The SWAN Hypothesis Manager in the Biomedical Knowledge Ecosystem

Elizabeth Wu
June Kinoshita
Gwen Wong

Alzheimer Research Forum

Tim Clark
Paolo Ciccarese
Marco Ocana

Harvard University and
Massachusetts General Hospital

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

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

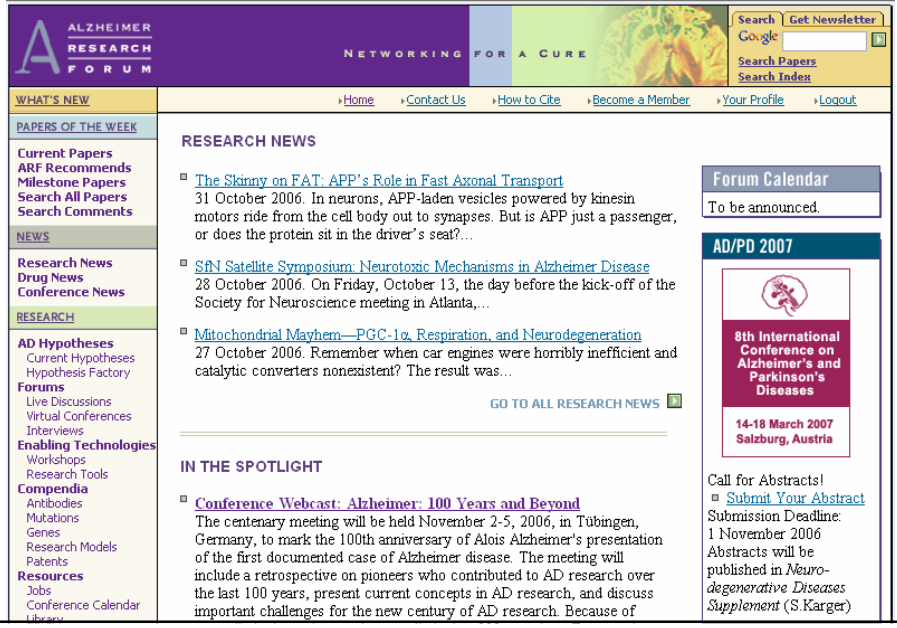
Alzheimer Research Forum
www.alzforum.org

was launched

Alzheimer Disease in 2006

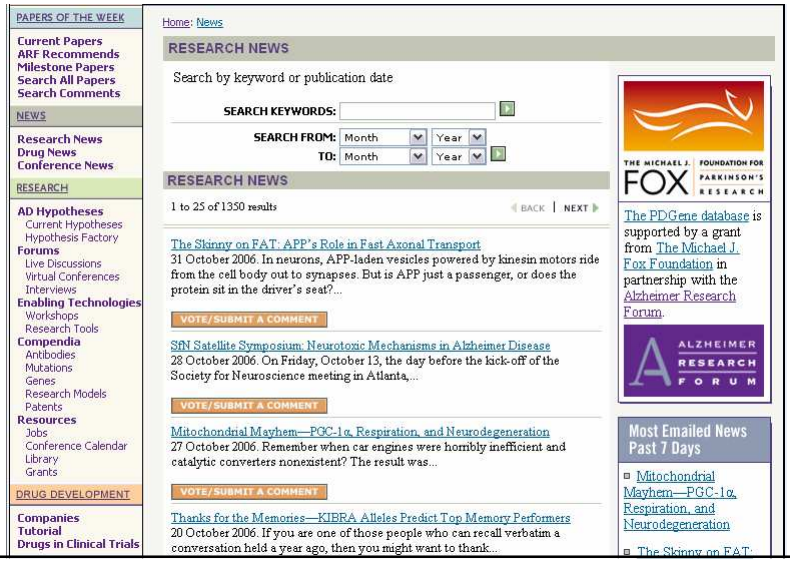
- 20 millions people worldwide suffer from Alzheimer Disease
- NIH funding for AD estimates at $ 650M per year
- 5,000 AD and related papers published in 2006 so far
- still…no effective treatment or therapy

