Ingenuity® Pathway Analysis (IPA®)

For the analysis and interpretation of 'omics data

IPA is a web-based software application for the analysis, integration, and interpretation of data derived from 'omics experiments, such as RNAseq, small RNAseq, microarrays including miRNA and SNP, metabolomics, proteomics, and small scale experiments that generate gene and chemical lists. Powerful analysis and search tools uncover the significance of data and identify new targets or candidate biomarkers within the context of biological systems.

IPA goes beyond pathway analysis by:

- Identifying key regulators and activity to explain expression patterns
- Predicting downstream effects on biological and disease processes
- Providing targeted data on genes, proteins, chemicals, and drugs
- Building interactive models of experimental systems

Target identification and validation
Biomarker discovery
Drug mechanism of action
Drug mechanism of toxicity
Disease mechanisms

Table 1. Applications supported by IPA.

RNAseq
Microarray
miRNA
mRNA
qPCR
Proteomics
Metabolomics

Table 2. Experimental approaches supported by IPA.

Insightful data analysis and interpretation

Data analysis and interpretation with IPA builds on the comprehensive, manually curated content of the QIAGEN Knowledge Base. Powerful algorithms identify regulators, relationships, mechanisms, functions, and pathways relevant to changes observed in an analyzed dataset. Analytics go beyond pathway analysis to understand experimental results within the context of biological systems (Tables 1 and 2) and interactive tools allow detailed exploration of results,

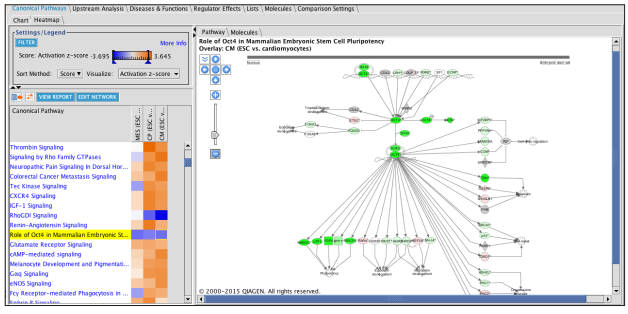

Figure 1. Interactive tools to explore and compare datasets. Trends and similarities across analyses can be quickly compared using heatmaps and interactive pathway graphics within the context of canonical pathways, analysis of downstream effects, and examination of potential upstream regulators.

including comparisons across multiple analyses (Figure 1), discovery of novel biological connections, and generation of testable hypotheses.

Unlock insights and develop novel hypotheses

The Core Analysis in IPA quickly identifies relationships, mechanisms, functions, and pathways relevant to a dataset. Upstream Regulator Analysis surfaces molecules, including miRNA and transcription factors, which may be causing observed gene expression changes (Figure 2) while Downstream Effects Analysis predicts downstream biological processes that are increased or decreased based on the analyzed data (Figure 3).

Integrating results about potential regulators and effects, the Regulator Effects tool highlights connections to create hypotheses about upstream triggers responsible for downstream phenotypic or functional outcomes. To further explore potential hypotheses, Molecule Activity Predictor (MAP) enables the user to interrogate subnetworks and canonical pathways by selecting a molecule of interest, indicating up or downregulation, and simulating directional consequences on downstream molecules and the inferred activity upstream in the examined network or pathway (Figure 4).

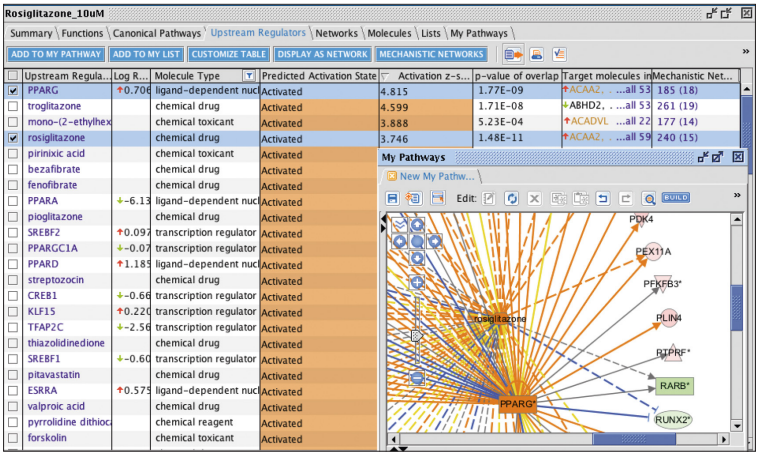

Figure 2. Interactive analysis of plausible upstream regulators and networks. Insightful analyses predict upstream molecules, including miRNA and transcription factors, which may be causing observed gene expression changes.

