# Biopharmaceuticals…

## Everyday drugs for all?

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**There are currently several very good reasons to take a closer look at biopharmaceuticals. After the introduction of „modern biologicals" at the beginning of the 1990s, including antibodies versus tumor necrosis factor (infliximab, adalimumab), more affordable generics/"biosimilars" are increasingly being expected to replace original compounds no longer under patent protection [1]. Moreover, cancer therapy in particular is a field where dramatic progress seems to be being made with bispecific antibodies [2], especially those termed "checkpoint" blockers [3] (some featuring kinase inhibitors).**

The promise shown by biopharmaceuticals is exemplified in the treatment of the "highly lethal" bronchial carcinoma: the low survival rate of approximately 5 % of patients five years after diagnosis results from the fact that tumor cells do not merely go "under the radar" of the body's immune system but actively suppress the immune response. This induced tolerance vis-à-vis the tumor is being investigated via ligands for "checkpoint" molecules such as CTLA-4 and PD-1, which downregulate lymphocytes. Solid tumors such as aggressive non-small cell lung cancer (NSCLC) express PD-L1, a PD-1 ligand suppressing antitumor response, at about 20 – 60 %. Nivolumab, an anti-PD-1 antibody, blows the tumor's cover in this respect. Building on the success of the Merck drug pembrolizumab, also an anti-PD-1 antibody, which showed success in a quarter of melanoma patients fully unresponsive to further treatment, initial pilot studies with nivolumab in lung cancer have resulted in progression-free survival of up to 36 months in individual cases and a one-year survival rate of 50 – 70% [3]. As a result of this promising data, the FDA permitted clinical trials in non-pretreated melanoma/lung cancer patients to go ahead following shortened drug approval first for pembrolizumab and then for nivolumab. In NSCLC, nivolumab is combined as a basic therapy with drugs such as cisplatin/gemcitabin or erlotinib, so as to rapidly determine the optimum combination therapy. The leading international immunologist Abdul Abbas (UC San Francisco) uses the following analogy to illustrate the dramatic breakthrough made by tumor immune therapy: "… letting up on the brake (the tumor immune response) is much more effective than flooring the gas pedal." (remark made at WIRM IX, Davos 2015).

At 80 – 85 %, conventional small-molecule pharmaceuticals continue to constitute the lion's share of prescribed medicines while biopharmaceuticals make up less than 10 % of prescription medicines. Following a rather sporadic development of new protein-based drugs, originally using biological sources such as swine pancreas, urine from menopausal women or human pituitary glands, 25 – 30 % of approval applications since the 1990s have been for genetically-engineered substances, most of which are antibody-based drugs. Research is focusing on lessening the specific problems raised by biopharmaceuticals, some resulting from their nature as foreign protein. Antibodies are "humanized", i.e. the protein sequence is adjusted to match human sequences. In addition, it is also necessary to mimic the typical human glycosylation pattern. The most practical approach here involves

bioreactors with eukaryotic cells such as Chinese hamster ovary cells or human embryonal kidney cells. Recent advances in genetic engineering now permit productive cells or mosaic viruses in tobacco plants to be equipped with human glycosyltransferases for the production of „humanized“ biopharmaceuticals in yeasts or plants. Despite problems at the purification stage [4], cerebrosidases for the treatment of congenital storage diseases and triple Ebola vaccines for passive immunization have already been manufactured in plants [5].

A “general” availability for all patients depends on cost factors and the attending physician’s level of knowledge. A hoped-for reduction in costs has been expected following the expiry of patent protection in the form of “biosimilars”, whose production would grant entry to the biopharmaceuticals market to other, smaller businesses. As regards rheumatism, psoriasis and IBD, some are advancing the controversial thesis that earlier, highly-effective treatment with biopharmaceuticals would benefit patients while being potentially more cost-effective. Costs could also be lowered by improvements in industrial manufacturing systems (yeasts, plants, milk, virus-mediated prokaryote transduction).

To prevent pharmaceutical companies’ commercial interests becoming an obstacle to combining biopharmaceuticals to treat cancer (for example), committees have been formed, some of which may even secure cooperation and joint clinical trials by means of administrative orders.

Nor have we exhausted the options for manufacturing “simple” biopharmaceuticals. Gene transfer to therapeutic cells, which then manufacture biopharmaceuticals “on demand”, directly at the active site of the disease in the patient’s body, is an exciting new development that is currently being trialed (also by the author’s lab).

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**Editor’s note**

Our special thanks to the author, who not only informed us about this topical issue after the close of this year’s World Immune Regulation Meeting (WIRM), held from March 18th to March 21st in Davos, Switzerland (www.wirm.ch), but also provided us with an article.

**Heinfried H. Radeke** studied medicine at the Hannover Medical School (MHH) and received his medical license in 1985. His Ph.D. thesis was recognized as the best research dissertation of 1986. After two years as an assistant physician at the Göttingen University Hospital, he began his career at MHH in 1987 with his research focus: the mechanisms of chronic inflammation in the field of molecular pharmacology. He completed his habilitation in this field in 1993 before further specializing as a consultant for general pharmacology and toxicology, consultant immunologist (DGfI), and consultant for clinical pharmacology (Frankfurt, 2004). Following a four-month research project at BASF Bioresearch in Cambridge (Boston) in 1992, Heinfried Radeke spent the period 1994–1997 completing further DFG-sponsored research in the USA. This involved one year at UC San Francisco (interleukin-1 alpha and carcinogenesis), followed by two years at Case Western Reserve University in Cleveland (nephritis, differentiation of T cells). Since 2001, Prof. Radeke has been aiding the realignment of pharmazentrum frankfurt (Prof. Josef M. Pfeilschifter, dean of medical faculty and director of the Institute of General Pharmacology and Toxicology) towards immunopharmacology, from 2001 to 2008 as the Dr. Hans Schleussner Foundation Lecturer for Immunopharmacology. He plays a decisive role in the training of medical and dental students, with past positions including that of deputy director of the DFG’s largest research training group, GRK1172 Biologicals, in which over 100 doctorates were awarded from 2005–2014.