Healthcare industry BW

Ralf Baumeister – tinkering, constructing and switching off genes

The focus of Ralf Baumeister's research, a small nematode that is known as Caenorhabditis elegans, is a rather simple organism. Nevertheless, the worm can be used to study complicated behaviour, including associated learning. This is how Prof. Dr. Ralf Baumeister from the Institute of Biology III at the University of Freiburg describes the animal that he works with on a daily basis. The worm has now got very little left to hide. Virtually everything has been studied in detail, its 302 neurons, its 959 body cells and its 19,253 genes. And the genetic information we learn from C. elegans is in many cases directly applicable to humans.

Bioinformatician and molecular biologist Prof. Dr. Ralf Baumeister.

His school biology teacher and his uncle, who was an eager ornithologist, have both helped shape Baumeister's passion for biology. Prof. Dr. Ralf Baumeister, head of the Department of Bioinformatics and Molecular Genetics at the University of Freiburg, was born in the southern German city of Schwabach close to Nuremberg in 1961. He originally wanted to study medicine and go into science, although not as a medical doctor. "I have always been interested in the mechanisms of disease," said Baumeister. Admission to medical studies proved difficult, which is why he decided to study chemistry. However, he soon realised that this was not right for him, and decided to turn to biology instead. "I've tremendously enjoyed this subject from the very first second," said Baumeister.

He did his degree and doctoral theses at the University of Erlangen in Wolfgang Hillen's laboratory

where he focused on the molecular mechanisms of the regulation of tetracycline resistance genes in the bacterium Escherichia coli. He was awarded his PhD in 1992. He became interested in organismic research when he heard of a small worm in which the synapses and connections of all 302 neurons were known. He was fascinated by the idea of finding out more about this by simulating and analysing the worm in silico using computers. Baumeister: “I became interested in Caenorhabditis elegans long before I even knew the worm’s name.”

Caenorhabditis elegans – a tiny animal for a broad range of experimental options

Baumeister found mouse research too complicated and far too time-consuming. That is why he turned to C. elegans, an organism that can be applied to many research questions and enables researchers to “tinker, construct and switch off genes”. It was as a postdoctoral researcher in Gary Ruvkun’s neurobiological laboratory at Harvard Medical School in Boston (USA) that Baumeister was first introduced to his preferred model organism, i.e. Caenorhabditis elegans (C. elegans). After all, this little creature is the model organism of six scientists who have been Nobel prizewinners in the last decade. “The experimental attributes of C. elegans make it a valuable research tool; it enables researchers to approach experimental issues with childlike naivety without having to take into account ethical and temporal restrictions. Moreover, research with C. elegans is not as costly as research involving other model organisms,” said the molecular biologist. “In addition, the worm’s genome is surprisingly similar to that of humans, which is why C. elegans has become an attractive organism for studying issues related to humans,” Baumeister added. It was therefore no coincidence that the laboratory where the first microRNAs were cloned and the regulatory mechanisms of C. elegans were analysed on all levels was a laboratory where the scientists were as keen as Baumeister on using C. elegans for experimental purposes.

The worm in us - C. elegans as a model of human disease

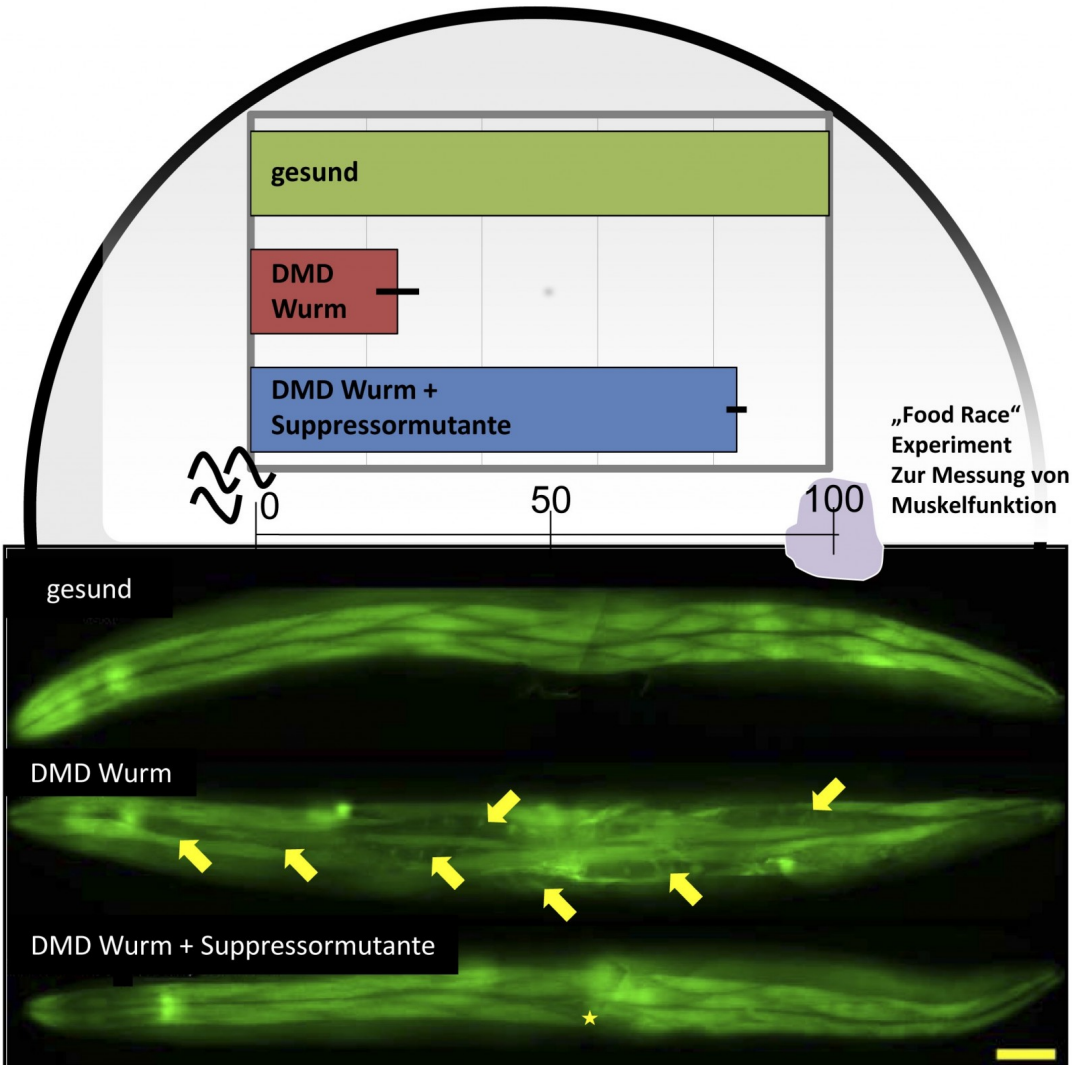
Following his stays at the Gene Center in Munich and the Ludwig Maximillian University in Munich, where he was professor of metabolic biochemistry, Baumeister became professor at the Institute of Biology III at the University of Freiburg in 2003. He was also instrumental in the establishment of the Center for Biological Systems Analysis (ZBSA) in 2008 and was director of the ZBSA until 2010.

