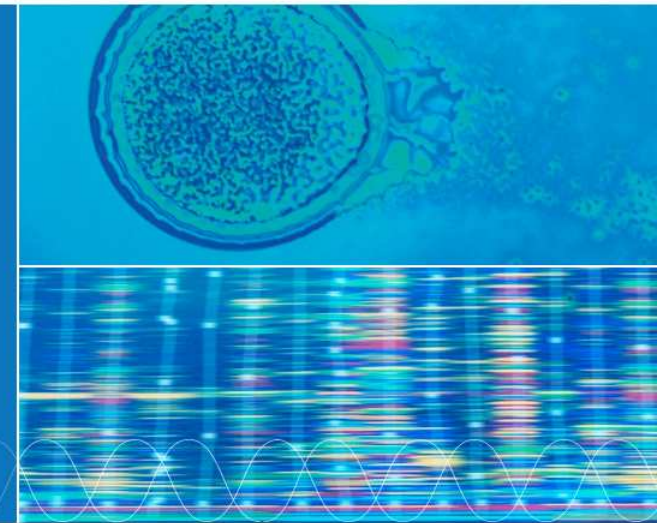




Semantic Search in Biomedical Science Content

Applications for an NLP Engine

Martin Griffies | October 2010.



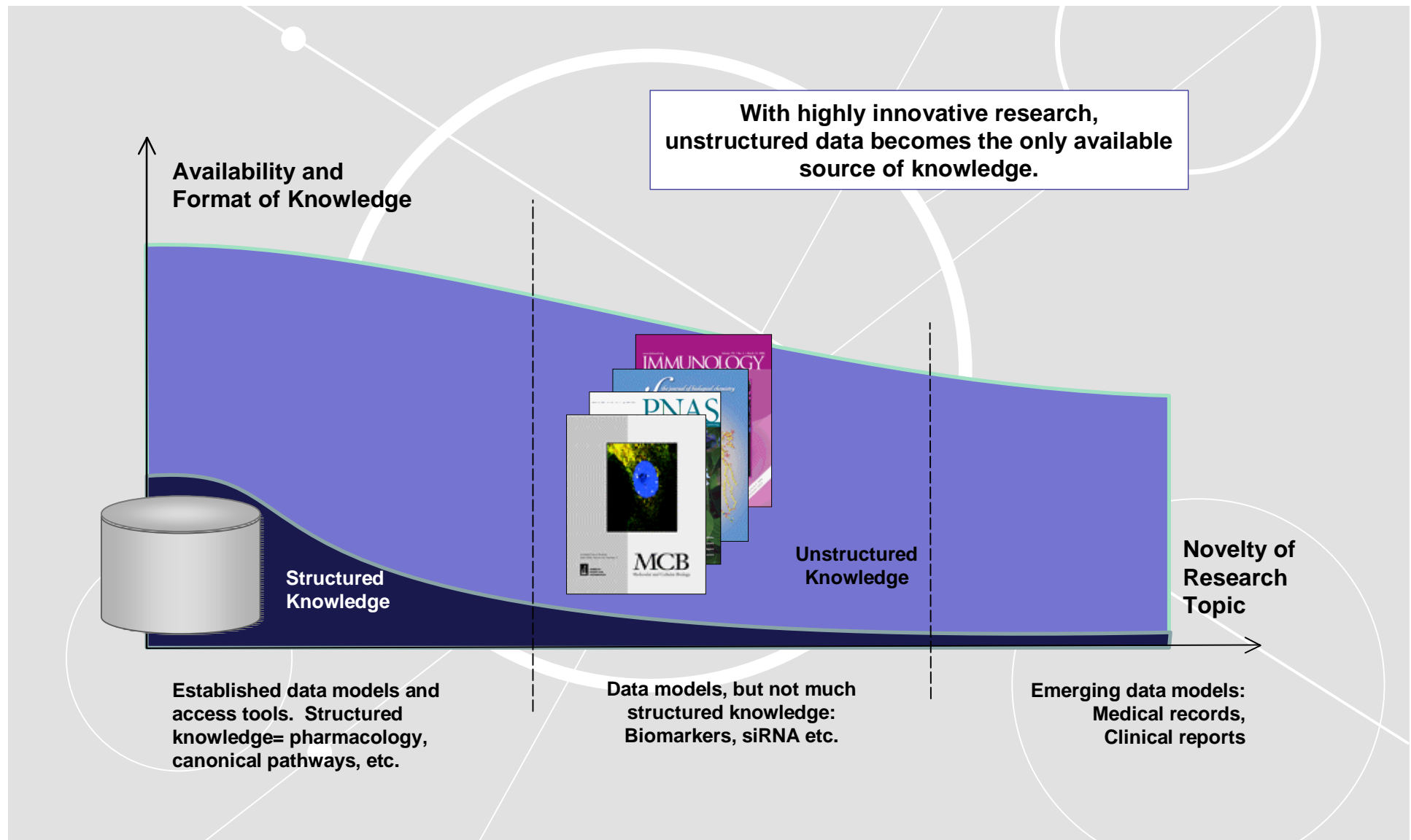
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We have a problem

Too much information, too little knowledge

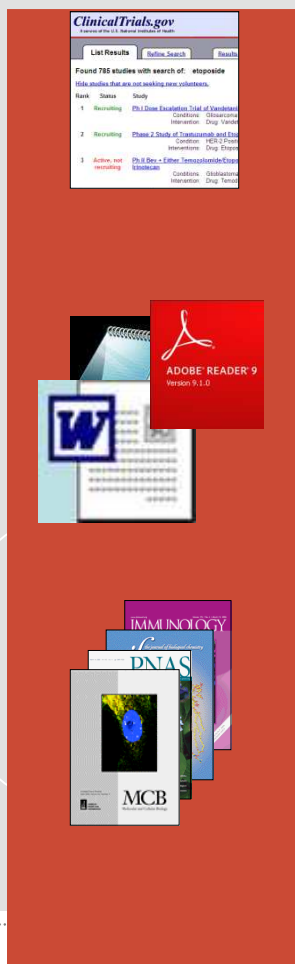
- External data
 - Free : PubMed, ClinicalTrials.gov, Open Access journals, Espace, ..
 - Subscription journals, digests, secondary sources
 - WWW search results
 - News feeds, advertisements
 - Conferences
 - etc
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 - Structured: databases, tables, curated data
 - Unstructured – reports, scanned documents.

