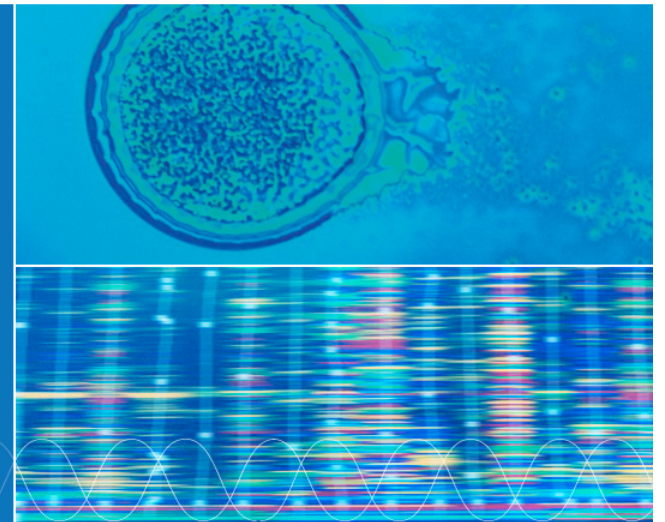




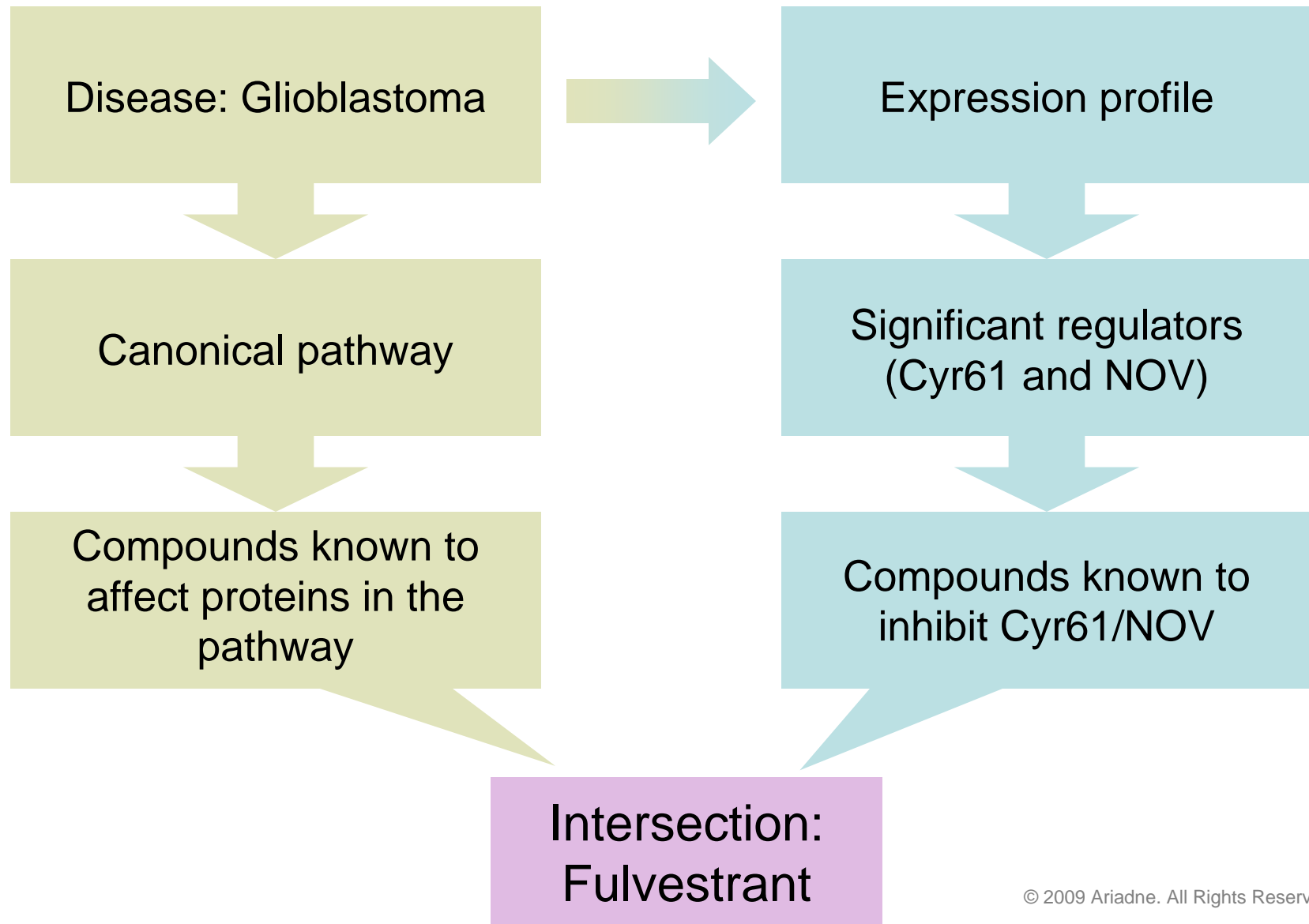
Knowledge Network Approach: Targets and Drugs.

