

Informatics approaches for agile biomedical research

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Harvard Medical School &
Massachusetts General Hospital

October 17, 2011

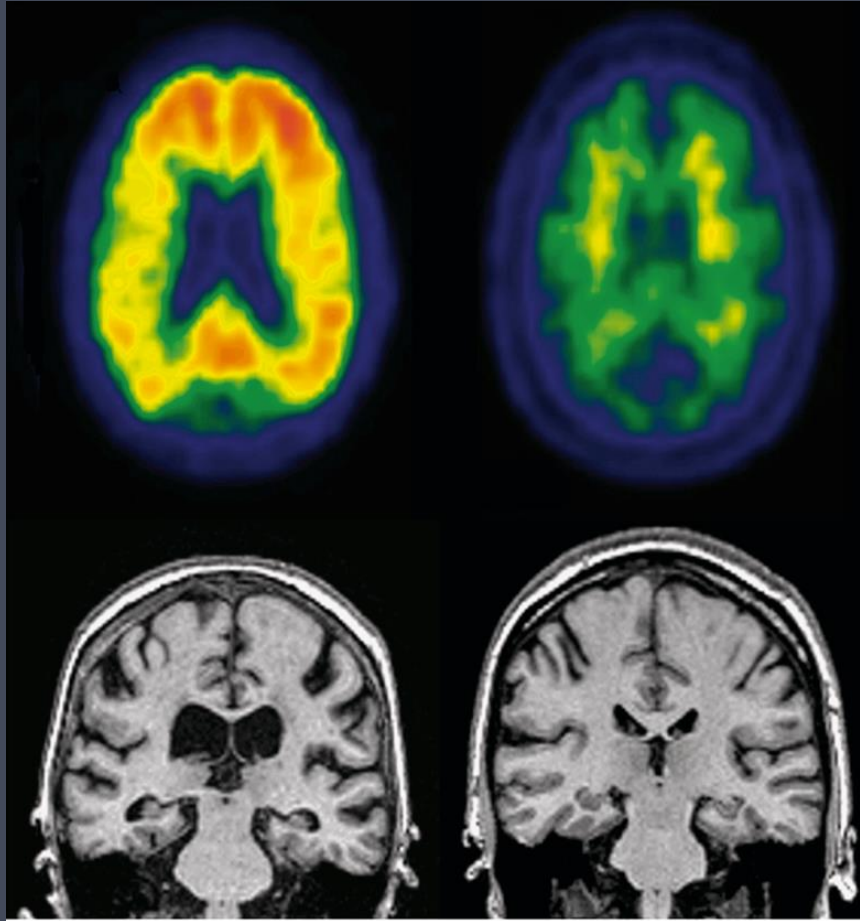


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Abstract

- 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 A β load predicted shorter time-to-progression”



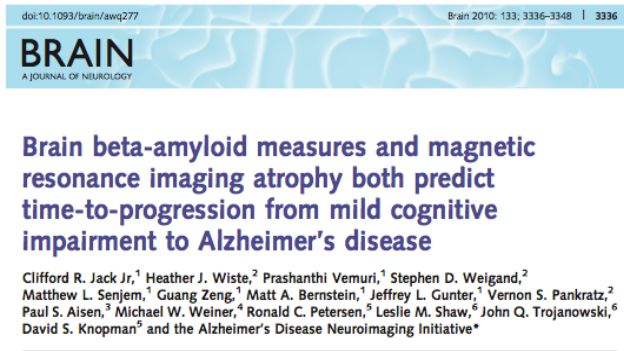
Brain. 2010 Nov;133(Pt 11):3336-3348.

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 unbelievable,...”*



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

**[rare event]*

Biomarkers of brain $\text{A}\beta$ amyloid deposition can be measured either by cerebrospinal fluid (CSF) or Pittsburgh compound B positron emission tomography imaging. Our objective was to evaluate the ability of $\text{A}\beta$ 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 $\text{A}\beta_{42}$ and Pittsburgh compound B positron emission tomography measures to produce equivalent measures of brain $\text{A}\beta$ 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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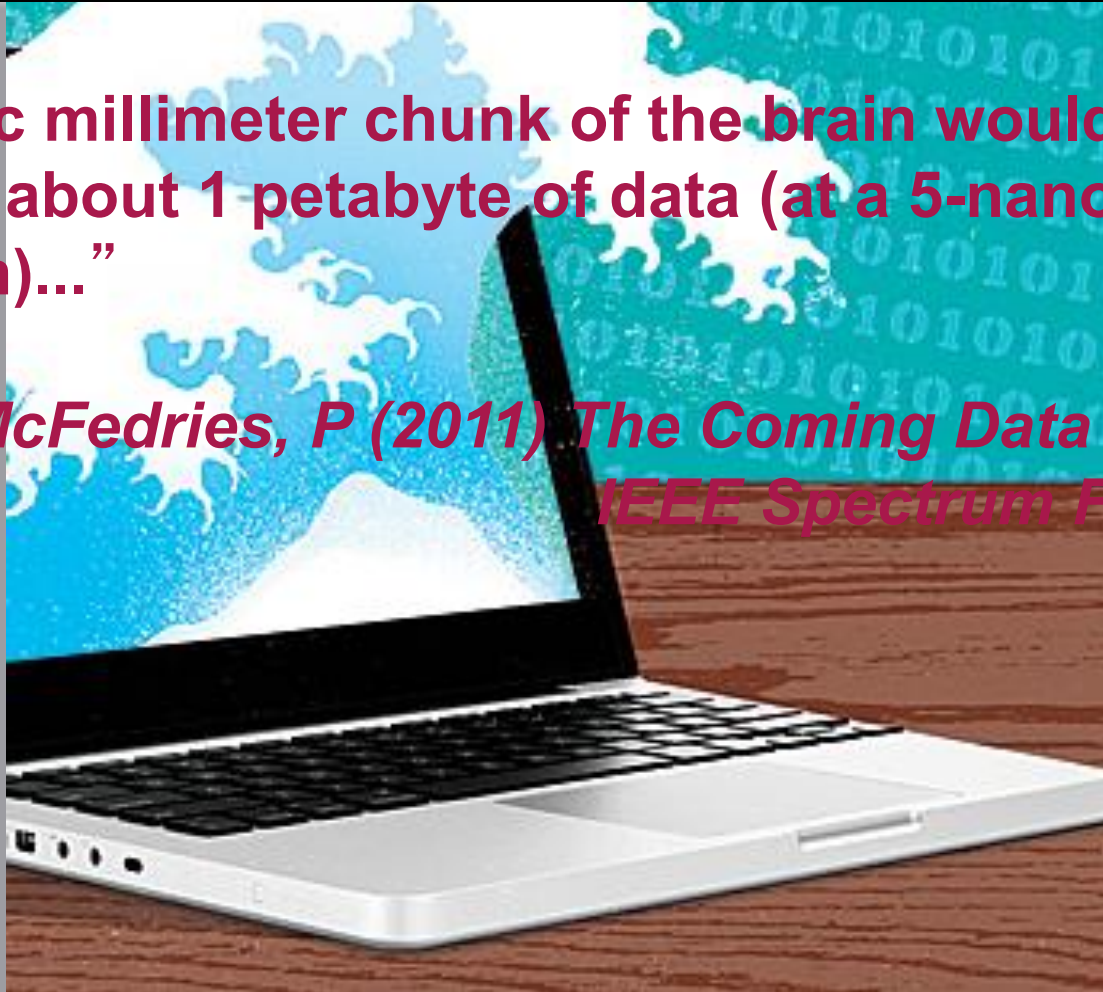
John Trojanowski, MD, PhD
U Penn Medical School

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

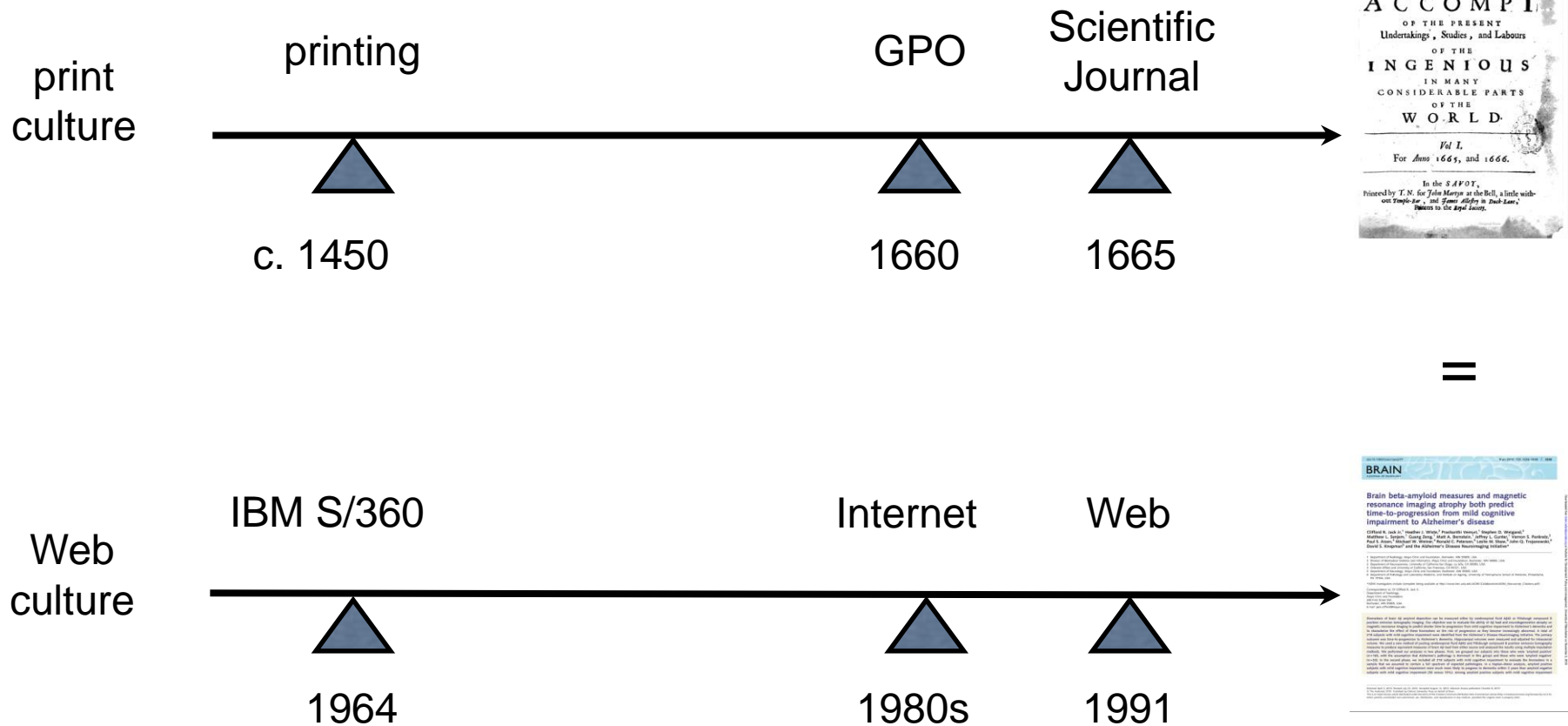
...with inadequately referenced primary data?