Alzforum in 2006

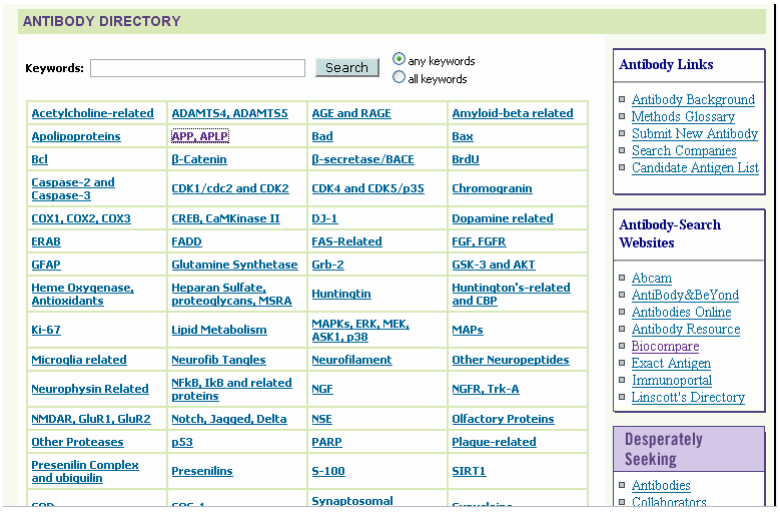


Collected 44,000 AD Related Papers

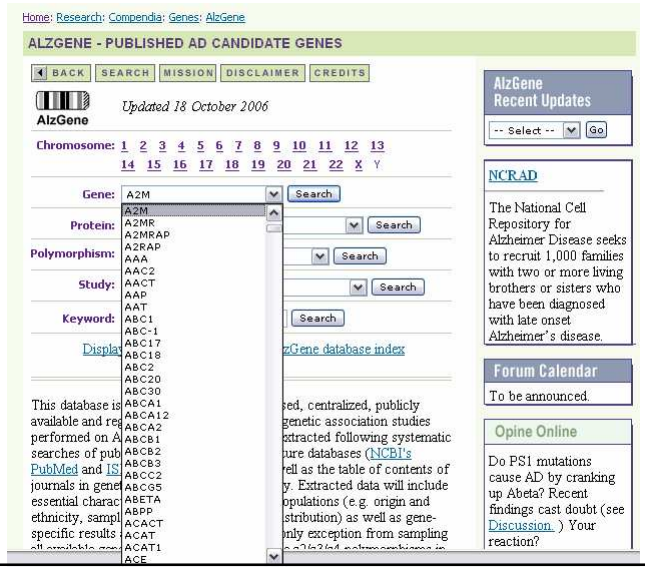
Published Over 1400 News Articles



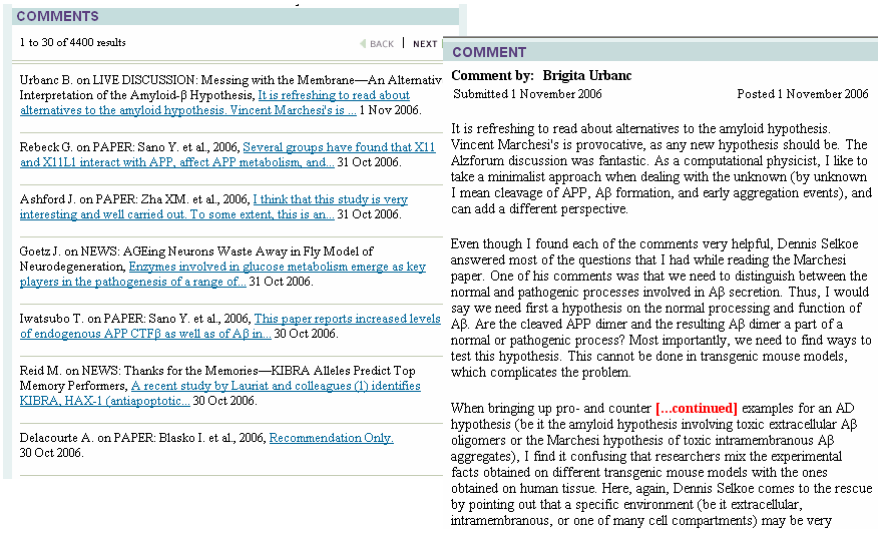
Curated 14,700 Antibodies



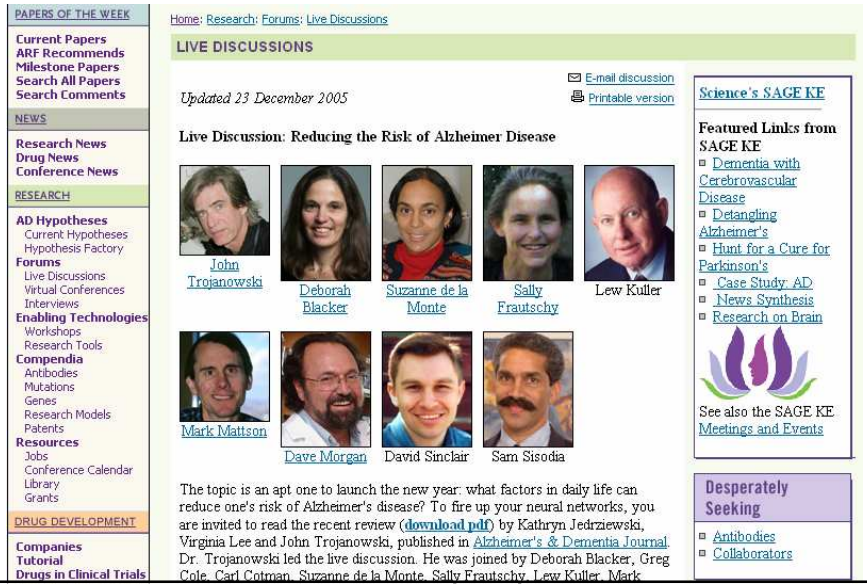
Curated 900 Genetic Association Studies and 366 Genes in AD



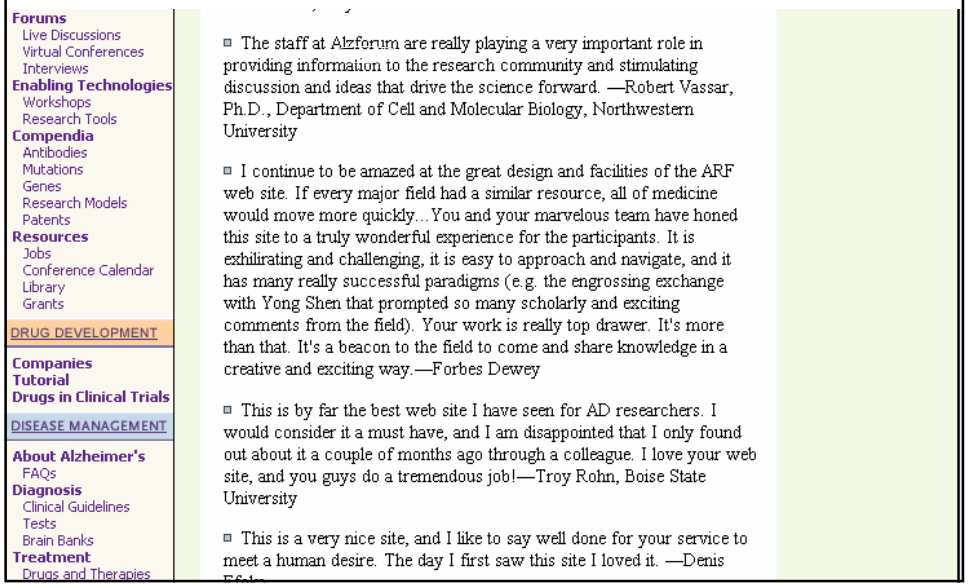
Scientists Sent in 4400 Comments



Participated in over 80 Live Discussions



Fan Mails



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 heros 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

Alzforum in 2006

ALZHEIMER RESEARCH FORUM — NETWORKING FOR A CURE

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RESEARCH
AD Hypotheses
Current Hypotheses
Hypothesis Factory
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Workshops
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RESEARCH NEWS

- 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?…
- SfN 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-1α, Respiration, and Neurodegeneration
  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

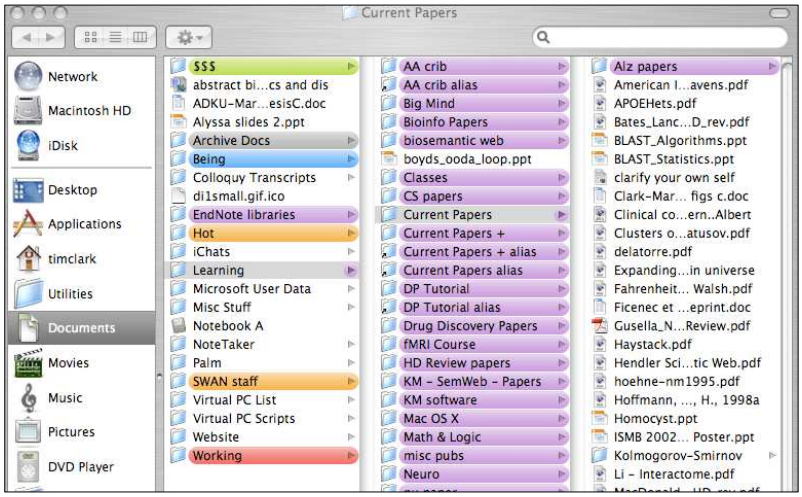
Forum Calendar
To be announced.

