

# Bio-IT's Leading Edge: Systems Biology's Revival

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# False Pretenses – Sorry

- **Bio-IT Trends...Sort of!**
  - ibid BIO 2005..
- **Systems Biology Revisited (aka Predictive Biology)**

# Why Look at SB Again

- **Industry Attitudes Changing**
  - **Steven Burrill says SB is R&D Driver**
    - **Devotes section to SB in Bio 2005 Report**
  - **Pharma's Growing Commitment**
    - **Pfizer appoints director of SB**
    - **Novartis – Compugen program**
  - **Harvard Med's SB Department**
  - **Few Early Successes**

# Sobriety Among SB Players

**“We’re at the very early stages still. I wish I could say something different. But we’re going beyond early adopters. We used to see a lot of requests from people to look at something they already knew the answer to. Now we were seeing requests for help with problems they cannot solve.”**

**-- James Karis, CEO of model-maker Entelos**

# Systems Biology: What Is It?

It is an approach to drug discovery and development that emphasizes identifying the key components in a particular biological system – usually a pathway relevant to disease – and determining how those components interact to produce a disease or normal state. This information is used to uncover methods of action, identify and prioritize targets and compounds, and to develop useful biomarkers.

Key technologies: data-mining, text-mining, computational modeling, and bio-simulation tools and diverse experimental assays. Vendors tend to emphasize either the *in silico* approach or experimental approach, but both are necessary.

# Building SB Businesses

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- **Pathway Pioneers**
- **Model Makers**
- **Experimentalists**
- **Full-fledged Drug Development**

# A Deeper Look at 5 Companies

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- **Business Model**
- **Technology**
- **Progress & Outlook**
- **PLUS: A few pharma SB case histories**

# Pathways – Ingenuity Systems

- **Snapshot - Founded in 1998; Mountain View, CA; First product six years later; Headcount ~ 100; early mover advantage**
- **Technology – IPA 3.0 and IKB (manually curated DB)**
- **Business – S/W license and DB access via web, expanding to customer hosted solution**

# Pathways – Ingenuity Systems

“Customers supply a list of genes that represent the state of a particular biological system. IPA computes these to pathways on the fly, and the output is a series of networks focused on the genes and proteins that you informed the system were most significant to you.”

“For some customers, it’s a choice of whether they want to read the literature for prior knowledge or do research. We’d like to make those things not mutually exclusive.”

-- Megan Laurance, Ingenuity.

# Pathways – Ingenuity Systems

- **Progress – Adopted in 9 of top 10 pharma; Citations jump (51 in '05); Merck/BMS deals; IPA 3.0 is significant; Global**
- **Competitive Issues - Lower on “value” chain; Market constraints; Religious war of DBs; Many competitors (Ariadne, GeneGo, etc)**
- **Outlook – Promising with a caveat**

# Top Down Models – Entelos

- **Snapshot – Founded 1996; Foster City, CA; Headcount ~ 90; Diverse business propositions**
- **Technology – “PhysioLab” platform (top-down); IT and KM expertise; Select domain expertise**
- **Business – R&D services but seeking IP participation and diversification**

# Top Down - Entelos

**“It’s hypothesis driven. We start by developing the platforms for a specific disease and specific questions we want to address. So with the RA PhysioLab, we were interested in what a therapies would we be investigating for the end points,”**

**– Michael French, former CBO.**

**“We’ve had a dozen or so customers and I think we’ve got that customer credibility [as a result.]. Now it’s about business growth. I think the fastest way to grow is to drive within a major customer.”**

**– James Karis, CEO**

# Top Down Models – Entelos

- **Progress – Organon co-marketing deal; DI acquisition; Unilever deal**
- **Competitive Issues – Few competitors; Models aren't cheap; Market acceptance; Scalability; Pharma seeks *own* modeling expertise; Need to grow**
- **Outlook – Promising but must support its size**

# State Models – Genstruct

- **Snapshot – Founded in 2001; Waltham, MA; Headcount ~ 20;**
- **Technology – “Molecular Epistemics” (knowledge assembly framework)**
- **Business – R&D collaboration...for now**

