

Nature_comments.txt

Date: Wed, 31 Oct 2007 02:29:06 UT
From: Decisions@nature.com
To: niko@brandeis.edu
Subject: Decision on Nature manuscript 2007-10-*****

30th October 2007

Dear Professor Grigorieff,

Thank you for submitting your manuscript entitled "Corrugated structure of an Abeta (1-40) amyloid fibril revealed by electron cryo microscopy", which we must decline on editorial grounds.

It is Nature's policy to decline a substantial proportion of manuscripts without sending them to referees, so that they may be sent elsewhere without delay. Such decisions are made by the editorial staff when it appears that papers are unlikely to succeed in the competition for limited space.

We do not doubt the technical quality of your work or its interest to others working in this and related areas of research. However, we feel that your findings are of insufficiently immediate interest to researchers in a broad range of other disciplines to justify publication in Nature.

I am sorry that we cannot be more positive on this occasion.

Yours sincerely,

Senior Editor, Nature

12 December 2007

Dr. Nikolaus Grigorieff
Department of Biology
Rosenstiel Center
Brandeis University
415 South Street
Waltham MA 02454

Ref: *****

Dear Dr. Grigorieff:

Thank you for submitting your manuscript "Corrugated structure of an A β (1-40) amyloid fibril revealed by electron cryo microscopy." We have now received the detailed reviews of your paper. Unfortunately they are not positive enough to support publication of the paper in Science. Although we recognize that you could likely address many of these specific criticisms in a revised manuscript, the overall nature of the reviews is such that the paper would not be able to compete for our limited space. We hope that you find the comments helpful in preparing the manuscript for submission to another journal.

We are grateful that you gave Science the opportunity to consider your work.

Sincerely,

Senior Editor

Review 1:

Report on the paper "Corrugated structure of an A β (1-40) amyloid fibril revealed by electron cryo microscopy" by Sachse et al.

An old riddle of structural biology is the structure of amyloid fibrils and in particular those formed by the Alzheimer peptides A β (1-40) and A β (1-42). Current structural investigations in this field show models for monomeric or dimeric subunits, and there were so far only coarse-grained pictures by electron microscopy. Here, the authors present an important cornerstone for building an understanding of amyloid fibrils formed by Alzheimer peptides. An EM study is presented showing fibrils of a certain morphology at considerable resolution (8 Å) which allows to draw a number of conclusions. One of the important ones is that 5 monomeric subunits form 1 blade of the two-bladed propeller, and the fine structure observed allows to speculate about the arrangement of the peptides. Since the authors present the to-date best resolved global structure of a paradigm example of fibrils, I recommend publication in Science. I'm certain that this paper will be of interest to a very wide readership.

Minor points:

A large part of the discussion (page 4, bottom) is devoted to short regions of the

peptides forming zipper-like structures. But the present structures of the A β -peptides are only mentioned in passing. The authors state that both models (A β (1-40) und A β (1-42)) cannot be fitted satisfactorily into the density observed. However, there is no quantification or no attempt for a joint refinement. It would also be nice to display one or both structures drawn at scale into Figure 2 for comparison. How does the morphology of the fibrils investigated by the Tycko and Riek groups compare to the morphology investigated here? It would be nice if the authors could improve the discussion with respect to these points. I would also like to mention that I have problems to see the 'corrugated' appearance of the electron density in all areas of Figure 2D. I wonder whether some of the features could be explained by segments adopting a α -helical conformation. Some of the sentences in the text require some imagination by the reader. The statement on page 4, top paragraph 'the cross section displays two U-shaped regions with head-to-head orientation.' is an example. I have to say that I did not quite get where the U is and where the head of the U is.

Review 2:

Authors: Sachse, Fandrich, & Grigorieff
Ms 1152507

The strengths of this report are the significantly increased resolution of the cryo-microscopic images achieved by Sachse et al. The earlier work at 24 Å resolution showed a similar but less detailed image than the work here, which is at a nominal resolution of 8 Å. Another significant strength of the work is the measurement of the mass per unit length of the fibril. Here it is measured at 5 Abeta units per 0.48 nm rise of the fibril.

The limitation of the work is that even the new resolution falls short of that needed to propose an atomic model. So the frank truth is that we know no more after this communication than we did before about the atomic contacts that bring about fibril formation of Abeta (1-40), or how fibril formation might be stopped.

The present resolution, which is just coarser than the level necessary for a chain trace, seems to raise many questions. The conjecture of the authors seems reasonable that each wing of the fibril consists of two beta sheets. This would make four Abeta molecules per layer. Do the authors believe that the 5th Abeta suggested by the mass per unit length measurement is non-existent, or does the 5th bridge the two wings? What is the especially strong density near the central 2-fold axis? Do Abeta chains all lie in a single layer normal to the fibril axis, or do one or more cross to the next layer. The authors do not discuss the longitudinal view.

On page 6, the authors suggest that the observed 'corrugation' of the fibril explains the torsional stability of the fibrils. However, it would seem that stability is not explained alone by this blurry feature. What is needed is the nature of the chemical bonding between units.

