

Semantic Resources Project
***PRO (Protein Ontology) Use Cases
for Scientific Communities***

Paolo Ciccarese, PhD



Mass General Hospital



Harvard Medical School

Semantic Resources Project

- Collaboration between
 - Mass General Hospital
 - Science Commons
 - Alzforum
- Goal: creating a set of semantic resources
 - Of interest for SWAN and SCF projects
 - Following best practice
- Two examples of PRO related resources:
 - Proteins of interest in AlzSWAN (APP, Tau, Synuclein)
 - Antibodies (immunogens and antigens)

SWAN (Semantic Web Application in Neuromedicine)

- It is a Web-based collaborative program that aims to organize and annotate scientific knowledge about neurodegenerative disorders.
- Collaboration of Mass General Hospital with Alzforum (www.alzforum.org)
- Its goal is to facilitate the formation, development and testing of hypotheses about neurodegenerative diseases.
- It is about scientific discourse

AlzSWAN (SWAN for Alzheimer)

SWAN Alzheimer Knowledge Base beta

Semantic Web Applications in Neuromedicine

[Log in](#)

[SWAN Terms of Use](#)

[Home](#) [Statements](#) [Genes-Proteins](#) [Evidence Maps](#) [About](#)

Welcome to the SWAN Alzheimer Knowledge Base

SWAN is the participatory knowledge base of Alzheimer Disease that YOU can help develop. SWAN is all about how you interpret, debate, ask questions and advance the science.

» FEATURED CONTRIBUTIONS



H The $\alpha 7$ Nicotinic Acetylcholine Receptor gene mediates cognitive deficits and synaptic pathology.
Dziewczapolski Gustavo et al.



H Abraham comment on Pollio et al hypothesis "Increased expression of the oligopeptidase THOP1 is a neuroprotective response to A β toxicity."
Abraham C R



H NMDA receptor hypoactivity (NRHypo) may have an important contributory role in Alzheimer disease.
Olney J W et al.

click on the title to browse the full content and use the arrows to scroll the list

» HOT TOPICS ([browse all hypotheses](#))

- A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis
- Soluble oligomeric aggregates of A β are toxic to neurons and cause AD pathology
- Insoluble fibrillar A β leads to AD
- Defective mechanisms of A β clearance contribute to AD
- Tau dysfunction mediates neurodegeneration
- ApoE contributes to AD through multiple mechanisms
- Changes in calcium homeostasis may provide a common pathway for the neuropathological changes in AD
- Changes in presenilin function lead to dementia and neurodegeneration in Alzheimer Disease
- Misfolded proteins accumulated into protein aggregates characterizes the pathologic lesions of AD
- The molecular mechanisms of neuronal cell death are involved in the dysfunction and death of neurons in AD
- Synaptic loss appears to be the most powerful and ubiquitous proximate factor leading to the dementia of AD
- Failure of axonal transport might be the underlying basis for neurodegeneration in AD
- Cell membrane properties play a key role in AD Pathophysiology

» MECHANISMS

- Energetics
- Functional Changes of Proteins
- Structural Changes of Proteins

» HOW TO CONTRIBUTE

- BUILD A HYPOTHESIS
- CRITIQUE A HYPOTHESIS
- NOMINATE A KEY PAPER
- HELP FIND CONNECTIONS
- PROPOSE NEW FEATURES
- ADD SUPPORTING EVIDENCE

[Contact us!](#)

» KNOWLEDGE BASE

Statements

2137 Research Statements

» 173 Hypotheses

» 48 with Extended annotation

» 125 with Simple annotation

» 1964 Claims

60 Research Questions

45 Comments

Publications

2054 Journal Articles

8 Journal Comments

6 Journal News

33 Web Comments

AlzSWAN Curation Process

SWAN: browser



Curator

1. reading

Single Molecules of Highly Purified Bacterial Alkaline Phosphatase Have Identical Activity

Robert Palakowski, Doug B. Craig, Alison Skelley, and Norman J. Dovichi*

Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G1, Canada.

Received December 23, 1999; Revised Manuscript Received March 28, 2000

Abstract: The central paradigm of chemistry is that molecular structure determines molecular function. Details of this paradigm can be tested with single-molecule enzymology, where the activity of individual molecules is studied. In all cases reported thus far, there is a large molecule-to-molecule heterogeneity in activity and activation energy. This heterogeneity must arise from differences in structure. Replicate molecules on the same molecule yield consistent results; the structural heterogeneity must be stable over the time period of the experiment, which can extend over several hours. In this paper, we demonstrate that highly purified molecules of bacterial alkaline phosphatase possess identical activity; structurally identical molecules behave identically. In contrast, the glycosylated mammalian enzyme demonstrates a complex isoelectric focusing pattern and has a dramatic molecule-to-molecule variation in activity and activation energy. Glycosylation affects both the kinetics and energetics of this enzymatically catalyzed reaction.

Introduction

The stochastic activity of single molecules of lactate dehydrogenase, calf intestinal alkaline phosphatase, β -galactosidase, and cholinesterase has been reported.^{1–4} In most cases, the molecule-to-molecule activity was clearly heterogeneous. While there was a wide range in activity between molecules, the activity of any single molecule was stable over periods ranging from minutes to hours. The molecule-to-molecule heterogeneity also extends to activation energy, which varied by a factor of 2.5 for calf intestinal alkaline phosphatase.⁴

There are two explanations for this heterogeneity in molecular properties. In the energy landscape model, the molecule can exist in a number of different conformations that are separated by energy barriers of varying heights.⁵ Yung argued that the molecule-to-molecule heterogeneity in enzymatic properties of lactate dehydrogenase arises from molecules with identical primary structure that are trapped in different long-lived conformational substates; heterogeneity in molecular function is due to differences in the tertiary structure of the molecule.⁶ In contrast, we have argued that molecule-to-molecule differences in the behavior of calf intestinal alkaline phosphatase reflect differences in the posttranslational modification of the enzyme.⁷