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 *Neuro-degenerative 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?

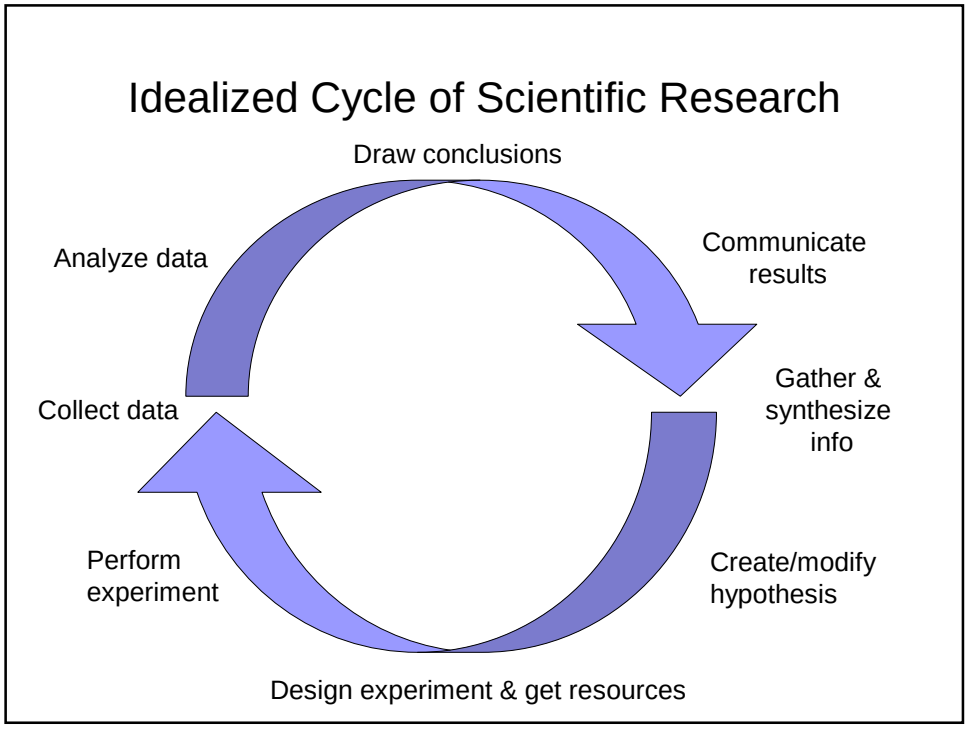
Semantic Web Applications in Neuromedicine

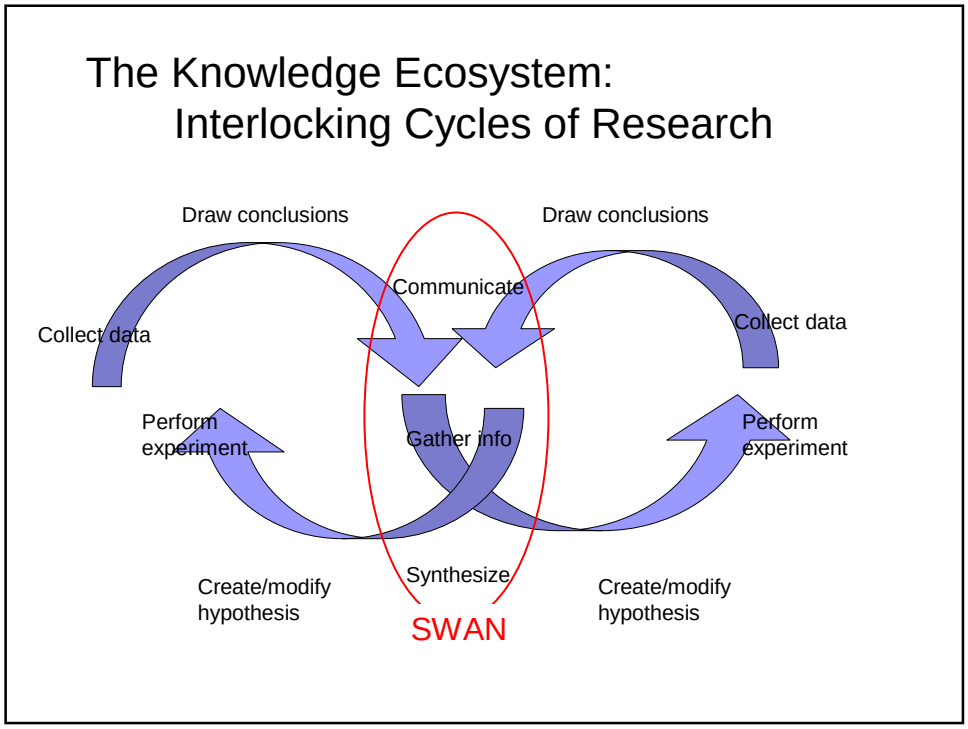
SWAN is a project to create

- 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

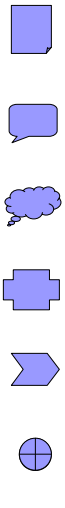
Fundamental Hypotheses

- 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


Idealized Cycle of Scientific Research
Draw conclusions
Communicate results
Gather & synthesize info
Create/modify hypothesis
Design experiment & get resources
Perform experiment
Collect data
Analyze data


The Knowledge Ecosystem:
Interlocking Cycles of Research
Draw conclusions
Draw conclusions
Communicate
Collect data
Collect data
Perform experiment
Gather info
Perform experiment
Synthesize
Create/modify hypothesis
Create/modify hypothesis
SWAN

