



Pharma-Epistemology: the Semantic Web in Practice

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March 2008



Ramon Llull – Computational Epistemologist



Ramon Llull (1232 – 1315)

- Ramon Llull was a writer and philosopher born into a wealthy family in Palma, Mallorca, then part of the Crown of Aragon.
- His first major work was *Art Abreujada d'Atrobar Veritat* (The Art of Finding Truth).
- Llull believed that there were a limited number of basic, undeniable truths in all fields of knowledge, and that we could understand everything about these fields of knowledge by studying combinations of these elemental truths.

- Glymour, Ford and Hayes; Ramon Llull and the Infidels *AI Magazine* (1998)
- http://en.wikipedia.org/wiki/Ramon_Llull



The Automation of Discovery

1. Pick something out of the haystack; subject it to a severe test. Decide if it is a needle. Continue until you find the needle or until civilization comes to an end. → **HARD SCIENCES**
2. Pick something you like out of the haystack. Subject it to a severe test. If it doesn't pass test, find weaker test that it can pass. → **PSYCHOLOGY, ECONOMICS**
3. Try 1 for a while, and if no needle turns up, start studying hay.
4. Try 1 for a while, if no needle turns up, change the meaning of "needle". → **POST-MODERNISM**
5. Set haystack on fire and blow away the ashes to find the needle. → **QUANT FINANCE, FINANCIAL ENGINEERING**
6. Run a magnet through the haystack. Sort out screws, paper clips, nails and needles. → **APPLIED COMPUTATIONAL PHARMA-EPISTEMOLOGY**

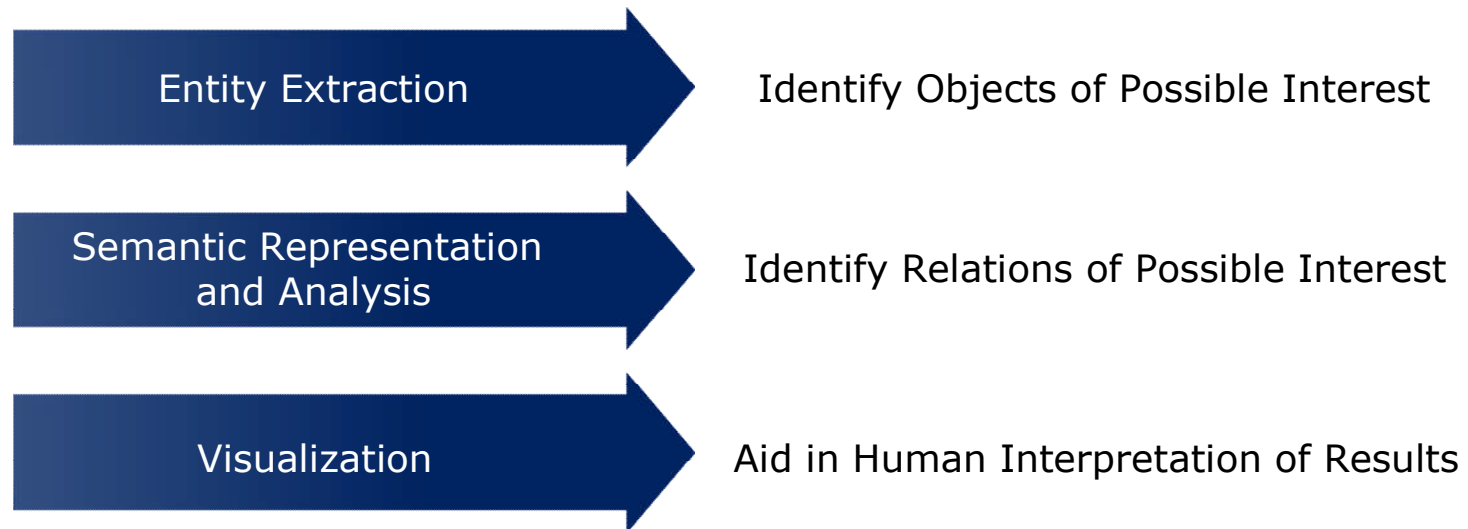


Example Application Approach

- ▶ **Latent Semantic Indexing (LSI)** - LSI is a technique in natural language processing, in particular in vectorial semantics, of analyzing relationships between a set of documents and the terms they contain by producing a set of concepts related to the documents and terms.
- ▶ LSI enables three comparisons of interest:
 - How semantically similar are two terms?
 - How semantically similar are two documents?
 - How associated are term i and document j ?



