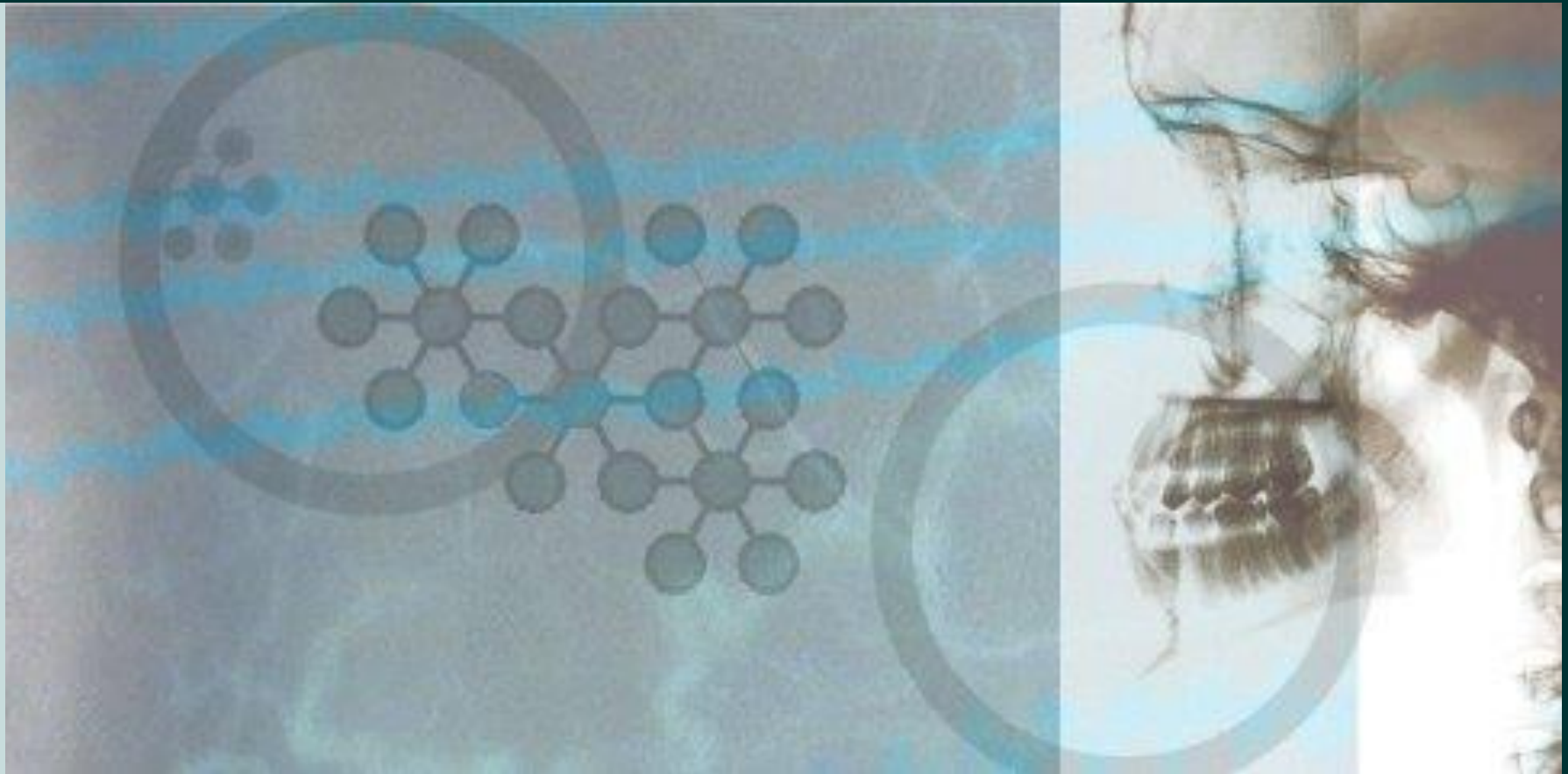


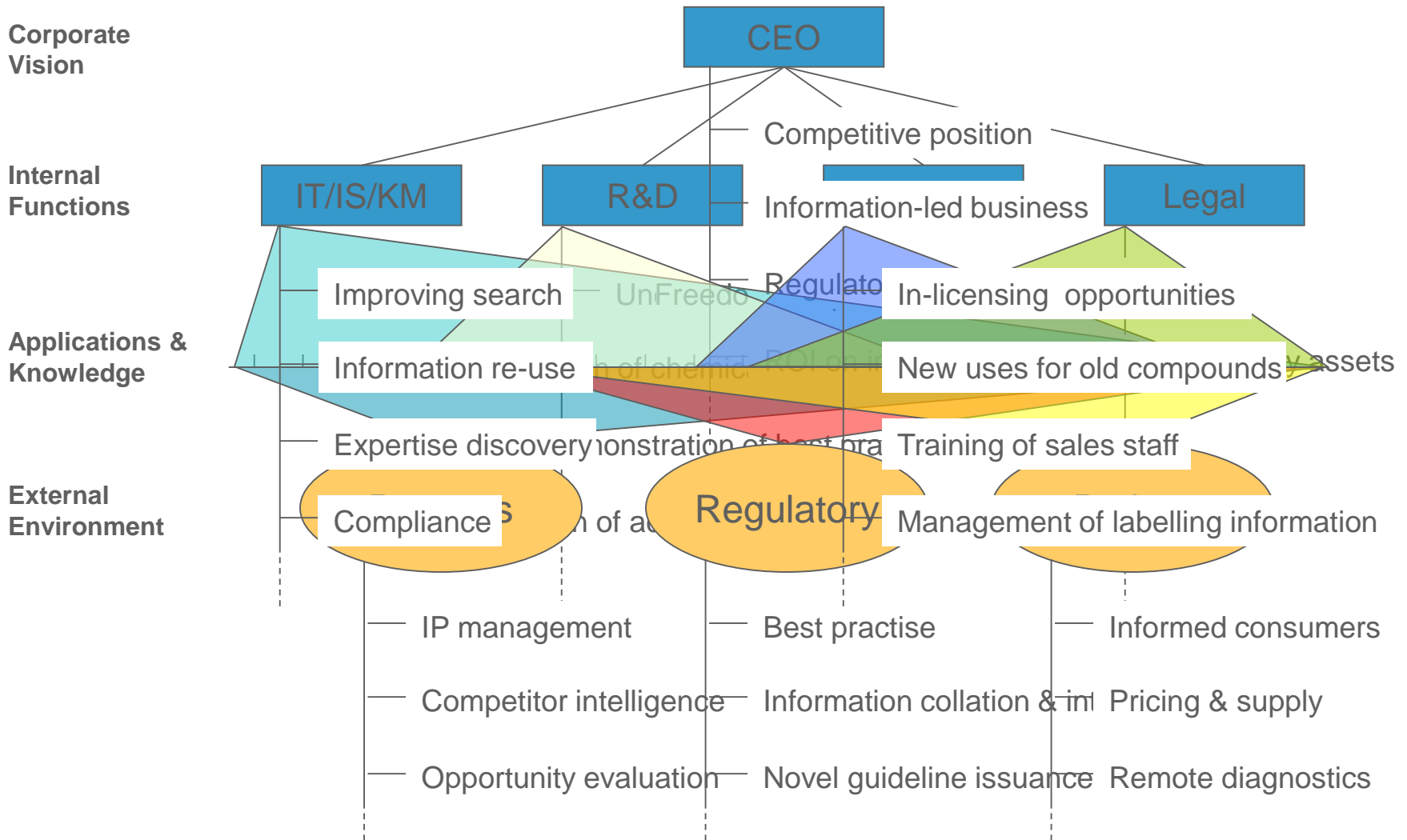
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Knowledge Representations

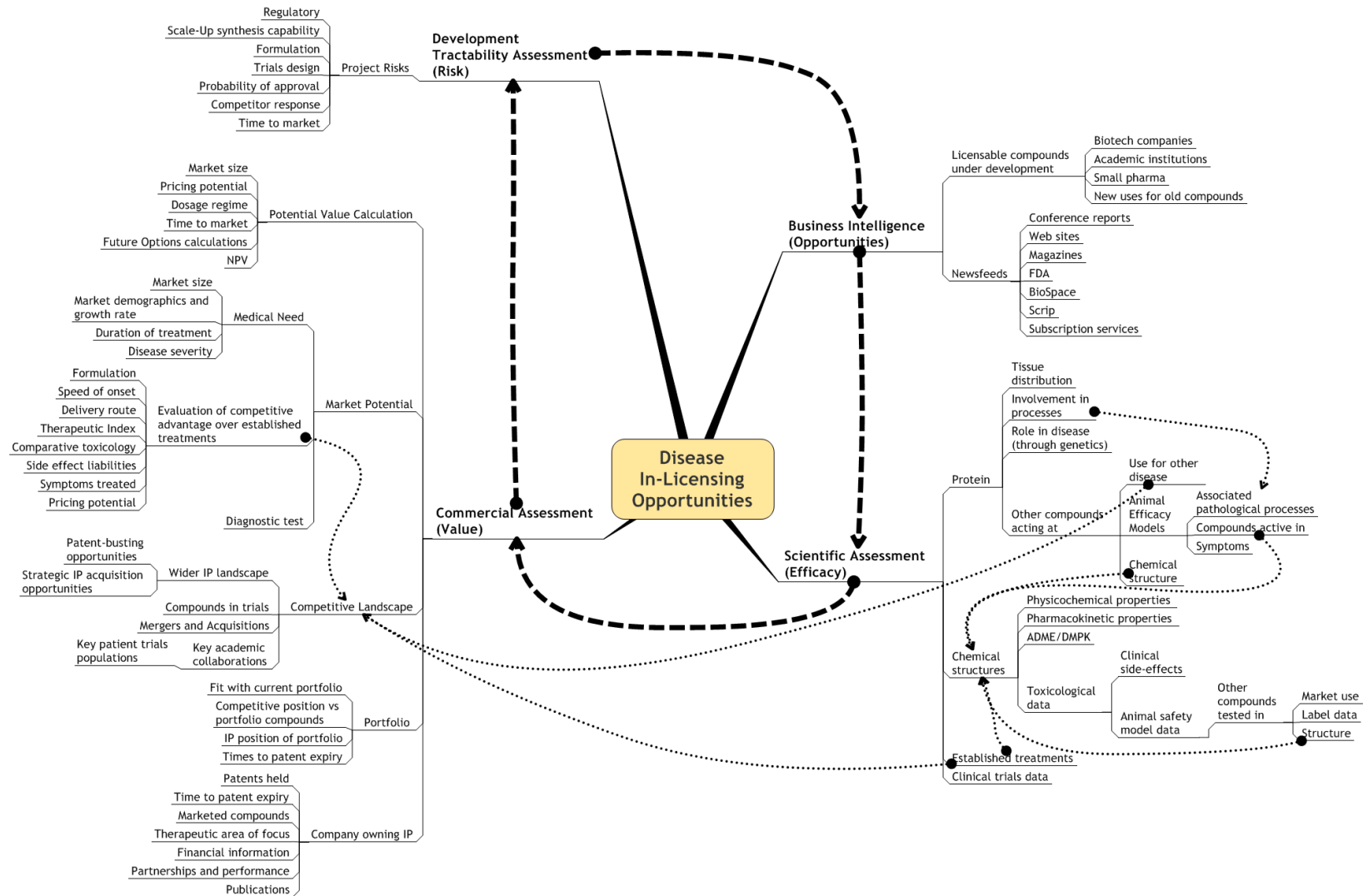
Prepared for PRISM Forum Oct 6th 2004



Integrated Intelligence for Business



In-Licensing Sources



Data Integration Methodologies

- Rules based
 - Matches values in tagged fields
- Data warehousing
 - Specialised database schema developed to optimise repetitive analysis in 'same question, different data' applications
- Federated middleware
 - Use of middleware to connect distributed data sources to various client applications via shared data model
- Ad hoc query optimization
 - Query normalisation and distribution across multiple source databases

The Importance of Semantics

- Identity based semantics are very limiting
 - is-equivalent-of, is-same-as, is-a, is-part-of
- Descriptive relationships are much more valuable

COMPOUND	COMPOUND	AFFECTS
COMPOUND	COMPOUND	CONTAINS
COMPOUND	COMPOUND	HAS AFFINITY FOR
COMPOUND	COMPOUND	HAS DERIVATIVE
COMPOUND	COMPOUND	INCREASES
COMPOUND	COMPOUND	INDUCES
COMPOUND	COMPOUND	INHIBITS
COMPOUND	COMPOUND	INTERACTS WITH
COMPOUND	COMPOUND	IS ACTIVE INGREDIENT IN
COMPOUND	COMPOUND	IS ADMINISTERED WITH
COMPOUND	COMPOUND	IS ANALOGUE OF
COMPOUND	COMPOUND	IS INDUCED BY
COMPOUND	COMPOUND	IS METABOLITE OF
COMPOUND	COMPOUND	REDUCES
mRNA	COMPOUND	IS AFFECTED BY
mRNA	COMPOUND	IS DECREASED BY
mRNA	COMPOUND	IS DOWNREGULATED BY
mRNA	COMPOUND	IS INCREASED BY
mRNA	COMPOUND	IS INDUCED BY
mRNA	COMPOUND	IS INHIBITED BY
mRNA	COMPOUND	IS REGULATED BY
mRNA	COMPOUND	IS UPREGULATED BY
mRNA	PROTEIN	CODES FOR