“... 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



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	8	7	6 40	4	3 3	7 3	.
1	9	8	7 45	4	6 3	10 3	2.
2	11	10	8 50	4	9 4	0 3	4.
2	0 1	11	9 55	5	0 4	3 3	6.
3	0 1	1 0	10 60	5	2 4	6 3	8.
3	1 2	1	11 65	5	4 4	8 3	10
4	0 1	4 1	0 70	5	7 4	10 3	.
4	6 1	5 1	7 5	5	9 5	0 4	2.
5	0 1	6 1	1. 80	5	11 5	2 4	5

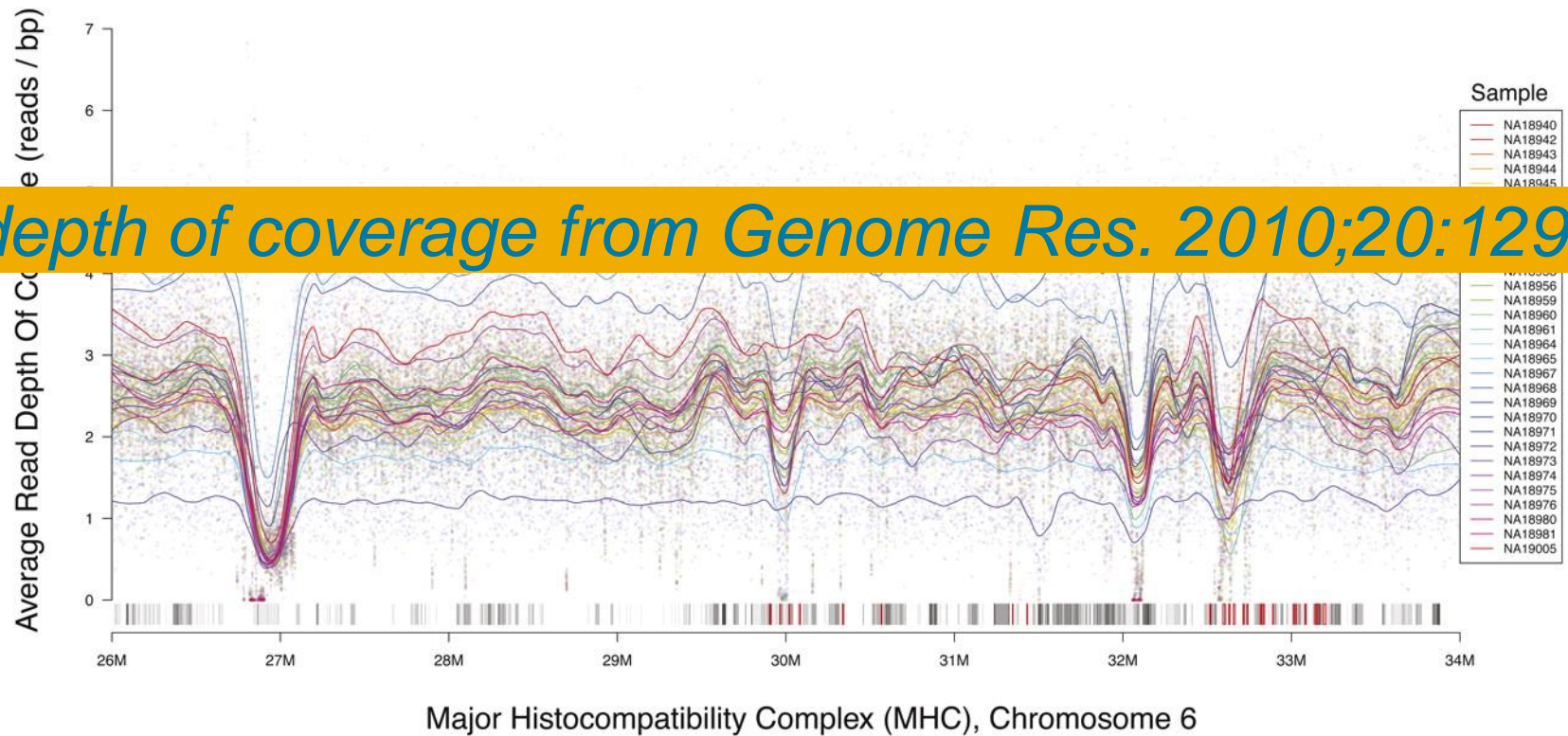
table of data from Philos Trans R Soc Lond 1(4):56

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.

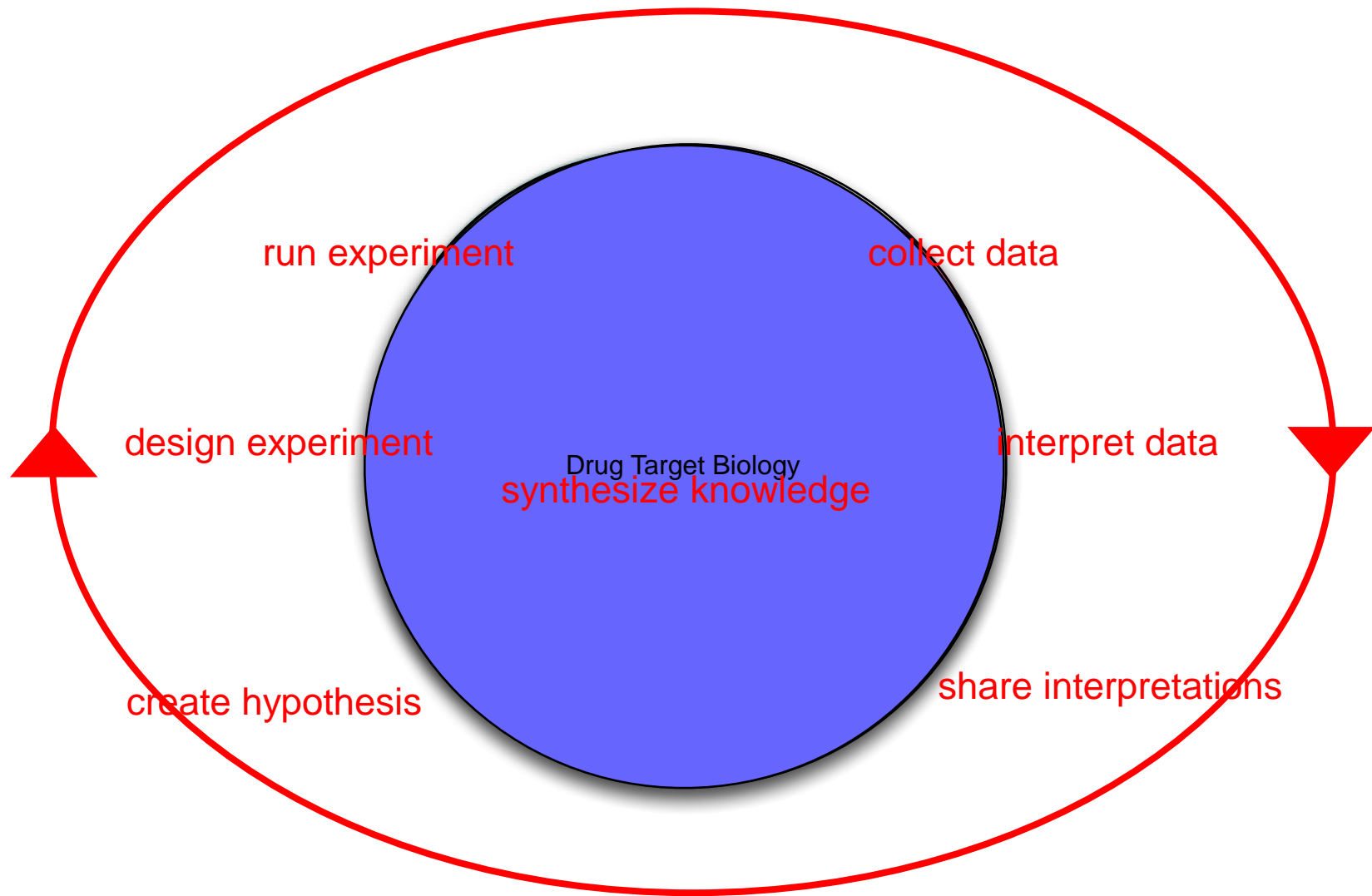
In the above-mentioned *French Tra&*, there are, besides several other particulars, to be represented in due place, contained some *Considerations* of Monsieur *Auzout* upon Mr. *Hook's* New Engine for grinding *Optick-Glasses*. Where he premises in *General* his thoughts touching the working of *Great 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