*Corresponding author. E-mail: ndovichi@chem.ualberta.ca; Phone: 780-492-2280.
Present address: Department of Chemistry, University of Winnipeg, Winnipeg, Manitoba R3B 2T9, Canada.
1. De, S. Yung, F. S. Arai, *Chem Phys Lett* 199, 481–482 (1992).
2. De, S., W. M. Edwards, M. A. Wang, T. C. Li, R. H. Dowling, N. J. Dovichi, *J. Am. Chem. Soc.* 1994, 116, 520–523.
3. De, S., R. H. Dowling, N. J. Dovichi, *J. Am. Chem. Soc.* 1996, 118, 415.
4. De, S., R. H. Dowling, N. J. Dovichi, *J. Am. Chem. Soc.* 1997, 119, 1077–1082.
5. De, S., X. Li, B. P. J. *Acc. Chem. Res.* 1994, 27, 1047–1070.
6. De, S., J. P. F. *Protein Pap. P. Biomol. Sci. Rep. Chem. Phys.* 1999, 27, 11–22.
7. Palakowski, R., S. G. Wojcik, P. G. *Science* 1991, 252, 1038–1043.

molecule heterogeneity in molecular function reflects heterogeneity in the primary structure of the molecule.⁸ In this paper, we demonstrate that the activities of single molecules of highly purified *Escherichia coli* alkaline phosphatase are identical. *E. coli* alkaline phosphatase is a monofunctional protein that is coded by a single *phoA* gene. The enzyme exists in three forms, designated isoenzymes 1, 2, and 3. The isoenzymes differ by an N-terminal sequence that is present in isoenzyme 1 but absent in isoenzymes 2 and 3. Isoenzyme 2 represents a heterodimer of isoenzyme 1 and 3. We used isoelectric focusing to purify each isoenzyme and laser-assisted fluorescence to monitor the activity of individual enzyme molecules.

Experimental Section
Enzyme synthesis. *E. coli* strain 600 of bacteriophage phi-80, as a weakly fluorescent substrate for alkaline phosphatase, was used by P. Scudiero (Sanofi-Sintelabo, CA) and converted to the highly fluorescent product 7-(2-hydroxyethyl)-2-(4-hydroxyphenyl)-6-methyl-4-methyl-3-methyl-5-methyl-4-methyl-3-methyl-2-methyl-1,3-bisphosphonate.
***E. coli* Alkaline Phosphatase Purification.** The purification is described in the Supporting Information section of this paper. Briefly, complex was separated by isoelectric focusing and visualized with Alk-Blue. Bands corresponding to isoenzymes were excised from the gel. Enzymes were purified by centrifugation through an appropriate buffer. To avoid proteolytic digestion of the enzyme, procedures were performed in a cold room and the purified enzyme was protected with a chemical protease inhibitor.

Single-Molecule Activity. The assay was performed in a 17 μ m \times 10 μ m \times 0.125 μ m long capillary (part of the chamber) was coated in a poly- α -methylacrylate sheath. To perform the single-molecule experiments, a 3 \times 10⁷ M solution of purified enzyme was injected into the capillary by application of a 400-Vdc voltage field for 2 s. The fluid from the injection was used to calculate:
(1) Haskins, R. A., Casanovi, J., Iversen, L. L., Norman, P. A., *Protein Sci.* 1992, 1, 2475–2477.
(2) De, S., J. P. F. *Protein Pap. P. Biomol. Sci. Rep. Chem. Phys.* 1999, 27, 11–22.

© 2000 American Chemical Society
Published on Web 05/05/2000

2. extracting

Hypothesis
Discourse List, Citations
Genes, Proteins

3. organizing and encoding

5. publishing

4. connecting

SWAN: workbench

Hypothesis list

SWAN Alzheimer Knowledge Base beta
Semantic Web Applications in Neuromedicine

Home Statements Genes-Proteins Evidence Maps About

» Statements » All Hypotheses

7 Hypothesis filtered from 173 originally ([Reset All Filters](#))

sorted by: [status](#) and [firstAuthor](#); then by... • grouped as sorted

Extended Annotation (6)

1. Plaque removal is not enough to halt progressive neurodegeneration in Alzheimer Disease. Hypothesis
Holmes Clive - Boche Delphine, Wilkinson David, Yadegarfar Ghasem, Hopkins Vivienne, Bayer Anthony, Jones Roy W, Bullock Roger, Love Seth, Neal James W, Zotova Elina, and Nicoll James A [2008]
Contains 33 statements: [32 with evidence](#) [1 without evidence](#) and a total of [56 citations](#)
Relationships with external statements: [9 consistent](#) [7 inconsistent](#) [5 alternative to](#)
Genes-Proteins: [Homo sapiens: Beta-amyloid protein 42;](#)

2. Ap Plaques Lead to Aberrant Regulation of Calcium Homeostasis In Vivo Resulting in Structural and Functional Disruption of Neuronal Networks. Hypothesis
Kuchibhotla Kishore V - Goldman Samuel T, Lattarulo Carli R, Wu Hai-Yan, Hyman Bradley T, and Bacskai Brian J [2008]
Contains 10 statements: [10 with evidence](#) [0 without evidence](#) and a total of [26 citations](#)
Relationships with external statements: [4 consistent](#) [7 inconsistent](#)
Genes-Proteins: [Homo sapiens: PSEN1, APP, Amyloid beta A4 protein;](#)

3. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Hypothesis
Meyer-Luehmann Melanie - Spires-Jones Tara L, Prada Claudia, Garcia-Alloza Monica, de Calignon Alix, Rozkalne Anete, Koenigsnecht-Talboo Jessica, Holtzman David M, Bacskai Brian J, and Hyman Bradley T [2008]
Contains 40 statements: [37 with evidence](#) [3 without evidence](#) and a total of [54 citations](#)
Relationships with external statements: [14 consistent](#) [10 inconsistent](#) [9 discussed](#) [11 alternative to](#)
Genes-Proteins: [Homo sapiens: Amyloid beta A4 protein, APP, Presenilin-1;](#)

4. Brainstem neurons are initiators of neuritic plaques Hypothesis
Muresan Zoia - Muresan Virgil [2008]
Contains 27 statements: [27 with evidence](#) [0 without evidence](#) and a total of [96 citations](#)
Relationships with external statements: [12 consistent](#) [2 inconsistent](#) [1 discussed](#) [2 alternative to](#)

Selectors
Search this page:

