

Written Evidence for inquiry on Scientific Publication by Science and Technology Committee, UK House of Commons

PART I: EDITORIAL AND PUBLISHER CORRUPTION

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Ian Gibson MP,
Chairman of the Committee,
Science and Technology Committee,
7 Millbank, London SW1P 3JA
UK

8 February 2004

**Re: The Committee invitation for written evidence on an inquiry into scientific publications;
my e.mail correspondence with Emily Commander, January 5-6, 2004¹**

1. INTRODUCTION

1.1 Author background information

I am M.D., Ph.D., neuroscientist, biochemist and editor. For over a decade I have been involved in Alzheimer's disease research and the basic science on the role of fats in brain function, memory, and brain disorders. I have published more than one hundred refereed articles, scientific correspondence items, and meeting abstracts, and lead the free-access no-publication-charge international peer-review scholar publication, *Neurobiology of Lipids* (ISSN 1683-5506) that I founded and publish since April 2002. My dual expertise as neuroscientist and electronic journal publisher provides the grounds for two parts of my personal written evidence for the inquiry on

¹ Available at: <https://ar1.org/Lists/SPARC-OAForum/Message/413.html>

Scientific Publication by Science and Technology Committee of the UK Parliament. Part I of my written evidence is provided below.

1.2 Competing interest declaration

I declare that I do not have any competing financial interest. I aim free information dissemination and an unbiased development of Alzheimer's neuroscience. I observe the Society for Neuroscience Guidelines for Responsible Conduct Regarding Scientific Communication. I am a founding, managing and publishing editor of the *Neurobiology of Lipids*, an unpaid position. *Neurobiology of Lipids* (ISSN 1683-5506) has no affiliation with any professional association, publisher, industry member, commercial enterprise, public, educational or government organization. The viewpoint presented in this written evidence is my personal view.

2. EDITORIAL AND PUBLISHER CORRUPTION

2.1 Conclusions to draw

- A. The unfair practices of major scientific journals (including representing conventional subscription-based publishing system journal *Nature*; *Science* magazine; Elsevier's Cell Press *Neuron* and *Cell*; Elsevier's *Brain Research*; and free access *Journal of Clinical Investigation*) illustrate editorial and publishing institution corruption, and their apparent inability to serve public interest.
- B. The presented evidence show that questioned journals serve a private interest, and that there is no working mechanism to force these journals or their publishing institutions to amend things and thus observe their own broken self-declared ethical guidelines.
- C. Described events (particularly an unpublishing a correspondence item at *Science's SAGE KE*, and the rejection of article at *Dialysis & Transplantation* after objections from marketing department^{*}) additionally illustrate the lack of true editorial independence from the publisher, publishing institution (American Association for the Advancement of Science in case of *Science's SAGE KE*) or other bodies (The journal marketing Department in case of *Dialysis & Transplantation*).

^{*} Dyer O. *British Medical Journal* Vol. 328: pp. 244-b (2004)

- D. There is a boring timing match between amyloid treatment, severe deterioration of UK Alzheimer's patient; and the presump sales of shares by Dennis Selkoe, academic professor and director of Ireland-based Elan corporation.

2.2 Recommendations

- A. To introduce rules to protect public interest of biomedical publication;
- B. To introduce rules on personal responsibility and penalties for those helping to conceal the dishonesty by others in biomedical publications;
- C. To introduce rules to safeguard true independence of editors of biomedical publications;
- D. To investigate whether there is a secret deal between hiding for two years experimental amyloid treatment failure, severe deterioration of Alzheimer's patient in a UK clinic, the following sales of shares by Elan Corporation Alzheimer's expert Dennis Selkoe and other Elan insiders, and the consequent disastrous turndown of Elan.

2.3 Preamble

Editorial material of one of the major world medical journals, *Nature Medicine*, wrote in 1999: "Science, and biomedical science in particular, is competitive, and for many is a pursuit that generates considerable passion and emotion. No wonder, then, that competing scientists working in the most competitive disciplines occasionally come to blows... Research into... Alzheimer disease seems to suffer more than most in this respect. Judging by recent events, this reputation seems justified..."² This events were summarized in an accompanying *Nature Medicine* essay,³ and in two earlier general media reports, a *Wall Street Journal's* "Did ties to Alzheimer's test maker sway NIH report?"⁴ and *The Boston Phoenix's* "Science for Sale: A Harvard researcher stands to profit from a product he "independently" reviewed for the National Institutes of Health",⁵ a reading material for students taking a course on Medical Ethics at Case Western Reserve University.

² Nature Med. Vol. 5(7): p. 713, p. 717 (1999)

³ Birmingham K, Ready T. Conflict-of-interest problems lead to policy changes. Nature Med. Vol.5(7), 717-8 (1999)

⁴ Waldholz M, King RT, Jr. The Wall Street Journal. (30 Nov 1998)

⁵ Ready T. (29 April 1999). Available at: <http://www.bostonphoenix.com/archives/1999/documents/00521742.htm>

Another major general medicine journal, UK-based *British Medical Journal (BMJ)* in a recent Education and Debate essay stated that “journals are caught between publishing the most relevant and valid research and being used as vehicles for drug company propaganda”.⁶

The facts provided below indicate that the major worlds’ general science and neuroscience journals impede not biased scientific development of the research into the causes and treatment of Alzheimer’s disease, obstruct public interest and their own guidelines, and apparently serve one’s secret private interest. It is explained how such wrongdoing *i)* is associated with a severe competing financial interest of Alzheimer’s expert Dennis Selkoe, a hero of *Wall Street Journal* and *The Boston Phoenix* reports; and *ii)* could cause a severe deterioration of at least one Alzheimer’s patient in England.

2.4. Journal Nature

In April 2002 I was forced to enter struggling to protect my fields' unbiased developed after UK-based journal *Nature* (Macmillan Publishers Ltd, Registered No. 785998, England; a “prestigious, long-running multidisciplinary journal and a must-have for libraries”, as defined on 6 Oct. 2003 by *The Guardian*) published the article⁷ co-authored by Harvard professor Dennis Selkoe. Prof. Selkoe is known as an Alzheimer’s field lead authority and an architect of a decade-long amyloid hypothesis. This hypothesis blames a small protein called amyloid beta as a cause of Alzheimer’s disease. The hypothesis dominated the stage for more than a decade and retarded the development of many other promising approaches.⁸ *Nature* article favored Selkoe hypothesis. What the article failed to report was apparent financial conflict of interest by Selkoe, and the balanced discussion that amyloid beta is an essential brain chemical, as was convincingly shown by others.⁸ The accompanied *Nature News* report⁹, however, announced in the title that “smoking gun found for Alzheimer's”. I covered both issues in my correspondence arising item submitted to *Nature*. *Nature* editor asked me to present evidence of Selkoe conflict, and finally rejected my communication. The rejection response included the following determination on an allegation of a not disclosed competing financial interest by Dr. Selkoe: “regarding the competing financial interests statement, Dr Selkoe no longer has any connection with the companies you list because of the 1997 ruling by Harvard University prohibiting such connections among its faculty members. Selkoe's amyloid-

⁶ Available at: <http://bmj.com/cgi/content/full/326/7400/1202>

⁷ *Nature*. Vol. 416, pp.535-53 (April 4, 1999)

⁸ Koudinov A. Amyloid beta is an essential synaptic protein, NOT neurotoxic junk. See Appendix 1 below.

⁹ Available at: <http://www.nature.com/nsu/020402/020402-5.html>

beta vaccine patent was independent of Elan/Schenk's."¹⁰ This belonging to *Nature* scientific correspondence, along with some evidence of Selkoe conflict, appeared as a Rapid Response in *British Medical Journal* on 15 May 2002.¹¹

In August 2002 Dublin-based *The Sunday Business Post* in two publications¹² confirmed that Dr. Selkoe is not only Harvard Professor, but also Elan Corporation Director, and "Elan Alzheimer's expert in pre-slump share sale". Growing fast internet search capabilities allowed me to discover in mid-summer 2002 publicly available US Security and Exchange Commission (SEC) information on sale of shares by Dennis Selkoe and other Elan insiders. This sale of shares happened a year before the company publicly announced poor results in its' trial of amyloid-based Alzheimer's disease treatment with a vaccine.¹³ I also discovered another apparent conflict by D. Selkoe, an award in 2001 the major American Alzheimer's Potamkin Prize to Elan scientist Dr. Dale Schenk. This prize is managed by American Academy of Neurology (AAN) Potamkin Prize selection committee chaired since 1999 by Professor Selkoe, who's service as Director for Elan was not disclosed in any AAN document.¹⁴

As previously requested, I delivered the information on Selkoe conflict to *Nature*, and asked *Nature* to disclose Dr. Selkoe conflict to meet the journal own published guidelines.¹⁵ The response of Phillip Campbell (dated 11 September 2002) serving Editor for journal *Nature* and Editor-in-Chief for *Nature publications* seemed missing the point of the latest publicly available info. Dr. Campbell stated: "My colleagues have examined the situation with patents and we are also satisfied that our conflict of interest guidelines have been adhered to."¹⁰

I believe that the above statement contradicts Dr. Campbell other official statement that "there are circumstances where selection of evidence, interpretation of results or emphasis of presentation might be inadvertently or even deliberately biased by a researcher's other interests"¹⁵

