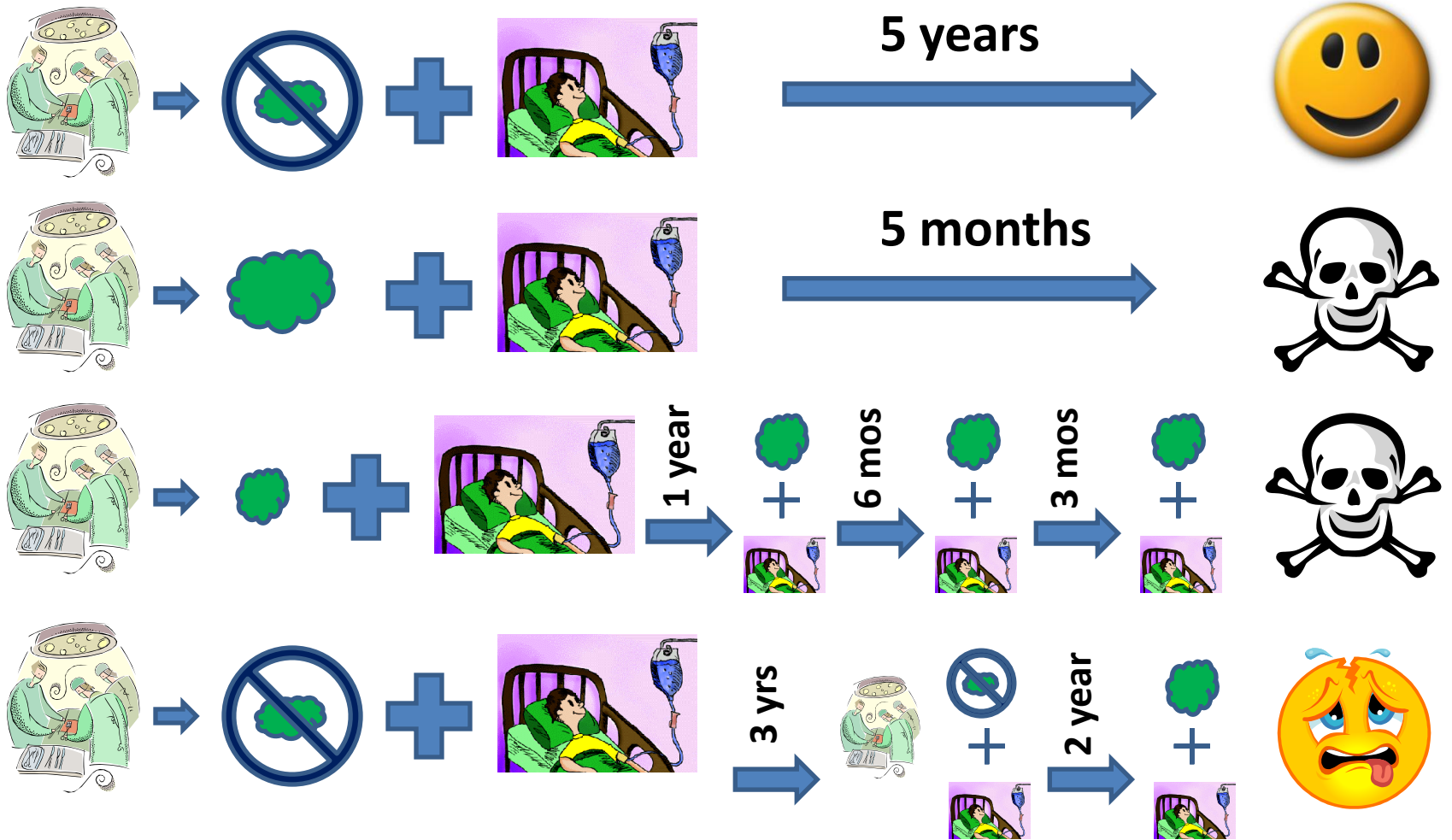# Validated Targets associated with Curatively Treated Advanced Serous Ovarian Carcinoma

Joyce N. Barlin, Narciso Olvera, Faina Bogomolniy, Fanny Dao, Dennis S. Chi, Petar Jelinic, Douglas A. Levine

