Informatics approaches for agile biomedical research

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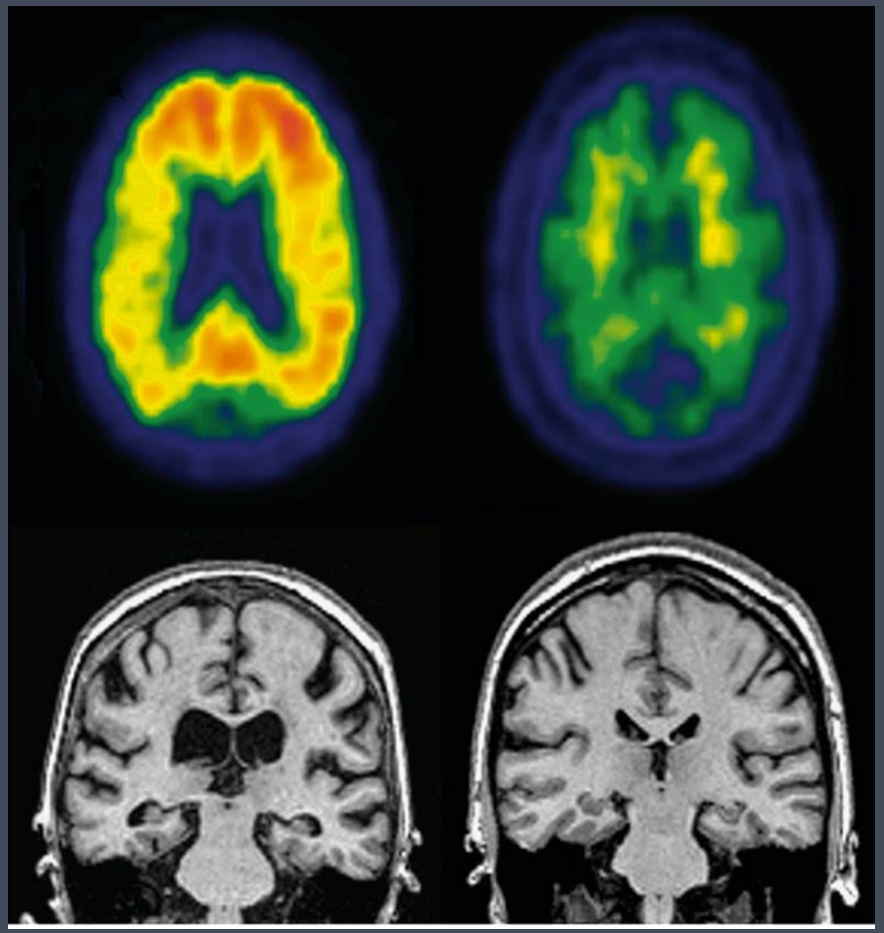
October 17, 2011

Abstract

- Biomedical communications now undergoing fundamental change due to the Web.
- Pharmaceutical research should take advantage of these advances for agile collaboration & internal productivity gains.
- "Nanopublications" and related models for rapid, agile information awareness, sharing and preservation support .

"hippocampal atrophy and Aβ load predicted shorter time-to-progression"



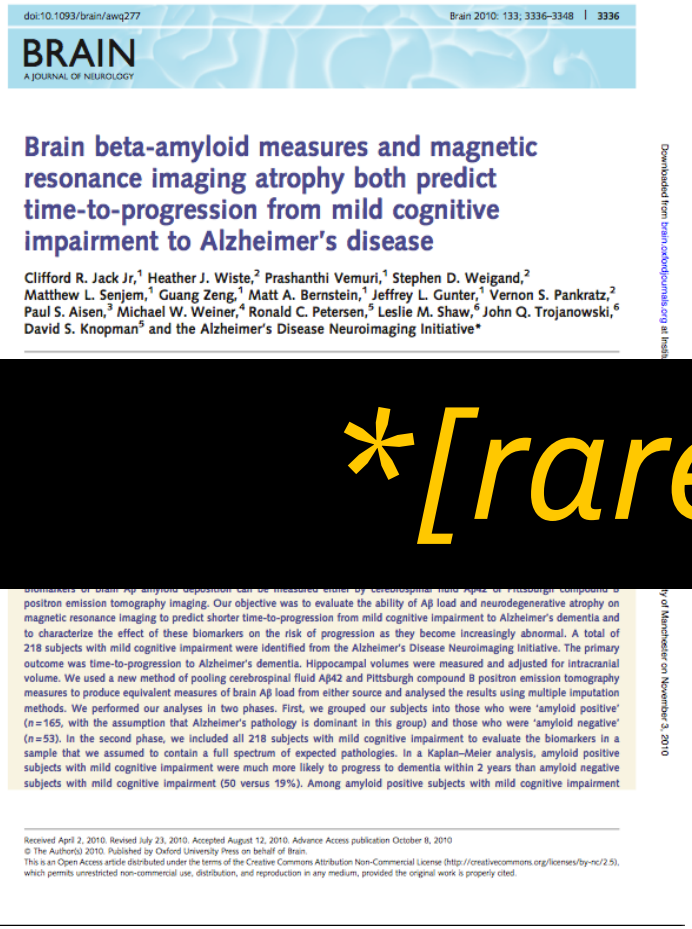
Brain. 2010 Nov;133(Pt 11):3336-3348.

PET imaging of PIB (radiolabelled compound binds amyloid beta A4 protein)

MRI imaging of brain structure showing loss of hippocampal volume

MCI progressors + non progressors = *218 subjects*

Trojanowski: “It was unbelieveable,…*



doi:10.1093/brain/awq277 Brain 2010: 133; 3336–3348 | 3336

BRAIN
A JOURNAL OF NEUROLOGY

Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease

Clifford R. Jack Jr,[1] Heather J. Wiste,[2] Prashanthi Vemuri,[1] Stephen D. Weigand,[2] Matthew L. Senjem,[1] Guang Zeng,[1] Matt A. Bernstein,[1] Jeffrey L. Gunter,[1] Vernon S. Pankratz,[2] Paul S. Aisen,[3] Michael W. Weiner,[4] Ronald C. Petersen,[5] Leslie M. Shaw,[6] John Q. Trojanowski,[6] David S. Knopman[5] and the Alzheimer's Disease Neuroimaging Initiative*

positron emission tomography imaging. Our objective was to evaluate the ability of Aβ load and neurodegenerative atrophy on magnetic resonance imaging to predict shorter time-to-progression from mild cognitive impairment to Alzheimer's dementia and to characterize the effect of these biomarkers on the risk of progression as they become increasingly abnormal. A total of 218 subjects with mild cognitive impairment were identified from the Alzheimer's Disease Neuroimaging Initiative. The primary outcome was time-to-progression to Alzheimer's dementia. Hippocampal volumes were measured and adjusted for intracranial volume. We used a new method of pooling cerebrospinal fluid Aβ42 and Pittsburgh compound B positron emission tomography measures to produce equivalent measures of brain Aβ load from either source and analysed the results using multiple imputation methods. We performed our analyses in two phases. First, we grouped our subjects into those who were 'amyloid positive' (n=165, with the assumption that Alzheimer's pathology is dominant in this group) and those who were 'amyloid negative' (n=53). In the second phase, we included all 218 subjects with mild cognitive impairment to evaluate the biomarkers in a sample that we assumed to contain a full spectrum of expected pathologies. In a Kaplan–Meier analysis, amyloid positive subjects with mild cognitive impairment were much more likely to progress to dementia within 2 years than amyloid negative subjects with mild cognitive impairment (50 versus 19%). Among amyloid positive subjects with mild cognitive impairment

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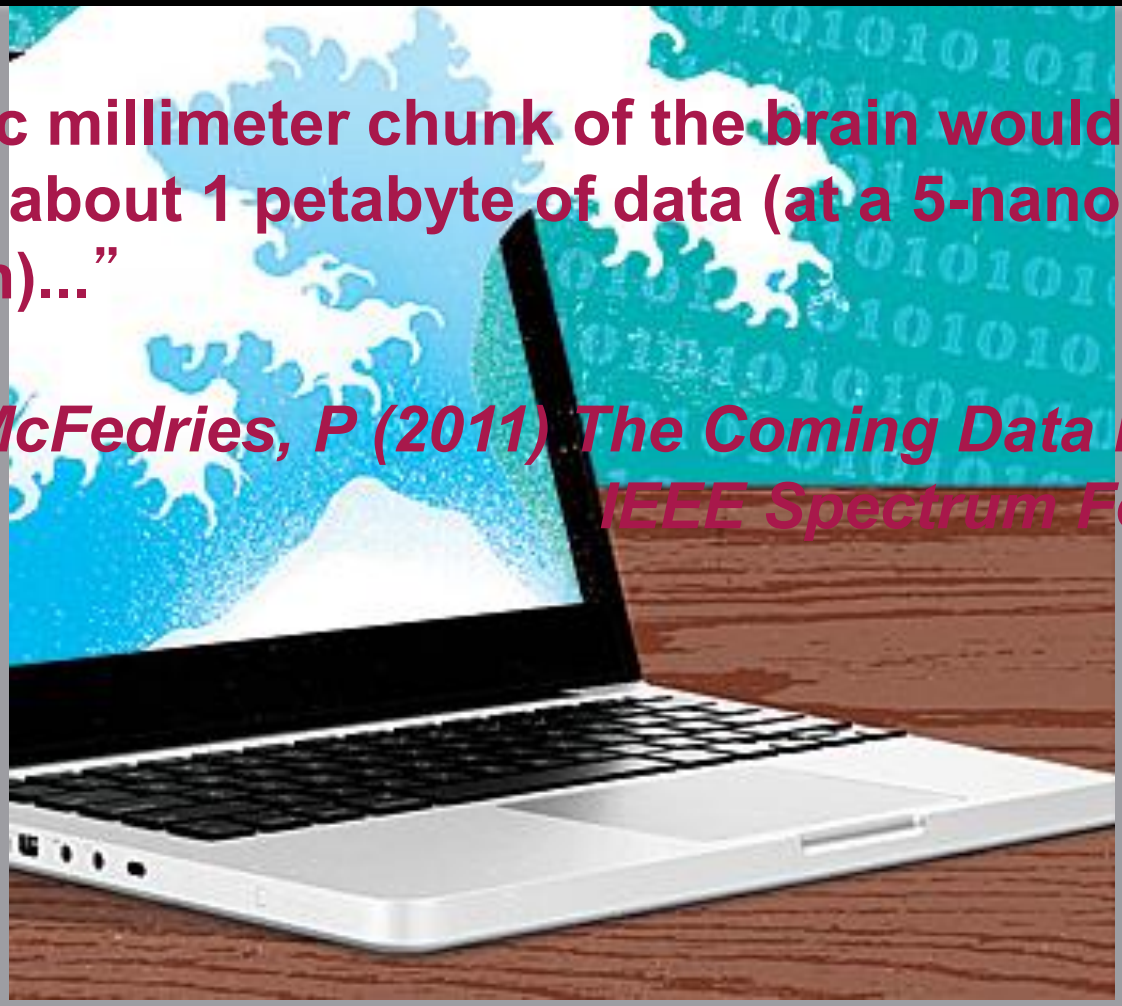
…[we] parked our egos and intellectual-property noses outside the door and
agreed

*[rare event]

John Trojanowski, MD, PhD
U Penn Medical School

Sharing of Data Leads to Progress on Alzheimer’s, NY Times, 12 Aug 2010

…with inadequately referenced primary data?