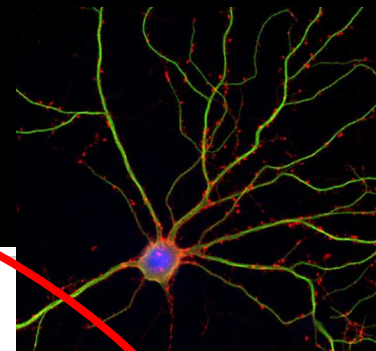
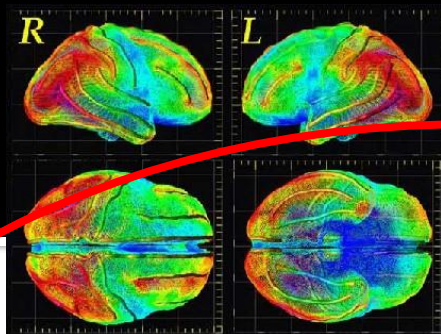
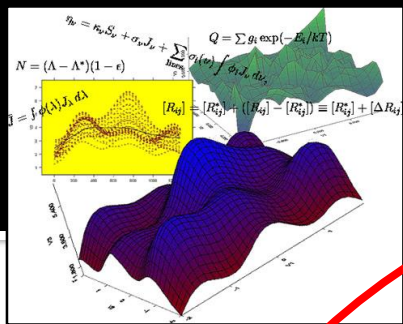
MHC depth of coverage in JPT samples of the 1000 Genomes Project pilot 2, calculated using the GATK depth of coverage tool.



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

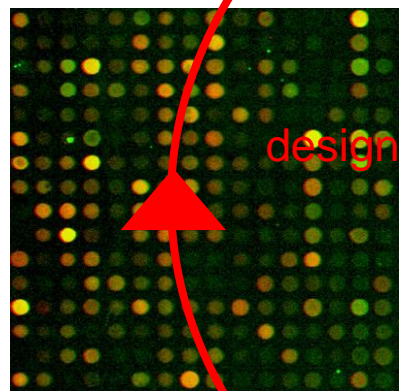




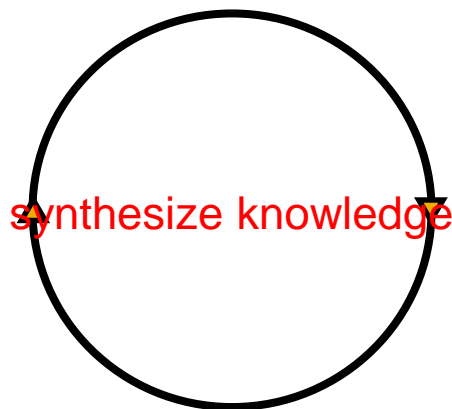


run experiment

collect data



design experiment



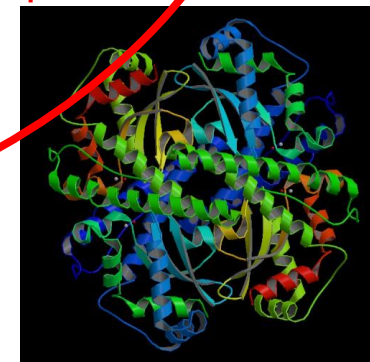
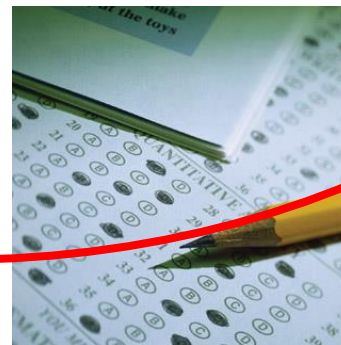
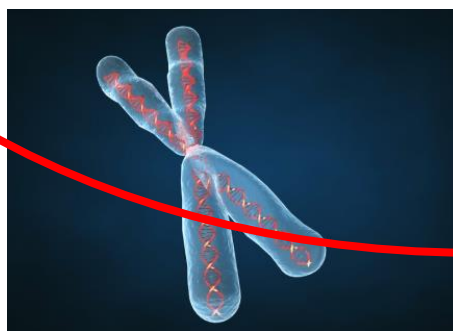
synthesize knowledge

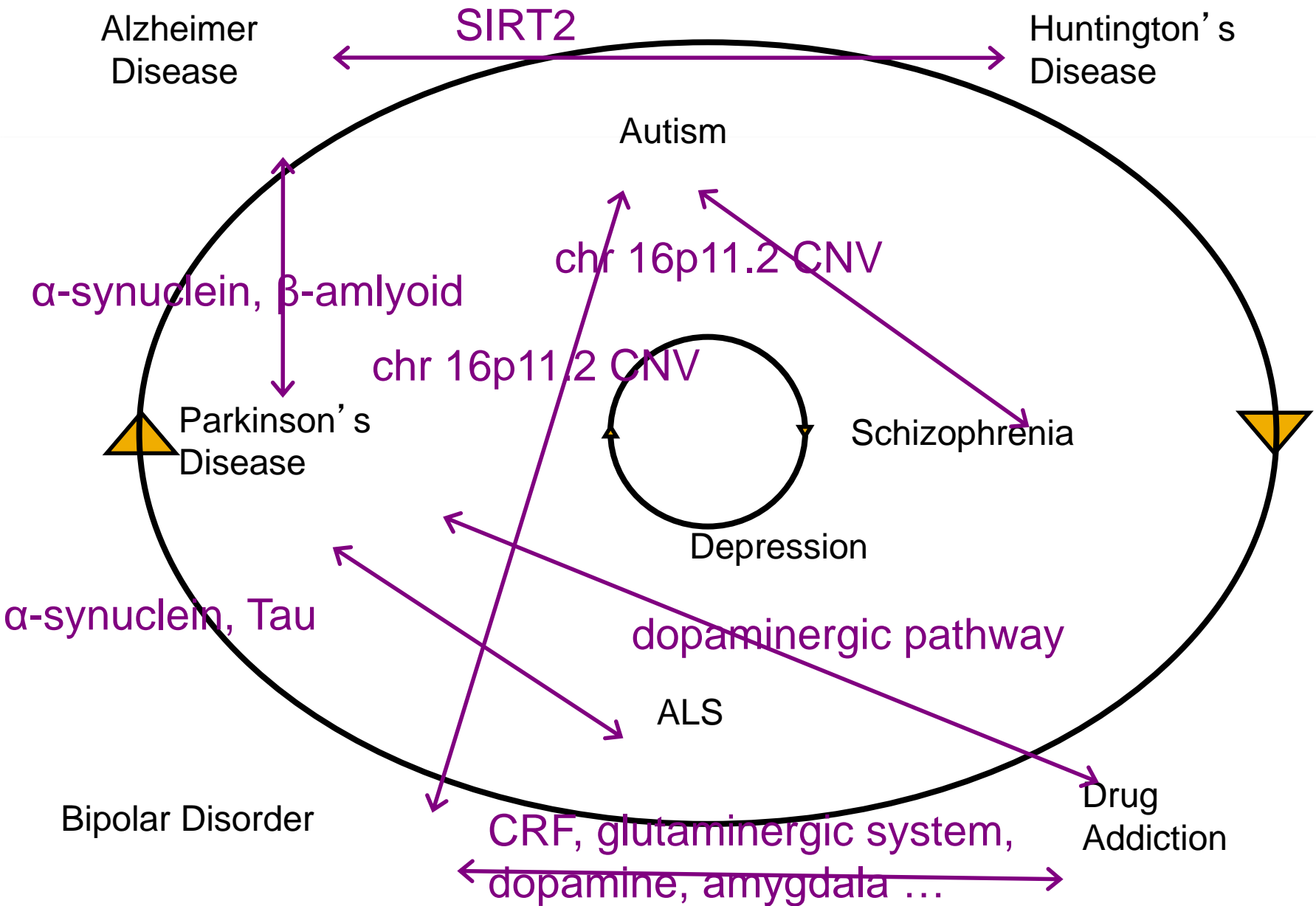
interpret data



create hypothesis

share interpretations





Web 2.0: Biomedical “collaboratories”



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Create or view entries with a click
Search within a Lab Notebook
Improved navigation
Jump between entries and blogs

New! One-click setup

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See all new users.

OWW Community Blog

SB5.0: The Fifth International Meeting on Synthetic Biology (Stanford, June 15-17, 2011)

Dear Synthetic Biology Community, We are excited to announce The Fifth International Meeting on Synthetic Biology (SB5.0) on June 15 – 17, 2011 at Stanford University.

UPDATE: Glitch with user pages

Update - 12:30am Monday November 8, 2010 We have fixed a bug that caused the Biblio extension, which was disabled until we can devise a fix.

BioBricks Foundation now managing OWW tech support


The BioBricks Foundation is pleased to announce that we are now managing technical support for OpenWetWare. The BBF is a nonprofit organization



News

LRK2 and Biomarkers: Funding Opportunities

The Michael J. Fox Foundation for Parkinson's Research announced two funding opportunities focused on LRRK2 and biomarkers. >>



Latest News

6th Annual Meeting of The Genetic Epidemiology of Parkinson's Disease Consortium (GEO-PD)

The 6th Annual Meeting of The Genetic Epidemiology of Parkinson's Disease Consortium (GEO-PD) will be held in Evanston Chicago from September 19 to 21, 2011. ...

See more: [Research News](#) 06 Jul 2011

The Michael J. Fox Foundation Announces the Generation of a Novel LRRK2 Antibody for PD Research

NEW YORK, June 30, 2011 — The Michael J. Fox Foundation for Parkinson's Research (MJFF) is announcing the availability of new mouse monoclonal antibodies directed against Leucine-Rich Repeat Kinase 2 ...

