

The SWAN Hypothesis Manager in the Biomedical Knowledge Ecosystem

Elizabeth Wu
June Kinoshita
Gwen Wong

Tim Clark
Paolo Ciccarese
Marco Ocana

Alzheimer Research Forum

Harvard University and
Massachusetts General Hospital

Workshop for W3C Semantic Web Health Care & Life Sciences Interest Group
Athens, GA
6 November 2006



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100 Years Ago in 1906



On November 3, 1906 Alois Alzheimer presented an unusual case of dementia at the university city of Tübingen, Germany. Auguste D. would become known as the first documented case of Alzheimer's disease (AD) – a disorder of the brain's nerve cells that impairs memory, cognition and behavior.

10 Years Ago in 1996

Alzheimer Research Forum

www.alzforum.org



was launched

Alzheimer Disease in 2006

- 20 millions people worldwide suffer from Alzheimer Disease
- NIH funding for AD estimates at \$ 650M per year
- 5,000 AD and related papers published in 2006 so far
- still...no effective treatment or therapy

Alzforum in 2006

Collected 44,000 AD Related Papers

Published Over 1400 News Articles

Home: News

RESEARCH NEWS

Search by keyword or publication date

SEARCH KEYWORDS:

SEARCH FROM: Month Year

TO: Month Year

RESEARCH NEWS

1 to 25 of 1350 results [BACK](#) | [NEXT](#)

[The Skinny on FAT: APP's Role in Fast Axonal Transport](#)
 31 October 2006. In neurons, APP-laden vesicles powered by kinesin motors ride from the cell body out to synapses. But is APP just a passenger, or does the protein sit in the driver's seat?...

[SN Satellite Symposium: Neurotoxic Mechanisms in Alzheimer Disease](#)
 28 October 2006. On Friday, October 13, the day before the kick-off of the Society for Neuroscience meeting in Atlanta,...

[Mitochondrial Mayhem—PGC-1 \$\alpha\$, Respiration, and Neurodegeneration](#)
 27 October 2006. Remember when car engines were horribly inefficient and catalytic converters nonexistent? The result was...

[Thanks for the Memories—KIBRA Alleles Predict Top Memory Performers](#)
 20 October 2006. If you are one of those people who can recall verbatim a conversation held a year ago, then you might want to thank...

ANTIBODY DIRECTORY

Keywords: Search any keywords all keywords

Acetylcholine-related	ADAMT54, ADAMT55	AGE and RAGE	Amyloid-beta related
Apolipoproteins	APP, APLP	Bad	Bax
Bcl	β-Catenin	β-secretase/BACE	BrdU
Caspase-2 and Caspase-3	CDK1/cdc2 and CDK2	CDK4 and CDK5/p35	Chromogranin
COX1, COX2, COX3	CREB, CaMKinase II	DJ-1	Dopamine related
ERAB	FADD	FAS-Related	FGF, FGFR
GFAP	Glutamine Synthetase	Grb-2	GSK-3 and AKT
Heme Oxygenase, Antioxidants	Heparan Sulfate, proteoglycans, MSRA	Huntingtin	Huntington's-related and CBP
KI-67	Lipid Metabolism	MAPKs, ERK, MEK, ASK1, p38	MAPs
Microglia related	Neurofib Tangles	Neurofilament	Other Neuropeptides
Neurophysin Related	Nfkb, Ikb and related proteins	NGF	NGFR, Trk-A
NMDAR, GluR1, GluR2	Notch, Jagged, Delta	NSE	Olfactory Proteins
Other Proteases	p53	PARP	Plaque-related
Presenilin Complex and ubiquitin	Presenilins	S-100	SIRT1
...	...	Synaptosomal	...

Antibody Links

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- [Methods Glossary](#)
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Antibody-Search Websites

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- [Biocompare](#)
- [Exact Antigen](#)
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- [Linscott's Directory](#)

Desperately Seeking

- [Antibodies](#)
- [Collaborators](#)

Curated 14,700 Antibodies

6 November 2006

Curated 900 Genetic Association Studies and 366 Genes in AD

The screenshot shows the AlzGene website interface. At the top, it says "ALZGENE - PUBLISHED AD CANDIDATE GENES". There are navigation buttons for BACK, SEARCH, MISSION, DISCLAIMER, and CREDITS. Below that, it says "Updated 18 October 2006". A chromosome selector is visible, showing chromosomes 1 through 22, X, and Y. A search bar is present with the word "Gene:" and a dropdown menu showing "A2M". Below the search bar, there are sections for "Protein:", "Polymorphism:", "Study:", and "Keywords:". A list of genes is displayed, including ABC17, ABC18, ABC2, ABC20, ABC30, ABCA1, ABCA12, ABCA2, ABCB1, ABCB2, ABCB3, ABCG5, ABETA, APP, APOE, APOE2, APOE3, APOE4, APOE5, APOE6, APOE7, APOE8, APOE9, APOE10, APOE11, APOE12, APOE13, APOE14, APOE15, APOE16, APOE17, APOE18, APOE19, APOE20, APOE21, APOE22, APOEX, APOEY. On the right side, there are several boxes: "AlzGene Recent Updates", "NCRAD" (The National Cell Repository for Alzheimer Disease), "Forum Calendar" (To be announced), and "Opine Online" (Do PS1 mutations cause AD by cranking up Abeta? Recent findings cast doubt (see Discussion.) Your reaction?).