The authors' conclusion that 'these findings are specifically important in the context of amyloid pathogenicity that may arise from structural precursors of these fibrils and for biotechnological applications that intend to exploit the properties of physical stability of these fibrils' reaches too far. I can see no way in which the understanding of amyloid pathology is advanced by the present work.

In summary, the improved reconstruction and imaging of Abeta over earlier studies will be of interest to workers in the field of Abeta structure, but will not have a wider impact, because the resolution is below the threshold of being able to establish an atomic model.

Some minor points:

1. The first sentence on page 4 cannot possibly be right, that the fibril possesses a width of 190 nm. Do the authors mean 19 nm?
2. In the same paragraph it is stated that the 'path of the polypeptide chain is visible in most parts of the structure'. If it is visible, please show the tracing. It is not evident to me.
3. It is not clear from the description and the Fig. 2 as to whether there are two sheets or four sheets.

Review 3:

The structure of a fibrillar form of the peptide Abeta 40 obtained from cryo-electron micrographs is described in this manuscript. The three-dimensional reconstruction presented by Sachse et al. suggests that the fibrils are not made of a continuous hairpin-like beta-sheet, as widely accepted based on solid state NMR data (Petkova et al., 2006 *Biochemistry* 45: 498-512) and mutagenesis studies (Shivaprasad and Wetzel, 2006 *J. Biol. Chem.* 281: 993-1000), but are instead made of several 2-3 amino acids beta-segments.

The manuscript is well written. However, I have several serious concerns with the data and a number of interpretations. The data presented neither allow the docking of the peptide Abeta 40 within the calculated electron density nor to account for the familial forms of Alzheimer's disease. I therefore believe that the data are neither sufficiently sound and innovative from the structural point of view nor of potential importance from the medical point of view to deserve publication in *Science*.

1- I looked very closely at the electron micrographs presented in Figure 1 and 3B. The fibrils displayed in these micrographs exhibit very significant variations in their pitch length. I therefore do not understand how the authors using pitches of 117-159 nm in Figure 1 and 78-122 nm in Figure 3B reach the model presented in Figure 2A with a pitch equal to 140nm. It is known that Abeta 40 fibrils exhibit a significant degree of heterogeneity (this is also accepted by the authors: Sachse et al. 2006 *J.Mol. Biol.* 362: 347-354). It is also perfectly fine to select a subset of fibrils "to reduce the problems associated with structural heterogeneity" as stated page 3, however, it is then critical to justify the selection used in particular when the selected segments represent about 13% of the segments the authors measured as one can derive from table S1. The authors do not provide any justification and the variations in pitch length I measured are inconsistent with the proposed model.

2- The authors propose that the two hairpin-like beta-sheets constituting the fibrils interact through their part that resembles a U-turn and that is at most 1 nm long, i.e. 3 amino acid residues (the distance between two carbon alpha within a beta sheet is about 0.32nm). I do not believe that such an interaction is of sufficient strength to hold the two "protofibrils" together. The authors neither propose, nor discuss alternative models that could fit equally well their data (for example the stacking of two flat peptides with a slight (2nm) shift).

3- The length of the peptide Abeta 40 calculated from the image reconstruction presented in Figure 2D is 18nm (9+7+2nm). The distance between two carbon alpha within a peptide ranges from 0.32 to 0.36 nm depending on whether the two amino acid residues are involved in a beta-sheet or an extended flexible loop. Thus, the length of the peptide Abeta 40 should be at most 14.4 nm. How do the authors account for the length measured here (18nm).

4- I do not believe that the authors provide any evidence other than visual (using image reconstructions) for their claim that "the fibrils do not consist of long and straight beta strands but of several short 2-3 amino acid beta-segments". In addition, the authors draw five 0.8-1.2nm arcs in Figure 3A and propose a two-fold symmetry. A central 1.2nm arc flanked by two 2nm arcs perfectly fit the reconstructed density map even when the proposed two-fold symmetry axis is held constant. One could also draw other patterns. The authors should justify their choice.

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5- The structural model proposed here should account for differences in the assembly propensities of mutant A β isoforms such as those associated with the familial dutch, flemish, arctic etc... Alzheimer forms. The authors should discuss this issue and propose structure-based explanations in a manner similar to what has been done recently by Fawzi et al., 2007 Biophys. J. doi:10.1529/biophysj.107.121467.

6- The authors suggest that the corrugated organization of the beta-sheet region proposed here may occur in other amyloid fibrils. They also propose a mechanistic scenario page 6. I have the feeling that such suggestions should be supported by structural and kinetic data. Sachse et al also claim that the corrugated organization of the beta-sheet region "readily provides a structural explanation for the observed stability of amyloid fibrils with respect to torsional stress or bending". The authors should develop their reasoning and explain in what this model accounts better for the physical properties of amyloid fibrils than the widely accepted model that is based on numerous mutagenesis and structural studies.

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American Association for the Advancement of Science