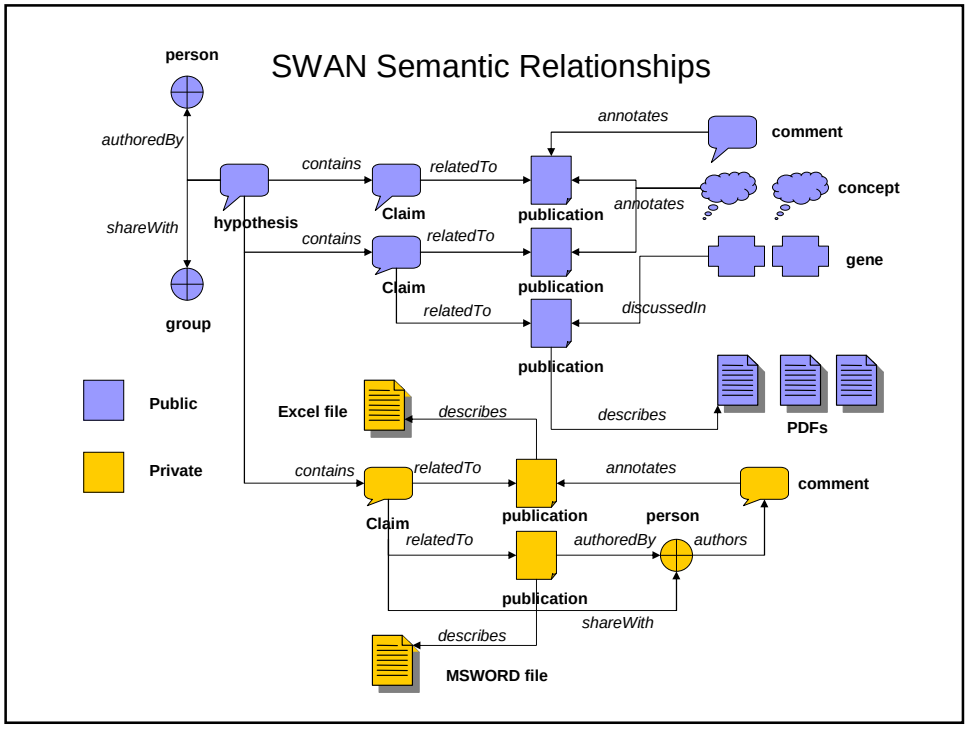
SWAN Ontology: Basic Concepts

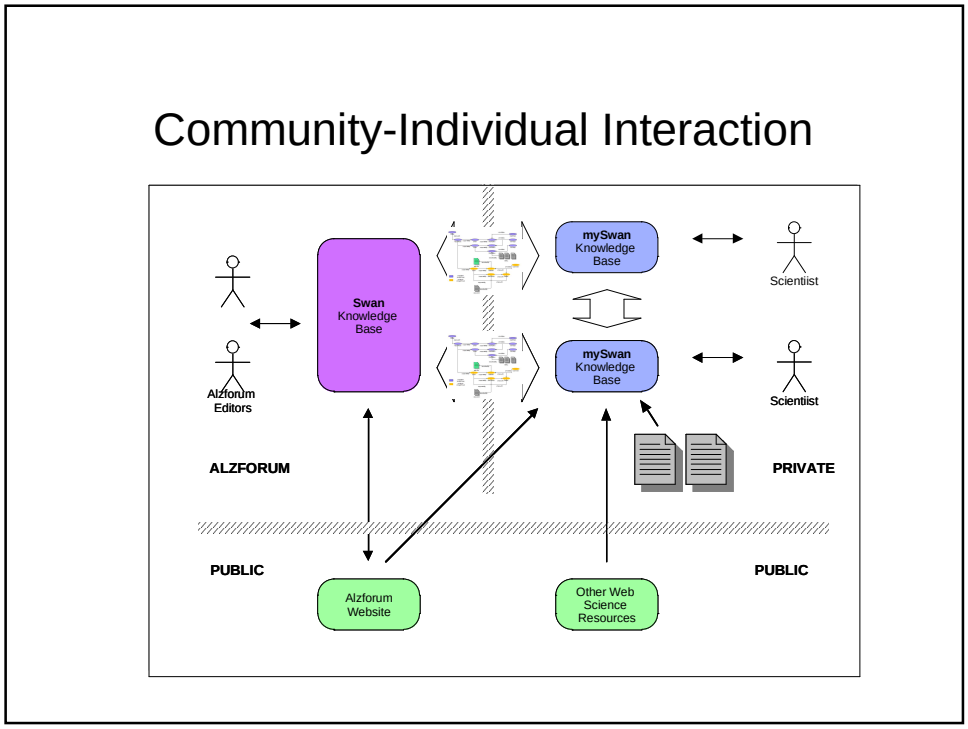


- **Digital Resource**
  journal article, manuscript, grant application, data, image, …
- **Research Statement**
  hypothesis, claim, structured comment, research questions
- **Domain Concept**
  personal concept (tag), formal concept (ontology)
- **Life Science Entity**
  gene, protein, organism, compound, …
- **Scientific Activity**
  experiment, study, review,…
- **Collaborator**
  person, community,…

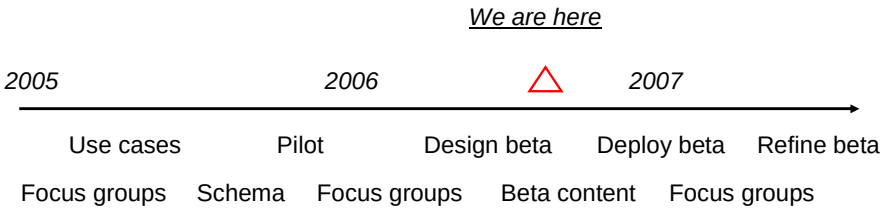
SWAN Ontology: Relationships

- 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 Semantic Relationships
person
authoredBy
shareWith
group
hypothesis
contains
Claim
relatedTo
publication
annotates
comment
concept
gene
discussedIn
Public
Private
Excel file
describes
PDFs
MSWORD file
person
authors


Community-Individual Interaction
Swan Knowledge Base
mySwan Knowledge Base
Scientiist
Alzforum Editors
ALZFORUM
PRIVATE
PUBLIC
Alzforum Website
Other Web Science Resources

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.