Search

Status
6 Extended Annotation
1 Simple Annotation

Hot Topics List 1

- 7 Aβ accumulation in the brain is the primary event in Alzheimer Disease pathogenesis
- 13 ApoE contributes to Alzheimer Disease through multiple mechanisms
- 7 Cell membrane properties play a key role in AD Pathophysiology
- 5 Changes in calcium homeostasis may provide a common pathway for the neuropathological changes in AD
- 5 Changes in presenilin function lead to dementia and neurodegeneration in Alzheimer Disease
- 7 Defective mechanisms of Aβ clearance contribute to Alzheimer Disease
- 6 Failure of axonal transport might be the underlying basis for neurodegeneration in Alzheimer Disease
- 8 Genetic variants modulate risk of AD
- 7 **Insoluble fibrillar Aβ leads to AD**
- 3 Misfolded proteins accumulated into protein aggregates characterizes the pathologic lesions of Alzheimer Disease
- 7 Signaling mechanisms play a critical role in Alzheimer Disease
- 9 Soluble oligomeric aggregates of Aβ are toxic to neurons and cause AD pathology

Hypothesis

Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. 3 Comment(s)


 [Submit a comment](#)  [Show graph \(Experimental!\)](#)

Description:








This hypothesis confirms a temporal relationship between plaque deposition and neuritic architecture changes, utilizing data generated from longitudinal in vivo multiphoton microscopy. The authors test and confirm the fundamental tenet of the amyloid hypothesis that amyloid deposition precedes and induces the neuronal abnormalities that underlie dementia, and establish plaques as a critical mediator of neuritic pathology. Plaques form quickly, and lead to the activation and recruitment of microglia as well as increasingly dysmorphic neurites at plaque sites.

Authors: Meyer-Luehmann M Spires-Jones T Prada C Garcia-Alloza M de Calignon A Rozkalne A Koenigsnecht-Talboo J Holtzman D Bacskai B Hyman B



















Derived from:

 Meyer-Luehmann M, Spires-Jones T, Prada C, Garcia-Alloza M, de Calignon A, Rozkalne A, Koenigsnecht-Talboo J, Holtzman D, Bacskai B, Hyman B
[Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease.](#)
Nature. 2008 Feb 7;451(7179):720-4

Contains 40 Statements:

 37 with evidence  3 without evidence and a total of:  54 citations ; Related to external statements:  15 consistent  10 inconsistent  0 discussed  13 with alternatives



Expand All Details Collapse All Details

-  **A fundamental tenet of the amyloid hypothesis of Alzheimer's disease is that the deposition of amyloid-beta precedes and induces the neuronal abnormalities that underlie dementia.**
[SHOW Details](#)  Supporting(1)  Consistent(1)  Inconsistent(5)  Alternative to: (1)
-  **It has been suggested that alterations in axonal trafficking and morphological abnormalities precede and lead to senile plaques**
[SHOW Details](#)  Supporting(1)
-  **Longitudinal in vivo multiphoton microscopy has been developed to explore the formation of amyloid plaques and to determine the effects of newly formed dense-cored plaques on the microarchitecture of the brain.**
[SHOW Details](#)  Supporting(1)  Consistent(1)
-  **APP^{swe}/PS1^{d9xYFP} (B6C3-YFP) transgenic mice begin to show plaque appearance at 5 to 6 months age.**
[SHOW Details](#)  Supporting(2)  Genes/Proteins: (3)
-  **Tg2576 mice have a slower progression of disease than B6C3-YFP mice, but confirmed the rapidity of plaque development as demonstrated in the B6C3-YFP mice.**
[SHOW Details](#)  Supporting(1)
-  **New plaques do not form any closer to vessels than would be expected by chance, in accord with an earlier study of human Alzheimer's disease**
[SHOW Details](#)  Supporting(2)  Alternative to: (1)

Hypothesis

Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease 2 Comment(s)


4. **APP^{swe}/PS1^{d9xYFP} (B6C3-YFP) transgenic mice begin to show plaque appearance at 5 to 6 months age.**

[HIDE Details](#)  Supporting(2)  Genes/Proteins: (3)

Experimental Approach: Genetics, Animal models


Pathogenic Narrative Tags: [Pathologic change](#)

Supporting Evidence

 Jankowsky J, Slunt H, Ratovitski T, Jenkins N, Copeland N, Borchelt D

Co-expression of multiple transgenes in mouse CNS: a comparison of strategies.

Biomolecular engineering. 2001 Jun;17(6):157-65

 Jankowsky J, Fadale D, Anderson J, Xu G, Gonzales V, Jenkins N, Copeland N, Lee M, Younkin L, Wagner S, Younkin S, Borchelt D

Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for augmentation of a 42-specific gamma secretase.



Human molecular genetics. 2004 Jan 15;13(2):159-70

Genes/Proteins



Protein: [Presenilin-1 \[Homo sapiens\]](#)

Gene: [APP amyloid beta \(A4\) precursor protein \[Homo sapiens\]](#)

Protein: [Amyloid beta A4 protein \[Homo sapiens\]](#)

[SHOW Details](#)  Supporting(1)  Consistent(1)



4. **APP^{swe}/PS1^{d9xYFP} (B6C3-YFP) transgenic mice begin to show plaque appearance at 5 to 6 months age.**

[SHOW Details](#)  Supporting(2)  Genes/Proteins: (3)

