefore make more use of knowledge from basic research, which itself should be liberated as far as possible from the constraints of short-term commercial goals. His ideas were so convincing to Willy G. Stoll, Head of Research at Geigy AG, that it was decided to establish a joint research institute. This event preceded the complete merger of the two companies by a year. The institute – named after the 19th century Basel physiologist and discoverer of DNA, Friedrich Miescher – was to be a legally independent foundation. The Friedrich Miescher Institute (FMI) came into being almost exactly 100 years after the discovery of nucleic acids by the institute’s namesake. Following the signing of its Charter on April 8, 1970, Hubert Bloch was appointed as founding Director of the new joint venture. A Board of Trustees, with members representing both the sponsoring firms and Swiss universities, was nominated to oversee the Foundation.

To achieve its goals, the FMI was organized into project-defined research groups; the first six group leaders were selected and research activity was initiated just a few weeks after registration of the Foundation. The FMI was first allocated several laboratories in the research department of Ciba. Later, while waiting for promised space in a new building, the Institute rented space from the University of Basel and its members were the first occupants of the Biozentrum, which had just been built by the University. The sojourn in the Biozentrum turned out to be instrumental in cementing close ties between the FMI and the University of Basel – ties that still exist today.
In 1974, the FMI moved to its current site on the Rosental campus, where many of its successes have been realized. The first few months, however, were overshadowed by the unexpected loss of its inaugural Director, Hubert Bloch. Denis Monard, one of the first FMI group leaders, was called on to act as Director (a position he filled once again from 2002–2004). Soon, Matthys Staehelin, Professor of Medicine at the University of Basel and a director of the Ciba-Geigy Corporation, was chosen to lead the FMI, and in 1976 the Directorship was transformed into an Executive Committee, with Matthys Staehelin as Chairman. This arrangement persisted until 1982, marking a period of steady growth and scientific expansion. The institute trained students as well as postdoctoral fellows, and collaborated with the University of Basel and other institutes worldwide; interactions with Ciba-Geigy increased considerably.

A Scientific Advisory Board (SAB), as envisaged in the FMI Charter, was constituted and held its first meeting in June 1976. The inaugural members were Howard Rickenberg (Chairman), Michael Stoker, Charles Weissmann, Efraim Racker and Edmond Fischer. Over the years, the FMI has been fortunate in being able to recruit many of the world’s leading biologists as members of its SAB – benefiting its Director and staff, and the Board of the Foundation enormously.

The plant era

Also in 1976, the Institute extended its interests into plant biology, where the impact of rapidly evolving molecular genetic techniques was just being felt. The FMI Board of Trustees was convinced that the commercial future of agriculture lay in the breeding of plants guided by the molecular biology of desirable traits and their manipulation at the genetic level. The FMI accordingly looked for and hired several outstanding plant molecular biologists. The following decade saw a marked expansion of plant research at the FMI. Of the 24 FMI research groups, 8 were working with plant models around 1985, accounting for more than 40% of the 170 research personnel then employed at the Institute.

Globally, molecular plant biology hardly existed as a discipline before the early 1970s; the FMI was thus setting the trend. It soon became recognized as a leader in plant transgenesis, ushering in the era of genetically improved crops. In 1984, close collaboration between several FMI plant groups culminated in the publication of two protocols that allowed foreign genes to be expressed in whole plants. With this important breakthrough, the “FMI protocols” had their heyday in the 1980s. Subsequently, however, other techniques were developed, and the FMI focus turned to other topics such as plant development, the action of plant
hormones and plant-microbe interactions. Many patents were filed, and several are now owned and exploited by Syngenta attesting to the innovative research of this era.

**A new generation**

As the plant era reached its zenith in the 1980s, the FMI as a whole experienced numerous – sometimes dramatic – changes in both personnel and research direction. Following the arrival of Edward Reich as Director in 1982, new appointments concentrated on chemistry and biochemistry, which opened up new technical opportunities for the Institute and led to increased cross-group collaboration, especially in cancer research.

In 1987, Max Burger arrived at the FMI as the new Director. Aided by the Scientific Advisory Board, which he valued highly for its critical yet constructive advice, he identified areas of expertise to be encouraged. The appointment of a series of junior group leaders was used to fill gaps and build bridges.

Believing it essential for the future of the FMI that group leaders get involved in university science education, Max Burger used his connections to academic life in the city – especially at the Biozentrum – to open the way for FMI-led courses and lecture series.
at the University of Basel. The pay-off was an increasing number of excellent graduates and postgraduates who chose to pursue their studies at the FMI. During Max Burger’s directorship, the Institute was able to move into a specially refurbished building on the same grounds, which provided not only more space but also direct access from the street. The building enhanced the physical identity of the FMI and provided convenient access for the many University students and visitors to FMI lectures.