"... a cubic millimeter chunk of the brain would comprise about 1 petabyte of data (at a 5-nanometer resolution)..."

—McFedries, P (2011) The Coming Data Deluge. IEEE Spectrum Feb 2011

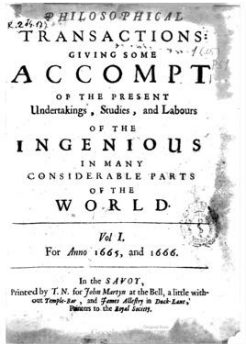
A little history

print culture

printing — c. 1450

GPO — 1660

Scientific Journal — 1665


PHILOSOPHICAL
TRANSACTIONS:
GIVING SOME
ACCOMPT
OF THE PRESENT
Undertakings, Studies, and Labours
OF THE
INGENIOUS
IN MANY
CONSIDERABLE PARTS
OF THE
WORLD.
Vol. I.
For Anno 1665, and 1666.
In the SAVOY,
Printed by T. N. for John Martyn at the Bell, a little without Temple-Bar, and James Allestry in Duck-Lane;
Printers to the Royal Society.

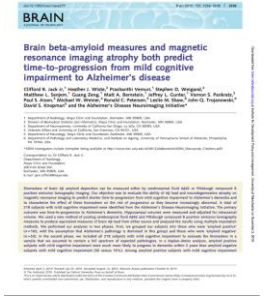
=

Web culture

IBM S/360 — 1964

Internet — 1980s

Web — 1991


BRAIN
Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease

A TABLE of the Apertures of Object-Glasses.

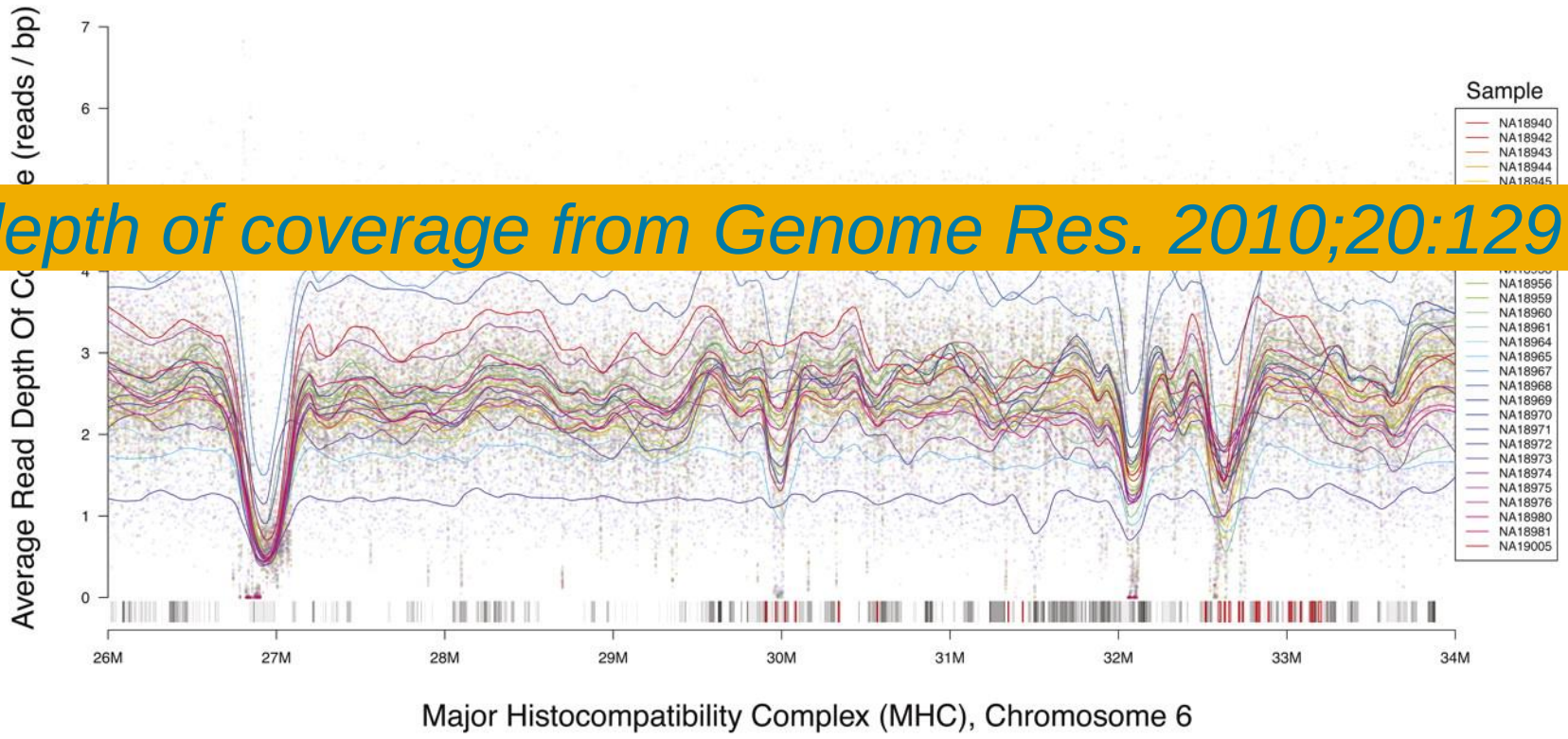
The Points put to some of these Numbers denote Fractions.

Lengths of Glasses. Feet, Inches.	For excellent ones. Inch. Lines.	For good ones. Inch. Lines.	For ordinary ones. Inch. Lines.	Lengths of Glasses. Feet, Inches.	For excellent ones. Inch. Lines.	For good ones. Inch. Lines	For ordinary ones. Inch. Lines.
4	4	4	3	25	3 4	2 10	2 4.
6	5	5	4	30	3 8	3 2	2 7
9	7	6	5	35	4 0	3 4.	2 10
1 0	8	7	6	40	4 3	3 7	3 .
1 6	9	8	7	45	4 6	3 10	3 2.
2 0	11	10	8	50	4 9	4 0	3 4.
2 6	1 0	11	9	55	5 0	4 3	3 6.
3 0	1 1	1 0	10	60	5 2	4 6	3 8.
3 6	1 2	1 1	11	65	5 4	4 8	3 10
4 0	1 4	1 2	1	0.70	5 7	4 10	3 .
4 6	1 5	1 3	1	.75	5 9	5 0	4 2.
5 0	1 6	1 4	1	1.80	5 11	5 2	4 5
10	2 1	1 10	1	6 200	9 6	8 0	6 9
12	2 4	2 0	1	8 250	10 6	9 2	7 8.
14	2 6	2 2	1	9. 300	11 6	10 0	8 5
16	2 8	2 4	1	11. 350	12 6.	10 9	9 0
18	2 10	2 6	2	1400	13 4	11 6	9 8
20	3 0	2 7	2	2.			

