Design of two single-domain intrabodies to reduce intracellular Aβ production

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Introduction
Alzheimer’s disease is the major cause of dementia in the elderly population, and its figures will increase as aging is the major risk and the population’s lifespan is increasing. There is a promising gene-based therapy which turns the humoral immune system outside in for intracellular immunization. Intracellular antibodies (intrabodies) are antibody fragments fused to signal sequences which allow them to stay within the cell and, if desired, direct them to specific compartments and organelles. In the present work we present a therapeutic alternative for combating intracellular amyloid-β production.

APP processing and Alzheimer
The amyloidogenic hypothesis affirms that initiation of Alzheimer’s Disease (AD) is elicited by excessive amyloidogenic processing of the Amyloid Precursor Protein (APP), producing toxic amyloid-β. Significant in vitro and human pathological data suggest that intraneuronal accumulation of Aβ peptides plays an early role in the neurodegenerative cascade.

Intrabody approach
Intrabodies are intracellularly retained antibodies fused to signal sequences specific for intracellular compartments. Originally intrabodies derive from single-chain variable fragments (scFv), but recently smaller versions are being developed (i.e. single-domain intrabodies (sdAb)).

Methodology

Expected results

<table>
<thead>
<tr>
<th>Time to complete Morris Water Maze</th>
<th>Cytosolic sdAb</th>
<th>sdAb-KDEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs control</td>
<td>Slower progression of AD</td>
<td></td>
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<tr>
<th>Amount of Aβ42 deposits</th>
<th>vs control</th>
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More promising results of the ER-retained version (sdAb-KDEL) are expected, since the processing of APP occurs mainly in the secretory pathway. However, results from this sdAb format are expected to overcome those obtained with conventional intrabodies formats.

References

Images in Methodology come from: [2] and [3]