In 1996, Sandoz and Ciba-Geigy gave birth to Novartis, and in the following year the Friedrich Miescher Institute became part of the Novartis Research Foundation. After the merger, the new company decided to divest its plant breeding and plant protection interests in the form of Syngenta. The FMI consequently expanded its focus on neurobiology, epigenetics and growth control. Its name was subsequently changed to “Friedrich Miescher Institute for Biomedical Research”.

The most impressive research results emanating from the FMI during Max Burger’s time concerned the discovery and characterization of protein kinases and their control over cancer cell growth. It was Max Burger’s own interests that led the expansion in molecular cancer research, and he encouraged the development of supporting technologies and inter-group collaboration. Interactions with Ciba-Geigy’s Head of Oncology, Alex Matter, fostered important contacts that would later be transferred to Novartis. Under Max Burger’s leadership, the FMI achieved worldwide recognition for excellence in research.
Signaling and Cancer

The Signaling and Cancer program at the FMI has sought a comprehensive understanding of signaling circuits and mechanisms regulating the growth, division and death of cells. A deeper knowledge of these processes facilitated the development of novel, mechanism-based therapeutics to combat human disease. Success was based on long-term persistence coupled with a healthy impatience, and extensive exchanges and synergies among research groups at the FMI and at Ciba Geigy, or later Novartis. Contacts with the University of Basel and other institutes around the world generated valuable ideas, data, technology and expertise, benefiting FMI’s sponsor.

Two projects in particular were readily taken up by Novartis. First, the discovery of the key signaling kinase PKB (Akt) and the demonstration that it plays a central role in cancer cell signaling kick-started the Ciba-Geigy project that led to Novartis’ Gleevec® – a targeted inhibitor of the Bcr-Abl tyrosine kinase and a blockbuster anti-leukemia treatment. Second, work on ribosome protein phosphorylation turned out to be not only excellent science, but also a perfect example of the founders’ vision for the FMI. It was to contribute, many years later, to Novartis’ 2009 release of Afinitor® as a cancer treatment. The FMI similarly contributed to the development of a PI3 kinase inhibitor and has filed numerous patents on novel kinases of relevance to cancer.

Another significant finding was the discovery that the gene for the human epidermal growth factor receptor 2 (ErbB2) is amplified in around 25% of primary breast tumors. Over the years, research at FMI further dissected the role of ErbB2 signaling in the pathogenesis and prognosis of breast cancer. Although not all breast cancer patients with an ErbB2 defect respond to therapy, important progress has been made, and an antibody-based treatment is in clinical trials.
Neurobiology

The formation of neuronal connections during development and their maintenance in adulthood are crucial determinants of nervous system function in health and disease. Research at the FMI has used molecular and genetic techniques to explore the cellular mechanisms that determine how circuits are first made and later modified to support animal behavior.

One of the earliest and most colorful contributions of FMI neuroscience involved the early application of green fluorescent protein (GFP) for the visualization of cytoskeleton-binding proteins in cultured hippocampal neurons. Live video recordings revealed actin-dependent changes in dendritic spine shape within seconds, suggesting that anatomical plasticity at synapses can be extremely rapid. Another long standing research interest concerns factors influencing the stability of the neuronal network. PN-1, a serine protease inhibitor, was identified early on, and its role in synaptic plasticity as well as in cancer metastasis was elucidated over the years.

Neurobiology research at the FMI has gone from strength to strength in the last few years, with the advent of an organismal approach to tracking and dissecting neuronal circuits as they function in intact tissue. Several lines of research are investigating the circuitry of vision, olfaction, movement, memory, learning and anxiety during different stages of development, using an impressive array of model systems. The FMI's impact on neurobiology worldwide is evidenced by the fact that FMI scientists organize one of the most high-profile neurobiology meetings – the Ascona meeting – biannually. Importantly, FMI neurobiologists are starting to apply their accumulated knowledge of synapse plasticity and neuronal circuitry to investigate mechanisms of human disease and sensory malfunction, seeking novel treatments for retinal diseases and diagnostics for neurodegeneration.
The state of the art

The history of research in biology is as much a history of technological innovations as of novel insights. Many, if not most, techniques arise out of necessity – in the course of efforts to find a tailor-made way of testing a burning hypothesis. Some methods remain home-made, while others gain worldwide recognition as crucial tools. Among the latter is Western blotting, a technique that was published in PNAS in 1979 by scientists at the FMI, simultaneously with a protocol from Stanford.