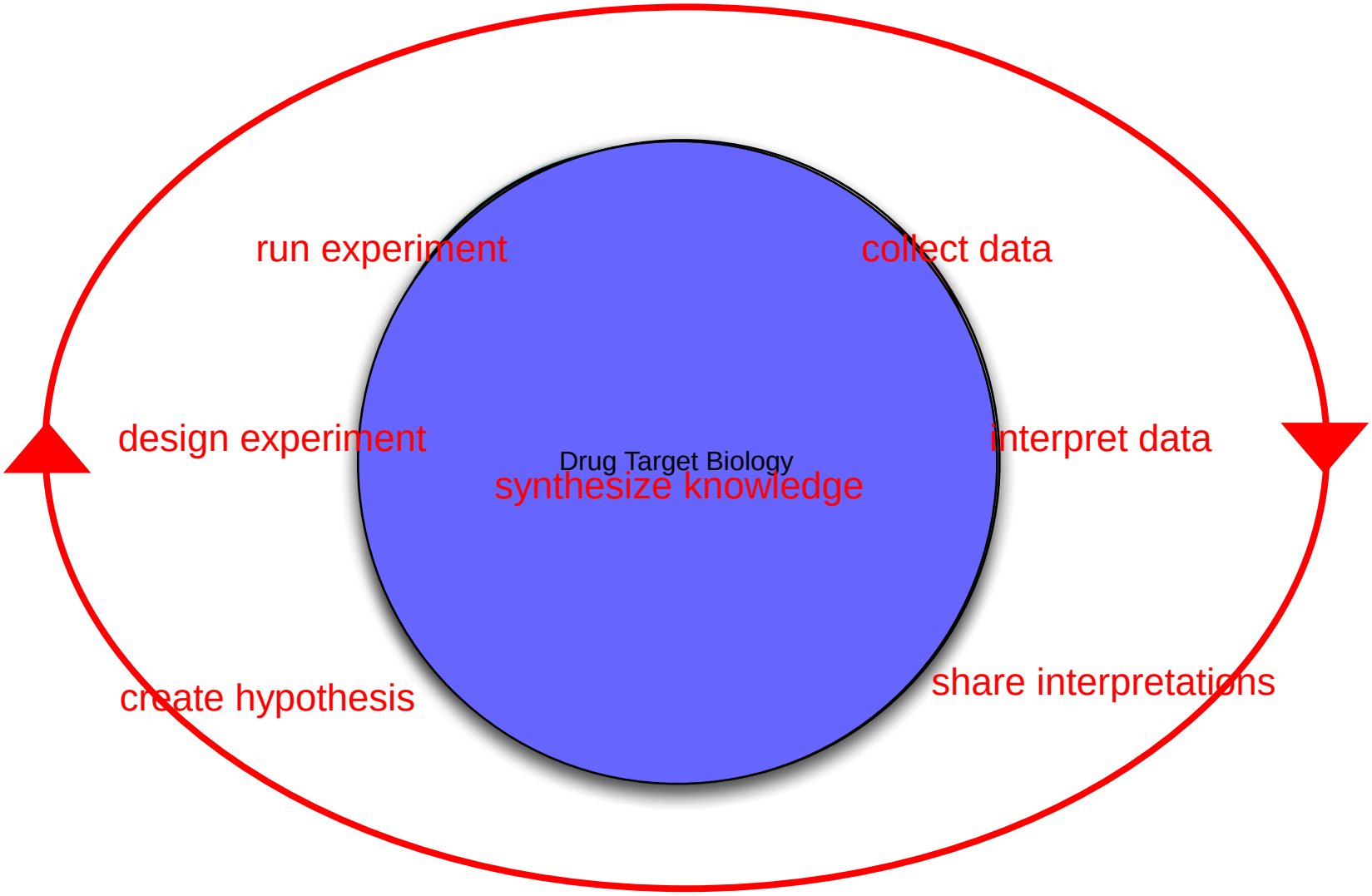
Considerations of Monsieur Auzout *upon Mr.* Hook's *New Instrument for grinding of* Optick-Glasses.

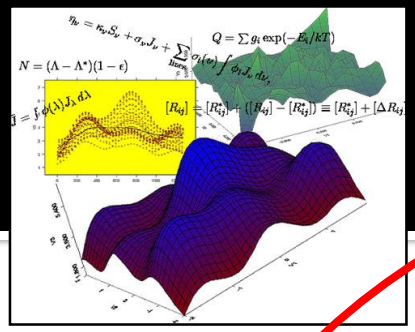
In the above-mentioned *French* Tract, there are, besides several other particulars, to be represented in due place, contained some *Considerations* of Monsieur *Auzout* upon Mr. *Hook*'s New *Engine* for grinding *Optick-Glasses*. Where he premises in *General* his thoughts touching the working of *Great* Optick-Glasses, and that by the help of a *Turn lathe*; affirming first of all, that not only the *Engine* is to be considered for giving the *Figure*, but the

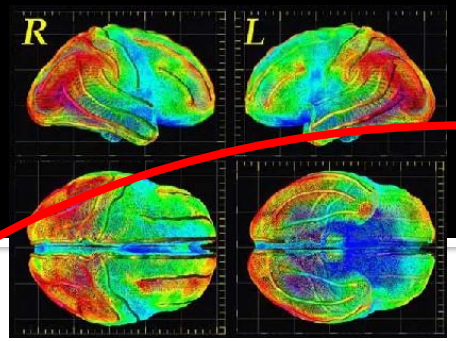
MHC depth of coverage in JPT samples of the 1000 Genomes Project pilot 2, calculated using the GATK depth of coverage tool.

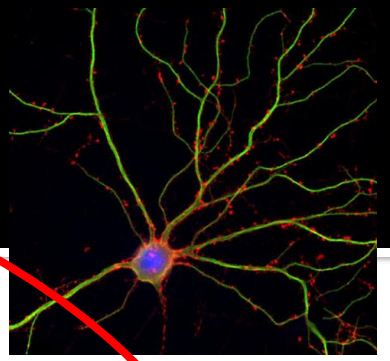


McKenna A et al. Genome Res. 2010;20:1297-1303


run experiment
collect data
design experiment
interpret data
Drug Target Biology
synthesize knowledge
create hypothesis
share interpretations

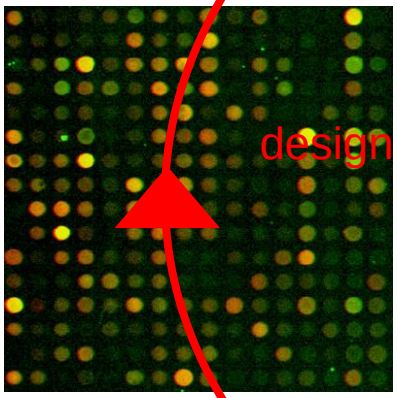






run experiment

collect data



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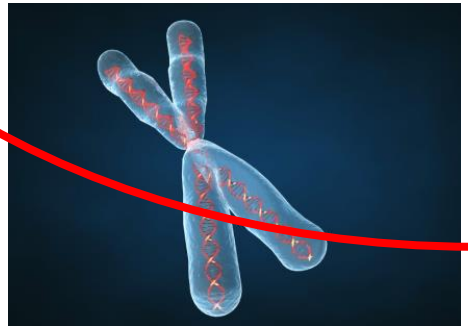
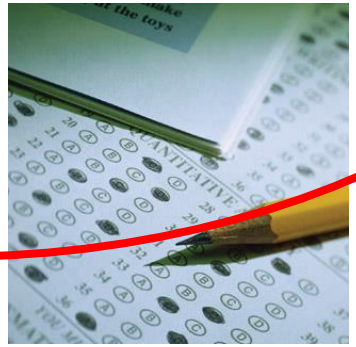
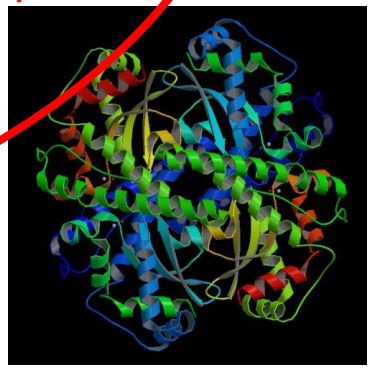
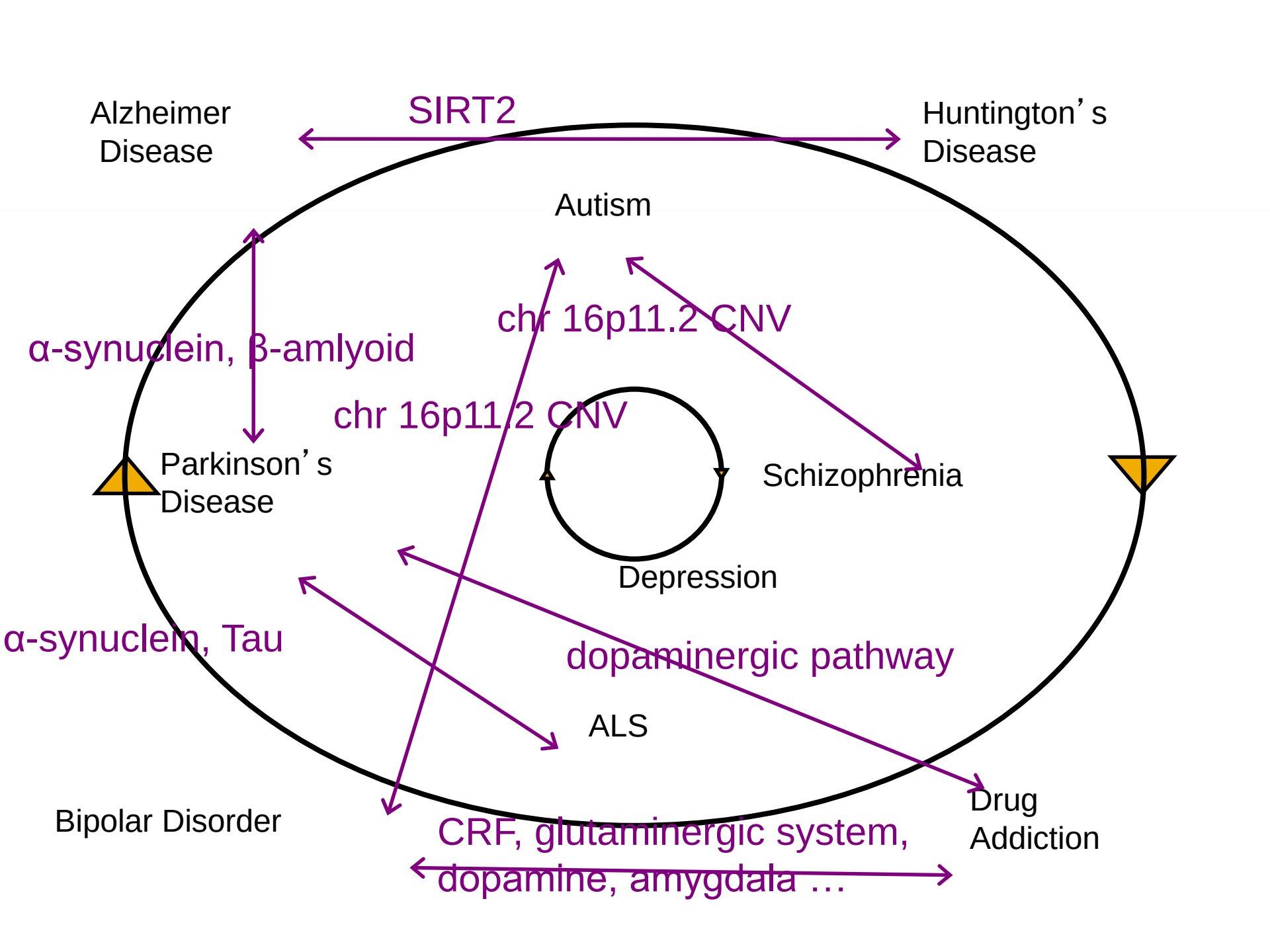