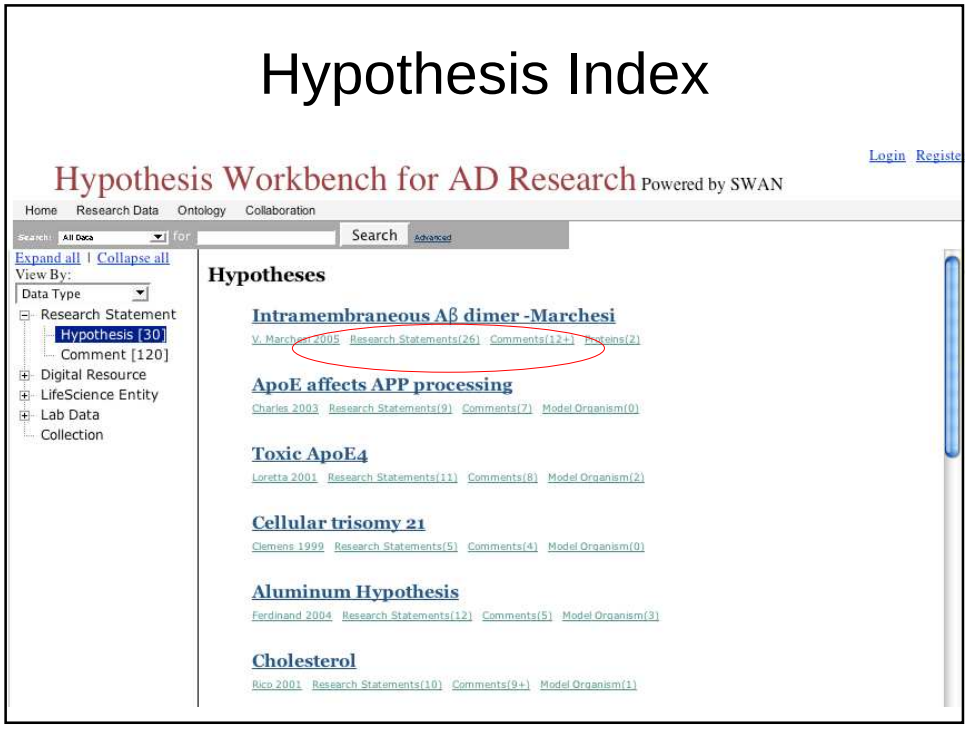
Research communities, laboratories,science administrators, and Individual scientists can organize their own data, manuscripts, grants, publications and other digital resources around key hypotheses, observations, or biomedical concepts. They can also selectively share their knowledge with colleagues 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.

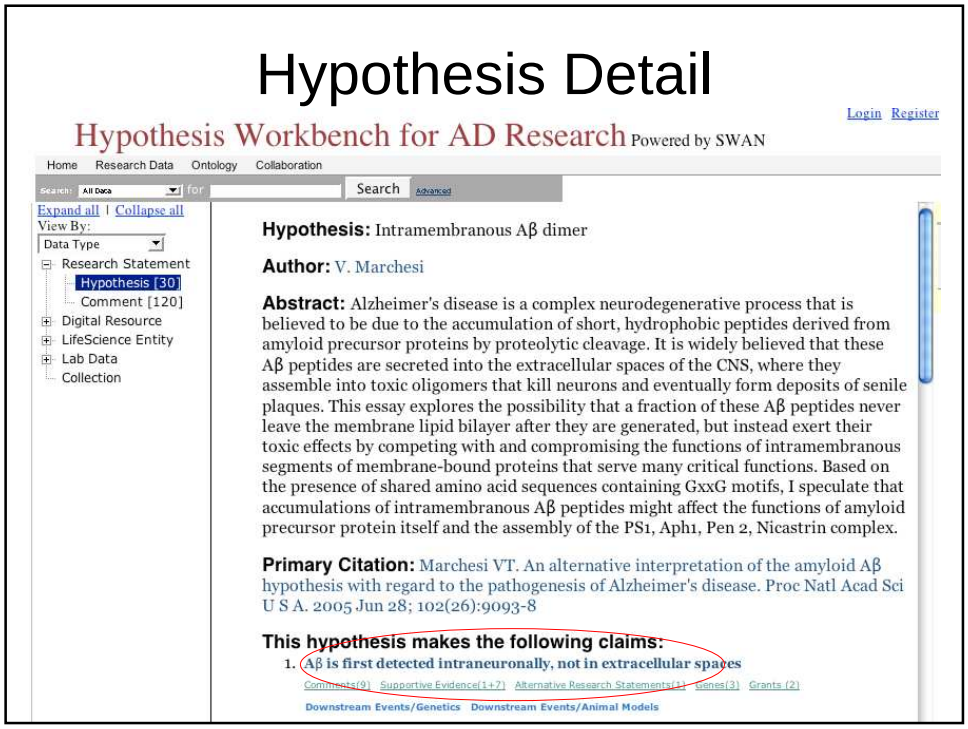
Our approach is based on semantically organizing and enriching the scientific information in the system, using the new technologies of the Semantic Web (Berners-Lee et al, 2001).

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.