Exploiting LSI



The banner features a collage of images: an oil rig, power lines, a scientist in a lab coat, and industrial machinery. The title 'Pfizer Project Overview' is centered in white text on a dark blue background.

Pfizer Project Overview

- ▶ Text mine biomedical literature to identify putative [molecular] biomarkers by tumor type
 - Ovarian, NSLC, colorectal, pancreatic, melanoma, gastric, HRPC, breast
- ▶ There were two chief questions relevant to this project:
 - Can you tell us something we didn't already know (find me a new biomarker)?
 - Can you find what we may already know and organize it in ways that are simpler to search and analyze?





It all begins with the query - Prognostic Lung Tumor Biomarker Queries

Prognostic significance of clinical factors and Akt activation in patients with bronchioloalveolar carcinoma

Junji Tsurutani^{a,d}, Seth M. Steinberg^b, Marc Ballas^a, Matthew P. Jaclyn LoPiccolo^a, Hiroshi Soda^d, Shigeru Kohno^d, Valgardur Egilsson^c, Phillip A. Dennis^{a,*}

^a Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, United States

^b Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, United States

^c Department of Pathology, National University Hospital, 101 Reykjavik, Iceland

^d Second Department of Internal Medicine, Nagasaki University School of Medicine, 17-1 Sakamoto, Nagasaki, Japan

Received 22 June 2006; received in revised form 12 July 2006; accepted 20 September 2006

P-606 Prognostic factor analysis of locally advanced non-small cell lung cancer with surgical resection: Poor disease-free survival in patients with low expression of bax

J. Choi, H. Lim, J. Park, H. Lee, Y. Jung, H. Kim, Y. Oh, S. Hwang, H. Choi, J. Han, *Aju University School of Medicine, Suwon, South Korea*

Background: The prognosis of locally advanced non-small cell lung cancer (NSCLC) patients (pts) who underwent surgical resection is generally poor even with adjuvant treatment (TX).

Methods: We investigated the prognostic significance of various clinicopathologic characteristics including apoptosis related proteins, p53, bax, and galectin-3 in 104 pts with locally advanced NSCLC who underwent surgical resection (stage II: 47, IIIA: 40, IIIB: 10, IV: 7). Eighty-two pts (79%) received adjuvant TX (chemotherapy: 9, radiotherapy: 17, both: 56).

Results: With a median follow-up of 54 months (26-120 months) in survivors, 4-year disease-free survival (DFS) and overall survival (OS) of total pts were 29% and 42%, respectively, excluding 6 deaths from postoperative complications. High expression of p53, bax, and galectin-3 was observed in 43 (41%), 20 (19%), and 46 (44%) pts using immunohistochemistry in multivariate analysis, while large tumor size ($p < 0.0001$), non-squamous

$p = 0.001$),
with poor
adjuvant
pression of
d NSCLC

Prognostic significance of vessel architecture and vascular stability in non-small cell lung cancer

Niels Reinmuth^{a,c,*}, Elisabeth Piegelbrock^a, Miriam Raedel^a, Nicole Fehrmann^a, Heike Hintelmann^a, Ruth Wagner^a, Wolfgang E. Berdel^a, Michael Thomas^c, Lutz Freitag^d, Rolf M. Mesters^{a,b}

^a Department of Medicine/Hematology and Oncology, University of Muenster, Muenster, Germany

^b IZKF Muenster, University of Muenster, Muenster, Germany

^c Clinic for Thoracic Diseases, University of Heidelberg, Amalienstr. 5, D-69126 Heidelberg, Germany

^d Clinic for Pulmonary Diseases, Hemer, Germany

Received 14 March 2006; received in revised form 12 July 2006; accepted 20 September 2006

Query Corpus of Literature

User: Jim Golden (goldenj)

Search Repository:

JGolden-Medline-1995up-1

Minimum Score

0

+/~ keywords

Disallow Optimizer?