The Importance of Semantics

- Semantic Normalization

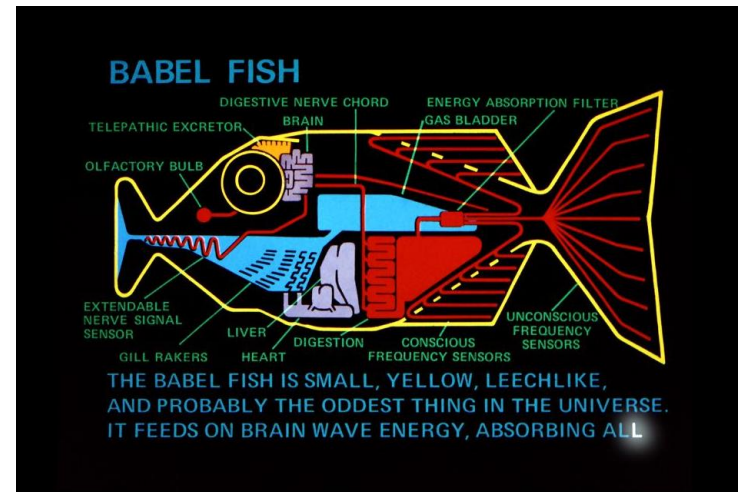
- Disambiguation

- Cold – rhinoviral disease or Chronic Obstructive Lung Disorder

- Aggregation

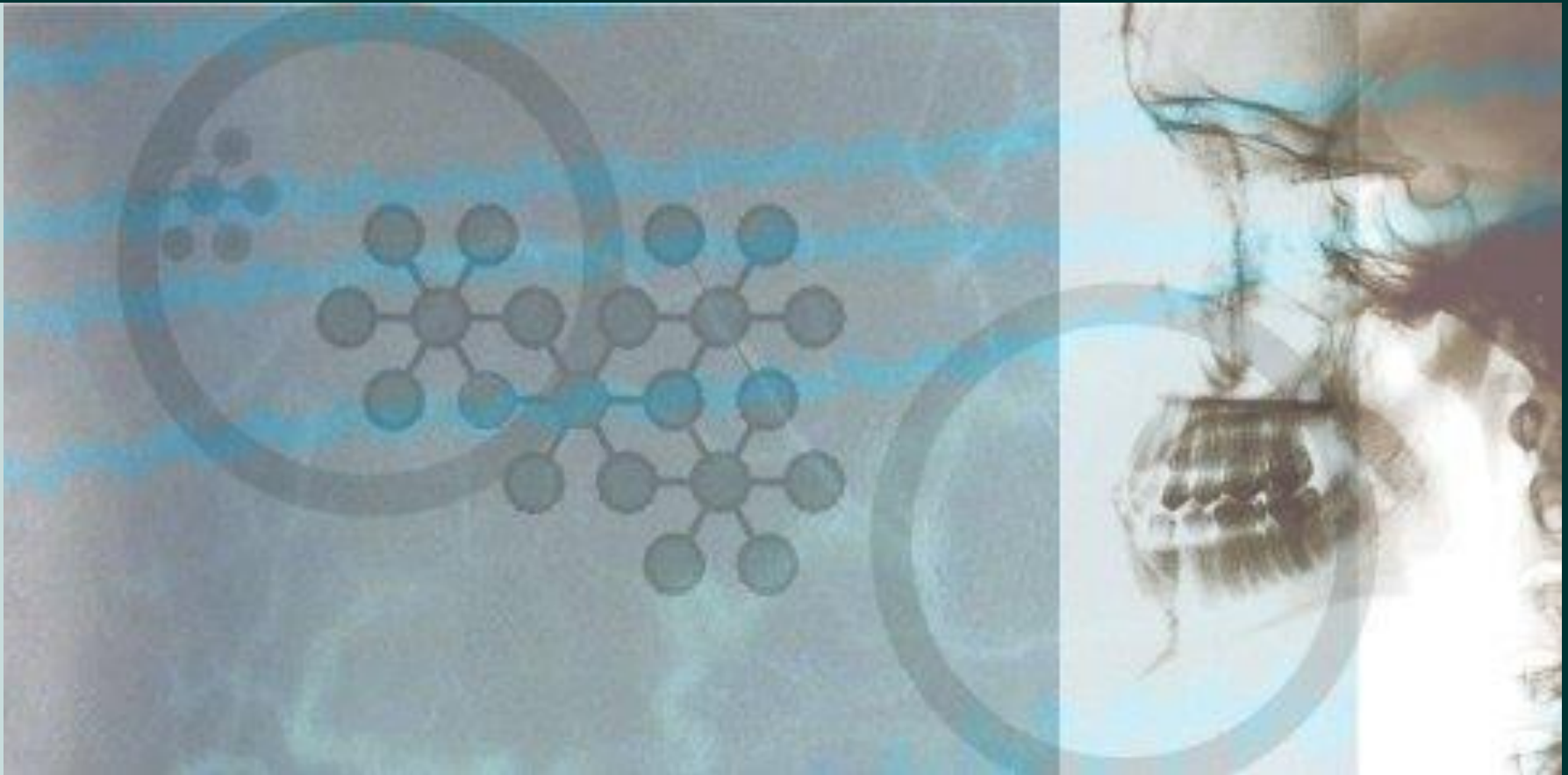
- Diazepam – 197 synonyms

Aliseum; Amiprol An-Ding Ansilive Ansiolin Ansilisina Antenex Anxicalm Anxionil Apaurin Apo-diazepam Apozepam Armonil Arzepam Assival Atensine Atilen Azedipamin BRN 0754371 Baogin Bensedin Benzopin Best Betapam Bialzepam Britazepam CB 4261 CCRIS 6009 Calmaven Calmocitene Calmociteno Calmod Calmpose Caudel Centrazepam Cercine Ceregulart Chuansuan Condition D-Pam DZP Desconet Deslonge Diacepan Diaceplex Dialag Dialar Diapam Diapax Diapine Diaquel Diastat Diatran Diazemuls Diazepan Diazepan leo Diazepin Diazetard Dienpax Dipaz Dipezona Disopam Dizac Domalium Doval Drenian Ducene Duksen Dupin Duxen EINECS 207-122-5 Elcion CR Eridan Euphorin P Eurosan Evacalm Faustal Faustan Freudal Frustan Gewacalm Gihitan Gradual Gubex HSDB 3057 Horizon Iazepam Jinpanfan Kabivtrum Kiatrium Kratium Kratium 2 LA III LA-111 Lamra Lembrol Levium Liberetas Lizan Lovium Mandro Mandro-Zep Medipam Mentalium Metamidol Methyl diazepamone Methyl diazepamone Methyl diazepamone Metil Gobanal Morosan NSC 169897 NSC-77518 Nellium Nerozen Nervium Neurolytril Nivalen Nixtensyn Noan Notense Novazam Novodipam Ortopsiqum Paceum Paralium Paranten Parzam Pax Paxate Paxel Paxum Placidox 10 Placidox 2 Placidox 5 Plidan Pomim Propam Prozepam Psychopax Quetinil Quiatril Quievita Radizepam Relaminal Relanium Relax Reliver Renborin Ro 5-2807 Ruhsitus Saromet Sedipam Seduksen Seduxen Serenack Serenamin Serenzin Setonil Sibazon Sico Relax Simasedan Sipam Solis Sonacon Stesolid Stesolin Tensopam Tranimul Trankinon Tranqdyn Tranquirit Trazepam Umbrium Unisedil Usempax AP Valaxona Valeo Valiquid Valitran Valium Valrelease Valuzepam Vanconin Vatran Vazen Velium Vival Vivol WY-3467 Winii Zepaxid Zipan e-Pam



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Background of Knowledge Representation



What do we Mean, Knowledge Representation?

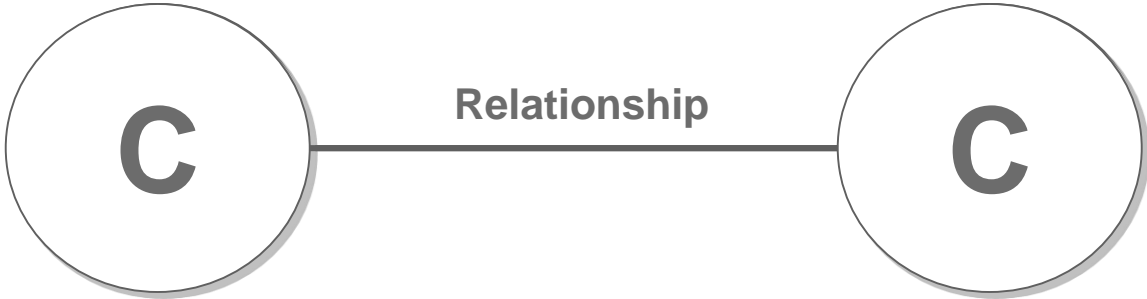
- Based in philosophy, applied in artificial intelligence
- 3 main components:
 1. Logic – provides the formal structures and rules of inference
 2. Ontology – defines the kinds of things that exist in the application domain and the relationships between them
 3. Computation – supports the business applications

Knowledge Representation: Logical, Philosophical and Computational Foundations, John F. Sowa
ISBN 0-534-94965-7

What is Logic?

- Aristotle's syllogisms
- Predicate calculus and conceptual graphs
- Graph theory

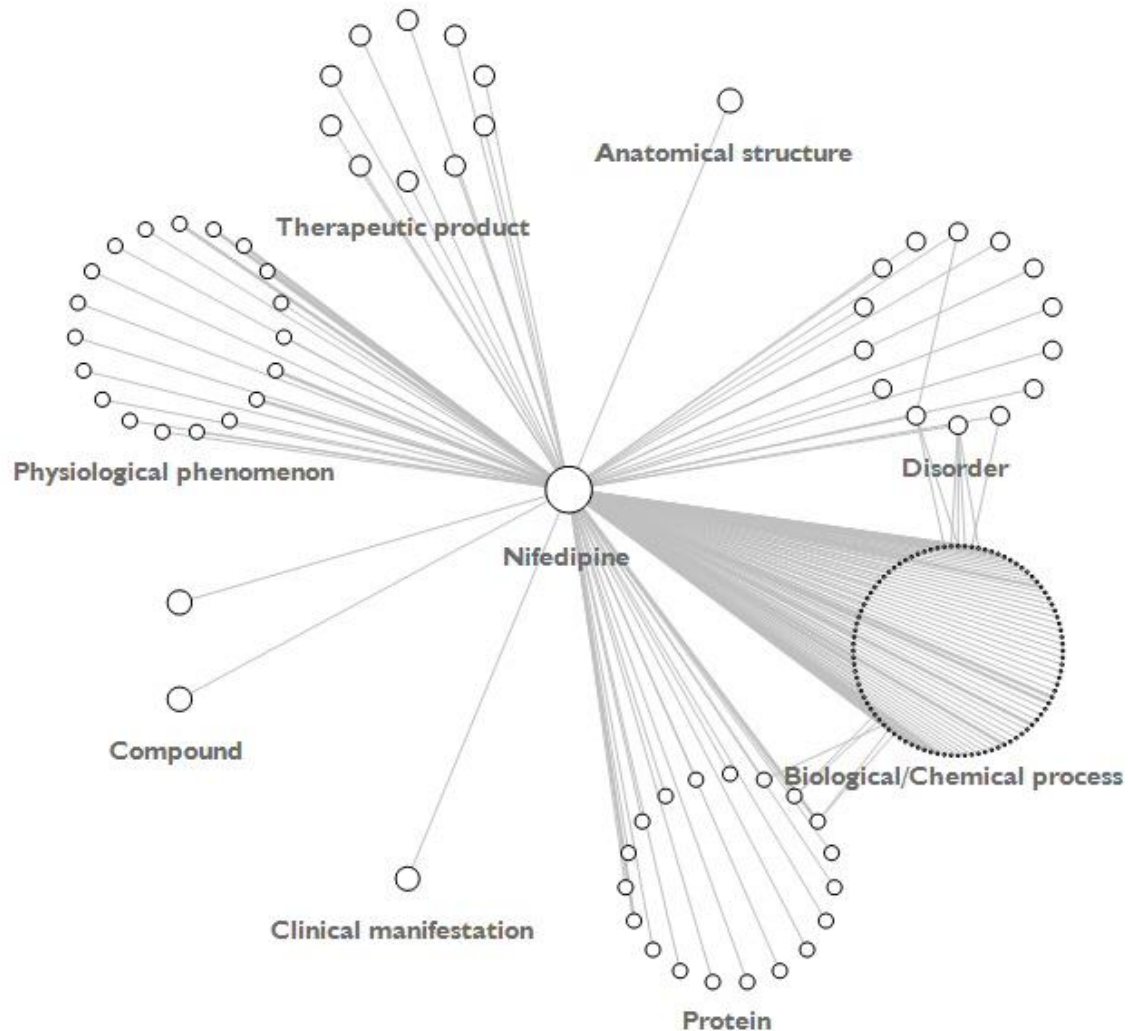
Building Blocks of Ontology



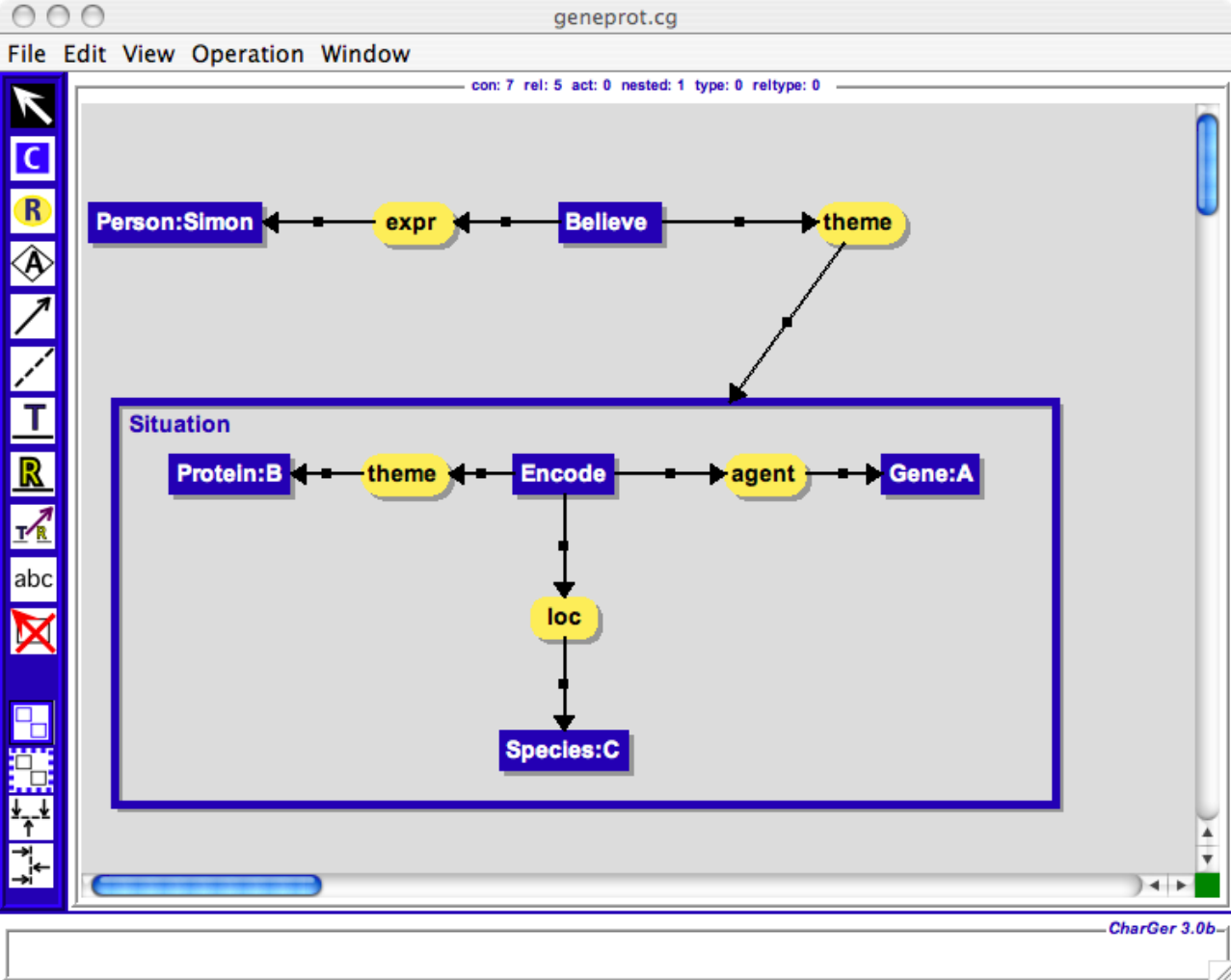
<subject> <predicate>
 <object>



Graph Theory Representations



Binary vs n-ary



What is Ontology?

- Quirn's fundamental question of ontology:

Q: What is there?

A: Everything

- The study of 'things' that exist and the relationships that exist between them

What is Computation?

- Reasoning
- Path-finding
- Inference

Path-Finding

BioWisdom Sofia Knowledge Suite - PathLab V0.1

File Network Search Window Help

Inspector

Compound: Tolcapone

1444
Compound
Tolcapone

myoglobin -> Rhabdomyolysis

Path Graph

Console

```

Species:HUMAN=[contains (2.0)]=>Disorder:Rhabdomyolysis
[path cost:6.0/2.0]

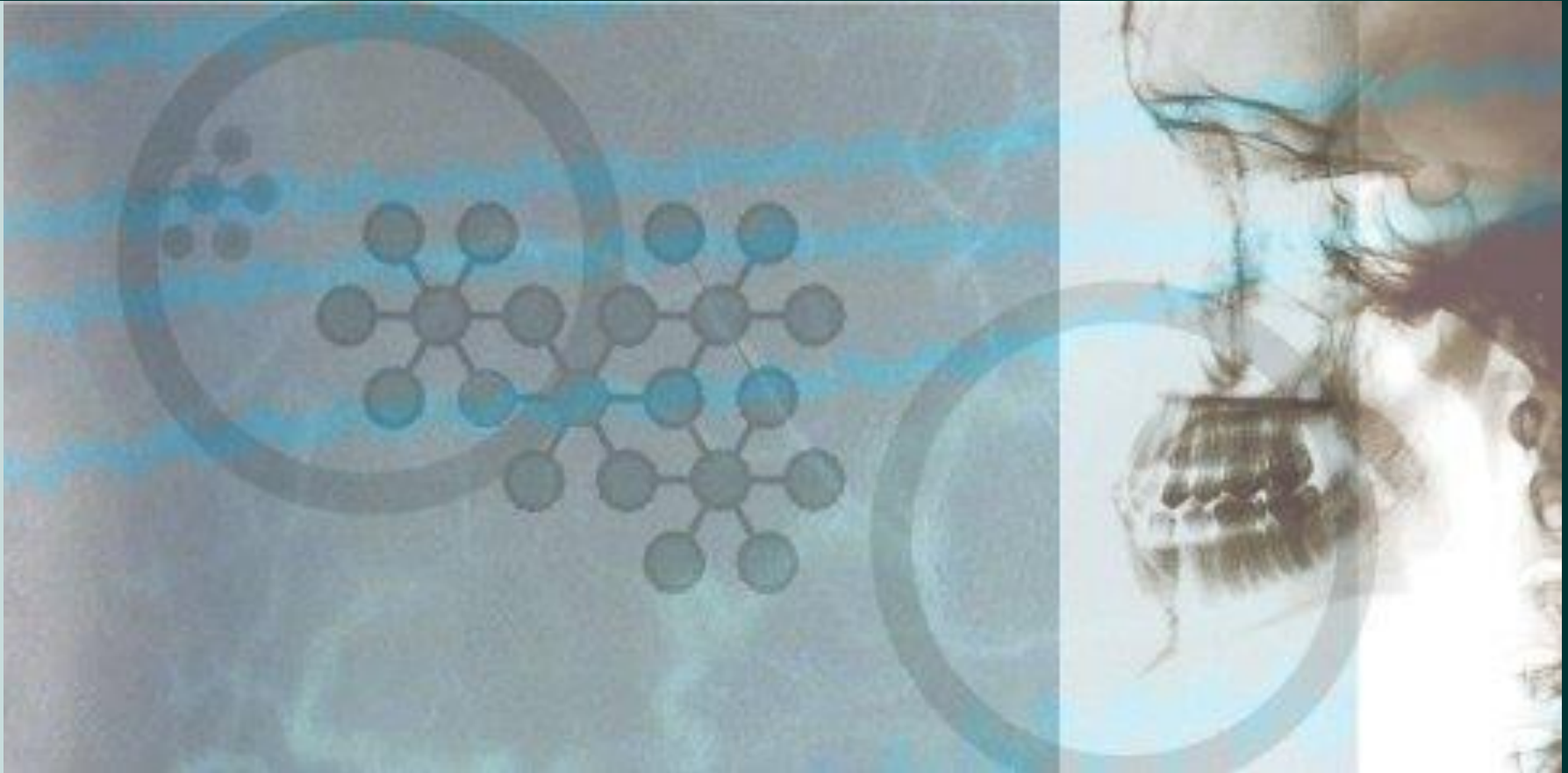
Protein:myoglobin=[may be elevated in diseases associated with (2.0)]=>Anatomical structure:Skeletal Muscle
Anatomical structure:Skeletal Muscle=[is found in (2.0)]=>Species:HUMAN
Species:HUMAN=[contains (2.0)]=>Disorder:Rhabdomyolysis
[path cost:6.0/2.0]
    
```


What is Computation In the Real World?