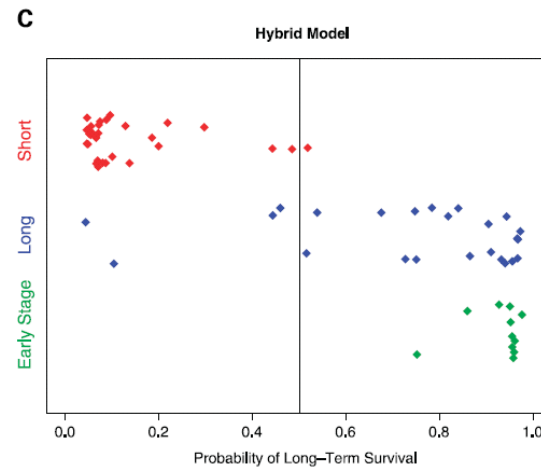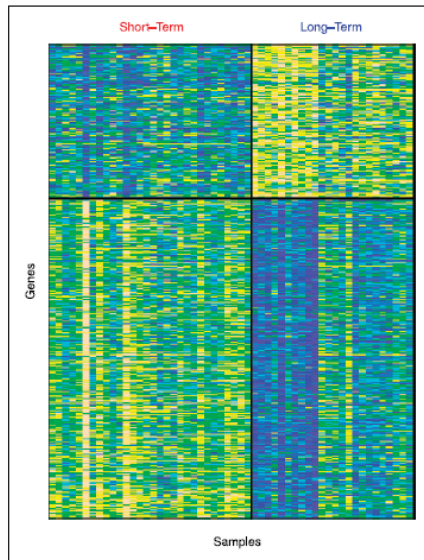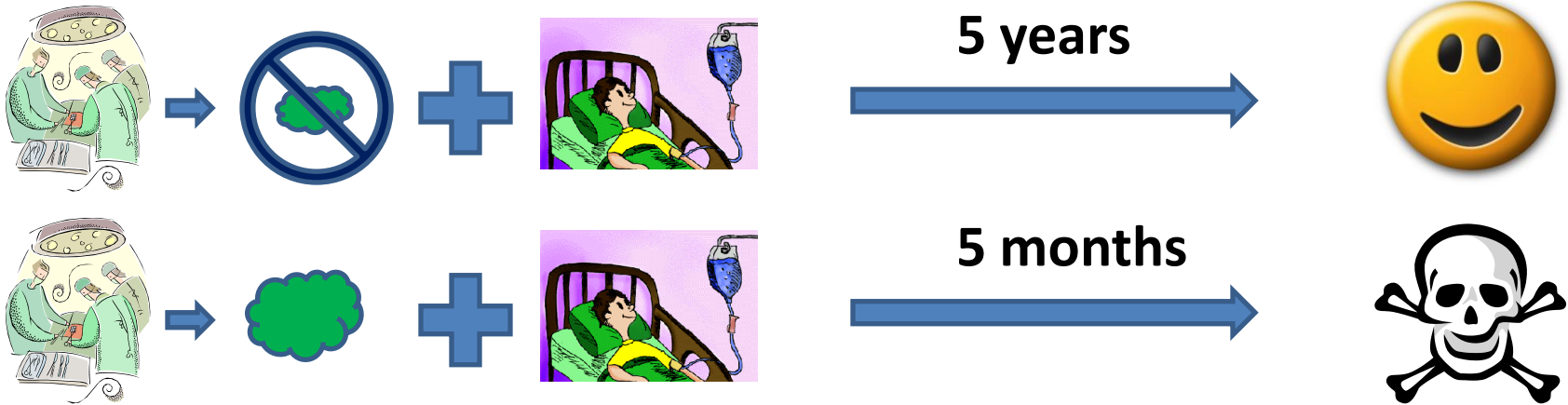Memorial Sloan-Kettering Cancer Center, New York, NY

Cancer Genomics

- Cancer genomics – discovery and technology development

- Applied cancer genomics – address clinical observations

- TCGA well suited for applied cancer genomics due to richly annotated clinical data