Scientists Sent in 4400 Comments

The screenshot shows a forum page titled "COMMENTS". It indicates "1 to 30 of 4400 results". The first comment is by Urbanc B. on LIVE DISCUSSION: Messing with the Membrane—An Alternative Interpretation of the Amyloid- β Hypothesis. It is refreshing to read about alternatives to the amyloid hypothesis. Vincent Marchesi's is ... 1 Nov 2006. The second comment is by Rebeck G. on PAPER: Sano Y. et al., 2006, Several groups have found that X11 and X11L1 interact with APP, affect APP metabolism, and... 31 Oct 2006. The third comment is by Ashford J. on PAPER: Zha XM. et al., 2006, I think that this study is very interesting and well carried out. To some extent, this is an... 31 Oct 2006. The fourth comment is by Goetz J. on NEWS: AGEing Neurons Waste Away in Fly Model of Neurodegeneration, Enzymes involved in glucose metabolism emerge as key players in the pathogenesis of a range of... 31 Oct 2006. The fifth comment is by Iwatsubo T. on PAPER: Sano Y. et al., 2006, This paper reports increased levels of endogenous APP CTF β as well as of A β in... 30 Oct 2006. The sixth comment is by Reid M. on NEWS: Thanks for the Memories—KIBRA Alleles Predict Top Memory Performers, A recent study by Launiat and colleagues (!) identifies KIBRA, HAX-1 (antiapoptotic)... 30 Oct 2006. The seventh comment is by Delacourte A. on PAPER: Etasko I. et al., 2006, Recommendation Only. 30 Oct 2006. A "COMMENT" box is also visible, containing a comment by Brigita Urbanc submitted on 1 November 2006. The comment text reads: "It is refreshing to read about alternatives to the amyloid hypothesis. Vincent Marchesi's is provocative, as any new hypothesis should be. The Alzforum discussion was fantastic. As a computational physicist, I like to take a minimalist approach when dealing with the unknown (by unknown I mean cleavage of APP, A β formation, and early aggregation events), and can add a different perspective. Even though I found each of the comments very helpful, Dennis Selkoe answered most of the questions that I had while reading the Marchesi paper. One of his comments was that we need to distinguish between the normal and pathogenic processes involved in A β secretion. Thus, I would say we need first a hypothesis on the normal processing and function of A β . Are the cleaved APP dimer and the resulting A β dimer a part of a normal or pathogenic process? Most importantly, we need to find ways to test this hypothesis. This cannot be done in transgenic mouse models, which complicates the problem. When bringing up pro- and counter [...] examples for an AD hypothesis (be it the amyloid hypothesis involving toxic extracellular A β oligomers or the Marchesi hypothesis of toxic intramembranous A β aggregates), I find it confusing that researchers mix the experimental facts obtained on different transgenic mouse models with the ones obtained on human tissue. Here, again, Dennis Selkoe comes to the rescue by pointing out that a specific environment (be it extracellular, intramembranous, or one of many cell compartments) may be very

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LIVE DISCUSSIONS

Updated 23 December 2005

[E-mail discussion](#)
[Printable version](#)

Live Discussion: Reducing the Risk of Alzheimer Disease

[John Trojanowski](#) [Deborah Blacker](#) [Suzanne de la Monte](#) [Sally Frautschy](#) [Lew Kuller](#)
[Mark Mattson](#) [Dave Morgan](#) [David Sinclair](#) [Sam Sisodia](#)

The topic is an apt one to launch the new year: what factors in daily life can reduce one's risk of Alzheimer's disease? To fire up your neural networks, you are invited to read the recent review ([download pdf](#)) by Kathryn Jedrzewski, Virginia Lee and John Trojanowski, published in *Alzheimer's & Dementia Journal*. Dr. Trojanowski led the live discussion. He was joined by Deborah Blacker, Greg Cole, Carl Cotman, Suzanne de la Monte, Sally Frautschy, Lew Kuller, Mark

Science's SAGE KE

Featured Links from SAGE KE

- [Dementia with Cerebrovascular Disease](#)
- [Detangling Alzheimer's](#)
- [Hunt for a Cure for Parkinson's](#)
- [Case Study: AD](#)
- [News Synthesis](#)
- [Research on Brain](#)

See also the [SAGE KE Meetings and Events](#)

Desperately Seeking

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PAPERS OF THE WEEK

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RESEARCH

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Fan Mails

Forums

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DISEASE MANAGEMENT

About Alzheimer's

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- [Brain Banks](#)

Treatment

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□ The staff at Alzforum are really playing a very important role in providing information to the research community and stimulating discussion and ideas that drive the science forward. —Robert Vassar, Ph.D., Department of Cell and Molecular Biology, Northwestern University

□ I continue to be amazed at the great design and facilities of the ARF web site. If every major field had a similar resource, all of medicine would move more quickly... You and your marvelous team have honed this site to a truly wonderful experience for the participants. It is exhilarating and challenging, it is easy to approach and navigate, and it has many really successful paradigms (e.g. the engrossing exchange with Yong Shen that prompted so many scholarly and exciting comments from the field). Your work is really top drawer. It's more than that. It's a beacon to the field to come and share knowledge in a creative and exciting way. —Forbes Dewey

□ This is by far the best web site I have seen for AD researchers. I would consider it a must have, and I am disappointed that I only found out about it a couple of months ago through a colleague. I love your web site, and you guys do a tremendous job! —Troy Rohn, Boise State University

□ This is a very nice site, and I like to say well done for your service to meet a human desire. The day I first saw this site I loved it. —Denis


