Michael Schindler: HI virus and host interactions

Prof. Dr. Michael Schindler explores the interaction between viruses and their human host cells on the molecular level. His specific interest is HI virus infections and the mechanisms the virus uses to attack the human immune system. Schindler's eventual aim is to identify a new target for the therapy of HIV infections. In April 2014, Schindler was appointed head of the Department of Molecular Virology of Human Infectious Diseases at the University Hospital in Tübingen.

Prof. Dr. Michael Schindler has been chair of the Department of Molecular Virology of Human Infectious Diseases at the University Hospital in Tübingen since April 2014.

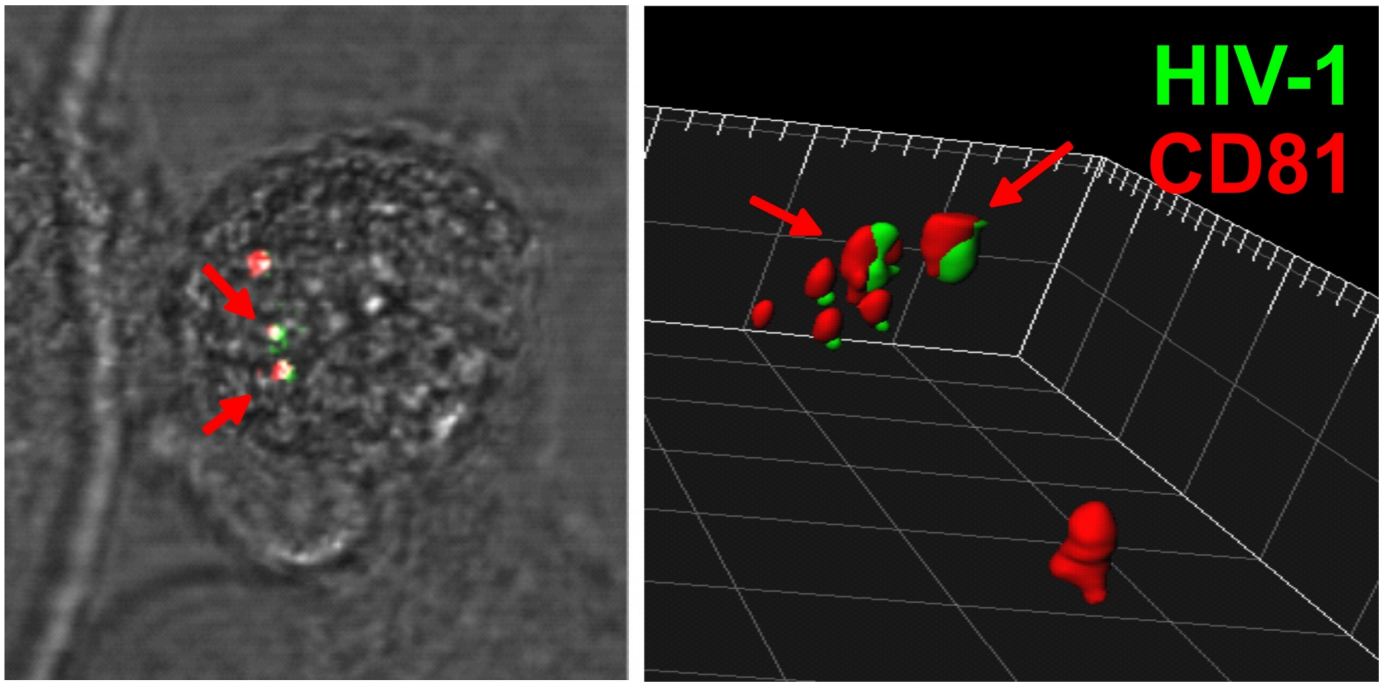
The appointment of Prof. Dr. Michael Schindler in April 2014 reinforces the field of viral research at the University Hospital in Tübingen. The 36-year-old scientist studies the interaction between the human host and HIV and other human viruses and has had a number of high profile publications during his professional career. Schindler studied biology at the University of Ulm and laid the foundation for his current career in 2002 when he became the first graduate student in Prof. Dr. Frank Kirchhoff's team, then recently appointed professor at Ulm University. Schindler also did his PhD in Kirchhoff's laboratory (2006). His doctoral work led to new insights into HIV research, which generated a huge response among the scientific community.

Schindler discovered why the simian immunodeficiency virus (SIV; from the Latin simia, meaning monkey), which is closely related to HIV, does not lead to AIDS in monkeys. He compared the function of a specific viral protein called Nef during the infection of human hosts with that of the corresponding protein in monkeys and found that the two types of Nef proteins – presumably for evolutionary reasons – are so different that they even have opposing effects. While SIV Nef proteins prevent the activation of specific immune system lymphocytes, HIV Nef proteins enhance the activation of these T-helper cells. This causes the human immune system to break down and the infected person to develop AIDS.

Inspired by this first major research success, Schindler continued with his research into the molecular mechanisms of virus-host interactions, but broadened his outlook. When he was appointed head of a group of researchers at the Heinrich Pette Institute in Hamburg, Schindler extended his investigations to other HIV proteins and the hepatitis C virus (HCV). "We were mainly interested in what is known as viral immune evasion, i.e. the mechanisms that viral proteins use to manipulate host cells in a way that enables the virus to evade the human immune response," says Schindler. He began his investigations into HCV in 2009, but it was not until spring 2014 that the researchers' findings led to the first HCV-related publication in the renowned journal "Molecular and Cellular Proteomics"[1]. The paper focussed on the entire interaction network of viral proteins in live liver cells.