The Evolving Challenge



The challenge of volume

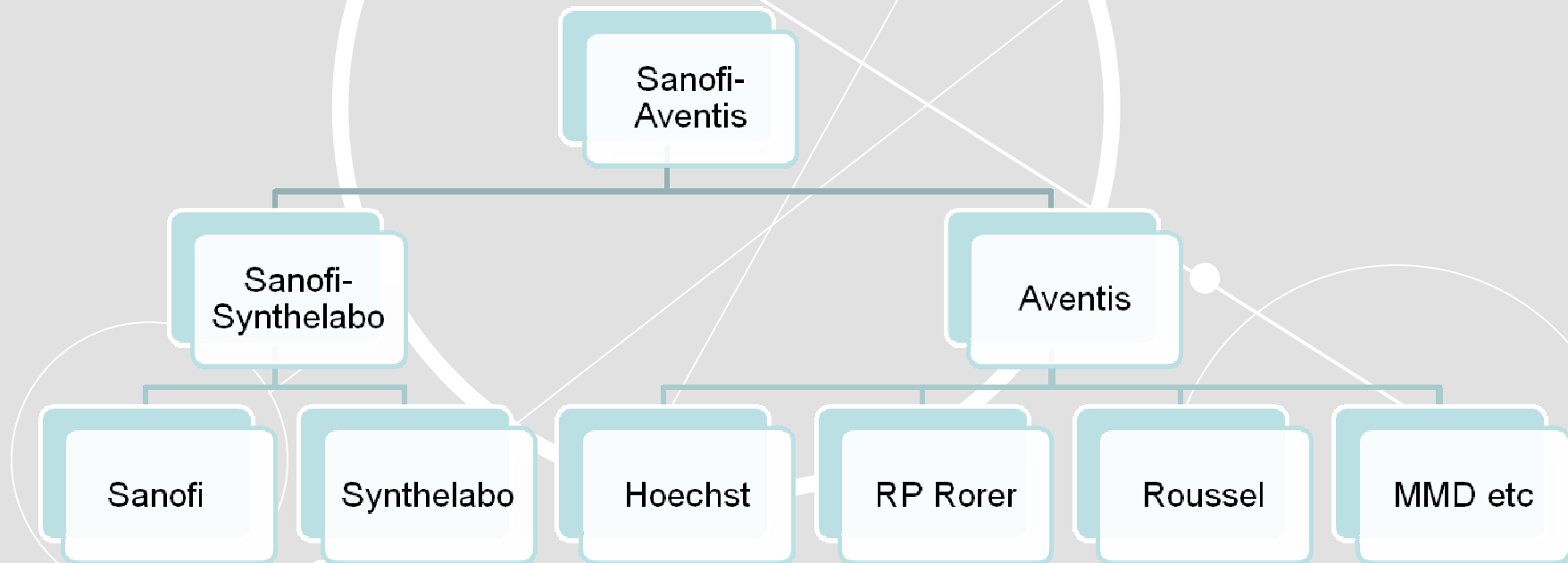
More is not necessarily better



- 20 million PubMed abstracts
- 500.000 USPTO applications / year
- PubChem: 72 million records / 28 m structures.

The challenge of Origin

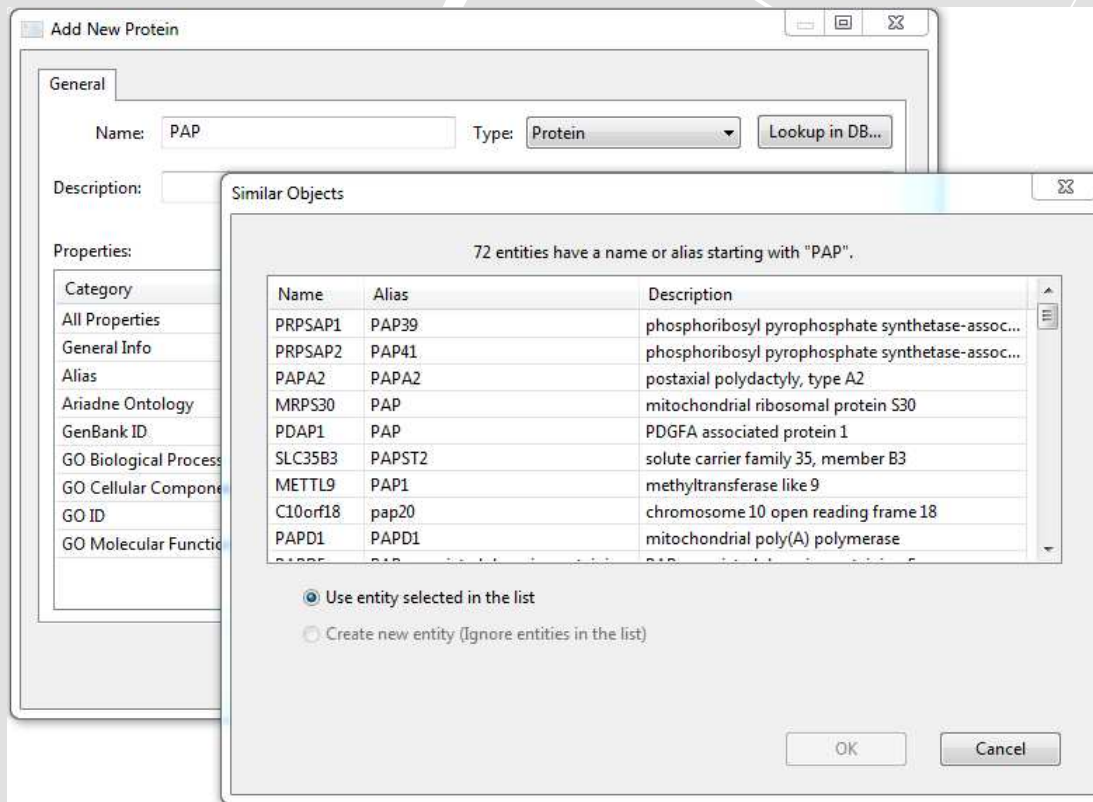
Time, location, language: **Integration.**



The challenge of Meaning

The need for Semantics

- 1700 synonyms for APAP
- 70+ entities named “PAP”



The screenshot shows a software interface for adding a new protein. The main window is titled "Add New Protein" and has a "General" tab. The "Name" field contains "PAP", the "Type" is set to "Protein", and there is a "Lookup in DB..." button. A "Description" field is also present. Below these are "Properties" including "Category" and a list of ontology terms like "All Properties", "General Info", "Alias", "Ariadne Ontology", "GenBank ID", "GO Biological Process", "GO Cellular Component", "GO ID", and "GO Molecular Function".

A "Similar Objects" dialog box is overlaid on top, displaying a table of 72 entities with names or aliases starting with "PAP". The table has three columns: "Name", "Alias", and "Description".

Name	Alias	Description
PRPSAP1	PAP39	phosphoribosyl pyrophosphate synthetase-assoc...
PRPSAP2	PAP41	phosphoribosyl pyrophosphate synthetase-assoc...
PAPA2	PAPA2	postaxial polydactyly, type A2
MRPS30	PAP	mitochondrial ribosomal protein S30
PDAP1	PAP	PDGFA associated protein 1
SLC35B3	PAPST2	solute carrier family 35, member B3
METTL9	PAP1	methyltransferase like 9
C10orf18	pap20	chromosome 10 open reading frame 18
PAPD1	PAPD1	mitochondrial poly(A) polymerase

Below the table, there are two radio buttons: "Use entity selected in the list" (which is selected) and "Create new entity (Ignore entities in the list)". At the bottom of the dialog are "OK" and "Cancel" buttons.

The Search for meaning

90% of Searches are Keyword-based



- Retrieves documents, not facts.
- But facts / assertions / relationships are (usually) what users want.
- RELEVANCE is needed

11940574:7 Because **Axin2**⁶ has been shown to_{Main} **associate**¹ with and **inhibit**³ **beta-catenin**³ abundance and function._{Main}
 we **hypothesized** that_{Main} **That**_{Main} **Axin 2**⁴ which is affecting⁷ **proliferation of MEF cell line**_{NPmod} **can work**³ in a **negative feedback pathway**_{Main} **5** **regulating**⁵ **Wnt signaling** and thus **2** **controlling**² **apoptotic process**_{VPmod}.

Syntactic normalization:

1. Verbal conjunction
2. VP conjunctions
3. NP conjunctions
4. NP modifiers
5. VP modifiers
6. Some syntactic movements
7. NP prepositional structure
8. Relational clauses
9. Nominalizations

Decomposed primitive sentences (triplets):

Axin2	associate	beta-catenin abundance
Axin2	associate	beta-catenin function
Axin2	inhibit	beta-catenin abundance
Axin2	inhibit	beta-catenin function
Axin2	affect	MEF cell line proliferation
Axin2	work	negative feedback pathway
Axin2	regulate	Wnt signaling
Axin2	control	apoptotic process

From Text to Relations

“Axin binds beta-catenin and inhibits GSK-3beta activity in hepatocytes.”



