Healthcare industry BW

# Manfred Jung: drug discovery and the epigenetic code

**Environmental factors can influence the tightness of DNA packaging. Loosely wrapped DNA is more readily accessible and therefore more easily transcribed than tightly wrapped DNA. These epigenetic modifications are inherited by daughter cells when the cells divide and passed on to offspring; the epigenetic memory also helps cells to maintain their identity. Over the last ten years, researchers have also provided increasing evidence as to how the epigenetic memory influences the behaviour of tumour cells. Prof. Dr. Manfred Jung's team at the University of Freiburg are chemical epigeneticists, whose research involves the development of methods that enable them to identify and optimise new therapeutic drugs which are able to alter the epigenetic code of cancer and other cell types. The team use a perfidious worm for their research.**

Schistosoma trematodes, commonly known as flukes, are parasitic flatworms whose development involves two different hosts – snails and humans: the flatworm uses ramshorn snails which live in tropical and subtropical waters as intermediate hosts. The snails excrete the Schistosoma larvae into the water where people, for example if they have rough skin, can be infected and develop schistosomiasis (also known as bilharzia or snail fever). This disease affects around 300 million people worldwide, mainly in developing countries. Once the parasite has entered the human blood system, it changes the way it behaves and starts to feed on blood components. The move from the snail to the human host requires the worm to change genetic programmes. "Epigenetic chromatin modifications determine which parasite genes are transcribed under specific environmental conditions," said Prof. Dr. Manfred Jung from the Chemical Epigenetics Group in the Department of Pharmaceutical Chemistry at the University of Freiburg. "Cancer cells are able to continue dividing indefinitely as a result of epigenetic modifications, without alterations to the genetic code."

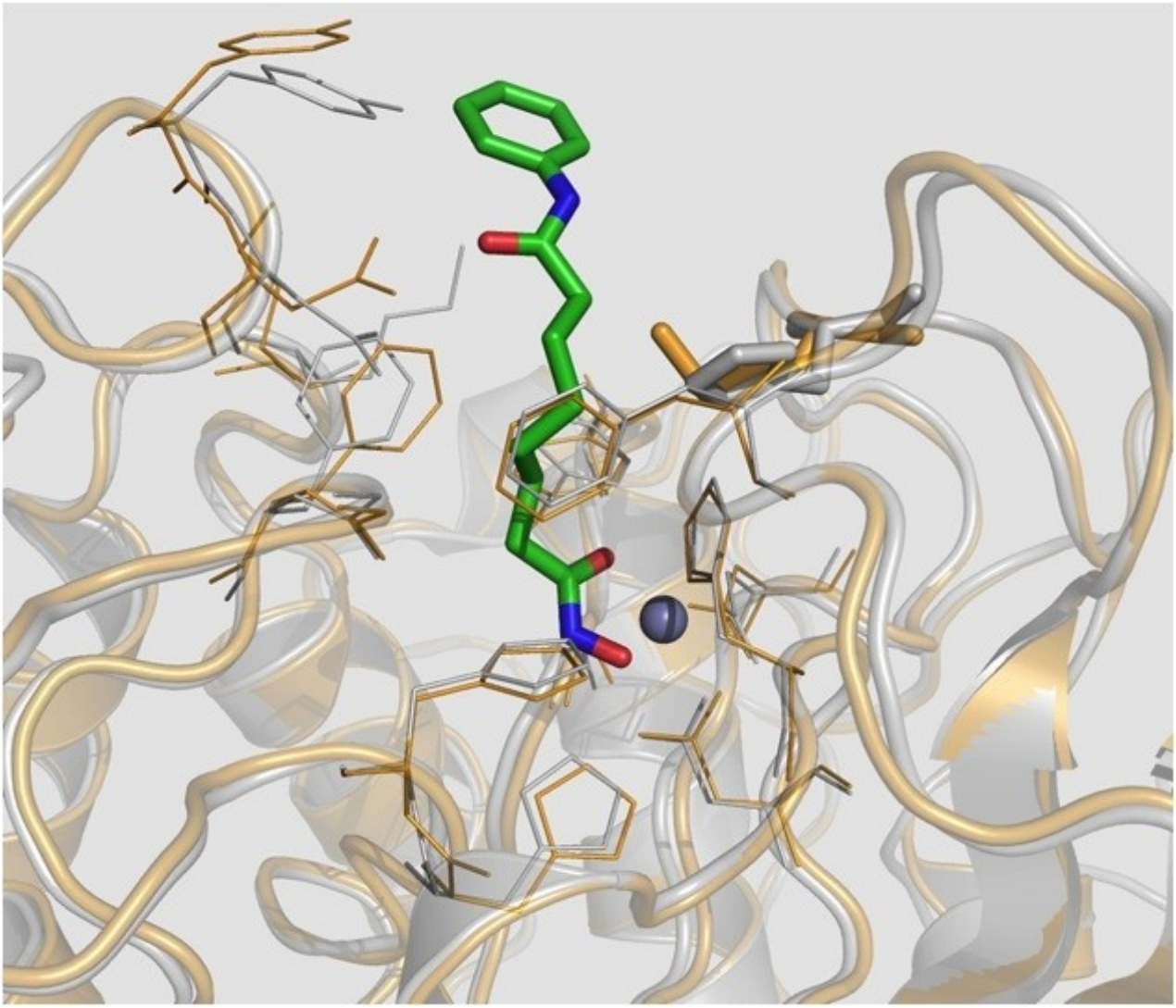
Chemical Epigenetics Group led by Prof. Dr. Manfred Jung (fifth from the left).


