Werner Franke and the significance of his research results for medicine

Although based at a medically oriented institution dedicated to cancer research, basic biological research was at the center of Werner Franke's scientific life and thinking. Only from basic research - this was his firm conviction - can fundamentally new results emerge that can then be introduced into medicine and provide the impetus for diagnostic and therapeutic innovations there. In 1980, the author of these lines was the first medical employee to join his hitherto purely scientific, basic research-oriented group at the German Cancer Research Center in Heidelberg as a post-doc (several others followed). The assigned task was to help implement one of his central concerns: Where are there medical applications of his cell biological discoveries? At that time, natural science - especially cell and molecular biology - and medicine were still often separated by walls; there was little communication between the fields in cancer research, rather mutual distrust. Werner Franke, however, was one of the few basic researchers who, even back then, asked with every biological discovery, with every newly discovered protein, to what extent it could be used in medical diagnostics, in tumor diagnostics, i.e. in the real world of medicine. With this interdisciplinary approach, he was far ahead of his time.

One of his main discoveries was the cell type-specific expression of intermediate filament proteins. From his very first work, in the late 1970s, he sought cooperation with interested medical professionals, especially pathologists, to find out whether these proteins, or specific antibodies directed against them, could be used to diagnose cancer metastases. As a result of these collaborations with physicians, many of his cellular and molecular biological discoveries have since entered the diagnostic panel in tumor medicine, especially clinical pathology, and have become part of routine pathological diagnostics.

One example is vimentin, the intermediate filament protein of mesenchymal cells of connective tissue (Franke et al. 1978). He created the name - as so often - from Latin (vimentum = the wickerwork). Today, every pathological institute worldwide has antibodies against vimentin for the immunohistochemical diagnosis of soft tissue tumors.

A prominent area in Werner Franke's work is then represented by the cytokeratins, the complex multigene family system of intermediate filament proteins of epithelial cells. It was his discovery in the early 1980s that the diverse cytokeratin proteins are expressed in different epithelial tissues in different cell type-specific patterns (Franke et al. 1981a, Moll et al. 1982), and these results have been widely applied in clinical tumor pathology. In a tumor, intermediate

filaments of the cytokeratin type prove the presence of a carcinoma, even in metastasis, which is why in clinical tumor pathology a pan-cytokeratin antibody is used as the first immunohistochemical examination step in any unclear tumor. The molecular cytokeratin subtypes - classified in a cytokeratin catalog - then allow conclusions to be drawn about the specific organ of origin, such as cytokeratin 20 in colorectal carcinomas, cytokeratin 5 in head and neck squamous cell carcinomas, or specific cytokeratin combinations in urinary bladder carcinomas. Thus, cytokeratins and their subtypes have become indispensable in pathological tumor diagnostics.

Not only pathology, but also clinical oncology has been enriched by his research. One example is CYFRA 21-1, a serological tumor marker based on soluble cytokeratin 19. This marker can be determined in the blood for therapy control and recurrence monitoring, especially in patients with non-small cell lung cancer.

Besides the intracellular cytoskeleton, it was the cell-cell junctions that fascinated Werner Franke strongly and increasingly. A major component of the desmosomes, a junction type characteristic of epithelial cells, is desmoplakin, which he described in 1981-1983 (Franke et al. 1981b; Müller et al. 1983); for this name he resorted to the Greek. Here, too, Werner Franke demonstrated clinical applications in cooperation with physicians at an early stage (Franke et al. 1983). It turned out that desmoplakin could also be used as an immunohistochemical tumor marker in clinical pathology and neuropathology, for confirmation of an epithelial tumor or even a meningioma in the meninges.