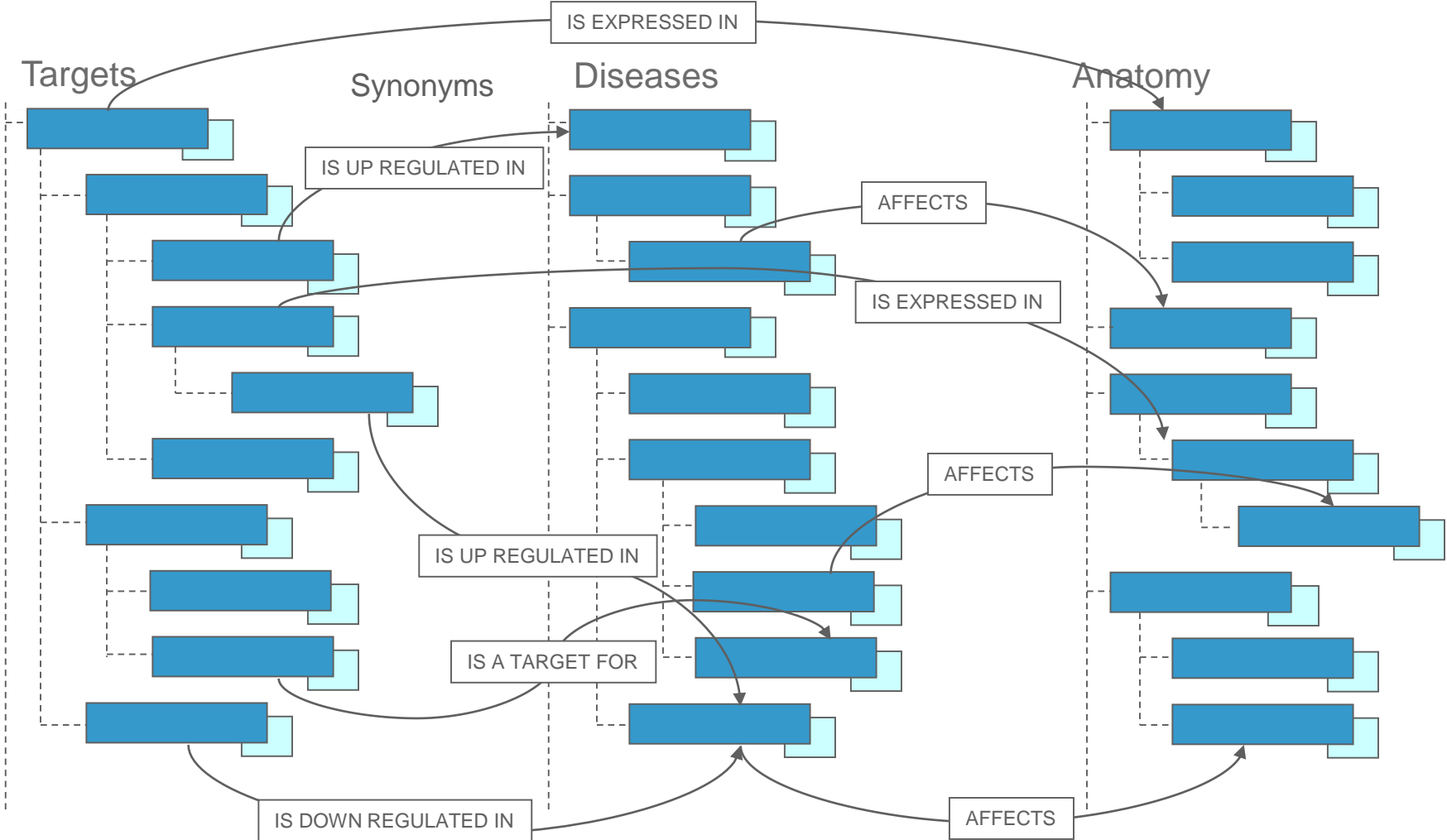
- Hypothesis generation for mechanisms of side effect liability
- Identification of potential biomarkers
- Structure based freedom to operate searches
- Extended high-dimensional SAR analysis using biological and chemical information
- Risk/reward evaluation for in-licensing opportunities
- Information auditing for regulatory compliance
- Smart spell-checker
- Smart phone book with expertise location
- 21st century search

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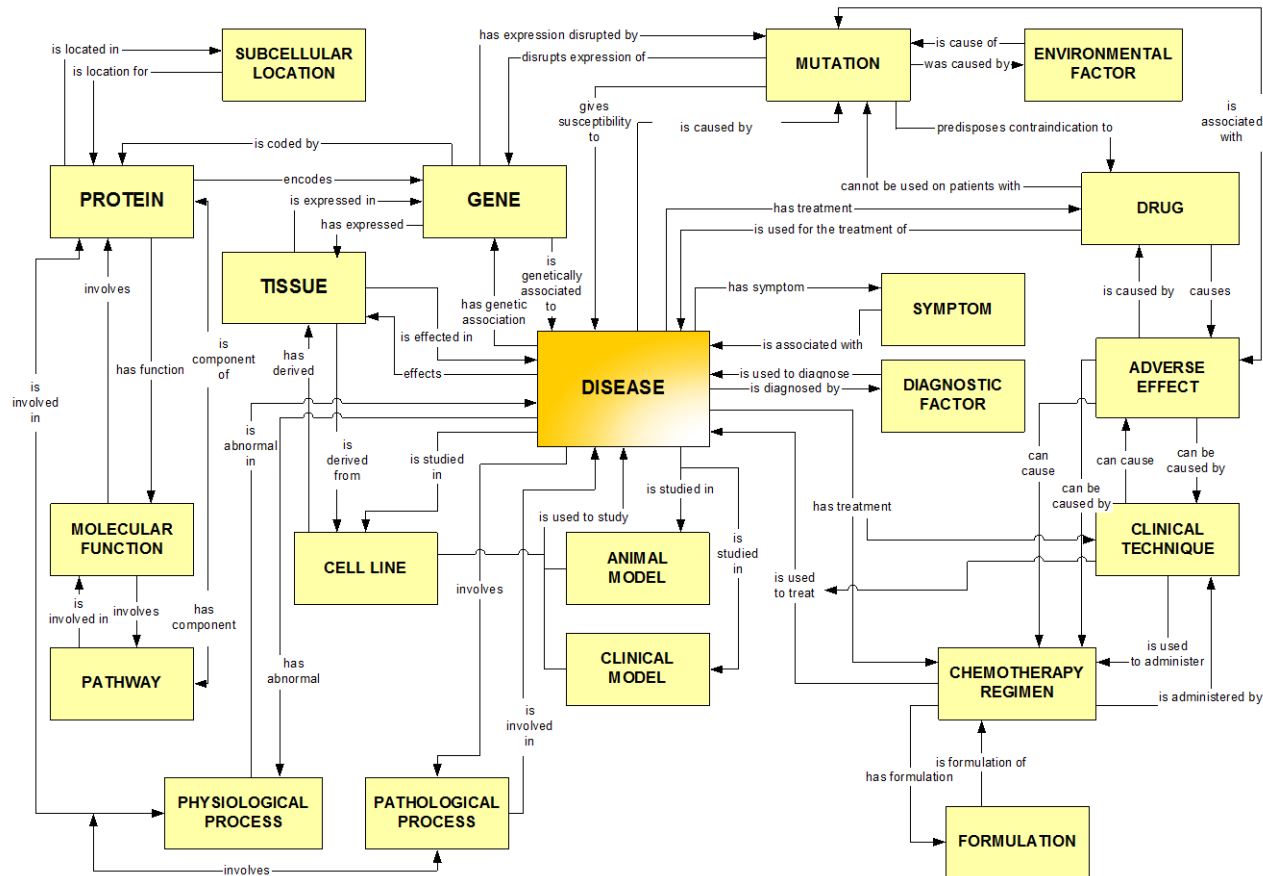
Types of Knowledge Representation



Knowledge Representations- Ontologies

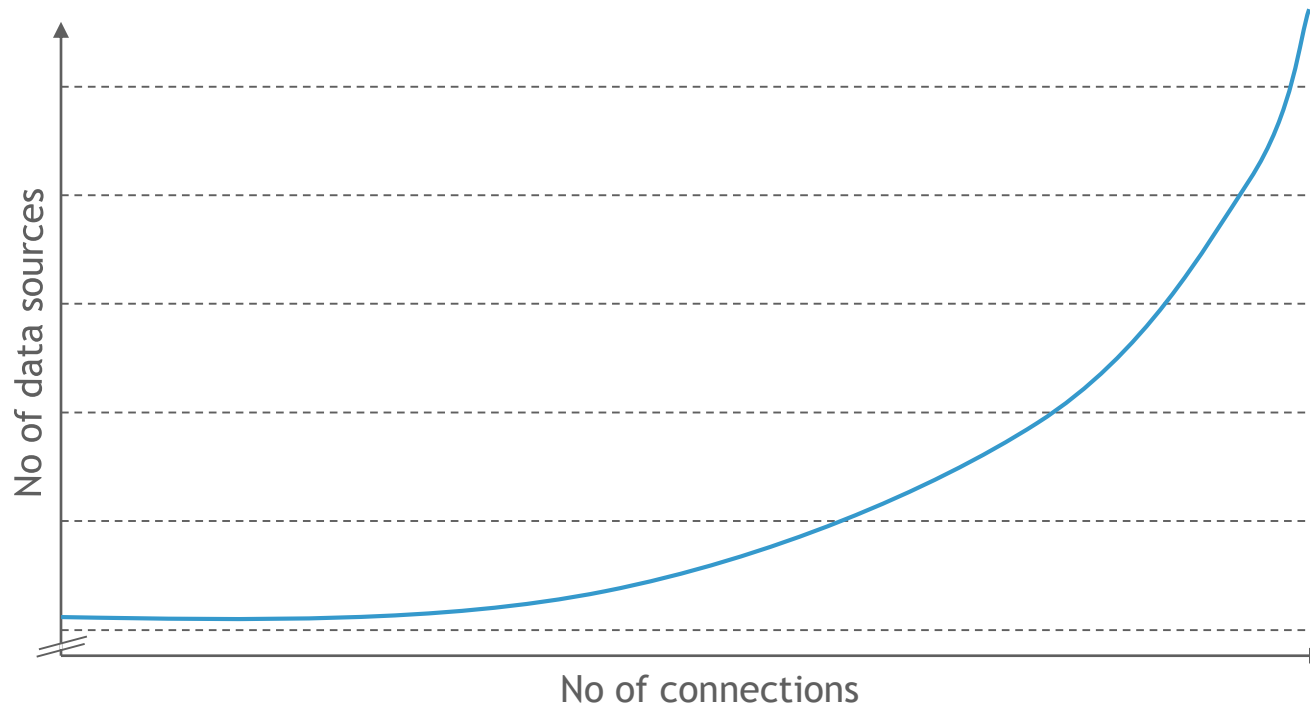


Multi-Relational Ontology



- Integrates information from multiple sources into single coherent view
- Connections are made at a semantic level, not by a common rule

Scalable Multi-Relational Ontology



- Constant level of effort results in an exponential increase in number and complexity of relationships between concepts
- Power of an ontology based system grows as the coverage, content and number of relations grows

Knowledge Representation

Taxonomies

- Manually curated
- Simple parent-child relationships
- Connect single type of concept
- Tend to invisibility
- Become harder to use as they grow
- Become harder to maintain as they grow
- Limited reusability

Ontologies

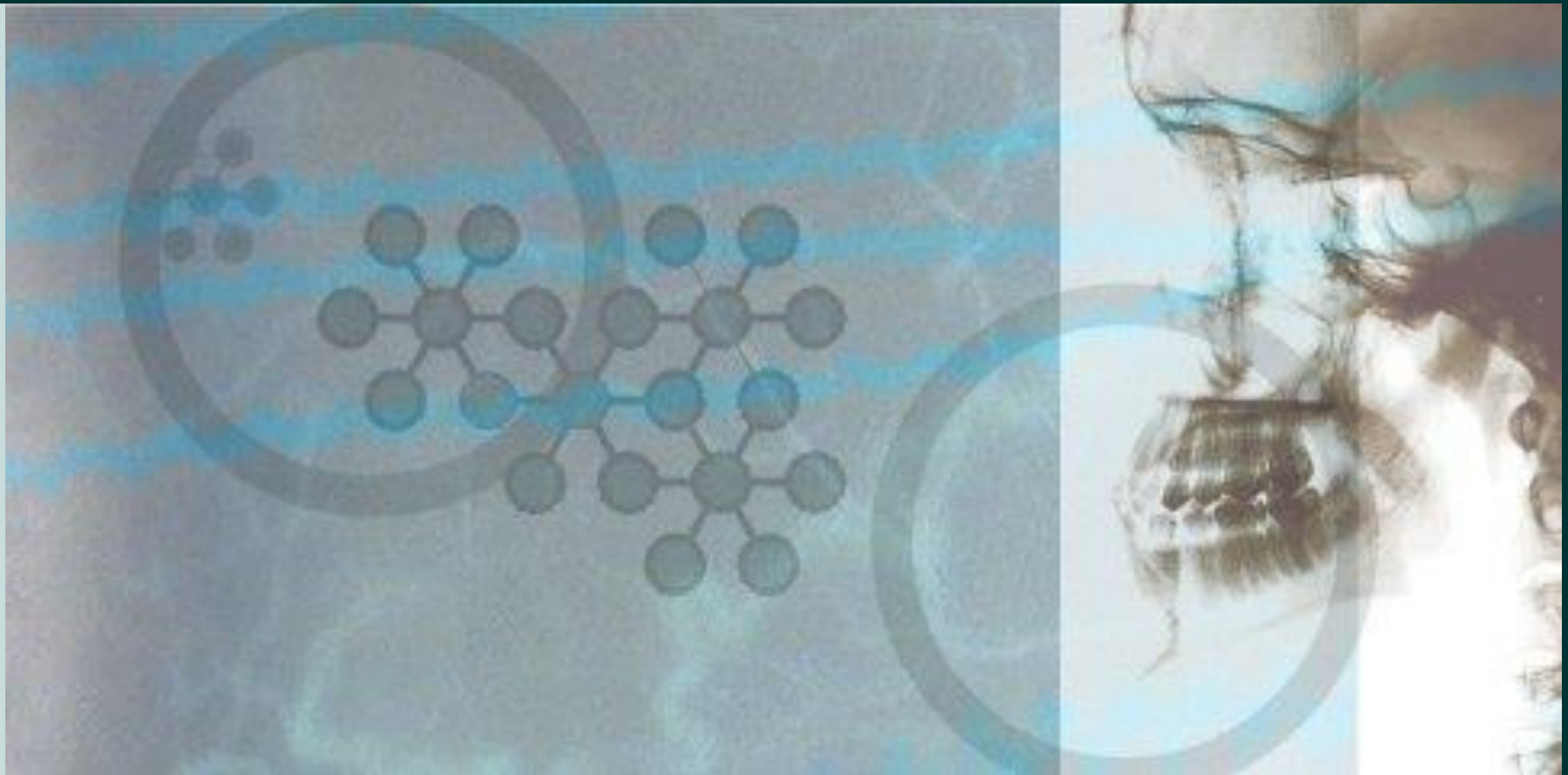
- Semi-automatic curation
- Multiple descriptive relationships
- Connect multiple types of concepts
- Tend to visibility
- Become more valuable and as they grow
- Become easier to maintain as they grow
- Widely reusable

