1. Introduction

At the beginning of the last century, Alois Alzheimer, the head of the Anatomical Laboratory at the Royal Psychiatric Clinic in Munich, presented the clinical and neuropathological characteristics of the disease that was subsequently named after him. In the brain of Auguste D., a 51-year-old patient who suffered from clinical symptoms such as progressive memory loss, delusions, and hallucinations, Alzheimer found proteinaceous deposits that were neuropathologically characteristic for this disease.[1] Today Alzheimer's disease is the most common neurodegenerative disease with more than 20 million patients worldwide and due to a consistently ageing society a further increase of cases appears to be unavoidable.[1] In recent years abnormal deposits of proteins and protein fragments with characteristics similar to those observed for Alzheimer's disease, have furthermore turned out to be common for a whole class of disorders called amyloid and amyloid-like diseases.[2,3] Some of the most prevalent examples are diseases like Type II diabetes (often referred to as late-onset diabetes) and various neurodegenerative disorders such as Parkinson's disease, Huntington's disease, and various prion diseases such as Creutzfeld-Jakob.[4,5] Thus, amyloidoses include some of the most feared and costly diseases in the western world.[3]

As mentioned above, all of these diseases are accompanied with deposits of proteins, which are normally soluble. Depending on the disease, these deposits can be in the brain, in skeletal tissue, or in other organs, and the amount of protein involved ranges from hardly detectable quantities to kilograms.[3] Despite their different origins and quantities, characteristic amyloid fibrils with remarkably similar structural features are found throughout. These fibrils possess a diverse fibrous morphology in which 2 to 6 individual filaments, termed protofilaments, are wound around one another. The internal structure within these protofilaments is characterized by a lamellar cross-β quaternary structure, which is composed of thousands of non-covalently associated peptide and protein strands.[2] This exceptional macroscopic and microscopic structural appearance led to the assumption that the involved proteins, regardless of their native conformation, have an unusual ability to adopt an amyloid structure. Therefore, the association of proteins into fibrillar amyloids was considered as a major cause of the above mentioned diseases. This "amyloid hypothesis" is still widely accepted but has to be viewed with a healthy dose of skepticism because recent investigations have provided evi-

dence that much more complex mechanisms cause cellular pathology and neurodegenertaion.[2] Firstly, Dobson and co-workers showed that non-disease related proteins may also associate into a characteristic amyloid structure at *in vitro* conditions with a morphology that is indistinguishable from that found in pathologic conditions. Based on these findings, it was reasoned that the ability to adopt an amyloid structure under certain conditions is not an unusual feature of a limited number of disease related proteins but instead a general property of all polypeptide chains.[3,5-7] Secondly, several *in vitro* experiments clearly demonstrated that early aggregates, which are formed during the amyloid assembly process are more deleterious to cells than matured fibrils. Also prefibrillar intermediates of non-disease related proteins yielded similar cell-toxic effects.[8,9] On basis of these investigations it appears likely that the toxicity of early amyloid aggregates results from defined interactions with cellular membranes, which causes oxidative stress and elevated concentrations of free Ca^{2+}.[5] However, a detailed knowledge of the molecular processes of amyloid formation and, more importantly, of the structure of prefibrillar intermediates that presumably yield neurodegeneration remains elusive.

The fact that most of the proteins involved in amyloid-like diseases usually possess a well defined conformation in the native, often functional state inescapably shifts the attention to the required conformational transition that allows self-assembly into amyloid to begin.[10,11] It is commonly accepted that mutations in the primary structure, as observed for most of the familial cases of amyloid like diseases, yields structural changes and rapid progression of amyloidosis.[1,2,12] This is usually caused by either a destabilization of the native conformation or a changed selectivity of involved proteinases as observed for early onset familial Alzheimer's disease.[1,2] More importantly, a changed environment to which natural proteins are exposed at translocation or stress conditions can promote misfolding and aggregation. In other words, changing the environment of a peptide or protein can alter its conformation and has therefore to be considered as potential trigger for amyloid formation.[13] In principle, various factors such altered pH value, ionic strength, local protein concentration, and the presence of transition metal ions or membranes can induce conformational transitions that subsequently induce the association into amyloids.[13] Also post translational modifications or the presence of a small quantity of a misfolded protein fragment might yield similar amyloid promoting effects.[13] Consequently, changed environmental conditions have to be considered as the most critical events in the entire process of amyloidogenesis and have attracted increased attention of many researchers in recent years.

Most of the above-mentioned amyloid like diseases are reckoned as incurable to date. Several strategies ranging from fairly unselective amyloid inhibition strategies to immunization approaches have been reported but no convincing therapy is available at present.[2,14,15] In many cases even the diagnosis of the disease is exclusively based on rather doubtful clinical symptoms. Thus, a detailed understanding of the molecular events and intermediates that occur during the process of amyloid formation and the way how this pathway is affected by the environment might pave the way for further diagnosis and treatment approaches. However, the low solubility of amyloid forming peptides, their intrinsically high tendency to aggregate, and a mostly poor synthetic accessibility restrict the spectrum of analytical techniques and consequently complicate a detailed characterization. To overcome these drawbacks, the development of small and manageable model peptides that can serve as tools for the characterization of amyloid formation processes on a molecular level is of paramount importance.

In this thesis, the *de novo* design and characterization of coiled coil based amyloid forming model peptides that perceptibly react on the environmental factors pH and transition metal ions is described.