Similarly, time-lapse imaging of microtubule dynamics with green fluorescent protein (GFP) was undoubtedly the harbinger of remarkable developments in imaging that have since evolved at the FMI. In recent years, there have been several major developments in the area of imaging technologies. Light activated events for quantitative physiological read-out are now readily exploited, and novel fluorescence-tagging methods are used to track single macromolecules in living cells, neuronal networks, and dynamic changes in cellular substructures. The 3D reconstitution of tissues from serial sections viewed by scanning electron microscopy is another new technology harnessed by the FMI.

As well as leading-edge microscopy and imaging technologies, the FMI established several other new technology platforms. These include platforms for protein structure determination, single- and few-cell genomic profiling, next-generation sequencing and computational biology, which provides crucial support to FMI scientists as they try to cope with the digital data explosion. Coincident with the development of these technologies, an innovative method for mapping genome-wide cytosine methylation was published by FMI scientists under the acronym MeDIP. MeDIP has been rapidly integrated into the study of heritable methylation and is now widely used by international consortia to map epigenetic changes in cancer cell genomes.
Epigenetics

Epigenetic modifications determine cell fate, help guard genome integrity, and maintain differentiated states, thus playing crucial roles in diseases such as cancer or in stem cell de- and re-differentiation therapies. The interdisciplinary approach of the FMI allows its scientists to exploit a variety of model organisms, and its epigenetic focal area now includes nine research teams studying the range of molecular mechanisms that regulate tissue- and stage-specific gene expression.

Originally, the interest in epigenetics at the FMI stemmed from the study of plant transgenesis. Epigenetic research in 1991 focused on small interfering RNAs in plants and their pervasive RNA silencing networks. Since that time, and especially under the directorship of Susan Gasser (appointed in 2004), the FMI has developed an interdisciplinary approach that exploits various model organisms to understand the molecular mechanisms of epigenetic control.

The pioneering development of protocols to monitor and quantify chromatin and DNA modifications genome-wide have been one of the FMI’s major contributions to the new research field of “epigenomics”. In addition, FMI scientists discovered key players in RNA interference (RNAi) and miRNA function, and have elucidated the roles of histone deacetylases in gene repression and cell cycle control. Such research has made the institute a world-class center of epigenetics, and the impact of this blossoming field on pharmaceutical developments is now being realized.

The recent past and future

Following Denis Monard’s second successful stint as FMI Director, the Institute welcomed Susan Gasser as Director at the end of 2004. With six of the Institute’s group leaders approaching retirement, she had an unprecedented opportunity to rebuild the FMI. The Novartis Research Foundation defined her mission as “making the FMI a world-class research institute”, and provided generous support to this end.
From 2004 to 2010, the FMI engaged 11 new group leaders in all three focal areas, successfully attracting world-class junior and senior scientists from top universities and institutes across the United States and Europe. Expertise in RNA biology, C. elegans genetics, innovative imaging technologies, transgenetic tools and novel approaches to cancer biology complemented existing expertise within the FMI and raised the Institute’s research to new heights. Publications in top-ranked journals increased to between 20 and 30 *Nature, Science* or *Cell* journal articles per year, and competitive third-party funding has been granted to most FMI teams. At the latest count, the Institute’s staff was 320 strong, with over 100 PhD students and 90 postdoctoral fellows. Two thirds of the latter had won competitive fellowships to join the FMI. The Institute’s International PhD program alone attracts 1200 applications per year, and the selected students follow a training program alongside their research activities. Networking within the Institute is a daily process, as is networking in the outside world.

With the sharpening of the FMI’s biomedical focus, its interactions with Novartis research teams have also increased dramatically. Despite the wide geographical distribution of Novartis operations, the FMI is currently pursuing about 50 collaborative projects with Novartis colleagues in Cambridge, Basel, La Jolla, Shanghai and Singapore. Promising projects include the targeting of novel protein kinases, regulatory enzymes for the deposition or erasure of epigenetic marks, and the restoration of photoreceptor activity to cone cells compromised by retinitis pigmentosa, a progressive hereditary eye disease. Diagnostic markers and tumor-specific extracellular matrix proteins are among the by-products of FMI research that represent valuable tools for Novartis’ pharmaceutical efforts.

Today, the FMI figures prominently in the Swiss and European science communities and – perhaps more than in the past – the Institute is defined by its position at the interface of academia and industry. While institutes of this nature have come and gone over the years, there is currently a trend in the pharmaceutical sector to establish new centers operating precisely at this interface, hoping to understand the molecular basis of disease and to funnel ideas and cutting-edge science into drug discovery. The FMI has vast experience in this enterprise and aims to continue on its established trajectory at the forefront of biomedical research, making new discoveries and helping to translate these into treatments that meet unmet medical needs.

This extract is taken from a 40-year retrospective history of the FMI written by Pat King, former FMI group leader. The FMI thanks Pat King for many years of skillful scientific writing.