More Fan Mails

Fan Mail Support Us

RETURN TO TOP

- Once again it is Forums like yourselves who connect people. Thanks for the incredible work that you all do behind the scenes. Also to the researchers and scientists who selflessly work to find a cure or even some clues to this disease which makes strangers of our loved ones. Bless you all and warm South African greetings and thanks. —Love, Karen Borochowitz
- I think that the work of foundations such as yours is one of the great untold stories of American altruism. My congratulations. —Sanford M. Simon, Professor and Head of the Laboratory of Cellular Biophysics, Rockefeller University
- I appreciate you allowing me to express our family's deepest gratitude, admiration and hopefully encouragement, to all of you involved in this struggle. Thank you for contacting me and for helping us. You truly are our heroes and our hope for the future. —Most gratefully, Linda Clark
- I spend many hours searching databases and other sites on the Web, and I believe that the Alzheimer's Disease Forum is probably the best maintained and most useful medically oriented site that I know of. The purpose of this note is to congratulate you for your efforts... Every time I open your site, usually stimulated by your weekly e-mails, I find something interesting going on, such as, for example the call for suggestions for the identification of problems that need more emphasis and additional support. Thank you for performing an extraordinarily valuable service. —Vincent T. Marchesi, MD Ph.D., Professor of Pathology and Cell Biology, Director Boyer Center for Molecular Medicine, Yale University

Alzforum in 2006



ALZHEIMER RESEARCH FORUM

NETWORKING FOR A CURE

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WHAT'S NEW

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RESEARCH NEWS

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 27 October 2006. Remember when car engines were horribly inefficient and catalytic converters nonexistent? The result was...

[GO TO ALL RESEARCH NEWS](#)


IN THE SPOTLIGHT

- [Conference Webcast: Alzheimer: 100 Years and Beyond](#)
 The centenary meeting will be held November 2-5, 2006, in Tübingen, Germany, to mark the 100th anniversary of Alois Alzheimer's presentation of the first documented case of Alzheimer disease. The meeting will include a retrospective on pioneers who contributed to AD research over the last 100 years, present current concepts in AD research, and discuss important challenges for the new century of AD research. Because of

Forum Calendar

To be announced.

AD/PD 2007



8th International Conference on Alzheimer's and Parkinson's Diseases

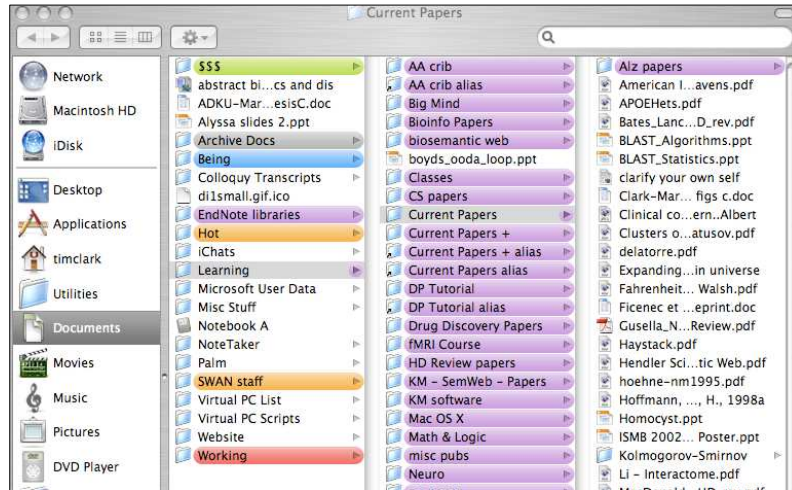
14-18 March 2007
Salzburg, Austria

Call for Abstracts!

- [Submit Your Abstract](#)

Submission Deadline:
1 November 2006
Abstracts will be published in *Neurodegenerative Diseases Supplement* (S.Karger)

Each scientist's digital resources also have
his or her own form of organization



The SWAN Project: Problem Statement

- Knowledge is information in context
- Scientific information content is currently not transferred with its context because:
 - Scientific information is currently only exchanged digitally as individual documents and data files
 - Knowledge annotation and organization performed independently by websites and researchers
 - Knowledge schemas are therefore idiosyncratic, incompatible and not easily transferable
- We want to create and exchange semantic context (metadata) along with digital scientific information
- Creation of metadata must be a sustainable process

What is SWAN?