This once again shows that researchers working in the field of molecular biology require a great deal of patience. When he was in Hamburg, Schindler had become increasingly interested in how HIV infects macrophages, which is a key component of viral pathogenesis and AIDS progression. "Back then, macrophages were not yet the major focus of HIV research as the T cells are the principal targets of HIV in the human body. However, some researchers had already suggested that macrophages possibly played an important role in the pathogenesis and progression of AIDS," says the researcher going on to add, "our work was instrumental in substantiating this hypothesis."

An ideal refuge for the HI virus: membrane-coated vacuoles in the macrophages



Left: Microscopic image of an HIV-1 infected macrophage showing the intracellular accumulation of viruses (green). The cellular CD81 factor (red) is found in the same regions. Right: Three-dimensional reconstruction of the area shown on the left.
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In 2011, Schindler became head of a group of researchers at the Helmholtz Centre in Munich where he continued his work with macrophages. Together with his team, Schindler studied how new HI viruses are assembled and released by macrophages. His persistence paid off: working with some of his former colleagues from Hamburg, Schindler discovered a previously unknown immune evasion mechanism, which turned out to be of huge clinical relevance. HI viruses are assembled in the intracellular compartment of macrophages where they accumulate in vacuoles, which protects them

against antibodies and from where they can be directly transferred to T cells. "Cell-to-cell transmission is a process during which the viruses do not come into contact with the extracellular space and are thus protected against immune system attacks," says Schindler.

Macrophages survive for weeks and even months and are also able to pass through the blood-brain barrier. This makes them an ideal and particularly dangerous reservoir and transport vehicle for HI viruses. In 2012, Schindler's team published their results in the Journal of Virology[2], the top journal for virologists. "I would have liked to publish our findings in a journal with an even higher impact factor, but I am quite impressed with the number of times the paper has already been quoted by other researchers, and that is what really counts," says Schindler.

He has been head of the Department of Molecular Virology of Human Infectious Diseases at the University Hospital of Tübingen since April 2014 and continues to focus on the interactions between HIV and the human immune system. Thanks to the academic department, Schindler is now not only able to expand his work to other viral infections and factors, but also extend his team's technological repertoire. In Hamburg and Munich, Schindler was already involved in the optimization of the life cell imaging of viruses in host cells. "Modifying the viruses with fluorescence dyes in a way that retains their infectious capacity and also enables them to reproduce is a huge challenge," says the researcher. Schindler has also developed methods that help him distinguish the large number of different virus-host interactions from each other.

Schindler and his team have combined a method that enables the measurement of the energy transfer between two chromophores (FRET = Förster resonance energy transfer) with a method known as FACS (fluorescence-activated cell sorting) with the aim of analysing as many cells as possible along with their viral cargos within the shortest possible time period. "I get rather frustrated when I have to characterize a single protein interaction because it is both time-consuming and complex. FACS-FRET enables us to quantify and visualize protein-protein interactions in live host cells. Our department now has access to all the devices and methods we need for this type of work, and this is an excellent position to be in," says Schindler. "The appeal of our method is that it is not limited to viruses, we are able to study any molecular interaction we are interested in. In addition to identifying and characterizing interactions, we are also able to look for substances that inhibit defined interactions."

This work takes Schindler closer to achieving one of his ambitions, namely the identification of conserved interactions between different viruses and a specific host protein and the subsequent use of this structure as a target for antiviral therapy.

Demonstrating the feasibility of functional healing

Ultimately, all these investigations are aimed at improving the treatment of viral infections as well as making it possible to help HIV patients in particular. Nevertheless, Schindler is very cautious when it comes to talking about a 'cure' for HIV. "The question is, do we refer to a sterile cure, by which I mean the complete elimination of all HI viruses or do we refer to a functional cure? A functional cure has the potential to control HIV infections – possibly without therapy – and improve the quality of life of people with HIV as well as enabling people to live much longer with HIV than was previously possible." Schindler believes that the second option is currently the most realistic and hopes that his work will be able to contribute to this goal. "Understanding how viral infections are able to evade immune response mechanisms is essential for finding out how the immune system can be strengthened." If it were possible to make the human host so fit that it could control HIV infections on its own, this would be a big step forward in HIV therapy. Schindler believes that identifying and analysing immune response components that are not destroyed is crucial. "We would then be able to specifically strengthen these components, for example with a vaccine."

Many advances in HIV treatments which have dramatically improved the life of HIV patients have been made in recent years. "Around 25 HIV drugs have been approved for the treatment of AIDS in industrial countries. And these drugs enable people to live longer without dying of AIDS. Ageing with HIV poses a number of challenges and we need to build information on how the adverse effects of the drugs can be minimized in order to enable AIDS patients to live as normal a life as possible."

[1] Hagen N, Bayer K, Rösch K, Schindler M: The Intraviral Protein Interaction Network of Hepatitis C Virus, in:Mol Cell Proteomics 2014 Jul;13(7):1676-89
https://www.gesundheitsindustrie-bw.dewww.mcponline.org/content/13/7/1676.abstract?sid=9e8fa35d-58d7-420e-a034-16b8f8eea6ea

[2] Koppensteiner H, Banning C, Schneider C, Hohenberg H, Schindler M: Macrophage Internal HIV-1 Is Protected from Neutralizing Antibodies, in: J virol 2012 Mar;86(5):2826-36
https://www.gesundheitsindustrie-bw.dejvi.asm.org/content/86/5/2826

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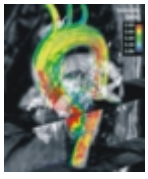

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