Nikolai Daraselia PhD | 01.23.2009



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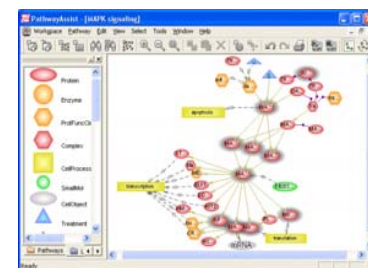
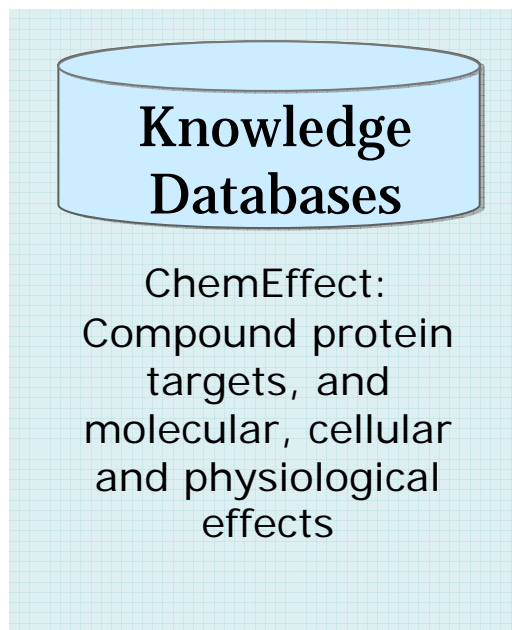
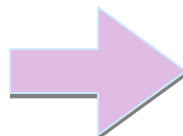
Workflow



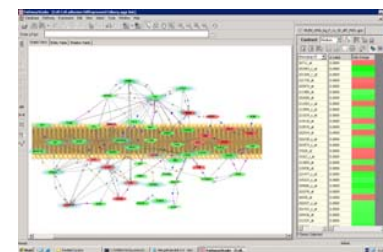
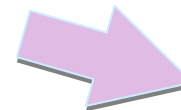
Ariadne Pathway Studio

Knowledge databases:

- ResNet® Mammalian
- ChemEffect®



Pathway Building



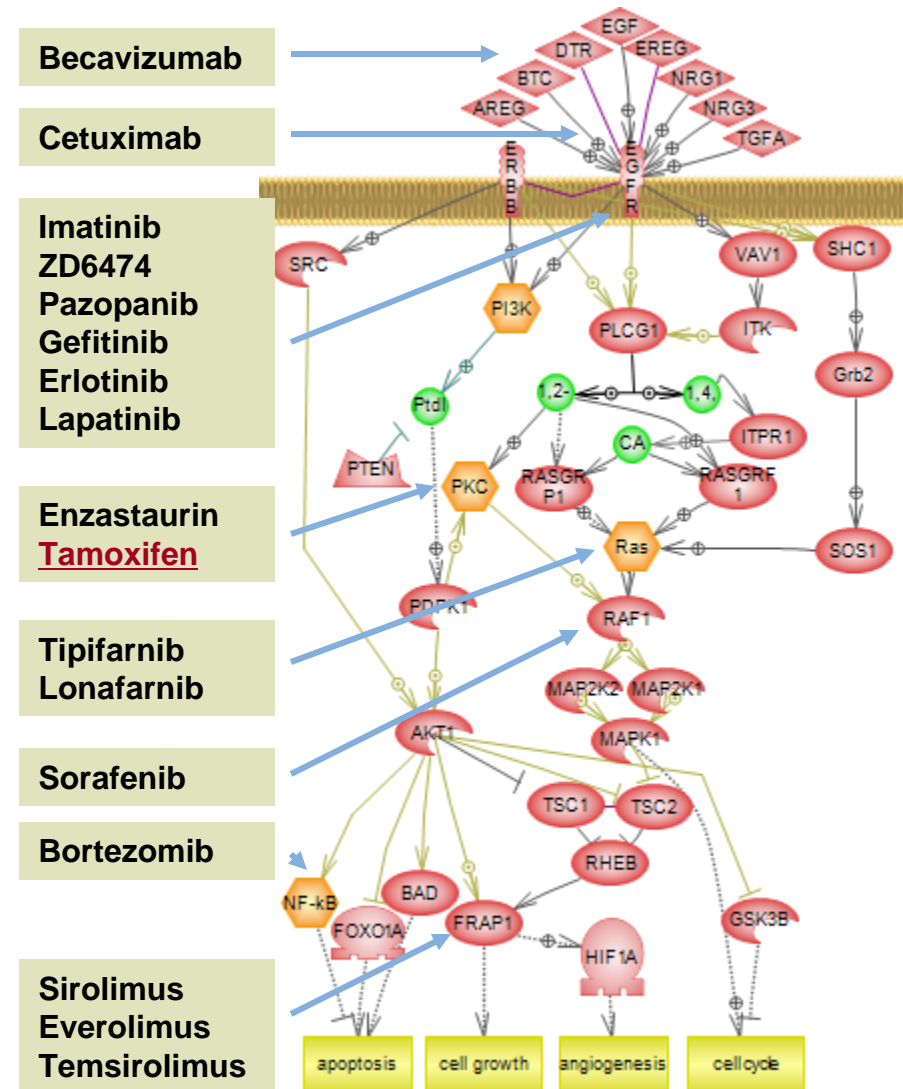
Gene expression
analysis

Glioblastoma Pathway

- Main signaling pathways (PKC, NFkB, MAPK, mTOR, beta-Catenin) and other key proteins were identified and combined on a single pathway
- Inhibitors of glioblastoma pathway are in various stages of clinical trials with mixed outcome
- Current opinion: targeting multiple proteins may be more efficient

ChemEffect:

- 750+ compounds in down-regulating pathway
- 40 compounds targeting 5 and more proteins