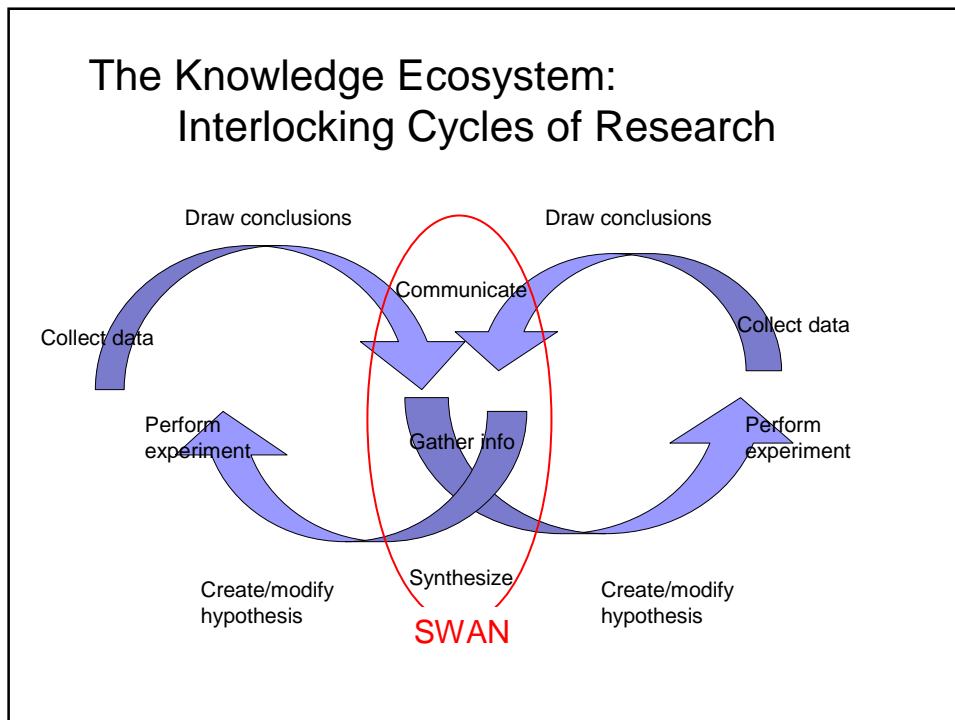
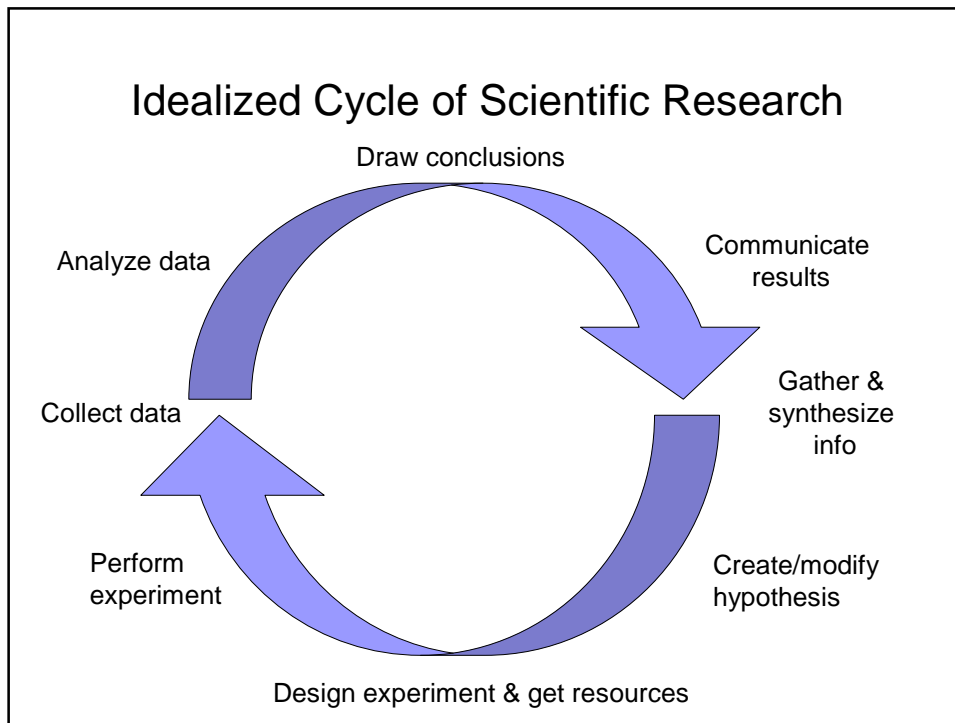
Semantic Web Applications in Neuromedicine

SWAN is a project to create

- A common digital framework for sharing knowledge annotation and organization in AD research
 - Immediately useful software to implement this framework
 - Software & framework built using Semantic Web technology (Berners-Lee et al. 2001)
- A robust community process for sharing knowledge via the framework

Fundamental Hypotheses

- Knowledge **context** can be digitized and exchanged along with digital **content**
- SWAN software can make this process **simple** and **highly useful** to the biological researcher
- Using SWAN, a scientist's **personal** knowledge management activity can add value to the **community** knowledge base, and vice versa
- Wide adoption would increase **research productivity** in AD research



SWAN Ontology: Basic Concepts



Digital Resource

journal article, manuscript, grant application, data, image, ...



Research Statement

hypothesis, claim, structured comment, research questions



Domain Concept

personal concept (tag), formal concept (ontology)



Life Science Entity

gene, protein, organism, compound, ...



Scientific Activity

experiment, study, review, ...

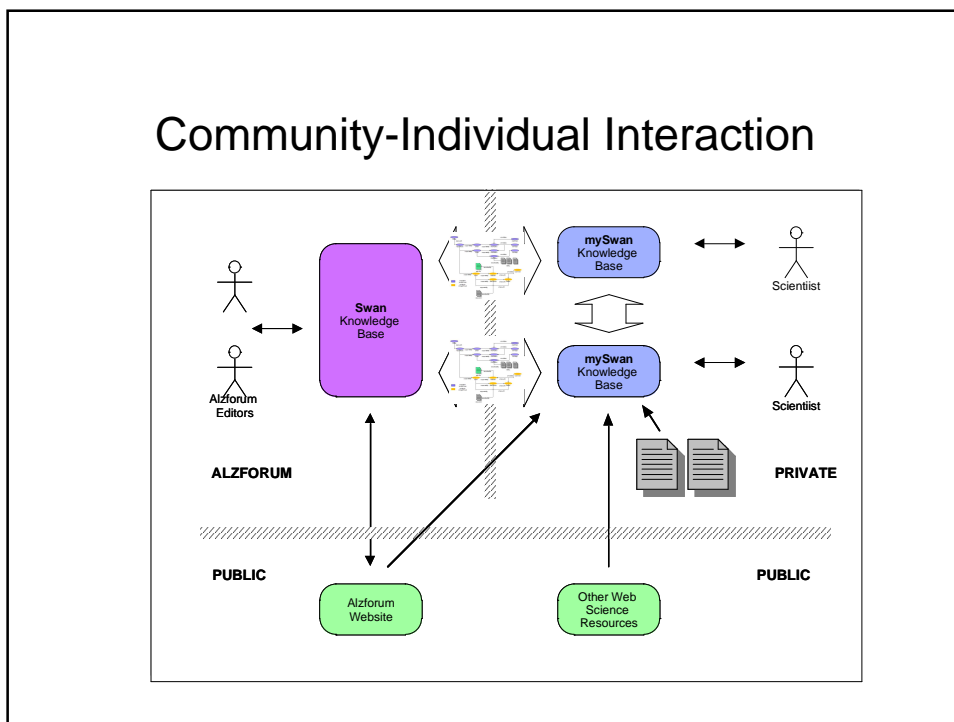
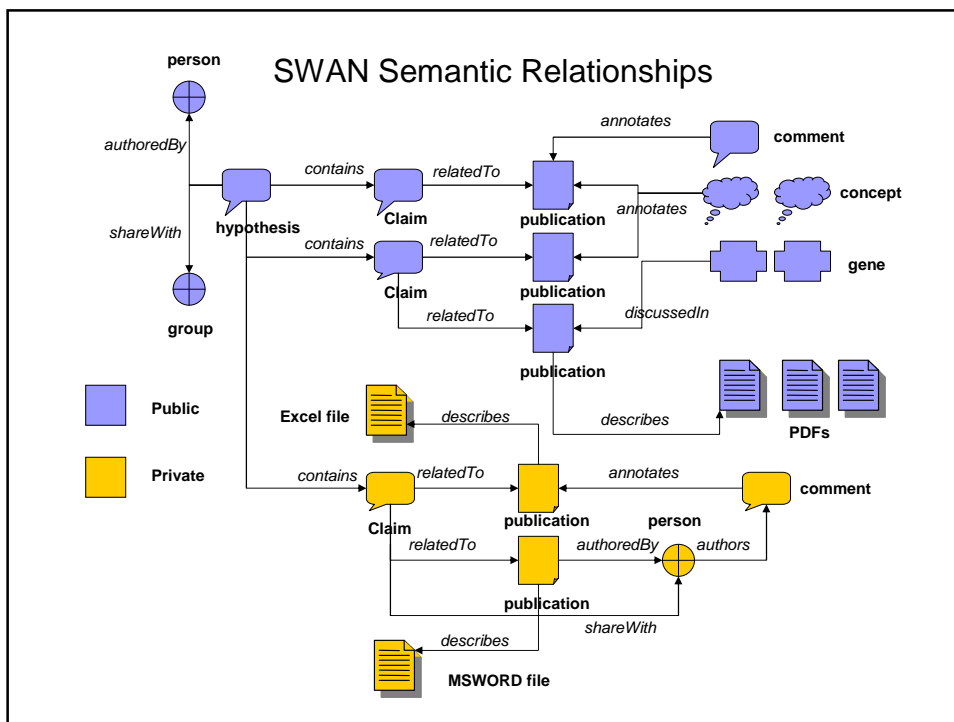