Top-Down vs Bottom-Up

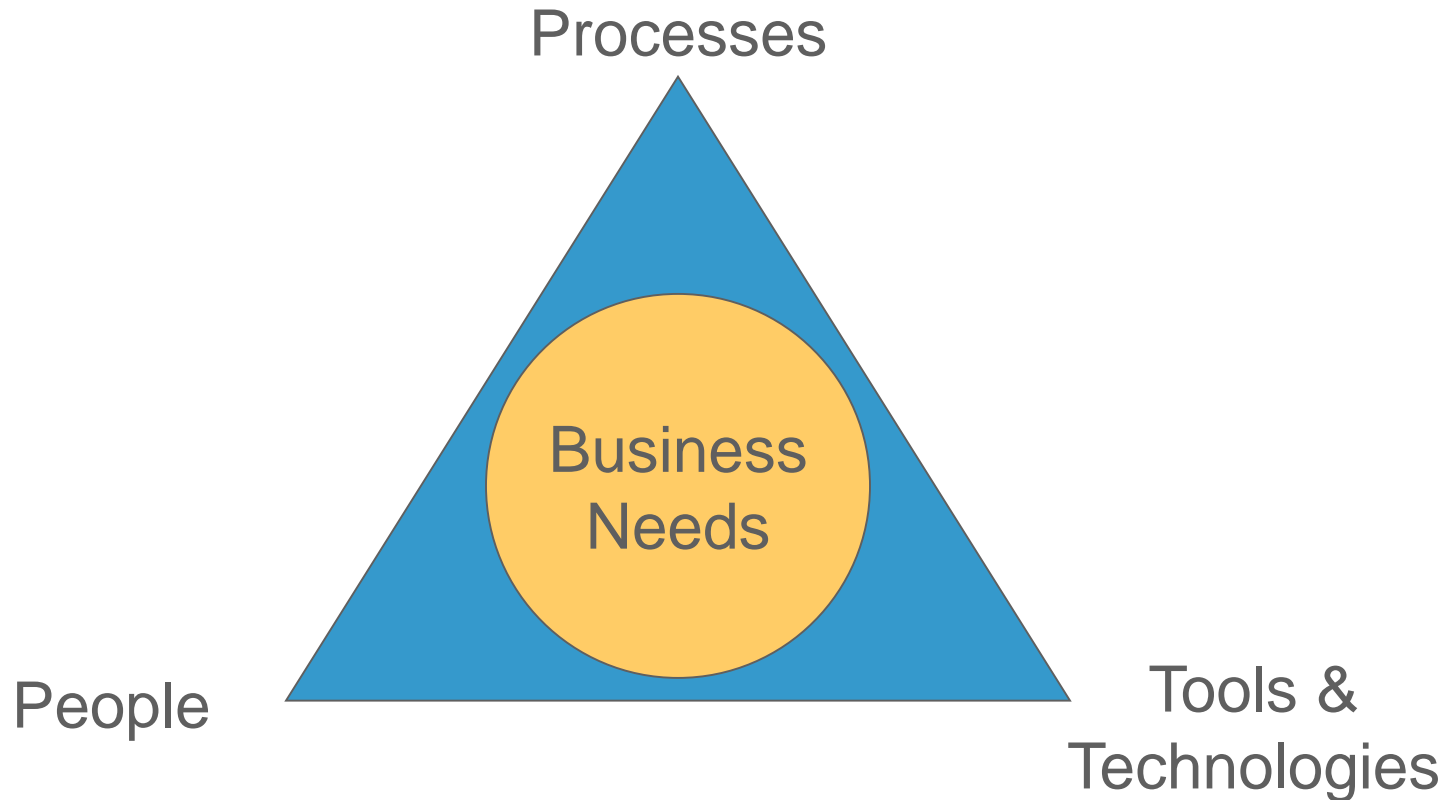
- Top-down approach
 - Segregation into Abstract ! Concrete classes
 - Limited relational complexity
 - Manual design and population
 - Guaranteed computability, but limited data
- Bottom-up approach
 - Analyse available data
 - Semi-automated identification of concepts and relationships in data
 - All concepts and relationships structured
 - Potentially limited computability

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Applications of Ontology



Background to Knowledge Management



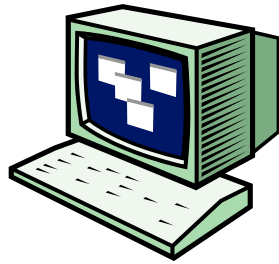
Knowledge Management Pitfalls

- 60% of KM budgets is spent on high-risk, closed architecture data integration projects
- Lack of business buy-in
 - Often caused by focussing too much on the tools and technologies
 - ‘So what does it mean to me?’
- Too complex a vision means that nothing is delivered until after the business needs have changed
- Poor execution and risk management

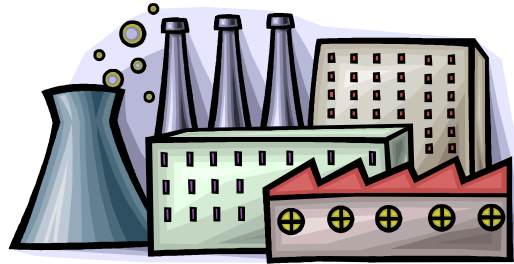
4 Pillars of Knowledge Management



People



Tools

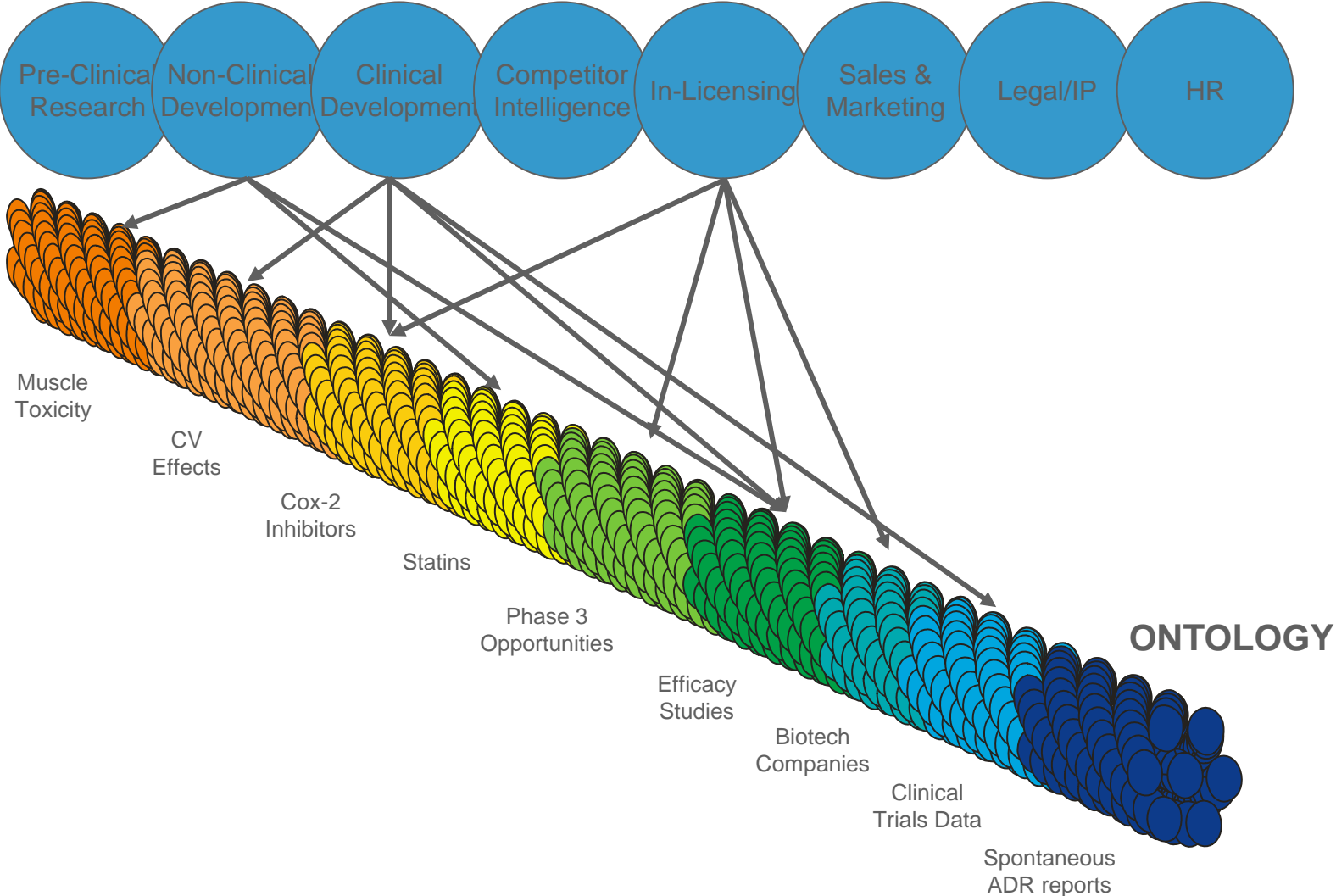


Organizational
Network



Global
Network

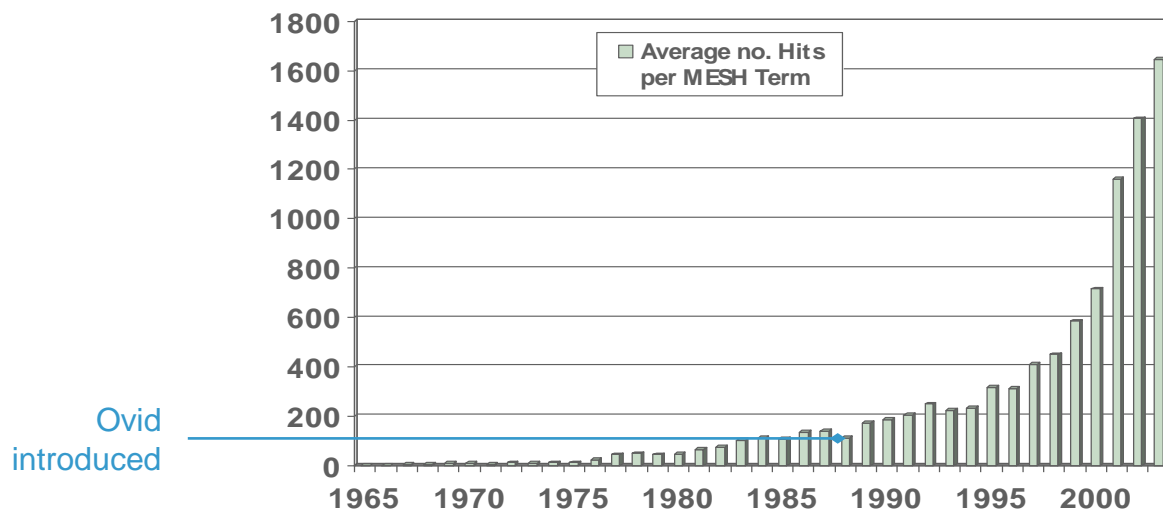
Reusing the Thread of Knowledge



The Tools Don't Work Anymore

- Average scientist or business analyst spends 20-25% of their time looking for information in text sources
- Search recall is only 25-35% as they miss synonyms
- Co-occurrence of terms only works across whole documents
- They get thousands of hits, so they skim the top 100 titles
- They read the top 10 abstracts, and select the top 5 papers

- Chance of reading the 'right' paper is <2%
- Cost to business is \$900 per scientist per week *



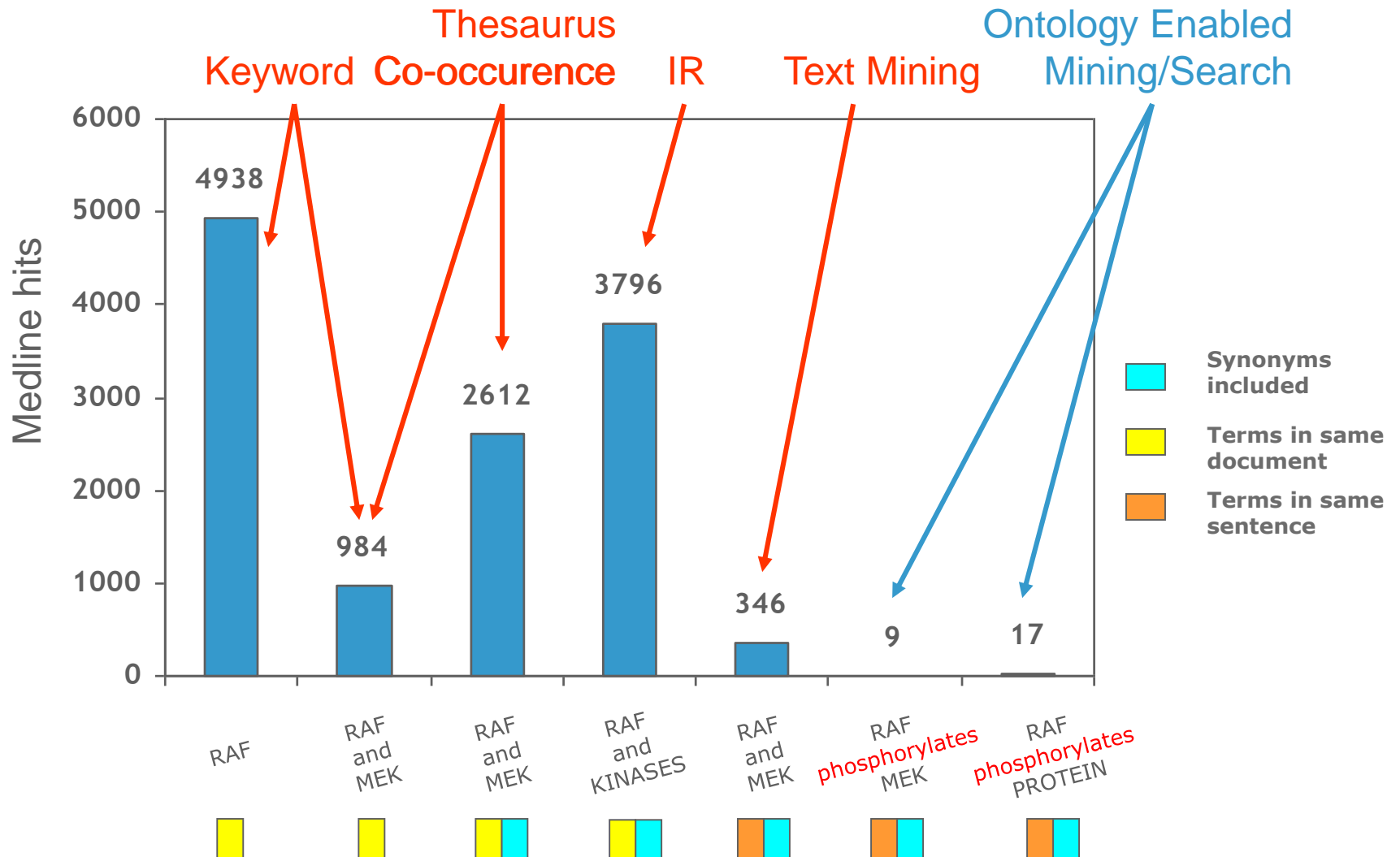
*Based on \$200K/yr FTE rate

Progression of Searching

Example Query: 'RAF phosphorylates MEK'

- PubMed keyword:
 - Articles that contain the word 'RAF'
- Taxonomy/thesaurus based search:
 - Articles that contain 'RAF' or any synonym
- Co-occurrence:
 - Articles that contain both 'RAF' and 'MEK' (or any synonym)
- Information Retrieval (Verity, Convera, Inxight etc.):
 - Articles that are about 'RAF' and other kinases
- Text Mining (ClearForest, Inxight, I2E etc.):
 - Articles that contain the concepts 'RAF' and 'MEK' (or synonym) linguistically bounded in phrase, sentence or section with verb
- Thematic (Ontology):
 - Articles that contain references to 'RAF phosphorylating MEK' or any concept/relationship synonym
 - All other things that 'RAF' (or its synonyms) interacts with grouped by type or relationship

