

Alzheimer's disease: The amyloid cascade hypothesis: An update and reappraisal

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Abstract. Here I recap the scientific and personal background of the delineation of the amyloid cascade hypothesis for Alzheimer's disease that I wrote with Gerry Higgins and the events leading to the writing of that influential review.

My former and wise Head of Department, Bob Williamson, used to quip that the greatest thing about molecular genetics was that knowledge was a handicap and this is certainly why I have enjoyed a career in genetics. By that he meant that all you needed to know about a disease was its mode of inheritance. Positional cloning would lead you to the mutant gene which, unambiguously, caused disease. And after that, there would be no argument: pathogenesis would start from there.

In the 1970's and 1980's there were huge numbers of ideas, mostly rather vague and untestable, about what was the cause of Alzheimer's disease: slow viruses, aluminum exposure, "accelerated aging" (whatever that is, beyond a smokescreen for sloppy thought, has never been clear to me), or an environmental toxin were among the favorite notions. There was also some confusion about the relative importance of, and the relationships between, the different elements of the disease pathology: the plaques, which Glenner [2] and Masters and Beyreuther [12] had shown were made of the amyloid- β peptide in the mid 1980s, the tangles, which

Wischik and Goedert [5] had shown was made of tau in the late 1980s, and the neuronal loss.

We geneticists made some missteps: the original linkage report was wrong, and yet had pointed at a chromosomal 21 gene [14]. It took us some time to realize the disease was genetically heterogeneous [15]: however, with this realization and because of the linkage of the amyloid gene to Hereditary Amyloidosis, Dutch Type [11,16], our group suddenly understood that the simplest interpretation of all the genetic data was that A β PP mutations caused a minority of early onset autosomal dominant Alzheimer's disease. We focused our attention on those families that showed evidence for linkage to chromosome 21 markers and immediately began to find mutations in A β PP, close to the amyloid- β part of the molecule [4]. These data were important because they gave us the first defined cause of the disease, and they also gave us the possibility to make transgenic models of the disease. I realized that these findings proved one cause of disease. More importantly, I realized they implied that all causes of disease would share mechanistic relationships with this first cause. Over-

expression of A β PP in Down syndrome immediately became an obvious second defined cause, as Glenner had been suggested many years before [3].

Emboldened by these ideas, but aware of my limitations as a discussant of amyloid processing, I contacted David Allsop [1], who had originally worked out the amino acid composition of amyloid, and together we wrote the widely cited review for Trends in Pharmacological Sciences [6]. Dennis Selkoe had also understood the significance of our genetic data and reviewed the field for Cell [13], and these reviews, together with the Science review are widely seen as the start of the dominance of the "Amyloid Cascade Hypothesis" for Alzheimer's disease. I think this attribution is a little unfair: presumably, Glenner [3] and Masters and Beyreuther [12] had isolated amyloid and cloned the amyloid gene because they believed something along the lines of the amyloid cascade hypothesis although they never expressed their ideas clearly.

The story of how the review was written is a little complicated. In late 1991, I had visited the United States to give a talk to Gerry Higgins' group at the National Institute on Aging (coincidentally, my current employer, though no longer Gerry's: in fact, Gerry's former secretary is my Senior Administrator). While I was visiting Gerry's lab, he and I had got on very well, and he showed me a manuscript he had in press in Nature [10], describing the production of transgenic amyloid mice with fulminant Alzheimer pathology, both plaques and tangles. He offered to show me slides from the mice, but he couldn't lay his hands on them at that time. I didn't mind because looking down a microscope is always a waste of time for me. However, the manuscript was stunning, and ostensibly described the full modeling of the disease process. After I was back in London, Gerry and I spoke by 'phone several times, and I suggested we review the genetic and animal data together. He agreed, and contacted a friend of his who was an editor at Science to see if they were interested. To my surprise, they were, and I drafted the paper immediately, with him correcting the draft and supplying the figure: the title was also his choosing. The review took possibly a week to write. At the time, I was organizing a small meeting in London about Alzheimer's disease and I invited him to be the Plenary Lecturer. But as this was all brewing, he began to tell me that people didn't believe him about the pathology in his mice. At last, the day before we were to have the meeting, he 'phoned to say he couldn't come: he was having serious problems at work, and perhaps he should withdraw his name from the paper.

