Alzheimer’s disease (AD) is the major cause of dementia in our senior community. It is a progressive and incurable illness of the brain that causes extensive loss of neuronal cells and results in the impairment of memory and cognitive functions. It affects 1 in 20 people over the age of 60, and 1 in 3 over the age of 85. AD has become an increasing socio-economic burden, as the illness develops slowly for over a decade, and the patients have to stop their professional and most social activities, and they progressively fully dependent and in need of full care, usually from close relatives and family.

The various underlying risk factors for AD, such as lifestyle, stroke, high blood pressure and hypercholesterolemia, diabetes, oxidative stress and inflammation, all converge to molecular mechanisms centred on the amyloid cascade theory. For over a century, AD has been traditionally diagnosed post-mortem by the accumulation of amyloid plaques and tau neurofibrillary tangles in the brain cortical regions and hippocampus. The major component of the amyloid plaques was identified nearly thirty years ago as a protein fragment, termed amyloid β peptide (Aβ). Since then, extensive research has aimed to reveal the pathological mechanisms that lead to AD and to discover strategies to lessen amounts of Aβ in the brain, as it is commonly accepted that an imbalance between the production and clearance of Aβ peptides results in the formation of toxic Aβ aggregated species that trigger the dysfunction and death of neuronal cells.

The amyloid theory is strongly supported by genetic studies that have revealed disease-causative mutations in the genes encoding the Aβ amyloid precursor protein (APP) and the presenilins, which are the active subunits of γ-secretase, the proteolytic enzyme that dictates the length of Aβ isoforms being generated, thus their aggregating and toxic properties. Therefore, researchers and pharmaceutical companies are working towards therapeutic strategies to either prevent Aβ production, or to interfere with its aggregation using metal modulators or competing molecules, or to facilitate its clearance through immunotherapy. To prevent or reduce Aβ production, researchers target the secretase enzymes that cleave the amyloid precursor to release the toxic Aβ fragment.

Aβ is produced by the sequential action of β-secretase and gamma-secretase. Many inhibitors for these enzymes have been developed in the pharmaceutical industry, but none of these are yet available in the clinic. Our research group is particularly interested in BACE1, which is the β-secretase enzyme that mediates the first proteolytic cut in the sequential process of Aβ formation. This is a well-characterized enzyme that can be targeted with chemical inhibitors, and some of these...
are currently in advanced clinical trials. Studies from our laboratory have shown that BACE1 levels and enzymatic activity are abnormally elevated in the brain of patients with Alzheimer's disease and that BACE1 activity is increased in the cerebrospinal fluid of AD patients. One of our current goals is to improve knowledge of the biological function of BACE1 in order to foresee the potential side-effects of inhibiting its activity. This is done using cellular and animal models. Another of our major objectives is to establish if BACE1 has the potential to become a blood biomarker in AD by comparing RNA, protein and enzymatic levels in the blood of patients with Alzheimer’s disease, mild cognitive impairment, and controls. This would allow to identify the patients who could benefit from a treatment with BACE1 inhibitors and to monitor the effectiveness of the treatment.

In conclusion, although Alzheimer’s disease remains today incurable, intensive research into rational therapies offer promise that it will become treatable in the near future, particularly if it can be diagnosed at a very early stage.
