

# **SIX YEARS OF COLLABORATIVE ALZHEIMER'S DISEASE RESEARCH IN GERMANY**

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This special issue of "Neurodegenerative Disease" is devoted to a six-year program of the Deutsche Forschungsgemeinschaft (DFG), which supported up to 13 projects on cellular mechanisms of Alzheimer's disease with 7.5 Million Euros. Since the maximum funding by the DFG for such initiatives is six years, the program will terminate in June 2006. The members of this program will use this occasion to present their projects, their major findings and the collaborative network in form of summarizing articles.

At the International Conference on Alzheimer's Disease (AD) in Amsterdam in 1998, Volker Herzog (University of Bonn) and C. Haass discussed for the first time the idea to initiate a nation wide priority program on AD research with a special focus on cellular mechanisms leading to Amyloid  $\beta$ -peptide ( $A\beta$ ) production and tau aggregation. We both felt that this was about time, since a collaborative research program on this hot topic did not exist in Germany. For us this was quite surprising, since we were used for many years to run collaborative projects with scientists throughout Europe and the United States. Moreover, we had the strong feeling that by this time Germany's AD researchers were split into two opposing groups, the "Baptists and the Tauists". This dogmatic separation of the field prevented coordinated and collaborative research for decades in Germany. Moreover, we also found it surprising that in Germany only a small number of research teams existed. This was even more surprising, knowing that Germany looks back to a fantastic tradition of excellent AD research. Needless to say, that it all started in Germany, when Alois Alzheimer described for the first time the brain pathology of a heavily demented patient exactly 100 years ago (November 1906). Furthermore, Germany is also the place where the  $\beta$ -Amyloid Precursor Protein ( $\beta$ APP) gene was cloned. This major breakthrough was possible due to the pioneering work of Konrad Beyreuther, who is now regarded to be the father of modern AD research. A number of the members of this network are his "children" or "grand children".

The idea behind our initiative was to bring together molecular biologists working in AD research from complementary fields and opinions and to provide a novel platform for collaborations. In addition interdisciplinary collaborations should be initiated by including cell biologists. Finally, we wanted an opportunity for young investigators to start their own and independent research.

The DFG sponsored priority program represents an optimal opportunity to support such collaborative nation wide research on novel ideas, which allows all interested scientists throughout the country to work in the field and to benefit from a collaborative network. The program runs for six years, with international reviews at the beginning and after every other year.

After a first and very successful review the program started under the name “Priority Program *SPP1085* Cellular Mechanisms of Alzheimer’s Disease” in spring 1999. We covered many aspects of modern AD research centered around the cell biology of APP, the three different secretase activities and tau. These included, in vivo analysis of APP transport, functional analysis of presenilin, identification and reconstitution of  $\gamma$ -secretase, assembly of the  $\gamma$ -secretase complex, identification of novel  $\gamma$ -secretase substrates,  $\gamma$ -secretase function in animal models (*C. elegans* and *Drosophila*), cellular analysis of  $\gamma$ -secretase complex components, life imaging of  $\gamma$ -secretase trafficking, identification  $\gamma$ -secretase like proteases, functional analysis of APP and its homologues in mice and primary neurons, effects of cholesterol on Amyloid  $\beta$ -peptide generation, functional analysis of BACE and its dimerization, phosphorylation of secretases, the role of  $\alpha$ -secretase in the prevention of A $\beta$  production, tau aggregation, and effects of abnormally phosphorylated tau on cellular transport. In addition projects related to novel therapeutic strategies based on the cellular and molecular mechanisms discovered in our program were initiated. Drugs were screened for their potential to block tau aggregation and its detrimental effects on cellular transport,  $\gamma$ -secretase modulators were investigated for their potential to selectively inhibit Amyloid  $\beta$ -peptide generation without affecting Notch signaling, and novel compounds were designed to block and investigate secretase activities. The outcome of these projects will be summarized by the members of the *SPP1085* in their articles in this special issue of “Neurodegenerative Diseases”. In addition a list of publications originating from the *SPP1085* projects can be found below. By going through these articles one can immediately appreciate that AD research in Germany grew together to a group of internationally competitive scientists. Tauists are now even working with Baptists! Moreover, we established a growing number of novel research teams led by young investigators (Drs. Weggen, Kaether, Lichtenthaler, Kins,

and Steiner). Furthermore, several members of the *SPP1085* obtained major positions at German Universities (Drs. Baumeister, Hartmann, Pietrzik, Schmidt, Multhaup, Walter, Müller, and Haass) and laboratories focusing on Alzheimer's disease are now distributed throughout Germany (Fig. 1).