Alzheimer Disease
SIRT2
Huntington's Disease
Autism
α-synuclein, β-amlyoid
chr 16p11.2 CNV
chr 16p11.2 CNV
Parkinson's Disease
Schizophrenia
Depression
α-synuclein, Tau
dopaminergic pathway
ALS
Drug Addiction
Bipolar Disorder
CRF, glutaminergic system, dopamine, amygdala …

Web 2.0:
Biomedical "collaboratories"

Supervised automatic annotation

Genes

Proteins

Biological Processes

Chemical Compounds

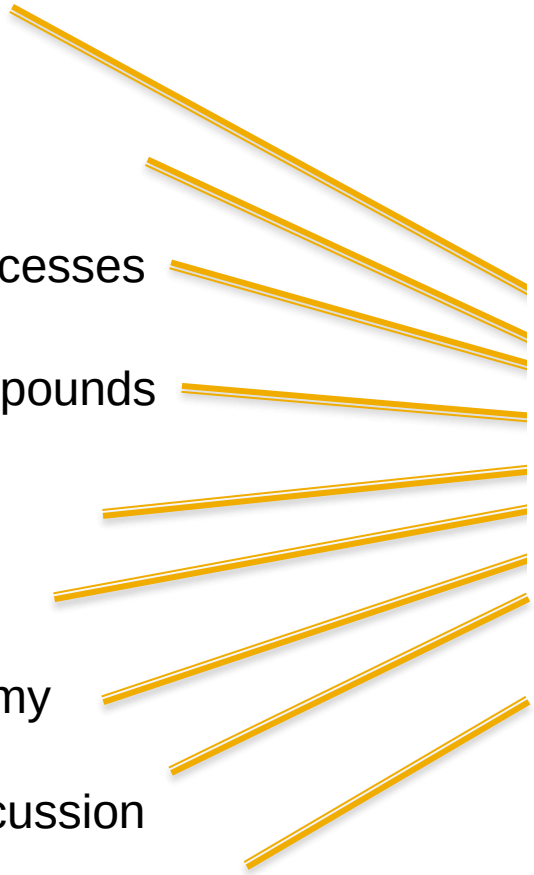
Antibodies

Cells

Brain anatomy

Threaded discussion

Direct data & methods citation



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1 Department of Radiology, Mayo Clinic and Foundation, Rochester, MN 55905, USA
2 Division of Biomedical Statistics and Informatics, Mayo Clinic and Foundation, Rochester, MN 55905, USA
3 Department of Neurosciences, University of California-San Diego, La Jolla, CA 92093, USA
4 Veterans Affairs and University of California, San Francisco, CA 94121, USA
5 Department of Neurology, Mayo Clinic and Foundation, Rochester, MN 55905, USA
6 Department of Pathology and Laboratory Medicine, and Institute on Ageing, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

*ADNI investigators include (complete listing available at http://www.loni.ucla.edu\ADNI\Collaboration\ADNI_Manuscript_Citations.pdf).

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Rochester, MN 55905, USA
E-mail: jack.clifford@mayo.edu

Biomarkers of brain Aβ amyloid deposition can be measured either by cerebrospinal fluid Aβ42 or Pittsburgh compound B positron emission tomography imaging. Our objective was to evaluate the ability of Aβ load and neurodegenerative atrophy on magnetic resonance imaging to predict shorter time-to-progression from mild cognitive impairment to Alzheimer's dementia and to characterize the effect of these biomarkers on the risk of progression as they become increasingly abnormal. A total of 218 subjects with mild cognitive impairment were identified from the Alzheimer's Disease Neuroimaging Initiative. The primary outcome was time-to-progression to Alzheimer's dementia. Hippocampal volumes were measured and adjusted for intracranial volume. We used a new method of pooling cerebrospinal fluid Aβ42 and Pittsburgh compound B positron emission tomography measures to produce equivalent measures of brain Aβ load from either source and analysed the results using multiple imputation methods. We performed our analyses in two phases. First, we grouped our subjects into those who were 'amyloid positive' ($n = 165$, with the assumption that Alzheimer's pathology is dominant in this group) and those who were 'amyloid negative' ($n = 53$). In the second phase, we included all 218 subjects with mild cognitive impairment to evaluate the biomarkers in a sample that we assumed to contain a full spectrum of expected pathologies. In a Kaplan–Meier analysis, amyloid positive subjects with mild cognitive impairment were much more likely to progress to dementia within 2 years than amyloid negative subjects with mild cognitive impairment (50 versus 19%). Among amyloid positive subjects with mild cognitive impairment

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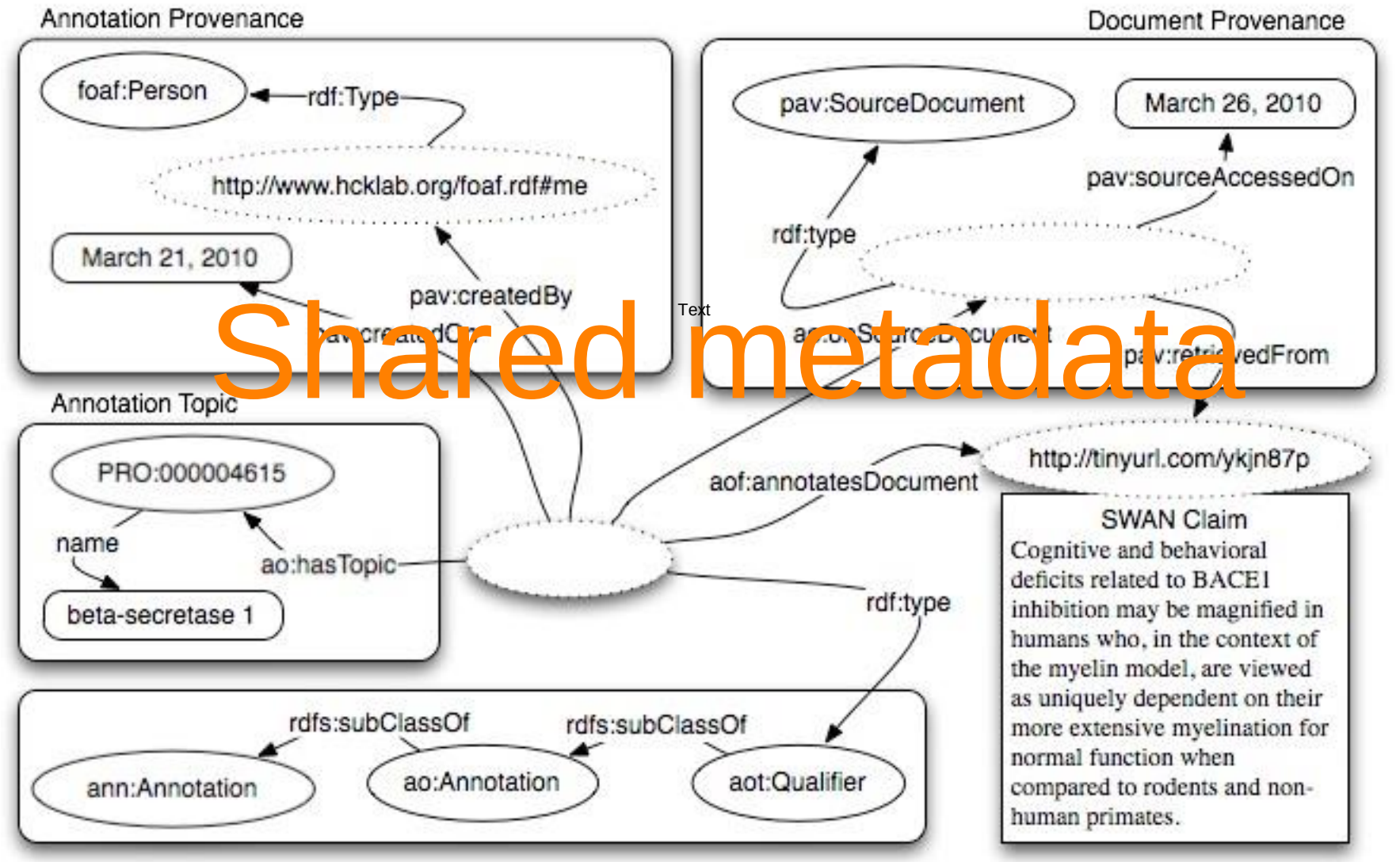
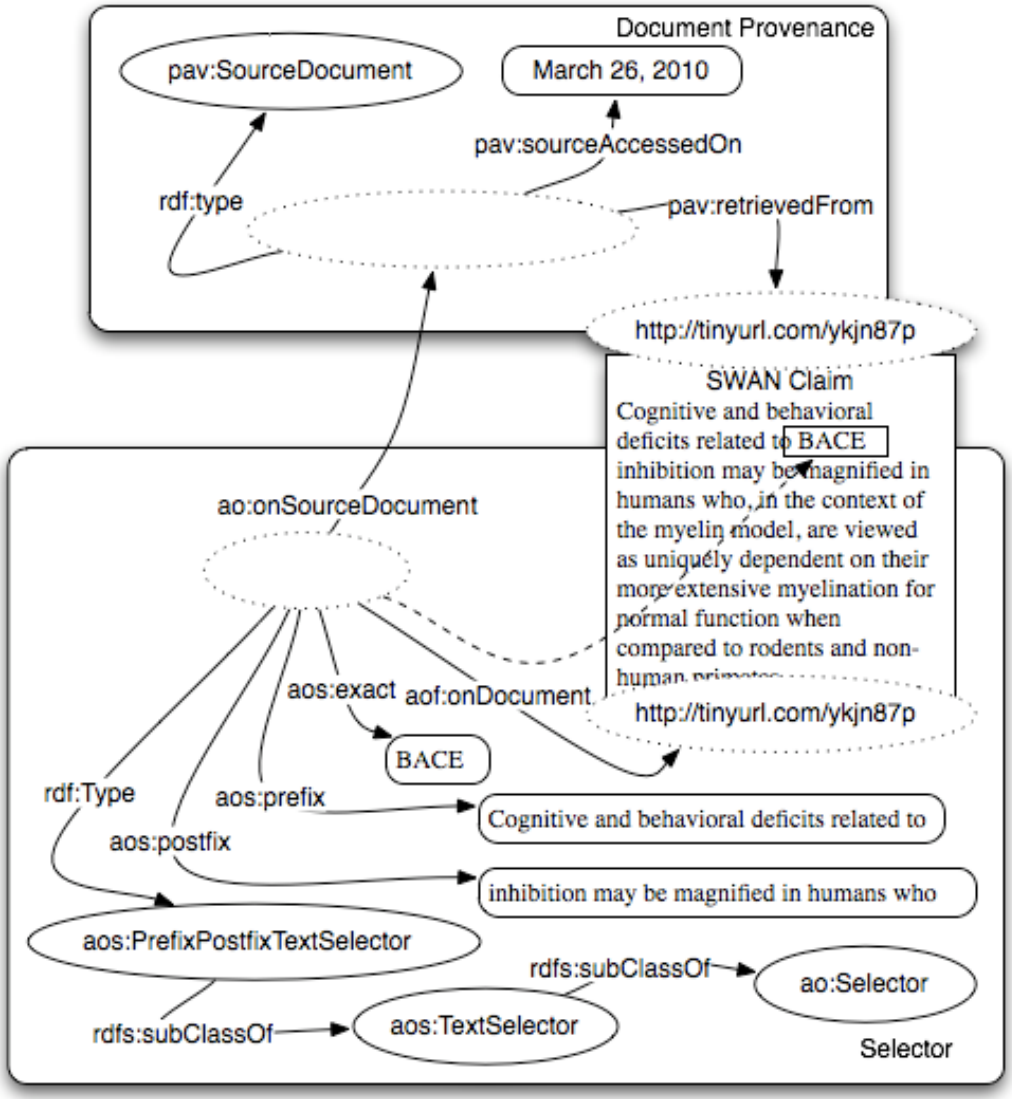
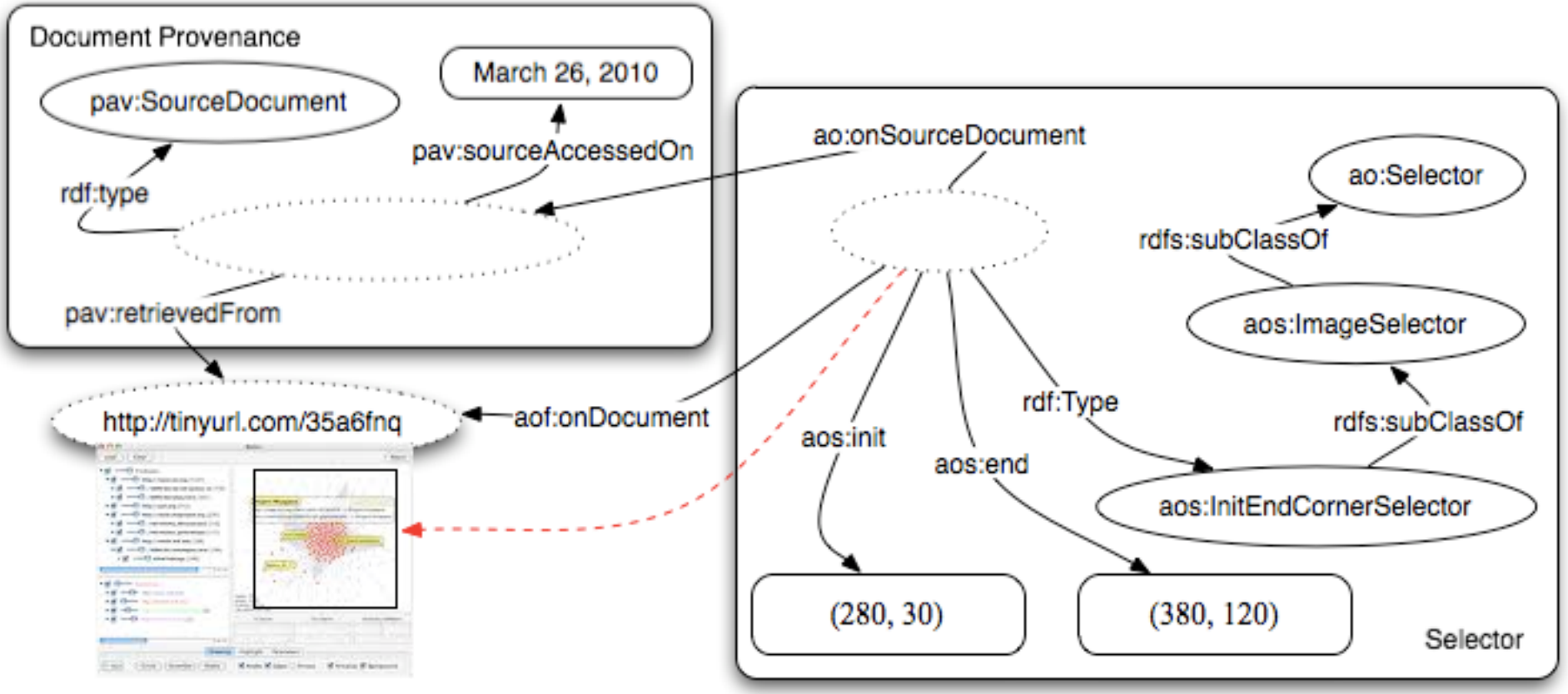
Annotation Ontology (AO)