NLP: short statements (key facts in the form of triplets)

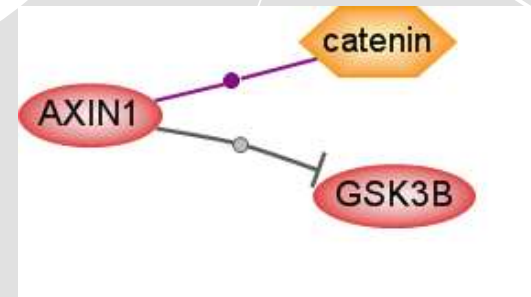
Axin	<u>binds</u>	beta-catenin
Axin	<u>inhibits</u>	GSK-3beta activity



Extracting relations

Axin - beta-catenin, relation: Binding













Axin -> GSK-3beta, relation: Regulation,
effect: Negative

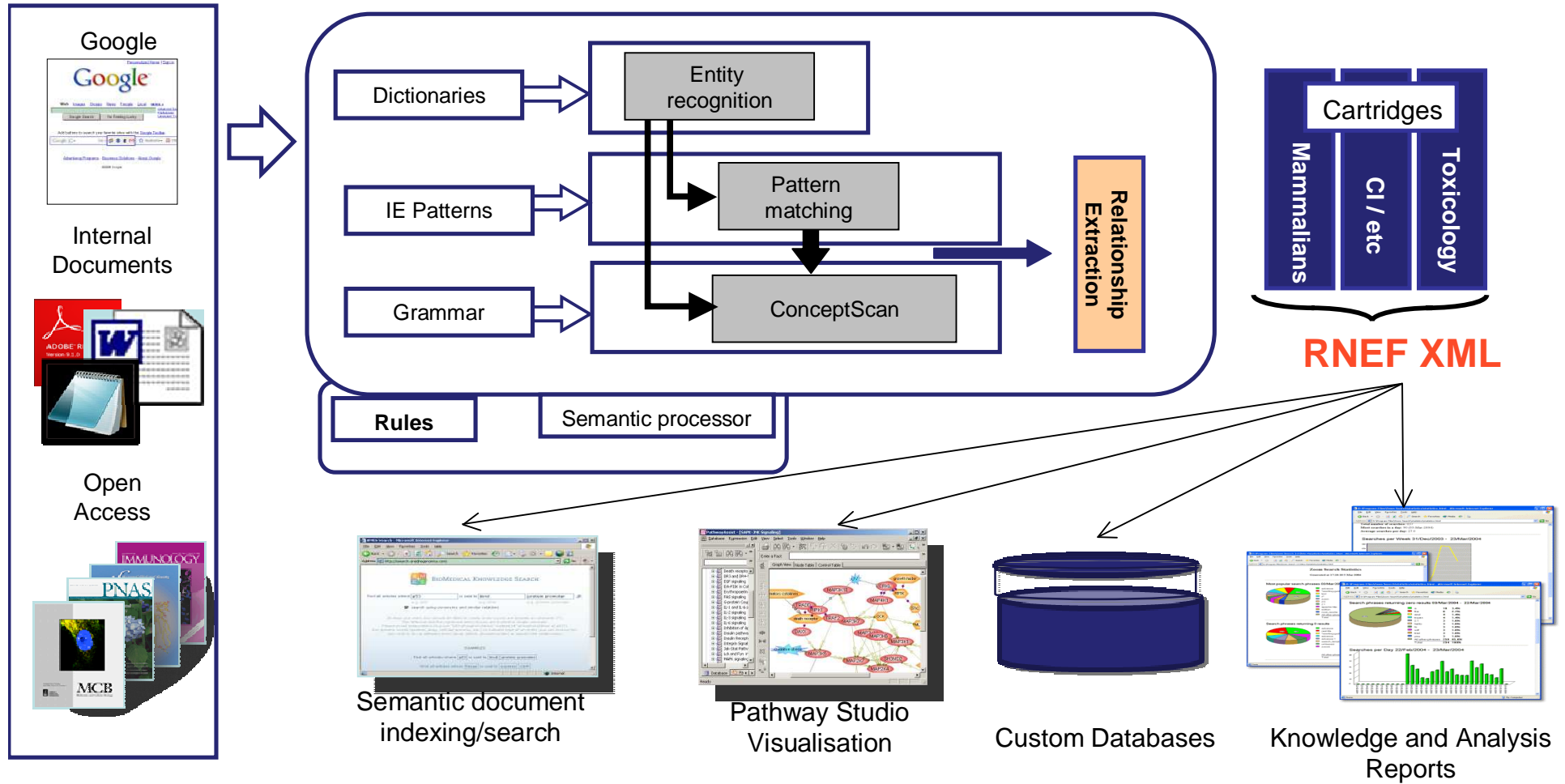


Semantic Search System

- Finds the right documents
- Summarizes / precis findings
- Can also answer natural language questions:
 - “what causes migraine?”


Can be tailored for specific domains by adding *ontologies*

- [Brivaracetam inhibits spreading depression in rat neocortical slices in vitro.](#)
 PubMed  PubGet 
 Margineanu DG, Klitgaard H
 Seizure (2009) [Show Abstract »](#)
 Epilepsy and migraine are episodic neurological disorders with marked co-morbidity, making migraine common among epileptic patients.
- [Influence of MTHFR genotype on contingent negative variation and MRI abnormalities in migraine.](#)
 PubMed  PubGet 
 de Tommaso M ... Livrea P »
 Headache (2007) [Show Abstract »](#)
 The hyper-homocysteinemia may favor the vascular and neuronal mechanism underlying migraine, and the risk of stroke.
- [Metoclopramide for migraine-associated hiccup.](#)
 PubMed  PubGet 
 Gupta VK
 Int J Clin Pract (2006) [Show Abstract »](#)
 Metoclopramide can swiftly control both hiccup and migraine headache.
- [Chronic daily headache: when to suspect sinus disease.](#)
 PubMed  PubGet 
 Houser SM, Levine HL
 Curr Pain Headache Rep (2008) [Show Abstract »](#)
 Migraine may be responsible for many headaches thought to be caused by the sinuses.
- [\[Genetics of migraine\]](#)
 PubMed  PubGet 
 Evers S ... Ringelstein EB »
 Nervenarzt (1996) [Show Abstract »](#)
 This would lead to further clues to the pathogenesis underlying migraine and, thus, to therapeutic developments.
- [Alzheimer's disease and other neurological disorders.](#)
 PubMed  PubGet 



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[kainic acid](#)
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[mecamylamine](#)


RELATIONSHIP-DRIVEN
BIOMEDICAL SEARCH

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Keyword Results (28,080)

Applied Filters
Expand all Relationships
Turn Highlighting Off
Sort by Date

None

Filters

Also Containing

Published Within

Publication Type

Key Concepts

- 1 Elevated corticosteroid levels block the memory-improving effects of nootropics and cholinimetics. (PubMed)**

Mondadori C ... Häusler A »
 Psychopharmacology (Berl) (1992) [Show Abstract](#) »

The improvement of **memory induced** by **physostigmine**, **arecoline**, and **tacrine (THA)** was similarly inhibited.
- 2 Effects of U-50,488H on scopolamine-, mecamylamine- and dizocilpine-induced learning and memory impairment in rats. (PubMed)**

Hiramatsu M ... Kameyama T »
 J Pharmacol Exp Ther (1998) [Show Abstract](#) »

Administration of U-50,488H (0.17 or 0.51 μmol/kg s.c.) 25 min before the acquisition **trial** reversed the impairment of learning and **memory induced** by scopolamine and **mecamylamine**.

» [More Relationships](#)
- 3 Cholinesterase inhibitors ameliorate behavioral deficits induced by MK-801 in mice. (PubMed)**

Csemansky JG ... Dong H »
 Neuropsychopharmacology (2005) [Show Abstract](#) »

Three separate experiments were conducted to test the effects of **physostigmine**, **donepezil**, or **galantamine** on deficits in learning and **memory induced** by **MK-801**.

» [More Relationships](#)
- 4 Nicotinic interactions with antipsychotic drugs, models of schizophrenia and impacts on cognitive function. (PubMed)**

Levin ED, Rezvani AH
 Biochem Pharmacol (2007) [Show Abstract](#) »

Cartridges & Ontologies

Flexibility & Domain Coverage

- Single engine, multiple domains
 - In-house dictionaries: canonical / preferred terms
 - Standard terminologies:
 - MeSH,
 - GO,
 - SNOMED,
 - MedDRA etc
- Clinical, AE records,
- Toxicology, Plants, Proteins,
- Competitive Intelligence

BMKS App – Semantic Search (Plants)

Key Concepts

\$smallmol

auxin	ammonium
GA	selenite
IAA	pectin
GA3	silicon
C2H4	GA(4)
ABA	quinclorac
cytokinin	citric acid
FC	glyphosate
BR	silver
RS	Ca2+
methionine	haemin
BL	tryptophan
NaCl	ZEN
CO2	AA
catechin	CFM
sterol	anthocyanin
ETH	PAA
benzyladenine	GA(14)
TIBA	SA
Kinetin	
Ozone	
oligosaccharides	
H+	
lysine	
Cadmium	
lanolin mixture	
JA	
2,4-D	
1-NAA	
Na+	
octopine	

Q \$smallmol induces growth

Search ?