Ontology Improves Search Accuracy

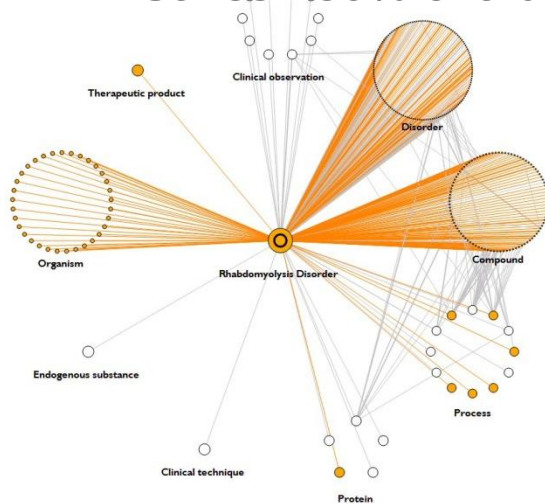


RAF - phosphorylates - TARGET

v-raf-1 murine leukemia viral oncogene 1	phosphorylates*/vg	target	Sentence	Link	Score
v-raf-1 murine leukemia viral oncogene 1 (<i>Raf-1</i>)	efficiently phosphorylate	mitogen-activated protein kinase kinase (<i>MAP kinase kinase</i>)	B-Raf and Raf-1 both efficiently phosphorylate MAP kinase kinase (MEK-1).	doc10741	99
v-raf-1 murine leukemia viral oncogene 1 (<i>Raf-1</i>)	phosphorylated	mitogen-activated protein kinase kinase 1 (<i>MKK1</i>)	Raf-1 phosphorylated MKK1 on one major tryptic phosphopeptide, the phosphorylation of which increased with time.	doc10965	100
v-raf-1 murine leukemia viral oncogene 1 (<i>Raf-1</i>)	was extensively phosphorylated	camp-dependent protein kinase (<i>PKA</i>)	in vitro phosphorylation experiments showed that Raf-1 was extensively phosphorylated by PKA, while ERK2 and MEK were not.	doc17924	99
v-raf-1 murine leukemia viral oncogene 1 (<i>Raf-1</i>)	phosphorylates	mitogen-activated protein kinase kinase (<i>mitogen-activated protein kinase kinase</i>)	upon activation, Raf-1 phosphorylates mitogen-activated protein kinase kinase (MEK), which in turn activates mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK/ERKs), leading to the propagation of signals.	doc22168	100
v-raf-1 murine leukemia viral oncogene 1 (<i>Raf-1</i>)	phosphorylate	mitogen-activated protein kinase kinase 1 (<i>MKK1</i>)	this could be partly explained by the inability of Raf-1 to phosphorylate MKK1 C-terminal deletion mutants even though the phosphorylation sites were intact in these mutants.	doc24780	99
v-raf-1 murine leukemia viral oncogene 1 (<i>both Raf-1</i>)	are phosphorylated	p21 activated kinase 1 (<i>PAK1</i>)	here we show that both Raf-1 and MEK1 are phosphorylated by PAK1 and that mutations at PAK1 phosphorylation sites in either protein prevent cross-cascade activation.	doc26770	97
		protein kinase c-like 1 (<i>PAK1</i>)	here we show that both Raf-1 and MEK1 are phosphorylated by PAK1 and that mutations at PAK1 phosphorylation sites in either protein prevent cross-cascade activation.	doc26770	97
v-raf-1 murine leukemia viral oncogene 1 (<i>Raf-1</i>)	phosphorylate	mitogen-activated protein kinase kinase 1 (<i>MEK1</i>)	phosphorylation of MEK1 on serine 298 does not appear to regulate the interaction between Raf-1 and MEK1, but rather the ability of Raf-1 to phosphorylate MEK1 with which it is complexed in vivo.	doc26770	99

Finding Information Effectively Using Ontology

- Text resources have been mined for all concepts and relationships
- Recall is >90% as synonyms are automatically appended to the search
- User can choose the themes and topics that they wish to see
- Precision is >90% for the specific relationship between the terms
- Users get presented with an overview of the contexts in which their concept occurs, and the best papers connecting multiple concepts
- Saves >80% of a user's search time - \$720/scientist/yr*



Name	Type	Relationship	Name
<input checked="" type="checkbox"/> Rhabdomyolysis	Disorder	IS CAUSED BY	Cerivastatin
<input type="checkbox"/> Acute Rhabdomyolysis	Disorder	IS CAUSED BY	Cerivastatin

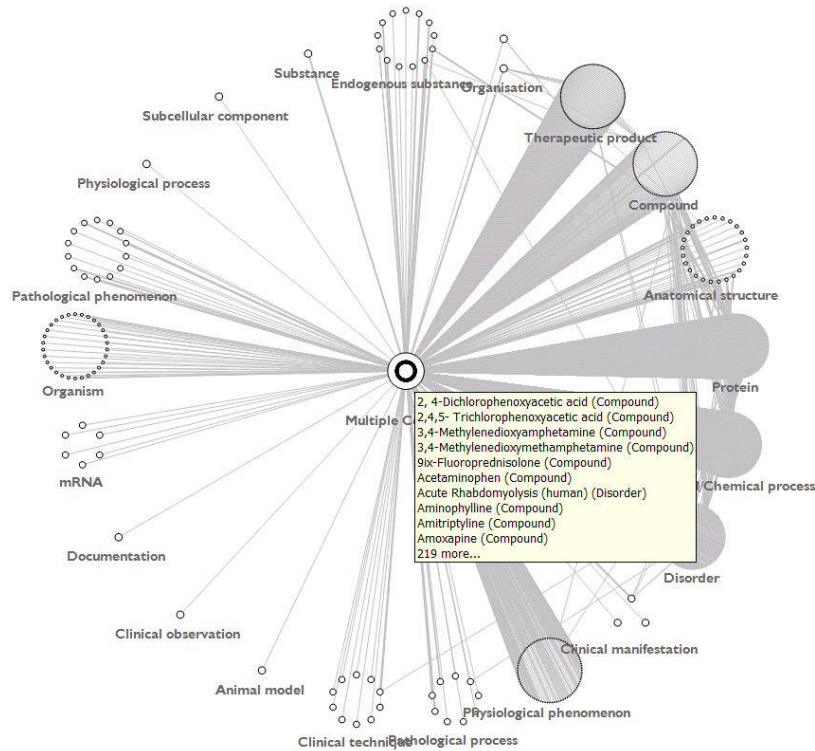
Assertion Evidence		
Data Source	Version	Record
Disase Database	1	
MEDLINE	1	12151857
MEDLINE	1	12372976
MEDLINE	1	12456749
MEDLINE	1	11838874
MEDLINE	1	12033959
MEDLINE	1	11502127
MEDLINE	1	1258018
MEDLINE	1	12463921
MEDLINE	1	11189157
MEDLINE	1	11417566
MEDLINE	1	11371708
MEDLINE	1	11723116
MEDLINE	1	12063668
MEDLINE	1	12036707
MEDLINE	1	12030671
MEDLINE	1	11856503
MEDLINE	1	11718617
MEDLINE	1	11562335
MEDLINE	1	11502587
MEDLINE	1	11718614
MEDLINE	1	11525593
MEDLINE	1	11539690
SBA	1	081102en.pdf

The myotoxicity of statins.
 Evans M, Rees A.
 Department of Diabetes and Endocrinology, University Hospital of Wales, Heath Park, Cardiff, UK. evans2@uaf-wales.com

PURPOSE OF REVIEW: Since hypercholesterolaemia is a chronic condition, the long term safety of statins is important. Adverse reactions involving skeletal muscle are the most common (reported incidence 1-7%). The recent withdrawal of cerivastatin because of deaths from rhabdomyolysis, of which 25% were related to gemfibrozil-cerivastatin combination therapy, has focused attention on myotoxicity associated with statins and in particular with statin-therapeutic combinations. We review the safety profiles of the individual statins, and discuss the mechanisms that may account for myotoxicity associated with statins and these agents and how these may relate to the different myotoxic potential of individual agents. **RECENT FINDINGS:** The statins, particularly the first generation agents, have been well evaluated from the perspective of safety and efficacy. Cerivastatin was associated with a 10-fold higher incidence of myotoxicity than any other statin, suggesting that there may be differences in myotoxic potential between agents. Statin-associated myotoxicity is complex, involving effects on cell membrane structure and function, mitochondrial dysfunction and impaired myocyte duplication. Potential differences in myotoxicity between agents may relate to the physico-chemical, pharmacokinetic and pharmacodynamic properties of individual drugs. The etiology of myotoxicity associated with statin-therapeutic combination therapy is complex and multifactorial, with recent studies suggesting that there may be differences in myotoxic potential between individual therapies. **SUMMARY:** Recent evidence suggests that there may be differences in myotoxic potential between individual agents. Thus, the choice of hypolipidemic therapy needs to be based not only on outcome evidence and cost-effectiveness analysis, but also on safety considerations for individual agents.

*Based on \$200K/yr FTE rate

Searches Lead to More Relevant Knowledge



Imported from array - Sofia Export - [Scatter Plot]

Glutathione S-Transferase M1
 Glutamic-Pyruvate Transaminase
 GTP Cyclohydrolase 1
 Epidermal Growth Factor (beta.1)
 Endothelin 1
 Diarrhegin and Metalloproteinas
 Cytochrome p450, Subfamily IIIA
 Cytochrome p450, Subfamily IIC
 Cytochrome p450, Subfamily IIB
 Cytochrome p450
 Creatine Kinase
 Coagulation Factor
 Chemokine (C-C motif) Ligand 2

US 2004/0092574 A1
 May 13, 2004

STATIN-Lp(a) INHIBITOR COMBINATIONS
 FIELD OF THE INVENTION
 [0001] This invention concerns a combination of a statin [0008] The combinations of this invention can also be pharmaceutically acceptable salts of the respondents.

effective amount of an Lp(a) inhibitor. More particularly, one embodiment of the invention is a combination of a statin with an Lp(a) inhibitor which is a retinoid.

retinoids are those described in U.S. Pat. especially preferred compositions employ beta or 13-cis-retinoic acid. Also preferred are trans-retinol, as well as 13-cis-retinol, tretinoin, and 9-cis-retinol.

class of preferred Lp(a) inhibitors to be inorganic phosphates of the Formula I

C1=CC=C(C=C1)C(=O)O

Entrez PubMed - Microsoft Internet Explorer provided by BioWisdom

Search PubMed for []
 Limits Preview/Index History Clipboard Details
 Display Abstract Show 20 Sort Send to Text

NCBI PubMed National Library of Medicine

Search PubMed for []
 Limits Preview/Index History Clipboard Details
 Display Abstract Show 20 Sort Send to Text

SBA 2 workspace.jws - Jump! Enterprise Navigator

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 Departm
 UK, man

PURPO
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PMID: 1

Reviewer: John Zhanqing Gong
 NDA No. 21-366

Page 4 of 143

PHASE 2B TOXICITY CONCLUSION:
 The sponsor submitted data which document for rats and mice 2-year carcinogenicity studies on November 23, 1998 and June 21, 1999. The 2-year carcinogenicity study in mice was initiated in June 19, 1998. The rat AC conducted with the data submission on January 19, 2000.

MOUSE CARCINOGENICITY:
 Cancer incidences in both sexes at dose of 200 mg/kg in the 2-year carcinogenicity study. The response level of 200 mg/kg in mice is about 100 fold the human response based on the individual FDA approved MHD of 10 mg.

MOUSE TUMOR FINDINGS:
 The spectrum of neoplastic findings in the control groups was consistent with that expected in mice of this age, sex, and strain.

In the liver of mice of the 200 mg/kg/day groups of both sexes, there was a clear increase in incidence of both hepatocellular adenomas and carcinomas which correlated with the mean and found distribution described at necropsy. In many cases, the tumors were also multiple. The histology of the tumors varied from small well-differentiated adenomas to which only the histology could not have been distinguished from large and pleomorphic carcinomas. The incidence of these tumors was significantly higher in the 200 mg/kg/day groups than in the control groups in both sexes.

Generally, higher incidence of hepatocellular adenomas/carcinomas was observed in males than females. In cases of hepatocellular adenomas/carcinomas were noted at 100 mg/kg in both sexes, with significant increases not observed at 200 mg/kg in both sexes. Higher incidence of hepatocellular carcinoma was only observed at 200 mg/kg in both sexes. These results are consistent with the findings with other studies, where higher incidence of hepatocellular adenomas/carcinomas was also observed in both sexes.

Incidence of selected neoplastic findings

Tumor	Sex	Control	100 mg/kg	200 mg/kg	100 mg/kg	200 mg/kg
Hepatocellular adenoma	Male	0	0	10	10	10
Hepatocellular carcinoma	Male	0	0	0	0	0
Hepatocellular adenoma	Female	0	0	0	0	0
Hepatocellular carcinoma	Female	0	0	0	0	0
Total tumor-bearing		0	0	10	10	10

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Systematic Knowledge Analysis

What is the mechanism of toxicity associated with a class of drugs?

Identify all known side effects

- Identified forms of side effect (42)
- Search PubMed extract clinical subset
- 500,000 papers
Read 100/day
20 man years

Extract all compounds

- Read abstracts
- Extract all references to compounds (140)

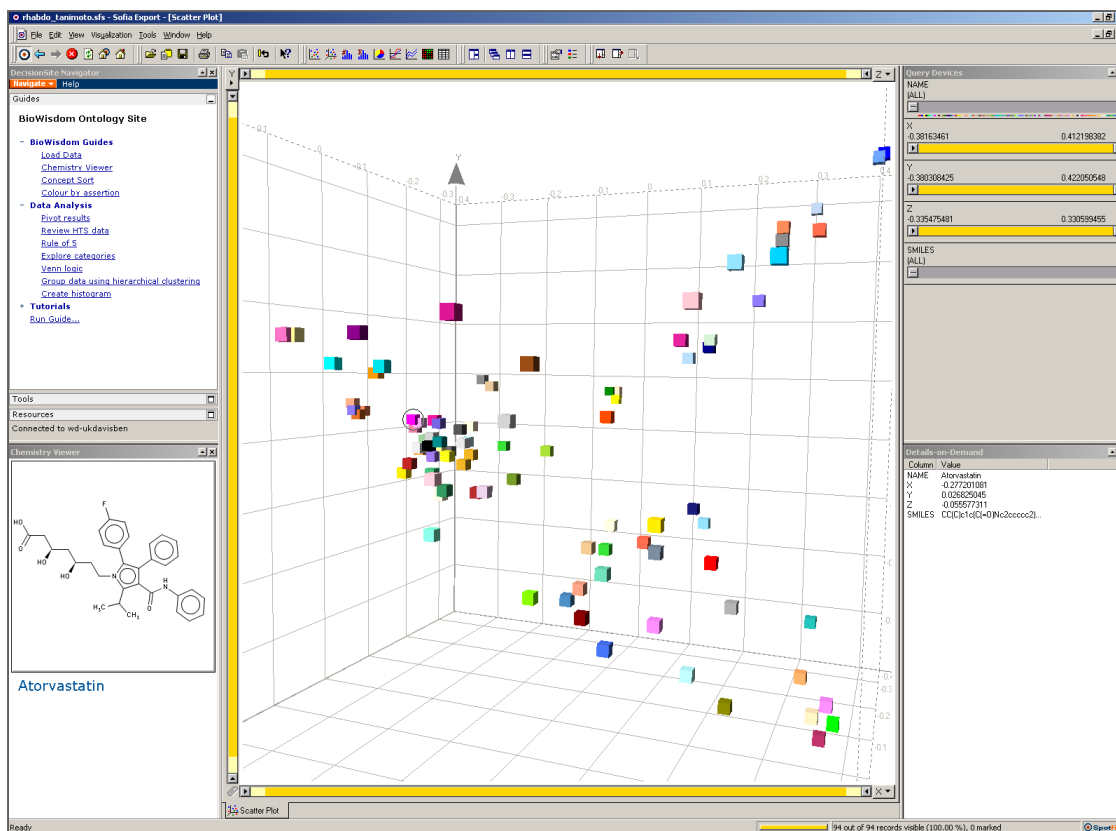
Identify all proteins

- Search Pubmed for protein interactions for each of 140 cmpds
- 3,000,000 papers
Read 100/day
120 man years
- Proteins (500)

Manual, systematic aggregation of all the knowledge to enable comparative analysis is not tractable

Analysis and Data Mining

- Aggregates relevant information from many sources
- Exported for analysis in data mining tools of choice, e.g. Spotfire



Linking Structure to Function for Medicinal Chemists/Toxicologists

The screenshot displays the BioWisdom Sofia Ontology Browser interface. A 'Structure Editor' window is open, showing search options and chemical structures for Mibefradil, Haloperidol Decanoate, Cerivastatin, and Atorvastatin. The main window shows a network graph with 'Cerivastatin' at the center, connected to various concepts like 'Organisation', 'Clinical observation', 'Disorder', 'Protein', 'Process', 'Compound', 's substance', and 'Product'. An 'Evidence' table is visible at the bottom right.