I said of course he should be an author: we had written the paper together, and that is how we left it. Apart from taking him to lunch 5 years later, during a visit of his to Florida to interview to become an administrator at NASCAR, I have never seen or spoken to him since. As the probable fraud of his mouse analysis was uncovered, he resigned, left science and disappeared. So this paper, while it could be seen as the beginning of the amyloid cascade hypothesis, was Gerry's last.

What do I think of it today? First, it is simple, clear and short: too many articles are complicated, muddy and long: even a venture capitalist or a corporate CEO can read to the end of it. Second, while adjudication of final truth depends on successful therapy, I think there can be little doubt that it is largely correct, as we have recently reviewed [8]. Third, as an idea, the amyloid cascade hypothesis has been extremely valuable in focusing research. Fourth, I have found it irritating to be asked time and time again to present and defend it, rather like Procul Harem being asked endlessly to sing "A Whiter Shade of Pale".

Subsequent findings which have supported the basic tenet of the article have included (see ref. [8]):

- 1) the observation that presenilin mutations have the same effect on amyloid processing as A β PP mutations and presenilin is in fact, part of the enzyme complex which produces A β from A β PP,
- 2) the realization that tau mutations lead to tangles, cell loss and dementia, indicating that tau is indeed downstream from A β ,
- 3) the observation that the crossing of an A β PP transgene into a tau transgenic mouse does indeed push tangle formation and this effect is rescued by reducing the amyloid load: (thus, years later, we were indeed able to make mice with pathology similar to those fraudulently described by Gerry).
- 4) the genetic linkage screens for late onset Alzheimer's disease show up both the A β PP gene and a locus on chromosome 10 which influence A β PP metabolism.

Amyloid-based treatments, the final test of the amyloid cascade hypothesis, are showing some hopeful results, but they are certainly not yet conclusive.

The amyloid cascade hypothesis has been extensively criticized particularly by those who point out that by "amyloid" we originally meant "plaque amyloid" (although I note that at the time, the official name for what we now call A β was amyloid- β peptide). While I accept this criticism because most people, including me, now think it is some smaller oligomeric species,

I find it tiresome. Of course, our ideas have changed. If they hadn't, we would have wasted the last 13 years doing research: the article in *Science* was intended to generate ideas and act as a framework for a research agenda, not to be a definitive statement. I re-read it for the first time in at least 10 years to write this article: when I wrote it, I certainly didn't mean it to be laid down on a tablet of stone and consulted to ascertain ultimate wisdom about Alzheimer's disease. Other criticisms have seemed, to my intolerant ear, to be merely vague murmurings of malcontents who have consistently failed to come up with a viable alternative.

Writing this short memoir enables me to spread the thanks for this work. I wrote the widely cited review, but my thoughts at that time were influenced by the conversations I had with my boss, Bob Williamson, with my postdocs, Alison Goate, Mike Owen, Marie-Christine Chartier-Harlin and Mike Mullan and also with Christine Van Broeckhoven and Peter St George Hyslop. There was a community of ideas and our discussions, both within our group and with Christine and Peter, were free and open: I wish it were always so. Karen Duff, Mike Hutton and Jada Lewis have led subsequent transgenic work, which I think has almost proved the amyloid hypothesis beyond reasonable doubt. Colleagues like these and Dave Morgan have made science both productive and fun for me and most of the collaborations started in those days continue today.

I believe we are close to a therapy for Alzheimer's disease based on the amyloid cascade hypothesis, but time will tell.