Another clinical field of application of Werner Franke's basic research has opened up in cardiology. In the heart, the cell junctions of the myocardium are naturally of vital importance, especially the intercalated discs that maintain the tissue stability of the heart muscle. Werner Franke has intensively studied these junctions connecting the myocardial muscle cells and their unique and highly complex molecular structure. In the areae compositae, as he named these special cell-cell junctions, he discovered and described a special protein, plakophilin 2, in addition to a large number of other structural proteins including desmoplakin. As an essential component of the area composita, plakophilin 2 has an important function for the cohesion of the heart muscle tissue. There is now a failure of plakophilin 2 in some people due to congenital gene mutations. The resulting functional loss of this protein is, as we now know, one of the most common causes of an inherited cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), which can lead to sudden cardiac death. The molecular identification of plakophilin 2 as a research result of Werner Franke and his co-workers (Mertens et al. 1996)

and its transfer into medical application (Gerull et al. 2004) opened the possibility of genetic diagnostic testing for such mutations. Thus, in positive cases, appropriate measures and treatments can be initiated on the part of cardiologists, also for relatives possibly affected by the mutation. The same applies to other genes coding for cell junction proteins in the area composita of the cardiac muscle cell, such as desmoglein 2, which was also discovered by Werner Franke and his co-workers (Koch et al. 1991), whereby gene mutations here are also associated with ARVC, but also with dilated cardiomyopathy.

The examples compiled here impressively demonstrate how fundamental new findings can arise from knowledge-oriented cell and molecular biological basic research not primarily oriented towards application, which are then successfully transferred to the clinical world. In Werner Franke's scientific work, the medical fruits were numerous and they will endure forever.

Finally, I would like to take this opportunity to express my great gratitude for his support, on behalf of many other colleagues in medicine, to whom he has given the decisive impetus for professional scientific work in basic research and how the basic results obtained can then be transferred into medical practice, ultimately for the benefit of patients, and Werner Franke has personally advised not a few cancer and heart patients.

Prof. Dr. Roland Moll
Philipps-Universität Marburg, Institute of Pathology, Marburg, Germany

References:

Franke WW, Schmid E, Osborn M, Weber K (1978) Different intermediate-sized filaments distinguished by immunofluorescence microscopy. Proc Natl Acad Sci USA 75: 5034-5038.

Franke WW, Schiller DL, Moll R, Winter S, Schmid E, Engelbrecht I, Denk H, Krepler H, Platzer B (1981a) Diversity of cytokeratins. Differentiation specific expression of cytokeratin polypeptides in epithelial cells and tissues. J Mol Biol 153:933-959.

Franke WW, Schmid E, Grund C, Müller H, Engelbrecht I, Moll R, Stadler J, Jarasch ED (1981b) Antibodies to high molecular weight polypeptides of desmosomes: specific localization of a class of junctional proteins in cells and tissues. Differentiation 20:217-241

Franke WW, Moll R, Mueller H, Schmid E, Kuhn C, Krepler R, Artlieb U, Denk H (1983) Immunocytochemical identification of epithelium-derived human tumors with antibodies to desmosomal plaque proteins. Proc Natl Acad Sci USA 80:543-547.

Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, Lerman BB, Markowitz SM, Ellinor PT, MacRae CA, Peters S, Grossmann KS, Michely B, Sasse-Klaassen S, Birchmeier W, Dietz R, Breithardt G, Schulze-Bahr E, Thierfelder L (2004) Mutations in

the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet 36:1162-1164

Koch PJ, Goldschmidt MD, Walsh MJ, Zimbelmann R, Franke WW (1991) Complete amino acid sequence of the epidermal desmoglein precursor polypeptide and identification of a second type of desmoglein gene. Eur J Cell Biol 55:200-208.

Mertens C, Kuhn C, Franke WW (1996) Plakophilins 2a and 2b: constitutive proteins of dual location in the karyoplast and the desmosomal plaque. J Cell Biol 135:1009-1025

Moll R, Franke WW, Schiller DL, Geiger B, Krepler R (1982) The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell 31:11-24

Müller H, Franke WW (1983) Biochemical and immunological characterization of desmoplakins I and II, the major polypeptides of the desmosomal plaque. J Mol Biol 163:647-671