See more: [PDOR Spotlight](#) 30 Jun 2011

Buck Institute study: Lithium may help halt progression of Parkinson's

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Article describes evidence gaps affecting clinical practice

Dealing With Data Overload? A New Tool Automates Meta-analysis of fMRI Studies

A conversation with NeuroSynth developer Tal Yarkoni

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Discussions

2011 Meeting of The Genetic Epidemiology of Parkinson's Disease Consortium (GEO-PD)

The Genetic Epidemiology of Parkinson's Disease

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News

Lancet Review: Most Chronic Pain Treatments Don't Work

Article describes evidence gaps affecting clinical practice

Dealing With Data Overload? A New Tool Automates Meta-analysis of fMRI Studies

A conversation with NeuroSynth developer Tal Yarkoni

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Specificity Versus Patterning Theory: Continuing the Debate

Allan Basbaum

Does the brain process and interpret innocuous noxious stimuli differently? ...

Pain Research Forum

Specificity Versus Patterning Theory: Continuing the Debate

Neurologists have by tradition separated disorders of the central nervous system from those affecting the peripheral nervous system. Arguments for...

Discussions

2011 Meeting of The Genetic Epidemiology of Parkinson's Disease Consortium (GEO-PD)

The Genetic Epidemiology of Parkinson's Disease

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Trichostatin A, Angiotensin II, and Neuregulin-1 in ALS

9 July 2011. Sometimes a history of research can help to solve a problem...

Faster, Safer Ways to Cook Up Dopaminergic Neurons

9 July 2011. Effective cell replacement therapy for Parkinson's disease has been an elusive target...

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thesis about where and how e starts off is gaining ground vide clues in its support. feiko Braak and Kelly Del : University of Ulm in scribed the distribution of hallmarks of PD central and peripheral f deceased patients.

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Parkinson's GWAS—Genes Could Explain a Quarter of Late-Onset PD Risk

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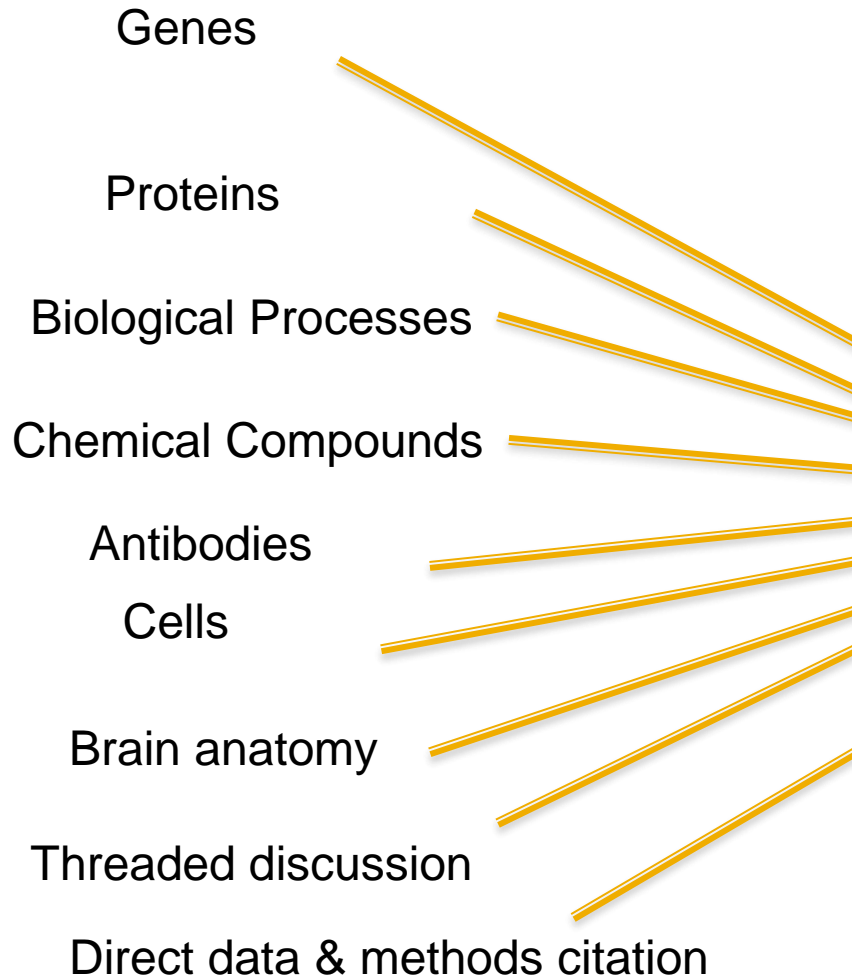
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Supervised automatic annotation



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. Knopman⁵ and the Alzheimer's Disease Neuroimaging Initiative*

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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/ADNII/Collaboration/ADNI_Manuscript_Citations.pdf).

Correspondence to: Dr Clifford R. Jack Jr,
Department of Radiology,
Mayo Clinic and Foundation,
200 First Street SW,
Rochester, MN 55905, USA.
E-mail: jack.clifford@mayo.edu