*“We skipped the light fandango
Turned cartwheels cross the floor.
I was feeling kind of sea sick,
The crowd called out for more.
The room was humming harder
As the ceiling flew away.
When we called out for another drink
The waiter brought a tray
And so it was that later
As the miller told his tale
That her face at first just ghostly
Turned a whiter shade of pale.”*

References

- [1] D. Allsop, M. Landon and M. Kidd, The isolation and amino acid composition of senile plaque core protein, *Brain Res* **259**(2) (24 Jan 1983), 348–352.
- [2] G.G. Glenner and M.A. Murphy, Amyloidosis of the nervous system, *J Neurol Sci* **94**(1–3) (Dec 1989), 1–28.
- [3] G.G. Glenner and C.W. Wong, Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein, *Biochem Biophys Res Commun* **122**(3) (16 Aug 1984), 1131–1135.
- [4] A.M. Goate, M.C. Chartier-Harlin, M.C. Mullan, J. Brown, F. Crawford, L. Fidani, L. Giuffra, A. Haynes, N. Irving, L. James, R. Mant, P. Newton, K. Rooke, P. Roques, C. Talbot, M. Pericak-Vance, A. Roses, R. Williamson, M.N. Rossor, M. Owen and J. Hardy, Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease, *Nature* **349** (1991), 704–706.
- [5] M. Goedert, C.M. Wischik, R.A. Crowther, J.E. Walker and A. Klug, Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau, *Proc Natl Acad Sci USA* **85**(11) (June 1988), 4051–4055.
- [6] J. Hardy and D. Allsop, Amyloid deposition as the central event in the aetiology of Alzheimer's disease, *Trends Pharm. Sci.* **12** (1991), 383–388.
- [7] J. Hardy, K. Duff, K. Gwinn-Hardy, J. Pérez-Tur and M. Hutton, Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau, *Nature Neurosci* **1** (1998), 95–99.
- [8] J. Hardy and D.J. Selkoe, The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics, *Science* **297**(5580) (19 Jul 2002), 353–356.
- [9] J.A. Hardy and G.A. Higgins, Alzheimer's disease: the amyloid cascade hypothesis, *Science* **286** (1992), 184–185.
- [10] S. Kawabata, G.A. Higgins and J.W. Gordon, Amyloid plaques, neurofibrillary tangles and neuronal loss in brains of transgenic mice overexpressing a C-terminal fragment of human amyloid precursor protein, *Nature* **354**(6353) (12 Dec 1991).
- [11] E. Levy, M.D. Carman, I.J. Fernandez-Madrid, M.D. Power, I. Lieberburg, S.G. van Duinen, G.T. Bots, W. Luyendijk and B. Frangione, Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type, *Science* **248**(4959) (1 June 1990), 1124–1126.
- [12] C.L. Masters and K. Beyreuther, Neuronal origin of cerebral amyloidogenic proteins: their role in Alzheimer's disease and unconventional virus diseases of the nervous system, *Ciba Found Symp* **126** (1987), 49–64.
- [13] D.J. Selkoe, The molecular pathology of Alzheimer's disease, *Neuron* **6**(4) (April 1991), 487–498.
- [14] P.H. St George-Hyslop, R.E. Tanzi, R.J. Polinsky, J.L. Haines, L. Nee, P.C. Watkins, R.H. Myers, R.G. Feldman, D. Pollen, D. Drachman et al., The genetic defect causing familial Alzheimer's disease maps on chromosome 21, *Science* **235**(4791) (20 Feb 1987), 885–890.
- [15] P. St. George Hyslop et al., Genetic linkage studies suggest that Alzheimer's disease is not a single homogenous disorder, *Nature* **347** (1990), 194–197.
- [16] C. Van Broeckhoven, J. Haan, E. Bakker, J.A. Hardy, W. Van Hul, A. Wehnert, M. Vegter-Van der Vliet and R.A.C. Roos, The beta-amyloid precursor protein gene is tightly linked to the locus causing Hereditary Cerebral Hemorrhage with Amyloidosis of Dutch Type, *Science* **248** (1990), 488–490.