Authors ?

Journals ?

Clear All

relationships (263) ?

Keyword Results (10,292) ?


Selected: 0 Export

Expand All Relationships

Turn Highlighting Off

Sort by Date

[nisiccocin- and IAA-induced elongation growth share the same pattern of K⁺ dependence.](#)


PubMed 

ode K, Lüthen H
Exp Bot (2001) [Show Abstract »](#)

ne potassium channel blocker tetraethylammonium (TEA) reversibly inhibited FC-induced growth.

[More Relationships](#)

[volvement of oxyradicals in promotion/inhibition of expansion growth in cucumber cotyledons.](#)


PubMed 

ataria S ... Guruprasad KN »
dian J Exp Biol (2005) [Show Abstract »](#)

ytokinins reduced the level of oxyradicals in dark grown cotyledons, while promoting growth.

[More Relationships](#)

[Auxin Conjugation by Tobacco Mesophyll Protoplasts : Correlations between Auxin Cytotoxicity under Low Density Growth Conditions and Induction of Conjugation Processes at High Density.](#)


PubMed 

aboche M ... Leguay JJ »
lant Physiol (1984) [Show Abstract »](#)

ne induction of growth by 2,4-dichlorophenoxyacetic acid and picloram was not affected by cell density.

[More Relationships](#)

BMKS Application – Translational Medicine



BIO-MEDICAL
KNOWLEDGE
SEARCH

?

?

?

∞ ResNet Relations (155) ?
🔑 Keyword Results (1,320) ?

[Turn Highlighting Off](#)

Applied Filters ?

None

Filters

🔑 **Key Entities** ?

- 12000006
- 12003066
- 14-3-3
- ABCA1
- ADAM10
- ADRB2
- AHSG
- AKT1
- ALB
- ALDH2
- ALOX5
- ALOX5AP
- APBA3
- APBB1
- APBB3
- APOA4
- APOA5
- APOC1

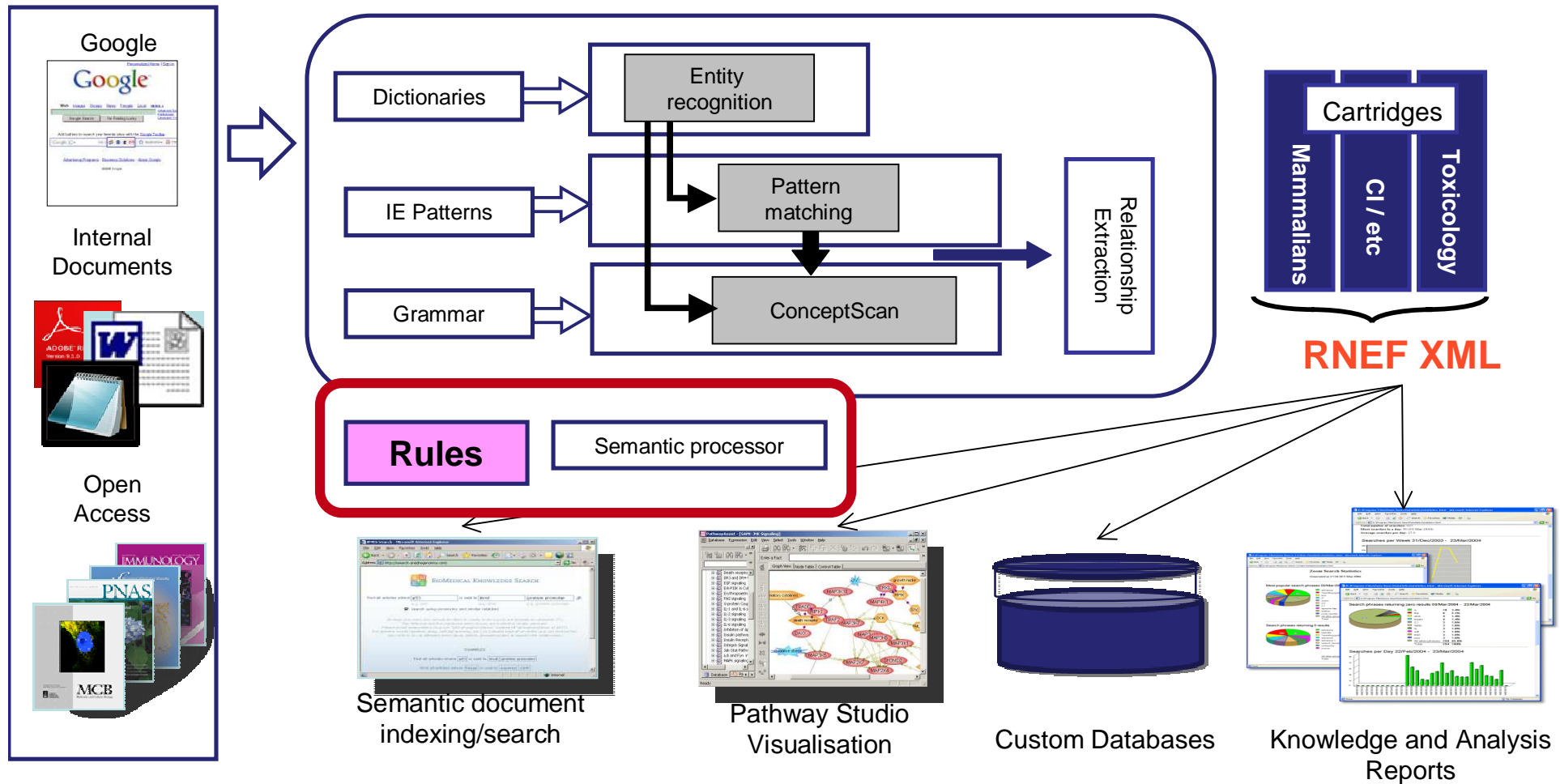
→ **StateChange: Alzheimer Disease -> CYP2D6 (mutation)**

Pharmacogenetics 11: 237-245. [CrossRef] [Medline] Tanaka S, Chen X, Xia Y, Kang DE, Match N, Sundsmo M, Thomas RG, Katzman R, Thal LJ, Trojanowski JQ, et al. (1998) Association of CYP2D microsatellite polymorphism with Lewy body variant of **Alzheimer's disease**.
 16033950:10298; Organ: brain, Organism: Homo sapiens
 3 More References »

→ **positive StateChange: Alzheimer Disease -> PPARG (mutation)**

« Fewer References

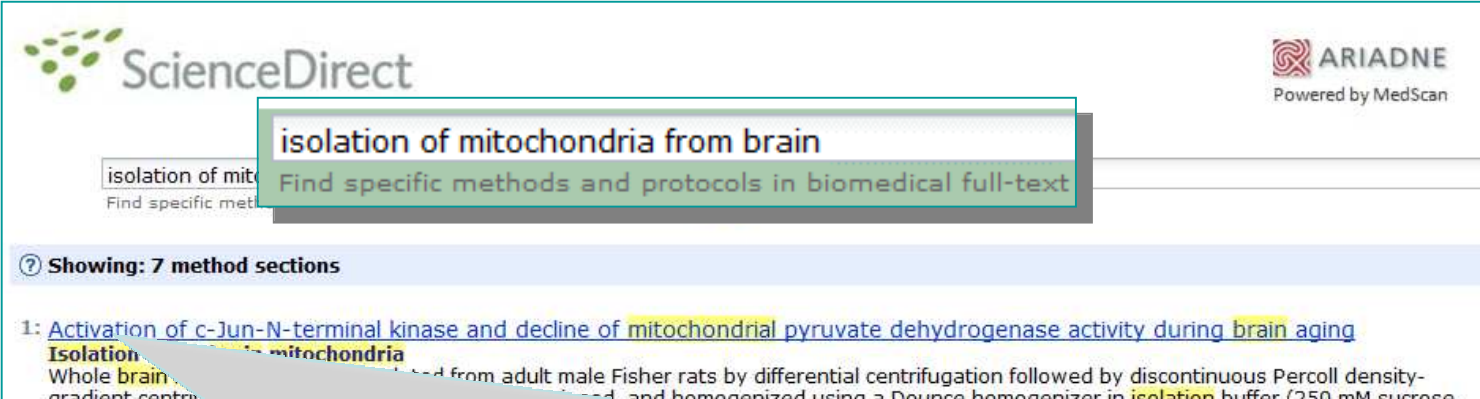
- [1] Because both **COX** and **PPARG** expression are increased in **Alzheimer brains** (Kitamura et al., 1999), it is likely that at least some effects of ibuprofen on AD pathology are mediated through changes in the activities of these enzymes.
 10908610:10199; Tissue: microglia
- [2] It has been reported that the expression of cyclooxygenase-2 (COX-2) and peroxisome proliferator-activated receptor-gamma (PPARG) is elevated in **Alzheimer's disease**, and certain nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the risk and delay the onset of **Alzheimer's disease**.
 15033806:3; CellLineName: PC 12
- [3] **Alzheimer's disease** is associated with elevated levels of Abeta, and enhanced expression of **PPARG**.
 15993441:1;
- [4] In addition, this polymorphic mutation in **PPARG** is associated with other aspects of human diseases, including **cancers, polycystic ovary syndrome, Alzheimer disease** and aging.
 19390629:4; Tissue: fat, Organism: Homo sapiens