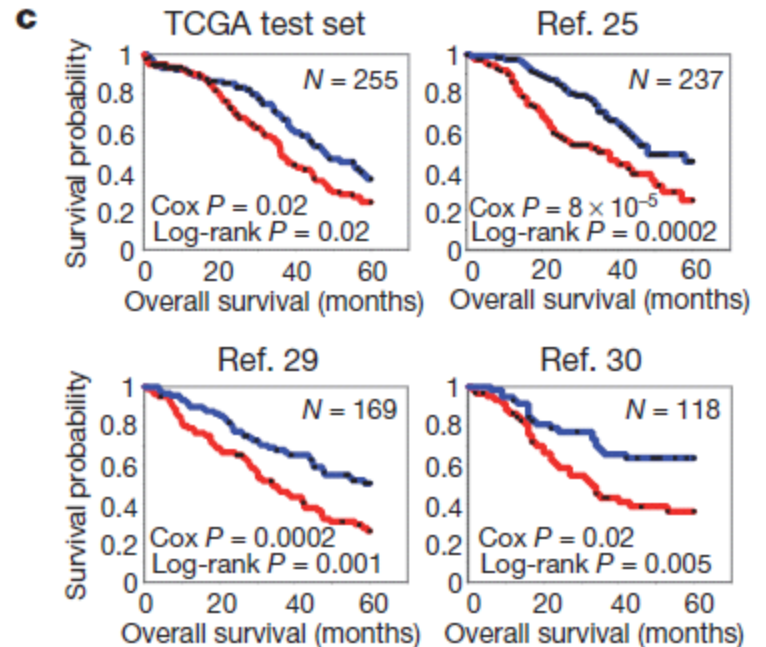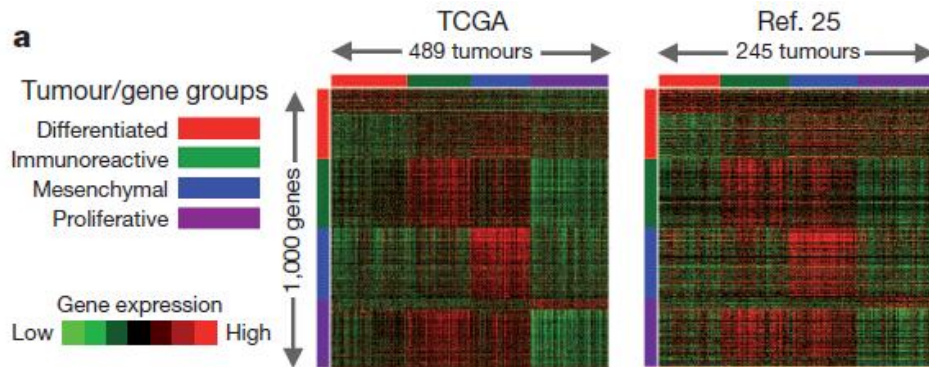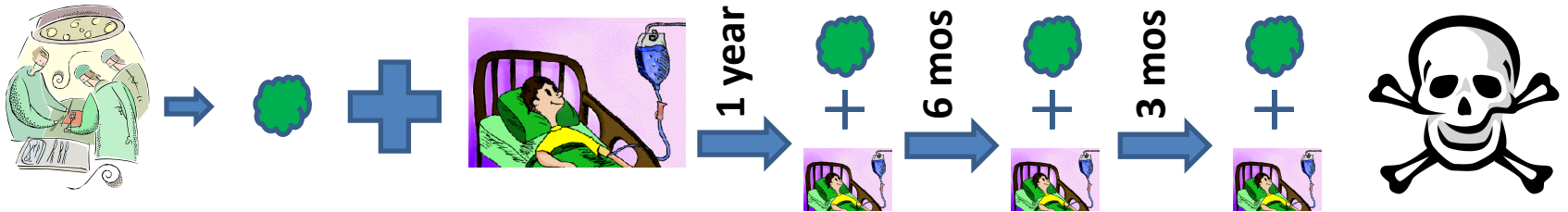- Will improve in parallel with tools and data access

Ovarian Cancer

Ovarian Cancer – Short/Long

5 years

5 months

Short-Term   Long-Term

Genes

Samples

C   Hybrid Model

Short   Long   Early Stage

Probability of Long–Term Survival

Overall Survival - Typical

One and Done – Pts doing well

5 years

Fig. 1. Overall survival, stage IIIC ovarian cancer, 1989–2003.