Localization in text



Localization on image



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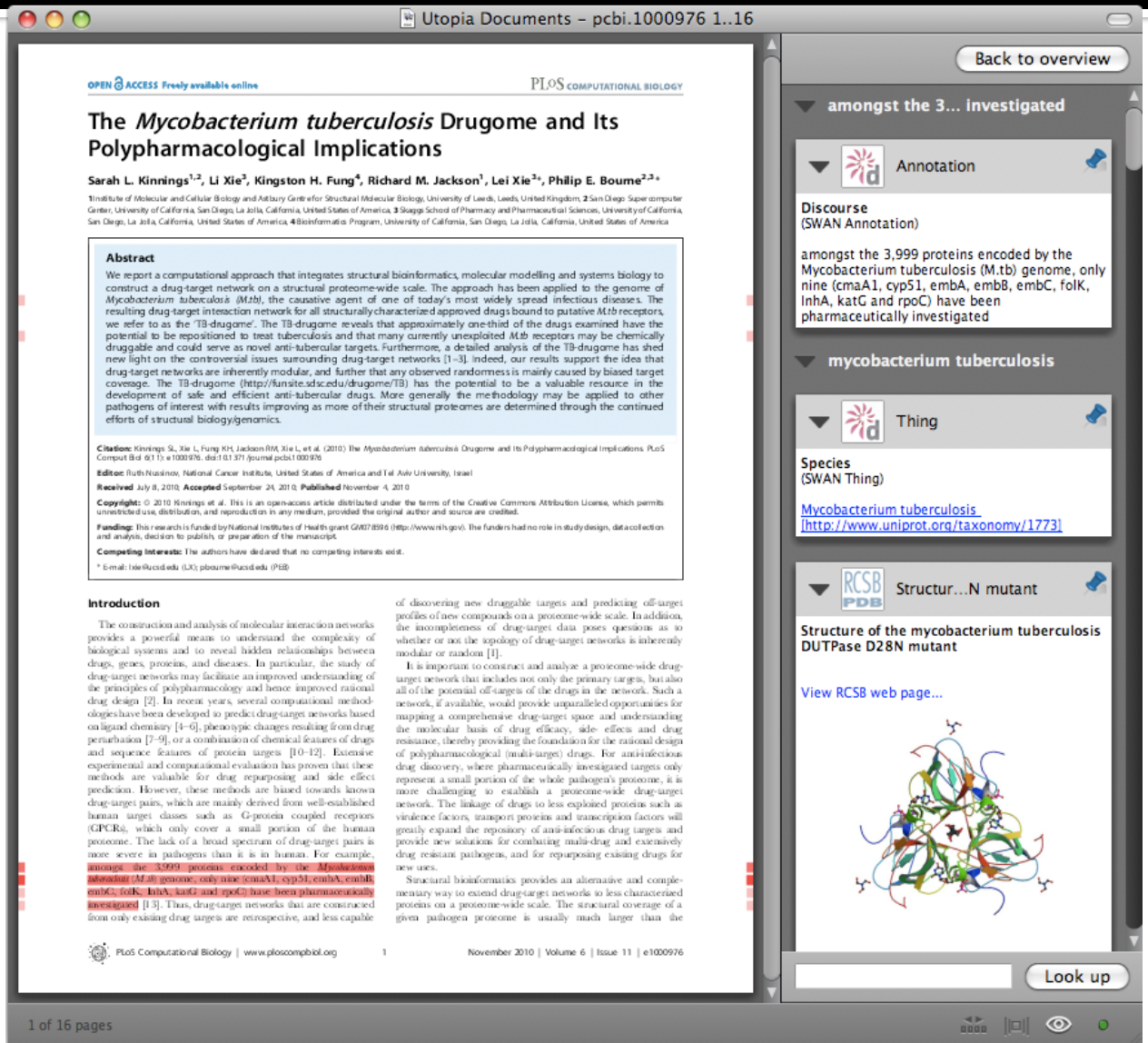
In PDF viewer:
Data mashups linked to text locations