Examples of MedScan customization projects performed for customers:

- 1) Immunology: facts about cell types
- 2) Biomarkers: automatic classification of biomarkers
- 3) ClinicalTrials.gov: import of XML formatted clinical trial reports
- 4) Phosphosites: extraction of protein phosphorylation sites
- 5) Mutations: extraction of mutations linked to diseases

Use of Rules: Materials & Methods



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Find specific methods and protocols in biomedical full-text

isolation of mitochondria
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Showing: 7 method sections

1: Activation of c-Jun-N-terminal kinase and decline of mitochondrial pyruvate dehydrogenase activity during brain aging
Isolation of rat brain mitochondria
Whole brain mitochondria were isolated from adult male Fisher rats by differential centrifugation followed by discontinuous Percoll density-gradient centrifugation and homogenized using a Dounce homogenizer in isolation buffer (250 mM sucrose

Material and
Methods Section

Organelle

Method

Organ

Isolation of rat brain mitochondria

Whole brain mitochondria were isolated from adult male Fisher rats by differential centrifugation followed by discontinuous Percoll density-gradient centrifugation [24]. Brains were excised, rinsed, and homogenized using a Dounce homogenizer in isolation buffer (250 mM sucrose, 20 mM HEPES, 1 mM EDTA, 1 mM EGTA, 1 mM dithiothreitol, protease inhibitor (100 µl per brain), 0.5% bovine serum albumin (BSA), pH 7.4). The homogenate was centrifuged at 1330×g (5 min) to remove nuclei and cell debris and the resulting supernatant was centrifuged at 21 200×g (10 min). The pellet was resuspended in 15% Percoll and was centrifuged 21 000×g for 10 min. The resulting loose pellet was layered onto a preformed discontinuous Percoll gradient and centrifuged at 31 000×g for 10 min. Mitochondrial fractions were collected and washed twice with isolation buffer followed by washing in BSA-free isolation buffer. The purity of the mitochondrial fraction was assessed as previously described [12] by measuring markers of microsomal (NADPH-cytochrome P450 reductase) and cytosolic (lactic dehydrogenase, β-actin) contamination. Activities of NADPH-cytochrome P450 reductase and lactic dehydrogenase were negligible when compared to those in the crude homogenate. β-Actin was absent in the mitochondrial fraction when assessed by immunoblot analysis (shown in Fig. 2).


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Article Outline X

- Summary
- Introduction
- Results and Discussion
- Experimental Procedures
- Acknowledgments
- Accession Numbers
- Supplemental Data
- References
- Publication Information

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 Cell, Volume 139, Issue 6, 1084-1095, 11 December 2009

doi:10.1016/j.cell.2009.11.015

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Article

The Structural Basis for mRNA Recognition and Cleavage by the Ribosome-Dependent Endonuclease RelE

Cajetan Neubauer^{1,4}, Yong-Gui Gao^{1,4}, Kasper R. Andersen^{2,4}, Christine M. Dunham^{1,5}, Ann C. Kelley¹, Jendrik Hentschel¹, Kenn Gerdes³, V. Ramakrishnan¹, and Ditlev E. Brodersen²

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Corresponding author

Corresponding author

⁴ These authors contributed equally to the work

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Summary

Translational control is widely used to adjust gene expression levels. During the stringent response in bacteria, mRNA is degraded on the ribosome by the ribosome-dependent endonuclease, RelE. The molecular basis for recognition of the ribosome and mRNA by RelE and the mechanism of cleavage are unknown. Here, we present crystal structures of *E. coli* RelE in isolation (2.5 Å) and bound to programmed *Thermus thermophilus* 70S ribosomes before (3.3 Å) and after (3.6 Å) cleavage. RelE occupies the A site and causes cleavage of mRNA after the second nucleotide of the codon by reorienting and activating the mRNA for 2'-OH-induced hydrolysis. Stacking of A site codon bases with conserved residues in RelE and 16S rRNA explains the requirement for the ribosome in catalysis and the subtle sequence specificity of the reaction. These structures provide detailed insight into the translational regulation on the bacterial ribosome by mRNA cleavage.

INTRODUCTION

Rapid adaptation to environmental stress is vital for free-living bacteria. During deprivation of nutrients, uncharged transfer RNAs (tRNAs) bind to the ribosome and stall synthesis of the signal nucleotide, (p)ppGpp. This alarmone regulates the *stringent response*, a far-reaching adaptation (Potrykus and Cashel, 2008). The stringent response also leads to activation of RelE, an effective inhibitor of protein synthesis. Under normal physiological conditions, RelE is inactive (Christensen and Gerdes, 2003; Christensen et al., 2001; Galvani et al., 2001; Gottfredsen and Gerdes, 1998; Li et al., 2009; Overgaard et al., 2009). Upon activation, RelE is able to bind the ribosome and specifically cleave messenger RNA (mRNA) in the A site (Christensen and Gerdes, 2003; Pedersen et al., 2003).

Such toxin-antitoxin pairs are very common in bacteria, and the RelE superfamily also encompasses HlgB, YoeB, YafQ, and YhaV, associated with a variety of functions (Gerdes, 2006; Grady and Hayes, 2003; Physak et al., 2009; Schmidt et al., 2007). The crystal structure of YoeB showed that its fold and catalytic mechanism (Kamada and Hanaoka, 2005). RelE is structurally similar to YoeB (Li et al., 2009; Takagi et al., 2005) but lacks the conserved catalytic histidine and glutamine residues. RelE has an intrinsic nuclease activity of the ribosome (Garza-Sanchez et al., 2008; Hayes and Sauer, 2003; Kamada and Hanaoka, 2005; Li et al., 2009; Sunohara et al., 2009). Pausing ribosomes are recovered for rescue by tmRNA in the absence of stringent response factors (Hayes and Sauer, 2003; Kamada and Hanaoka, 2005). The most likely result of the combined action of RelE-like endonucleases and exonucleases like RNase II (Garza-Sanchez et al., 2009). RelE-induced cleavage occurs at the A site codon, although it is occasionally also seen after the third nucleotide and, upon peptide release, even in the E site (Pedersen et al., 2003). The mRNA cleavage efficiency, with the UAG and UGA stop codons and sense codons like UCG and CAG, among the most efficiently cleaved (Pedersen et al., 2003). Together

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RelA

Protein | Chemical | Help

relA (b2784) ▼ E. coli

(p)ppGpp synthetase; ppGpp synthetase I; ATP:GTP 3'-pyrophosphotransferase

[Literature](#) [Sequence](#) [Structure](#) [Locus](#) [Domains](#)

MVAVRSAAHINKAGEFDPEKWIASLGITSGKSCCELAETWAYCLOQDQ

No information available

(P)ppGpp synthetase I/GTP pyrophosphokinase; In eubacteria ppGpp (guanosine 3'-diphosphate 5'-diphosphate) is a mediator of the

Molecular Cancer | Full text | Molecular portrait of cisplatin induced response in human testis cancer cell lines based on gene expression profiles

http://www.molecular-cancer.com/content/6/1/53

Reflect nature

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Acknowledgements

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Molecular portrait of cisplatin induced response in human testis cancer cell lines based on gene expression profiles

Nur Duale, **Birgitte Lindeman**, **Mitsuko Komada**, **Ann-Karin Olsen**, **Ashild Andreassen**, **Erik J Soderlund** and **Gunnar Brunborg**

Department of Chemical Toxicology, Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway

✉ author email ✉ corresponding author email

Molecular Cancer 2007, **6**:53 doi:10.1186/1476-4598-6-53

The electronic version of this article is the complete one and can be found online at: <http://www.molecular-cancer.com/content/6/1/53>

Received: 4 May 2007
Accepted: 21 August 2007
Published: 21 August 2007

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Abstract

Background

Testicular germ cell tumors (TGCTs) respond well to cisplatin-based chemotherapy and show a low incidence of these specific characteristics are not associated with TGCT cells'.

