

Summer 2006

Welcome to the Insider

Over the past seven years, the Ingenuity team has been focused on developing a solution for researchers who seek biological context and understanding from their experiments. Today we have thousands of researchers using Ingenuity Pathways Analysis on a regular basis and I want to take this opportunity to thank our customers for their support and for providing us with the feedback and motivation to continually improve on the products and services we deliver.

As the Ingenuity Pathways Analysis user base has grown, so have the applications and best practices and we thought it was time to share these user experiences with you in a quarterly newsletter. The *Ingenuity Insider* will highlight some of the exceptional research being done with Ingenuity Pathways Analysis and will keep you informed of the happenings at Ingenuity and our plans to extend the Ingenuity Pathways Analysis

solution. In this first issue, the focus is on the discovery and validation of biomarkers and highlights a recent publication from a group at Wyeth using Ingenuity Pathways Analysis in their biomarker research.

We are also pleased to announce the launch of the newest version of Ingenuity Pathways Analysis as well as partnerships with Spotfire, Rosetta and Agilent for the seamless integration of IPA into their research workflow.

We hope you find the *Ingenuity Insider* informative and as always your feedback and comments are appreciated.

Sincerely,



Jake Leschly
President & CEO, Ingenuity Systems

Announcing Ingenuity Pathways Analysis 4.0

Ingenuity Systems is pleased to announce the release of Ingenuity Pathways Analysis (IPA) 4.0. This newest version focuses on several themes that are critical to the community of researchers who are served by IPA.

SEARCH: Exploration of the Ingenuity Pathways Knowledge Base

With IPA 4.0, we have expanded our **Advanced Search** feature to support queries such as "Find all transporters that are involved in cardiac disorders", "Identify the known drug targets within that set of genes", or "Find all cytokines involved in arthritis". The ability to do combinatorial searches based on multiple types of gene annotations (Synonyms, Protein Family, Subcellular Location, Cellular/Disease Processes) will assist not only in building pathway models, but also in finding practical information that will help plan the next set of experiments. Any query can be saved in IPA.

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Publications

Defining Molecular Profiles of Poor Outcome in Patients With Invasive Bladder Cancer Using Oligonucleotide Microarrays. *J Clin Oncol.* 2006 Feb 10;24(5):778-89. Epub 2006 Jan 23. Sanchez-Carbayo M, Socci ND, Lozano J, Saint F, Cordon-Cardo C. [View Link...](#)

Molecular Classification of Crohn's Disease and Ulcerative Colitis Patients Using Transcriptional Profiles in Peripheral Blood Mononuclear Cells. *J Mol Diagn.* 2006 Feb;8(1):51-61. Burczynski ME, Peterson RL, Twine NC, Zuberek KA, Brodeur BJ, Casciotti L, Maganti V, Reddy PS, Strahs A, Immermann F, Spinelli W, Schwertschlag U, Slager AM, Cotreau MM, Dorner AJ. [View Link...](#)

Association of Activated Transcription Factor Nuclear Factor B With Chemoradiation Resistance and Poor Outcome in Esophageal Carcinoma. *J Clin Oncol.* 2006 Feb 10;24(5):748-54. Epub 2006 Jan 9. Izzo JG, Malhotra U, Wu TT, Ensor J, Luthra R, Lee JH, Swisher SG, Liao Z, Chao KS, Hittelman WN, Aggarwal BB, Ajani JA. [View Link...](#)

Gene Expression Profiling Of Localized Esophageal Carcinomas: Association With Pathologic Response To Preoperative Chemoradiation. *J Clin Oncol.* 2006 Jan 10;24(2):259-67. Epub 2005 Dec 12. Luthra R, Wu TT, Luthra MG, Izzo J, Lopez-Alvarez E, Zhang L, Bailey J, Lee JH, Bresalier R, Rashid A, Swisher SG, Ajani JA. [View Link...](#)

Gene Expression Profiling Differentiates Germ Cell Tumors From Other Cancers And Defines Subtype-Specific Signatures. *Proc Natl Acad Sci U S A.* 2005 Dec 6;102(49):17763-8. Juric D, Sale S, Hromas RA, Yu R, Wang Y, Duran GE, Tibshirani R, Einhorn LH, Sikic BI. [View Link...](#)