Wong, et al; *J Clin. Neurosci.* 2007 21: 301-308

Tuettenberg, et al; *Crit. Rev. in Onc. Hemat.* 2006 59: 181-193

Glioblastoma Gene Expression Analysis Workflow

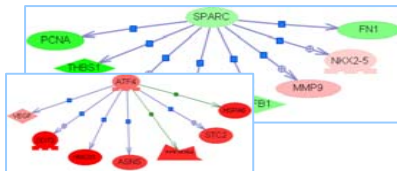
GE: Glioblastoma vs. Normal



Differential expression profile



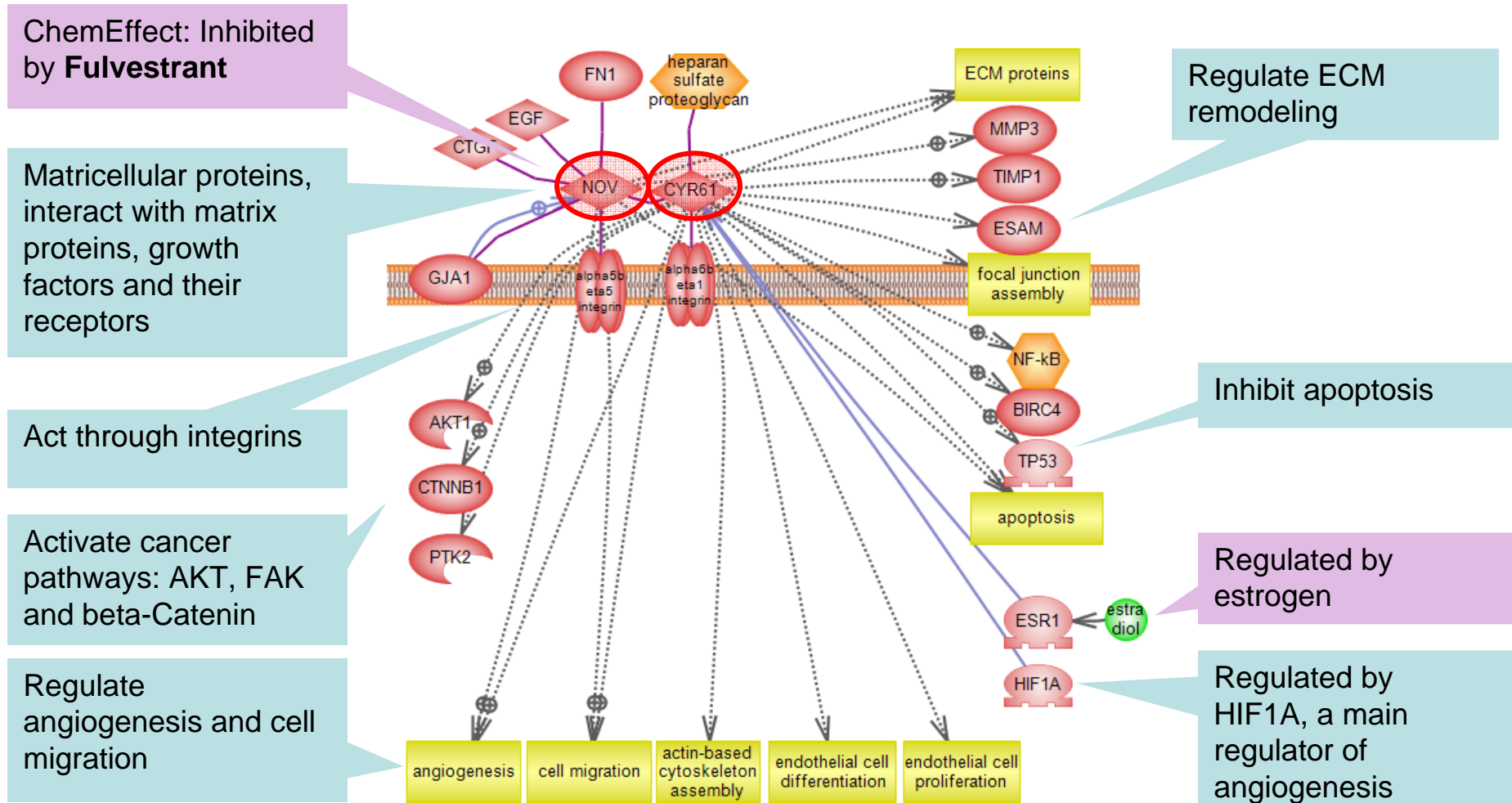
Sub-Network Enrichment Analysis



High-scoring components

- PathwayStudio 6 Sub-Network Enrichment Analysis Tool
- Statistical test, similar to Broad Institute Gene Set Enrichment Analysis (GSEA)
- Sub-networks are built dynamically around all proteins and represent their expression targets in the database (extracted from literature)
- Identify key regulators of differentially expressed genes

Cyr61 and NOV: Novel therapeutic targets ?



Fulvestrant: effective against Glioblastoma?



- Estrogen receptor antagonist
- Used in treatment of hormone receptor-positive metastatic breast cancer
- Tamoxifen, another ER antagonist and PKC inhibitor is partially effective against glioblastoma