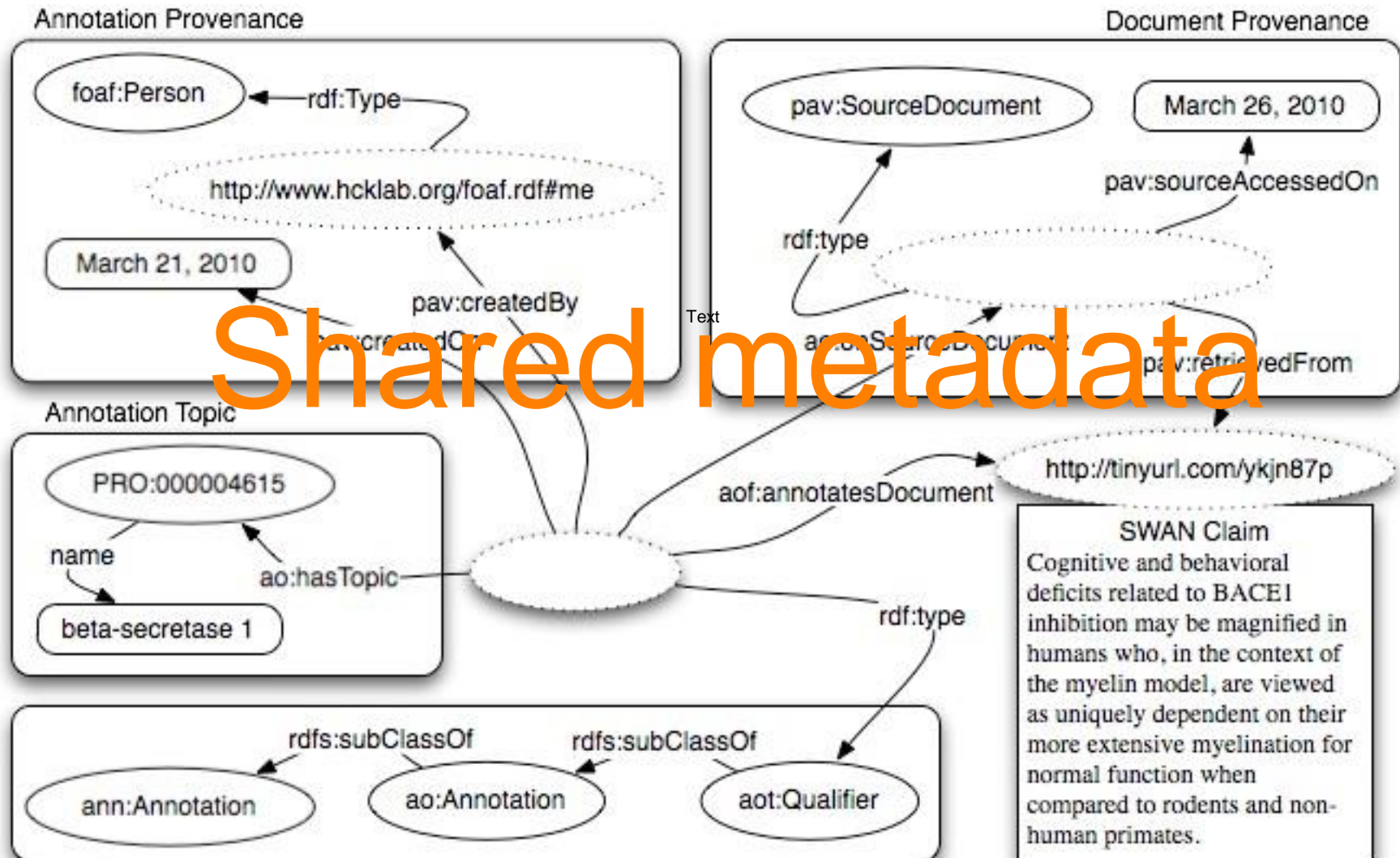
Biomarkers of brain A β amyloid deposition can be measured either by cerebrospinal fluid A β 42 or Pittsburgh compound B positron emission tomography imaging. Our objective was to evaluate the ability of A β load and neurodegenerative atrophy on magnetic resonance imaging to predict shorter time-to-progression 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 A β 42 and Pittsburgh compound B positron emission tomography measures to produce equivalent measures of brain A β 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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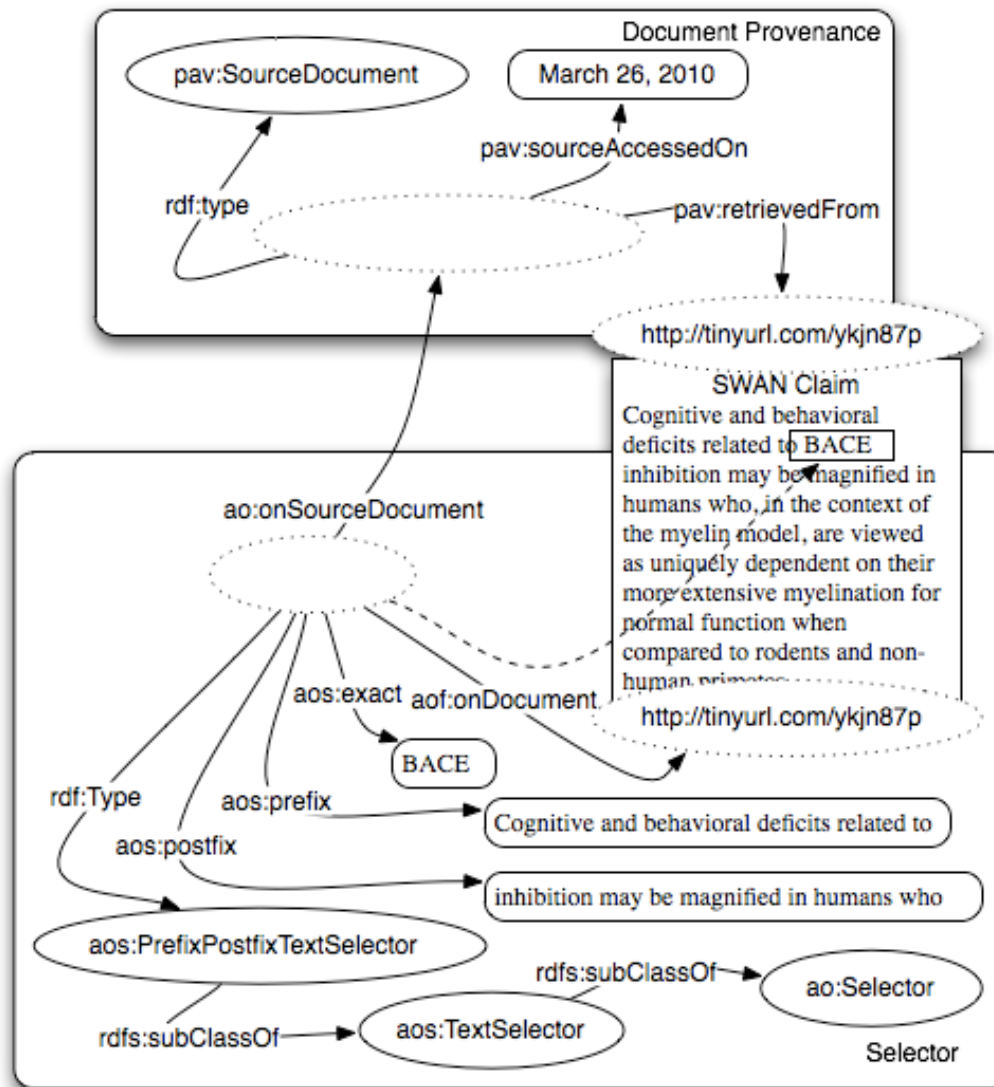
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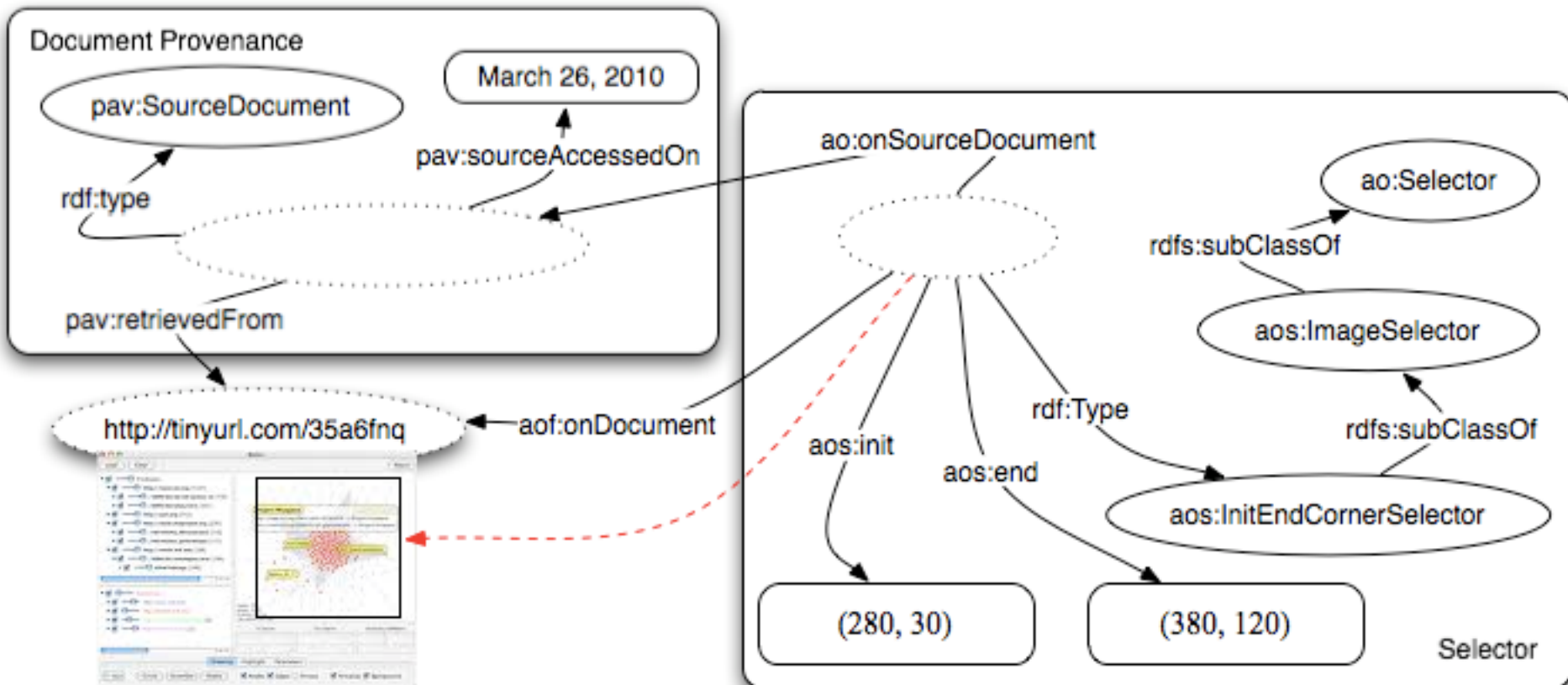
Annotation Ontology (AO)



Localization in text



Localization on image



Export AO RDF

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<rdf:type rdf:resource="http://purl.org/ao/AnnotationSet"/>
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In PDF viewer: Data mashups linked to text locations

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PLOS COMPUTATIONAL BIOLOGY

The *Mycobacterium tuberculosis* Drugome and Its Polypharmacological Implications

Sarah L. Kinnings^{1,2}, Li Xie³, Kingston H. Fung⁴, Richard M. Jackson¹, Lei Xie^{3*}, Philip E. Bourne^{2,3*}

¹Institute of Molecular and Cellular Biology and Arthur Centre for Structural Molecular Biology, University of Leeds, Leeds, United Kingdom, ²San Diego Supercomputer Center, University of California, San Diego, La Jolla, California, United States of America, ³Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, California, United States of America, ⁴Bioinformatics Program, University of California, San Diego, La Jolla, California, United States of America

Abstract

We report a computational approach that integrates structural bioinformatics, molecular modelling and systems biology to construct a drug-target network on a structural proteome-wide scale. The approach has been applied to the genome of *Mycobacterium tuberculosis* (*M.tb*), the causative agent of one of today's most widely spread infectious diseases. The resulting drug-target interaction network for all structurally characterized approved drugs bound to putative *M.tb* receptors, we refer to as the 'TB-drugome'. The TB-drugome reveals that approximately one-third of the drugs examined have the potential to be repositioned to treat tuberculosis and that many currently unexploited *M.tb* receptors may be chemically druggable and could serve as novel anti-tubercular targets. Furthermore, a detailed analysis of the TB-drugome has shed new light on the controversial issues surrounding drug-target networks [1–3]. Indeed, our results support the idea that drug-target networks are inherently modular, and further that any observed randomness is mainly caused by biased target coverage. The TB-drugome (<http://ksite.sdsc.edu/drugome/TB>) has the potential to be a valuable resource in the development of safe and efficient anti-tubercular drugs. More generally the methodology may be applied to other pathogens of interest with results improving as more of their structural proteomes are determined through the continued efforts of structural biology/genomics.

Citation: Kinnings SL, Xie L, Fung KH, Jackson RM, Xie L et al. (2010) The *Mycobacterium tuberculosis* Drugome and Its Polypharmacological Implications. *PLOS Comput Biol* 6(11): e1000976. doi:10.1371/journal.pcbi.1000976

Editor: Ruth Nussinov, National Cancer Institute, United States of America and Tel Aviv University, Israel

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Funding: This research is funded by National Institutes of Health grant GM078916 (<http://www.nih.gov>). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: lei@ksite.ucsd.edu (LX); pb@ksite.ucsd.edu (PEB)

Introduction

The construction and analysis of molecular interaction networks provides a powerful means to understand the complexity of biological systems and to reveal hidden relationships between drugs, genes, proteins, and diseases. In particular, the study of drug-target networks may facilitate an improved understanding of the principles of polypharmacology and hence improved rational drug design [2]. In recent years, several computational methodologies have been developed to predict drug-target networks based on ligand chemistry [4–6], phenotypic changes resulting from drug perturbation [7–9], or a combination of chemical features of drugs and sequence features of protein targets [10–12]. Extensive experimental and computational evaluation has proven that these methods are valuable for drug repurposing and side effect prediction. However, these methods are biased towards known drug-target pairs, which are mainly derived from well-established human target classes such as G-protein coupled receptors (GPCRs), which only cover a small portion of the human proteome. The lack of a broad spectrum of drug-target pairs is more severe in pathogens than it is in human. For example, amongst the 3,999 proteins encoded by the *Mycobacterium tuberculosis* (*M.tb*) genome, only nine (*cmaA1*, *cyp51*, *embA*, *embB*, *embC*, *folK*, *inhA*, *katG* and *rpoC*) have been pharmaceutically investigated [13]. Thus, drug-target networks that are constructed from only existing drug targets are retrospective, and less capable of discovering new druggable targets and predicting off-target profiles of new compounds on a proteome-wide scale. In addition, the incompleteness of drug-target data poses questions as to whether or not the topology of drug-target networks is inherently modular or random [1].