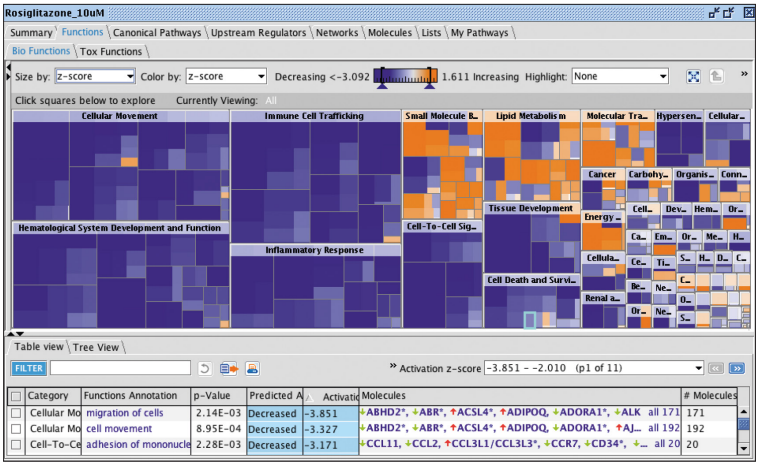

Figure 3. Detailed examination of downstream effects. Detailed heatmaps highlight significant downstream biological processes that are increased or decreased based on gene expression results.

Advanced Analytics to go beyond immediate connections

Building on the Core Analysis, Causal Network Analysis, a component of IPA Advanced Analytics, uncovers multi-level causal relationships relevant to experimental data by expanding upstream analysis to include regulators that are not directly connected to targets in the analyzed dataset. Another Advanced Analytics

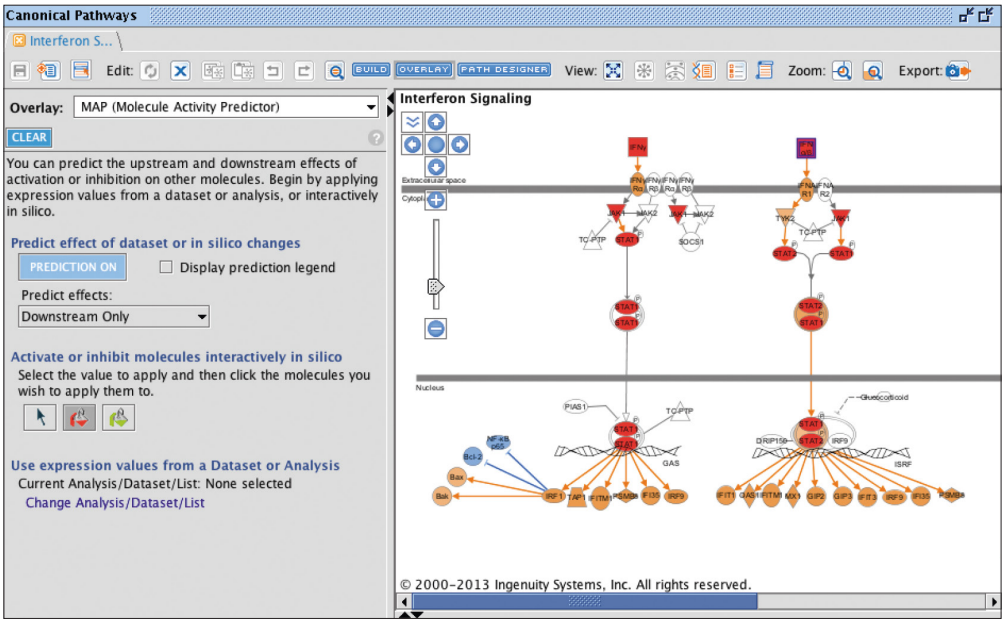

Figure 4. Simulation of perturbations in subnetworks and canonical pathways. Molecule Activity Predictor (MAP) interactively interrogates sub-networks and canonical pathways to simulate the downstream consequences of up or downregulating a molecule and to predict the inferred activity upstream.

component, BioProfiler, quickly surfaces molecules that are causally relevant to a disease or phenotype of interest, helping to identify potential therapeutic or toxicity targets, as well as associated known drugs and biomarkers.

