

How Can IPA Help Identify and Prioritize Biomarkers?

The Challenge: Identifying Better Biomarkers

Identifying biomarkers is a crucial endeavor across the entire drug development and discovery spectrum, from lead identification, target validation, and lead optimization in the discovery phase, all the way through proof of target, mechanisms, efficacy, and safety in the clinical phase. Being able to successfully identify, prioritize, and validate biomarkers leads to improved drug efficacy and safety, better patient diagnostics, an improved understanding of molecular mechanism, and improved clinical outcomes.

Datasets from microarray, proteomics, microRNA, RNA-Seq, and genotyping platforms are a common first step to identifying biomarker candidates. But accurately and effectively determining which biomarker candidates are most likely to have the fewest adverse side effects, the greatest efficacy, and are the best candidates for further experimentation is a more challenging task.

How can IPA help? IPA puts your data in the context of detailed biological information such as molecular function/chemical class, types of molecular events, detection in biofluids, and association with disease and biological processes, so you can quickly identify the most relevant and promising biomarker candidates from your dataset.

Key Biomarker Capabilities

- **Analyze** data across multiple biomarker lists to find biomarker candidates unique to a disease stage or common across all stages
- **Identify** biomarkers that are mechanistically based and causally associated with disease, adverse effects, or clinical endpoints
- **Prioritize** molecular biomarker candidates based on key biological characteristics (ex: secreted or detected in blood)
- **Prioritize** biomarkers most biologically relevant to disease model or patient population being studied
- **Tease out** mechanism linking potential markers to a disease or biological process of interest
- **Understand** the molecular differences between patient populations
- **Understand** if gene expression/protein signatures are enriched for biological functions and pathways relevant to the observed phenotype
- **Gain confidence** that co-regulation of biomarker candidates is not random but associated with patient phenotypes

Because IPA relies on a detail-rich knowledge base that allows you to drill down to the

Get started with step-by-step instructions.

- [How do I upload data into IPA?](#)
- [How do I create a biomarker analysis to identify biomarker candidates?](#)
- [How do I identify biomarkers that are common or unique across a disease, drug response, or sample?](#)
- [How do I overlay known biomarkers on a pathway?](#)
- [I'd like to see a training video on how to identify biomarkers in IPA](#)

(IPA access is required to open links.)

original published relationships, you can accomplish the above tasks with more confidence in your results and a deeper understanding of the biological relationships involved.

Biomarker Analysis Workflow in IPA: Example

1. Two sets of gene expression data (gene identifiers and expression ratios) were analyzed in IPA – one from normal samples one from samples of morbidly obese patients.

2. Analysis of key affected biological functions and pathways demonstrated a distinct difference between particular subsets of patients at the molecular level. See Figure 1.

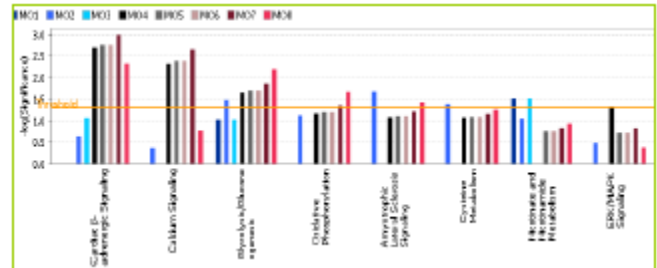


Figure 1

3. The datasets were filtered by several key biomarkers characteristics relevant to this study (including detection in specific bodily fluids and particular species) to identify the most relevant biomarker candidates. (For a closer look at this feature, see the Biomarker Filter section, below).