## Interfering with the code?

DNA in the cell nucleus is packaged into a condensed structure known as chromatin. The DNA is wrapped around spherical structures, i.e. nucleosomes consisting of histones and other proteins. More tightly packaged chromatin prevents transcription enzymes from accessing the DNA with the consequence that the genes encoded by this particular DNA stretch are turned off. The chemical modification of DNA and histones alters the local chromatin structure. Small chemical modifications, for example methyl and acetyl groups that are attached to histones by specific enzymes, form a kind of chromatin code that defines which genes are transcribed and which are not. This is also the reason why neurons behave differently from liver cells. The epigenetic modifications are passed on to daughter cells when the cells divide and can also be altered by environmental influences such as food consumed or the chemical environment that prevails in a specific host. “We are focused on finding drugs that are able to interfere with the epigenetic code,” said Jung.

In other words, Jung and his team are focusing on drug discovery. The researchers' drug targets include enzymes - histone acetylases, histone deacetylases and methyl transferases - that transfer acetyl and methyl groups to histones. How can inhibitors of such enzymes be found? In order to come up with an answer to this question, Jung and his team are working with a group of researchers led by Prof. Dr. Wolfgang Sippl at the University of Halle. Sippl and Jung are both part of the interdisciplinary research group programme at the Freiburg Institute for Advanced Studies (FRIAS). Sippl uses computers to simulate interactions between these enzymes and potential drugs, which enables him to make predictions on the chemical structure of a potential drug and reduce the number of drug candidates from a couple of million to a few hundred or even less.

Jung and his team subsequently use Sippl's most promising lead structures to test their efficiency in inhibiting chromatin- and DNA-modifying enzymes and optimise the structure of the molecules under investigation. In the future, Sippl and Jung's FRIAS project will also involve working in cooperation with the group of Prof. Dr. Oliver Einsle, a structural biochemist at the University of Freiburg.