Build custom pathways and gene or chemical list libraries

Create custom pathways with My Pathways and gene or chemical list libraries from a range of input data: gene lists from IPA search results, existing IPA networks or canonical pathways, uploaded lists of targets or biomarkers, or imported pathways using XGMML, BioPax, SBML, or GPML. Integrated tools guide the identification of upstream regulators or downstream targets of genes, enable layering of biological information or experimental data, and facilitate interrogation of hundreds of indexed subnetworks and canonical pathways to simulate effects and mechanisms of altered activity of target molecules (Figure 4). Highly interactive, these features afford intuitive exploration of connections between targets in a dataset to generate testable hypotheses and construct event-specific pathways such as:

- miRNA-mRNA target networks
- Transcriptional networks

- Phosphorylation cascades
- Protein-protein or protein-promoter interaction networks
- Chemical/drug effects on proteins

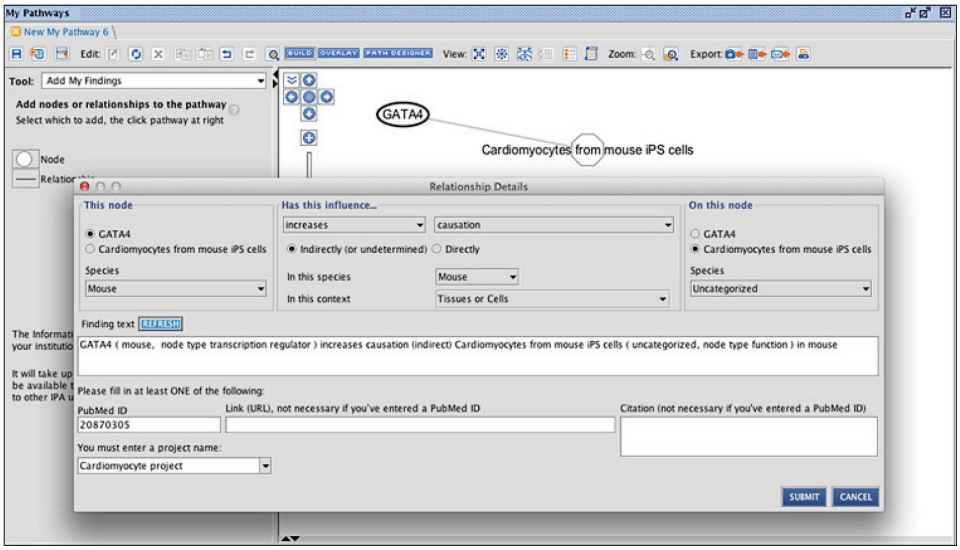

Figure 5. Quickly customize relationship content for analyses. My Findings incorporates your own or your institution's internal knowledge for a disease or therapeutic area to strengthen analyses and insights most relevant to your research question.

Explore pathways and interactions of interest

Path Explorer is an interactive tool that uncovers relevant relationships between genes of interest. By exploring these connections, the shortest paths between molecules associated with a disease or toxicity phenotype can be quickly identified, including access to supporting literature. Gene, Chemical & Pathway Search quickly generates and compares targeted lists of genes, druggable proteins, biomarkers, and chemicals.

Leverage internal knowledge for a better understanding

IPA can incorporate your own or your institution's internal data curation efforts for a disease or therapeutic area of interest. With the My Findings module, proprietary molecule-to-molecule relationship and molecule-todisease or function relationships are uploaded to a secure, customerdedicated repository, making the content accessible throughout IPA. Any hypothetical or empirically demonstrated relationships can be imported or drawn and annotated on a new or existing pathway and then used in subsequent analyses to increase confidence in predicted upstream regulators, interaction or causal networks, and downstream effects.