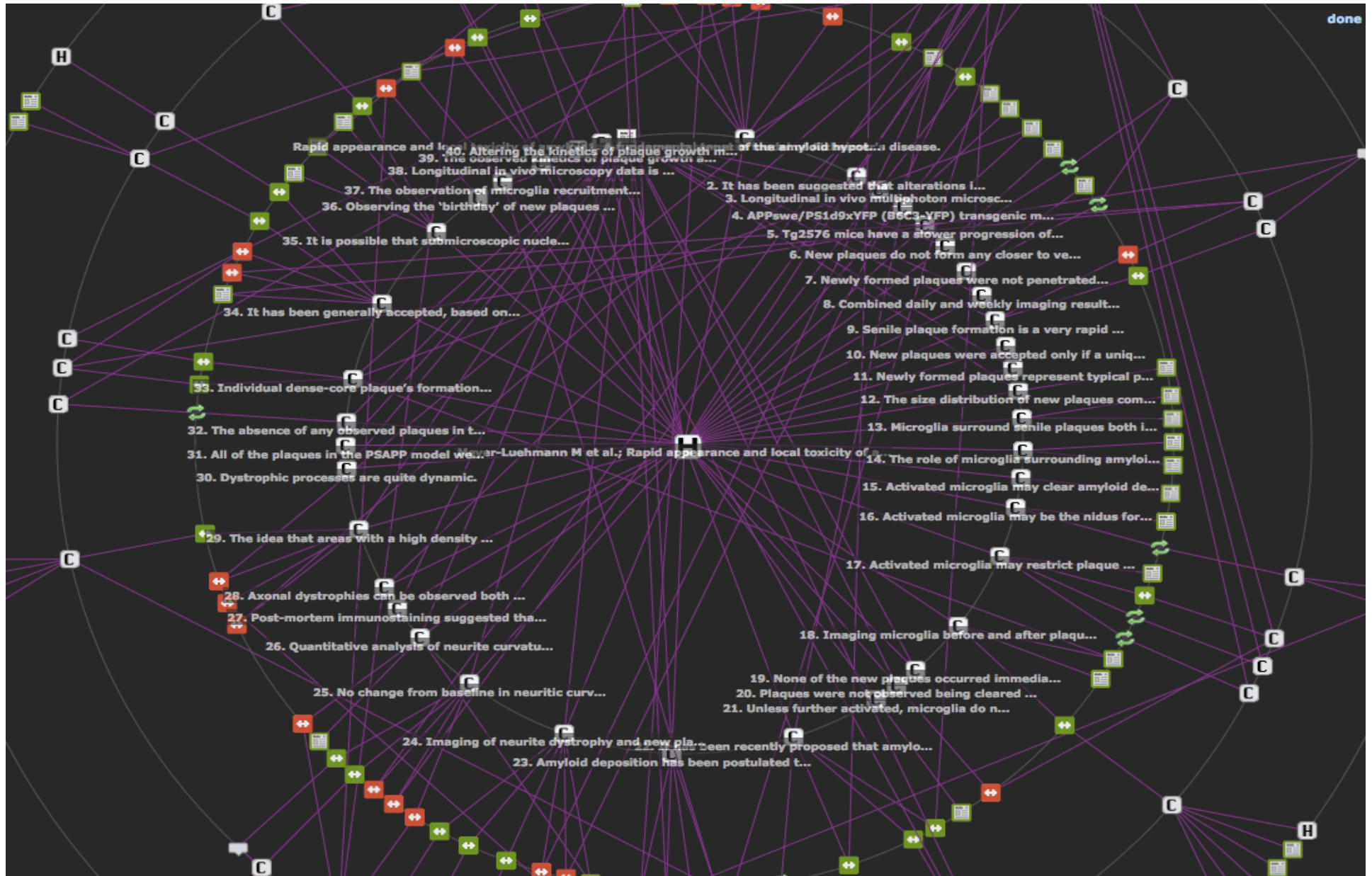
5. **Tg2576 mice have a slower progression of disease than B6C3-YFP mice, but confirmed the rapidity of plaque development as demonstrated in the B6C3-YFP mice.**

[SHOW Details](#)  Supporting(1)

6. **New plaques do not form any closer to vessels than would be expected by chance, in accord with an earlier study of human Alzheimer's disease**

[SHOW Details](#)  Supporting(2)  Alternative to: (1)

The hypothesis graph



AlzSWAN proteins management

- When the curators need a new protein they import it automatically from UniProt
- Data are stored according to the SWAN LSEs Ontology (<http://swan.mindinformatics.org/spec/1.2/lses.html>)
- UniProt does not give access to all the info we need (isoforms, cleavage products...)
- Willing to use PRO ontology and others when available (and demonstrate to cover our needs)

AlzSWAN

- In AlzSWAN we have statements related to gene or protein families that do not specify a single species (human vs mouse or rat), but we have also species specific statements
- Protein post-translationally modified have distinct roles:
 - Protein **isoforms** from a single gene have different physiological vs. pathological functions
 - **Cleavage products** have functions distinct from the parent protein
 - Example: APP protein → Abeta peptides, soluble APP, AICD
 - Proteins are assembled into **protein complexes**, and these are affected by isoform and post-translational modification
 - Example: Tau protein: how many microtubule binding domains (which exons used from gene), phosphorylation state of protein affect MT binding or fibril formation
 - Example: Abeta peptides form dimers, oligomers, amyloid plaque

APP is a gene that encodes a complexity of proteins

- A single locus: single copy per haploid genome
- Multiple splice variant mRNAs
- Multiple protein isoforms expressed
 - Some isoforms are ubiquitous, others neuron specific or T cell-specific
- Variety of conserved functional domains throughout length of protein
 - Isoform differences in major domains may have functional consequences
- APP interacts with multiple proteins
- Mutations throughout protein associated with familial Alzheimer Disease
- Cleavage products generated by α -, β - and γ -secretase are involved in both normal and pathogenic protein functions.

SWAN Protein Ontology is NOT just for APP

Ontology term	APP	Tau	Synuclein
Isoforms	10	8	3
Protein Domains	many	MT-binding domains	Tandem repeats
Mutations in disease	AD	FTDP	Parkinson Disease
Heteromultimeric Protein Complexes	many	Microtubules	many
Homomultimeric Protein Complexes	Oligomers, Plaques	PHF, Tangles Pick bodies	Fibrils, Lewy bodies

Summary of SWAN needs

- Protein Ontology needs vocabulary and relationships that include:
 - **Isoforms**
 - **Splice variants**
 - **Cleavage products**
 - **Mutations**
 - **Protein complexes: homomultimeric and heteromultimeric**
- Tissue-specific expression, protein complexes are important
- Intracellular protein trafficking and post-translational modifications are important

Goals for SWAN:

Research statements attributed to APP, can be specifically attributed to:

- an isoform of APP
- a cleavage product of APP
- a mutated form of APP
- a protein complex formed with APP or its cleavage products

AlzSWAN curators interaction with PRO

- APP isoforms and cleavage products have been modeled
- These required changes in the PRO model
- Currently working on Protein Complexes

Welcome to AlzSWAN

Where you explore scientific knowledge about Alzheimer disease and share your own ideas, comments and questions in a semantically structured system.