Moreover, just three months later *Nature* published an *Insight: Review* article by Dennis Selkoe and his business partner, Dr. Howard Weiner with no competing interest declaration.¹⁶ This article entitled "Inflammation and therapeutic vaccination in CNS diseases" is of particular relevance to

¹⁰ See my full corr. with Nature at: <http://anzwers.org/free/neurology/reports/eletters.html#let2nature>

¹¹ Available at <http://bmj.com/cgi/eletters/324/7338/656#22216>

¹² Sunday Business Post, Aug 18, 2002, available at: <http://archives.tcm.ie/businesspost/2002/08/18/story326047.asp>

¹³ See ARF news: <http://www.alzforum.org/new/detail.asp?id=410> , <http://www.alzforum.org/new/detail.asp?id=412>

¹⁴ Ethical conundrums: an Alzheimer's case. *BMJ* (2002) Available at: <http://bmj.com/cgi/eletters/325/7363/0/g#25404>

¹⁵ Nature statement on Competing interests: <http://www.nature.com/nature/submit/policies/competing/index.html>

¹⁶ *Nature* Vol. 420, pp. 879-84 (Dec 19, 2002)

Dr. Selkoe and Dr. Weiner amyloid entrepreneurship described in details in my correspondence "[Alzheimer's] Amyloid beta road show" commenting on another article co-authored by Weiner and Selkoe in *Journal of Clinical Investigation* (see below).¹⁷

Most lately *Nature* published another *Insight:Review* article by Selkoe entitled "Folding proteins in fatal ways".¹⁸ In this article D. Selkoe expanded his amyloid theory to other brain proteins and other neurodegenerative diseases. However, there were no competing interest disclosure made by *Nature* despite the fact that *Nature* is fully informed about it, and because amyloid hypothesis is the basis of Selkoe's Elan Corporation Alzheimer program.

Based on the above I can not call the conduct by *Nature* other then corruption. I therefore have no reason to believe to the response by *Nature* editor Dr. Campbell on my inquiry whether "Dr.Selkoe served as a referee for the *Nature* '99 article by [Elan] Schenk *et al.*¹⁹ (that was the basis for [Alzheimer's] vaccine development) and other Alzheimer's/amyloid related articles submitted previously to *Nature*."¹⁰ In his e.mail reply of Sept. 11, 2002 Dr. Campbell stated: "It is a strict policy of Nature that we do not discuss the identity of referees involved in our decision making. However, I can assure you that there is absolutely no basis for any suspicion that Dr. Selkoe might have abused his position as a possible referee."¹⁰

I believe that it is in the power of The Science and Technology Committee to request Nature to disclose their Alzheimer's amyloid vaccine articles referees. I further believe that such disclosure will confirm the drawn conclusion on *Nature* editorial corruption, and that there were no solid scientific grounds to publish the article by Elan's Dale Schenk and colleagues. This article triggered an unusually fast track 'development' of Alzheimer's amyloid vaccine, that could cause the severe deterioration of a patient in a UK clinic following amyloid treatment (see below).

2.5 Science Magazine by AAAS

Science is the major international general science scientific journal (published by the American Association for the Advancement in Science, AAAS with an UK office²⁰) that was called by *The Guardian* (6 Oct. 2003) a "major US player and perhaps the most widely read science journal in the world." Unfortunately, the conduct by *Science* and AAAS illustrate another example of editorial

¹⁷ *J Clin Invest* Vol.112, pp. 415-422 (Aug, 2003)

¹⁸ *Nature* Vol. 426, pp. 900-904 (Dec 22, 2003)

¹⁹ *Nature* Vol. 400, pp. 173-177 (1999)

²⁰ Peter Stern, Senior Editor, Science Europe Office, Bateman House, 82-88 Hills Road, Cambridge CB2 1LQ

and publishing institution corruption related to Alzheimer's disease research. The facts are provided below.

On one hand on my inquiry²¹ *Science* promptly handled the non-disclosure of competing interest in a 19 July 2002 review article by Hardy and Selkoe.²² Similarly to all mentioned above articles in *Nature*, the *Science* article represented a unipolar view of the amyloid beta protein as an Alzheimer's disease culprit and failed to provide a fair discussion of amyloid beta as essential brain chemical. The correction note published in *Science* on 27 September 2002 stated:

"The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics" by J. Hardy and D. J. Selkoe (19 July [2002], p. 353). The review should have been accompanied by the following conflict of interest declaration: "Dr. Selkoe is a founding scientist of Athena Neurosciences, now Elan PLC, and a Director of Elan." Science had failed to send the disclosure form at the time the manuscript was received."

The latter part of the correction transferred the non-disclosure responsibility from Dr. Selkoe to *Science*, indicating the magazine voluntary acceptance of the editorial misconduct (see my full correspondence²¹ with Donald Kennedy, *Science* Editor-in-Chief, for further details).

Just one month after the publication of the correction, however, on October 25, 2002, *Science* published another article by Selkoe that served to modify amyloid cascade hypothesis in favor of a specific physical form of amyloid, called oligomers.²³ It was a viewpoint article in a *Science* theme issue "The dynamic synapse" distributed free of charge at the 32nd Society for Neuroscience Annual Meeting, November 2-7, 2002, in Orlando, Florida, a major world forum for neuroscientists. This article (similarly to the mentioned above another *Science* article by Hardy and Selkoe) had no discussion of amyloid beta as good molecule. It also failed to provide honest disclosure of the competing financial interest by Selkoe and simplified the case by calling Dr. Selkoe "a consultant to Elan Pharmaceuticals, plc." in the last reference.

On my call for a true disclosure of competing interest by D. Selkoe, Harvard Professor, Elan Corporation Director, and "Elan Alzheimer's expert in pre-slump share sale"¹² *Science* Editor-in-

²¹ See my full corr. with *Science* at: <http://anzwers.org/free/neurology/reports/eletters.html# pmid12805530>

²² *Science* Vol. 297, pp. 353-356 (2002)

²³ *Science* Vol. 298, pp. 789-791 (25 Oct 2002)

Chief determined that “Dr. Selkoe's statement [that he is "a consultant to Elan Pharmaceuticals, plc."] is a sufficient announcement of what some might perceive as a conflict.”²¹

On April 22, 2003 I brought attention of *Science* Editor-in-Chief to another case of the violation of the *Science* and AAAS (American Association for the Advancement of Science, a publisher of *Science*) disclosure policy in another article on Alzheimer's disease amyloid oligomers. One of the senior authors of April 18, 2003 article on amyloid oligomers,²⁴ Dr. Carl Cotman failed to disclose that he is a co-founder, scientific director and consultant of the Cortex Pharmaceuticals, a company that has Alzheimer's disease as one of its' research areas.²⁵ This time Donald Kennedy did not reply on my non-disclosure alert and yet failed to publish a correction to fix this instance of the AAAS and *Science* policy breach. *Science* also refused my correspondence item describing experimental and data interpretation flaws of the article by Kaye *et al.*. Such scientific flaws were also noticed and publically sounded by Vincent Marchesi, Editor-in-Chief of *The FASEB Journal*.

Furthermore, on June 13, 2003 *Science* published a presidential address by Floyd Bloom, AAAS board chairman,²⁶ an immediate predecessor of Donald Kennedy at the post of *Science* Editor-in-Chief, and the sole Editor-in-Chief for Elsevier's Brain Research journal series (see below). This contribution included two-paragraph section on “Complex genetic diseases of the brain“. Defining “new strategies for the treatment of Alzheimer's” Dr. Bloom particularly mentioned “vaccines for absorbing the bad fragments of APP” (a chemical precursor of the amyloid beta protein) and “enzymes to block the abnormal proteolysis” [of APP yielding amyloid beta]. The related bibliography included citations of the above mentioned article by D. Selkoe in the *Science* theme issue,²³ and the article by vaccine developer Dr. Schenk of Selkoe's Elan Pharmaceuticals, plc.²⁷ What this *Science* publication by AAAS top official did not mention was Dr. Bloom competing financial interest.

The above issues were addressed in my correspondence with *Science* provided in my June 16, 2003 “Open letter to Donald Kennedy, Science Editor-in-Chief: AAAS, Science, Alzheimer's disease and academic dishonesty”.²¹ This letter also informed *Science* Editor-in-Chief that Floyd E. Bloom, AAAS Board of Directors Chair and Scripps Research Institute professor has competing financial interest as founder and CEO of Neurome, Inc.²⁸ Dr. Bloom did not disclose his financial interest in

²⁴ Kaye *et al.* *Science* Vol. 300, pp. 486-489 (18 April 2003)

²⁵ Research Areas. *Cortex Pharm web site* Available at: <http://www.cortexpharm.com/html/research/index.html>

²⁶ *Science* Vol. 300, pp. 1680-1685 (13 June 2003)

²⁷ *Nature Review Neuroscience* Vol. 3, pp. 824-828 (Oct 2002)

²⁸ Management team. *Neurome web site* <http://www.neurome.com/company/people.htm>

his *Science* "Presidential address. Science as a way of life: perplexities of a physician-scientist"²⁶ that AAAS made available free to all with no barrier for access (!) and that official AAAS news release called "Healing U.S. Health Care. AAAS Board Chairman Floyd E. Bloom calls for U.S. health care reform." (AAAS News release 13 June 2003).²⁹

There is another instance of financial conflict non-disclosure in articles on Alzheimer's disease that informed *Science* did not inform readers about. This is the article by Monsonogo and Weiner in the *Science* theme 'Brain Disease' issue (31 Oct 2003)³⁰ that apparently aimed free distribution among the global neuroscience audience at the Society for Neuroscience Annual Meeting 2003. I covered the above systemic wrongdoing by *Science* in my letter to colleagues,³¹ that generated November 7, 2003 response by Cambridge-based Peter Stern, Senior Editor of the Europe (UK) Office of *Science*: "Dear Dr. Koudinov, thank you for relaying your concerns to us. We have already started an investigation into that matter." Despite of this response by Peter Stern *Science* did not make public the competing financial interest by Howard Weiner. The typos correction, however, was published for the *Science* article by Monsonogo and Weiner.³²

Likewise, *Science* did not handle other non-disclosure cases described above, indicating that this is an editorial corruption, not incidental error. The facts described below further suggest that *Science* corruption may be endorsed by the leadership of AAAS, the publisher of *Science*.

