How the Next Generation Furthers **Insights while Healing Patients**

Clinician scientists work with patients as practicing physicians, while also pursuing scientific research in the lab. The huge time commitment this requires means fewer and fewer physicians are choosing this route. At the same time, it is becoming increasingly important for researching physicians to work in close collaboration with scientists – and for scientists to connect their research to diseases. Here, we take a look at TUM's up-and-coming scientists engaged in multiple sclerosis research.

For years now, university hospitals and the German Research Foundation (DFG) have been bemoaning the lack of fresh talent in medical research. The DFG highlighted this as far back as 2008, while physicians from several universities, including TUM, address the issue in a recent article on higher education research[1].

The research career path poses a formidable challenge for young physicians. Following their doctoral thesis and graduation, physicians generally spend several more years training as a specialist. If they are aiming for a parallel path in research, they also need to simultaneously engage in noteworthy research, establish a reputation in their field and network with peers. A 2006 survey by the German Society for Internal Medicine (DGIM) discovered that resident physicians spend around ten hours a day treating patients in the hospital. Most of them only have evenings and weekends available for research, making it almost impossible to pursue their projects at an internationally competitive level and build the necessary networks.

Taking multiple sclerosis (MS) research as a case in point, this article shows how TUM is creating room to maneuver within clinical training, promoting networking and thus bringing more researchers into medicine again. This also means supporting young families, which is why SyNergy, the Munich Cluster for Systems Neurology (p. 31), provides funding to help young academics pay for childcare, for example. ▷

1 Epstein et al., Beiträge zur Hochschulforschung 38, 1-2/2016
DFG, duz Special: „Karrierewege in der Hochschulmedizin", 2008

Picture credits: Jooss, Rothhammer

Rotation system: half doctor, half researcher

Dr. Benjamin Knier has been training to become a neurologist since July 2011 and is working as a resident in the neurological center (Neuro-Kopf-Zentrum) at TUM's university hospital, Klinikum rechts der Isar. His focus lies on changes to the optic nerve and retina as a result of neuroimmunological disorders – both in mouse models and in human patients. Knier is researching immunological processes accompanying optic neuritis (inflammation of the optic nerve), with a view to opening the door for new therapeutic approaches. At the same time, he is exploring the extent to which retinal changes in MS patients might serve as a prognostic factor for the subsequent course of the disease and its response to various treatment methods.

The young researcher is a member of Prof. Thomas Korn's working group. To date, he has invested over two years in "off-the-clock" research, pursuing his scientific endeavors after hours and on days off. But TUM has also given him room to maneuver – in several different ways. The specialized outpatient clinic for MS at TUM's Klinikum rechts der Isar hospital operates a rotation system, with two residents sharing a position alongside the specialists there. This means that each resident can spend half of their time with patients and the other half on research. Knier also used one and a half years in this clinic to advance his project, procure funding and apply for grants. Now, a faculty grant awarded by TUM's Commission for Clinical Research (KKF) is enabling him to devote 80 percent of his time to research. He reflects: "If you want to pursue an academic route as a physician, you have to make that decision early on. The field is becoming more and more competitive and the professors ever younger." In Knier's view, upcoming researchers have a window of seven to eight years to establish themselves in their chosen area. "If you're looking to conduct research and train as a specialist physician, there are few university hospitals in Germany with conditions to match those at Klinikum rechts der Isar. In neurology, we enjoy a supportive environment and excellent infrastructure."

Faculty grant: a year devoted to research

Dr. Viola Biberacher is currently training as a neurology specialist and working as a resident in the Department of Neurology at TUM's Klinikum rechts der Isar hospital. A member of Prof. Mark Mühlau's working group, she is developing her expertise in magnetic resonance imaging (MRI) changes in MS and thus acts as a link to clinical neuroimmunology. Biberacher is researching various parameters derived from MRI analysis, for instance of the spinal cord, as well as from blood and cerebrospinal fluid testing. The objective is to identify correlations between these parameters – on the one hand, to gain a better understanding of the disease, and on the other, to enable more accurate predictions about its progression. Alongside this research, her work in the MS outpatient clinic has given her a chance to experience patient care. A faculty grant from TUM's KKF research commission is now freeing up a year for Biberacher to focus on her research endeavors.

Doctor and geneticist

PD Dr. Dorothea Buck is the senior physician in the outpatient clinic for neuroimmunology at TUM's Klinikum rechts der Isar hospital – a role that involves caring for patients with MS and other neuroimmunological diseases. She also belongs to a working group led by Prof. Bernhard Hemmer and is researching the genetics of the immune response in MS. In her clinical studies, she is focusing on genetic factors that contribute to the onset of MS and influence disease progression and therapeutic response. Discussing her research, Buck explains: "It dovetails very well with my practice as a doctor, creating synergies that benefit everyone involved." Her view is that working with patients equips clinical researchers with a deeper understanding of disease patterns and direct contact with those affected, which in turn can inspire research topics relevant to patient care. ▷

Picture credits: Jooss

Three years of research in the US

After six years of neurological residency, Dr. Veit Rothhammer began working in the MS outpatient clinic at TUM's Klinikum rechts der Isar hospital. Funded by a grant from the German Research Foundation (DFG), he is now spending three and a half years conducting research in the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital, a teaching affiliate of Harvard Medical School in Boston. Rothhammer's research is focused on astrocytes – brain cells that exert local influence on inflammatory processes in the central nervous system of MS patients. Astrocytes govern the pathogenic potential of peripheral immune system cells that migrate to the brain in the course of disease, for instance. Moreover, they regulate repair processes in the brain which are relevant for the survival and functionality of neurons during chronic stages of MS.