Results

Genes identified in a variety of HCT116 cell lines after cisplatin treatment were strikingly different from that of differentiated TGCT cells. We identified 40 target genes for two microRNAs, hsa-mir-372 and hsa-mir-373 that may interfere with p53 signaling in TGCTs. The tumor suppressor genes *NEO1* and *LATS2*, and the estrogen receptor gene *ESR1*, all have binding sites for p53 and hsa-mir-372/373. *NEO1* and *LATS2* were down-regulated in TGCT cells following cisplatin exposure, while *ESR1* was up-regulated in TGCT cells. Cisplatin-induced genes associated with terminal growth arrest through senescence were identified, indicating associations which were not previously described for TGCT cells.

Conclusion

By linking our gene expression data to publicly available databases and literature, we provide a global pattern of cisplatin-induced cellular

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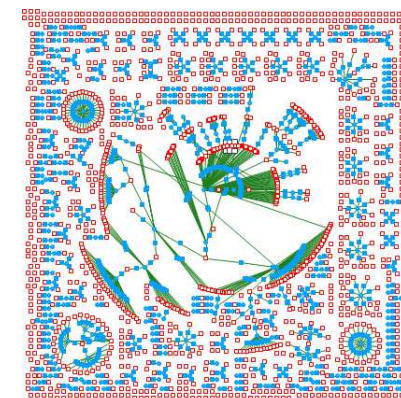
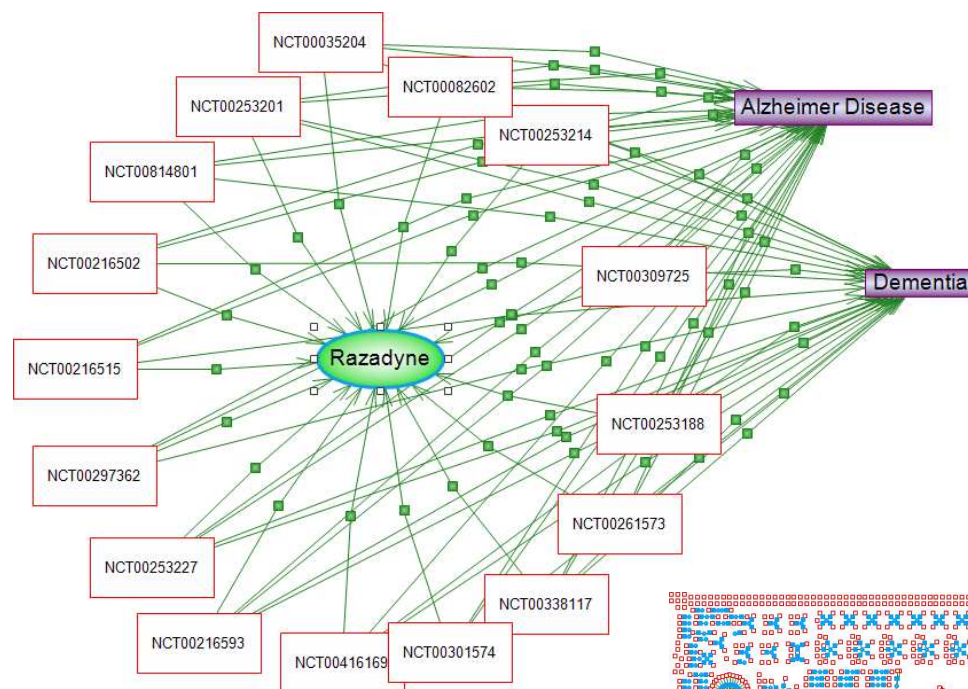
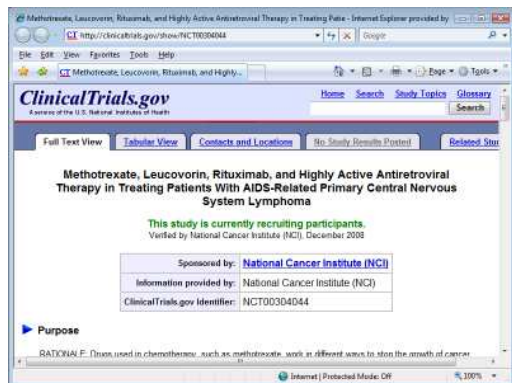
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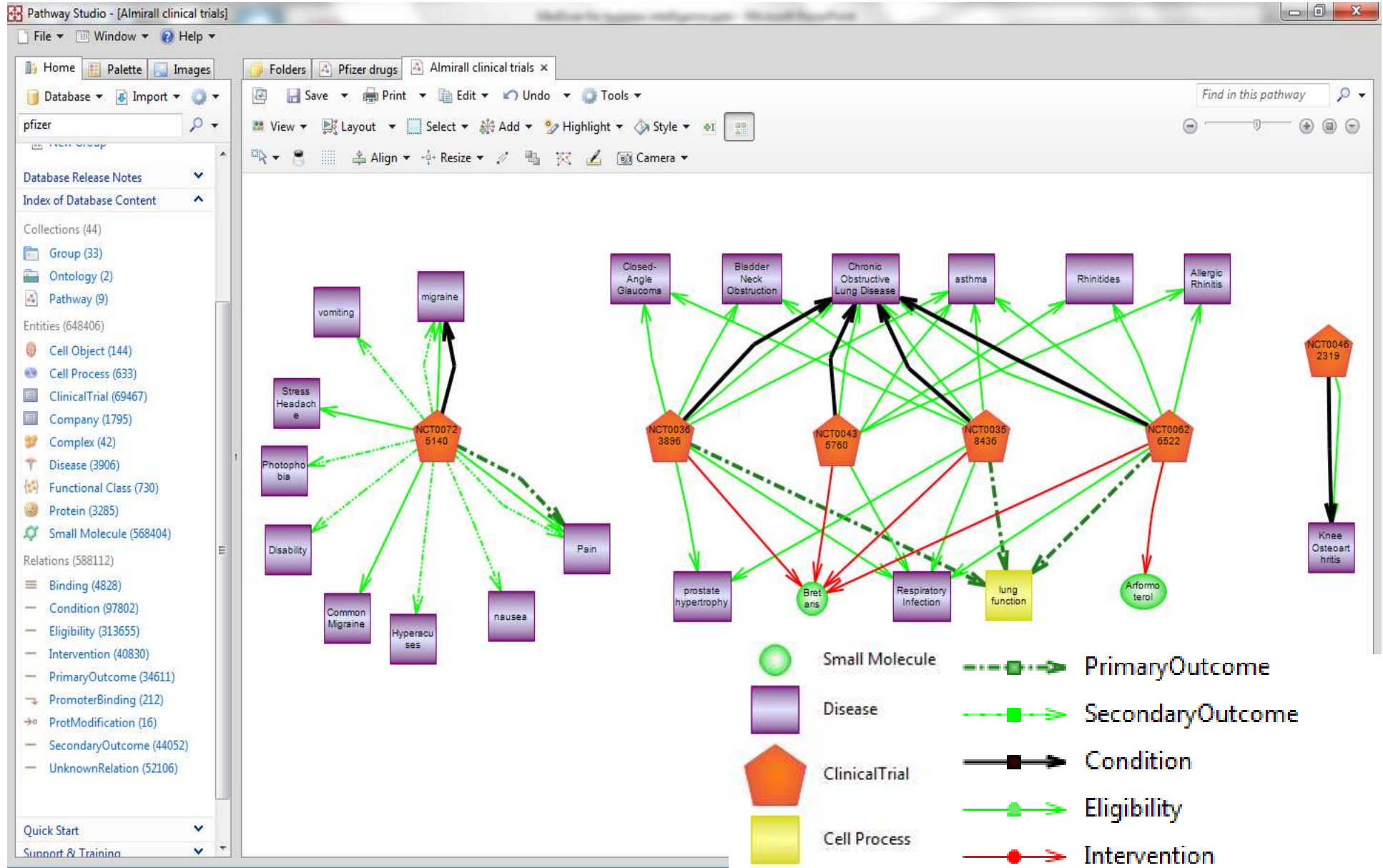