2.6 Is *Science* Magazine editorial misconduct endorsed by publisher leadership?

Let facts talk, so a reader of this section will justify himself/herself whether editorial misconduct by *Science* is endorsed by the American Association for the Advancement of Science (AAAS) leadership.

As noted above one of the *Science* articles that missed competing interest declaration was authored by Floyd Bloom, immediate past Editor-in-Chief of *Science*, AAAS Board of Directors Chair³³ 2003-2004 and Scripps Research Institute professor, and founder and CEO of Neurome, Inc.²⁸

²⁹ Available at: <http://www.aaas.org/news/releases/2003/0613bloom.shtml>

³⁰ *Science* Vol. 302, pp. 834-836 (31 Oct 2003)

³¹ Available at: <http://anzwers.org/free/neurology/reports/eletters.html#pmid14593170>

³² *Science* Vol. 303, p. 173 (9 Jan 2004)

³³ Board of Directors 2003-2004. AAAS web site Available at: <http://www.aaas.org/about/board.shtml>

Additional financial conflict of interest by AAAS official is illuminated in a news reports associated with the April 15, 2003 article published in the Proceedings of the National Academy of Sciences USA³⁴ (PNAS USA) having Floyd Bloom as senior author, and Neurome, Elan and Scripps Institute as organizations where this research was performed.³⁵

Quoting Floyd Bloom at the Press Release of Neurome: “Using our newly developed tools for visualizing brain structures, we were able to completely reconstruct the brains of the mice that model human Alzheimer's disease,” said Floyd E. Bloom, M.D., Founding CEO and Chairman of the Board of Neurome and Chairman of the Department of Neuropharmacology at The Scripps Research Institute. “In fact, embedded in the brain reconstruction, we generated a 3D reconstruction of the deadly deposits of amyloid, showing for the first time, how the amyloid deposits precisely correspond with key memory circuits -- the same key memory circuits that are affected early in human Alzheimer's disease...”

The Neurome web site³⁶ discloses further details of Dr. Bloom competing financial interest coming out of the collaboration between Neurome and Selkoe’s Elan corporation: “The research partnership with Elan has an initial term of 3 years and may generate up to \$4 million in service revenue for Neurome, together with shared ownership of the diagnostic and therapeutic applications of the genes, circuits and mechanisms identified in the research. The partnership will utilize Neurome's technologies to analyze a mouse model of Alzheimer's Disease with the goal of identifying and exploiting molecules and pathways relevant to diagnosis and treatment of the disease. The partnership will analyze Elan's proprietary mouse model of amyloid deposition in an attempt to answer a variety of scientific questions regarding amyloid deposition.”

2.7 Did Floyd Bloom’s Neurome and Selkoe’s Elan joint venture affect AAAS and Science integrity ?

Based on the above facts, I do think so. Moreover, there is an apparent unwillingness of AAAS to investigate and amend things, as illustrated by AAAS unpublishing my Open letter to Science Editor-in-Chief addressing the above issues. This letter was published on June 16, 2003 as a scientific correspondence item on *Science* article by Floyd Bloom²⁶ at an editorially independent division of AAA Science called *Science’s SAGEKE*. During seven weeks (till unpublished at the

³⁴ *Proceedings National Academy of Sciences USA* Vol. 100, pp. 4837-4842 (15 Apr 2003)

³⁵ 15 April 2003 Press Release *Neurome web site* available at: <http://www.neurome.com/news/press041503.htm>

³⁶ Neurome collaborations. *Neurome web site* available at: <http://www.neurome.com/company/collab.htm>

beginning of August 2003) this letter was read by more than one thousand online readers, indicating significant readers' interest. An unpublishing of the letter, however, did not preclude its' unlimited availability at my own web site.²¹

In his recent *Science* editorial³⁷ Editor-in-Chief Donald Kennedy wrote: "we have tried to give authors more guidance about disclosure, and we'll continue to help our readers make their own informed judgments." The above facts indicate that what Dr. Kennedy says is a letter of intent, not the policy *Science* adhered to.³⁸

Contrasting with Dr.Kennedy editorial the above facts show an apparent unwillingness of AAAS *Science* to inform readers about not-disclosed financial interests by *Science* authors, and AAAS *Science* obstruction of a disclosure made by others.

The situation is most dramatic because there is apparently no way to force AAAS (or *Nature*, as described in paragraph 2.4) to amend things. I therefore hope that the Science and Technology Committee inquiry will consider my recommendations, and will help to enforce by law editorial misconduct elimination and personal responsibility and penalties of those helping to conceal the dishonesty by others (see paragraph 2.2 above). This is especially important in biomedical publications as described below.

2.8 Did industry tie by AAAS leader affect the content of AAAS publications?

There is another far-reaching implication, a concern of the content quality of a major worlds' general science journals, as illustrated below.

In 2000 AAAS published the special *Science* issue entitled "The Best of Science - Neuroscience".³⁹ This special issue was available for purchase at the Society for Neuroscience Annual Meeting 2000 held 5-8 November 2000, New Orleans, LA. Among other articles "The best of Science – Neuroscience" issue included the article "Alzheimer's Disease - Genotypes, Phenotype and Treatment" by Dennis Selkoe (published earlier as *Science* perspectives article⁴⁰), and "Special introduction from Floyd E. Bloom, Editor-in-Chief of Science", according to the AAAS advertisement leaflet distributed at the New Orleans SFN Meeting 2000.

³⁷ *Science* Vol. 303 p. 15 (2 Jan. 2004)

³⁸ *SPARC OA Forum* (3 Jan. 2004) available at: <https://ar1.org/Lists/SPARC-OAForum/Message/406.html>

³⁹ AAAS News and Notes. AAAS web site available at: <http://www.aaas.org/news/newsandnotes/inside59.shtml>

⁴⁰ *Science* Vol. 275 pp. 630-631 (31 Jan. 1997)

“The Best of Science – Neuroscience” “limited-edition volume” of *Science* is also mentioned at the AAAS Annual Report 2000 Membership page.⁴¹ Quoting right side bar of this page: “Publications The Best of Science-Neuroscience. This new publication includes the best work published in this field from the pages of *Science*. This collection of cutting edge articles and research reports covers circadian rhythms, neurodegeneration, aging, and more.”

Based on the facts described above one may doubt that this issue presents a true “best of science”. One may further ask: Is AAAS inclusion of the article by Selkoe in the "Best of Science - Neuroscience" volume a support of Floyd Bloom business partner ? The latter seem true, based on an unfortunate time-match of the distribution of the *Science*'s “The best of Science – Neuroscience” at the 30th Society for Neuroscience Annual Meeting (5-8 Nov. 2000) and Floyd Bloom's Neurome announcement of “financing from... [Selkoe's] Elan Corporation...” and “research partnership with Elan Corporation's pharmaceutical subsidiary to study neurodegenerative disorders” (20 October 2000, as announced in *The Scientist* daily news report⁴² “New companies to commercialize neuroscience discoveries”).

The next question come then: Do *Science* articles on Alzheimer's amyloid hypothesis (by Selkoe,²³ by Kaye *et al.*,²⁴ by Bloom,²⁶ and by Monsonogo and Weiner³⁰ quoted above) serve to add a commercial value to Neurome, a company of Professor Floyd Bloom, an AAAS board of directors chair ?

If so, there is no wonder that another *Science* article⁴³ (covering presented at Stockholm World's Alzheimer's Congress 2002 wide range of Alzheimer's research projects expanding far beyond amyloid story) limits its' abstract (supposed to be fair representation of the article content) to the following amyloid beta endorsement: “STOCKHOLM--Alzheimer's researchers gathered here last month with a sense of urgency and optimism about possible treatments--and perhaps preventions--for the mind-robbing disease. The 4000 attendees heard about progress on several fronts, including possible vaccines and treatments aimed at either blocking formation of b amyloid, a small peptide thought to trigger the loss of brain neurons, or at dissolving the abnormal b-amyloid deposits that are a hallmark of the disease. This special focus also explores a debate over which drugs to test in a prevention trial.”