Structure Editor Search Options:

- Sub-Structure
- Exact Structure
- Not Sub-Structure
- Current Concept
- Tanimoto Similarity
- Tanimoto Dissimilarity
- Threshold: 1.0

Chemical Structures:

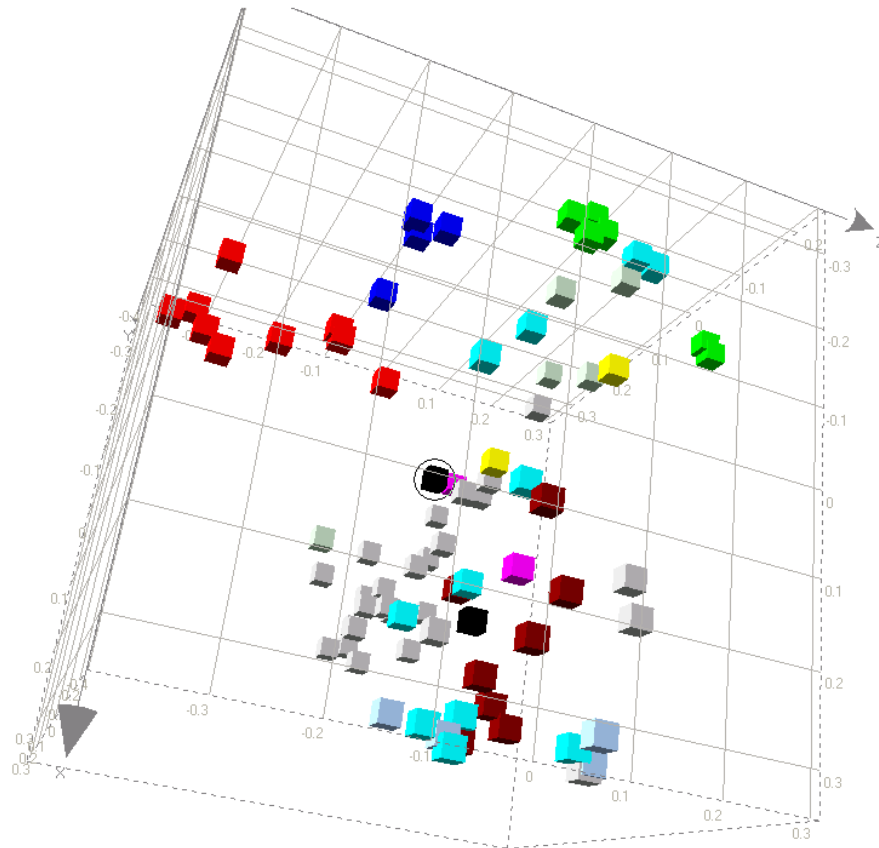
- Mibefradil
- Haloperidol Decanoate
- Cerivastatin
- Atorvastatin

Network Graph Labels: Organisation, Clinical observation, Disorder, Protein, Compound, Process, s substance, Product.

Evidence Table:

Evidence	Value
	(3R,5S,6E)-7-[4-(4-Fluorophenyl)-5-(Methoxymethyl)-2,6-Bi...
	145599-86-6
	459.55
	BAY W 6228
	C26H34FN05

Extended SAR using Biological + Chemical Data



Speeding up Analysis of FDA Documents for Regulatory Scientists

The screenshot displays the Jump! Enterprise Navigator interface. The main window shows a document titled "sba_21-366_crestor_pharmr_p1" with the following text:

Rosuvastatin induced fetal toxicity in rats at 25 mg/kg and rabbits at 3 mg/kg. In rats, both maternal toxicity (reduced body weight and food consumption, liver and renal toxicity) and fetal toxicity (lower number of pups live born, slight low fetal body weight, low incidence of pups with eyes open, and increase in startle amplitude, increases in visceral malformation and skeletal variations, and slightly retarded ossification) were observed at > 25 mg/kg with NOAEL for dams and fetus of 15 mg/kg. In rabbits, severe maternal toxicity (mortality, body weight loss, hypoactivity and debility, and marked histopathologic changes in liver, gallbladder, kidney, heart, and muscle) and fetal toxicity (increase in dead fetuses, decrease in fetal viability index) were observed at 3 mg/kg with NOAEL for dams and fetus of 1 mg/kg. The corresponding exposure levels for rats at 25 mg/kg were 3, 6, 13, and 28X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively. The AUC for pregnant rabbits at 3 mg/kg were not provided. Estimates based on the exposure (C_{max}) in male rabbits at dose of 5 mg/kg, the exposure for female rabbits at 3 mg/kg might be about 14, 1, 3, and 5X human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively.

There was a low distribution of rosuvastatin to fetus in rats (3% or 20% of maternal plasma concentration in fetal tissue or amniotic fluid, respectively) following a single oral dose of 25 mg/kg. Relatively higher distribution in fetal tissue (25% maternal plasma concentration) was observed in 1/4 fetus in rabbits following a single oral dose of 1 mg/kg. However, in the lactating rat, rosuvastatin was found in milk at concentrations up to 3 times those in plasma. These data suggested that rosuvastatin have risk to pregnant women and nursing mothers.

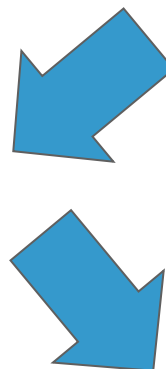
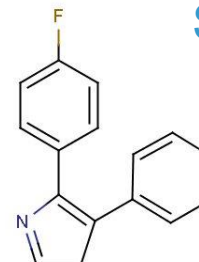
B. Pharmacologic Activity
Like other statins, rosuvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Rosuvastatin inhibited HMG-CoA reductase *in vitro*, and inhibit cholesterol synthesis *in vivo* with ED50 less than 1 mg/kg in rats and dogs (below NOAEL in toxicology studies).

C. Nonclinical Safety Issues Relevant to Clinical Use
Liver toxicity of rosuvastatin was observed across species in animal studies at exposure levels 1 to 7X the human exposure based on the Sponsor proposed high dose of 80 mg/day; about 2 to 16X the human exposure based on the human dose of 40

The sidebar on the right shows a search filter for "rosuvastatin;hmg coenzyme a" and a list of results under the heading "HMG Coenzyme A Reductase". The results include several entries related to HMG-CoA reductase inhibition in various contexts, such as "inhibited HMG-CoA reductase in vitro, a..." and "Rosuvastatin inhibited HMG-CoA reductase and inhibit cholesterol synthesis in vivo with ED50 less than 1 mg/kg in rats and dogs (below NOAEL in toxicology studies). C."

Freedom to Operate

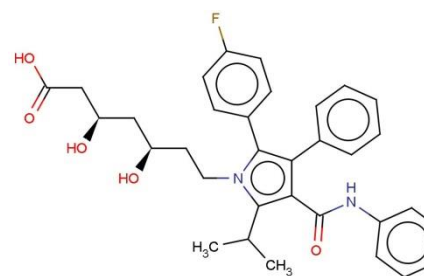
Search Input



Search Output

[R-(R*, R*)]-2-(4-fluorophenyl)-β, d-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Atorvastatin
Lipitor
PD155-158



US 2004/0092574 A1

May 13, 2004

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STATIN-LP(A) INHIBITOR COMBINATIONS

FIELD OF THE INVENTION

[0001] This invention concerns a combination of a statin compound, which is known to cause a reduction in plasma levels of low-density lipoproteins (LDL) cholesterol, and a compound which inhibits the formation of lipoprotein (a), Lp(a), which is a modified form of LDL, but which are unaffected by statins. The combination is useful for treating vascular disorders and diabetes mellitus.

BACKGROUND OF THE INVENTION

[0002] Several clinical studies have established that lowering certain forms of cholesterol in a mammal is an effective way to treat and prevent heart attacks, sudden death, and angina, both in subjects having higher than normal levels of circulating cholesterol, as well as those having normal levels of cholesterol. Lowering LDL, the bad form of cholesterol, is now one of the primary objectives of physicians treating patients who have, or who have a high risk of developing, cardiovascular diseases such as coronary heart disease, atherosclerosis, myocardial infarction, stroke, cerebral infarction, and even restenosis following balloon angioplasty. Many physicians are now utilizing cholesterol lowering agents purely as a prophylactic treatment in healthy subjects whose cholesterol levels are normal, thereby guarding against development of cardiovascular diseases.

[0003] The most commonly used cholesterol lowering agents are the statins, which are compounds which inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme responsible for catalyzing the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the cholesterol biosynthetic pathway.

[0004] There are several forms of circulating blood cholesterol which occur naturally in mammals. Some forms are considered "bad" cholesterol, while other forms are considered "good" cholesterol and are essential for good health. The good form of cholesterol has been established to be high density lipoprotein (HDL). Low density lipoprotein (LDL) is a "bad" cholesterol. Another form of LDL cholesterol, the primary bad form, is a modified form of LDL, called lipoprotein(a), or "Lp(a)". High levels of Lp(a) are now believed to be detrimental and can lead to cardiovascular diseases, and is one of the major risk factors leading to death from heart disease.

[0005] Because vascular diseases such as coronary heart disease, stroke, and even peripheral vascular disease, remain a leading cause of death and disability throughout the world, the need continues to develop new and improved treatments, as well as agents that will actually prevent the formation of these diseases.

[0006] We have now discovered that treatment and prevention of vascular diseases can be effected by administering a combination of a statin with an Lp(a) inhibitor. Typical Lp(a) inhibitors are the retinoids, as described in U.S. Pat. No. 5,489,611 incorporated herein by reference.

SUMMARY OF THE INVENTION

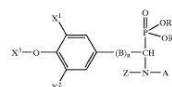
[0007] This invention provides a pharmaceutical composition comprised of an effective amount of a statin and an

effective amount of an Lp(a) inhibitor. More particularly, one embodiment of the invention is a combination of a statin with an Lp(a) inhibitor which is a retinoid.

[0008] The combinations of this invention can also employ the pharmaceutically acceptable salts of the respective active components.

[0009] Preferred retinoids are those described in U.S. Pat. No. 5,489,611. Especially preferred compositions employ 9-cis-retinoic acid or 13-cis-retinoic acid. Also preferred are trans-retinal and trans-retinol, as well as 13-cis-retinol, 13-cis-retinal, 9-cis-retinol, and 9-cis-retinal.

[0010] Another class of preferred Lp(a) inhibitors to be employed are aminophosphonates of the Formula I



[0011] wherein:

[0012] X¹ and X² independently are hydrogen, straight or branched C₁-C₆ alkyl and C₁-C₆ alkoxy, hydroxy, or nitro;

[0013] X³ is hydrogen or C₁-C₆ alkyl; or X³ or X² is an alkylidene dioxy ring having from 1 to 4 carbon atoms;

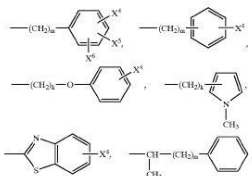
[0014] R¹ and R² independently are hydrogen, or straight or branched C₁-C₆ alkyl;

[0015] B is CH₂, -CH₂CH₂-, or CH=CH-;

[0016] n is 0 or 1;

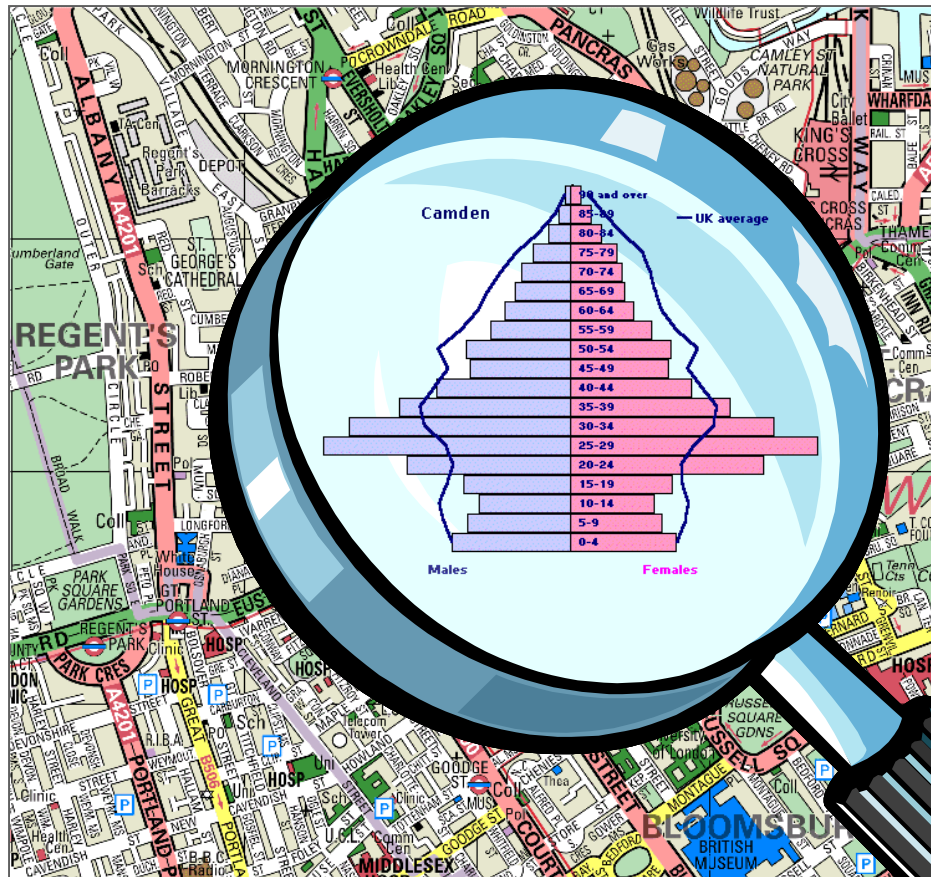
[0017] Z is hydrogen, straight or branched C₁-C₆ alkyl, an aryl group Ar, or R'CO₂ where R' is C₁-C₆ alkyl or perfluoro C₁-C₆ alkyl;

[0018] A is hydrogen, CH₂CH=CH₂, straight or branched C₁-C₆ alkyl or



Cc1cc(C(=O)Nc2ccccc2)c(-c3ccccc3)c(-c4ccc(F)cc4)n1CC[C@@H](O)C[C@@H](O)CC(O)=O

Semantic Lenses



- Semantic Lenses contain sets of filters and rules used to make the display of information more useful to a particular end-user
- Semantic Lenses enable specific data and evidence sources to be highlighted or ignored
- Semantic Lenses allow the display of information to be tailored to the type of data

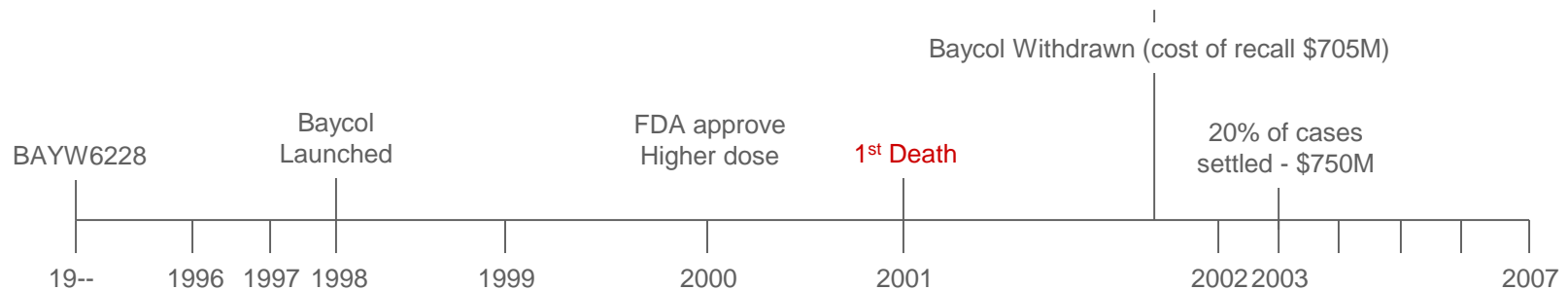
Return on Investment Calculations

- Opportunity based
 - Do things you want to but can't/don't do now
 - Comprehensive systematic analysis
 - Identification of new business opportunities
 - Objective knowledge-led decision making
- Risk based
 - Protection from costly or negative outcome
 - Avoid missing side-effect liabilities
 - Assess opportunities quickly enough to secure position
 - Evaluate project risks and market potential accurately
- Productivity based
 - Improvement of existing processes
 - Savings of time, headcount or money

What Ontology can do for R&D

- Helps eliminate liabilities early
- >100 killed, 1000's injured
- Many information sources
 - Human genome / proteome
 - Clinical & pre-clinical experience
 - Similar cases
- Investigation hampered by lack of 'system'
 - Different people, different jurisdiction, different locations