It is important to construct and analyse a proteome-wide drug-target network that includes not only the primary targets, but also all of the potential off-targets of the drugs in the network. Such a network, if available, would provide unparalleled opportunities for mapping a comprehensive drug-target space and understanding the molecular basis of drug efficacy, side-effects and drug resistance, thereby providing the foundation for the rational design of polypharmacological (multi-target) drugs. For anti-infectious drug discovery, where pharmaceutically investigated targets only represent a small portion of the whole pathogen's proteome, it is more challenging to establish a proteome-wide drug-target network. The linkage of drugs to less exploited proteins such as virulence factors, transport proteins and transcription factors will greatly expand the repository of anti-infectious drug targets and provide new solutions for combating multi-drug and extensively drug resistant pathogens, and for repurposing existing drugs for new uses.

Structural bioinformatics provides an alternative and complementary way to extend drug-target networks to less characterized proteins on a proteome-wide scale. The structural coverage of a given pathogen proteome is usually much larger than the

amongst the 3... investigated

Annotation

Discourse (SWAN Annotation)

amongst the 3,999 proteins encoded by the *Mycobacterium tuberculosis* (*M.tb*) genome, only nine (*cmaA1*, *cyp51*, *embA*, *embB*, *embC*, *folK*, *inhA*, *katG* and *rpoC*) have been pharmaceutically investigated

mycobacterium tuberculosis

Thing

Species (SWAN Thing)

[Mycobacterium tuberculosis](http://www.uniprot.org/taxonomy/1773)
<http://www.uniprot.org/taxonomy/1773>

RCSB PDB

Structur...N mutant

Structure of the mycobacterium tuberculosis DUTPase D28N mutant

[View RCSB web page...](#)

Look up

PLOS Computational Biology | www.ploscompbiol.org 1 November 2010 | Volume 6 | Issue 11 | e1000976

1 of 16 pages

Apache Clerezza / UIMA / AO integration

Clerezza integration with Apache UIMA

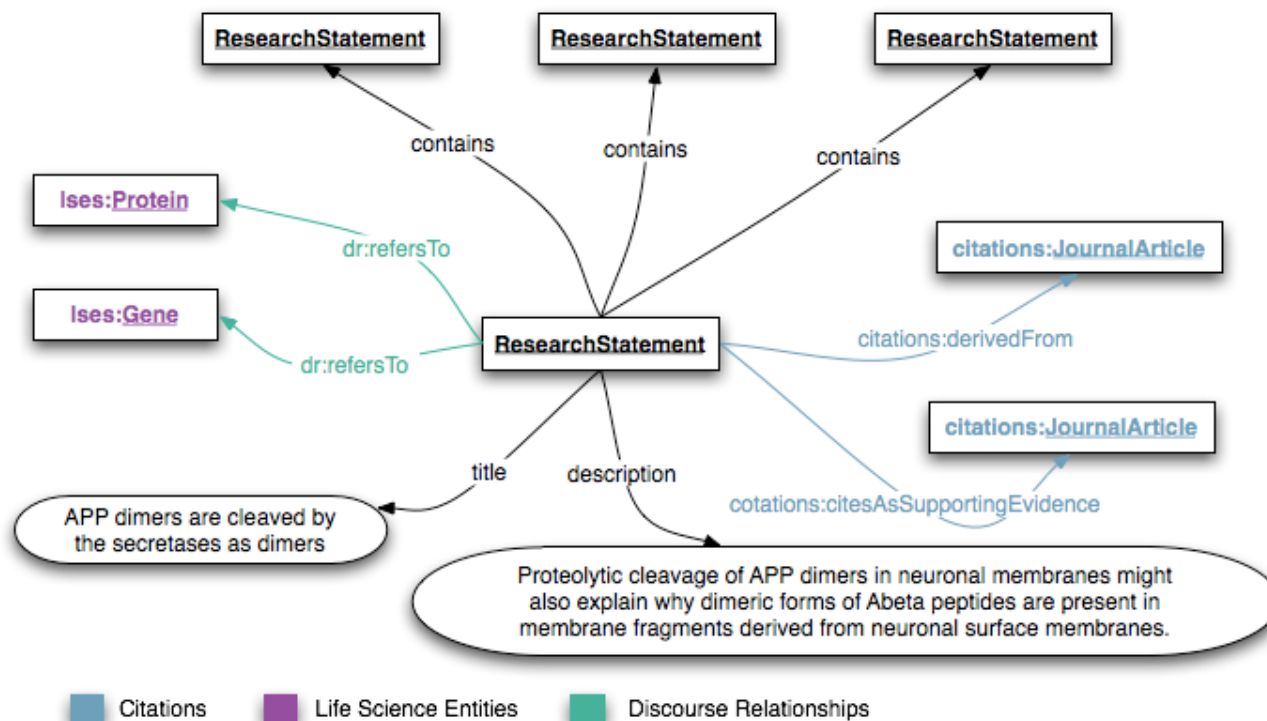
Introduction to Clerezza-UIMA integration

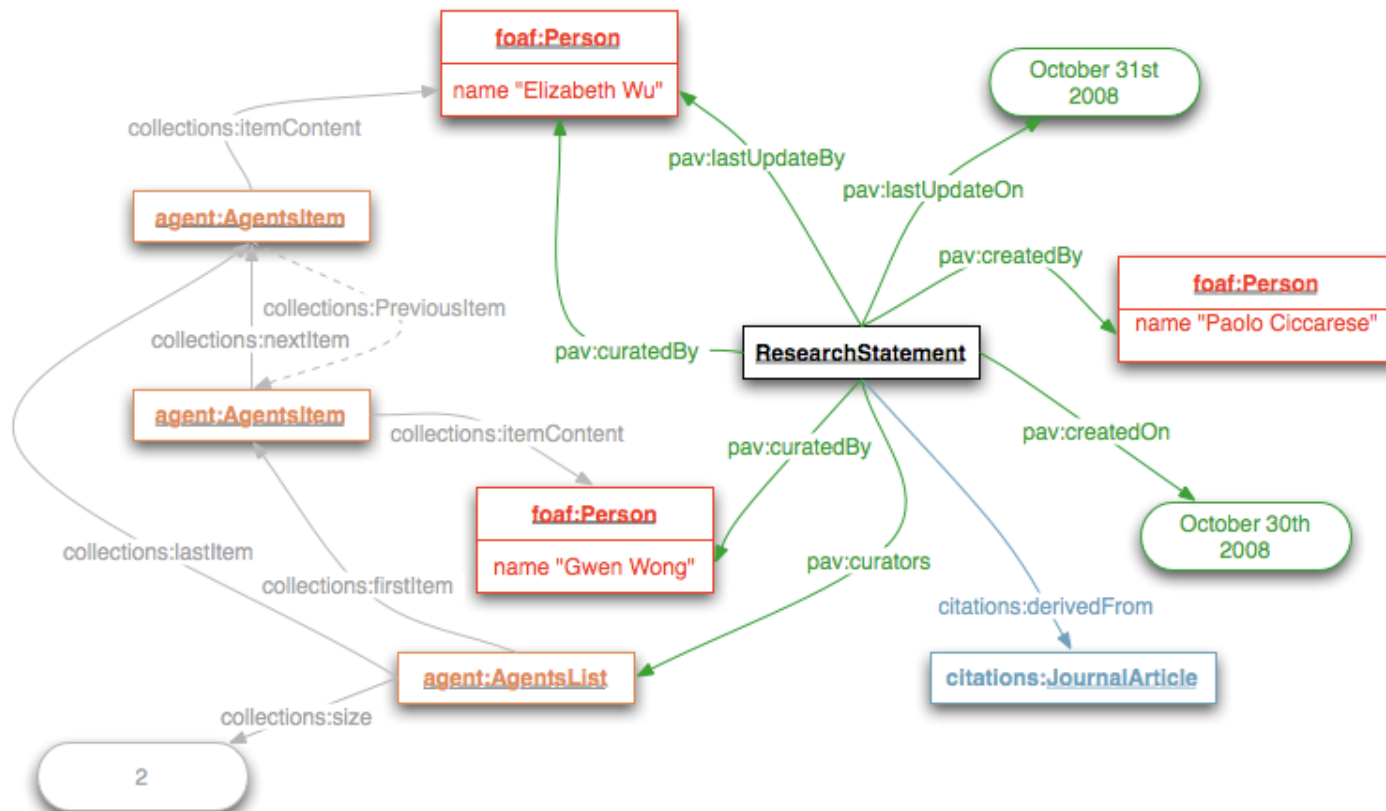
UIMA is an **OASIS** standard that allows the definition of analysis pipelines to manage unstructured information and extract structures and semantics around given data.

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!







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An Alzheimer hypothesis in SWAN

AlzSWAN Knowledge Base

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Loss of essential functions of presenilin can explain dementia and neurodegeneration in Alzheimer disease. 0 Comment(s)

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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 A β 40 peptide and AICD production, the effect of gamma secretase inhibitors on A β 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.