[View our tutorials](#) to learn how it works.

» FEATURED CONTRIBUTIONS



H Preclinical AD associated with progression to symptomatic AD is detected by PET Pittsburgh Compound B (PiB).
Morris John C et al.



H Clusterin (ApoJ) and Complement component receptor CR1 genes are associated with Late Onset AD.
Lambert Jean-Charles et al.



H The human brain has a unique vulnerability to Alzheimer disease (AD).
Bartzokis George

PRO not only for SWAN!

» HOT TOPICS (browse all hypotheses)

- Biomarkers are useful for predicting and staging Alzheimer disease
- A β accumulation in the brain is the primary event in Alzheimer Disease pathogenesis
- Soluble oligomeric aggregates of A β are toxic to neurons and cause AD pathology
- Insoluble fibrillar A β leads to AD
- Defective mechanisms of A β clearance contribute to AD
- Tau dysfunction mediates neurodegeneration
- ApoE contributes to AD through multiple mechanisms
- Changes in calcium homeostasis may provide a common pathway for the neuropathological changes in AD
- Changes in presenilin function lead to dementia and neurodegeneration in Alzheimer Disease
- Misfolded proteins accumulated into protein aggregates characterizes the

» MECHANISMS

- Energetics
- Functional Changes of Proteins
- Structural Changes of Proteins

» HOW TO CONTRIBUTE

- BUILD A HYPOTHESIS
- CRITIQUE A HYPOTHESIS
- NOMINATE A KEY PAPER
- HELP FIND CONNECTIONS
- PROPOSE NEW FEATURES
- ADD SUPPORTING EVIDENCE

» KNOWLEDGE BASE

Statements

2276 Research Statements

» 177 Hypotheses

» 53 with Extended annotation

» 124 with Simple annotation

» 2099 Claims

61 Research Questions

47 Comments

Publications

2277 Journal Articles

8 Journal Comments

6 Journal News

Science Collaboration Framework

- Reusable software that can be used to develop web-based, collaborative, scientific communities
- Support interdisciplinary scientists in publishing, annotating, sharing and discussing content such as articles, perspectives, interviews and news items, as well as assert personal biographies and research interests
- Applied for the development of the StemBook and PDOnline online communities



<http://www.sciencecollaboration.org/>

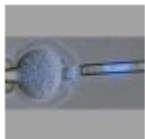
StemBook

HSCI
HARVARD STEM CELL
INSTITUTE

[Home](#) [About](#) [Contents](#) [Contributor Info](#) [Resources](#) [eAlerts](#)



STEMBOOK IS A COMPREHENSIVE, OPEN-ACCESS COLLECTION OF ORIGINAL, PEER-REVIEWED CHAPTERS COVERING TOPICS RELATED TO STEM CELL BIOLOGY. [READ MORE](#)



Cellular and nuclear reprogramming



Genomics and proteomics



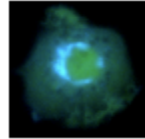
Renewal



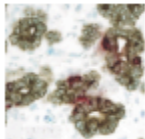
Ectoderm specification and differentiation



Germ cell and somatic stem cell biology in reproduction



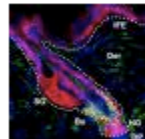
Stem cell immunology



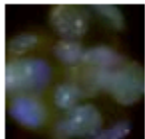
Endoderm specification and differentiation



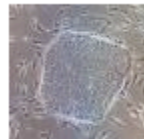
Mesoderm specification and differentiation



Therapeutic prospects



Epigenetics



Niche biology, homing, and migration



Tissue engineering

New Chapters

[The chromatin signature of pluripotent cells](#)
[Limbal epithelial stem cells of the cornea](#)
[Molecular imaging of stem cells](#)
[Stem cells, cancer, and epigenetics](#)

Commentary

Transdifferentiation – Cells Go From Point A to Point B Without "Passing Go"

Published: April 6, 2010

While many stem cell scientists are basking in the afterglow of induced pluripotency, and working on ways to de-differentiate and re-differentiate cells, a few researchers are already thinking about a shortcut.

To read more, [click here](#).

Past Commentaries

[Need For Standardization in Stem Cell Research Highlighted in AAAS Webinar](#)

[Advances in Imaging Techniques Help Drive Stem Cell Research](#)

E-mail address: *

Password: *

Log in

[recover password](#)

[Latest Posts](#) [PD Guide](#) [Funding Opportunities](#) [Home](#) [Resources](#) [Members](#) [News](#) [Research Questions](#)
[Conference Reports](#) [POTW](#) [Post here!](#) [Reporter Awards](#) [LRRK2 Antibodies](#)

search text here



News & Features

MJFF Awards More Than \$3 Million to Advance Parkinson's Disease Research

23 Apr 2010



The Michael J. Fox Foundation for Parkinson's Research today announced more than \$3 million in previously unannounced awards ending the first quarter of 2010. The funded projects complement the ...

Impax Pharmaceuticals Completes Enrollment in APEX-PD Phase III Trial of IPX066 in Parkinson's Disease

15 Apr 2010

HAYWARD, Calif., Apr 15, 2010 (BUSINESS WIRE) -- Impax Pharmaceuticals, the brand products division of Impax Laboratories, Inc., today announced that it has completed enrollment of its ...

ADAGIO Analysis Demonstrates That the Natural Progression of Clinical Symptoms in Parkinson's Disease May Be Slower in Earlier Stages

19 Apr 2010

JERUSALEM, Israel, Apr 19, 2010 (BUSINESS WIRE) -- --New findings provide further insights into the ADAGIO results which support early treatment initiation with Azilect(R) ...

NPF Awards Nearly \$1 Million for Clinical Research

14 Apr 2010



MIAMI—April 14, 2010—The National Parkinson Foundation (NPF) has awarded nearly \$1 million dollars to four investigators pursuing clinical research projects in 2010. The research NPF ...

[more](#)



Research Questions

Which behavioral outcomes are relevant in rodent models of dyskinesia?