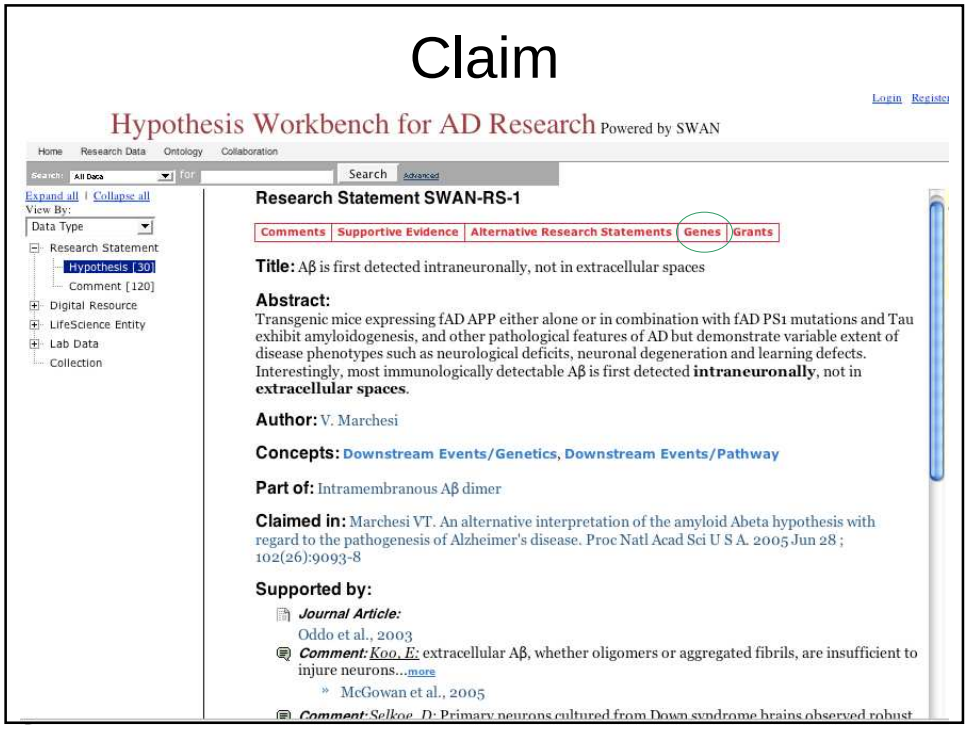
Hypothesis Index

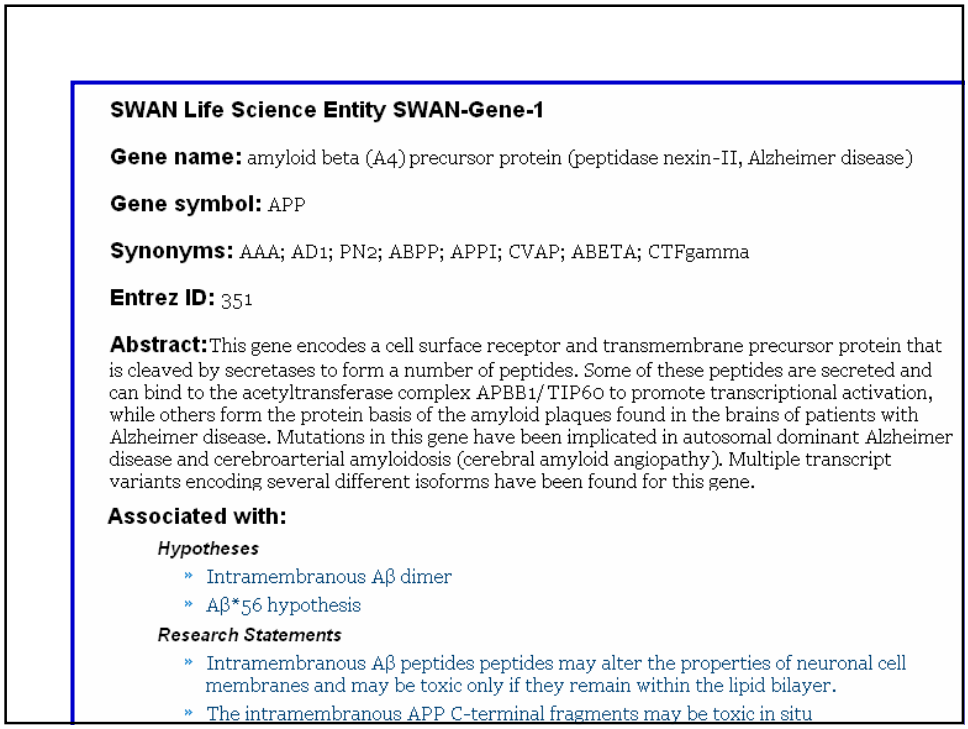


Hypothesis Detail

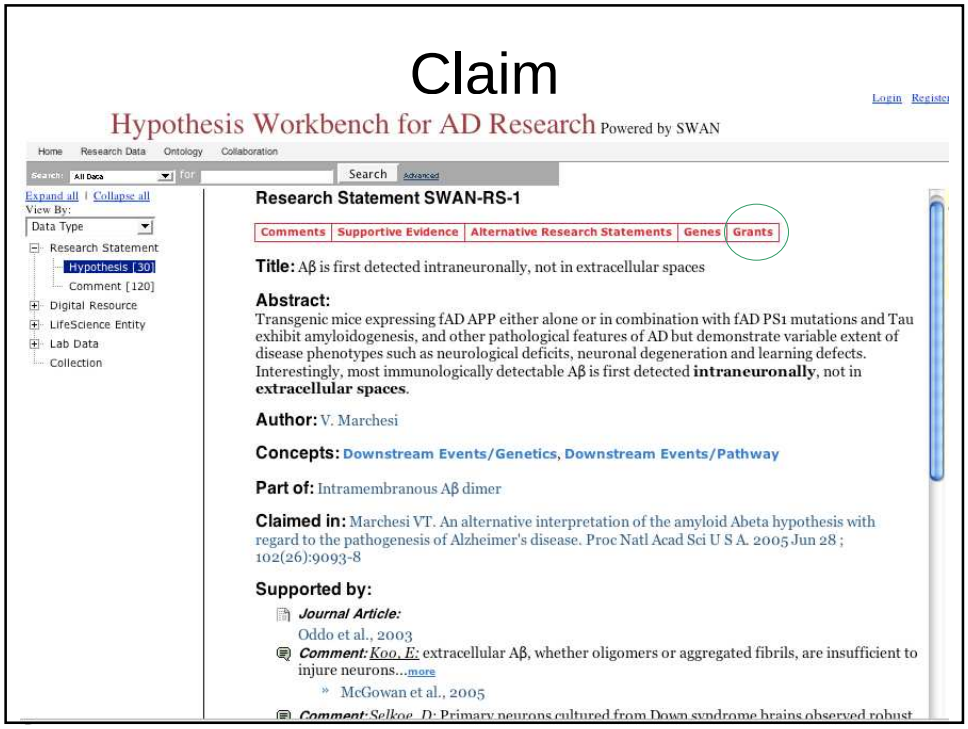


Claim

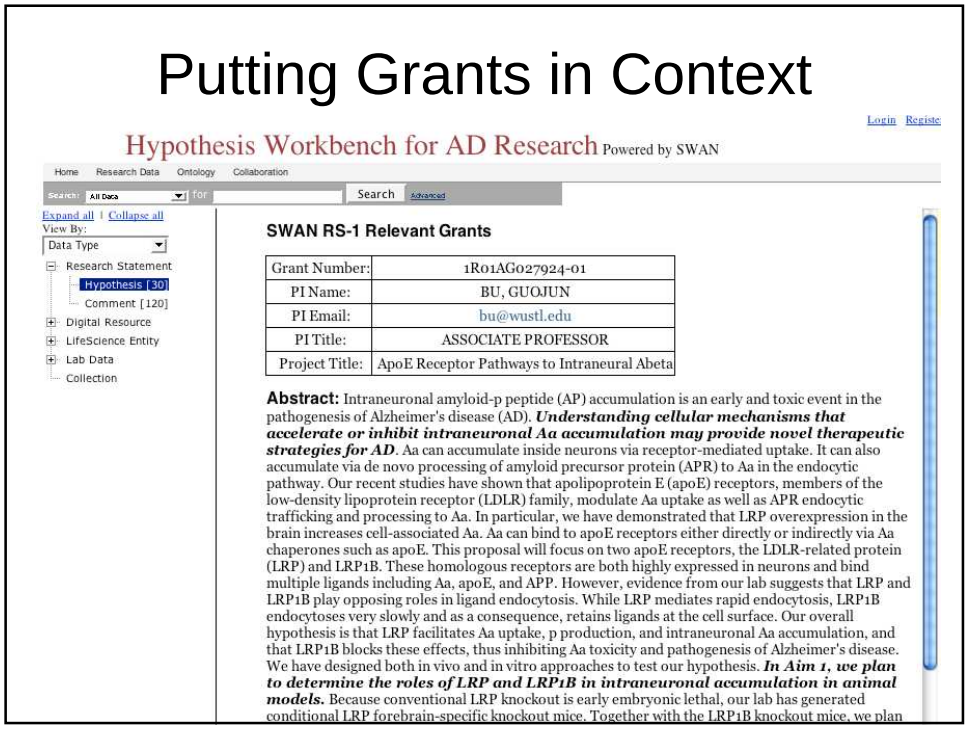

Login Register
Hypothesis Workbench for AD Research Powered by SWAN
Home Research Data Ontology Collaboration
Search: All Data for Search Advanced
Expand all | Collapse all
View By:
Data Type
Research Statement
Hypothesis [30]
Comment [120]
Digital Resource
LifeScience Entity
Lab Data
Collection
Research Statement SWAN-RS-1
Comments Supportive Evidence Alternative Research Statements Genes Grants
Title: Aβ 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 Aβ is first detected intraneuronally, not in extracellular spaces.
Author: V. Marchesi
Concepts: Downstream Events/Genetics, Downstream Events/Pathway
Part of: Intramembranous Aβ 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 Aβ, 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 Aβ dimer
» Aβ*56 hypothesis
Research Statements
» Intramembranous Aβ 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