Collaborator

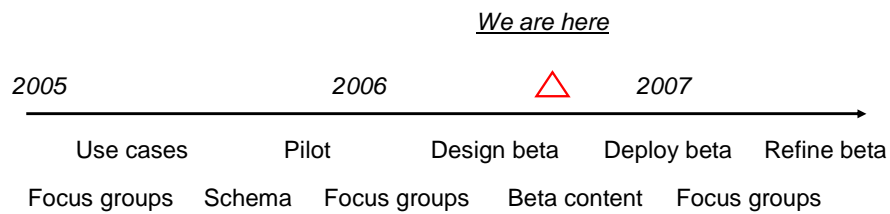
person, community, ...

SWAN Ontology: Relationships

- alternative to|alternative to
- counter to|counter to
- supports|supported by
- references|referenced by
- same as|same as
- evolved from|evolve to
- part of|contains
- related to|related to
- enters|entered by
- curates|curated by
- authors|authored by



SWAN Timeline



The SWAN Pilot

- Deployed via Web, hosted on servers at MGH
 - Two sites: mySWAN and Alzforum SWAN
 - Operates on RDF stores (a core Semantic Web technology)
- Designed to validate technology approach
- Basis for discussion with researchers on features

SWAN Beta Design Slides

- SWAN beta version will be constructed in two parts
 - Hypothesis workbench focused on overall structure of the discourse
 - labSWAN focused on private lab data management within the discourse
- The following slides are a design mockup for the SWAN Hypothesis Workbench
 - Basis for discussion with researchers & editors on needed features
- AD Workbench uses same navigation framework as the Pilot
 - Improved version of the discourse ontology
 - Improved clarity and user-friendliness of interface

AD Hypothesis Workbench

Hypothesis Workbench for AD Research Powered by SWAN

[Home](#) [Research Data](#) [Ontology](#) [Collaboration](#)

Welcome to the SWAN Hypothesis Workbench, a scientific knowledge organization tool for Alzheimer Disease Research.

Research communities, laboratories, science administrators, and individual scientists can organize their own data, manuscripts, grants, publications and other digital resources around key hypotheses, observations, or biomedical concepts. They can also selectively share their knowledge with colleagues and communities, and then compare and contrast their personal knowledge base with other organized knowledge deposited by colleagues in the SWAN community knowledge base at Alzheimer Research Forum (Alzforum), a trusted community knowledge repository.

This interplay of individual and community organized knowledge is designed to support the development of new insights, experiments, and research collaborations.

Our approach is based on semantically organizing and enriching the scientific information in the system, using the new technologies of the Semantic Web (Berners-Lee et al, 2001).

SWAN is a collaboration of the MIND Center for Interdisciplinary Informatics (Massachusetts General Hospital www.mindinformatics.org) and the Alzheimer Research Forum (www.alzforum.org). Funding is provided by the Ellison Medical Foundation, the NIH Human Brain Project (through a K-12 award) and by a private charitable foundation.

