DR CARSTEN KORTH

DISC1 discoveries

Questions still remain about chronic mental diseases such as schizophrenia, but **Dr Carsten Korth** believes he can help to paint a clearer picture of the biological mechanisms behind these diseases using the DISC1 protein

How will your research improve treatment for chronic mental diseases (CMD)?

The aim of my current research is to define the biology of CMD like schizophrenia by defining subgroups based on a distinct and clear biology, in particular a signature of protein pathology, ie. dysfunctional and aggregated proteins. Based on the definition of biology-based subgroups, the aim is to develop novel pharmacotherapies targeting the unique revealed molecular circuitry.

What evidence led you to the hypothesis that schizophrenia results in dysfunctional neurons which then accumulate misfolded proteins?

A particular feature of the main information-processing cells in the brain, the neurons, is that they have stopped dividing at a very early stage, many even before birth. That means that they cannot deal with arising cellular debris like a dividing cell that basically dilutes out its debris in cell division cycles. When a neuron becomes chronically dysfunctional, therefore, these clearing functions are thrown out of balance and protein aggregates result. The chronicity of most schizophrenia cases makes the existence of dysfunctional neurons very likely, and therefore led us to hypothesise that for identifying unique molecular signatures we should look for insoluble proteins in the (post mortem) brains of schizophrenia patients.

Through what methods do you plan to explore this hypothesis? Have you developed any novel approaches?

Our initial investigations focused on the purification of insoluble material from post mortem brains of patients with CMD, in particular with schizophrenia, and use individuals with no brain diseases, as well as those with unrelated brain diseases as controls. We modified methods that have been known in the field of protein conformational diseases to biochemically purify insoluble proteins. In one line of research, we took a candidate gene approach, ie. we investigated the protein products from genes that had been identified to be linked to familial forms of CMD, like the Disrupted-in-schizophrenia (DISC1) gene. We also analysed the insoluble proteins of post mortem brains by proteomics or a novel technique of disease-associated epitope discovery. In epitope discovery we generate antibodies against the insoluble proteome and screen for an exclusive and differential recognition of diseased tissue versus controls.

Amongst your findings to date, what has been most important?

Apart from our initial discovery of insoluble DISC1 in a subset of CMD cases, we have also been able to demonstrate that disease-associated polymorphisms within the DISC1 gene facilitate DISC1 aggregation, thus hinting at a possible mechanism of how these genetic changes act on the protein level. Recently, we have been able to demonstrate in cell culture models that DISC1 aggregates are cell-invasive, ie. they penetrate cells and can there recruit otherwise soluble proteins, like the schizophrenia candidate protein dysbindin. This research has recently been awarded the Ziskind-Somerfeld Award 2012 from the prestigious Society of Biological Psychiatry.

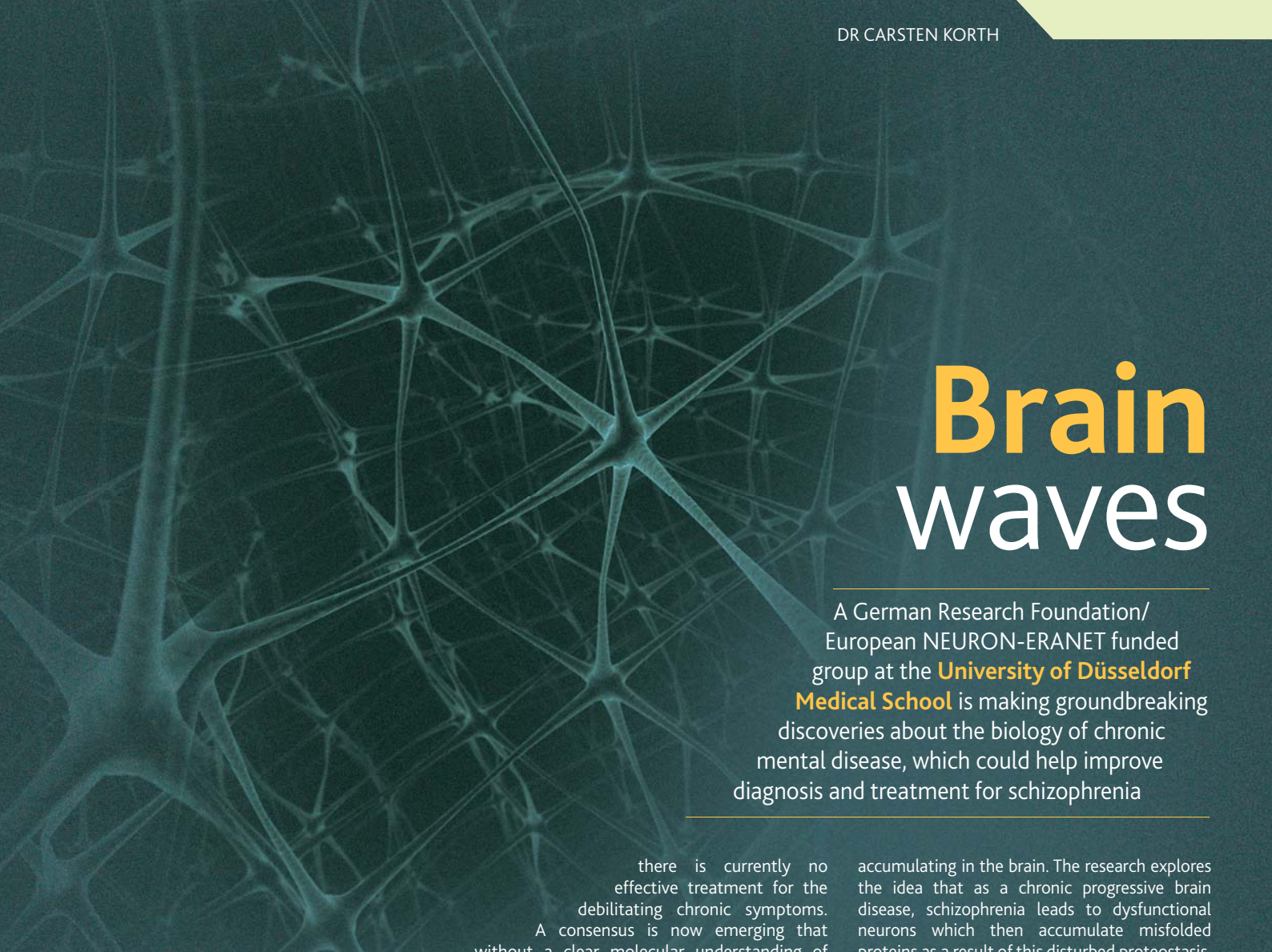
What are the most challenging aspects of this work?