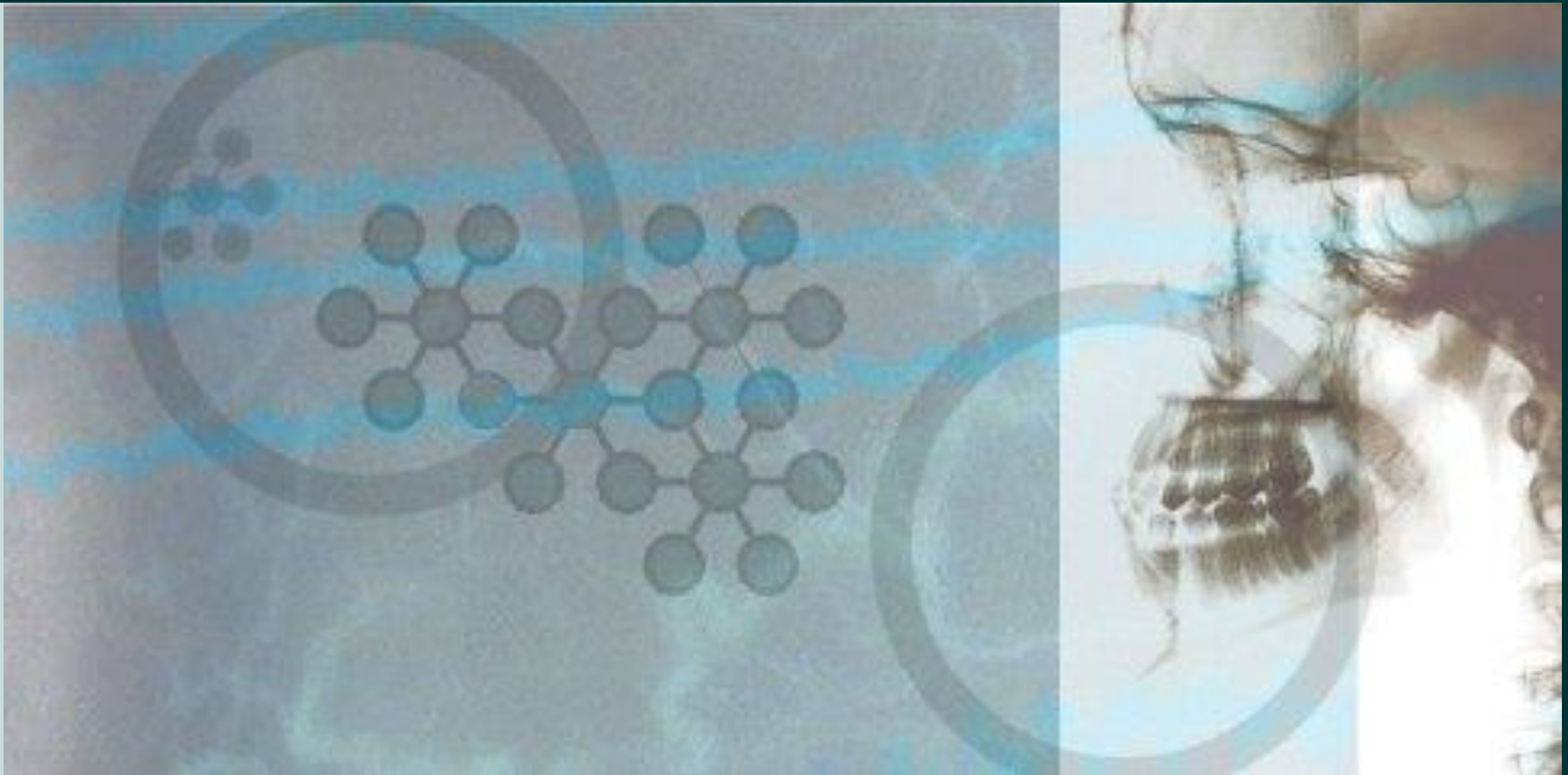
Cost
\$1-4B cash



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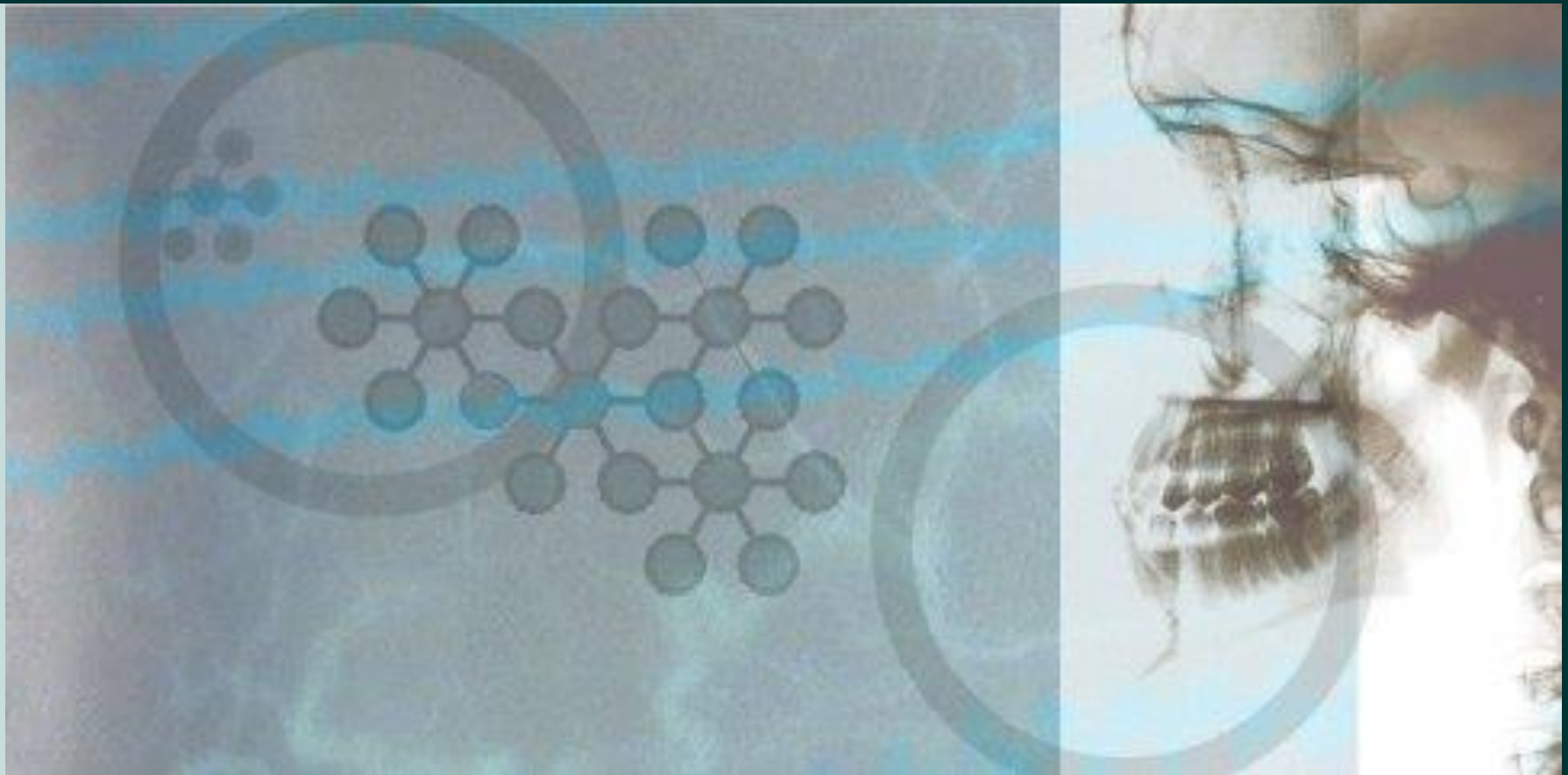
Case Studies

Sheryl Torr-Brown, Pfizer

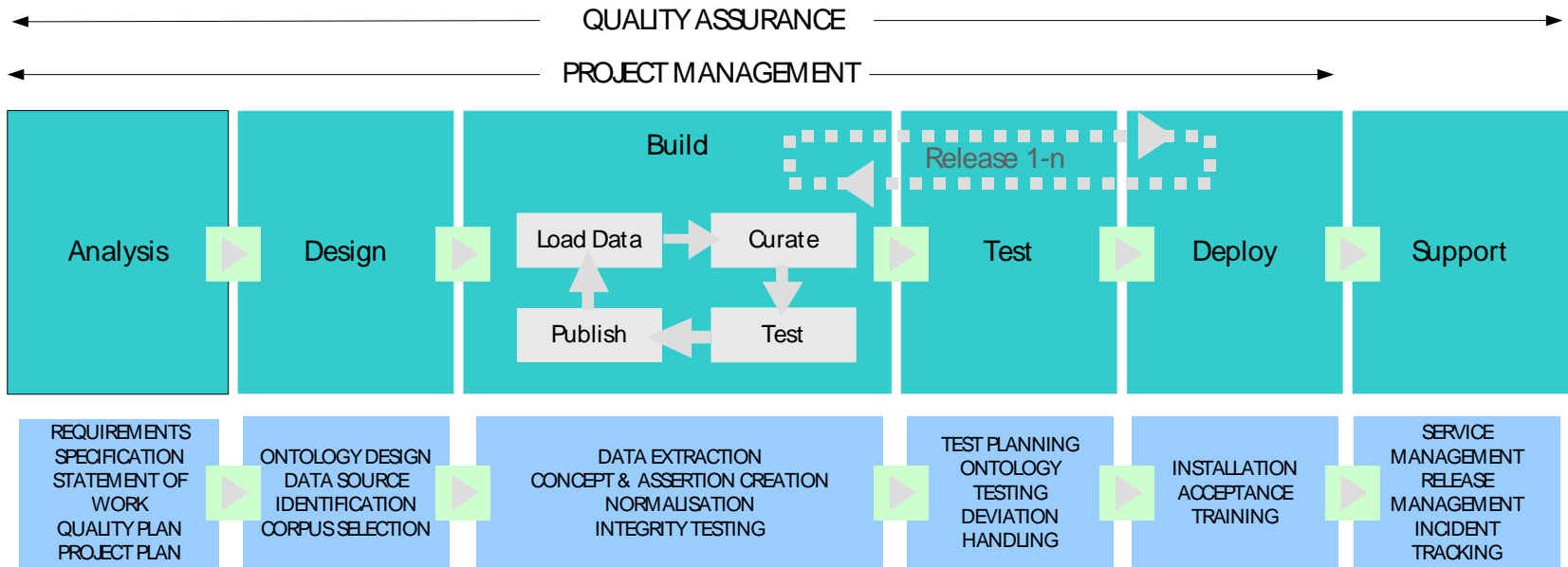


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Construction of Ontologies

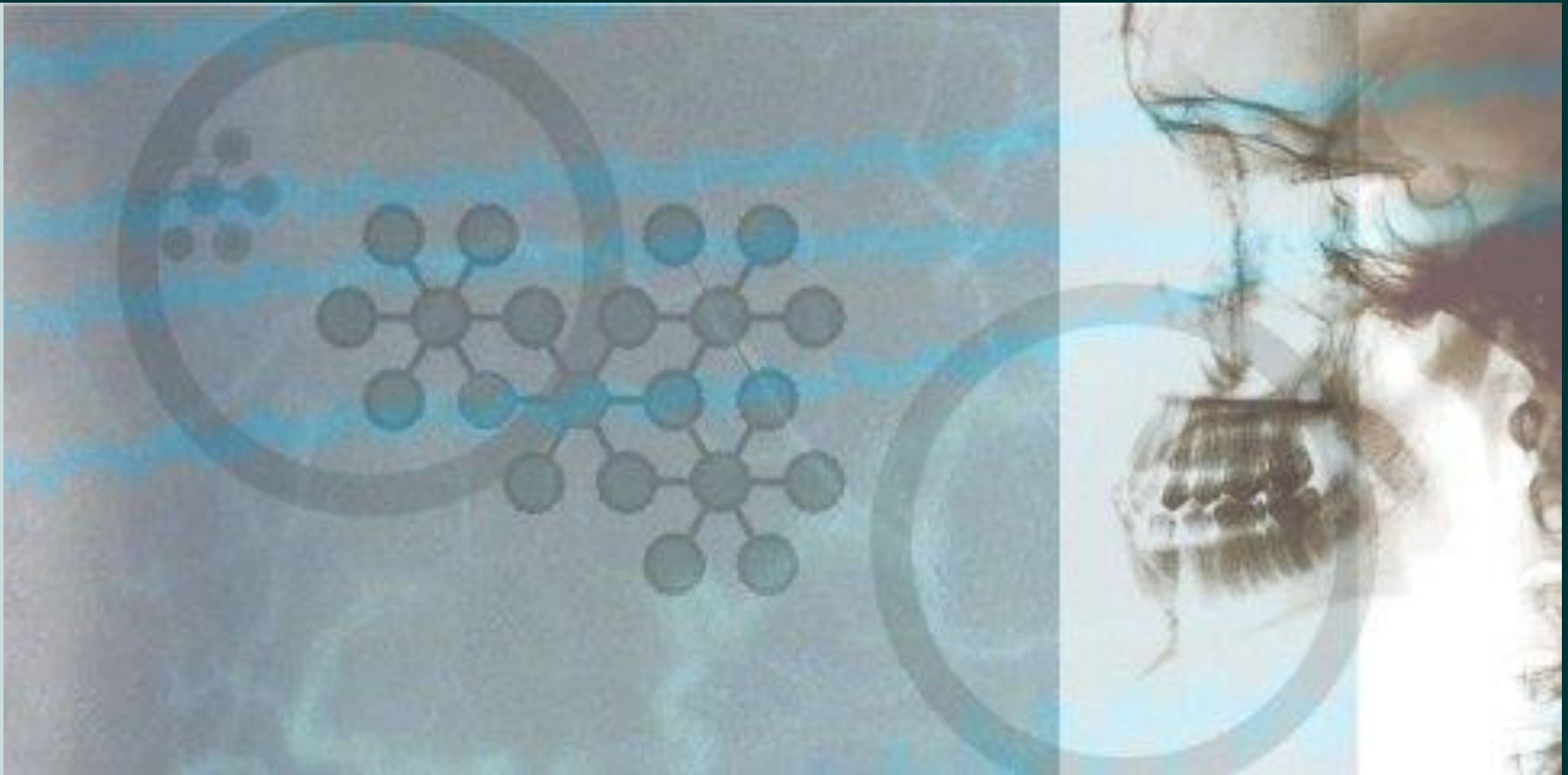


Ontology Curation Process



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Standards & Ontology Languages



Ontology Standards

- XML
 - Structured information interchange format
- RDF
 - Designed for classification/search applications
 - Oriented around <subject> <predicate> <object> triple
 - Uses URIs (e.g. LSIDs) for resource location
 - Each triple can be joined with other triples, but retains its unique meaning regardless of the complexity of the model
- OWL (Lite, DL, Full)
 - Lite – limited language subset supporting taxonomies
 - DL – simple extensions supporting Description Logics
 - Full – full blown semantic ontology, not guaranteed to be computationally complete



Example Ontologies

The screenshot displays the Protégé 2.0.1 ontology editor interface. The window title is "Artequakt5-WS04 Protégé 2.0.1 (C:\Documents and Settings\ha\Desktop\Artequakt5-WS04.pprj, Standard Text Files)". The menu bar includes "Project", "Edit", "Window", and "Help". The toolbar contains icons for file operations and editing, along with "A" and "R" buttons. The main interface is divided into three panes:

- Classes:** A hierarchical tree view showing the ontology structure. The root is ".THING", followed by "SYSTEM-CLASS", "E1.CIDOC_Entity", "E18.Physical_Entity", "E19.Physical_Object", "E22.Man-Made", "E23.Iconographic", "E26.Physical_Feature", "E2.Temporal_Entity", "E28.Conceptual_Object", "E36.Visual_Item", "Information_Text", "Document (46)", "Paragraph (374)", "Sentence (251)", "E39.Actor", "E40.Legal_Body", "Person (19)", "E52.Time-Span", "E53.Place (535)", "E54.Dimension", "E55.Type", "E59.Primitive_Value", "E61.Time_Primitive", "Extracted_Triple (9882)", "Class_Information (14)", and "Instance_Information (126)".
- Display Slot:** A pane showing the "name" slot for the selected class. It lists "Direct Inst." (Direct Instances) including: "<Person_105 name not set>", "<Person_108 name not set>", "<Person_13 name not set>", "<Person_132 name not set>", "<Person_133 name not set>", "<Person_26 name not set>", "<Person_27 name not set>", "<Person_43 name not set>", "Alfred Sisley", "Francisco Jose de Goya", "Gustave Courbet", "Mary Cassatt", "Mary Stevenson", "Pierre Auguste Renoir", "Rembrandt Harmenszoon van Rijn", "Rembrandt Peale", "Saskia van Uylenburgh", and "Sisley".
- Instance Form:** A form for the instance "Pierre Auguste Renoir (type=Person, name=Person_63)". It contains the following fields:
 - Name:** Pierre Auguste Renoir
 - Date Of Birth:** 25/2/1841
 - Date Of Death:** 3/12/1919
 - Date Of Marriage:** //1890
 - Painted:** a Tuke Henry, a Tissot James, a Sargent Singer, a Delacroix Eugene
 - Place Of Birth:** France
 - Place Of Death:** FranceBelow the form, there are three small image windows showing paintings: "Painting Style", "Painting Style", and "Painting Style".

Example Ontologies

The screenshot shows a Microsoft Internet Explorer browser window titled "Ontaria 0.8 - Microsoft Internet Explorer provided by BioWisdom". The address bar contains the URL "http://www.w3.org/2004/ontaria/basic?focus=mouse". The page header includes the W3C logo and the word "Ontaria", along with navigation links for "Home", "About", "Feedback/Forums", and "Help". A search bar contains the text "mouse" and a "Go" button, with links for "help" and "privacy".