Hypothesis Index

Hypothesis Workbench for AD Research Powered by SWAN

Home Research Data Ontology Collaboration

Search: All Data for Search Advanced

Expand all | Collapse all

View By: Data Type

- Research Statement
- Hypothesis (30)**
- Comment (120)
- Digital Resource
- LifeScience Entity
- Lab Data
- Collection

Hypotheses

- Intramembraneous A β dimer -Marchesi**
[V. Marchesi 2005](#) [Research Statements\(26\)](#) [Comments\(12+\)](#) [Revisions\(2\)](#)
- ApoE affects APP processing**
[Charles 2003](#) [Research Statements\(9\)](#) [Comments\(7\)](#) [Model Organism\(0\)](#)
- Toxic ApoE4**
[Loretta 2001](#) [Research Statements\(11\)](#) [Comments\(8\)](#) [Model Organism\(2\)](#)
- Cellular trisomy 21**
[Clemens 1999](#) [Research Statements\(5\)](#) [Comments\(4\)](#) [Model Organism\(0\)](#)
- Aluminum Hypothesis**
[Ferdinand 2004](#) [Research Statements\(12\)](#) [Comments\(5\)](#) [Model Organism\(3\)](#)
- Cholesterol**
[Rico 2001](#) [Research Statements\(10\)](#) [Comments\(9+\)](#) [Model Organism\(1\)](#)

Hypothesis Detail

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Hypothesis: Intramembraneous A β dimer

Author: V. Marchesi

Abstract: Alzheimer's disease is a complex neurodegenerative process that is believed to be due to the accumulation of short, hydrophobic peptides derived from amyloid precursor proteins by proteolytic cleavage. It is widely believed that these A β peptides are secreted into the extracellular spaces of the CNS, where they assemble into toxic oligomers that kill neurons and eventually form deposits of senile plaques. This essay explores the possibility that a fraction of these A β peptides never leave the membrane lipid bilayer after they are generated, but instead exert their toxic effects by competing with and compromising the functions of intramembraneous segments of membrane-bound proteins that serve many critical functions. Based on the presence of shared amino acid sequences containing GxxG motifs, I speculate that accumulations of intramembraneous A β peptides might affect the functions of amyloid precursor protein itself and the assembly of the PS1, Aph1, Pen 2, Nicastrin complex.

Primary Citation: Marchesi VT. An alternative interpretation of the amyloid A β hypothesis with regard to the pathogenesis of Alzheimer's disease. Proc Natl Acad Sci U S A. 2005 Jun 28; 102(26):9093-8

This hypothesis makes the following claims:

- A β is first detected intraneuronally, not in extracellular spaces**

[Comments\(9\)](#) [Supportive Evidence\(1+2\)](#) [Alternative Research Statements\(1\)](#) [Genes\(3\)](#) [Grants\(2\)](#)

[Downstream Events/Genetics](#) [Downstream Events/Animal Models](#)

Claim

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Research Statement SWAN-RS-1

[Comments](#) | [Supportive Evidence](#) | [Alternative Research Statements](#) | [Genes](#) | [Grants](#)

Title: A β is first detected intraneuronally, not in extracellular spaces

Abstract:
 Transgenic mice expressing fAD APP either alone or in combination with fAD PS1 mutations and Tau exhibit amyloidogenesis, and other pathological features of AD but demonstrate variable extent of disease phenotypes such as neurological deficits, neuronal degeneration and learning defects. Interestingly, most immunologically detectable A β is first detected **intraneuronally**, not in **extracellular spaces**.

Author: V. Marchesi

Concepts: [Downstream Events/Genetics](#), [Downstream Events/Pathway](#)

Part of: Intramembranous A β dimer

Claimed in: Marchesi VT. An alternative interpretation of the amyloid Abeta hypothesis with regard to the pathogenesis of Alzheimer's disease. Proc Natl Acad Sci U S A. 2005 Jun 28; 102(26):9093-8

Supported by:

- Journal Article:**
 Oddo et al., 2003
- Comment:** [Koo, E.](#) extracellular A β , whether oligomers or aggregated fibrils, are insufficient to injure neurons...[more](#)
- » [McGowan et al., 2005](#)
- Comment:** [Selkoe, D.](#) Primary neurons cultured from Down syndrome brains observed robust

SWAN Life Science Entity SWAN-Gene-1

Gene name: amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease)

Gene symbol: APP

Synonyms: AAA; AD1; PN2; ABPP; APPI; CVAP; ABETA; CTFgamma

Entrez ID: 351

Abstract: This gene encodes a cell surface receptor and transmembrane precursor protein that is cleaved by secretases to form a number of peptides. Some of these peptides are secreted and can bind to the acetyltransferase complex APBB1/TIP60 to promote transcriptional activation, while others form the protein basis of the amyloid plaques found in the brains of patients with Alzheimer disease. Mutations in this gene have been implicated in autosomal dominant Alzheimer disease and cerebroarterial amyloidosis (cerebral amyloid angiopathy). Multiple transcript variants encoding several different isoforms have been found for this gene.

Associated with:

Hypotheses

- » Intramembranous A β dimer
- » A β *56 hypothesis

Research Statements

- » Intramembranous A β peptides peptides may alter the properties of neuronal cell membranes and may be toxic only if they remain within the lipid bilayer.
- » The intramembranous APP C-terminal fragments may be toxic in situ

Claim

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Research Statement SWAN-RS-1

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Abstract:
 Transgenic mice expressing fAD APP either alone or in combination with fAD PS1 mutations and Tau exhibit amyloidogenesis, and other pathological features of AD but demonstrate variable extent of disease phenotypes such as neurological deficits, neuronal degeneration and learning defects. Interestingly, most immunologically detectable A β is first detected **intraneuronally**, not in **extracellular spaces**.