⁴¹ Annual report membership 2000 AAAS *web site* available at <http://www.aaas.org/annual/2000/membership.html>

⁴² *The Scientist* daily news (3 Nov. 2000) available at: <https://www.biomedcentral.com/news/20001103/01/>

⁴³ Helmuth. *Science* Vol. 297 1260-1262 (23 Aug. 2002) <http://www.sciencemag.org/cgi/content/short/297/5585/1260>

2.9 The lack of editorial independence at AAAS publications: A case of AAAS Science's SAGE KE

As noted above (see paragraph 2.7 “Did Floyd Bloom’s Neurome and Selkoe’s Elan joint venture affect AAAS and *Science* integrity ?”) my “Open letter to Donald Kennedy, Science Editor-in-Chief: AAAS, Science, Alzheimer’s disease and academic dishonesty”²¹ was published on 16 June 2003 in an online journal of AAAS Science called *Science of Aging Knowledge Environment* or *Science’s SAGE KE*. Despite of being the subscription based service by AAAS this wonderful web site provides unique opportunity for scientists in biomedical disciplines related to aging to meet colleagues and to provide scientific correspondence items on almost any article published elsewhere. I published at *Science’s SAGE KE* several scientific correspondence items that had total readership of 8,588 on February 1, 2004 (referenced at my web site scientific correspondence page⁴⁴). My scientific correspondence published in *Science’s SAGE KE* includes quoted above “Open letter to Science Editor-in Chief...”, my “Open letter to Public Citizen's Health Research Group on Alzheimer's disease research”⁴⁵ (also published at *British Medical Journal*⁴⁶), and the letters reporting the provided below facts on Elsevier Cell Press *Neuron* (“Hasta la vista, amyloid cascade hypothesis, OR will academic dishonesty yield Alzheimer's cure?”⁴⁷) and the *Journal of Clinical Investigation* (“Amyloid beta road show, or had the lure of profits corrupted Alzheimer’s neuroscience”⁴⁸).

The latter letter “Amyloid beta road show...”⁴⁸ was unpublished by *SAGE KE* along with my “Open letter to Science Editor-in-Chief...”²¹. *SAGE KE* editor Kelly LaMarco in the e.mail letter of 8 August 2003 wrote: “Dear Dr. Koudinov, Thank you for your recent postings in SAGE KE. Unfortunately, I have had to remove your comments from the site. We cannot post in SAGE KE letters that are addressed to the editors of other journals. We are happy to post comments on scientific findings. But we cannot post comments that criticize the editorial policies of other journals. Perhaps you can send your comments directly to Dr. Marks. Best wishes, Kelly LaMarco Editor, SAGE KE”.

⁴⁴ Freely available at: <http://anzwers.org/free/neurology/reports/eletters.html>

⁴⁵ Freely available at: <http://sageke.sciencemag.org/cgi/eletters/sageke;2002/34/or10#181>

⁴⁶ Freely available at: <http://bmj.com/cgi/eletters/325/7357/226/a#29825>

⁴⁷ Freely available at <http://sageke.sciencemag.org/cgi/eletters/pmid;12765607#191>

⁴⁸ Freely available at: <http://sageke.sciencemag.org/cgi/eletters/jci;112/3/415#218>

This response seemed explaining the reason to unpublish my 5 August 2003 letter on 1 August 2003 *Journal of Clinical Investigation* article co-authored by Selkoe. I, therefore, revised this correspondence and re-published it again with minor helpful revisions by Kelly LaMarco.

There were, however, no way to revise my Open Letter to AAAS *Science* Editor-in-Chief Donald Kennedy, also unpublished on this occasion, after this letter (published on 16 June 2003) generated in seven weeks the readership exceeding one thousand. I preferred to re-publish this Open letter at my web site where it is freely available. The Acrobat .PDF imprint of the Open Letter originally published at *Science's SAGE KE* is also available and is provided below (Appendix 2).

As *SAGE KE* user I enjoyed editorial management of this great online serial. I was, however, bothered by the following note in 8 August 2003 e.mail letter by Kelly LaMarco (see above): “Unfortunately, I have had to remove your comments from the site.”

I do qualify this statement by AAAS *Science's SAGE KE* editor, an editorially independent publication (ISSN 1539-6150) as an indication of a pressure exerted on *SAGE KE* editors, and a break of *SAGE KE* editorial independence.

No question the responsibility for such apparent editorial independence break rest with AAAS, a publisher of *SAGE KE*, not *SAGE KE* editors.

One may find convincing that there is a reason for publisher pressure on *SAGE KE editor*, a competing financial interest by AAAS top official, described in the unpublished letter (see paragraphs 2.5-2.7 above for details).

2.10 Elsevier Brain Research

Another eye-catching example of editorial and publisher wrongdoing is the case of Elsevier *Brain Research* named by UK *Gardian*⁴⁹ the most expensive UK library serial offering “a comprehensive look at events in neuroscience”. In June 2003 I informed Eric Merkel-Sobotta, Elsevier Corporate Relation Director, that *Brain Research* Editor-in-Chief,⁵⁰ Dr.Floyd Bloom (who also serves the sole Editor-in-Chief for the whole *Brain Research journal series*⁵¹ by Elsevier) has not disclosed

⁴⁹ Adam D. Scientists take on the publishers in an experiment to make research free to all. *The Guardian* (6 Oct 2003)

⁵⁰ Available at: <http://www.elsevier.com/inca/publications/misc/622287journals.html>

⁵¹ Available at: <http://www.elsevier.com/locate/brainres>

competing financial interest as illustrated above (see paragraphs 2.5-2.7 above). Since then Eric Merkel-Sobotta seems not bothered by the fact of impaired academic integrity by one of the most expensive Elsevier title. His only reply on my alerts (that I send him on several occasions since the publication on 16 June 2003 my Open letter to Science Editor-in-Chief that disclosed the conflict by Floyd Bloom) was 18 December 2003 e.mail note associated with my 17 December 2003 SPARC OA Forum posting “AAAS Science and academic integrity - breakdown of the year?”: "Would you please be so kind as to remove my name from your cc: distribution list? I am already on all of the usual listservs, and so do not need to receive your information separately. Thank you very much for your cooperation. With best regards, Eric Merkel-Sobotta". No other action were taken.

2.11 Proceedings of the National Academy of Sciences USA (PNAS USA)

Proceedings of the National Academy of Sciences USA (PNAS USA) is a flagship journal published by the National Academy of Sciences USA.

Paragraph 2.6 above is mentioning that “additional financial conflict of interest by AAAS official is illuminated in a news reports associated with the April 15, 2003 article published in the *Proceedings of the National Academy of Sciences USA (PNAS)* having Floyd Bloom as senior author, and Neurome, Elan and Scripps Institute as organizations where this research was performed.

It is important to note that *PNAS* article does not have competing interest declaration, as it is required by the *Uniform Requirements for the Manuscripts submitted to the Biomedical Journals*,⁵² and that it was “contributed by Floyd E. Bloom”.³⁴ *PNAS* information for authors⁵³ explains that the record “contributed by Floyd E. Bloom” indicates the manuscript submission to *PNAS* through Track III mechanism. It further says: “Track III: An Academy member [*PNAS* is a National Academy of Sciences USA publication] may submit his or her own manuscripts for publication. Members' submissions must be accompanied by the name of knowledgeable colleague(s) who reviewed the paper, along with the review(s)”. Is this an abuse of the *PNAS* submission policy associated with competing financial interest non-disclosure by Floyd Bloom?

I brought the above concerns to Nicholas Cozzarelli, *PNAS* Editor-in-Chief, in an e.mail letter (20 June 2003) on my Open letter to Science Editor-in-Chief and the above *PNAS* publication, and

⁵² Available at: <http://neurobiologyoflipids.org/submissions/uniformalreq.html>

⁵³ Submission and Review. Instructions for Authors *Proc Natl Acad Sci USA* <http://www.pnas.org/misc/iforc.shtml>

informed Dr. Cozzarelli of several other correspondence items quoted at length of this written evidence. In reply I received several confirmations from PNAS, including the one from Daniel Salsbury, Editorial Manager (21 Oct 2003) and Diane Sullenberger (5 Nov. 2003) similarly expressing thanks for my e-mails. I am not aware, however, that PNAS come to a determination on the case described above.

2.12 Journal *Neuron* by Elsevier's Cell Press and Other Cell Press titles

The non disclosed conflict by Selkoe (described in paragraphs 2.4 and 2.5) and others links the editorial corruption matter with a major neuroscience journal *Neuron* by Elsevier's Cell Press, as summarized below and described in details in *SAGE KE* letter "Hasta la vista, amyloid cascade hypothesis, OR will academic dishonesty yield Alzheimer's cure?"⁴⁷ and in *BMJ* letter "22 May 2003 *Neuron* article on Alzheimer's : 'valid research' or a 'drug company propaganda'?"⁵⁴

In my correspondence⁵⁵ with *Neuron* in August 2002 I requested editorial investigation and disciplinary action to punish Dennis J. Selkoe, non disclosure of competing financial interests in prior *Neuron* publication, and while serving *Neuron* editorial board member. Shortly thereafter I received a reply from *Neuron* senior scientist (currently serving a senior editor) Stacie Weninger. Dr. Weninger wrote to me: "I wanted to thank you for bringing this matter to our attention. We take these issues seriously, and we will look into the matter further".⁵⁰ Since then *Neuron* did not come to any action [that I expected to be] commensurate with the pattern of Dr. Selkoe misconducting academic nondisclosure dishonesty, as it is advised by the US Office of Research Integrity.⁵⁶ Moreover, February 2003 *Neuron* article by Sharon *et al.*⁵⁷ again hid D. Selkoe (a senior author) competing financial interest, disclosure that is required by the academic ethics and the uniform requirements for the manuscripts submitted to the biomedical journals.