Regarding the general research situation for this particular field, it would be desirable to have more research institutions providing an explicit focus on molecular psychiatry. A definite shortcoming in the field is the lack of systematic biobanking, where well documented and diagnosed CMD patients' tissues, including post mortem brains and fibroblasts are deposited and available.

In specific terms, one of the most challenging problems is to develop face valid animal models for CMD, ie. models that truly reflect a feature that is also present in the corresponding human disease subgroup. So far, animal models for CMD are mainly based on rather broad and sometimes far-fetched behavioural assays. Ultimately, identifying a solid and highly specific neuropathological feature like insoluble DISC1 in specific cells or brain regions could be one way to solve the problem of face validity of animal models.

Could you outline the next steps in your study?

We are currently analysing different animal models for DISC1 aggregation and also novel aggregated proteins in CMD that could possibly define yet other, different subcategories of CMD. We are actively searching for a biological signature for CMD defined by dysfunctional DISC1, that is DISC1opathies, for example by developing a blood test in collaboration with clinical psychiatrists or by investigating induced pluripotent stem cells from patients. Together with medicinal chemists we have started to look into the identification of pharmacotherapies able to influence DISC1 assembly such that it is beneficial for the cellular circuitry affected by DISC1 misassembly.



Brain waves

A German Research Foundation/ European NEURON-ERANET funded group at the **University of Düsseldorf Medical School** is making groundbreaking discoveries about the biology of chronic mental disease, which could help improve diagnosis and treatment for schizophrenia

ALTHOUGH CHRONIC MENTAL DISEASES (CMD) like schizophrenia are prevalent, effective treatments have remained elusive, largely because the biological mechanisms behind the disease processes are unknown. This means that in the absence of specific diagnostic tests like a blood test or radiological imaging, commonly used in the diagnosis of other medical conditions, CMD are still diagnosed in a clinical interview by self-reporting of patients.

Increasing evidence from genetic studies suggests that many CMD clinical phenotypes do not strictly segregate with only one genetic marker. Furthermore, epidemiological studies have demonstrated that there is an overlap of clinical disease entities on identical genetic backgrounds; for example the same individuals or close relatives of them can suffer from alternating schizophrenic or affective symptoms demonstrating that there is a continuum of clinical psychiatric symptoms rather than a categorical difference between them.

In the case of schizophrenia, although the acute episodes of psychosis can be sufficiently treated symptomatically with drugs that compete with the neurotransmitter dopamine in the brain, there is currently no effective treatment for the debilitating chronic symptoms. A consensus is now emerging that without a clear molecular understanding of CMD like schizophrenia or recurrent affective disorders, progress in developing effective treatments is unlikely to be made.

DEFINING SUBGROUPS OF CMD

Now, a research group based at the Heinrich Heine University of Düsseldorf Medical School in Germany is making headway in advancing a biological definition of CMD. Funded by the German Research Foundation/European NEURON-ERANET and led by Dr Carsten Korth, his group's strategy is to define subgroups of CMD based on a distinct protein pathology within the broadly defined clinical diagnosis of schizophrenia; an approach that has been very successful in investigating the mechanisms of other diseases such as Alzheimer's, where the study of how the characteristic, aggregating Abeta peptide is generated, has led to some profound insights.