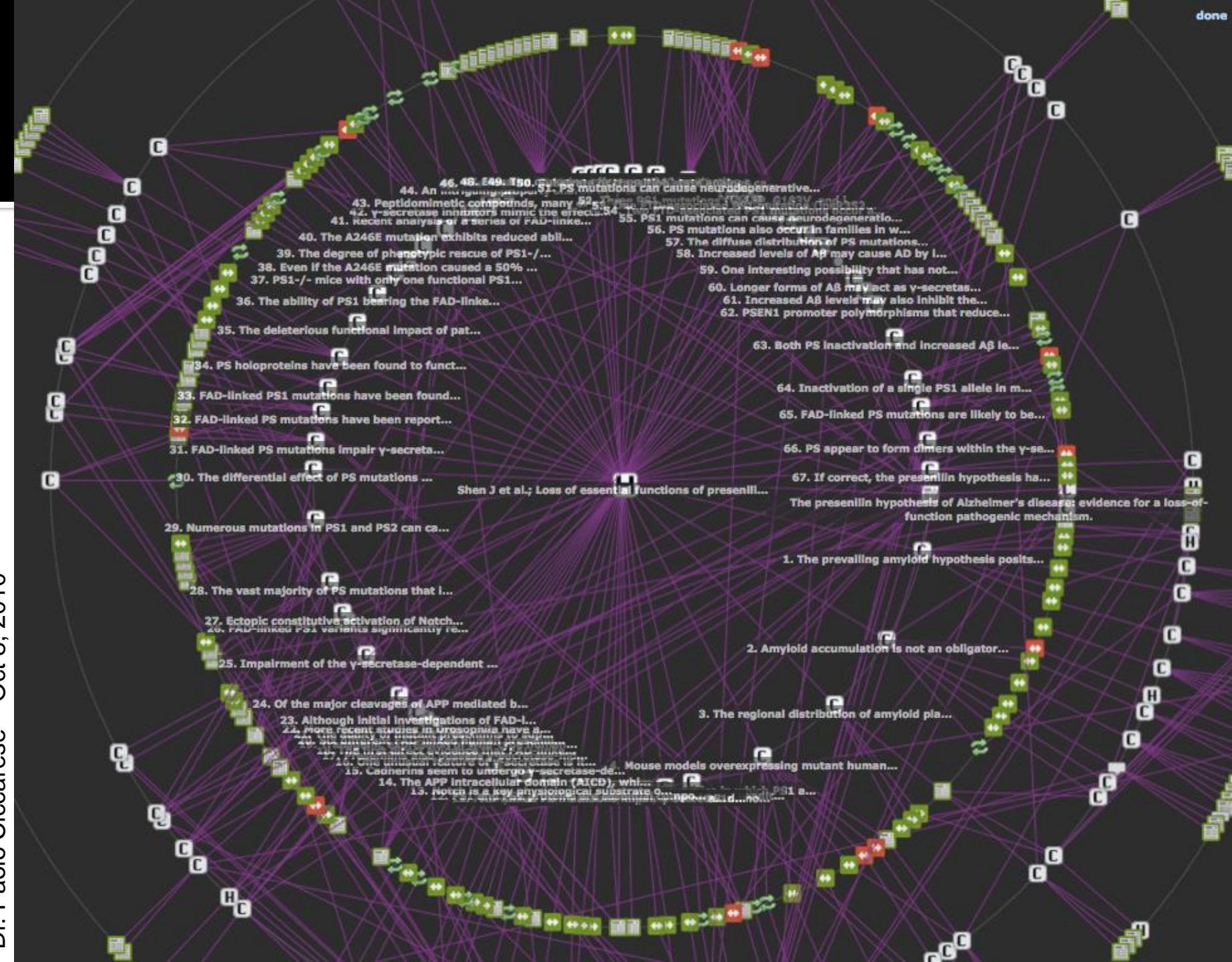
Proceedings of the National Academy of Sciences of the United States of America. 2007 Jan 9;104(2):403-9

Contains 66 Statements:

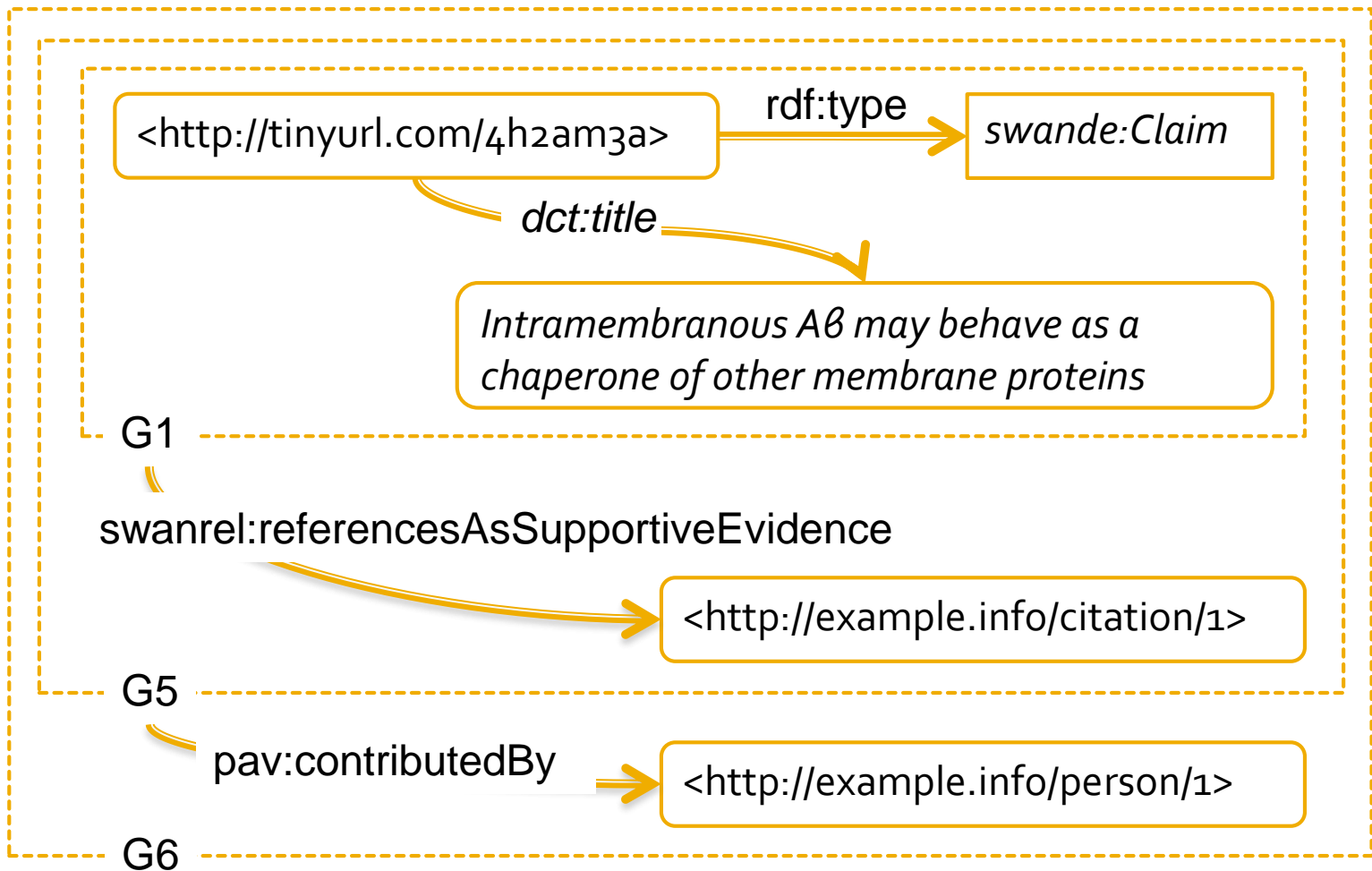
 67 with evidence  0 without evidence and a total of:  119 citations ; Related to external statements:  35 consistent  11 inconsistent  0 discussed  21 with alternatives

☒ Expand All Details ☐ Collapse All Details

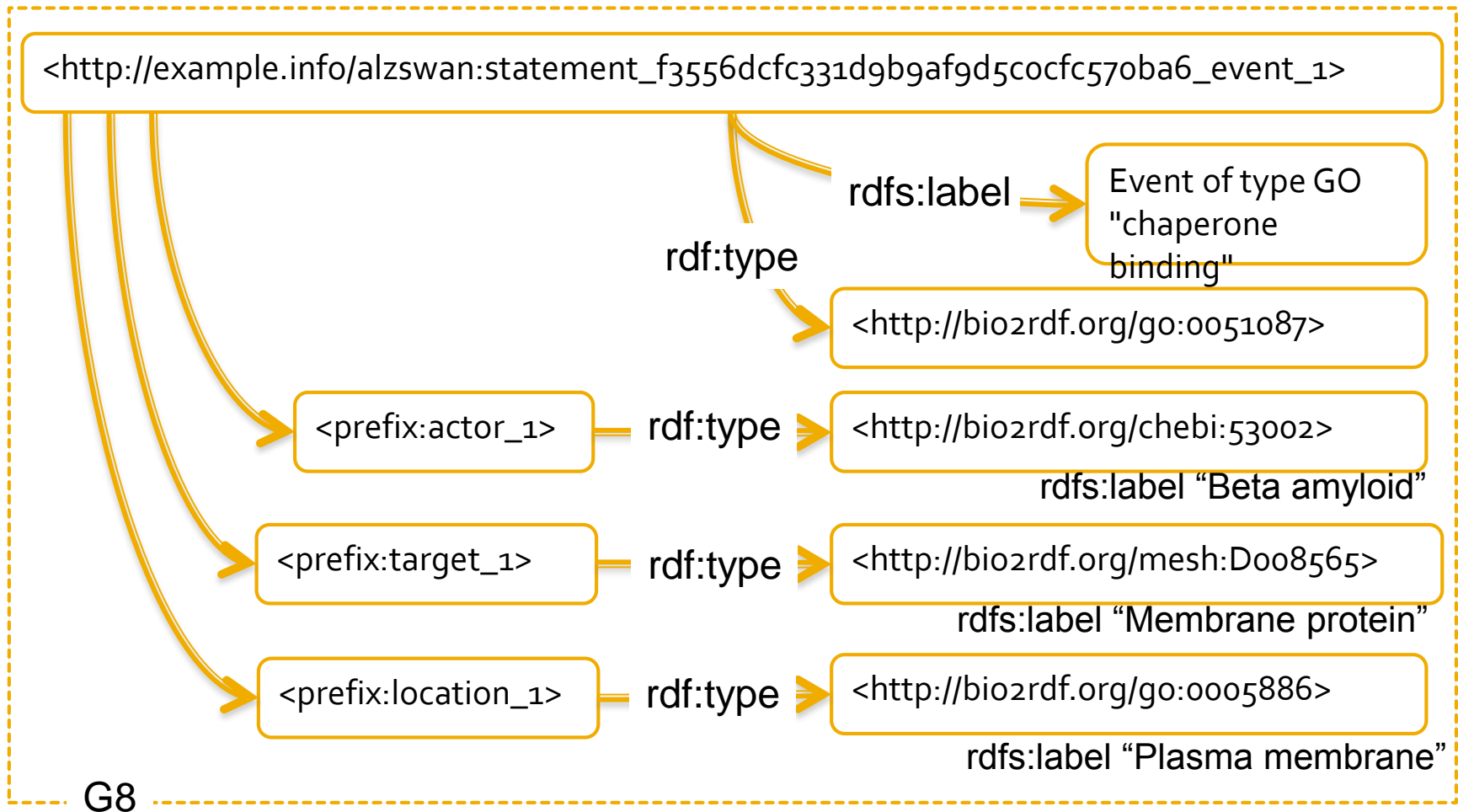
-  The prevailing amyloid hypothesis posits that accumulation of A β peptides, particularly the more hydrophobic and aggregation-prone A β 42, triggers a pathogenic cascade, leading to neurodegeneration in AD.
[SHOW Details](#)  Supporting(1)  Consistent(6)  Genes/Proteins: (1)
-  Amyloid accumulation 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)
-  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)
-  Mouse models overexpressing mutant human APP have reproduced overproduction of A β 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)
-  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)
-  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