Furthermore, on 22 May 2003 *Neuron* published featured article by Zurich researchers entitled "Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease".⁵⁸ The article was endorsed with the favoring *Neuron* commentary co-authored by *Neuron* editor Kenneth Blum.⁵⁹ The commentary conclusion enthusiastically stated that "the findings presented are important in

⁵⁴ Freely available at: <http://bmj.com/cgi/eletters/326/7400/1202#32842>

⁵⁵ See my full corr. with *Neuron* at: <http://anzwers.org/free/neurology/reports/neurology/eletters.html#let2neuron>

⁵⁶ Available at: <http://ori.dhhs.gov/html/misconduct/introduction.asp>

⁵⁷ *Neuron* Vol. 37, pp. 583-95 (2003)

⁵⁸ Winblad B, Blum KI. Hints of a Therapeutic Vaccine for Alzheimer's? *Neuron* Vol. 38, pp. 517-8 (22 May 2003)

⁵⁹ Hock C *et al.* *Neuron* Vol. 38, pp. 547-554 (22 May 2003)

providing further evidence for the validity of the prevailing working hypothesis, the Amyloid Cascade Hypothesis”.

I (as well as many other scientists) did not share the optimism of the *Neuron* article and associated commentary. Others found that “the title and some of the conclusions of this study are not yet justified.” I called both contributions “a bias in favor of the expired amyloid dogma-based Alzheimer’s therapy approach” due to the experimental flaws and the authors' apparently false statement on the financial interest in Selkoe’s Elan.

Hiding authors’ competing interest *Neuron* article by Hock *et al.* and its’ accompanying endorsement by the *Neuron* editor commentary serve an evidence for a conclusion in the *British Medical Journal* Editorial on financial interest in medicine: “Editorial coverage is much more valuable to drug companies than advertising, and scientific studies can be manipulated in many ways to give results favourable to companies.”⁶⁰

Since May 2003 there is no action taken by *Neuron*, Elsevier or Cell Press, indicating that there is an apparent corruption, and that *Neuron* and its’ publishers self interest (or ones’ private interest?) dominates the public interest of an unbiased development of Alzheimer’s neuroscience.

Neuron practices seems also exercised by another Cell Press title, worlds’ major biomedical journal *Cell*. An example follows: On 27 December 2003 I informed *Cell* Editor Emilie Marcus and Cell Press CEO Lynne Herndon that two 'breakthrough' articles⁶¹ in 26 December 2003 issue of *Cell* miss competing interest declaration by senior author, Dr. Eric Kandel. Dr. Kandel is a Nobel laureate, a Chairman of the Scientific Advisory Board and principal scientific founder of Memory Pharmaceuticals,⁶² and a reviews editor of Cell Press *Neuron*. The requirement for the disclosure of the conflict of interest is set in the Cell Conflict of Interest policy,⁶³ so, the break of it deserve the response. Again, there is no response over the past six weeks, however.

As in case of *Nature* and *Science* there is no working way to force Cell Press to amend things.

2.13 Journal of Clinical Investigation

⁶⁰ Available at: <http://bmj.bmjournals.com/cgi/content/full/326/7400/1155>

⁶¹ *Cell* Vol. 115, pp. 879-891, pp. 893-904 (26 Dec. 2003)

⁶² Advisory Board page. *Memory Pharm* web site available at: http://www.memorypharma.com/a_advisoryboard.html

⁶³ Available at: <http://www.cell.com/misc/page?page=authors>

The story of the *Journal of Clinical Investigation (JCI)* is based on the 1 August 2003 article by Monsonogo *et al.*⁶⁴ The major flaw of this report is the failure to provide a true competing financial interest declaration for senior authors, Dr. Dennis J. Selkoe and Dr. Howard L. Weiner. The Monsonogo *et al.* article footnotes' conflict of interest disclosure says that "the authors have declared that no conflict of interest exists." This statement is not true, as I described in mentioned above 5 August 2003 scientific correspondence letter "Amyloid beta road show or has the lure of profits corrupted Alzheimer's neuroscience".⁴⁸

This letter, however, was unpublished by *Science's SAGE KE* based on the editor reasoning that *SAGE KE* "cannot post comments that criticize the editorial policies of other journals" indicating *Journal of Clinical Investigation* unhappiness with my letter. I, therefore, revised this correspondence on a *JCI* article and submitted it again. *SAGE KE* editor email of 12 August 2003 stated: "We have now posted a slightly edited version of your letter. *JCI* has elected not to respond.", indicating that *JCI* is fully informed about my disclosure of the false competing interest declaration in the article under discussion. There is no correction published at *JCI* since then, so, any reader of the article by Monsonogo, Weiner, Selkoe and others at the free-access *JCI* web site remains dis-informed about the competing financial interest by the authors. See it yourself at the provided link.⁶⁴

2.14 Alzheimer's patient severe deterioration in a UK clinic

One of the recommendations of this written evidence is to investigate whether there is a secret deal between hiding for two years experimental amyloid treatment failure, deterioration of Alzheimer's patient in a UK clinic, the following sales of shares by Elan Corporation Alzheimer's expert Dennis Selkoe and other Elan insiders, and the consequent disastrous turndown of Elan. Such events match was reported by me to the Federal Drug Administration (FDA), US Securities and Exchange Committees (SEC) and noticed in the recent *Sunday Times* article "Selkoe's sale of Elan shares referred to SEC".⁶⁵ I am not aware that any action was taken to date by FDA or SEC.

The estimation of dates is based on 17 March 2003 *Nature Medicine* report "Neuropathology of Alzheimer's disease after immunization with amyloid-beta peptide: a case report"⁶⁶

⁶⁴ *J Clin Invest.* Vol. 112 pp. 415-422 (1 Aug. 2003) available at: <http://www.jci.org/cgi/content/abstract/112/3/415>

⁶⁵ Des Crowley. *The Sunday Times* (16 Nov 2003), <http://www.timesonline.co.uk/article/0,,2095-895532,00.html>

⁶⁶ Nicoll JAR *et al.* *Nature Medicine*, April 2003 Vol. 9, pp 448-452 (April 2003, published online 17 March 2003)

Let me quote the first paragraph of this *Nature Medicine* article. This quotation indicates that this Alzheimer's patient was immunized and become deteriorated before Elan Phase 2 clinical trial was launched, thus raising the question whether drug development regulatory bodies were properly and timely informed of this patient severe deterioration:

"A 72-year-old woman with a 5-year history of gradually progressive memory impairment presented with worsening confusion and disorientation. Her Mini Mental State Examination (MMSE) score (23/30) represented a three-point deterioration in two years. She had global cognitive impairment and satisfied the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association's criteria for probable AD, with no cardiovascular risk factors and a modified Haschinski score <4. Therapy with rivastigmine tartrate, a cholinesterase inhibitor, resulted in improvements in the Alzheimer's Disease Assessment Scale cognitive section (ADAS cog), MMSE, clock drawing and verbal fluency, but ten months later she had returned to baseline levels on all these parameters. The patient was then enrolled in a randomized, double-blind, multiple-dose immunogenicity study of Ab42 (AN-1792; Elan Pharmaceuticals). She received her first injection, containing 50 microg of AN-1792, in July 2000. This was repeated 4, 12 and 24 weeks later with no apparent adverse effects. A fifth injection with a reformulated preparation containing polysorbate-80, subsequently used in a multinational phase 2a trial, was given 36 weeks after the first injection. Four weeks after her last injection, her cognitive test results were unchanged (MMSE 23), but at six weeks she suddenly became unwell with dizzy spells, drowsiness, an unstable gait and fever. Two weeks after that, she deteriorated such that an MMSE could not be performed. Neuroimaging (Fig. 1a) showed extensive bilateral alterations in the cerebral white matter and enhancement on the brain surface. There was mild hydrocephalus; an isodense mass was identified above the splenium of the corpus callosum on the right side. The appearances were interpreted as representing either edema, possibly associated with an inflammatory process, or an infiltrating primary brain tumor. Therapy with dexamethasone was started. The patient remained relatively unchanged until she died in February 2002 from a pulmonary embolism 20 months after the first injection and 12 months after the last injection."

Lets' focus on the following sentences from the above paragraph:

"She received her first injection, containing 50 microg of AN-1792, in July 2000. This was repeated 4, 12 and 24 weeks later with no apparent adverse effects. A fifth injection with a reformulated preparation containing polysorbate-80, subsequently used in a multinational phase 2a trial, was given 36 weeks after the first injection. Four weeks after her last injection, her cognitive test results

were unchanged (MMSE 23), but at six weeks she suddenly became unwell with dizzy spells, drowsiness, an unstable gait and fever. Two weeks after that, she deteriorated such that an MMSE could not be performed... The patient remained relatively unchanged until she died in February 2002 from a pulmonary embolism 20 months after the first injection and 12 months after the last injection."