Data Components:

- Study
- Status
- Start
- Company
- Phase
- Primary Outcome

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A Trial Assessing LAS34273 in Moderate to Severe Stable Chronic Obstructive Pulmonary Disease (COPD)

This study has been completed.
 First Received: August 10, 2006 Last Updated: September 1, 2010 [History of Changes](#)

Sponsor:	Almirall, S.A.
Collaborator:	Forest Laboratories
Information provided by:	Almirall, S.A.
ClinicalTrials.gov Identifier:	NCT00363896

Purpose
 To evaluate the efficacy and safety of LAS 34273 compared to placebo in patients with moderate to severe COPD during one year of treatment.

Condition	Intervention	Phase
Chronic Obstructive Pulmonary Disease	Drug: Aclidinium bromide	Phase III

Study Type: Interventional
 Study Design: Allocation: Randomized
 Control: Placebo Control
 Intervention Model: Parallel Assignment
 Masking: Double-Blind

Official Title: Clinical Trial Assessing Efficacy and Safety of LAS34273 in Moderate to Severe Stable Chronic Obstructive Pulmonary Disease (COPD) Patients

Resource links provided by NLM:
[MedlinePlus related topics: COPD \(Chronic Obstructive Pulmonary Disease\)](#)
[Drug Information available for: Aclidinium bromide](#)
[U.S. FDA Resources](#)

Further study results provided by Almirall, S.A.:

Primary Outcome Measures:
 • Lung function

Secondary Outcome Measures:
 • Exacerbations and Quality of Life

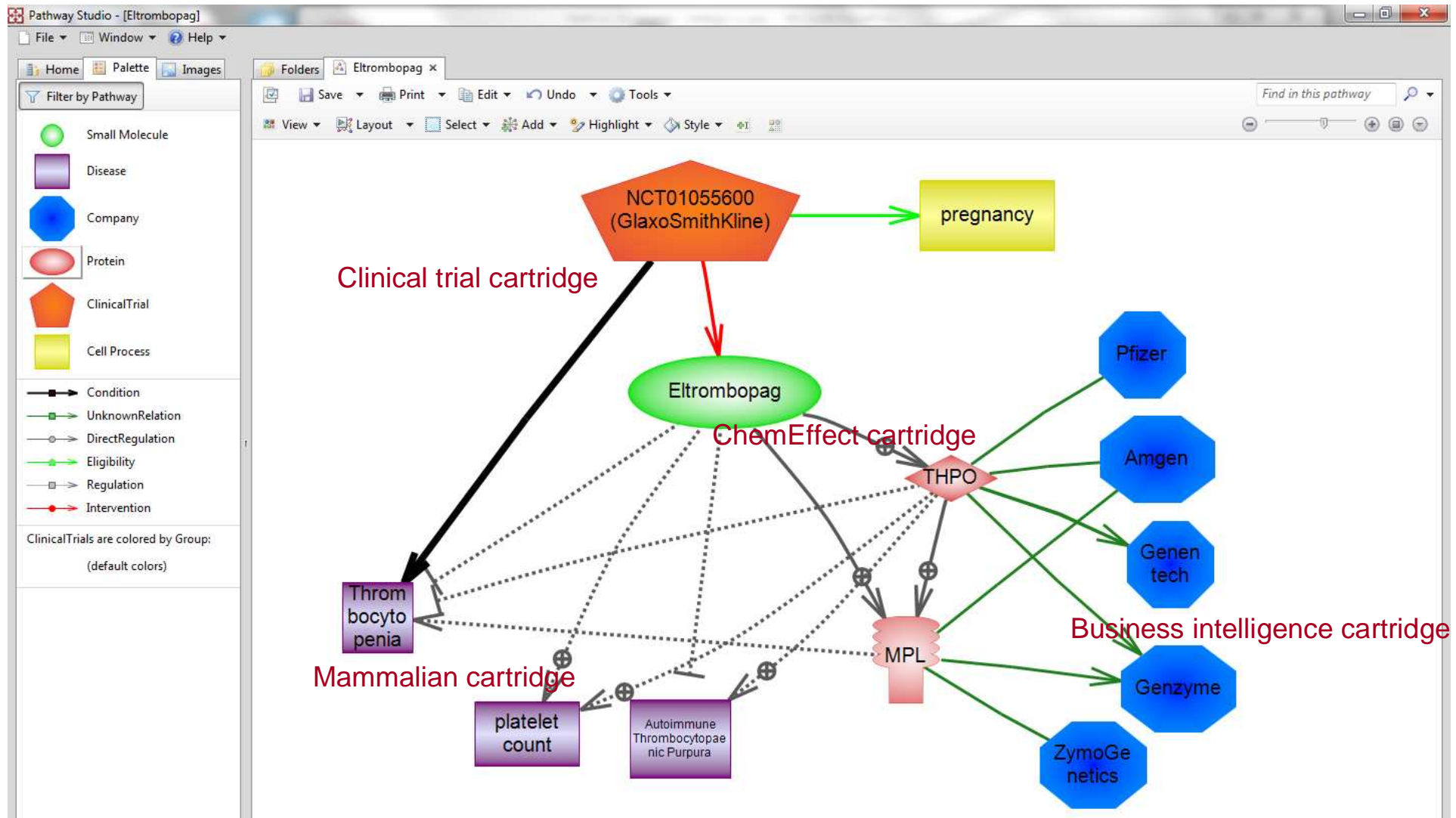
Study Start Date: August 2006
 Study Completion Date: May 2008
 Primary Completion Date: May 2008 (Final data collection date for primary outcome measure)

Eligibility

Ages Eligible for Study: 40 Years and older
 Genders Eligible for Study: Both
 Accepts Healthy Volunteers: No