In Munich, Rothhammer was a member of research groups led by Prof. Thomas Korn and Prof. Bernhard Hemmer. In Boston, he is part of the group of Prof. Francisco Quintana in multidisciplinary teams comprising physicians, biologists, biostatisticians, engineers and chemists. As he puts it: "You have to think outside the box and approach an issue from several different angles. That is the only way to gain insight of truly valuable nature." At Harvard University, his experience is one of close interaction with researchers from a wide range of educational and cultural backgrounds. Rothhammer emphasizes the key role of mentors in both the professional and personal development of researching physicians, providing guidance, support and tuition, and engaging them in dialog. "My mentors have shown me the value of training as a clinician scientist through their own example," he confirms. Following his return from Boston to Munich in 2018, Rothhammer hopes to set up a research group at TUM to continue his research. In addition, clinical practice remains an equally important career goal for him. In his view, the clinical facilities and scientific research groups are exceptionally well networked at TUM – and particularly in neurology, which boasts fruitful collaborations with the biological and immunological institutes of TUM and LMU, as well as with the Helmholtz centers.

Combining clinical and biological research

As part of her training, Dr. Marina Herwerth is working as a resident in the neurological center (Neuro-Kopf-Zentrum) at TUM's Klinikum rechts der Isar hospital. She is using an experimental mouse model to investigate the mechanisms underlying the onset of MS and related autoimmune disorders. Two-photon microscopy (p. 92) enables her to examine new disease sites occurring in the spinal cord and explore ways to prevent this. Herwerth played a key role in setting up a cooperation between two MS research groups at TUM – one focusing on clinical immunology (Prof. Bernhard Hemmer) and the other on basic research in neurobiology (Prof. Thomas Misgeld). A faculty grant from TUM's KKF research commission enabled her to conduct research alongside her role in the clinic. However, like all her colleagues, she also relies on obtaining external funding. The Hertie Foundation

is currently providing funds for her MS project, which she is using to finance her position for two years. Summarizing the most important requirements of a clinician scientist, Herwerth pinpoints a high degree of motivation and an environment with solid support structures. She also emphasizes the important role of mentors, whose contacts prove valuable in building networks within the research community, for instance.

Junior research groups for basic science

An essential feature of multiple sclerosis research at TUM is the close collaboration between scientists and physicians. This enables investigation of underlying disease mechanisms such as molecular links, which can then be directly translated into new therapeutic strategies. The SyNergy excellence cluster (p. 31) specifically fosters this approach by networking basic and clinical research.

Gaining early independence

As a TUM Junior Fellow at the Institute of Neuronal Cell Biology, Dr. Tim Czopka is head of an independent Emmy Noether Independent Junior Research Group, financed by the German Research Foundation (DFG) and currently comprising four doctoral students. Using young zebrafish as an animal model, he is researching the mechanisms of myelination. Myelin forms a protective coating around nerve fibers, and the state of ▷

Picture credits: Jooss, Rothhammer

this myelin sheath is crucial to signal transmission between neurons. In MS, this protective layer comes under attack – and also undergoes partial repair. Czopka was one of the first to successfully visualize the cellular mechanisms of myelination in a living animal using high-resolution optical imaging techniques. Gaining a conceptual understanding of the way our nervous system functions and identifying specific molecular switches is of vital importance to understanding diseases and developing therapeutic approaches. And for Czopka, that is the very essence of his work as a biologist. In basic biomedical and neuroscience research, the lines between biology and medicine tend to be fluid. Very often, neuroscientific questions regarding brain function also have a medical component, since disordered brain development or function often manifests in human disease patterns. Czopka was recently awarded a prestigious European Research Council (ERC) Starting Grant for his project examining the heterogeneity of myelinating cells and researching the influence of aging on cellular behavior.

Combining biology and medical research

Dr. Leanne Godinho leads a research group at TUM's Institute of Neuronal Cell Biology. Godinho's training is in developmental biology and neuroscience and she is interested in the basic principles that underlie the assembly of the nervous system during embryonic and postnatal development. Her group uses the zebrafish retina as a model system. Zebrafish are vertebrates and their retina is remarkably similar to that of humans. Visual disturbances are common in many neurological diseases, including MS, with retinal ganglion cells a prime target. Through her work, Godinho hopes to provide insights into possible mechanisms of repair when neural circuits and the cells that form them are damaged by disease. As part of a Collaborative Research Center (CRC) consortium, she currently holds a grant funded by the German Research Foundation (DFG) to enable her

work. "The added benefit of receiving such a grant is the network of people that you come into contact with," she explains, stressing that complementary expertise and resources are extremely valuable. "Collaborations and networks are driven by the people doing the work. TUM's strength lies in fostering both basic and clinical or disease-related research, permitting synergistic interactions between scientists to occur naturally." Godinho works in close contact with the groups in her institute, with weekly joint meetings that allow for free exchange of ideas and provide opportunities to collaborate on projects of mutual interest. Some of these groups have a more medical bent to their work, for instance using mouse models of human diseases such as multiple sclerosis, and she has collaborated with them on a number of occasions to provide an efficient pipeline for testing tools in the zebrafish model prior to their use in mice.

Karsten Werth

Picture credit: Jooss