Query Text Locale:

en

Result Docs per Page:

10

Number of Result Terms:

10

Save This Query:

Save

Query:

Last successful query

Retrieve

Delete

Query successful and saved as "Last successful query".

Query Text

Prognostic significance of clinical factors and Akt activation in patients with bronchioloalveolar carcinoma
Junji Tsurutania,d, Seth M. Steinbergb, Marc Ballasa, Matthew Robertson a, Jaclyn LoPiccoloa, Hiroshi Sodad, Shigeru Kohnod, Valgardur Egilssonc, Phillip A. Dennisa,~
a Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, United States
b Biostatistics and Data Management Section, Center for Cancer Research, National Cancer

Like DocIDs:

Run this query

The query represents a concept around which all other documents in the repository are compared for meaning

Query Results

Query Date: Fri Dec 01 09:02:51 EST 2006

Found 10 Terms: (Best Score = 10000)

	Term	Score
1.	prognoses	4108
2.	cox's	3772
3.	kaplan-meir	3697
4.	tumor-node-metastasis	3681
5.	substage	3672
6.	iaslc	3657
7.	substaging	3626
8.	tnm	3612
9.	contre	3487
10.	nonsmall	3472

Semantically related concepts derived from query document



Semantically Related Documents in Corpus

1. Document [5867542](#) of set [5867542](#) and locale "en_US" (score 8465)
Summary: c-erbB-2 expression in small-cell lung cancer is associated with poor prognosis.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0433.xml
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2. Document [6075592](#) of set [6075592](#) and locale "en_US" (score 8329)
Summary: Identification of HER-2/neu overexpression and the clinical course of lung carcinoma in non-smokers with chronic lymphocytic leukemia.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0442.xml
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3. Document [7647114](#) of set [7647114](#) and locale "en_US" (score 8308)
Summary: Phospho-akt expression is associated with a favorable outcome in non-small cell lung cancer.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0508.xml
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4. Document [4403459](#) of set [4403459](#) and locale "en_US" (score 7687)
Summary: Association of immunoreactive hepatocyte growth factor with poor survival in resectable non-small cell lung cancer.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0370.xml
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5. Document [6649032](#) of set [6649032](#) and locale "en_US" (score 7569)
Summary: Carbonic anhydrase IX is an independent predictor of survival in advanced renal clear cell carcinoma: implications for prognosis and therapy.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0467.xml
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6. Document [7694783](#) of set [7694783](#) and locale "en_US" (score 7545)
Summary: Overexpression of S100A2 protein as a prognostic marker for patients with stage I non small cell lung cancer.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0510.xml
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7. Document [6714852](#) of set [6714852](#) and locale "en_US" (score 7540)
Summary: Phosphorylation, but not overexpression, of epidermal growth factor receptor is associated with poor prognosis of non-small cell lung cancer patients.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0469.xml
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8. Document [7083119](#) of set [7083119](#) and locale "en_US" (score 7525)
Summary: Synchronous overexpression of epidermal growth factor receptor and HER2-neu protein is a predictor of poor outcome in patients with stage I non-small cell lung cancer.
Source: file:/home/mhobson/medline/medline2006/load/medline06n0485.xml
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Summarize NSLC Document

Summarize Text

Prognostic significance of clinical factors and Akt activation in patients with bronchioloalveolar carcinoma
Junji Tsurutania,d, Seth M. Steinbergb, Marc Ballasa, Matthew Robertson a, Jaclyn LoPiccolo, Hiroshi Sodad, Shigeru Kohnod, Valgardur Egilssonc, Phillip A. Dennisa,~
a Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, United States

Summarize

Summary of Given Text

Best concept 1 (1): Forty-six patients with histopathologically proved BAC, in accordance with the WHO classification of lung tumors revised in 1999 [20], were enrolled in this study, Please cite this article in press as: Tsurutani J et al., Prognostic significance of clinical factors and Akt activation in patients with bronchioloalveolar carcinoma, Lung Cancer (2006), doi:10.1016/j.lungcan.2006.09.026
Prognostic significance of clinical factors and Akt activation 3 Table 1 Patient characteristics n = 46 Median age (range) 65 (38—84)
Gender Female 28 Male 17 Unknown 1 Clinical stage I 16 II 11 III 8 IV 9 Unknown 2 Smoking Never smoker 9 Smoker 23 Unknown 14
Histology Mucin 8 Non-mucin 37 Unknown 1 and median age was 65 years old (range 38—84).