Besides funding the research projects the DFG also supported annual meetings to allow discussion and exchange of data. To these meetings all members and their co-workers, the reviewers, and selected speakers from all over the world were invited. The meetings took place at a rather remote place in the Bavarian Alps and is now known as *the* Eibsee Meeting. Six such meetings were held throughout the funding period including satellite meetings of the project leaders in Hamburg and Berlin where the co-speaker of the SPP has taken a chair for Biochemistry during the funding period (G. Multhaup, Free University of Berlin). These conferences turned out to be an excellent platform for generating new collaborations and for bringing together German AD researchers. This meeting developed to an internationally well-recognized conference. Importantly, the very special "Eibsee atmosphere" allowed detailed informal discussion during hiking and at the fireplace in the evening (Fig. 2 & 3). Here many novel ideas and collaborations developed, frequently with inclusion and advice of our international guest speakers and reviewers. The Eibsee Meeting is now *the* German platform for AD research. We are extremely excited that the Hans & Ilse Breuer Foundation generously supports this meeting in the future. At this years Eibsee VI conference (the last meeting sponsored by the DFG), the foundation already invited Dr. Dennis Selkoe as a keynote speaker. Moreover, the Hans & Ilse Breuer Foundation will not only help to keep German AD researchers together by supporting the Eibsee conference, but will also directly support AD research in Germany by offering a major research award (100.000.- Euro) and several stipends for Ph.D. students. It is our great pleasure to congratulate Dr. Harald Steiner as the first recipient of this award.

Finally we want to thank the DFG for the strong support throughout these years. We also greatly acknowledge the tremendous work and important scientific advice from the international board of reviewers (Drs. St George Hyslop, Glabe, Heppner, Kloetzel, van Leuven, Saftig, and Aguzzi). They not only had to review numerous applications but many of them had to travel long distances for the final board meetings and our conferences.

We are looking forward to fruitful and long lasting excellent AD research in Germany based on this successful DFG program!

## Figure Legends

**Fig. 1 Alzheimer laboratories of the Priority Program SPP 1085 in Germany (only members of the last funding period are shown).** Red: newly established laboratories; Green: previously established laboratories.

**Fig. 2 The sixth Eibsee Meeting**

**Fig. 3 Impressions from the Eibsee V & VI conferences**

(A) Left to right: Eckhard Mandelkow (MPI, Hamburg), Raymond Kelleher (M.I.T.), Rudi Tanzi (MGH & Harvard Medical School), Tobias Hartmann (Center for Molecular Biology Heidelberg), Dora Kovacs (MGH & Harvard Medical School), Jee Shen (Harvard Medical School), and Eva Maria Mandelkow (MPI Hamburg). (B) Peter St George Hyslop (University of Toronto). (C) Christoph Hock (University of Zürich). (D) Charles Glabe (University of California, Irvine). (E) Frank LaFerla (University of California, Irvine). (F) Michael Shelanski (Columbia University). (G) Gang Yu (University of Texas). (H) Zugspitze, Eibsee, and the lake at sunrise. (I) Fred van Leuven (University of Leuven). (J) Peter Kloetzel (Charite, Berlin) and (right) Gerd Multhaup (Freie University Berlin). (K) Peter Breuer announcing the first Award of the Hans & Ilse Breuer Foundation. (L) Harald Steiner (Ludwig Maximilians University Munich) receiving the Hans & Ilse Breuer Award for Alzheimer's Disease Research. (M) Dietrich Reinhardt (Dean of the Medical Faculty of the Ludwigs Maximilian University of Munich) holding the laudatio on Harald Steiner.