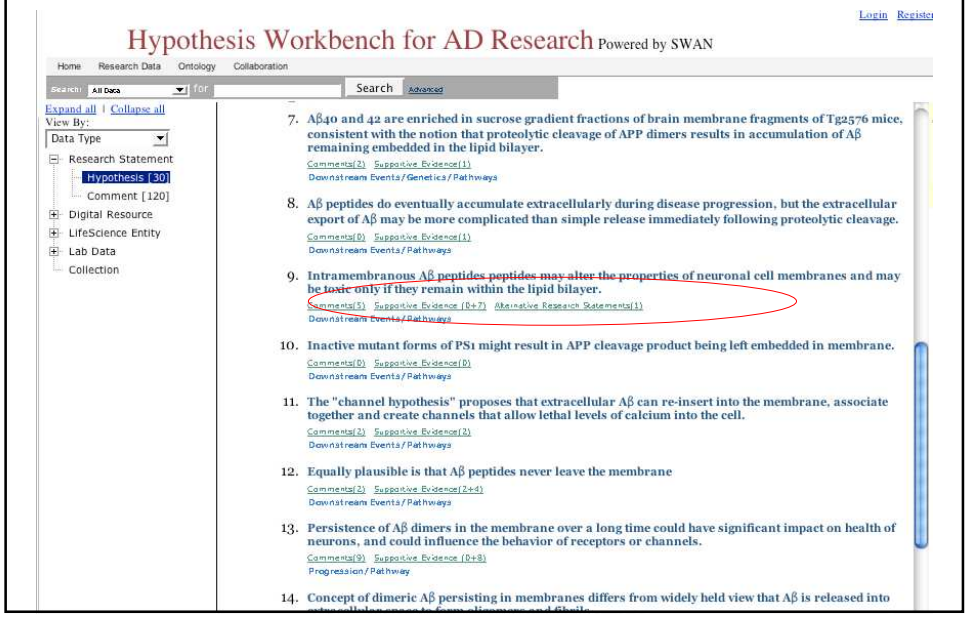
Claim



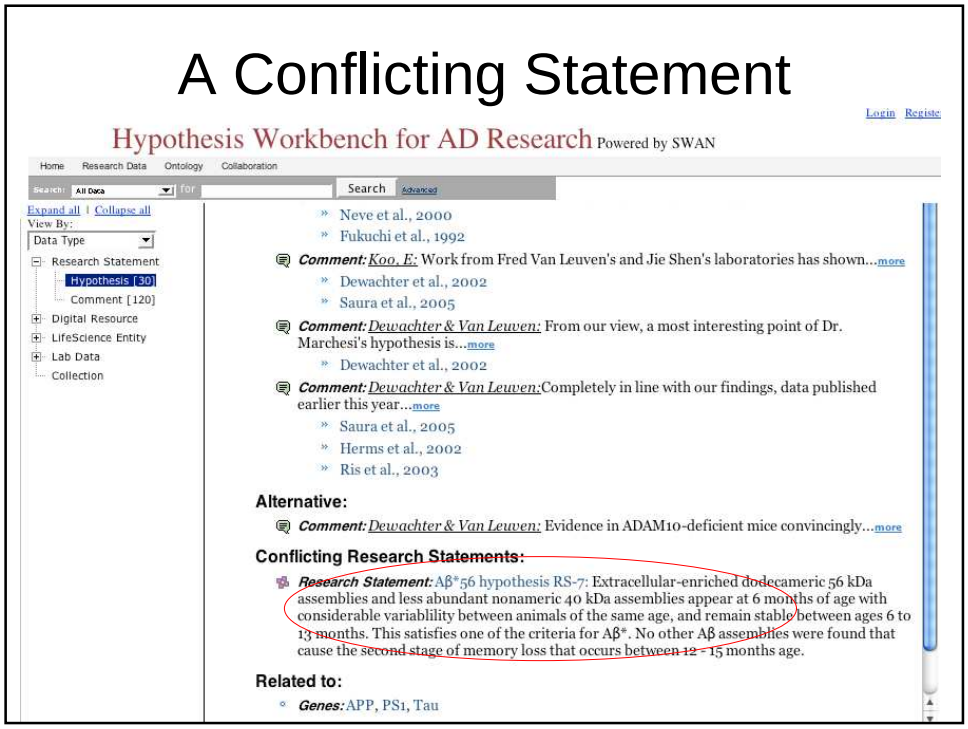
Putting Grants in Context



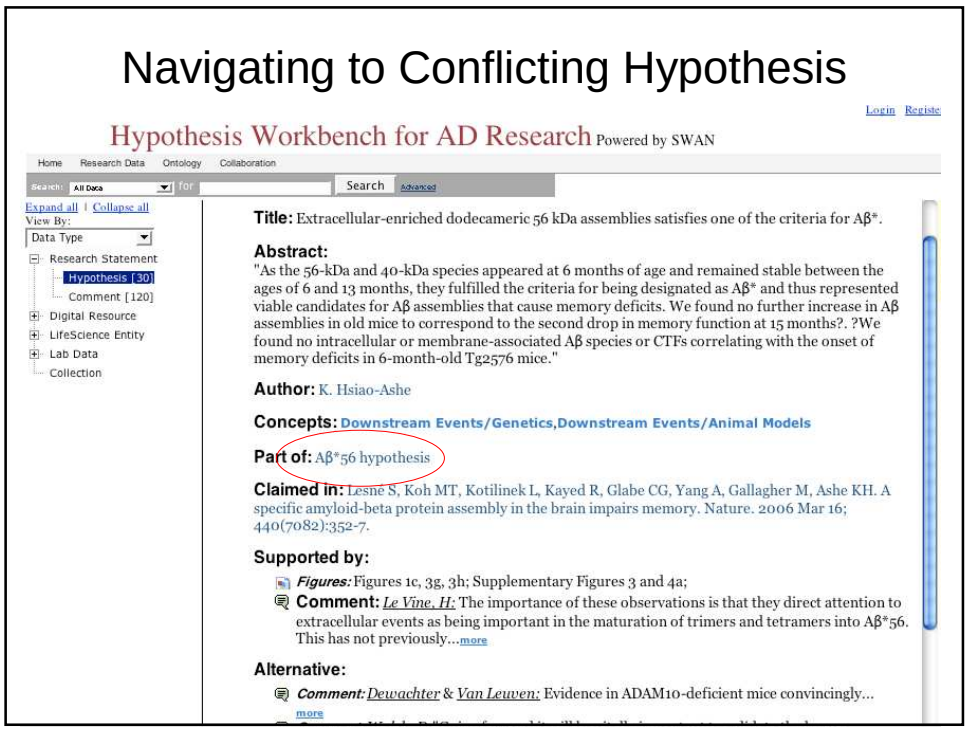
Linking Across Hypotheses



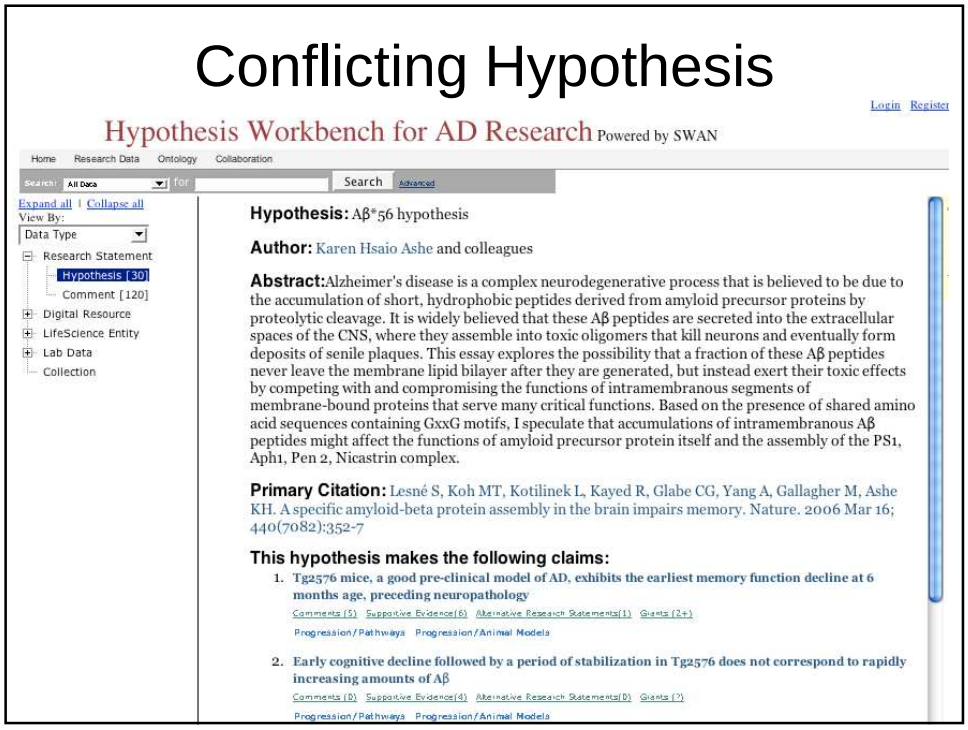
A Conflicting Statement



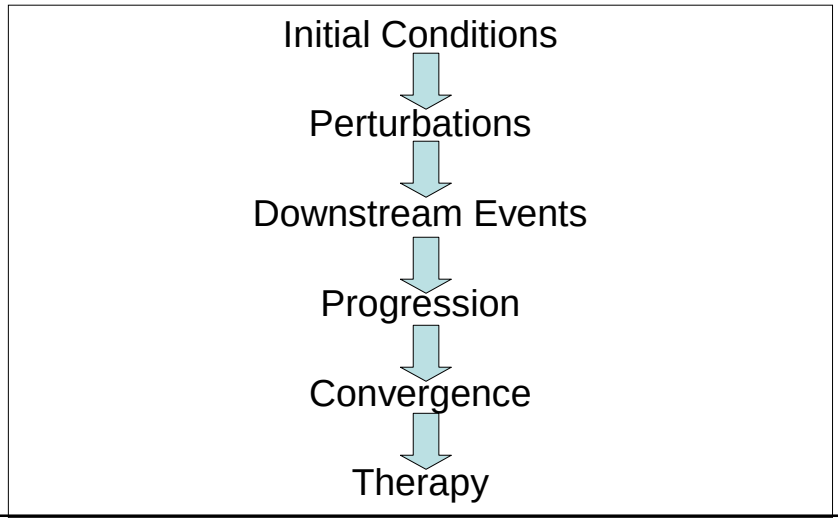
Navigating to Conflicting Hypothesis



Conflicting Hypothesis



Pathologic Narratives



Comparing Hypotheses with Pathogenic Narratives

Title	Initial Conditions	Perturbations	Downstream Events	Progression	Convergence	Therapy
Intraneuronal Aβ dimers (Marchesi 2005)	APP, PS1, GPA, ErbB,		Intramembranous Aβ40 and Aβ42, APP dimers,	Channels of Aβ40 allow lethal Ca2+ into cells,	Intramembranous Aβ dimers reduces receptor function,	Therapies directed to extracellular Aβ may miss toxic species,
Aβ*56 (Lesne et al, 2006)	APP, PS1 bram,		Soluble Aβ assemblies disrupt memory.		Tg2576 exhibit early memory decline preceding neuropathology,, Aβ*56 can cause memory deficit in healthy rats	Therapies to Aβ*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 Aβ	Aβ oxidizes membrane cholesterol, liberates H2O2 and increases oxidative stress	Aging is associated with progressive oxidation of circulating lipoprotein, leads intracellular accumulation in lysosomes		Statins
Pathways of Aβ oligomerization (Bitan et al., 2003)			Photocrosslinking reveals Aβ42 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 Ciccarese, 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.

website: http://swan.mindinformatics.org

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