Best concept 2 (0.8152): Dennisa,~ a Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, United States b Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, United States c Department of Pathology, National University Hospital, 101 Reykjavik, Iceland d Second Department of Internal Medicine, Nagasaki University School of Medicine, 17-1 Sakamoto, Nagasaki 852-8501, Japan Received 22 June 2006; received in revised form 19 September 2006; accepted 24 September 2006 KEYWORDS Bronchioloalveolar carcinoma; Prognostic factor; NSCLC; Akt; Smoking Summary Purpose: Lung cancer is the leading cause of cancer related mortality in the world.

Best concept 3 (0.7449): Evaluating an additional phosphorylation site (T308) appeared to improve the prognostic value of Akt activity Table 5A Final Cox proportional hazard model based on 43 patients with complete data (except for smoking) Variable Parameter estimate p-Value HR 95% CI for HR Gender Stage 0.81 0.77 0.032 0.049 2.24 2.17 1.07—4.71 1.004—4.71 HR, hazard ratio; CI, confidence interval.



Prognostic Lung Tumor Taxonomy

Home Documents

Document Taxonomy

Log

Compute taxonomy

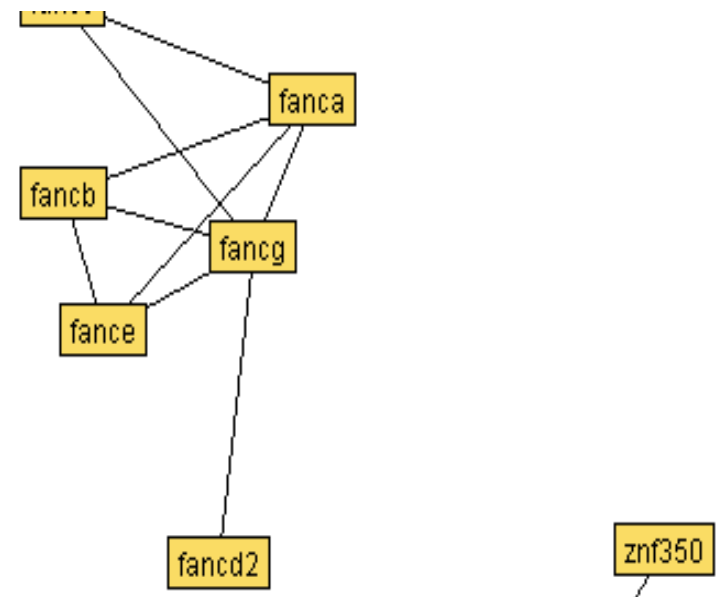
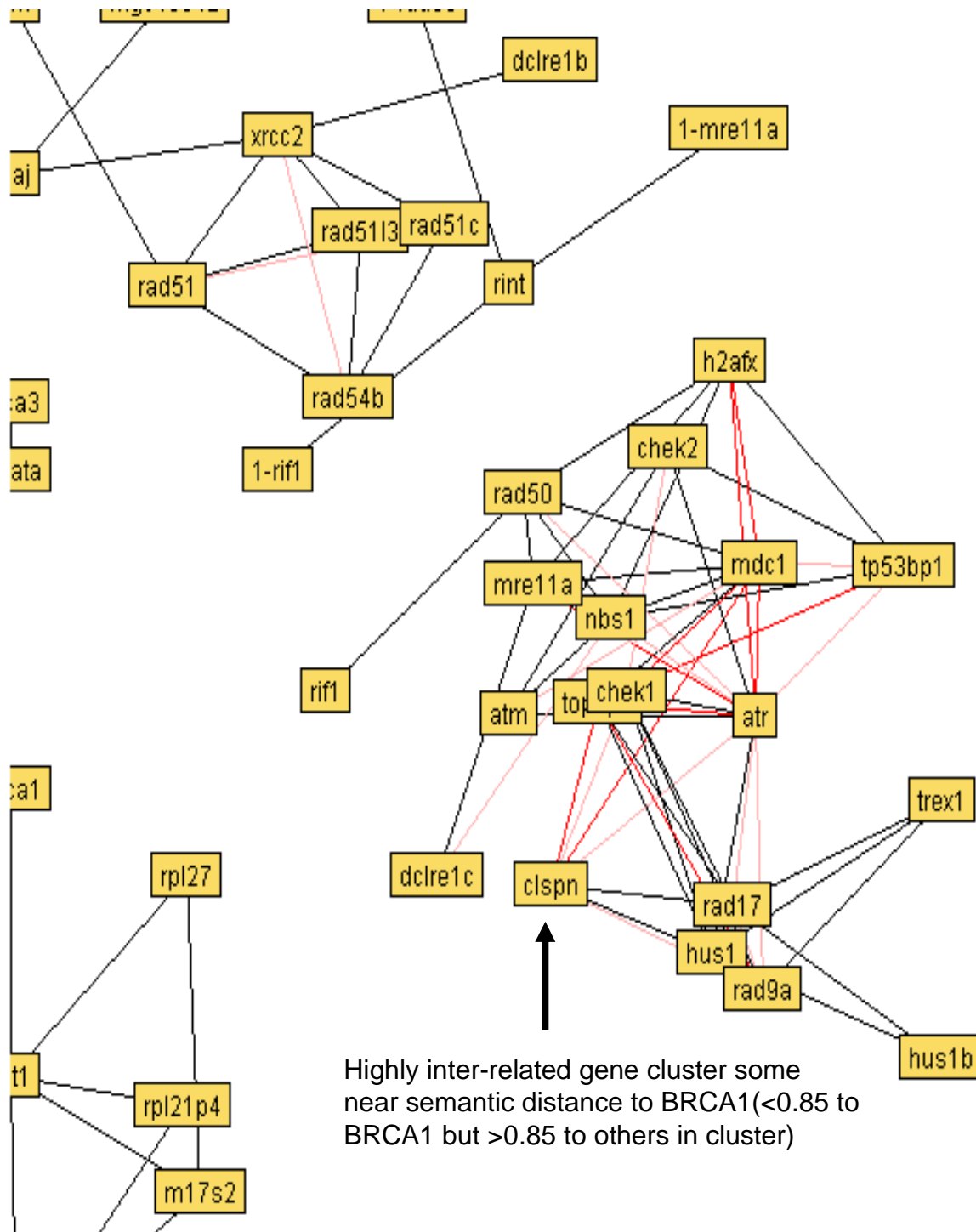
- 1P-607 Evaluation of two phosphorylation sites establishes Akt activation as a poor prognostic factor for all stages of NSCLC tumorsP Dennis, J. Tsuruta
- 74 Cells, Treatment, Growth (941 docs)
 - 66 Small (71 docs)
 - 64 Normal, Role (31 docs)
 - 62 Tensin, Pleckstrin (23 docs)
 - 60 Node, Lymph, PTNM (46 docs)
 - 59 Effects (39 docs)
 - 59 Nuclear, NF-kappaB, Akt1 (17 docs)
 - 58 Follow-up, Long-term (111 docs)
 - 58 Period (98 docs)
 - 58 Mutant, PTEN, Ser473 (44 docs)
 - 58 Chest, Type, Surg (22 docs)
 - 58 (22 docs)
 - 57 (66 docs)
 - 57 Erk, Extracellular, P38 (50 docs)
 - 56 Glottic (21 docs)
 - 55 Nodal, PN (17 docs)
 - 54 Renal, Gr (17 docs)
 - 54 Rapamycin (17 docs)
 - 53 Local, Cor (17 docs)
 - 53 Data (27 docs)
 - 52 (54 docs)
 - 49 ASCO, Annual, Vol (46 docs)

