Nucleic Acid Aptamers As Research Tools And Diagnostic Reagents In Amyloid Disease

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Title of project or programme

Title of PI Nucleic Acid Aptamers As Research Tools And Diagnostic Reagents In Amyloid Disease

Principal Investigators of project/programme grant

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Source of funding information

Medical Research Council

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01-02-2010

Total duration of award in months

36

The project/programme is most relevant to

- Alzheimer’s disease and other dementias

Keywords

Research abstract in English

The misfolding and aggregation of normally soluble proteins and peptides leads to a range of grave human pathologies that represent a major threat to human health in our aging society. First identified more than a century ago, and vigorously studied by both academia and industry in recent decades, amyloid disease still represents a major unmet clinical need. Although low molecular weight

compounds have been identified that can reverse, halt, or alter the pathway of protein/peptide aggregation in vitro, potent reagents for clinical diagnosis and intervention in amyloidosis remain remote. There are on-going needs for better understanding of the molecular mechanisms of amyloid fibril formation as well as the structure(s) and biological properties of the final fibril product(s). This will allow the critical pathological species and the best therapeutic targets to be identified, and used to develop sensitive reagents for early diagnosis and effective intervention.

Here we propose to address these issues using two medically-important systems: (i) Abeta1-40/42 the peptide(s) famously associated with Alzheimer's disease (AD), as an example of neuropathic amyloidosis and (ii) beta2-microglobulin (beta2m): the molecular culprit of dialysis related amyloidosis (DRA), a major problem of potential threat in all patients undergoing long-term renal dialysis, as an example of protein aggregation in systemic amyloidosis. By exploiting and developing the power of RNA aptamers as potential new reagents for intervention in amyloid disease we propose to:

select biologically stable RNA aptamers able to recognise different species formed during the assembly of Abeta1-40/42 and beta2m into amyloid fibrils in vitro,as the fibrils themselves

determine the structural basis of aptamer:target recognition and its effect on amyloid assembly;

investigate the potential of the RNA aptamers selected above for: a)early detection of amyloidosis in vivo, and therefore provide proof of principle of their utility as diagnostic reagents; b)possible therapeutic intervention.

Overall, our aim is to use detailed biophysical analysis to identify, isolate and characterise intermediates of amyloid assembly and different fibril polymorphs, and to use this knowledge to select monomer-, oligomer-, or fibril-specific RNA aptamers able to recognise each of these species specifically. Our goals are to provide new and powerful reagents to advance fundamental studies of the structural molecular mechanism of amyloid assembly, as well as providing proof of principle of the utility of RNA aptamers for amyloid diagnosis and therapy.

Lay summary
In which category does this research fall?

- Basic research