Powerful tools for deep analysis of NGS and miRNA data

Every feature of IPA is aimed at maximizing the impact of the information that surfaces in an analysis so that the interpretation of a dataset is comprehensive. For example, the Human Isoform

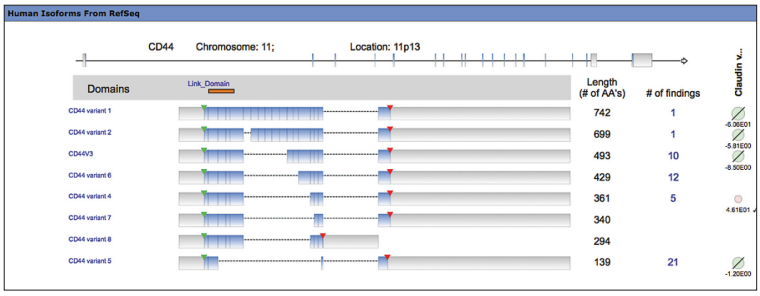

Figure 6. Intuitive visualization of RNAseq data. Significantly regulated isoforms in experimental data are intuitively displayed to facilitate exploration of their impact on functional protein domains with links to isoform-specific publications.

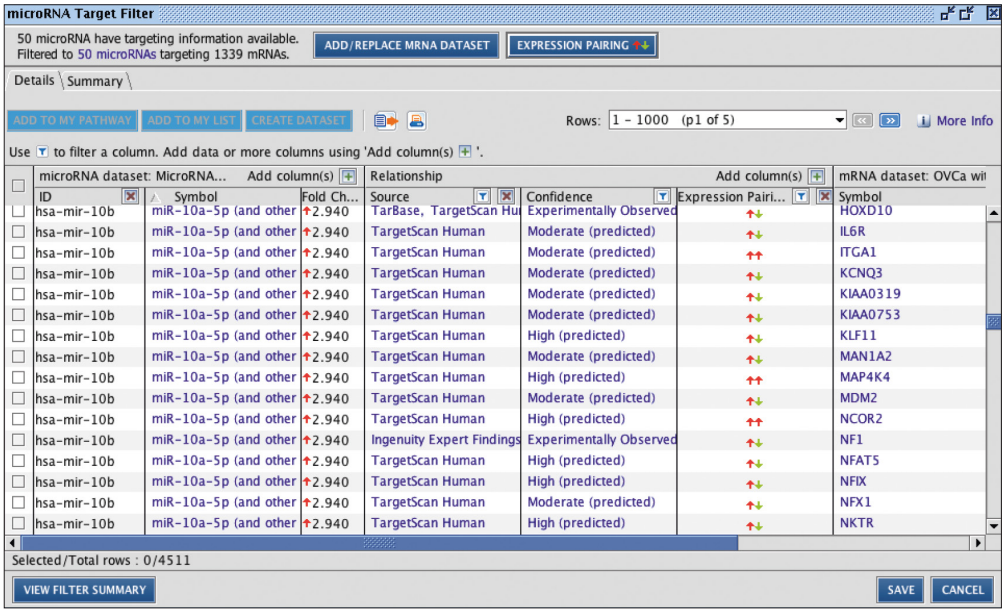

Figure 7. Comprehensive filtering tools to confidently identify mRNA targets. The miRNA Target Filter in IPA provides insights into the biological effects of miRNA, based on experimentally validated interactions from TarBase and miRecords, predicted miRNA-mRNA interactions from TargetScan, and miRNA-related findings from peer-reviewed literature.

View displays expression data associated with each isoform from uploaded RNAseq data in an intuitive graphical overview. Significantly regulated isoforms are listed in this view along with impacted functional protein domains and links to supporting publications (Figure 6). Another powerful capability, the MicroRNA Target Filter, combines interactive filtering and comprehensive content to identify and prioritize miRNA-mRNA target pairings and provide insight into the biological effects of miRNA (Figure 7). Additionally, Upstream Regulator Analysis predicts miRNAs that may be regulating genes of an experimental dataset.