**New taxonomy
for NSCLC based
on new query
containing 941
documents**

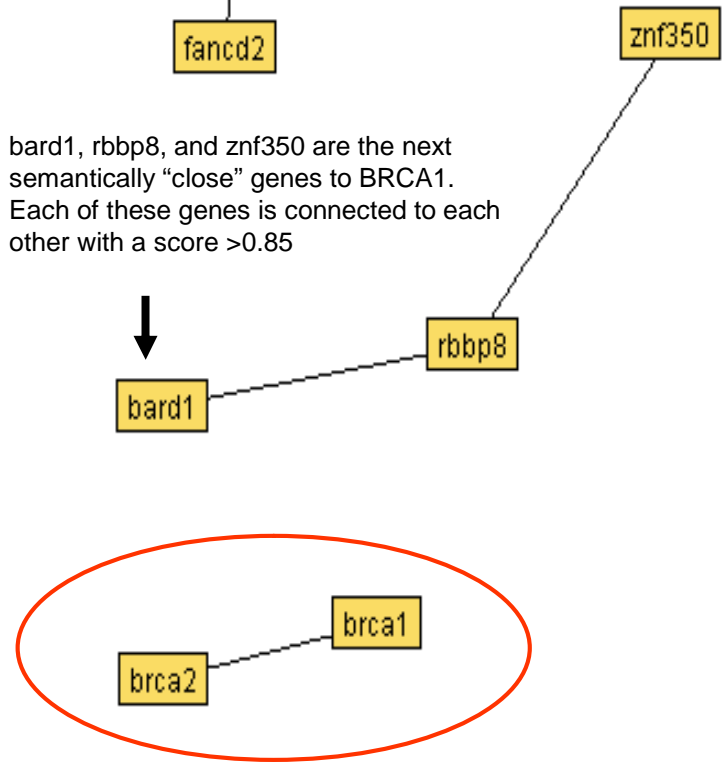
Taxonomies (or conceptually organized clusters of documents) are generated specifically for the query – the query is used to organize the corpus of documents and each cluster is given an appropriate title. All documents are then placed in their most relevant conceptual cluster.

Knowledge Presentation

Therapeutic Area	Indication	Biomarker	Biomarker Panel	Journal Reference	Protein/Gene ID	Synopsis
Oncology	Ovarian Carcinoma	angiopoietin-2		Mast cell density, angiogenesis, blood clotting, and prognosis in women with advanced ovarian cancer. Chan JK, Mawardi A, Leimic H, Liu F, Berman J	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	Many hold angiopoietin-2 responsible for progression of brain, ovarian, hepatocellular and bladder cancers. In addition to speculation about
Oncology	Ovarian Carcinoma	AP-2g		The AP-2g transcription factor is upregulated in advanced-stage ovarian carcinoma. Elin Ødegaard, Anne Cathrine	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	AP-2g expression is upregulated in advanced-stage ovarian carcinoma compared to early-stage carcinomas, borderline tumors, and the ovarian
Oncology	Ovarian Carcinoma	ARHI	ARHI, p21(WAF1/CIP1)	Expression of the tumor suppressor gene ARHI in epithelial ovarian cancer is associated with increased expression of p21 WAF1/CIP1 and prolonged	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	PURPOSE: ARHI, an imprinted putative tumor suppressor gene, is expressed in normal ovarian epithelial cells, but its expression is down-regulated or lost in most ovarian cancer cell lines.
Oncology	Ovarian Carcinoma	p21(WAF1/CIP1)	ARHI, p21(WAF1/CIP1)	Expression of the tumor suppressor gene ARHI in epithelial ovarian cancer is associated with increased expression of p21 WAF1/CIP1 and prolonged	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	PURPOSE: ARHI, an imprinted putative tumor suppressor gene, is expressed in normal ovarian epithelial cells, but its expression is down-regulated or lost in most ovarian cancer cell lines.
Oncology	Ovarian Carcinoma	B7-H4		B7-H4 overexpression in ovarian tumors. Tringler B, Liu W, Corral L, Torkko KC, Enomoto T, Davidson S, Lucia MS	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	Despite great advances in therapeutic management, the mortality rate for ovarian cancer has remained relatively stable over the past 50
Oncology	Ovarian carcinoma	bone morphogenetic protein-7	beta8 integrin subunit, bone morphogenetic protein-7, claudin-4, collagen type IX	Differential gene expression in ovarian carcinoma: identification of potential biomarkers. Hibbs K, Skubitz KM, Pambuccian SE, Casey RC, Burleson	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	Ovarian cancer remains the fifth leading cause of cancer death for women in the United States. In this study, the gene expression of 20 ovarian
Oncology	Ovarian carcinoma	claudin-4	beta8 integrin subunit, bone morphogenetic protein-7, claudin-4, collagen type IX	Differential gene expression in ovarian carcinoma: identification of potential biomarkers. Hibbs K, Skubitz KM, Pambuccian SE, Casey RC, Burleson	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	Ovarian cancer remains the fifth leading cause of cancer death for women in the United States. In this study, the gene expression of 20 ovarian
Oncology	Ovarian carcinoma	collagen type IX alpha2	beta8 integrin subunit, bone morphogenetic protein-7, claudin-4, collagen type IX	Differential gene expression in ovarian carcinoma: identification of potential biomarkers. Hibbs K, Skubitz KM, Pambuccian SE, Casey RC, Burleson	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uid=105322	Ovarian cancer remains the fifth leading cause of cancer death for women in the United States. In this study, the gene expression of 20 ovarian