Although the article missed specific dates the above allows the following calculation and notes:

- A. This patient was immunized with AN-1792, that was latter used in FDA approved Phase2 clinical trial ("...A fifth injection with a reformulated preparation containing polysorbate-80, subsequently used in a multinational phase 2a trial...")
- B. last immunotherapy injection was at the end of year 2000 (24 weeks after the first injection in July 2000)
- C. patient remained unchanged during January 2001 ("four weeks after her last injection")
- D. patient became unwell at the beginning of February 2001 ("at six weeks [after her last injection] she suddenly became unwell")

Especially dramatic could be the possibility that this patient deterioration caused presump shares sale by Elan directors. Quoting Des Crowley's *The Sunday Times* article:

"Selkoe... sold 20,000 shares for around \$1m on February 6, 2001. Other insiders at Elan declared sales of more than \$43.5m in the months following Selkoe's disposal. After the American Food and Drug Administration (FDA) refused to endorse the drug in January 2002, the share price fell to a low of \$2."

I believe that specific dates in medical record of this patient may add clarity to the above timing match, and therefore warrants your investigation.

Quoting my senior colleague from Australia:

"did you realise that the new *Nature Medicine* article by Nicholls et al shows that this case of meningoencephalitis occurred 6 months before Elan's Phase 2A [clinical] trials were begun? You may be interested in exploring the implications of this timing."

It is thus possible that Selkoe's Elan failed to report in time this case reaction on a vaccine. If so, should Elan Phase2 Trial be ever launched, yielding many more patients' illness, following the vaccine withdrawal a year latter,⁶⁷ further threatening Alzheimer's research community with a rush movement of the not-validated hypothesis to the clinic and making harm to patients, while serving ones' commercial interest. Based on the facts, provided in earlier paragraphs of this written evidence, it is regrettable to realize that major scientific journals are involved in this unfair play.

I am not along in my belief. Below are voices of my two colleagues, senior professors:

"...Many thanks for all the information... I was going to do an article more than a year ago saying that a clinical trial of A-beta vaccination was too hazardous to try, but never got around to it. Then the disaster that many of us predicted would result came to pass. I thought common sense would then prevail and this whole idea would be abandoned. But as you have pointed out, the dogma is too strong to be dropped, and now it is the application, and not a faulty theory that is being blamed. More AD cases are in danger..."

"I agree whole heartily with your letter to Science concerning Alzheimer's disease and the amyloid beta protein. It is amazing how this field has been led down the "amyloid hypothesis" trail to the exclusion of other viable hypotheses. If you don't go along with the amyloid dogma, you have difficulty publishing and extreme difficulty being funded. The anti-intellectual, anti-science mentality displayed by many in this field has slowed progress to a crawl. This is a shame."

Also, please note that American Academy of Neurology (AAN) Potamkin Prize 2001 (chaired by Elans' D.Selkoe, see paragraph 2.4 above for further details) was awarded to Elan scientist Dr. Dale Schenk. This Prize 2001 apparently was awarded to Dr. Schenk [at AAN Meeting 2001] after the above UK Alzheimer's case was deteriorated and after Selkoe sale of Elan shares in early 2001.^{46,64}

3. CONCLUSION

I do believe that an unfortunate story of an UK Alzheimer's patient subjected to the Selkoe's amyloid-hypothesis-based treatment, became possible due to the editorial and publisher corruption in biomedical publications.

⁶⁷ Weiss R. *The Washington Post*. (1 March 2002).

It is therefore my responsibility to bring the above facts to The Committee Attention. The corrupted practices by biomedical journals is a threat to the public interest and to the public health.

I therefore hope that The Committee will follow my recommendations *i)* to introduce rules to protect public interest of biomedical publication; *ii)* to introduce rules on personal responsibility and penalties for those helping to conceal the dishonesty by others in biomedical publications; *iii)* To introduce rules to safeguard true independence of editors of biomedical publications; and *iv)* to investigate UK Alzheimer's patient case.

4. APPENDIX

The printout of all documents quoted at length of this written evidence is available upon request. Appendix 1 below represents the article (quoted above⁸) submitted for publication in a peer reviewed journal

**A matter-of-fact: Alzheimer's amyloid beta ($A\beta$) is an essential synaptic protein,
NOT neurotoxic junk**

Alexei R. Koudinov *et al.*

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Israel

Running title:

Amyloid beta is good, not bad

Key words:

competing financial interest, Dennis Selkoe, dementia, dogma, Down syndrome, institutional corruption in medicine, lipoprotein receptor, neurodegeneration, Parkinson's, peer review, responsible conduct regarding scientific communication, research integrity

Abstract

Despite a decade long universal publication and grant review bias in favor of the view on amyloid beta (A β) as Alzheimer's disease culprit (solely neurotoxic for neurons and brain tissue), current scientific evidence leaves little doubt that as an HDL apolipoprotein apoA β (apoAbeta) serves an essential role at synapse and in synaptic structure-functional plasticity that underlie learning and memory. Therefore, the change of A β biology in Alzheimer's disease (as well as in a number of other human pathologies, including cardiovascular disease, neuromuscular junction disorders and Down syndrome) may represent physiological mechanism aiming to compensate impaired brain structure or function. In our own recent study A β 1-40 rescued long term potentiation (LTP, a major model for activity-dependent CNS plasticity, *Neurobiol Lipids*, **1**, 8, 2003, <http://neurobiologyoflipids.org/content/1/8/>), while cholesterol synthesis inhibition abolished the restorative action of the A β peptide. This study confirms that apoA β protein is a functional component of synaptic structure-functional plasticity and of neurochemical pathways for neural cholesterol, lipoproteins, and other lipids. The article also calls for a need to critically re-evaluate a universal belief that transgenic mice with a transgene for amyloid precursor protein (APP) is a true model for Alzheimer's type neurodegeneration.

INTRODUCTION

What Alois Alzheimer saw in early 1900s in brain samples from the first Alzheimer's disease (AD) case ever to be described in medical literature were senile plaques, composed of many components, including amyloid beta protein (A β) (Enserink 1998). A β (first described by Glenner and Wong (1984) is derived from amyloid β precursor protein (APP or β PP) via still missing details complex proteolytic pathway catalyzed by a number of secretases (Koudinova et al. 1999, Koudinova and Koudinov 2003d). Short amino-acid sequence of A β (having A β 1-40 and A β 1-42 as major species) allows easy synthesis of the peptide and explains why the vast majority of *in vitro* experimentation with A β was performed with the synthetic peptides. The past experimentation with A β were performed at very high peptide concentrations that would never occur physiologically or even possible under pathological condition. Such *in vitro* studies yielded easy experimental amyloid β fibril formation that contributed to the predisposition that A β is just a biological waste. Despite of claimed abundance in AD brain, naturally occurring human A β was never purified in preparative condition to allow further experimentation with natural protein.**

Many years of intense research and millions of research dollars did not help to resolve the role for A β in AD. Oppositely, in 1992 several reports have shown that there is a soluble form of A β which is normally produced by cells in culture (implying that the secretion of soluble (s) A β is physiologic) and can be detected in plasma, cerebrospinal fluid (CSF) and brain tissue (Koudinova et al. 1999). In our own contribution we further showed that in plasma and CSF sA β circulates as a part of high density lipoproteins (HDL), and that sA β is secreted by cells as an apolipoprotein constituent of lipoproteins (Koudinov et al. 1994, 1996a, 2001c, Koudinova et al. 1996a, Koudinov and Koudinova 1997a). Several reports (referenced in Koudinov et al. 2001c) latter confirmed our

** Our detailed method for preparative purification of soluble A β from human cerebrospinal fluid lipoproteins (Koudinova et al. 1997, 1998) remained overlooked for many years.

discovery. We further showed that natural apoA β does not cross link with other apolipoproteins in normal CSF HDL (indicating a priority of monomeric apoA β -to-lipid interaction under normal condition) and that an interaction of apoA β with apolipoproteins is a characteristic of Alzheimer's CSF HDL samples. We explained the latter condition as a break in the lipoprotein structural integrity in a way that favors interaction of A β -to-A β (that creates oligomers) or apoA β -to-other apolipoprotein (shown for ApoE and ApoJ) (Koudinov et al. 2001c, Koudinova 2003c). Such reasoning met the support by others (Matsubara et al. 2004). A β association with lipoproteins is also a property of apparent direct relevance to the role of A β in the homeostasis of cholesterol and other lipids as discussed below (Koudinova et al. 2000, Koudinov and Koudinova 2001a).

APP processing (leading to its A β -bearing C-terminal fragments) is strongly conserved in animals from insecta to mammalia, suggesting that sA β is involved in very basic and important metabolic pathways (discussed in Koudinova et al 1999a, Koudinov and Koudinova 1997a). Moreover, current scientific evidence assigns to A β an essential role in the mechanisms of synaptic function, plasticity, learning and memory (discussed below). These scientific facts make it hard to accept amyloid cascade hypothesis. Till recently amyloid hypothesis was the major hypothesis of Alzheimer's disease research. Over a decade it has gradually become a dogma. Amyloid hypothesis not successfully attempted to explain the disease pathogenesis through the prism of pathogenetic primacy of amyloid deposition in the brain tissue of affected individuals. This not-validated hypothesis was the basis for Alzheimer's therapeutic approach tackling brain amyloid by anti-amyloid vaccination or immunotherapy (reviewed in Robinson et al. 2003). Anti-amyloid vaccination, however, was halted at the beginning of 2002 due to severe adverse effects in a number of phase 2 trial participants.