	Deaths	Censored	Total
Microscopic	20	47	67
< 0.5 cm	24	46	70
0.5-1 cm	61	38	99
1-2 cm	43	10	53
> 2 cm	145	31	176

	Total	Deaths
None grossly visible	114	28
1-5 mm	50	20
5-10 mm	33	33
10-20 mm	18	12
> 20 mm	42	21

Log-rank p = 0.005
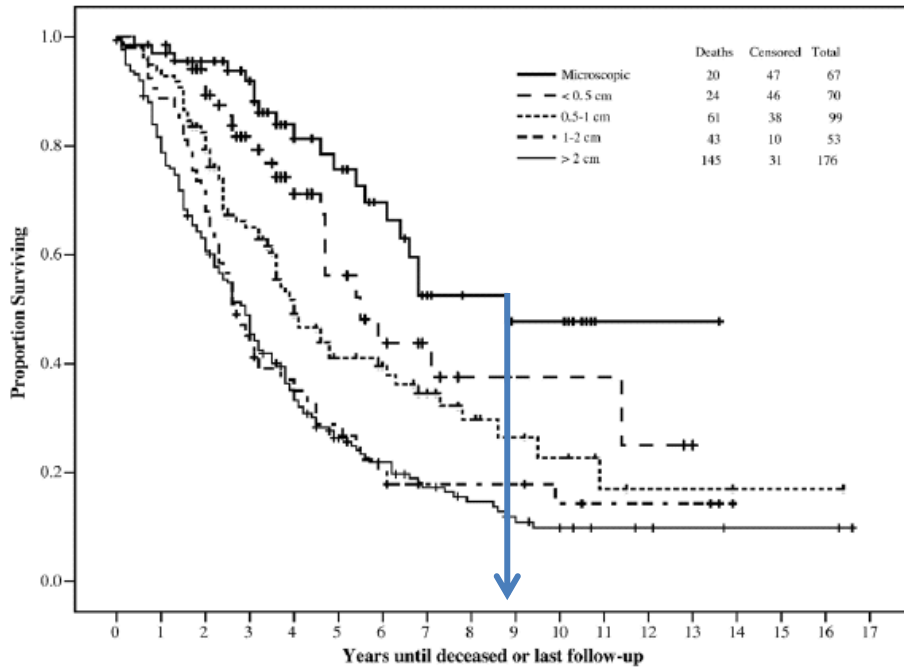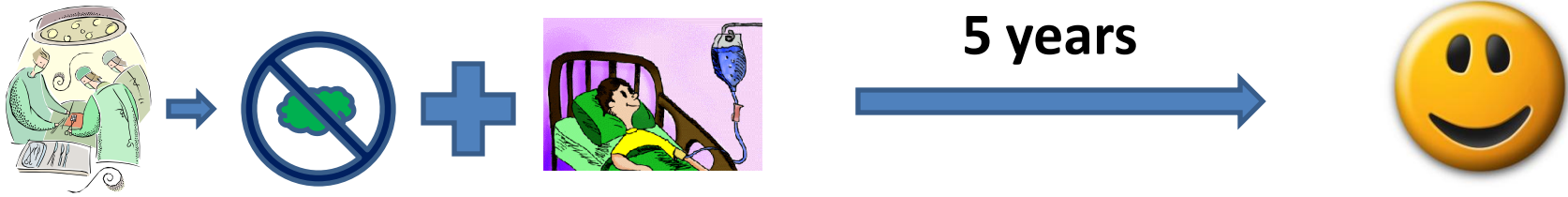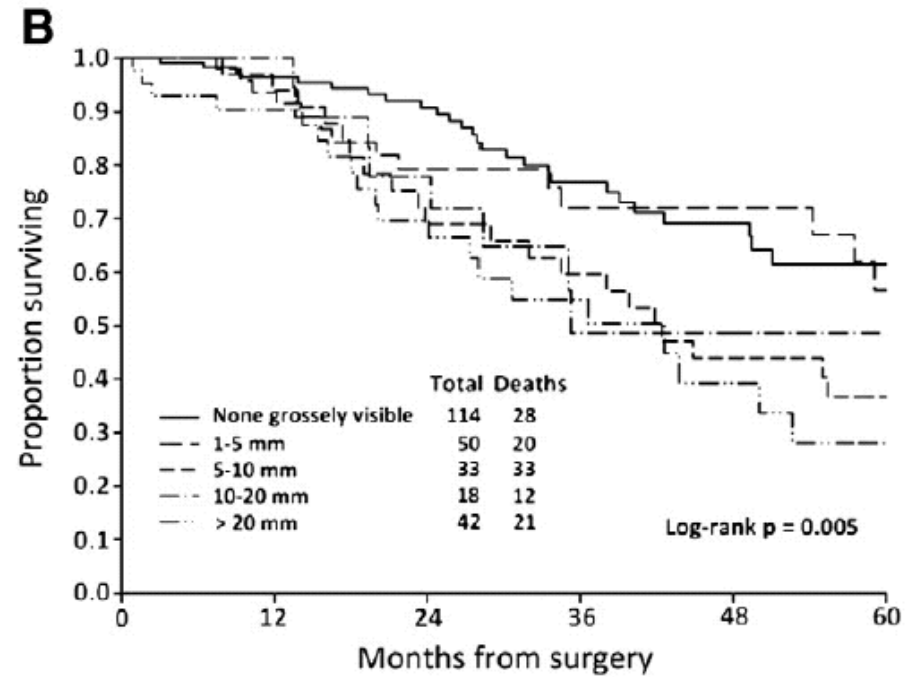
One and Done Hypothesis