Apache Clerezza / UIMA / AO integration

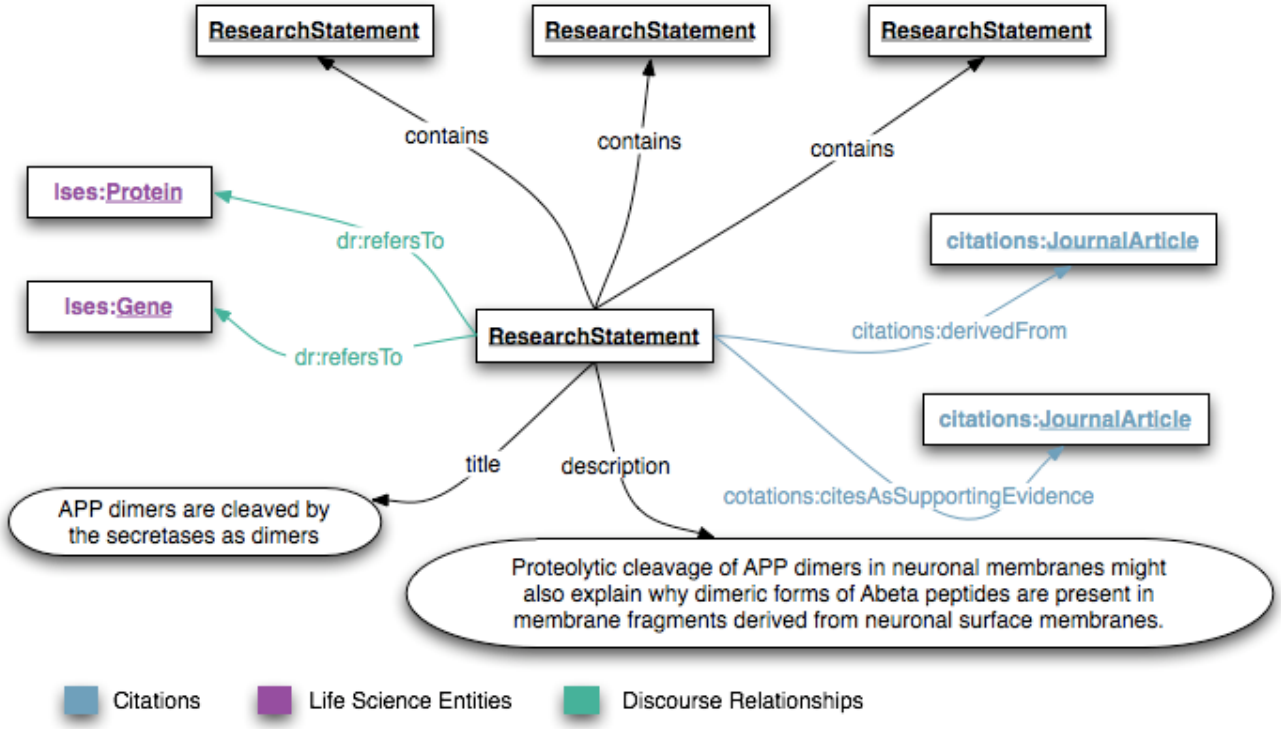
Clerezza integration with Apache UIMA

Introduction to Clerezza-UIMA integration

UIMA is an OASIS standard that allows the definition of analysis pipelines to manage unstructured information and extract structures and semantics around given data.

The Clerezza-UIMA integration brings the power of UIMA inside Clerezza providing reuse of existing UIMA components, definition of new ones in a linked data oriented system.

- AO now integrated w/Clerezza in Apache code…
- AO/RDF output now a standard Clerezza option!


ResearchStatement
ResearchStatement
ResearchStatement
contains
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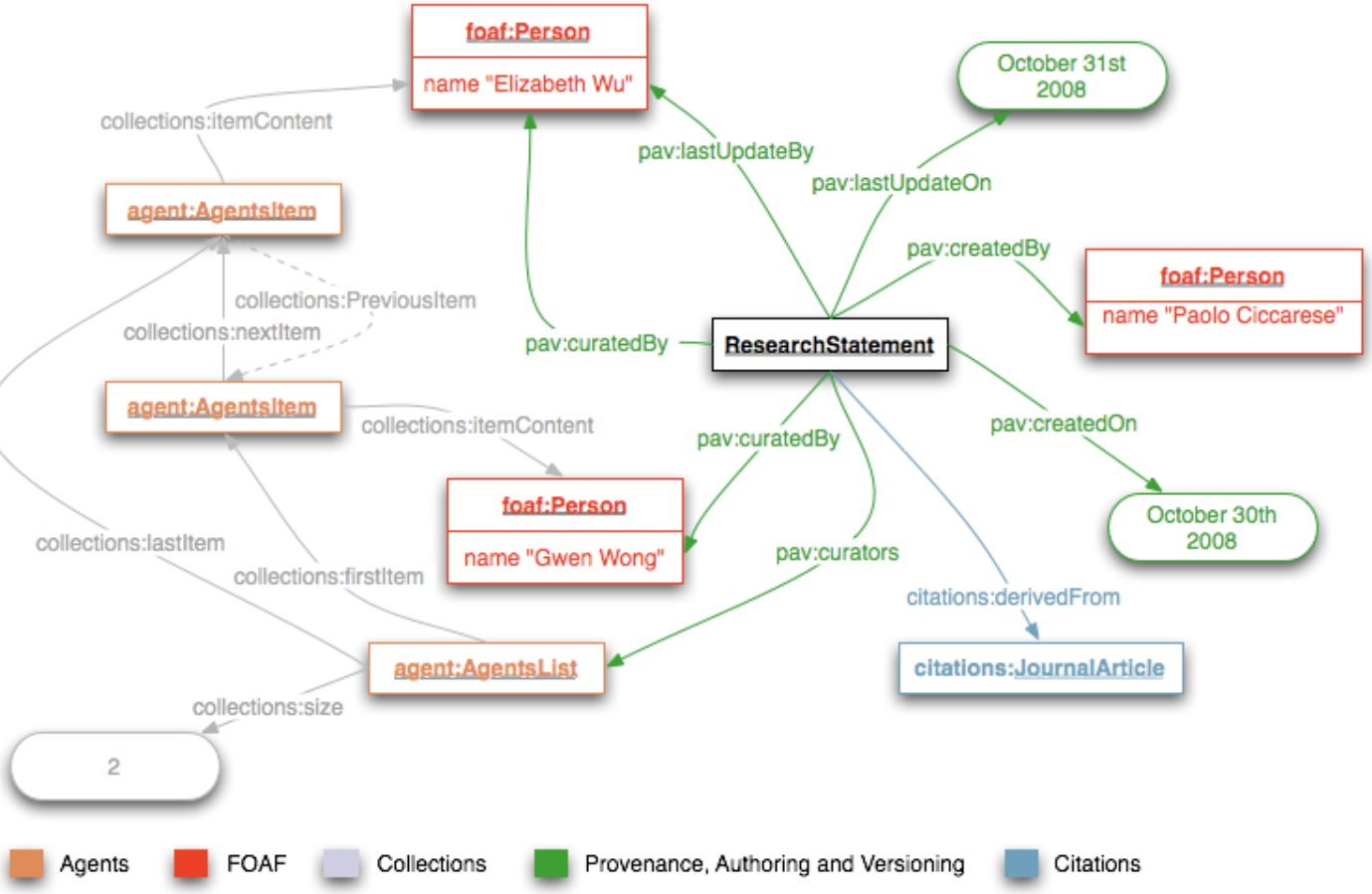
description
APP dimers are cleaved by the secretases as dimers
Proteolytic cleavage of APP dimers in neuronal membranes might also explain why dimeric forms of Abeta peptides are present in membrane fragments derived from neuronal surface membranes.
Citations
Life Science Entities
Discourse Relationships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October 31st 2008
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Agents
FOAF
Collections
Provenance, Authoring and Versioning
Citations

An Alzheimer hypothesis in SWAN

AlzSWAN Knowledge Base

Powered by SWAN (Semantic Web Applications in Neuromedicine)

Log in

search

Home | Statements | Genes-Proteins | Evidence Maps | About

» Statements » Hypotheses

Navigation History

Loss of essential functions of presenilin can explain dementia and neurodegeneration in Alzheimer disease.

0 Comment(s)

Submit a comment | Show graph (Experimental!)

Description:

This hypothesis suggests that pathogenic FAD PS1 mutations cause a general impairment of PS function affecting both γ-secretase-dependent and -independent activities. In this hypothesis, the authors propose that loss of essential functions of presenilins explains the pathologies of AD, and base their hypothesis on their studies of conditional PS1 knockout mice, the effects that FAD PS1 and PS2 mutations have on Aβ40 peptide and AICD production, the effect of gamma secretase inhibitors on Aβ peptide production, and the observations of mutant PS in Frontotemporal Dementia in the absence of amyloid.

Authors: Shen J Kelleher R

Derived from:

Shen, Jie

Kelleher, Raymond J

Shen J, Kelleher R

The presenilin hypothesis of Alzheimer's disease: evidence for a loss-of-function pathogenic mechanism.

