Hartmut Wekerle

In October 2002 **Prof. Hartmut Wekerle**, *Director at the* **Max Planck Institute for Neurobiology**, *was awarded the "Foundation Louis D." science prize by the Institut de France. The prize, worth 750,000 euros, recognizes Wekerle's pioneering research on autoimmune diseases of the central nervous system, in particular multiple sclerosis. Thirty years ago such disorders, according to the beliefs of the time, were considered "impossible". Wekerle played a vital role in overturning this dogma, consequently founding the field of neuroimmunology – a research field where scientists work together with medics in trying to untangle the "self" destructive attacks of the immune system.*

Photos: Wolfgang Filser

Hartmut Wekerle was born in 1944 in Waldsut, studied medicine at the University of Freiburg and began his scientific career in 1967 at the Max Planck Institute for Immunobiology, Freiburg. "That happened purely by chance", relates Wekerle. "I had just read an article in the Zeit-Magazine about the Max Planck Society and then discovered immunobiology listed in the lecture program at the MPI. Since I wanted to pursue immunology in my Ph.D. work I overcame my awe of the elite prefix "Max Planck" and knocked on their door ..."

The knocking was heard – and so as a Ph.D. student Wekerle came under Herbert Fischer's wing, who inspired his passion for immunology. Wekerle submitted his dissertation in 1971. After this he worked until 1973 as postdoc at the Weizman Institute in Rehovot – where, through Michael Feldman, he came across the themes that have occupied him for some 30 years: the problem of self tolerance of the immune system and the phenomenon of autoimmunity, immuno-aggression against the body's own structures.

When Wekerle returned from Rehovot to the Freiburg Max-Planck Institute for Immunobiology in 1973 he had several items in his baggage that in the following years would set off scientific explosions: data that planted serious doubts about the then accepted concept of self tolerance of the immune system – about a key element of the so-called clone selection theory of the Australian immunologist and Nobel prize winner Sir Macfarlane Burnet.

This theory addressed the basic organization of T-lymphocytes, a class of white blood cells that play a central role in the immune defense: they have the task of recognizing "antigens" on molecular structures foreign to the body. This immune recognition is highly specific, since each T-lymphocyte is tuned to one single, very exact "enemy profile": it carries receptors on its surface, a kind of feeler, that are tailored to its "personal" antigen like a key that fits a lock. Therefore, from all lymphocytes only those that carry the proper receptor respond upon contact with foreign molecules: lymphocytes with identical specificity are called clones.

New Theories for Old – Dismantling Dogmas

According to Burnet the immune system should retain millions of lymphocyte clones of different specificities in order to ensure that every thinkable antigen will, in fact, be recognized. Upon contact with an antigen the lymphocytes of the "responsible" clone should replicate and start the immune reaction.

The specific arsenal of the immune defense apparently encompasses the entire antigen repertoire of the outside world, in other words is prepared for every thinkable defense situation. At the same time it must tolerate the body's own structures – and Burnet explained this with a selection process before birth: during the embryonal phase all lymphocytes with "self" recognizing receptors should be eradicated, the immune defense should undergo targeted disarmament. This theory held until the end of the 1970's – until Wekerle and his colleagues painted another picture: that the healthy immune system certainly includes T-lymphocytes that recognize the body's own structures, i.e. that are tuned to "auto" antigens.

This meant departing from an attractive and convincing picture of a pre-formed immune defense purely tuned to foreign structures. "Some immunologists", according to Wekerle, "found this departure extremely difficult. And because a dominant dogma also has dedicated champions, in the early 1980's we had to withstand conflicts from all sides. Moreover, it was not our aim to dismantle a dogma. Rather, we wanted to explain our results – which was then not compatible with contemporary wisdom."

This was soon followed by a second, no less hard to follow "trick" that also affected an entrenched dogmatic view – the theory that the central nervous system is exempt from any immune reaction: what is known as the blood-brain barrier should shield the brain and spinal cord from T-lymphocytes that are otherwise found throughout the body. In a multinational cooperation Wekerle showed that this does not apply, at least not in this general fashion. It became apparent that although the central nervous system is exempt from "routine" immune surveillance, activated T-lymphocytes taking part in an ongoing defense reaction outside the nervous system receive selective access to the brain and spinal chord. Furthermore, in certain cases brain cells were found to cooperate closely with the immigrant lymphocytes, taking part in the immune reaction in the nervous system.

Thus the brain and spinal chord are in no way "immunological no man's-land". In retrospection, Wekerle finds it almost curious that this conclusion caused such a sensation amongst experts: "At that time it was actually almost impossible to assess whether there were diseases of the central nervous system where the immune system definitely took part."

In 1982 the focus of Wekerle's research settled on one of these dis-

eases: that year he was appointed director of the clinical research group for multiple sclerosis established by the Max Planck Society at the Neurological Clinic of the University of Würzburg with money from the "Herman and Lilly Schilling Foundation".

This group united researcher scientists with clinical practitioners and their goal was to elucidate the immunological processes involved in multiple sclerosis – namely, the autoimmune reaction against a component of myelin, a substance made of fat and protein that forms an isolating layer surrounding the individual nerve fibers.