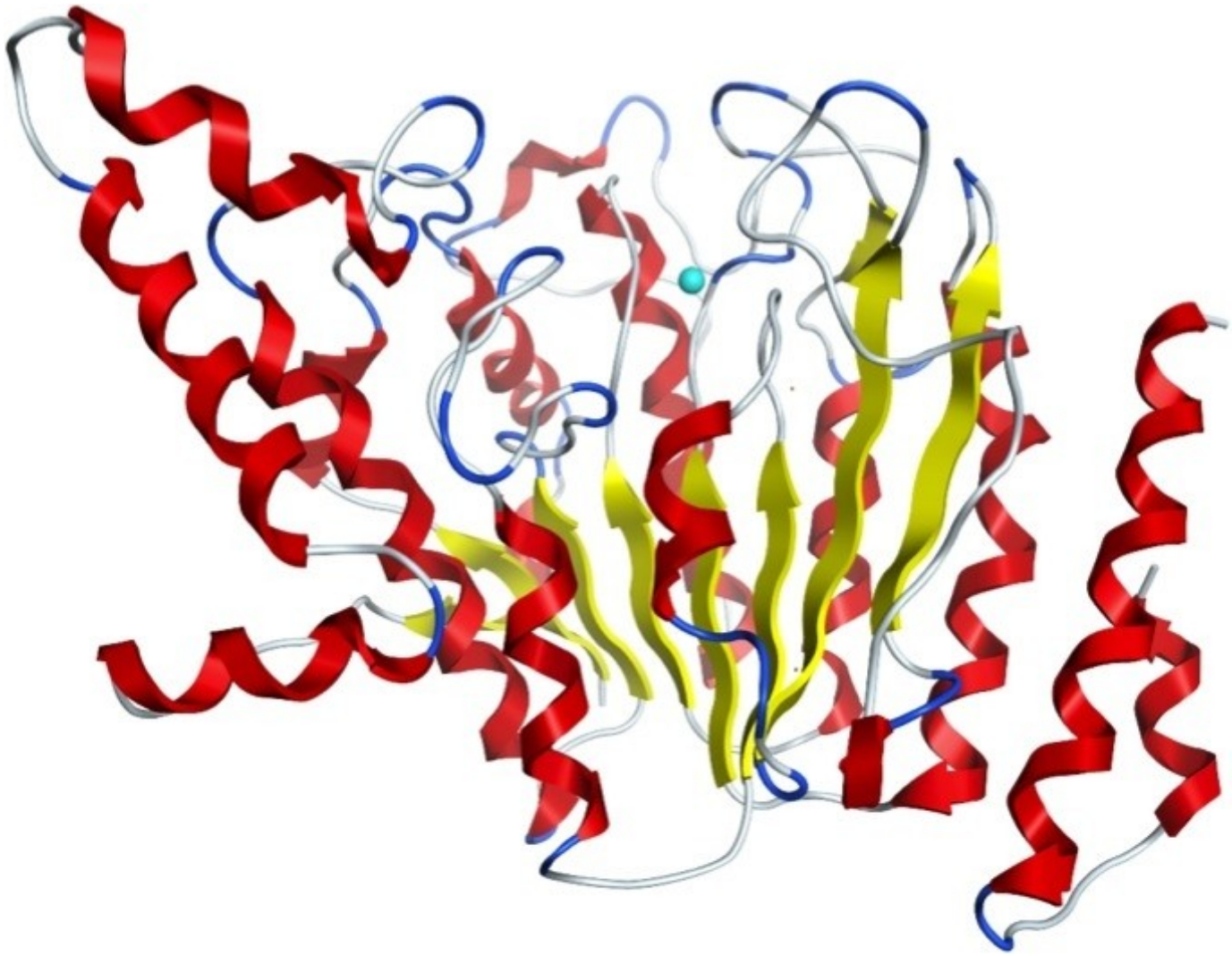
Computer predicted interaction between a histone deacetylase (orange and grey) and a histone deacetylase inhibitor (green).


Structural investigations of the interaction between the enzymes and potential inhibitors will then provide the researchers with more information on the inhibitory mechanisms.

## From basic research to application?

Over the last few years, the researchers from Freiburg have identified two inhibitors, one that blocks a histone deacetylase enzyme and one that blocks an enzyme known as arginine methyltransferase. These substances have been found to control the in-vitro growth of tumour cells, but their clinical application is still a long way off. A major difficulty is the fact that the inhibitors of DNA- and chromatin-modifying enzymes have a global effect, which means they do not exclusively target tumour cells and genes that regulate cell division activity.

The Schistosoma project is confronted with a similar problem: a drug that has the potential to kill the parasite must not affect the epigenetic profile of the human host cells. Despite this problem, Jung still believes that the chosen approach has enormous potential. Four epigenetic inhibitors have already received marketing authorisation as anti-cancer drugs and others are currently undergoing clinical testing. "Maybe at some stage in the future we will also be able to come up with an epigenetic drug," said Jung.



X-ray crystal structure of the Schistosoma histone deacetylase HDAC8.
© Prof. Dr. Wolfgang Sippl

As head of an academic group of researchers, Jung mainly sees himself as a basic researcher. He is mainly concentrating on the development of new methods that enable the discovery of new drugs. High-throughput screening approaches that enable the effect of hundreds of thousands of potential molecules to be tested at the same time as making it possible to run preclinical and clinical studies to assess and validate the effects and adverse effects of concrete substances are highly costly and can therefore only be carried out by industry. Although the researchers from Freiburg are unable to carry out such studies on their own, they nevertheless contribute important ideas to the field.

In order to establish an optimal drug discovery infrastructure in the field of epigenetics, the Freiburg researchers are working with Prof. Dr. Roland Schüle from the Centre of Clinical Research at Freiburg University and Prof. Dr. Thomas Jenuwein from the Freiburg-based Max Planck Institute (MPI) of Immunobiology and Epigenetics. The research partners are aiming to establish a new cooperative research centre that will offer support to researchers in their endeavour to translate ideas into concrete drug targets. The future cooperative research centre will also involve partners from industry. The Schistosomas project has also made some progress; Jung and his colleagues have identified an inhibitor that specifically targets the epigenetic code of the flatworm. "We will now focus on the optimisation of this inhibitor," said Jung.

**Further information:**

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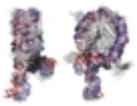

Epigenetics – heritable traits without changing the DNA sequence