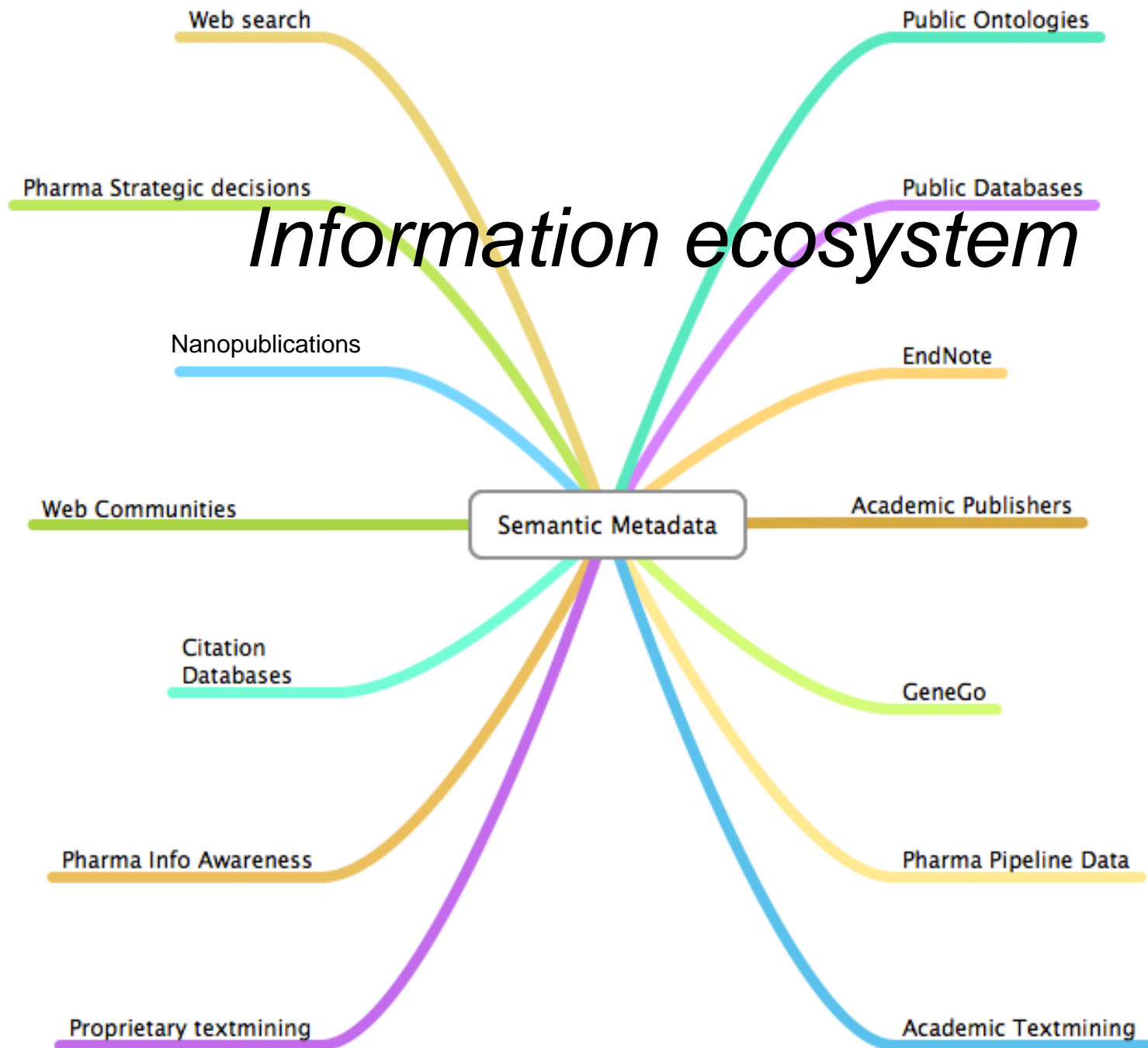


Ciccarese-Groth nanopublications: “triplified” claims

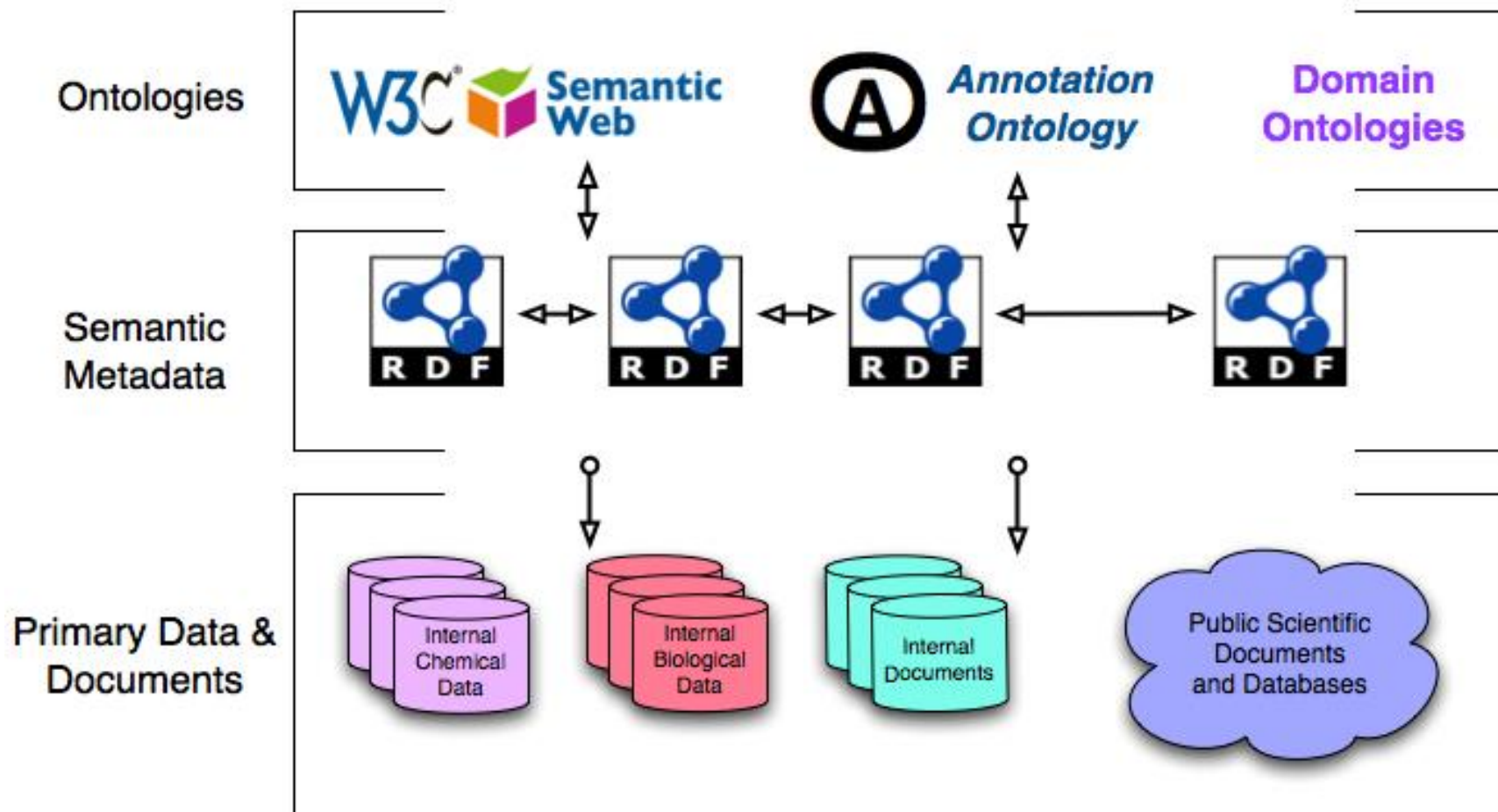


With many thanks to Nigam Shah, Stanford University

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.