USE OF SMALL INHIBITORY NUCLEIC ACIDS FOR DOWN-REGULATION OF GENES INVOLVED IN ALZHEIMER'S DISEASE

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According to the amyloid hypothesis, accumulation of Aβ is a primary factor driving Alzheimer's disease pathogenesis [1]. Lowering of Aβ secretion can be achieved by decreasing of β-secretase activity, rather than by down-regulation of the APP substrate protein. Therefore, BACE is a primary target for anti-amyloid therapeutic drug design [2]. Several approaches have been undertaken to find an effective inhibitor of human β-secretase, mostly in the field of peptidomimetic, non-cleavable substrate analogues [3].

Small inhibitory nucleic acids (siNAs) able to down-regulate gene expression include antisense oligodeoxy*ribo*nucleotides (antisense DNA), catalytic nucleic acids (ribozymes and deoxyribozymes) and short interfering RNAs (siRNAs).

While antisense oligonucleotides were first used to identify an aspartyl protease with β-secretase activity, all the strategies now demonstrate that siNAs are able to inhibit BACE biosynthesis in a sequence-specific manner, measured both at the level of its mRNA and the level of protein [3]. Moreover, knock-out of BACE reduces the intra- and extracellular population of Aβ40 and Aβ42 peptides. This anti-amyloid effect of siNAs was observed in a wide spectrum of cell lines as well as in primary cortical neurons. Thus targeting BACE with small inhibitory nucleic acids may be beneficial for the treatment of Alzheimer's disease and for future drug design.

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