While there is no question on a certain role for A β in AD, the anti-amyloid vaccination challenges triggered many scientists' concern whether the amyloid hypothesis is a true approach for Alzheimer's disease research (referenced in Koudinov et al 2002b, Koudinov 2002e, 2003b, 2003c). This is especially important because associated with the amyloid dogma competing financial interests (Crowley 2002, 2003, Koudinov 2003c, 2003d) and universal publication and grant review bias (in favor of the view on A β as solely neurotoxic, a first author own experience as grant applicant and reviewer for a number of years) apparently retarded the development of several other promising approaches (Alzheimer's association: Research overview: amyloid hypothesis. 2002). The sad reality became illuminated on March 26, 2003 when *Neuron* (a major neuroscience journal) published a feature electrophysiological study on APP and A β synaptic function (Kamenetz et al 2003). This article by Kamenetz *et al.* (2003) was published near three years after it was first submitted and communicated at the Society for Neuroscience Annual Meeting in 2000 (Kamenetz et al. 2000).

ROLE OF A β IN MEMORY AND SYNAPTIC FUNCTION: RECENT STATE OF THE ART

The three early electrophysiological studies reported A β -mediated increase of long-term potentiation (LTP, an experimental cellular model of learning and memory) in rat dentate gyrus in *in vitro* experiments, indicating facilitation of synaptic plasticity by A β . Thus, it was shown (Wu et al. 1995a) that whereas acute treatment of young rat (70-120 days) hippocampal slices with the low concentration (100-200 nM) of bath applied A β 1-40 did not change basal synaptic transmission, there was an increase in tetanus induced LTP. Moreover, intracellular (100 nM, via the recording pipette) or bath (200 nM) application of A β 1-40 triggered the slow onset potentiation of the NMDA receptor-mediated synaptic currents (Wu et al. 1995b) in the hippocampal slices from young rats (70-120 g weight), and did not affect the basal AMPA receptor-mediated transmission, resting

membrane potential or input resistance of the granule cells. It is very unfortunate that authors oversight these two articles (Wu et al. 1995a, 1995b) in their latter publication on the neurotoxicity of A β (Walsh et al 2002, Koudinov and Koudinova 2002c) co-authored by a major proponent of the amyloid cascade hypothesis (Crowley 2002, 2003, Koudinov 2003c, 2003d). Similar results (of A β being a molecule essential for synaptic function) were presented by Schulz (1996), who showed no effect of A β 1-42 on AMPA currents, and demonstrated the increase of NMDA currents by the peptide. This report proposed that A β peptides (A β 1-42, A β 1-28 and A β 1-40) increase the probability of LTP under the paradigm that induced little LTP in control slices. Another report (Chen Q.S. et al. 2000) presented data on A β 1-42 and A β 25-35 inhibition of hippocampal LTP at the concentration of 200 nM to 1 μ M and no effect at 20 nM. This paper, however, employed different from earlier reports (Wu et al. 1995a, 1995b, Schulz, 1996) protocol (particularly, Sprague-Dawley, not Wistar, rats; 30^oC recording temperature; stimulus duration of 0.1 msec delivered through sharpened monopolar tungsten electrodes; the decline of bath-applied peptide just prior to the tetanic stimulation), and missed detailed consideration of A β 1-40, also proposed in the article (despite of the lack of experimental data) to inhibit the hippocampal LTP.

Several other articles reported on infusion of A β into the rat brain followed by electrophysiological (Cullen et al. 1996, Freir et al. 2001, Itoh et al. 1999, Trubetskaya et al. 2003) or behavioral analysis (McDonald et al. 1994, Sweeney et al. 1997, Malin et al. 2001). The paper of Cullen *et al.* showed no effect of A β 1-40 (0.4 or 3.5 nmol in 5 μ l, equal to the I.V. injection of 5 μ l of 0.8 mg/ml (a very high concentration of A β , see a note above) solution for 3.5 nmol A β 1-40) on the ability to induce LTP in hippocampal slices *in vitro*, and the delayed (presented 24 and 48 hrs after the injection and not observed 75 min after injection) reduction in the NMDA receptor-mediated responses recorded *in vivo* (Cullen et al. 1996). It is important to note that the other study concluded that “NMDA receptor regulation by amyloid-beta does not account for its inhibition of LTP in rat hippocampus”

(Raymond et al. 2003). Another article (Freir et al. 2001) investigated the effect of intra-cerebroventricular injection of A β fragments (A β 15-25, A β 25-35 and reverse sequenced A β 35-25) on synaptic transmission and LTP in the CA1 region of the hippocampus *in vivo*. This report (Freir et al. 2001) showed an impairment of LTP in a time- (for A β 25-35) and concentration-dependent manner (for A β 25-35 and A β 35-25) but left open the question (as did another recent study by Trubetskaya et al. 2003) what would be the effect of A β 1-40 or A β 1-42 in such experimental condition. The authors suggested that injection of A β 1-40 at a dose of 300 pmol/day (the volume of injection, however, remained unclear) for 10-11 days impaired the hippocampal LTP (Freir et al. 2001). Another earlier article (Itoh et al. 1999) recorded waveforms in *in vitro* hippocampal slices at 25°C (and not at standard 32°C) after the injection of A β 1-40, and expressed LTP as a population spike (PS, not evoked post synaptic potential, EPSP) change versus time. Similarly, LTP was expressed as PS change versus time in early article on A β oligomers (Lambert et al. 1998); this article (Lambert et al. 1998) also missed representative waveforms presentation. Another earlier report showed no evidence of A β 1-40 accumulation or neurotoxicity after the injection of the peptide into rat hippocampus (McDonald et al. 1994). Recent behavioral study reported increase of the synaptic APP with learning capacity in rats (Huber et al. 1997). APP was also shown to modulate long-term depression (LTD), another important parameter of neuronal plasticity. Thus, bath application of the soluble APP (100 nM, 1 h) adsorbed the ability of rodent hippocampal slices to maintain LTD (referenced and discussed in Koudinov et al. 2001e). Behavioral analyses were characterized by both the absence and the presence of A β effect on learning and memory in different behavioral experiments (McDonald et al. 1994, Sweeney et al. 1997, Malin et al. 2001).

Several reports further addressed the puzzling issue of the role of the structural properties of A β for neural function. These reports showed that oligomeric (Walsh et al. 2002, Lambert et al. 1998, Wang et al. 2002, Gong et al. 2003) and plaque (Koudinov et al. 2001e, Chen G. et al. 2000,

Stephan et al. 2001, Kim et al. 2001) amyloid is capable to impair synaptic or behavioral plasticity, possibly due to the break of neuronal microcircuitry (discussed in Koudinov et al. 2001e). All cited above studies of oligomeric A β (as well as the latest study by Kaye et al. (2003), while concluding on A β neurotoxicity, however, miss consideration of the physiological association of A β with lipoproteins, that potently arrest the peptide toxicity (Cedazo-Minguez et al. 2001, Farhangrazi et al. 1997, Koldamova et al. 2001). Such lack of important experimental consideration creates critical flaw for all studies of A β oligomers (Walsh et al. 2002, Koudinov and Koudinova 2002c, Lambert et al. 1998, Wang et al. 2002, Gong et al. 2003) and must warn all of a well possible lack of the pathophysiological relevance of A β oligomers (Koudinova 2003c, Marchesi 2003).

One other recent investigation suggested age-related impairment of synaptic transmission (but not synaptic plasticity) in transgenic mice that overexpress human APP possessing “Swedish” mutation (Fitzjohn et al. 2001), while the report by Richardson et al. (2003) showed that ultrastructural and behavioural changes precede amyloid deposition in a transgenic model of AD. The latter study implies a need to critically re-evaluate another dogma, a universal belief that transgenic animals expressing normal or mutated transgene for APP represent a true model for Alzheimer’s type neurodegeneration (to be discussed in details elsewhere). Would amyloid hypothesis survive should one pay close unbiased but not commercial (Dalton 2000a, 2000b, Younkin and Stoddard 2000) overdue attention to an inability of early APP transgenic mice (reported a decade ago, Wirak et al. 1991, Jucker et al. 1992, Marx 1992) to yield A β deposition? Would this inspire a deserved quest for another promising approaches long time ago (AlzForum Current hypotheses 2003)?

It is impossible to unite cited above *in vitro* and *in vivo* electrophysiological and behavioral studies of A β protein, and conclude on the relevance of their experimental conditions to brain physiology and Alzheimer’s disease. The same is true for several most recent articles aiming to clarify the receptor machinery and signaling cascades involved in A β -mediated modulation of synaptic

plasticity (Freir et al. 2003a, 2003b, Chen et al. 2002, Vitolo 2002, Nakagami and Oda 2002). For this reason in our own recent study (see below) we focused on a different experimental condition (Koudinov and Koudinova 2001a, 2001b, 2002a, 2003a, 2003e). There are, however, two clear-cut conclusions. The first conclusion represents the title of this article: Alzheimer's amyloid beta ($A\beta$) is an essential synaptic protein, NOT neurotoxic junk. The second one is a sad fact that the vast majority of articles concluding on $A\beta$ as bad neurotoxic molecule oversight (thus failing to agree with the "Uniform requirements for manuscripts submitted to biomedical journals", available at: <http://neurobiologyoflipids.org/submissions/uniformalreq.html>) critical studies by others on an essential role for $A\beta$ in brain neurochemistry, the peptide beneficial effect on synaptic plasticity, and the competing financial interests by the amyloid hypothesis proponents (Crowley 2002, 2003, Koudinov 2003b, 2003c, 2003d, 2003g).