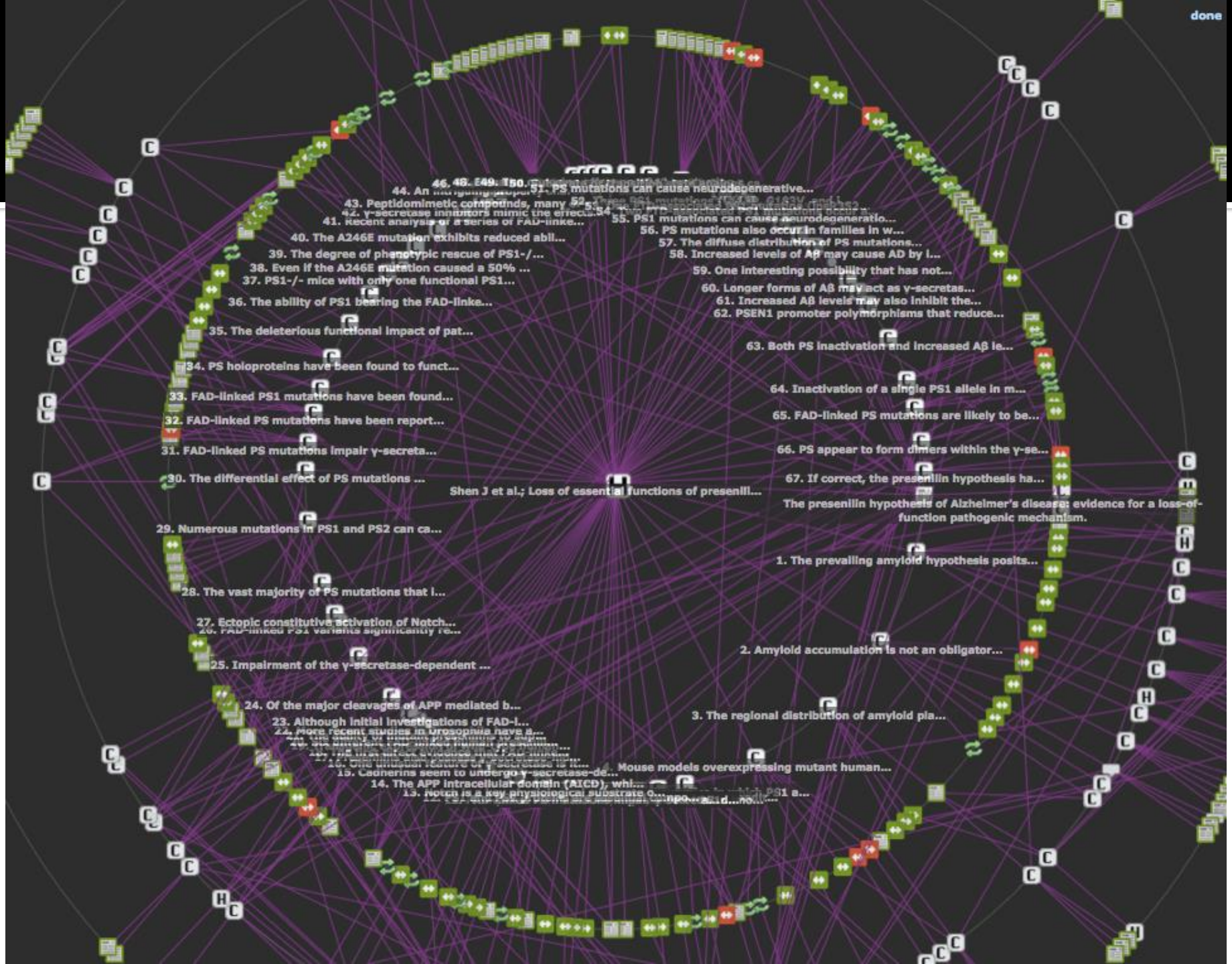
Proceedings of the National Academy of Sciences of the United States of America. 2007 Jan 9;104(2):403-9

Contains 66 Statements:

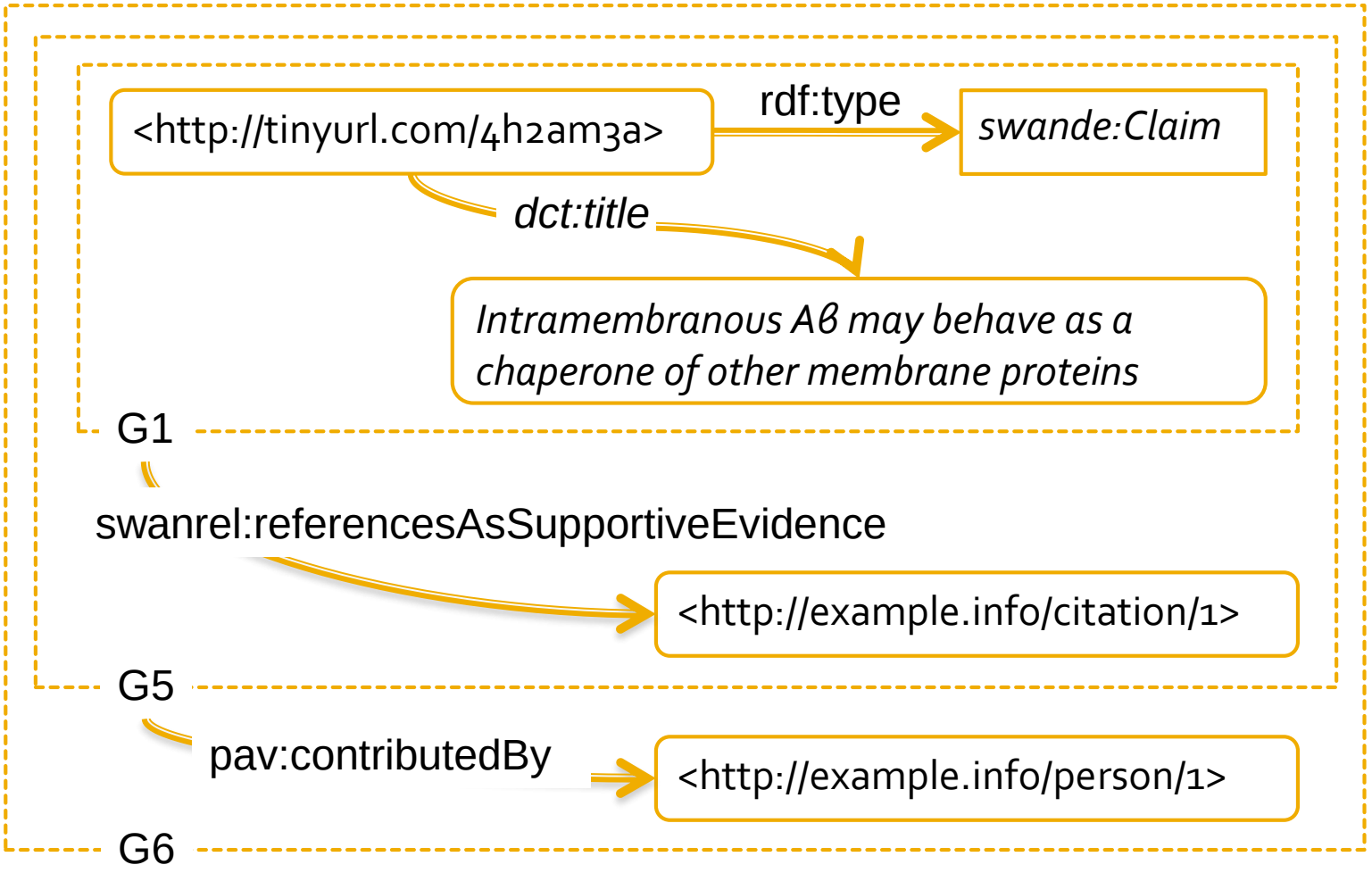
67 with evidence | 0 without evidence | and a total of: 119 citations ; Related to external statements: 35 consistent | 11 inconsistent | 0 discussed | 21 with alternatives

Expand All Details | Collapse All Details

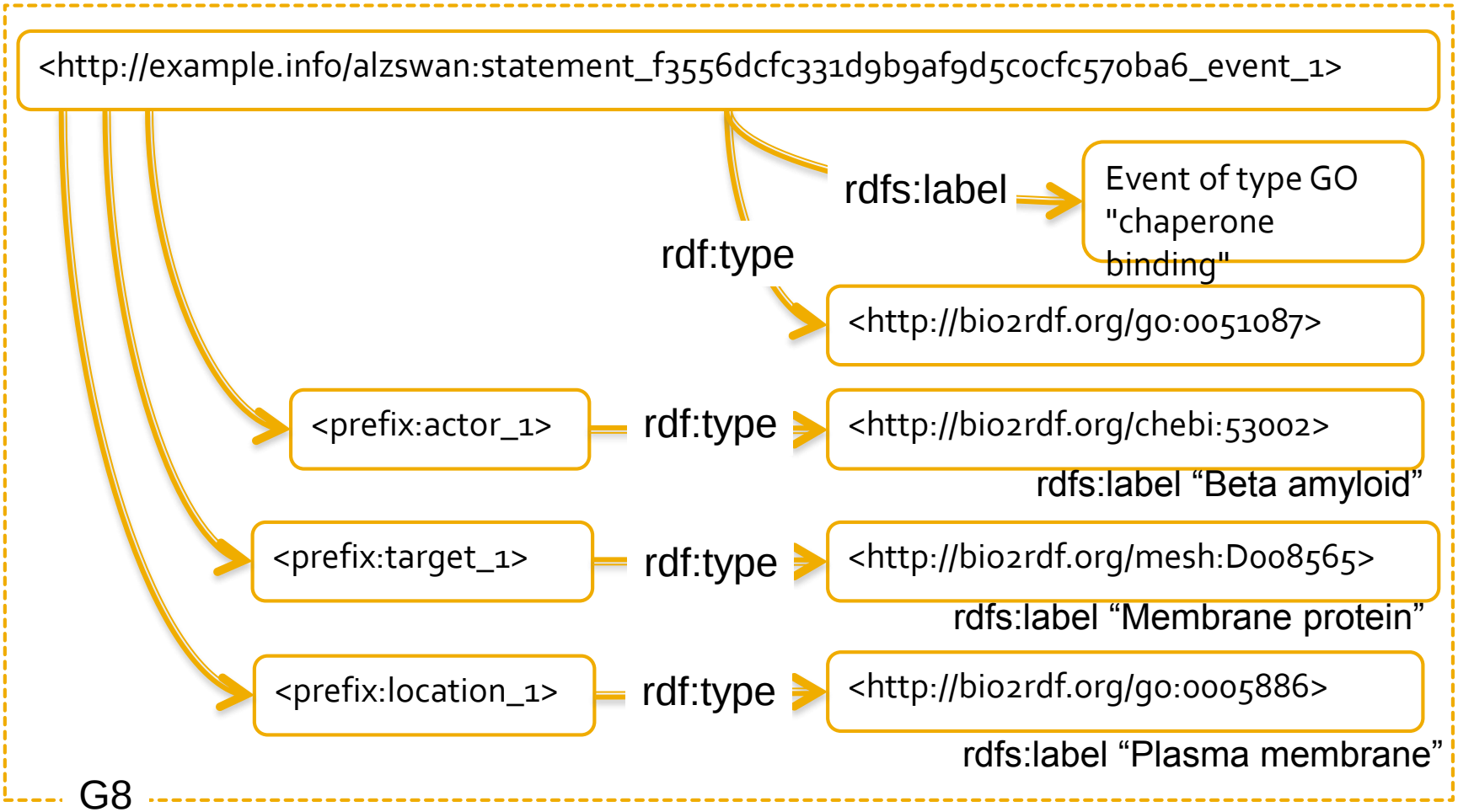
1. The prevailing amyloid hypothesis posits that accumulation of Aβ peptides, particularly the more hydrophobic and aggregation-prone Aβ42, triggers a pathogenic cascade, leading to neurodegeneration in AD.
   SHOW Details | Supporting(1) | Consistent(6) | Genes/Proteins: (1)
2. Amyloid accumulation is not an obligatory feature of dementia or neurodegeneration because neurodegenerative dementias lacking amyloid pathology (e.g., FTD) have been well described.
   SHOW Details | Supporting(1) | Consistent(5) | Inconsistent(1) | Alternative to: (1)
3. The regional distribution of amyloid plaques correlates poorly with the pattern and severity of dementia in AD, whereas synaptic loss correlates well with these clinical features.
   SHOW Details | Supporting(1) | Consistent(3)
4. Mouse models overexpressing mutant human APP have reproduced overproduction of Aβ peptides and progressive amyloid deposition, but they have largely failed to reproduce neurodegeneration.
   SHOW Details | Supporting(1) | Consistent(3) | Inconsistent(2) | Alternative to: (2) | Genes/Proteins: (1)
5. Conditional knockout mice in which PS1 and PS2 are selectively inactivated in the adult cerebral cortex develop age-related, progressive neurodegeneration characterized by hallmarks of AD neuropathology, including synaptic loss, neuronal cell death, astrogliosis and tau hyperphosphorylation.
   SHOW Details | Supporting(1) | Consistent(1) | Inconsistent(1) | Alternative to: (1) | Genes/Proteins: (2)
6. Inactivation of PS1 expression in conditional knockout mice occurs at 4 weeks of age postnatally, and neurodegeneration becomes evident by 4 months of age. By the age of 9 months, 24% of cortical neurons