Genome-Wide Monocytic mRNA Expression in Polytrauma Patients for Identification of Clinical Outcome. *SHOCK.* July 1, 2005; 24(1): 11-19. Biberthaler P, Bogner V, Baker HV, Lopez MC, Neth P, Kanz KG, Mutschler W, Jochum M, Moldawer LL. [View Link...](#)

Asbestos Exposure, Pleural Mesothelioma, And Serum Osteopontin Levels. *N Engl J Med.* 2005 Oct 13;353(15):1564-73. Pass HI, Lott D, Lonardo F, Harbut M, Liu Z, Tang N, Carbone M, Webb C, Wali A. [View Link...](#)

Science Solutions

For access to more than 50 scientific publications citing Ingenuity Pathways Analysis, [click here.](#)

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Ingenuity User Group Meeting

July 24-26, 2006 is the date for the Ingenuity User Group Meeting held at the Hilton Boston Back Bay Hotel in historic Boston, Massachusetts. Presenters from industry and academia will share their expertise using Ingenuity Pathways Analysis.

Our keynote speaker is the esteemed Prof. Dr. Peter van der Spek, Professor and Head of Bioinformatics at Erasmus MC, Rotterdam, The Netherlands. We are pleased to have Dr. Jin Shang, Merck Research Laboratories, discuss "Networks and Pathways of Pancreatic Islet Beta-Cell Compensation to Insulin Resistance in a Mouse Model of Type 2 Diabetes" and Dr. Ken Paigen, The Jackson Laboratory, discuss "Using Ingenuity Pathways Analysis to Map the Functional Organization of the Genome".

You may register for the User Group Meeting at www.ingenuityusergroup.com.

Using IPA's Advanced Search Feature to Find Secreted Proteins and Drug Targets Associated With Diseases

With the implementation of IPA 4.0's Advanced Search functionality, you now have the ability to query the Ingenuity Pathways Knowledge Base with combinations of terms to identify subsets of genes. For example, before embarking on a diagnostic biomarker discovery research project for a particular disease, it would be helpful to understand which genes have already been associated with that disease and are secreted (detectable in the extracellular space).

To answer this question, click on the "Advanced" search button.

ADVANCED

Enter the disease of interest in the Functions and Diseases field (in this case "colitis").

Functions and Diseases

Select "extracellular space" from the drop down menu in the Subcellular Location field. Click the Search button.

Results from this search identified genes that could be investigated as potential biomarker candidates, including MUC3A, IL10, IL4, F10, IL12A, IL6, IL7, EB13, LGALS4, TNF, IL2 and CD30L.

Subcellular Locations:

In addition, by sending this list of genes to a pathway (select all and click),

ADD TO PATHWAY

and utilizing the Drug Overlay feature, IPA can quickly identify genes on the list that are targets of clinical candidates and FDA-approved drugs for the treatment of ulcerative colitis and Crohn's Disease, namely Remicade - an anti-TNF antibody approved for Crohn's disease, CDP870 - and anti-TNF antibody in Phase III trials for Crohn's disease, and deligoparin - an F10 inhibitor in Phase III trials for ulcerative colitis.



IPA 4.0 Features Enable Modeling of Drug Mechanism of Action

IPA 4.0 provides a bridge between bevacizumab (Avastin), its target VEGF, and the process targeted by Avastin, angiogenesis.

SEARCH

Search Ingenuity Pathways Knowledge Base for genes associated with angiogenesis of tumors. Add them to a My Pathway.