bard1, rbbp8, and znf350 are the next semantically "close" genes to BRCA1. Each of these genes is connected to each other with a score >0.85



BRCA1 and BRCA2 are the only two genes connected with a semantic cosine score >0.85

News Letters RSS

TBE
Generally speaking, a biomarker is used to indicate or measure a biological process (for instance, levels of a specific protein in blood or spinal fluid, genetic mutations). Detecting biomarkers specific to a disease can aid in the identification, diagnosis, prognosis and

Research Paper

Low Blood Pressure
Blood pressure is the force exerted by circulating blood on the walls of blood vessels, and constitutes one of the principal vital signs. Blood pressure is generated by the heart pumping blood into the arteries and is regulated by the response by the arteries to the flow of blood.

By convention, an individual's blood pressure is expressed as systolic/diastolic blood pressure, for example, 120/80. The systolic blood pressure (the top number) represents the pressure in the arteries as ↻

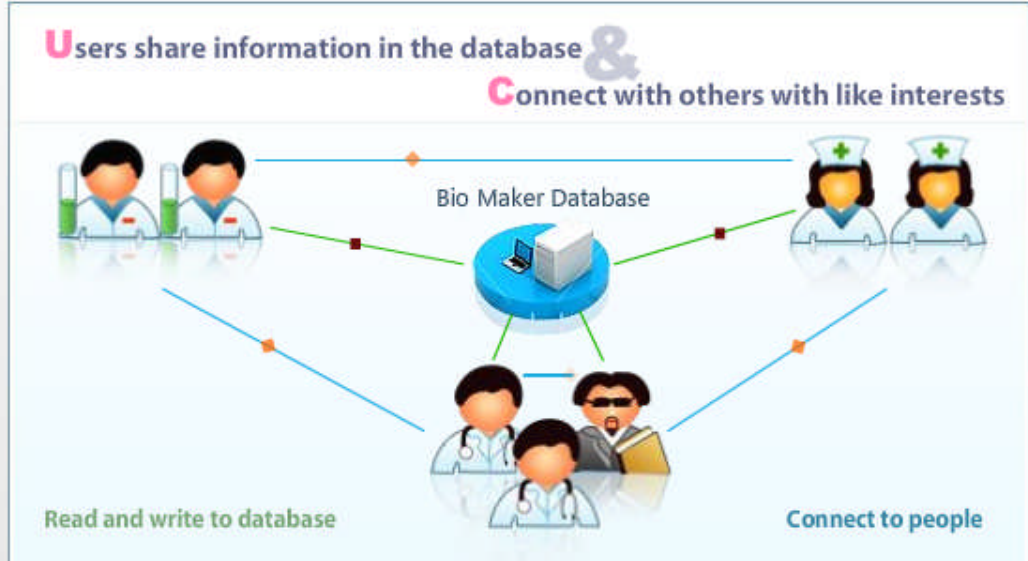
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Refine Search (optional):