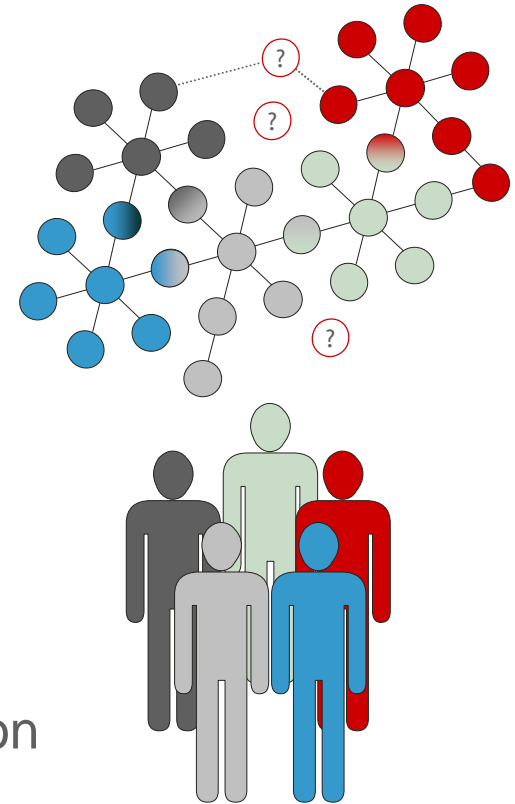
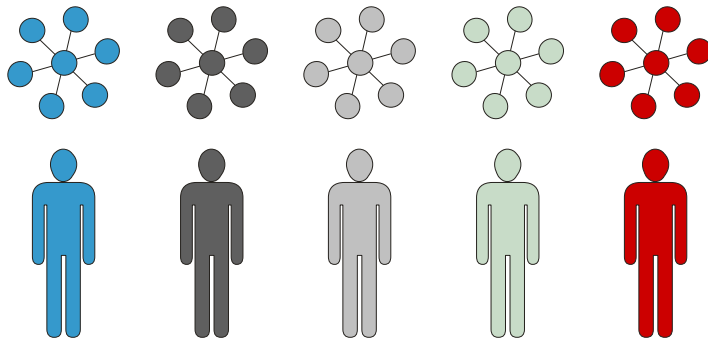
The search results are displayed in a list format:

- Result 1**
H_5_2_6_Input_Devices_And_Strategies Class [Visit](#)
no description or comment available
Dereference not yet attempted.
Some uses: [classification_dam1](#)
- Result 2**
Mouse Class [Visit](#)
Mouse
Dereference not yet attempted.
Some uses: [hedwig.xml](#)
- Result 3**
Rat Class [Visit](#)
A Rodent that has a hairless tail like a Mouse but that is larger than a Mouse.
Dereference not yet attempted.
Some uses: [Mid-level-ontology.owl](#)
- Result 4**
Tangible Thing Class [Visit](#)
Something which is not intangible, something which is physical, made of matter. It does not matter whether things are real of imaginary. Therefore we consider Mickey Mouse's car and a hippogriff as tangible things
Dereference not yet attempted.
Some uses: [AKT Reference Ontology \(Portal Ontology\)](#), [AKT Reference Ontology \(Support Ontology\)](#)

Public Domain Ontology Initiatives

- W3C
<http://w3c.org/>
- Ontaria - 858 sources, 2.5M assertions
<http://www.w3.org/2004/ontaria/>
- Ontoweb
<http://ontoweb.aifb.uni-karlsruhe.de/>
- OpenRDF
<http://www.openrdf.org/>
- Protégé
<http://protege.stanford.edu/>
- Gene Ontology
<http://www.geneontology.org/>
- Biological Processes Ontology
<http://smi-web.stanford.edu/projects/helix/pubs/process-model/>
- HL7-RIM
<http://www.ics.mq.edu.au/~borgun/Software.html>

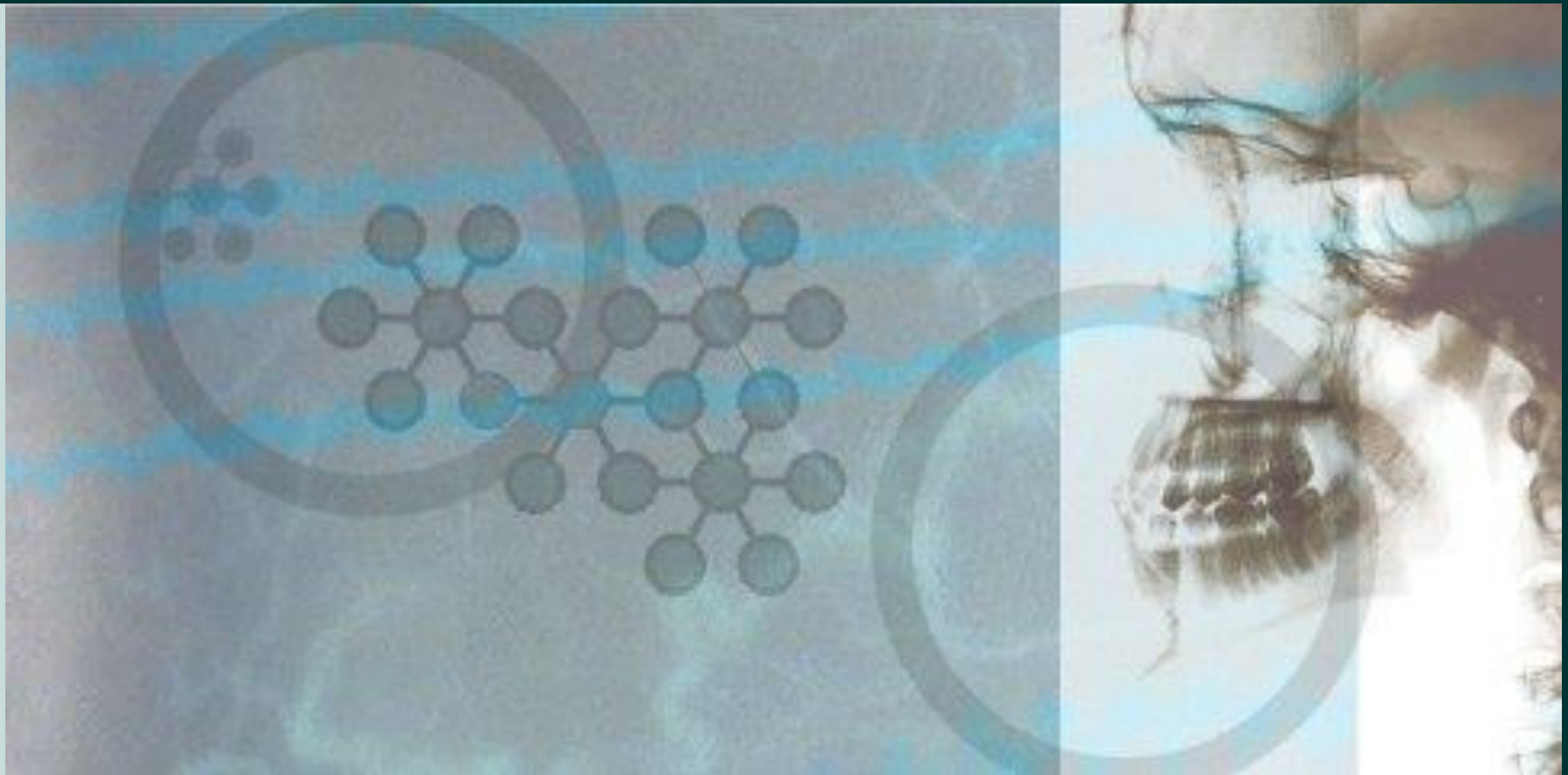
Value of Ontology



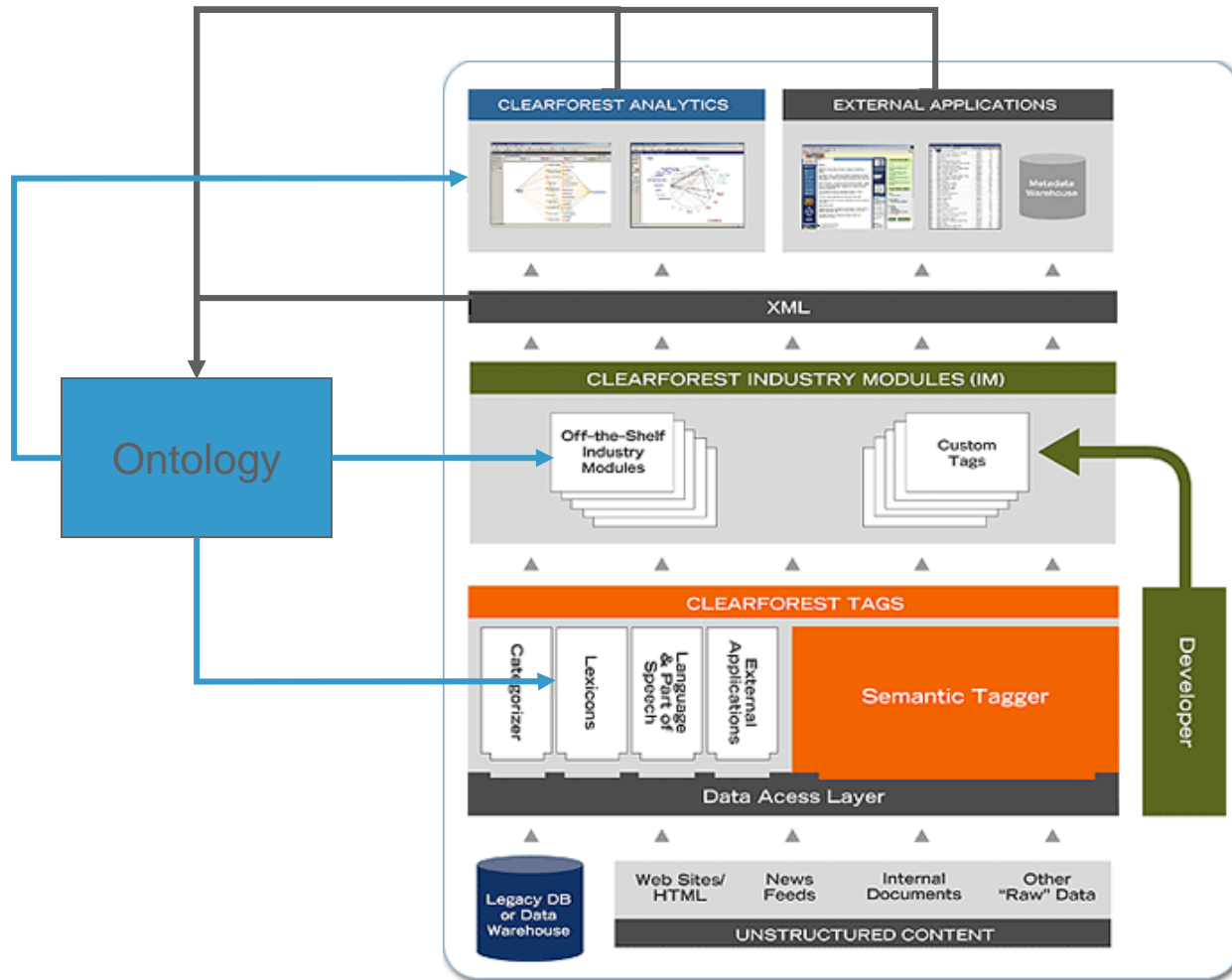
- Makes teams' knowledge visible
- Facilitates collaboration and communication
- Identifies knowledge gaps
- Supports multiple business applications
- Makes knowledge available for re-use on new projects

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steve.gardner@biowisdom.com



Potential Integration with ClearForest



An Ontology is an Atlas

- Contains the names of all important things (places)
- Contains attributes of all things (size, postcode, counties, population, etc)
- Contains the links between one thing and all others it is connected to (routes)
- Everybody has ontologies in their head – they are our way of looking at and interpreting the world
- Relationships depend on context (tube, bus or car)



Concept Typing by Rules

Microsoft Excel - Concept Cleanup and Typing - EntityBasic_Method 061.xls [Read-Only]

File Edit View Insert Format Tools Data Window Help Adobe PDF

Arial 10 B I U

D660

A	B	C	D	E	F	G	H	I	J
624	16	Use PubMed Id to look up journal title (A putative concept typing step).							
625		Annotate each record with a putative type according to journal it appears in.							
626									
627									
628	17	Type the concept on the string pattern within the concept string itself (A putative concept typing step).							
629		If concept has the following form, then type as...							
630		KEY: <i>italics</i> = actual string, X = letter, N = number, C = carriage return (ie: end of term), S = Space, [] = optional, () = numbers of							
631		form of concept	putative concept ty notes	suggested score					
632		X(2-3){S}(N)(5-9)C	SUBSTANCE	ie: Two or three let	20				
633		X(n){S}muscle(s)C	ANATOMICAL STRUCTURE		20				
634		X(n){S}tissue(s)C	ANATOMICAL STRUCTURE		15				
635		X(n){S}cell(s)C	ANATOMICAL STRUCTURE		15				
636		X(n){S}vein(s)C	ANATOMICAL STRUCTURE		15				
637		X(n){S}artery C	ANATOMICAL STRUCTURE		15				
638		X(n){S}arteries C	ANATOMICAL STRUCTURE						
639		X(n){S}arteries C	ANATOMICAL STRUCTURE						
640		X(n){S}neuron(s)C	ANATOMICAL STR	eg: capture... "fast motoneurons"					
641		X(n){S}neuron(s)C	ANATOMICAL STRUCTURE						
642		X(n){S}fibre(s)C	ANATOMICAL STRUCTURE						
643		X(n){S}fiber(s)C	ANATOMICAL STRUCTURE						
644		X(n){S}layer(s)C	ANATOMICAL STRUCTURE						
645		X(n){S}lopsy(s)C	ANATOMICAL STRUCTURE		20 or BIOMEDICAL TECHNIQUE ???				
646		X(n){S}lopsiess(s)C	ANATOMICAL STRUCTURE		20 or BIOMEDICAL TECHNIQUE ???				
647		X(n){S}atroph(s)C	DISORDER	atrophy itself is a process, but usually a word before atropy refers to a disorder					
648		X(n){S}pathy C	DISORDER						
649		X(n){S}plegia C	DISORDER						
650		X(n){S}disease C	DISORDER						
651		X(n){S}disorde(r)C	DISORDER						
652		X(n){S}syndrome C	DISORDER						
653		X(n){S}agomist C	SUBSTANCE						
654		X(n){S}antagomist C	SUBSTANCE						
655		X(n){S}protein C	SUBSTANCE						
656		X(n)in C	SUBSTANCE						
657		X(n){S}surgery C	BIOMEDICAL TECHNIQUE						
658		X(n){S}ligation(s)C	BIOMEDICAL TECHNIQUE						
659		X(n){S}toxicity C	???????????????????????????? - need to discuss at a "Concept meeting"						
660									
661									
662									
663									
664		malformation	always is a DISORDER						
665		abnormal - often signifies	CLINICAL MANIFESTATIUN						
666		in born error	always signifies DISORDER, and always is a METABOLIC DISOREDR						
667									
668									
669									
670									
671									
672									
673									
674	18	Type the concept on the context of the sentence (A putative concept typing step).							
675		form of concept	putative concept ty notes						
676		1 X(n){S}(define1)C	SUBSTANCE	define1 = to pick out concentrations after a compound, eg: CCK-8 (1 mMol)					
677									
678		definitions for more complex forms...							
679		define1	contains	numbers (1234567 OR					
680				commas (,) OR					
681				full stops (.) OR					

putative new rules / applied Julie's rules / entity_basic_sample /

Ready

Curation and Document Analysis Tools for Information Scientists

The screenshot displays two main windows from the BioWisdom software suite. The background window is the 'Sofia Ontology Editor', which shows a hierarchical ontology tree on the left and a 'Relationship Types' panel on the right. An 'Add Relationship Type' dialog box is open, showing fields for 'Concept type' (set to 'Protein'), 'Related concept type' (set to 'Process'), and 'Relationship name'. The foreground window is the 'Sofia Text Prototype', which displays a MEDLINE record (10592346) with a text snippet: 'Severe rhabdomyolysis following massive ingestion of oolong tea: caffeine intoxication with coexisting hyponatremia.' Below the text, a 'Term Selection' panel shows 'IS CAUSED BY (Disorder, Disorder)' as the selected relationship. A 'Candidate Assertions' table is shown at the bottom, listing relationships between terms from the text and the ontology.

Name	Type	Relationship	Name	Type
Hypokalaemic Disorder	Disorder	IS CAUSED BY	Hyponatraemic Disorder	Disorder
Rhabdomyolysis (HUMAN)	Disorder	IS CAUSED BY	Caffeine	Compound
Rhabdomyolysis (HUMAN)	Disorder	OCCURS WITH	Water Intoxication	Disorder
Rhabdomyolysis (HUMAN)	Disorder	IS CAUSED BY	Caffeine Intoxication	Disorder
Water Intoxication	Disorder	IS CAUSED BY	Caffeine	Compound