Author: V. Marchesi

Concepts: [Downstream Events/Genetics](#), [Downstream Events/Pathway](#)

Part of: [Intramembranous A \$\beta\$ dimer](#)

Claimed in: Marchesi VT. An alternative interpretation of the amyloid Abeta hypothesis with regard to the pathogenesis of Alzheimer's disease. Proc Natl Acad Sci U S A. 2005 Jun 28; 102(26):9093-8

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 Oddo et al., 2003
- Comment:** [Koo, E.](#) extracellular A β , whether oligomers or aggregated fibrils, are insufficient to injure neurons...[more](#)
 » [McGowan et al., 2005](#)
- Comment:** [Selkoe, D.](#) Primary neurons cultured from Down syndrome brains observed robust

Putting Grants in Context

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SWAN RS-1 Relevant Grants

Grant Number:	iR01AG027924-01
PI Name:	BU, GUOJUN
PI Email:	bu@wustl.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	ApoE Receptor Pathways to Intraneural Abeta

Abstract: Intraneuronal amyloid-p peptide (AP) accumulation is an early and toxic event in the pathogenesis of Alzheimer's disease (AD). ***Understanding cellular mechanisms that accelerate or inhibit intraneuronal Aa accumulation may provide novel therapeutic strategies for AD.*** Aa can accumulate inside neurons via receptor-mediated uptake. It can also accumulate via de novo processing of amyloid precursor protein (APR) to Aa in the endocytic pathway. Our recent studies have shown that apolipoprotein E (apoE) receptors, members of the low-density lipoprotein receptor (LDLR) family, modulate Aa uptake as well as APR endocytic trafficking and processing to Aa. In particular, we have demonstrated that LRP overexpression in the brain increases cell-associated Aa. Aa can bind to apoE receptors either directly or indirectly via Aa chaperones such as apoE. This proposal will focus on two apoE receptors, the LDLR-related protein (LRP) and LRP1B. These homologous receptors are both highly expressed in neurons and bind multiple ligands including Aa, apoE, and APP. However, evidence from our lab suggests that LRP and LRP1B play opposing roles in ligand endocytosis. While LRP mediates rapid endocytosis, LRP1B endocytoses very slowly and as a consequence, retains ligands at the cell surface. Our overall hypothesis is that LRP facilitates Aa uptake, p production, and intraneuronal Aa accumulation, and that LRP1B blocks these effects, thus inhibiting Aa toxicity and pathogenesis of Alzheimer's disease. We have designed both in vivo and in vitro approaches to test our hypothesis. ***In Aim 1, we plan to determine the roles of LRP and LRP1B in intraneuronal accumulation in animal models.*** Because conventional LRP knockout is early embryonic lethal, our lab has generated conditional LRP forebrain-specific knockout mice. Together with the LRP1B knockout mice, we plan

Linking Across Hypotheses

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- Aβ₄₀ and 42 are enriched in sucrose gradient fractions of brain membrane fragments of Tg2576 mice, consistent with the notion that proteolytic cleavage of APP dimers results in accumulation of Aβ remaining embedded in the lipid bilayer.
Comment(2) Supportive Evidence(1)
 Downstream Events / Genetics / Pathways
- Aβ peptides do eventually accumulate extracellularly during disease progression, but the extracellular export of Aβ may be more complicated than simple release immediately following proteolytic cleavage.
Comment(0) Supportive Evidence(1)
 Downstream Events / Pathways
- Intramembranous Aβ peptides may alter the properties of neuronal cell membranes and may be toxic only if they remain within the lipid bilayer.
Comment(3) Supportive Evidence (0+7) Alternative Research Statement(1)
 Downstream Events / Pathways
- Inactive mutant forms of PS1 might result in APP cleavage product being left embedded in membrane.
Comment(0) Supportive Evidence(0)
 Downstream Events / Pathways
- The "channel hypothesis" proposes that extracellular Aβ can re-insert into the membrane, associate together and create channels that allow lethal levels of calcium into the cell.
Comment(2) Supportive Evidence(3)
 Downstream Events / Pathways
- Equally plausible is that Aβ peptides never leave the membrane
Comment(2) Supportive Evidence(2+4)
 Downstream Events / Pathways
- Persistence of Aβ dimers in the membrane over a long time could have significant impact on health of neurons, and could influence the behavior of receptors or channels.
Comment(3) Supportive Evidence (0+3)
 Progression / Pathway
- Concept of dimeric Aβ persisting in membranes differs from widely held view that Aβ is released into the extracellular space.
Comment(0) Supportive Evidence(0)
 Downstream Events / Pathways

A Conflicting Statement

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Neve et al., 2000
 Fukuchi et al., 1992

Comment: Koo, E: Work from Fred Van Leuven's and Jie Shen's laboratories has shown...
 Dewachter et al., 2002
 Saura et al., 2005

Comment: Dewachter & Van Leuven: From our view, a most interesting point of Dr. Marchesi's hypothesis is...
 Dewachter et al., 2002

Comment: Dewachter & Van Leuven: Completely in line with our findings, data published earlier this year...
 Saura et al., 2005
 Herms et al., 2002
 Ris et al., 2003

Alternative:
Comment: Dewachter & Van Leuven: Evidence in ADAM10-deficient mice convincingly...

Conflicting Research Statements:
Research Statement: Aβ⁵⁶ hypothesis RS-7: Extracellular-enriched dodecameric 56 kDa assemblies and less abundant nonameric 40 kDa assemblies appear at 6 months of age with considerable variability between animals of the same age, and remain stable between ages 6 to 13 months. This satisfies one of the criteria for Aβ*. No other Aβ assemblies were found that cause the second stage of memory loss that occurs between 12-15 months age.

Related to:
 Genes: APP, PS1, Tau

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Title: Extracellular-enriched dodecameric 56 kDa assemblies satisfies one of the criteria for A β *.

Abstract:
 "As the 56-kDa and 40-kDa species appeared at 6 months of age and remained stable between the ages of 6 and 13 months, they fulfilled the criteria for being designated as A β * and thus represented viable candidates for A β assemblies that cause memory deficits. We found no further increase in A β assemblies in old mice to correspond to the second drop in memory function at 15 months?. We found no intracellular or membrane-associated A β species or CTFs correlating with the onset of memory deficits in 6-month-old Tg2576 mice."