Ciccarese-Groth nanopublications: Claim + Author's evidence

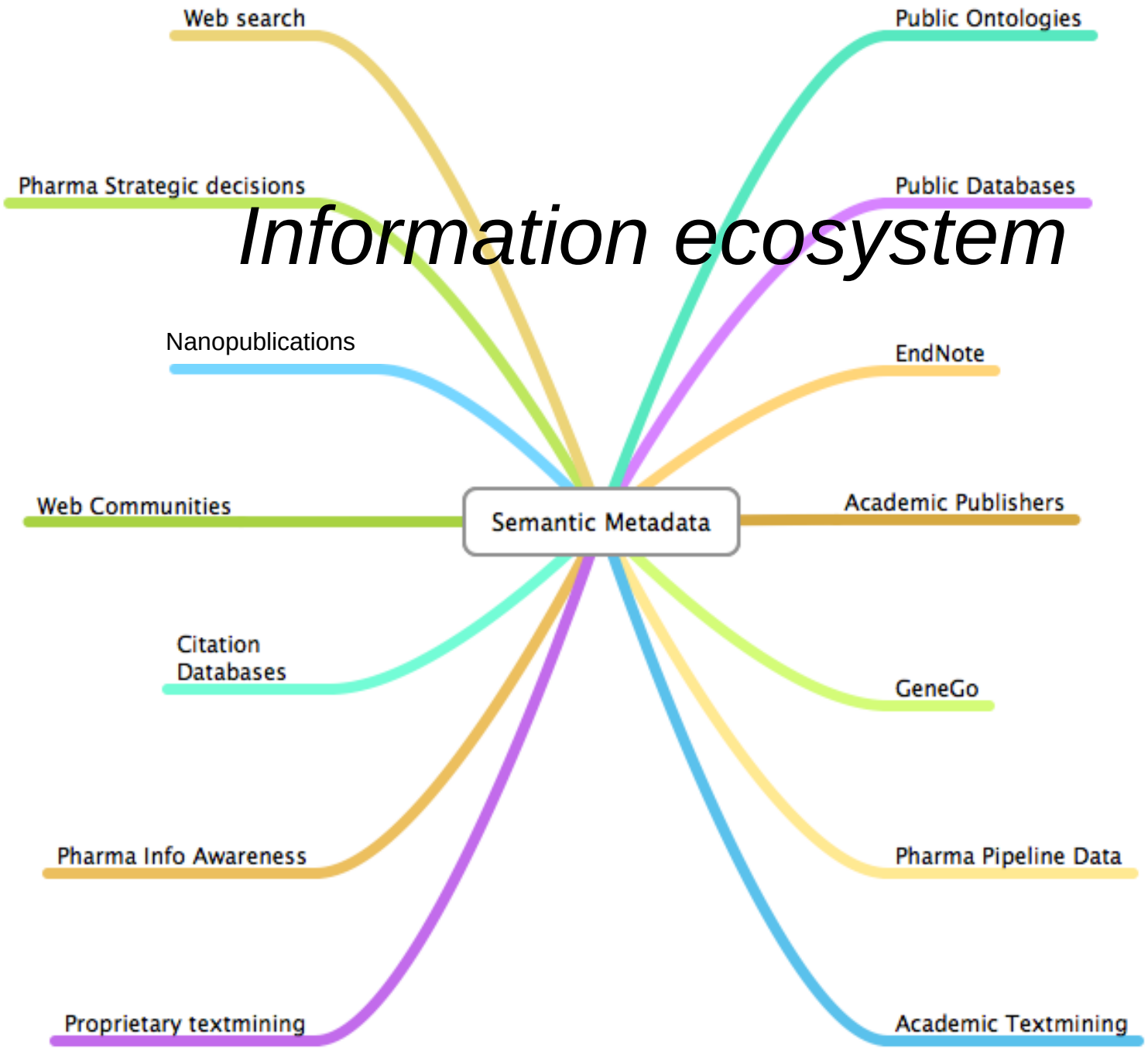


Ciccarese-Groth nanopublications: "triplified" claims

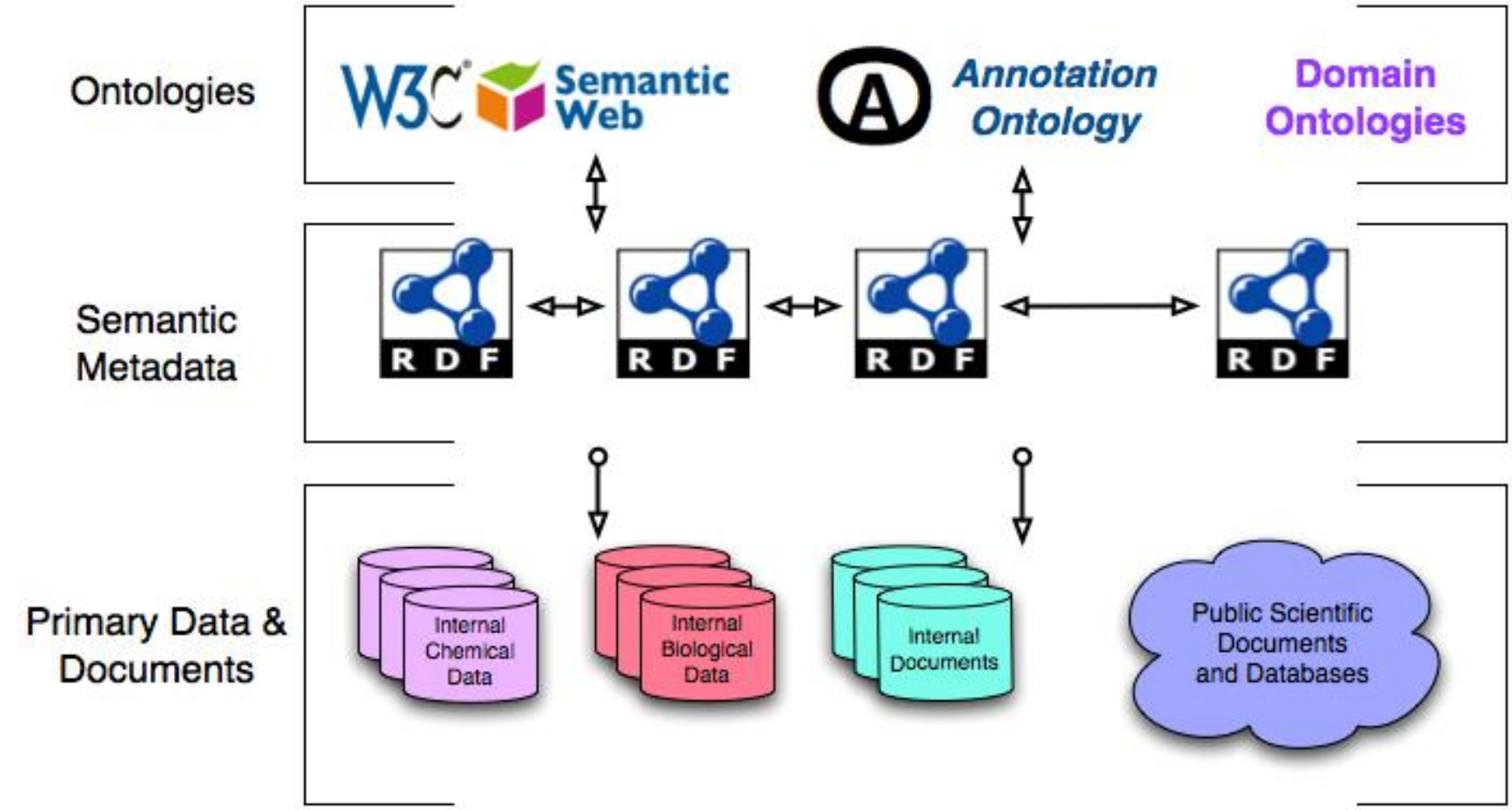


With many thanks to Nigam Shah, Stanford University

Information ecosystem



Open Enterprise Semantic Model



Summary

- Curing complex medical disorders goes hand in hand with next-gen biomedical communications
- Web 3.0 provides the technology framework
- Semantic annotation, hypothesis management, nanopubs: tools for next-gen biomed comms .
- Requires / enables international collaborations of biomedical researchers and informaticians.
- Open enterprise model with semantic metadata.
- Semi-open privacy model: targeted sharing.