The development of rodent models of LID has improved our ability to conduct studies into the molecular mechanisms of LID as well as to screen new therapeutic strategies. However, it is much harder to detect and analyze rodent behavior relevant to L-DOPA-



Contributions

Most Recent

Editor's Choice

Comment on Pfeiffer and McLaughlin (2010)

By: Lorraine Iacovitti, Thomas Jefferson 23 Apr 2010 11:30

AM EST

PRO is attractive for our communitites

- AlzSWAN (<http://hypothesis.alzforum.org/>)
- StemBook (www.stembook.org)
- PDOnline (<http://www.pdonlineresearch.org/>)
- Others coming up...

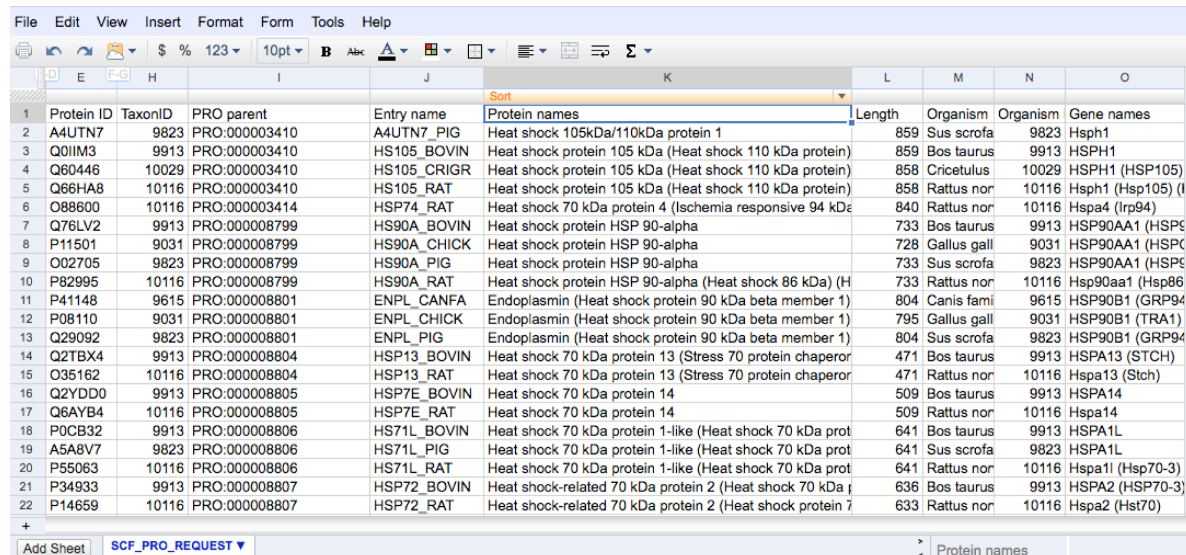
Some thoughts about the
PRO terms submission process

PRO terms are submitted by hand

- RACE-PRO web form
 - UniprotKB identifier
 - Annotations
 - Database xrefs
 - “comments”
- Some requests can't be submitted through RACE-PRO
 - Protein families are submitted through SourceForge

The screenshot shows the RACE-PRO web interface. At the top, there is a header for the Protein Information Resource (PIR) with a navigation menu including 'About PIR', 'Databases', 'Search/Analysis', 'Download', and 'Support'. Below the header, the main title is 'RACE-PRO Rapid Annotation interface for Protein Ontology (?)'. There are input fields for '*Annotator name:', '*E-mail:', and '*Institution:', along with 'Save', 'Submit', and 'Reset' buttons. A note states: 'Note: Your e-mail address is for internal use only and will not be shared with third parties.' The main section is titled 'Definition of the Protein Object' and contains five numbered steps: 1. Enter a UniProtKB identifier (with a 'Retrieve' button and examples: Q15796; Q15796-2; VAR_011378). 2. Specify sequence region (with options for 'Full-length' or 'Region' from a start to an end position). 3. Indicate post-translational modifications (with a field for 'Amino acid number' and a 'choose PTM' dropdown). 4. Protein Object name (with a note to separate multiple names using ';'). 5. Evidence Source (with a 'choose Db' dropdown and an 'IDs' field). Below this section is 'Annotation of the Protein Object' with a 'Domain' field and a 'Link to PFAM' button.