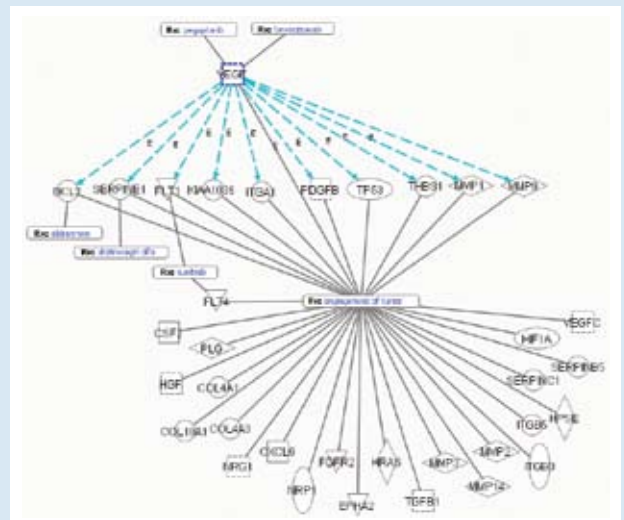
Use IPA 4.0's new Path Explorer to find relevant molecular paths from VEGF to angiogenesis genes.



Incorporate all drugs relevant to VEGF/angiogenesis pathway.



Represent "angiogenesis of tumor" in pathway.



An Integrated Approach to Analyzing Affymetrix Copy Number Data Using Ingenuity Pathways Analysis

Identification of copy number alterations using Affymetrix SNP (single nucleotide polymorphism) chips is being widely adopted in the Oncology community as a way to further understand mechanism of disease. To better demonstrate how this type of data can be used to answer mechanistic questions regarding pathways and functions, scientists at Ingenuity Systems and Affymetrix have recently completed a case study. Dr. Megan Laurance, Ingenuity Systems, and Dr. Dione Bailey, Affymetrix, highlight the benefits of analyzing copy number data in the context of pathways, regulatory networks and biological functions by working with a previously published dataset generated by the Sellers lab at the Dana-Farber Cancer Institute ([Click Here to view](#)). The Sellers lab used Affymetrix SNP genotyping microarrays to characterize copy number abnormalities in various NCI60 cancer cell lines. Drs. Laurance and Bailey focused on a large amplification region within Chromosome 3 in melanoma cell lines to understand the biological implications of gene amplification events in that region on cancer-specific pathways and functions.

Their workflow involved generating copy number data using Affymetrix' CNAT software, identification of significant regions of amplification using Affymetrix Integrated Genome Browser (IGB), and then exporting the genes in that amplified region from IGB into a file which was analyzed in Ingenuity Pathways Analysis (IPA). By running a "standard" IPA analysis, as well as customizing the analysis using IPA's Search and My Pathways tools, they were able to identify several pathways specific to cancer-related processes and genes involved in development of melanomas that would be potentially perturbed as a result of copy number alterations. In particular, pathways centered on the tumor suppressor FHIT and the transcription factor MITF figured prominently, as did pathways highlighting interactions between MITF and genes implicated in melanoma cell adhesion, cell growth, and cell cycle events.

Learn more by joining us at our User Group Meeting where this case study and work flow will be presented.

Bio-IT World's Top 50 List



Ingenuity Systems was named by Bio-IT World as one of the top 50 companies that provide the most indispensable, enabling technologies for the biopharma industry. Ingenuity Systems'

key product, Ingenuity Pathways Analysis, is an important factor in driving the future of biomedical research and drug discovery.

Ingenuity Pathways Analysis 4.0, continued from page 1

PATH EXPLORER: Richer Pathway Models

When using the **Grow** feature, users can now specifically ask, "Find all genes that are transcriptionally downstream of this gene", or "Find all cytokines that are upstream of this set of genes".

By using the new **Path Explorer** feature, molecular paths can be built from a drug target (for example VEGF) to all genes that play a role in the process that is targeted by that drug (for example, angiogenesis). The enhancements in Advanced Search and Path Explorer can be combined into a powerful tool for understanding drug mechanism of action, mechanisms of disease, or any causal connections between genes of interest.

We have enhanced the **Overlay** features in IPA by enabling scientists to visualize the role of drugs, diseases, and cellular functions within pathways.

REPORTING: Supporting communication, publication, reporting of IPA results

IPA has become a tool that is central to the communication of biological results from large-scale "omics" experiments, as well as results from querying the Ingenuity Knowledge Base. In an effort to enable communication of those results to the scientific community, we have made improvements to the resolution of the graphics exported from IPA and have enabled export of additional analysis results.

