

New Paths towards combatting Alzheimer's Disease

Coupling clinical data with bio-chemical analysis has allowed DTU Chemistry to reveal molecular mechanisms behind the neuro-degenerative disorder. The implications to the field could be substantial.

Attempts to cure or at least halt Alzheimer's disease - the major neurodegenerative disease affecting millions of people worldwide - have so far been largely unsuccessful. But research at DTU Chemistry opens a new door of hope.

Previous drug candidates have been ineffective, because the mechanism behind this wide-spread neuro-degenerative disease has been wrongly perceived. A research group led by Associate Professor Kasper P. Kepp has combined information at the molecular level with genetic profiles of Alzheimer's disease patients. This unique approach has brought about a new understanding with large implications to the field.

"Unfortunately, we have to conclude that a number of recent and current drug candidates will never be successful because they target the wrong phenotypes. Continuing on this path will only give patients false hope and impose economic loss on shareholders and society as such. But the good news is that the direction can now be changed so that future drug candidates with substantially improved prospects can be developed," says Kasper P. Kepp.

Some of the new findings have just been published in the journal Dalton Transactions of The Royal Society of Chemistry, with Kasper P. Kepp and Postdoc Manish K. Tiwari, DTU Chemistry, as authors.

The key peptide

Alzheimer's disease patients typically suffer from impaired memory, gradual decline of cognitive abilities, and personality changes. The disease is strongly linked to aging and

mostly occurs sporadically. However, about 5 % of patients have inherited the disease risk. These cases are known as Familial Alzheimer's Disease (FAD). FAD cases are generally more severe and the disease on-set is earlier, in some cases down to 40-50 years of age.

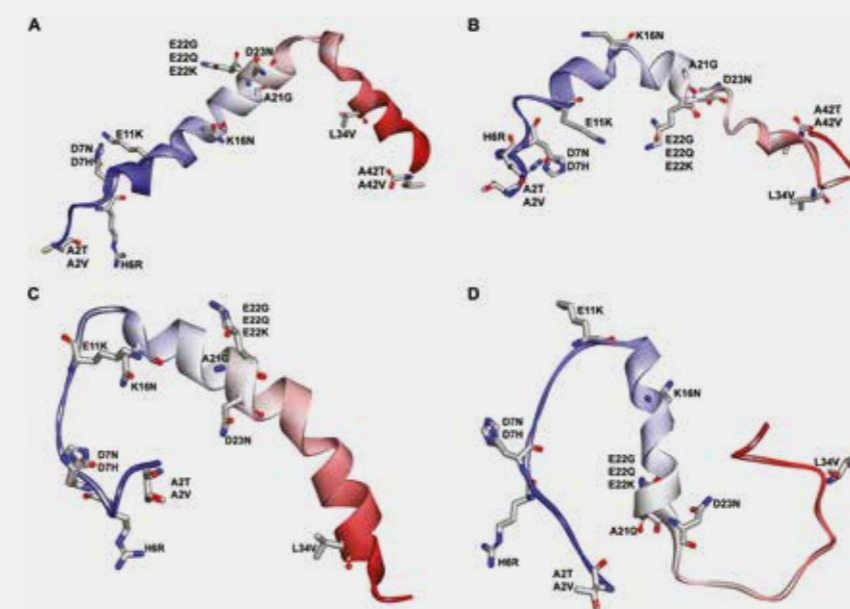
The relation between FAD and other cases of Alzheimer's has been a puzzle to researchers in the field. Some have assumed that two different mechanisms, and thus in reality two different diseases were in play. However, the DTU Chemistry group is working with a new hypothesis that at the molecular level the exact same phenomenon is occurring, only to a higher degree in the FAD cases.

It has been known for decades that the brains of Alzheimer's patients contain extracellular deposits of senile plaques consisting of the peptide β -amyloid ($A\beta$). The peptide is a cleavage product of a protein found in the membrane of the brain cells, namely Amyloid Precursor Protein (APP).

Plaques alone do not cause the disease

It has been assumed that the build-up of these plaques was closely linked to the disease - in other words that the brain would only be able to tolerate this build-up to a certain level.

As a logical consequence of this perception, several drug candidates by major pharmaceutical companies have been designed to limit the build-up of $A\beta$ in the anticipation that this would cure or at least halt the progression of Alzheimer's. However, this has not happened, while at the same time the patients have suffered side-effects. Furthermore, quite often,



Wild-type and mutant structures of $A\beta_{42}$ and $A\beta_{40}$. (A, B) The NMR structure of wild-type $A\beta_{42}$ (PDB codes 1IYT and 1Z0Q) and their 15 superimposed computational structures of $A\beta_{42}$ mutants. (C, D) The NMR structure of wild-type $A\beta_{40}$ (PDB codes 1BA4 and 2LFM) and their 13 superimposed structures of $A\beta_{40}$ mutants. The mutant residues are shown in stick-model. The peptide's secondary structure is shown with blue N-terminus and red C-terminus (the figure was generated using Discovery Studio (DS) 4.0 visualizer).

a pathological examination will reveal vast plaques without the deceased patient ever having experienced symptoms of Alzheimer's.

"Our findings strongly suggest that it is not the amount of $A\beta$ in itself which triggers the disease. The amounts observed for variants of this peptide simply do not correlate with disease tendency of patients having these variants. Instead, $A\beta$ can assume a number of different forms and properties of which only some are pathogenic," Kasper P. Kepp explains.

The group has found that, as a rule of thumb, the more disordered the structure of the peptide is, the more pathogenic will it tend to be. Furthermore, a strong correlation seems to exist between the disease and the water affinity of the peptide surface: A hydrophobic surface relates to disease, whereas a hydrophilic surface doesn't.

Keen to cooperate with pharma industry

The project benefits from the recent possibility of retrieving data from genetic profiling of Alzheimer's disease patients. The group has extracted its clinical data from a range of published clinical papers and from the international database on Alzheimer's and related diseases AD & FTD Mutations Database, where data from the sequencing of a little over 200 Alzheimer's patients are currently found. These data were compared with similar data from patients without the disease - that is, persons with "sound" forms of $A\beta$.

Unfortunately, the findings can't be translated directly into efficient anti-Alzheimer's drugs. "We have to remember that the main cause of the disease is aging, which again causes several changes in the bio-chemical processes of the brain. These changes are complex and are likely to occur no matter what we do - you can't cure aging. However, it is likely that drugs can be found which will delay or partly offset the tendencies leading to Alzheimer's. Also, this is yet another reason for recommending people to do exercise, both physically and mentally - by for instance solving Sudoku puzzles etc. Complex late-onset human diseases need to be tackled by a multitude of strategies, and medicine is only one of them."

The group is, however, keen to cooperate with the pharmaceutical industry based on the new findings, Kasper P. Kepp underlines:

"We will be able to carry out some of the basic design of drug candidates which may address the identified pathogenic structures of $A\beta$. But for taking these candidates into detailed design and further into clinical trials we will need participation from an industry partner with the necessary experience. Using existing compounds with drug-like and safe properties but with the special properties that we have found to be important for targeting Alzheimer's would speed up drug development."

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The text is based on the scientific article published in Dalton Transactions.

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Next step ...

To take the drug candidates into detailed design and clinical trials the research group at DTU Chemistry welcomes the participation from the pharmaceutical industry.

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