AMYLOID β RESTORES HIPPOCAMPAL

LONG TERM POTENTIATION: A CENTRAL ROLE FOR CHOLESTEROL

We recently attempted to dissect out the role for $A\beta$ in the synaptic plasticity in brain slices from adult male rat hippocampus under the condition that we characterized previously with regard to cholesterol and phospholipid synthesis (Koudinov and Koudinova 2001a, 2003f). The prolonged maintenance of slices in a test tube for more than twenty hours in our experimental setup preserved synaptic function (input/output curve (I/O), a basic measure of synaptic function, for example) but abrogated synaptic plasticity (LTP). $A\beta$ protein of the 1-40 aminoacids' molecule length (representing the major form of soluble $A\beta$, Koudinov et al. 1996a, Koudinova et al. 1996a) rescued LTP while cholesterol synthesis inhibition with a statin abolished LTP restoration by the peptide (Figure 1).

Our observation implies an intriguing perspective that A β protein is a functional player in an activity-dependent cholesterol neurochemical pathways and confirms important role for A β in synaptic structure-functional plasticity (Kamenetz et al. 2000, 2003, Wu et al. 1995a, 1995b, Schulz 1996, Koudinov and Koudinova 2001a, 2001b, 2003f). The finding also supports our proposed hypothesis that the change in A β biochemistry in Alzheimer's disease and related disorders is a functional (but NOT pathologic) compensatory phenomenon aiming to counterbalance impaired cholesterol dynamics and associated neurotransmission and synaptic plasticity, and that APP and A β represent integrated sensor-effector system for neural cholesterol and membrane dynamics regulation (Koudinov and Koudinova 2001a, 2001b, 2003a, 2003f, Koudinova and Koudinov 2003d). Such view received recent recognition in Neuron article (Wolozin 2004). The cholesterol mediated failure of synaptic function and neural degeneration in our view represents the cause of the major sporadic form of Alzheimer's disease (Koudinov and Koudinova 2001a, 2001b, 2003f, Koudinov et al. 2002d). We also proposed that cholesterol homeostasis failure is a unifying cause of synaptic degeneration in a number of degenerative diseases of the nervous system (Koudinov and Koudinova 2004).

The above data support previous reports on A β as 'good' molecule (Kamenetz et al. 2000, 2003, Wu et al. 1995a, 1995b, Schulz 1996) essential for neural/synaptic structure-functional plasticity (rather than synaptotoxicity claimed by amyloid hypothesis and A β neurotoxicity proponents, Hardy and Selkoe 2002, Walsh et al. 2002). Such viewpoint is additionally supported by several studies by others, particularly, by an increase of synaptic APP with learning capacity in rats (Huber et al. 1997), by neuronal activity dependent secretion of natural A β (Kamenetz et al. 2000, 2003) up-regulating a synaptic vesicle protein transcript by A β 1-42 (Heese et al. 2001), a transient increase of synaptic A β after the perforant pathway lesioning (Lazarov et al. 2002), detection of APP and its regulatory protein, FE65, in growth cones and synapses *in vitro* and *in vivo* (Sabo et al. 2003), and the modulation of the APP processing by several neurotransmission systems including

cholinergic (Isacson and Lin 2000, Hock et al. 2000), glutamatergic (Nitsch et al. 1997) and serotonergic (Nitsch et al. 1996) systems. There is a possibility of a bidirectional modulation between A β , APP and metabotropic and ionotropic receptor molecules and signaling pathways (Isacson and Lin 2000, Hock et al. 2000, Nitsch et al. 1996, 1997, Kar et al. 1996, Good et al. 1996, Blitzer et al. 2000, also see Koudinov et al. (2001e) for additional discussion). Thus, it was shown that the generation of A β is regulated by the phosphoinositide (PI) pathway, which commonly couples to transmitter receptors; and that A β peptide is capable to activate the PI pathway in *Xenopus* oocytes expressing rat brain RNA (Blitzer et al. 2000). A β also potentiates Ca²⁺ influx through voltage-sensitive Ca²⁺ channels (Ueda et al. 1997) and was reported to form calcium-permeable channels in lipid vesicles (Lin et al. 2001).

It is very important to notice that A β is not just structural but also functional apolipoprotein constituent of lipoproteins. A β affects cholesterol and phospholipids synthesis, cholesterol esterification and its' cellular uptake (Koudinov et al. 1994, 1996a, 1996b, 1997b, 1998a, 1998b, 2001c, Koudinov and Koudinova 1997a, 2001a, Koudinova et al. 1996a, 1996b, 1997, 2000, 2003a, Koudinova and Koudinov 2003b, 2003d, Koudinova 2003c). A β association with lipoproteins has apparent importance for the role of lipoproteins in the induction of the LTP that we proposed to depend on activity-dependent lipoprotein uptake necessary for an immediate cholesterol supply for dendritic outgrowth during early phases of the synaptic plasticity onset (Koudinov and Koudinova 2001a, 2002a, Zhuo et al. 2000). In such scenario, A β -mediated cholesterol synthesis (Figure 1) then facilitates cholesterol supply during later phases of the increase in the efficacy of the synaptic transmission (Koudinov and Koudinova 2001a, 2001c). On the other hand lipoproteins potently inhibit neural synaptotoxicity of A β (Cedazo-Minguez et al. 2001, Farhangrazi et al. 1997, Koldamova et al. 2001), the fact unfairly missed in articles serving to validate amyloid cascade hypothesis (Lambert et al. 1998, Walsh et al. 2002, Koudinov and Koudinova 2002c, Hardy and

Selkoe 2002, Gong et al. 2003, Kaye et al. 2003). As mentioned above, A β -to-lipoprotein association also serves to maintain A β solubility in the body fluids (Koudinov et al. 1997b, 1998a, 1998b, 1999, 2001c).

The evidence-based synaptic function for A β and the conceivable lack of the A β association with lipoproteins in the studies of oligomeric A β also called ADDLs (Lambert et al. 1998, Walsh et al. 2002, Wang et al. 2002, Gong et al. 2003, Kaye et al. 2003) may exacerbate the lack of the physiological relevance of the oligomers' neurotoxicity (Koudinova 2003c, Marchesi 2003) and face Alzheimer's field with the question whether amyloid lowering (by vaccination, a secretase modulation or by any other means) could ever be beneficial. This viewpoint is further supported by the "evidence suggesting that loss of endogenous amyloid beta by the pharmacological inhibition of amyloidogenesis results in a severe reduction in the viability of central neurons. In three different neuronal phenotypes, the pharmacological knock-down of amyloidogenic secretase activity resulted in cell death. This study further supports a key physiological role for the enigmatic amyloid beta peptide" (Plant et al. 2003). Finally, our latest report indicates a possibility of mistaken identity of lipoprotein-bound soluble monomeric apolipoprotein apoA β as plaque or oligomeric A β in a contemporary Alzheimer's research (Koudinova 2003c, Koudinova and Koudinov 2003b).

Conclusion. In accord with the research by others our data suggest that A β improves synaptic plasticity, and that this effect may be due to neural cholesterol dynamics modulation by the peptide (Koudinov and Koudinova 2001a, 2003e, 2003f). The role for A β (as a normal human protein) in mediating essential neurochemical pathways, however, is unlikely limited to cholesterol homeostasis. The other pathways can not be excluded and should be studied further in greater details. One such candidate is oxidative stress cascade (Koudinova et al. 2003a), also shown to be critical for synaptic function and plasticity (Berezov and Koudinov 2003, Kamsler and Segal 2003, Koudinov and Koudinova 2001d). The slow onset LTP (similarly pharmacologically induced by

vitamin E (Xie and Sastry 1993) and A β (Wu et al. 1995a, Schulz 1996), but impaired in the transgenic mice overexpressing enzyme SOD-1 (Koudinov and Segal 1998c) may be attributed to the lipid antioxidant properties modulation by vitamin E or A β (Xie and Sastry 1993, Kontush et al. 2001, Koudinova et al. 2003a) and dependency of slow LTP component on a unique molecular mechanism.

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ABBREVIATIONS

A β , amyloid beta protein

A β 1-40, amyloid beta protein of 40 amino acids length, the major form of apoA β

AD, Alzheimer's disease

AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid

ApoA β , apolipoprotein β -amyloid

APP, β PP, amyloid precursor protein

CSF, cerebrospinal fluid

HDL, high density lipoprotein

I/O, input/output curve, a measure of basic synaptic function

LTP, long-term potentiation, a synaptic plasticity measure

LTD, long-term depression, one of the characteristics of synaptic plasticity

NMDA, N-methyl-D-aspartate

PI, phosphoinositide

sA β , soluble form of β amyloid

SOD1, enzyme Cu/Zn superoxide dismutase

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