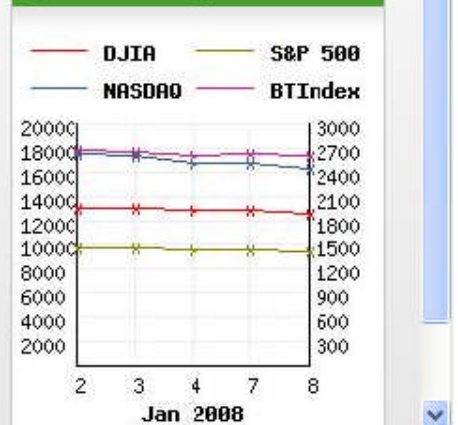
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- TBE



Tissue Exchange

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(www.thebiomarkerexchange.com)

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CAS/CSE1L PubMed Back

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Discussion

Research and Articles

CAS/CSE1L is the human homologue of the yeast gene CSE1. It was first cloned while searching for genes that rendered breast cancer cells resistant towards toxin induced apoptosis. Since depletion of CSE1 leads to cell-cycle arrest, CAS is thought to be involved in proliferation. CAS functions in the mitotic spindle checkpoint. CAS is located on chromosome 20q13, a locus often amplified in cancers of various origin, e.g. colonic or breast cancer. Since genetic instability is a hallmark of cancer, amplification or over expression of the CAS gene might interfere with or override its role in the mitotic spindle checkpoint. CAS is also implicated in the nuclear to cytoplasmic reshuffling of importin alpha, which itself is necessary for the nuclear transport of several proliferation activating proteins, transcription factors, oncogene and tumor suppressor gene products such as p53 and BRCA1. Inhibition of MEK1 mediated phosphorylation has been shown to enhance paclitaxel (Taxol) induced apoptosis in breast, ovarian, and lung tumor cell lines in-vitro. Since CAS is also phosphorylated (activated) by MEK1, and since the anti-cancer drug Taxol alters the microtubule assembly and activates pro-apoptotic signaling pathways, altering the activity/phosphorylation status of CAS via MEK1 inhibition may present a potential strategy in experimental cancer therapy.

Done

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[\[Prediction of response to docetaxel in breast cancer.\]](#)

Docetaxel, a second-generation taxane, is one of the most powerful anticancer drugs for breast cancer. It has been widely used in the metastatic setting but also in the adjuvant or neoadjuvant setting for breast cancer patients. However, docetaxel is not effective for all breast cancers. The respons...

[From plasma membrane to cytoskeleton: a novel function for semaphorin 6A.](#)

Class III beta-tubulin (TUBB3) overexpression has been reported in ovary, lung, breast, and gastric cancer patients. Currently, no clinical drugs are available for a specific targeting of TUBB3, whereas the investigational drug IDN5390 specifically interacts with TUBB3. To gain insight into the path...

[Isotype expression, post-translational modification and stage-dependent production of tubulins in er...](#)

Microtubules are cytoskeletal polymers containing repeating alpha/beta-tubulin heterodimers and are found in all eukaryotes including the malaria parasite Plasmodium falciparum. Diverse cellular functions such as chromosomal segregation, organelle transport and the determination of cell shape and mo...

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ACS :: Chemotherapy
of cancer cells called , which normally prompts cancer cells to grow. When combined with gemcitabine...
http://www.cancer.org/docroot/CRI/content/CRI_2_4_4X_Chemotherapy_34.asp?sitearea=

ACS :: What's New in Pancreatic Cancer Research and Treatment?
epidermal growth factor receptor . Several drugs that target are now being studied. One,...
http://www.cancer.org/docroot/CRI/content/CRI_2_4_6X_Whats_new_in_pancreatic_cancer_research_and_treatment_34.....

Dr. Len's Cancer Blog
be tested with a biomarker assay because the target of Avastin is not the cells...
<http://www.cancer.org/asp/blog/Comments.aspx?id=181...>

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