Author: K. Hsiao-Ashe

Concepts: [Downstream Events/Genetics](#), [Downstream Events/Animal Models](#)

Part of: [A \$\beta\$ *56 hypothesis](#)

Claimed in: Lesné S, Koh MT, Kotilinek L, Kaye R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. *Nature*. 2006 Mar 16; 440(7082):352-7.

Supported by:
Figures: Figures 1c, 3g, 3h; Supplementary Figures 3 and 4a;
Comment: [Le Vine, H.](#) The importance of these observations is that they direct attention to extracellular events as being important in the maturation of trimers and tetramers into A β *56. This has not previously...[more](#)

Alternative:
Comment: [Dewachter & Van Leuven](#): Evidence in ADAM10-deficient mice convincingly...[more](#)

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Hypothesis: A β *56 hypothesis

Author: Karen Hsiao Ashe and colleagues

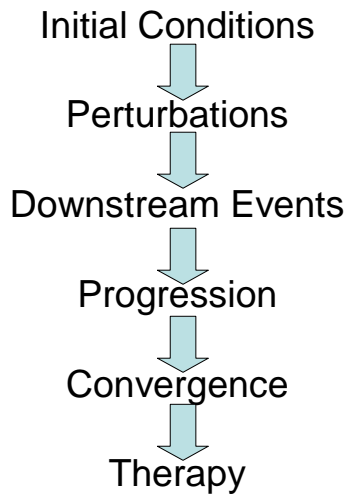
Abstract: Alzheimer's disease is a complex neurodegenerative process that is believed to be due to the accumulation of short, hydrophobic peptides derived from amyloid precursor proteins by proteolytic cleavage. It is widely believed that these A β peptides are secreted into the extracellular spaces of the CNS, where they assemble into toxic oligomers that kill neurons and eventually form deposits of senile plaques. This essay explores the possibility that a fraction of these A β peptides never leave the membrane lipid bilayer after they are generated, but instead exert their toxic effects by competing with and compromising the functions of intramembranous segments of membrane-bound proteins that serve many critical functions. Based on the presence of shared amino acid sequences containing GxxG motifs, I speculate that accumulations of intramembranous A β peptides might affect the functions of amyloid precursor protein itself and the assembly of the PS1, A β 1, Pen 2, Nicastrin complex.

Primary Citation: Lesné S, Koh MT, Kotilinek L, Kaye R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. *Nature*. 2006 Mar 16; 440(7082):352-7

This hypothesis makes the following claims:

1. Tg2576 mice, a good pre-clinical model of AD, exhibits the earliest memory function decline at 6 months age, preceding neuropathology
[Comments \(5\)](#) [Supportive Evidence \(6\)](#) [Alternative Research Statements \(1\)](#) [Quots \(2+\)](#)
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2. Early cognitive decline followed by a period of stabilization in Tg2576 does not correspond to rapidly increasing amounts of A β
[Comments \(0\)](#) [Supportive Evidence \(4\)](#) [Alternative Research Statements \(0\)](#) [Quots \(1\)](#)
[Progression/Pathways](#) [Progression/Animal Models](#)

Pathologic Narratives



Comparing Hypotheses with Pathogenic Narratives

Title	Initial Conditions	Perturbations	Downstream Events	Progression	Convergence	Therapy
Intraneuronal A β dimers (Marchesi 2005)	APP, PS1, GPA, ErbB,		Intramembranous A β 40 and A β 42, APP dimers,	Channels of A β 40 allow lethal Ca $^{2+}$ into cells,	Intramembranous A β dimers reduces receptor function,	Therapies directed to extracellular A β may miss toxic species,
A β *56 (Lesné et al, 2006)	APP, PS1 bram,		Soluble A β assemblies disrupt memory.		Tg2576 exhibit early memory decline preceding neuropathology., A β *56 can cause memory deficit in healthy rats	Therapies to A β *56 may provide reversibility in disease prior to permanent damage,
Ceramide and aging (Costantini et al, 2005)		Late onset AD associated with aging, hypercholesterolemia, atherosclerosis, head trauma, stroke. Ceramide involved in neurodegeneration.	Smase generates ceramide,, nSMadse2 regulated by p75 neurotrophin receptor	Chronic increase in intracellular ceramide inhibits axonal elongation and activates cell death.		
Cholesterol and aging (Costantini et al, 2005)		High concentration of cholesterol in brain or cells can increase A β	A β oxidizes membrane cholesterol, liberates H $_{2}$ O $_{2}$ and increases oxidative stress	Aging is associated with progressive oxidation of circulating lipoprotein, leads intracellular accumulation in lysosomes		Statins
Pathways of A β oligomerization (Bitan et al., 2003)			Photocrosslinking reveals A β 42 Pentamers and hexamers as basic units for further assembly		Oligomers of Ab42 assemble into paranuclei which leads to fibrillar structures. Ab40 lacks ability to form paranuclei	

Summary

- SWAN is a project to share information *content and context* for AD researchers
- SWAN is designed to map onto the *scientific knowledge lifecycle*
- SWAN will include *software, content, and community process*
- SWAN pilot completed, beta being developed

The SWAN Team

- MGH/MIND: Marco Ocana, Paolo Cicarese, Tim Clark
www.mindinformatics.org
- Alzforum: Elizabeth Wu, Gwen Wong, June Kinoshita
www.alzforum.org
- Thanks to: Anne Young, Brad Hyman, Zane Hollingsworth, Marian DiFiglia & Dora Kovacs - MGH; Dean Hartley - BWH; Andy Seaborne & Steve Cayzer - HP Labs, Bristol, UK; Sean Martin - IBM Advanced Technology Group.



The Beautiful Swan - by William Nicholson, British (1872-1948), color lithograph after a woodcut, 1900. Campbell 73b.

website: <http://swan.mindinformatics.org>