NEW CONTENT: Access to additional High Quality Content

With each quarterly release of IPA, customers are given access to additional high quality, manually-curated content. Customers will benefit from a large boost in gene-to-gene relationships in networks (with a particular boost in protein:DNA and protein:promoter interactions), as well as 17 new Canonical Pathways, and the addition of Phase III clinical candidates to the Drug View feature.

MAC ENABLEMENT

IPA now fully supports the community of researchers utilizing the Macintosh platform.

Free Trial

Register today for a free trial of
Ingenuity Pathways Analysis at
www.ingenuity.com/trial

Upcoming Events

**Integrative Proteomics: Structure,
Function, Interaction**
July 12–14, 2006

Hinxton Hall Conference Centre
Cambridge, UK

Ingenuity Systems User Group Meeting
July 24–25, 2006

Back Bay Hilton Hotel
Boston, MA

Chips to Hits 2006
September 25–28, 2006

Hynes Auditorium
Boston, MA
Visit Ingenuity at Booth 408

Training Schedule

For a complete list of training sessions,
[click here](#).

IPA in Expression Analysis

Thursday, July 6, 2006
7:00 am, Pacific Daylight Time
[Click for more information](#)

**Using IPA as a Knowledge &
Discovery Tool**

Thursday, July 13, 2006
7:00 am, Pacific Daylight Time
[Click for more information](#)

IPA Case Studies

Thursday, July 20th, 2006
7:00 am, Pacific Daylight Time
[Click for more information](#)

Publications Highlighting the Utility Of IPA in Biomarker Discovery

Our publication spotlight this month highlights recent work from the Biological Technologies research team and Andrew Dorner, Senior Director, Molecular Profiling and Biomarker Discovery, at Wyeth Research. Their work provides excellent examples of how gene expression profiling of sentinel tissues such as peripheral blood mononuclear cells (PBMCs) can be combined with pathways analysis for the discovery of pharmacogenomic markers of drug response and diagnostic markers of disease.

In their publication "Risk factors associated with beta-amyloid(1-42) immunotherapy in pre-immunization gene expression patterns of blood cells", the Wyeth research team combined gene expression analysis of PBMCs from patients treated with a novel immunotherapy for Alzheimer's disease with Ingenuity Pathways Analysis to identify predictive biomarkers that would help stratify patient populations into those that were likely to mount a proper response to the immunotherapy and those that were likely to have an adverse

event in response to that therapy. IPA's Functional Analysis feature was used to narrow in on the subsets of genes from those expression profiles that were associated with biological processes and pathways relevant to the phenotypes observed in each patient population.

In a subsequent publication "Molecular Classification of Crohn's Disease and Ulcerative Colitis Patients Using Transcriptional Profiles in Peripheral Blood Mononuclear Cells", the Wyeth team utilized IPA's functional annotations and Canonical Pathway analysis of gene expression profiles to help identify molecular biomarkers that could complement the standard diagnosis of Ulcerative Colitis and Crohn's Disease.

Their approach of assaying gene expression changes in PBMCs with subsequent analysis of expression profiles in Ingenuity Pathways Analysis provides a robust strategy for identifying biomarker candidates that are mechanistically based and causally connected to the observed clinical endpoint – whether the goal is disease subclassification or prediction of drug response.

Publications, continued from page 1

New Data-Analysis And Mining Approaches Identify Unique Proteome And Transcriptome Markers Of Susceptibility To Autoimmune Diabetes. Mol Cell Proteomics. 2005 Oct 16; [Epub ahead of print]. Gerling IC, Singh S, Lenchik NI, Marshall DR, Wu J.
[View Link...](#)

Risk Factors Associated with Beta-amyloid (1-42) Immunotherapy in Preimmunization Gene Expression Patterns of Blood Cells. Arch Neurol. 2005 Oct;62(10):1531-6. O'Toole M, Janszen DB, Slonim DK, Reddy PS, Ellis DK, Legault HM, Hill AA, Whitley MZ, Mounts WM, Zuberek K, Immermann FW, Black RS, Dorner AJ. [View Link...](#)