München (TUM), the German Center for Neurodegenerative Diseases (DZNE) and the Max Planck Institutes for Biochemistry, Neurobiology and Psychiatry will participate in the venture. Indeed, its protagonists hope to place a whole new field on the map – systems neurology – and the new Cluster of Excellence, with the catchy name “SyNergy”, could turn Munich into the European headquarters of the discipline.

Placing a whole new field on the map

The first job is to tear down fences. Neurological disorders have traditionally been classified as either neurodegenerative, inflammatory or vascular in origin. “These have generally been viewed in isolation, and studied in separate compartments,” says Martin Dichgans, Head of the Institute for Stroke and Dementia Research at the Medical Center in Großhadern. “For my part, I have worked mainly on Alzheimer’s disease, and seldom looked over the garden wall,” remarks Christian Haass, Professor of Metabolic Biochemistry at LMU and Coordinator for the Cluster (his Co-Coordinator is Professor Thomas Misgeld, Chair of Biomolecular Sensing at the TUM). “I just concentrated on my own Alzheimer’s projects. But sooner or later, one comes up against an impasse. I had always closed my eyes to the fact that Alzheimer’s patients, without exception, also show signs of inflammation and vascular pathology in the brain”. In other words, he had ignored two important markers of Alzheimer’s dementia, because he focused on the so-called amyloid plaques, the toxic protein deposits found in the affected brain cells, as playing the key role.

Conversely, most of his colleagues in other laboratories that focused on inflammatory diseases or on the molecular mechanisms underlying strokes failed to notice, for example, that dementia symptoms often appear in the aftermath of a stroke. Haass says that when one raises the issue in leading labs around the city, the expression “tunnel vision” often comes up. SyNergy was specifically conceived to change this by getting disparate research groups, some of them very well known in their special fields, to collaborate.

The Cluster is also a response to recent research findings, which have uncovered unexpected mechanistic parallels between apparently very different neuropathological conditions, such as Alzheimer’s and Parkinson’s, multiple sclerosis (MS) and the devastating amyotrophic lateral sclerosis (ALS). The common features may be involved in their genesis, progression or amelioration. “But what is important is how
each factor interacts with others, and what this tells us about how best to treat the disorder in question,” says Haass. Multiple sclerosis, for example, is an inflammatory disease, but the inflammation promotes secondary neurodegenerative processes, making the condition much more difficult to manage. “We have so far overlooked the similarities and overlaps between these different areas.”

**Taking risks – to make real breakthroughs**

With stroke a similar picture emerges. Factors like hypertension, diabetes, defects in fat metabolism that contribute to stroke are also statistically associated with increased risk for Alzheimer’s. “We have begun to recognize that these conditions often develop in parallel,” says Martin Dichgans, which suggests that they should also be investigated in parallel. Dichgans recalls the case of an 80-year-old with memory difficulties, who was referred to his stroke unit. Tests revealed not only neurodegenerative changes, but also alterations in the tiny capillaries in the brain, which would have a negative effect on cerebral blood flow. “Both together increase the risk of dementia,” says Dichgans. The two factors potentiate each other, both acting to impair cognitive performance. One may predominate in one case, the other in the next.

So researchers from diverse backgrounds will now work together to tease out common mechanisms of neurological disorders. In addition to facilitating such “horizontal” connections, the creators of SyNergy intend to forge links in the “vertical” plane. Thus, they wish to integrate basic research more closely with what clinicians encounter in their daily consultations, so as to ensure that laboratory findings are translated into therapeutic benefits as quickly as possible. This in turn implies that clinical observations should feed back into experimental paradigms. In this context, there are high hopes for so-called tandem projects, in which specialists in different fields collaborate on the design and realization of a common program. An expert on neurodegeneration might cooperate with an authority in the area of inflammatory reactions or vascular dynamics, for example. In fact, SyNergy will only provide support for projects of this sort. “That sounds rather contrived at first,” says Haass. “But in this way, we can bring together people who have been working on related phenomena unawares.”

A rather large ALS project is a perfect example of the approach. Six different research groups, ranging from stem-cell researchers to clinicians, are taking part. As Haass points out, “It had never occurred to clinicians that vascular disturbances might play a role in the pathogenesis of ALS.” The first indications came from genetic experiments on zebrafish. When Haass and his colleague Bettina Schmid, also a member of the SyNergy Cluster, recently knocked out the zebrafish version of a gene known to be associated with ALS in humans, they observed striking defects in blood flow in the spinal cord and brain of the mutants. Abnormalities like this can often be seen in intact specimens of the 3-cm-long fish, which are almost transparent during early development. When he and Schmid gave a joint lecture on their findings at the LMU Graduate School of Systemic Neurosciences, Haass was approached by Marianne Dieterich, Director of the Neurological Clinic in Großhadern. “Together, we sketched out the idea for a tandem project within 10 minutes”, he recalls. Another member of the ALS project, Dieter Edbauer, Professor of Translational Neurobiochemistry at the German Center for Neurodegenerative Diseases (DZNE) in Munich, hopes to...
develop a cell-culture model for the disease. “Such cell-based models are ideal for testing the effects of potential drugs, for instance,” says Haass. As he explains, ALS research has been greatly boosted by the discovery of a series of genes that are linked with this form of dementia. “We now have the opportunity to study this disease virtually from scratch.” The Cluster of Excellence also allows researchers to explore entirely new avenues, and try out things that German grant agencies would shy away from. “To make real breakthroughs, one must be willing to take risks,” says Haass. For Martin Kerschensteiner, a professor at the Institute of Clinical Neuroimmunology, high potential is synonymous with high risk. The SyNergy teams want to foster this taste for risk by confronting different perspectives with each other. “The best thing would be if representatives of diverse disciplines were to meet casually in the course of the day, in the corridors, at a coffee-break, over a beer in the evening,” Haass muses. “Those are the settings that give rise to the most exciting ideas.” So now he’s thinking about setting up a “SyNergy Club”. Regular meetings between basic researchers and clinicians, at which the physicians give case reports and the experimentalists present the latest data from the bench, are also part of the SyNergy concept. “It is often a moving and motivating experience for a researcher to see a patient,” says Kerschensteiner. “It reminds one of the real point of one’s work and what one wants to achieve.” And, he adds, it is important for basic researchers to see which of the therapeutic concepts that emerge from cell-culture and animal models actually make it into the hospital wards.

SyNergy is “patient centered”, and this distinguishes it from many other research networks. To strengthen this focus further, neurologist Dieterich and stroke researcher Dichgans have begun to build a large-scale patient database, in which all SyNergy members can record their individual observations relevant to each case – blood profiles, clinical, neuropsychological, genetic and imaging data. This can then serve as a basis for future studies.

The new interdisciplinary community of experimentalists and clinicians will soon have its own habitat too, made of glass, steel and concrete. Beginning in 2014, a large fraction of the SyNergy team will move into a new building – near the Medical Center and the other institutes in Großhadern.

Munich Cluster for Systems Neurology

The Munich Cluster for Systems Neurology (“SyNergy”) has chosen an integrative approach to dissecting the interactions between the various pathogenic mechanisms that contribute to the development of neurological disorders. The Cluster, a new venture set up with funding from the German Excellence Initiative, creates a collaborative network made up of basic and clinical researchers and specialists in systems analysis. LMU will act as the coordinating institution, and is joined by the Technische Universität München, the German Center for Neurodegenerative Diseases (DZNE), the Helmholtz Center Munich – German Research Center for Health and Environment, and the Max Planck Institutes for Biochemistry, Neurobiology and Psychiatry.