Seamless sharing and communication of results

IPA functions as a central platform for the analysis of biological data, generation of testable hypotheses, and construction and visualization of molecular models of experimental systems. The communication and collaboration tools of IPA enable collaborative work on models and creation of interactive reports to share with colleagues. Collaborators with a license for IPA can be invited to share datasets and analyses or a customized Collaboration Workspace can serve as a shared results repository within or across institutions or consortia. The Professional Dynamic Reports of IPA are detailed summaries of analysis results that highlight the broader biological and therapeutic relevance of a particular pathway, gene, or molecule list (including uploaded proprietary lists). The detailed tabular data and dynamic features of these reports enable fast decision making and hypothesis generation. Finally, Path Designer transforms networks and pathways into publicationquality, colored graphics with species-specific nomenclature, biological icons, and organelles, and customized text, fonts, and backgrounds. Path Designer pathways are intuitive, fully interactive graphics supported by the comprehensive content of IPA.

Understanding biological connections in a variety of applications

Biomarker discovery

Prioritize molecular biomarker candidates based on key biological properties and elucidate mechanisms linking markers to disease or phenotype of interest.

Metabolomics

Leverage critical biological context in IPA to overcome the challenges of analyzing metabolomics data and infer impacted cell function from metabolite lists.

miRNA research

Predict miRNAs regulating gene expression patterns and find mRNA targets based on content from miRBase, TargetScan, and the QIAGEN Knowledge Base.

NGS/RNAseq data analysis

Streamline data analysis with rapid identification of expressed isoforms and integration of statistical analysis tools, like CLC Genomics Workbench.

Proteomics

Uncover mechanistic links in complex proteomics data, identify potentially implicated regulators, and predict impacted downstream processes or diseases.

Toxicogenomics

Generate focused toxicity and safety assessments of candidate compounds and gain insight into pharmacological response and mechanism of action and toxicity.

Powered by content of the QIAGEN Knowledge Base

The QIAGEN Knowledge Base is a data repository like no other. The Knowledge Base organizes biological interactions and functional annotations created from millions of individually modeled relationships between proteins, genes, complexes, cells, tissues, drugs, and diseases. These modeled relation-

Entrez Gene
RefSeq
OMIM
ClinVAR
GWAS Database
Gene Ontology (GO)
Human Metabolome Database (HMDB)
GNF Tissue Expression Body Atlas
NCI-60 Cell Line Expression Atlas
HumanCyc metabolic pathway information
BIND, DIP, MINT, MIPS, BioGRID, IntAct, Cognia protein-protein interactions
Clinicaltrials.gov
Drugs@FDA
Mosby's Drug Consult
Goodman & Gilman's Pharmacological Basis of Therapeutics
DrugBank
Hazardous Substance Database (HSDB)
Chemical Carcinogenesis Research Information System Database (CCRIS)
TargetScan
miRBase
miRecords
TarBase
COSMIC
The Mouse Genome Database (MGD) from The Jackson Laboratory (JAX)

Table 3. Additional sources of content in IPA.

Affymetrix®
Affymetrix SNP ID
Agilent®
CAS Registry Number
CodeLink
dbSNP
Ensembl
Entrez Gene
GenBank
Gene Symbol – mouse (Entrez Gene)
Gene Symbol – rat (Entrez Gene)
Gene Symbol – human (Hugo/HGNC)
GenPept
GI Number
Human Metabolome Database (HMDB)
Illumina
Ingenuity
International Protein Index
KEGG
Life Technologies (Applied Biosystems®)
miRBase (mature)
miRBase (stemloop)
PubChem CID
Refseq
UCSC (hg18)
UCSC (hg19)
Unigene
Uniprot/Swiss-Prot Accession
Species-specific Identifiers supported in IPA
Human
Mouse
Rat
Additional species via ortholog mapping

Table 4. Identifiers supported in IPA.

ships, or Findings, are manually reviewed for accuracy and include rich contextual details and links to original publications. The QIAGEN Knowledge Base enables access to relevant and substantiated knowledge from primary literature, as well as public and third-party databases (Tables 3 and 4), for the comprehensive interpretation of experimental results within the context of larger biological systems.

Ingenuity Pathway Analysis (IPA) is intended for molecular biology applications. This product is not intended for the diagnosis, prevention or treatment of a disease. For up-to-date licensing information and product-specific disclaimers, see the respective Ingenuity product site. Further information can be requested from AdvancedGenomicsSupport@qiagen.com or by contacting your local account manager.

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