Much of what had previously only been discovered in experiments with "animal" immune cells could be confirmed and extended in Würzburg with material from the blood of patients with multiple sclerosis. For example, they succeeded in isolating T-lymphocytes that react against the auto antigen myelin from the blood of not only patients with the disease but also from healthy individuals. Not only that: practically every brain substance, apparently, is perceived as a potential antigen by self-recognizing T-lymphocytes and can be attacked – facts Wekerle now generalizes: "I would go as far as saying that not only components of nerve tissue but every organ-specific protein in the body is in principle recognized by self-reacting T-lymphocytes and under unfortunate circumstances can become the target of an autoimmune reaction."

Green Light on Autoimmune Reactions

This prognosis marks the fundamental change brought about by Wekerle's research. The defense system initially considered "blind" to the body's own structures, now seems only an organ actively choosing between "self" or "non-self" – and that can also make mistakes and instigate a "civil war". Such mistaken attacks against self had been explained earlier as regeneration of "forbidden" lymphocyte clones by chance; now it's known that what lies behind this are faults or failures in the controls that underpin immune reactions against the body's own structures.

"Unfortunately", according to Wekerle, "we still know very little about how self-reactive T-lymphocytes are normally prevented from performing their job. Nevertheless it is wrong to think of them as time bombs in the body, since it has been shown that they are only activated by exceptional processes and spiced up by pathogens."

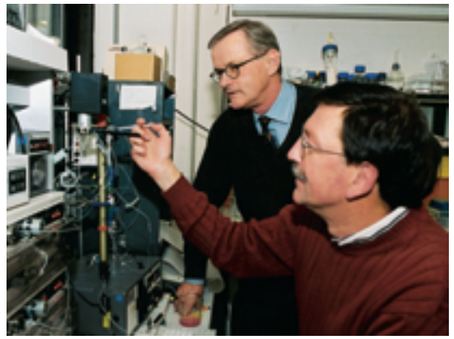
Since 1988 Wekerle has been pursuing his research as director of the Max Planck Institute for Neurobiology at Martinsried near Munich, leading the department of Neuroimmunology. The focus of the work, as before, is the interaction between nerves and the immune system. As in Würzburg, there is also a close connection with clinical research in Martinsried – based on a model cooperation with Prof. Reinhard Hohlfeld, the director of the Institute for Neuroimmunology at the Clinic of the Ludwig Maximilian University of Munich.

Wekerle describes this "integrative lab", in which the Max Planck and University invest jointly, as a stroke of luck: "It allows us to integrate experimental research directly with clinical human immunology and carry out neuroimmunology from the bedside to the molecule – a unique model that we are proud of."

Currently, they are investigating in detail what happens during the course of an autoimmune attack against brain tissue, using what is basically a simple yet very effective "pioneering" method: using specific retroviruses that can be genetically manipulated to produce a green fluorescent protein. Autoimmune T-lymphocytes that attack myelin in the myelin sheaths of nerve cells are then infected with these retroviruses. The manipulated retroviruses integrate into the genome of the infected T-cells – and as a result, according to Wekerle, make ideal probes: "The T-cells remain functionally intact and do exactly what is expected of autoimmune, myelin-specific lymphocytes. At the same time they produce the green dye – and can therefore be followed while they go about their business."

If myelin-activated T-lymphocytes are injected into the blood of rats, several – because they are activated – penetrate the blood-brain barrier. "Such experiments were previously of little use," reports Wekerle, "as we soon lost track of these lymphocytes: for days on end we didn't know where they were hiding."

Now, the green dye has thrown light on this puzzle: the activated T-lymphocytes were found to wander through the periphery immune tissue of the rat and finally collect in the spleen. Here, they are completely genetically deprogrammed and take on a new phenotype; for instance, the activation signs on their surface disappear and they develop receptors for chemical signaling molecules that act as a signpost to show them the way.



After three days these converted lymphocytes then migrate en mass out of the spleen and stream into the brain where they cause acute, inflammatory autoimmune disease of the myelin sheath. To the amazement of the immunologists a good 90 percent of all the lymphocytes taking part in this inflammation light up green and act as "effectors", or attackers – contrary to previous views that only a few activated cells force their way into the brain and that the immune reaction is primarily taken on by passively recruited "helper troops".

Answers Bring More Questions

This knowledge can perhaps be put to good use, thinks Wekerle: "We now know that the T-lymphocytes adopt a new phenotype before their attack, that is another external appearance. Perhaps we can find a structural feature that unequivocally distinguishes these lymphocytes, thus providing a possibility of trapping them before they invade the brain." Moreover, it is conceivable that the retroviruses carrying the gene for the green fluorescent protein could be equipped with genes for therapeutically effective proteins. A range of proteins are known that affect regeneration of damaged nerve cells – and that, through manipulated retroviruses and T-lymphocytes, can be targeted to their site of action.

However, the path from the lab to the clinic will be long and arduous, since the immune system has shown itself to be an extraordinarily complex organ in which numerous different cells via similarly numerous signaling molecules work together in an as yet perplexing network. Understanding this functioning network, according to Wekerle, requires patience: "Previously it was believed that with the answer to an apparently vital question 'almost everything' was known. Our experience has shown that every answer always yields new, for the most part even more difficult questions. And we have learned that it is not enough to study isolated cells or even the interaction between two cells, rather we must approach things a whole. In immunology nowadays whole 'milieus' are characterized; that is, summarizing functional networks rather than individual functions. This is what we are concentrating on – and there is still quite a lot to do."

WALTER FRESE

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