

## Interview with Dr. Andrew Sleight

Head of Central Nervous System Research, F.Hoffmann-La Roche

On January 25, 2006, the MorphoSys partner Roche filed all necessary applications to commence a European phase 1 clinical trial with a HuCAL-derived antibody to treat Alzheimer's disease. An international study has shown that Alzheimer's disease costs US\$ 130–150 billion worldwide, and is consequently one of the greatest burdens on our health system. Currently available therapies range from being inadequate to ineffective.

Dr. Andrew Sleight joined Roche as a Laboratory Head in February 1993. In 2003 he became responsible for the global strategy for Neuroscience Research and the Neuroscience Portfolio at Roche with staff in Basel, Switzerland, and Palo Alto (California/U.S.A). Prior to joining Roche he held various research positions in the U.S, England and France. Dr. Sleight is married and has two children.



**MorphoSys** What was Roche's main aim when it began the project, and why was MorphoSys involved?

**Dr. Sleight** There is an enormous unmet need to combat this illness. Worldwide, approximately 3% of those over 60 suffer from Alzheimer's. The likelihood of developing dementia increases with increasing age—one in five people over 80 is afflicted. Alzheimer's disease is therefore one of the main focuses of central nervous system research at Roche. We are working on various approaches to explore new ways of treating this illness. One very promising therapeutic approach requires antibodies that can bind certain protein deposits in the brain with high specificity. We identified MorphoSys's HuCAL technology as the most appropriate technology for this purpose.

**MorphoSys** What happens to people when they develop Alzheimer's?

**Dr. Sleight** Initially, people often have problems with their memory. They gradually develop difficulties with other mental tasks, such as recognizing situations, objects, or familiar people. They can suffer from severe mood swings and may become depressed or lose touch with reality, suffering from delusions. Patients undergo personality changes and their personal relationships suffer. In the final stages, they find even simple, everyday tasks such as washing and dressing more difficult or may be completely unable to manage them. Alzheimer's disease is not yet fully understood, but various hallmarks are associated with it. During the illness, certain nerve cells become functionally impaired and eventually die off. The brains of Alzheimer's patients characteristically contain enormous deposits of a protein, beta amyloid, in a form known as plaques. Many studies indicate a connection between these plaques and disease symptoms. Dissolving these plaques is therefore potentially a way of treating the disease.

**MorphoSys** How is Alzheimer's disease currently treated and why are new drugs needed?

**Dr. Sleight** There are various treatments for Alzheimer's disease: for example, it can be treated with drugs that reduce the breakdown of the transmitter acetyl choline in the brain, which improves patients' general performance. However, these drugs can only temporarily delay the cognitive impairment for about six to twelve months and are not interfering with the progression of the illness. Another class of compounds, those based on the drug memantine, attempt to maintain the learning capacity of the brain. Other symptoms of the disease, such as restlessness, depression, or aggressive behavior can be treated with various antipsychotic drugs. There is no cure yet, since all these approaches do not treat the underlying cause of the problem but only try to reduce the symptoms. What's more, these treatments become less effective after only a few years.

**MorphoSys** What more can the therapeutic antibody do?

**Dr. Sleight** The problem is the need to go deeper into the possible causes of the illness, rather than to treat it superficially. The antibody was developed to specifically attack the plaques of beta amyloid protein in patients' brains. It is administered intravenously as a drug and transported into the brain through the bloodstream. It binds the plaques in the brain and helps the body to break them down.

**MorphoSys** What is the particular challenge in developing an antibody against Alzheimer's disease?

**Dr. Sleight** The main obstacle to such an approach is the brain itself. The human brain is surrounded by a protection mechanism, known as the blood-brain barrier, which prevents various substances from leaving blood capillaries and gaining access to the brain. For many years, scientists believed that this barrier could not be crossed by large molecules such as antibodies. However, it has been shown that antibodies can in fact penetrate into the brain—admittedly only about 0.1% of the amount administered. It is therefore essential for this therapeutic approach that the antibodies are highly effective and bind their target molecules very strongly.

**MorphoSys** Are there other approaches to the treatment of Alzheimer's?

**Dr. Sleight** There are methods to immunize Alzheimer's patients against beta amyloid protein or parts of it. This approach also involves antibodies against beta amyloid produced by the patient's own immune system. However, this strategy suffered a setback in 2002 when a vaccine failed in clinical trials. Although the vaccine improved some of the patients' conditions and also caused the plaques to be broken down, many patients developed severe side effects of brain inflammation. This inflammation was a direct result of immunization. If purified antibodies are given, this problem should disappear.

**MorphoSys** What has Roche achieved so far by using an antibody?

**Dr. Sleight** The successes that Roche has shown so far are from early laboratory experiments and also from an animal model for Alzheimer's disease. The antibody dissolved aggregates of beta amyloid molecules in a test tube. Most significantly, the antibodies bound with very high specificity to amyloid plaques in tissue slices taken from Alzheimer's patients. To build on this success, the human antibody was also tested in a living system. In the studies conducted by Roche, a mouse model of Alzheimer's disease was used. The antibody accumulated in the brain of these animals and efficiently bound amyloid plaques with high selectivity. Additional studies have shown that the antibody is effective in breaking down amyloid plaques.

**MorphoSys** How is the first clinical study of the antibody designed and what will it show?

**Dr. Sleight** The goal of a phase 1 study is generally to establish safety and tolerability of new drug candidates. Side effects will therefore be studied in a relatively small number of patients. Furthermore, the first results of the study will show how often and in what amount the drug should be administered to optimize its effects.

**MorphoSys** Thank you very much for the interview, Dr. Sleight.