NPM01, A MARINE NATURAL PRODUCT, AND ITS DERIVATIVES AS A-SECRETASE ACTIVATORS

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Introduction: The amyloid precursor protein (APP) is constitutively shed by a protease activity called α-secretase, generating soluble α-peptide (sAPPα) and preventing the generation of β-amyloid peptide (βA), one of the major hallmarks of Alzheimer’s disease (AD). The activation of this cellular process is considered a promising strategy for preventing the pathogenic amyloid cascade.

Aims: To exploit the marine environment as a source of novel compounds to identify inhibitors of the amyloid cascade acting as α-secretase activators and to confirm their value in several cell lines.

Methods: Several stable cell lines overexpressing APP and SH-SY5Y cells have been used to evaluate the biological activity of the compounds.

Results: NPM01 is a marine compound identified in a program for neuroprotection against oxidative stress. This compound is able to significantly reduce βAsecretion in different APP-transfected cell lines. This effect correlates with an increase of sAPPα, suggesting that activation of the α-secretase pathway is involved in its mode of action. The possible pathways involved in this process are discussed. In addition, an active medicinal chemistry program has led to several compounds with improved properties.

Conclusions: NPM01 is able to prevent neuronal death under oxidative stress conditions and to reduce βA levels as observed in several cell lines. The compound seems to promote the α-secretase pathway as increased levels of sAPPα have been detected. From this project an active synthesis program is being developed in Noscira with promising results.