His main interest is the study of the genetic regulation of ageing and the mechanisms involved in the development of neurodegenerative diseases such as Parkinson's and Alzheimer's as well as Duchenne muscular dystrophy (DMD). "Two-thirds of all human disease genes have a counterpart in C. elegans," said Baumeister referring to the similarity of the worm genome with that of humans, "and it often shows that although the phenotype may be different, the underlying regulatory mechanisms are the same."

Baumeister, who has also studied computer sciences at university level, adopted a systematic approach to finding answers to his questions. His major tools come from the field of genetics, a field that enables the creation of mutations and hence the manipulation of phenotypes. Mutants can be produced from any gene whatsoever, for example by knocking out specific genes. Duchenne muscular dystrophy, one of the most common genetic disorders in humans, is caused by a mutation of the dystrophin gene. The loss of dystrophin (ed. note: dystrophin is part of the dystrophin-glycoprotein complex which provides mechanical stability to the sarcolemmma, i.e. cell membrane of a muscle cell) leads to the progressive wasting of skeletal muscles, eventually resulting in cardiac and respiratory failure, which is a major reason for the early death of those affected. “We are interested in finding out how certain genetic defects and their effects can be prevented or reversed,”

said the geneticist.

Minus times minus gives plus



“Food race“ experiment for measuring muscular activity using worms. Worms with different genetic backgrounds migrating in a Petri dish on a scale from 0 to 100 (food source, purple) in 120 min. Above: percentage of worms that reach the food source. Bottom: photo showing a wild-type specimen (no defective muscles), a DMD mutant (defective muscles are indicated by arrows) and a DMD/suppressor mutant (where muscle degeneration is efficiently reduced; indicated by an asterisk).

Modification of the dystrophin gene in C. elegans also has far-reaching effects: dystrophin mutation gives rise to a worm that lacks some of its 95 muscle cells and has difficulties moving around. In many cases, it is impossible to repair the defective gene. “Now the exciting question is whether it is possible to knock out any other of the remaining 19,252 genes in addition to the gene mutation that normally leads to muscle weakness and whether knocking out another gene is able to compensate the dystrophin gene mutation?” Baumeister provides the unexpected answer to the question himself: “This actually works!” The geneticist works systematically, switching off one gene after the other and studying what happens. In the majority of cases, knocking out other genes tends to worsen muscle weakness. “However, I came across three cases where the worms recovered although they were still carrying the disease-causing defect,” said Baumeister enthusiastically. What happened in this case? Every cell has a surveillance system that controls whether all protein components function as they should. If a mistake is identified, then the defective proteins are taken to the proteasome where they

are degraded. In the case of DMD, the cell guardian has realised that the stabilising dystrophin-glycoprotein complex is defective and the cell is damaged to a degree that prevents it from living as long as a healthy one. The defective cell is eliminated, which leads to the degeneration of the muscles. "Each of the three genes that we have knocked out in addition to the disease-causing gene, are part of this garbage system," said Baumeister explaining that this does not solve the underlying problem as the cell remains defective. However, the intervention prevents the cell from being labelled as garbage and destroyed." In the suppressor mutant, one genetic defect is therefore compensated by a second. Sometimes it seems better to operate a cell at only eighty percent of its normal performance level rather than with zero performance.

Smart synthesis of work and free time

Baumeister and his team found five genes for Alzheimer's and 17 genes for Parkinson's that were able to at least partially compensate disease-causing mutations. However, Baumeister does not yet want to disclose any more findings. "Moments like this where we find something are real highlights of our lives as researchers," said Baumeister, a tango dancer in his spare time, and hopes that the competition between scientists will eventually give way to interdisciplinary cooperation so that the huge amount of data produced in biological disciplines can be dealt with intelligently. But, in the meantime, as Baumeister points out, there is also life beyond the laboratory to enjoy.

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Article

25-Mar-2013
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BioRegion Freiburg

The article is part of the following dossiers

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