Korth is focusing on the protein biochemical elements of brain pathophysiology in schizophrenia and in particular on disturbed proteostasis – where dysfunctional neurons are unable to correctly build up and degrade proteins – which results in aggregated or insoluble proteins accumulating in the brain. The research explores the idea that as a chronic progressive brain disease, schizophrenia leads to dysfunctional neurons which then accumulate misfolded proteins as a result of this disturbed proteostasis. "The identification and characterisation of these proteins would provide a handle to uncover a disturbed cellular process, since in other chronic brain diseases, the same proteins that are mutant in familial forms of these diseases have also been shown to have accumulated in sporadic forms of the diseases," Korth explains.

DISC1OPATHIES

Results so far have been groundbreaking and have led them to develop a novel CMD disease category defined by the involvement of the Disrupted-in-schizophrenia 1 (DISC1) protein, which the researchers have termed 'DISC1opathies'. The DISC1 protein has been shown to be a key regulator in behavioural control, since the presence of mutant DISC1 causes different cellular distribution, interactions, cortical development and behaviour in transgenic animals expressing mutant or no DISC1. By investigating an established collection of post mortem brains from individuals with CMD, Korth's group discovered that in about 20 per cent of cases, insoluble DISC1 immunoreactivity was present in the cingulum cortex, a brain region that had previously been assigned important functions

IDENTIFICATION OF MISFOLDED PROTEINS IN SCHIZOPHRENIA – DISC1OPATHIES AND MORE

OBJECTIVES

- To define distinct biology-based subgroups of schizophrenia, in particular by their protein pathology
- To generate face valid, novel animal models displaying those disturbed biological pathways and use them for developing novel pharmacotherapies
- To translate insights generated by modelling biology-based subgroups of schizophrenia in animals back into clinical diagnostics and therapy

KEY COLLABORATORS

Joseph P Huston, University of Düsseldorf, Germany • **Akira Sawa**, Johns Hopkins University Medical School, USA • **William Hennah**, University of Helsinki, Finland • **Jesus Requena**, University of Santiago, Spain • **Orly Reiner**, Department of Medical Genetics, Weizmann Institute, Israel • **Vishwanath Lingappa**, University of California San Francisco/Prosetta, USA

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CARSTEN KORTH completed his residency in psychiatry at the Max Planck Institute, earned his PhD at the Free University of Amsterdam and received postdoctoral training at the University of California San Francisco. He co-founded the company Prionics AG. Since 2002 Korth has served as Research Group Leader at the University of Düsseldorf.

in behavioural control. They therefore reasoned that insoluble DISC1 may be a defining marker of a subgroup: "By defining a subcategory of CMD based on a DISC1-dependent pathophysiology, our goal of defining mental diseases based on their biology can be jump-started," he adds.

In addition, it has been shown in cell models that DISC1 aggregates both lose molecular interactions with other key proteins and gain new interactions, for example with other proteins independently linked to schizophrenia, such as dysbindin, thereby profoundly changing neuronal functions and communication. Moreover, DISC1 aggregates display – like protein aggregates from other classical neurodegenerative diseases – a key feature of protein conformational diseases: cell-invasiveness.

DISC1opathies are diseases where the molecular origin can be traced back to a dysfunctionality of the extended DISC1 pathway and thereby be defined independently from their behavioural phenotype like schizophrenia or depression. This method of defining mental diseases is a paradigm change to current clinical diagnostics in that the classification is made by subgroups based on biology rather than on clinical phenotypes. The advantage of this approach is that biology-based classifications have more potential to facilitate the translatability of experimental *in vitro* or *in vivo* disease models to patients and therefore accelerate the development of novel pharmacological therapies.

REVOLUTIONISING CMD DIAGNOSIS AND TREATMENT

Other proteins have also been identified that are insoluble in the brains of CMD patients. The project members are currently investigating their cellular biology, genetics and disease pathways in collaboration with experts from behavioural neuroscience and genetics.
Work is also done in collaboration with clinical psychiatrists in developing blood-based diagnostics of CMD, and specifically to identify a blood-based identification of DISC1opathies. "I believe that the availability of objective testing for CMD will remove much of the stigma that still exists for CMD, because the patients will be able to say 'I have been tested positive for X' rather than receiving a perceived verdict based on an interview," Korth predicts. Ultimately, this research is a first step in defining biology-based subgroups which could lead to the abolishment of the diagnosis schizophrenia as it is now used. His vision is that it will be replaced by a variety of 'X'-opathies, each designating a biology-defined disease category with different pharmacological targets for each.

Clinical psychiatrists, patients and pharmaceutical companies agree that a causal therapy, primarily for the irreversible chronic symptoms of CMD like schizophrenia is urgently needed and the establishment of a biological test or signature can be separated from the development of novel pharmacotherapies because patients need to be identified based on whether their biological subgroup will respond to such therapies. Thus defining subcategories opens the door for novel diagnostics, animal modelling and the development of novel therapies. The researchers have already begun to develop pharmacotherapies counteracting the misassembly or aggregation of DISC1 or other misassembled proteins in CMD. Furthermore, several top research laboratories around the world have now also begun to characterise misfolded proteins in CMD, including pharmaceutical companies; an indicator that the research Korth's group has initiated has gained recognition and acceptance in the field of molecular psychiatry.