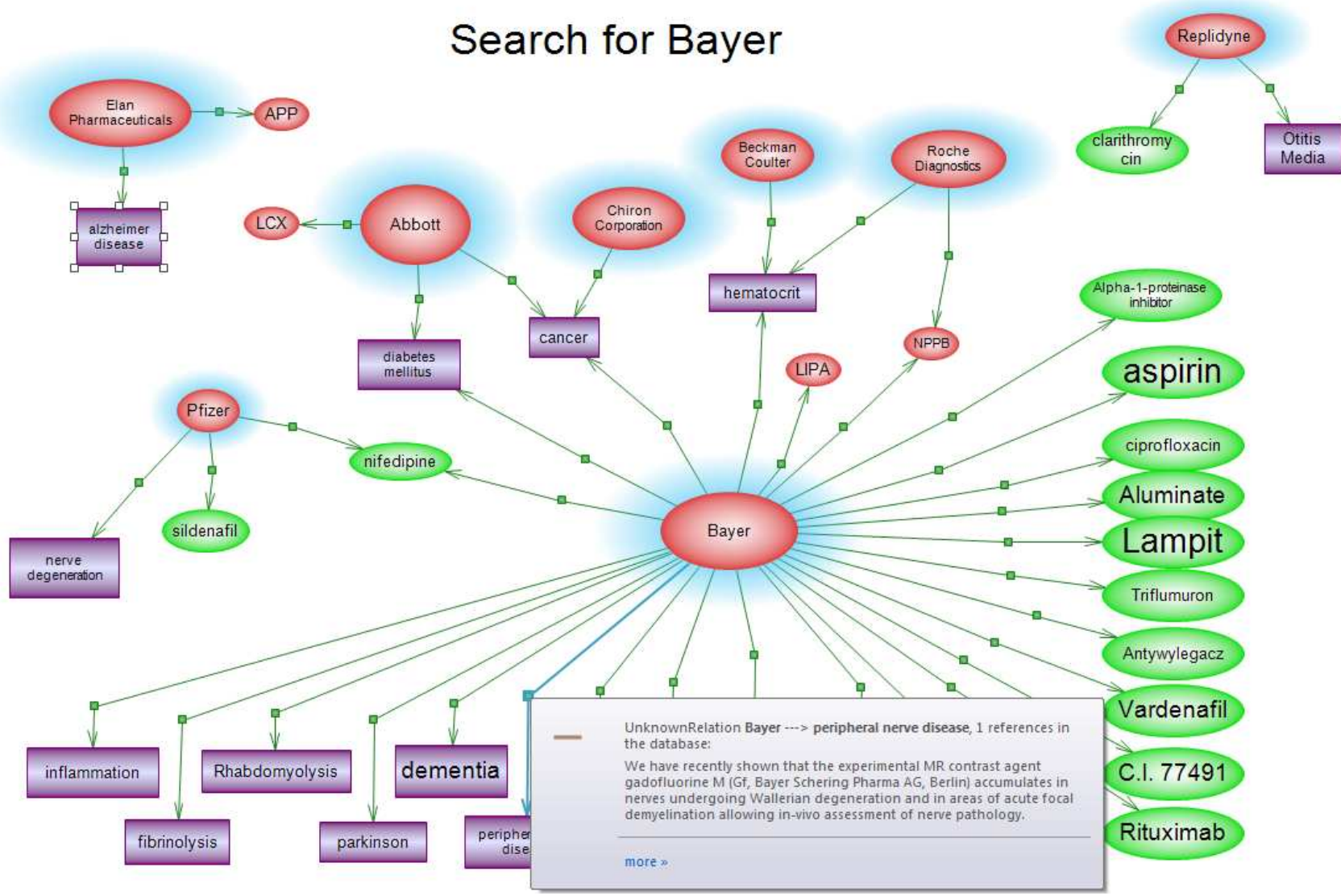
Criteria:
 Inclusion Criteria:
 • Males and females aged ≥ 40 years with a clinical diagnosis of moderate to severe stable COPD
 Exclusion Criteria:
 • History or current diagnosis of asthma, recent respiratory tract infection or acute COPD exacerbation, life expectancy of less than 1 year, known symptomatic prostatic hypertrophy, bladder neck obstruction or narrow-angle glaucoma

Combined cartridges: What companies are developing TPO therapies?



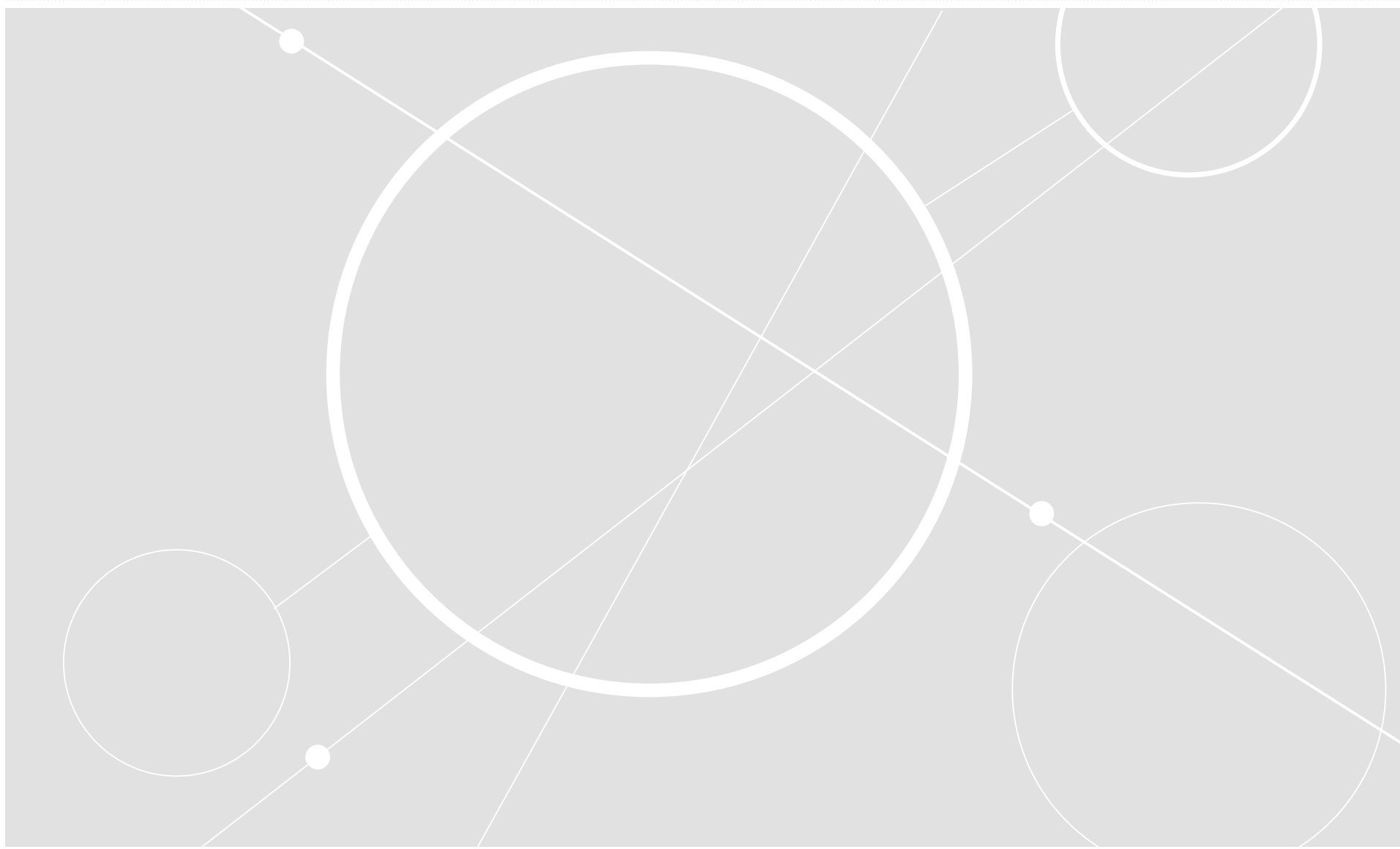
Project - Business Intelligence

Search for Bayer



Solution requirements

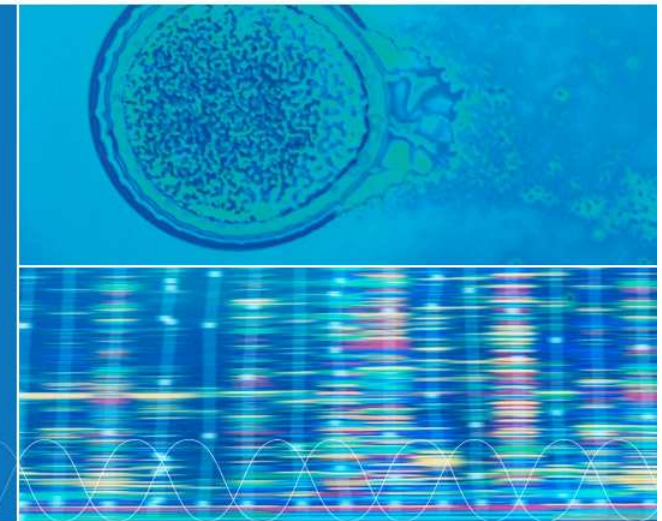
- Highly Curated Dictionaries and Patterns
 - On-going manual effort aided with statistical analysis
- Advanced NLP Algorithms:
 - Context sensitive disambiguation
 - Pattern / Dictionary based entity detection
 - Parallel Entity Detection
 - ConceptScan[®] Technology
- Curator
 - Statistical error model for rules-based
“error detection and correction” algorithm





Thank You.
Questions?
Applications for an NLP Engine

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