# State Models - Genstruct

**"Instead of using mathematical relationships to model the interactions, we use logic relationships. We can take any state change — gene-expression change, protein change, metabolite change, to phenotypic change — and infer causes and consequences related to those changes."**

**"Give me the 500 genes that changed when you treat this patient with glucose, and I'll tell you the interactions that had to take place from a signaling perspective to explain exactly the mechanism by which glucose will increase."**

**- Keith Elliston, co-founder, CEO, and president.**

# State Models – Genstruct

- **Progress – ADA validation work; Berlex (Schering) deal; Pfizer milestones**
- **Competitive Issues – Still young; Grow customer set; Prove technology; Scalability & Focus**
- **Outlook – Promising. Next year is important. Cash?**

# Microbial Models – Genomatica

- **Snapshot – Founded ~ 2000; San Diego, CA; Headcount ~ 20; Focused on bio-processing**
- **Technology – SymPheny platform; E. Coli and Yeast Models; Based on Bernhard Palsson's work**
- **Business – R&D collaboration, mostly non-therapeutic**

# Microbial Models - Genomatica

**“We’re striving to create and accelerate a broad range of different metabolism driven products based on an integrated computational-experimental platform. It's really a comprehensive description of metabolism in a genetic and biochemically consistent manner.”**

**Researchers can in silico delete genes, vary biochemical parameters, and perturb the environment to generate hypotheses.**

**– Christophe Schilling, CSO & President**

# Microbial Models – Genomatica

- **Progress – Dozen models; Long-term Dow collaboration; DSM deal; Fewer regulatory burdens; Cash flow neutral**
- **Competitive Issues – Few competitors yet (Synthetic Biology); Scalability; Expansion into therapeutics**
- **Outlook - Promising**

# Assayist – BioSeek

- **Snapshot – Founded ~ 2000; Burlingame, CA; Headcount ~ 15; Cell-based assays**
- **Technology - BioMAP (uses primary human cells); CSO is Ellen Berg; Eugene Butcher is a co-founder; *Nature Reviews DD Perspective* (June '05)**
- **Business – R&D collaboration and fee for service**

# Assayist - BioSeek

**“The reality is drugs work in a very complex setting. We turn on many pathways at once. Then we perturb them with the drug and measure a set of readouts. It turns out that changes in the protein level in the assay are surprisingly reproducible and robust, and it’s due to the reality that complex systems actually behave quite reproducibly.**

**“We’ve been able to identify profiles that tell us about mechanisms of action, so when we look at a new compound, we can make the interpretation immediately,”**

**– Ellen Berg, CSO and founder**

# Assayist – BioSeek

- **Progress – Tested 1000s of compounds; developed 15 assays; Dynavax Tech milestone; engaged with 3 of top 10 pharma**
- **Competitive Landscape – Many companies have similar approaches; Focused on compounds; IP important**
- **Outlook – Sounds promising**

# Evidence for Success

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- Roche/Entelos (found biomarker)
- Pfizer/Pharsight (killed program)
- J&J/Entelos (killed target)

# Compugen's Evolution

- **Evolving Business Model**
  - No S/W Licensing or Fee for Service
  - Build Models, Find Targets, Partner to develop them
- **Novartis deal is different**

# Miscellaneous SB Trends

- **Computer Language Development**
  - SBML; Little B
- **SB used in clinical trials**
  - Pharsight's 100
- **Hood's SB Incubator**
- **SB Literature Citations Grow**
- **Bio-IT World Launching an SB & *In Silico* Newsletter**

# The Wisdom of Enoch

- **Pharma's Pain Points**

- [http://www.bio-itworld.com/newsitems/2005/02/020405\\_report7382.html.news](http://www.bio-itworld.com/newsitems/2005/02/020405_report7382.html.news)

# Summary: SB's Future

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- **Pathways Providers**
- **Model Makers**
- **Experimentalists**
- **SB's Evolving Place in Predictive Biology**
  - **Biology as the Boeing 777**