Batch request format is better for integrating with applications



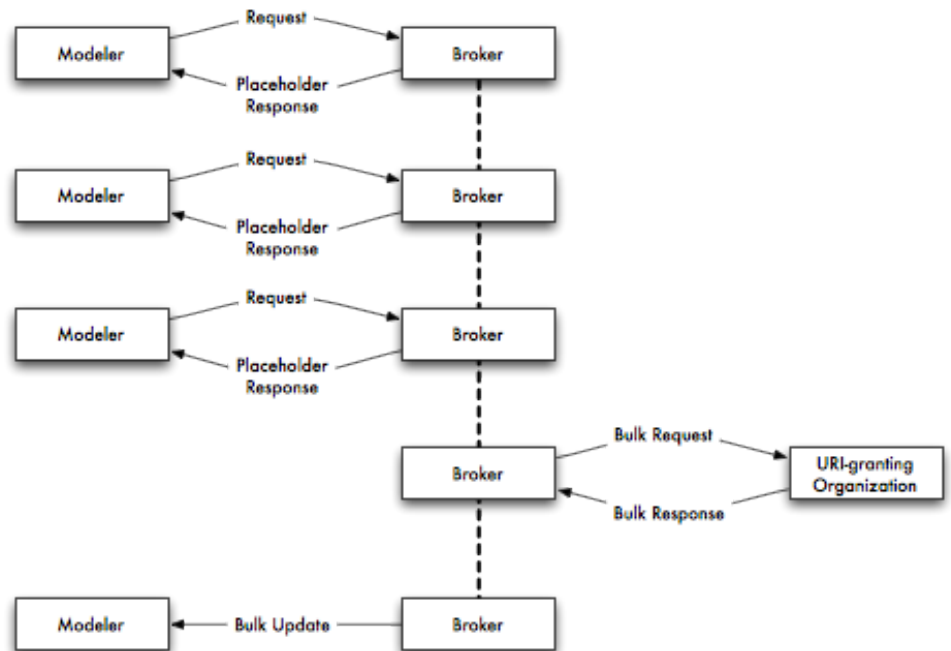
Protein ID	TaxonID	PRO parent	Entry name	Protein names	Length	Organism	Organism	Gene names
A4UTN7	9823	PRO:000003410	A4UTN7_PIG	Heat shock 105kDa/110kDa protein 1	859	Sus scrofa	9823	Hsph1
Q0IIM3	9913	PRO:000003410	HS105_BOVIN	Heat shock protein 105 kDa (Heat shock 110 kDa protein)	859	Bos taurus	9913	HSPH1
Q60446	10029	PRO:000003410	HS105_CRIGR	Heat shock protein 105 kDa (Heat shock 110 kDa protein)	858	Cricetulus	10029	HSPH1 (HSP105)
Q66HA8	10116	PRO:000003410	HS105_RAT	Heat shock protein 105 kDa (Heat shock 110 kDa protein)	858	Rattus nor	10116	Hsph1 (Hsp105) (Hsp105)
O88600	10116	PRO:000003414	HSP74_RAT	Heat shock 70 kDa protein 4 (Ischemia responsive 94 kDa)	840	Rattus nor	10116	Hspa4 (Irp94)
Q76LV2	9913	PRO:000008799	HS90A_BOVIN	Heat shock protein HSP 90-alpha	733	Bos taurus	9913	HSP90AA1 (HSP90)
P11501	9031	PRO:000008799	HS90A_CHICK	Heat shock protein HSP 90-alpha	728	Gallus gall	9031	HSP90AA1 (HSP90)
O02705	9823	PRO:000008799	HS90A_PIG	Heat shock protein HSP 90-alpha	733	Sus scrofa	9823	HSP90AA1 (HSP90)
P82995	10116	PRO:000008799	HS90A_RAT	Heat shock protein HSP 90-alpha (Heat shock 86 kDa) (Hsp90)	733	Rattus nor	10116	Hsp90aa1 (Hsp86)
P41148	9615	PRO:000008801	ENPL_CANFA	Endoplasmic (Heat shock protein 90 kDa beta member 1)	804	Canis fami	9615	HSP90B1 (GRP94)
P08110	9031	PRO:000008801	ENPL_CHICK	Endoplasmic (Heat shock protein 90 kDa beta member 1)	795	Gallus gall	9031	HSP90B1 (TRA1)
Q29092	9823	PRO:000008801	ENPL_PIG	Endoplasmic (Heat shock protein 90 kDa beta member 1)	804	Sus scrofa	9823	HSP90B1 (GRP94)
Q2TBX4	9913	PRO:000008804	HSP13_BOVIN	Heat shock 70 kDa protein 13 (Stress 70 protein chaperon)	471	Bos taurus	9913	HSPA13 (STCH)
O35162	10116	PRO:000008804	HSP13_RAT	Heat shock 70 kDa protein 13 (Stress 70 protein chaperon)	471	Rattus nor	10116	Hspa13 (Stch)
Q2YDD0	9913	PRO:000008805	HSP7E_BOVIN	Heat shock 70 kDa protein 14	509	Bos taurus	9913	HSPA14
Q6AYB4	10116	PRO:000008805	HSP7E_RAT	Heat shock 70 kDa protein 14	509	Rattus nor	10116	Hspa14
P0CB32	9913	PRO:000008806	HS71L_BOVIN	Heat shock 70 kDa protein 1-like (Heat shock 70 kDa prot)	641	Bos taurus	9913	HSPA1L
A5A8V7	9823	PRO:000008806	HS71L_PIG	Heat shock 70 kDa protein 1-like (Heat shock 70 kDa prot)	641	Sus scrofa	9823	HSPA1L
P55063	10116	PRO:000008806	HS71L_RAT	Heat shock 70 kDa protein 1-like (Heat shock 70 kDa prot)	641	Rattus nor	10116	Hspa1l (Hsp70-3)
P34933	9913	PRO:000008807	HSP72_BOVIN	Heat shock-related 70 kDa protein 2 (Heat shock 70 kDa p)	636	Bos taurus	9913	HSPA2 (HSP70-3)
P14659	10116	PRO:000008807	HSP72_RAT	Heat shock-related 70 kDa protein 2 (Heat shock protein 7	633	Rattus nor	10116	Hspa2 (Hst70)

* Manually curated
HSPs related antibodies

- Tabular format
 - Essential fields from RACE-PRO
 - “Tracer ID” tracks individual rows
- Supports automated terms management processes
 - Tracer ID can be used as a “temporary” URI

A “Term Broker” should manage interactions between PRO and applications

- A term broker is server software that assembles batch requests for PRO
 - Receives requests from the modeler
 - Produces placeholder URIs
- Submissions to PRO are made in batch
 - Additional protocol supports substitution of placeholder with final URIs



Antibodies modeling

- The ‘term broker’ can be used for improving our antibodies modeling process
- We are starting with 3k antibodies thaken from the AlzForum database (20k+ antibodies) (<http://www.alzforum.org/res/com/ant/>)
- The modeling starts with semi-automatic annotation of the record through our tool

Antibodies to Amyloid Precursor & Amyloid Precursor-related Proteins						
From the Manufacturers						
Antigen (Clone) IgG	Distributor (Producer)	Immunogen (Epitope)	Host (Formulation)	Methods glossary	Specificity	Reactivity top
APP (3E9) IgG ₁	Leinco Technologies cat# A121	immunogen = APP695 synthetic peptide (L E VPTDGNAGLLAEPQIAMFC)	monoclonal mouse (lyophilized, PBS, sucrose, affinity purified)	IH(P), WB	APP695, specific sequence	human, mouse (other species not tested)

Annotation Extracts Structured Information from Antibody Records

- Automatic dictionaries identify regions of structured text
- Java application allows curators to review, reject, or extend annotations
- Annotations exported to an OBI RDF format
- Terms requests submitted as batch request