4. Comparison of the two datasets identified common and unique biomarker gene to the subsets of patients. See Figure 2.

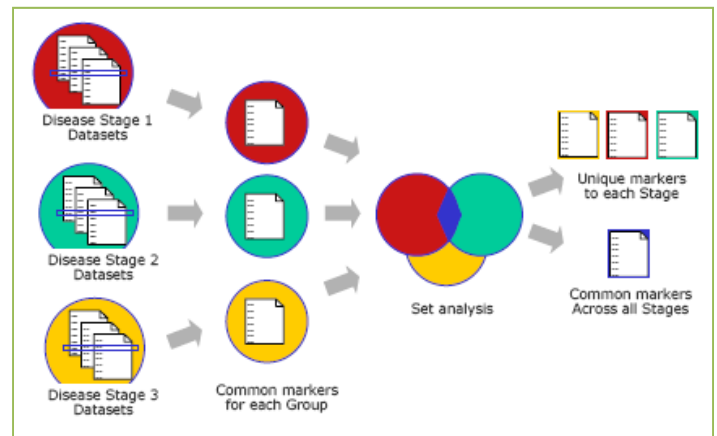


Figure 2

5. Candidate biomarkers were added to a pathway canvas, and overlaid with genes known to relate to obesity. Connecting the biomarkers to the genes identified key relationships (Figure 3), and drilling down to the literature findings helped interpret and validate the results (Figure 4).

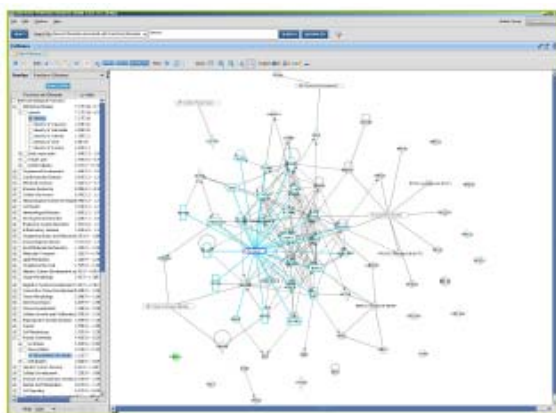


Figure 3

In neural tissue from mouse, mutant mouse **Stat3** gene (homozygous knockout) increases obesity of mouse.

18070774 Gao Q, Wolfgang MJ, Reschen S, Morino K, Horvath TL, Shulman GI, Fu XY. Disruption of neural signal transducer and activator of transcription 3 causes obesity, diabetes, infertility, and thermal dysregulation. *Proc Natl Acad Sci U S A* 2004 Mar 30;101(13):4661-6.

Mutant human **POMC** gene (C3804A) increases obesity of human.

9620771 Krude H, Biebermann H, Luck W, Horn R, Brobant G, Grotzer A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 1998 Jun 1;19(2):155-7.

ACTH deficiency and obesity in humans are associated with mutant human **POMC gene** (deletion 7133C, G7013T).

9620771 Krude H, Biebermann H, Luck W, Horn R, Brobant G, Grotzer A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 1998 Jun 1;19(2):155-7.

Obesity in female human is associated with mutant human **TNF-ALPHA [TNF] gene** (G-308A) (Biomarker status: biomarker statistic exist).

Experiment Type: polymerase chain reaction

10672452 Hoffstedt J, Eriksson P, Hallstrom L, Rosner S, Rydan M, Amar P. Excessive fat accumulation is associated with the TNF alpha-308 G/A promoter polymorphism in women but not in men. *Diabetologia* 2000 Jan;43(1):117-20.

Figure 4

Summary: IPA identified the biomarker candidates that are most highly connected to the disease genes, and used known biological functions and pathways to help explain the underlying interactions that associate potential biomarker candidates with the disease. We can also overlay functions, diseases, or pathways to identify additional functions and pathways these genes participate in to better understand the molecular events that lead to the development of morbid obesity and associated effects, such as weight gain and diabetes. We can then drill down to the original source of relevant reported relationships to further understand the relationship.

- **Want a closer look? View the [poster](#) for the above example.**
- **Want another example? View a [recorded seminar](#) on the biomarker capabilities in IPA.**

A Closer Look: Biomarker Filter

The Biomarker Filter in IPA rapidly identifies the most relevant biomarker candidates based on biological characteristics most relevant to the discovery study. It helps you:

- Determine if genes or proteins are detected in blood, urine, and PBMCs
- Discover what tissues, genes, or proteins are expressed
- Measure if genes or proteins are unregulated or downregulated in the dataset
- Assess if the candidate biomarker has a strong association with disease processes

Filter criteria include species, tissue & cell line, molecule types, diseases, biofluids, and biomarker application.