Antibody

```
----- anti:ABDateModified ----  
6/19/09  
----- anti:AGName ----  
"APP, APLF"  
----- anti:Directory ----  
APP  
----- anti:Name ----  
ABR Thermo Fisher Scientific  
----- anti:SortName ----  
"APP, APLF"  
----- anti:Title ----  
Antibodies to Amyloid Precursor & Amyloid Precursor-related  
Proteins  
----- anti:URL1 ----  
http://www.thermo.com/abr  
----- anti:antigenInfo ----  
IgG1  
----- anti:clonality ----  
monoclonal  
----- anti:cloneNum ----  
mAbP2-1  
----- anti:datasheet ----  
http://www.bioreagents.com/products/productDetails/productDetails  
.cfm?catnbr=OMA1-03132  
----- anti:datasheetLinkText ----  
APP  
----- anti:distributorInfo ----  
"Cat# OMA1-03132 Reference: Tampellini, 2007"  
----- anti:epitope ----  
"immunogen = N-terminal 100 amino acids from protease nexin-II  
(PN-II), which is the secreted form of human APP"  
----- anti:hostExtraInfo ----  
"purified IgG, PBS"  
----- anti:hostFastOutput ----  
monoclonal mouse  
----- anti:methodExtraInfo ----  
NULL  
----- anti:methodFastOutput ----  
"ELISA, IC, IP, WB"  
----- anti:reactivityFastOutput ----  
"human, primate (various)"  
----- anti:reactivityExtraInfo ----  
NULL  
----- anti:specificity ----  
N-terminus of APP
```

Annotations

1. www.bioreagents.com : [Reject](#) [Collapse](#) [Match](#)

- Comment:
- Annotates: <http://neurocommons.org/antibodies/4997>
- Property: <http://neurocommons.org/antibodies/datasheet>
- Text: www.bioreagents.com
- Span: 7,26
- Annotator: Timothy Danford
- Annotation Qualifiers:
 - automatic annotation
 - supplier
- Judgements:
 - accept (Timothy Danford 2010-03-01T08:44:10Z)

Show Rejected

Term Requests

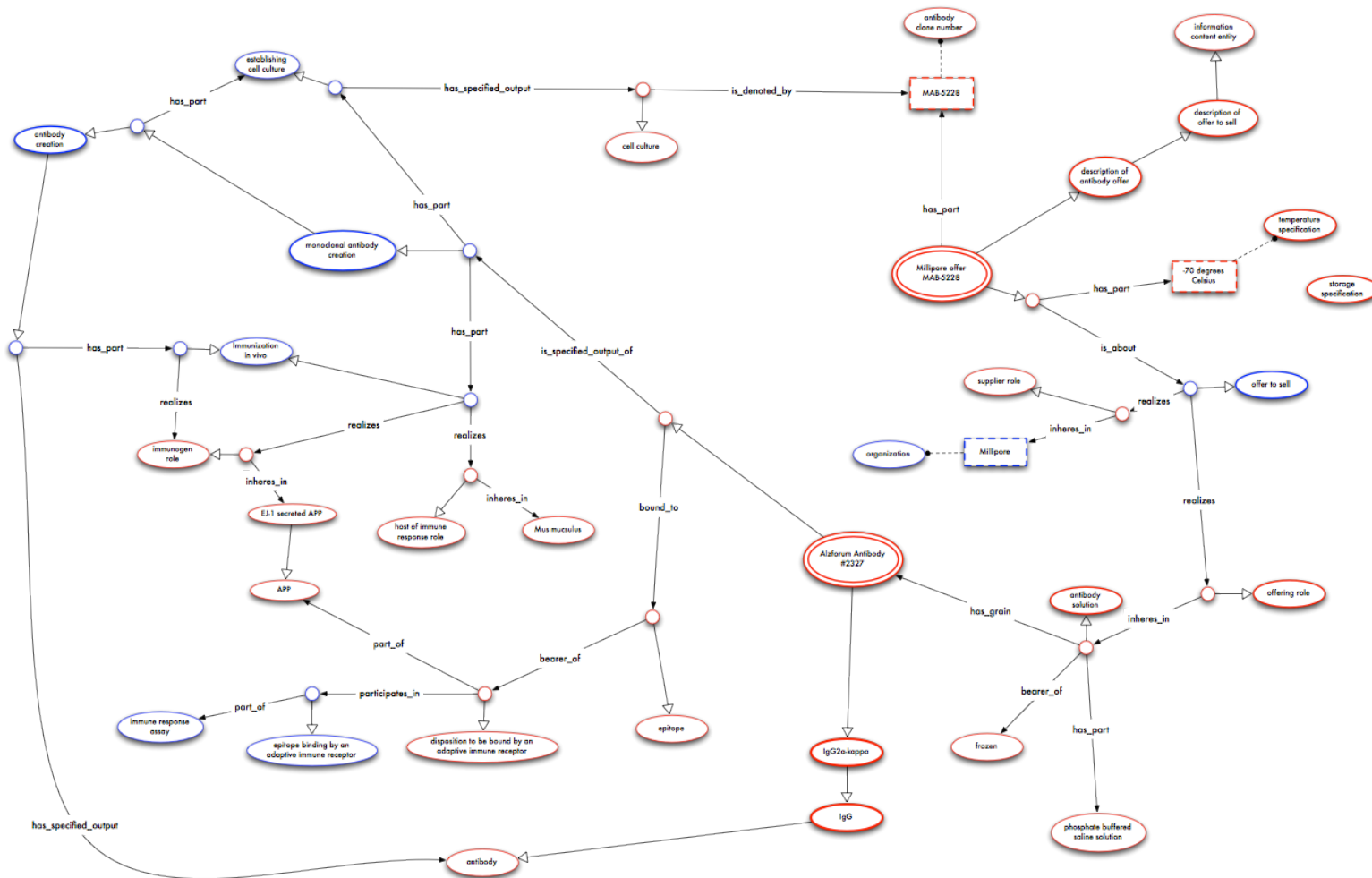
mAbP2-1
primate

Finished?

<- Lookup Scan ->

Add->Request Only Current Annotations

Annotations Translated Into OBI-Compliant RDF



Terms requests submitted as batch request

- We need to generate temporary IDs to be included in the request
- Temporary IDs are used in the application for regular functioning and for keeping track of the requests
- We need coded responses for the term requests in order to process them automatically in the application

People

Mass General Hospital

- Paolo Ciccarese
- Timothy Danford
- Tim Clark
- Sudeshna Das

Science Commons

- Alan Ruttenberg
- Jonathan Rees
- Kaitlin Thaney

Alzforum

- Elizabeth Wu
- Gwen Wong