- Why is a *small* subset of advanced ovarian patients apparently cured after initial surgery and chemotherapy alone?

- How are they different from long-term survivors who have recurred?

- Exclude multiple mechanisms of platinum resistance and early failure.

- Expression profiles that differ between apparently cured patients and other long-term survivors will shed light on mechanisms of drug resistance

Variation of PQ #19

Ovarian cancer disseminated? Yes.
One and done cured by chemotherapy alone? Sort of.

Inclusion Criteria

- Advanced-stage high-grade serous ovarian cancer patients who underwent primary cytoreductive surgery and platinum-based chemotherapy

- Case, One and Done: No recurrence and NED for at least 5 years

- Control, Recur and Survive: Recurrence but overall survival at least 5 years (long-term survivors)

- Affy U133A arrays available from TCGA or MSK

Patient Samples/Datasets

- MSKCC (non-overlapping with TCGA)
    - 14 patients curatively treated
    - 42 patients who recurred and survived > 5 years
- TCGA (from Table S1.1)
    - 16 patients curatively treated
    - 42 patients who recurred and survived > 5 years

TCGA

Dendrogram for clustering experiments,
using centered correlation and average linkage.

MSKCC

Dendrogram for clustering experiments,
using centered correlation and average linkage.
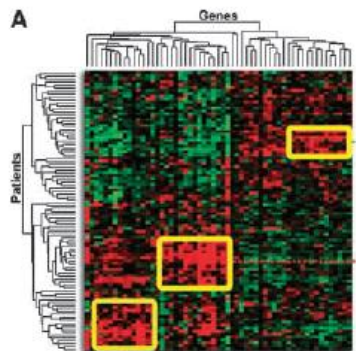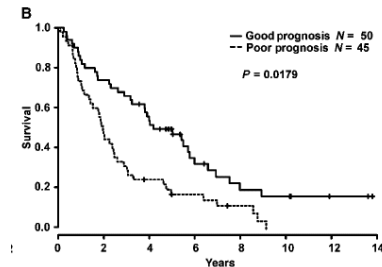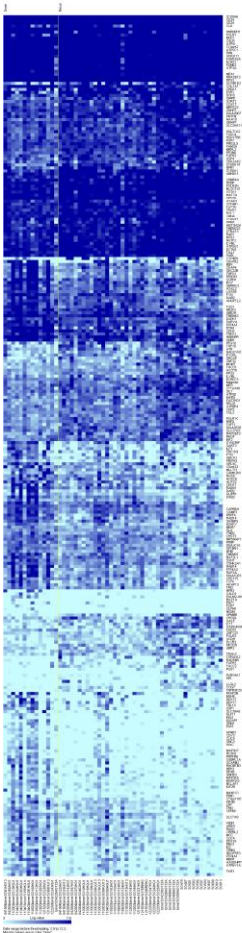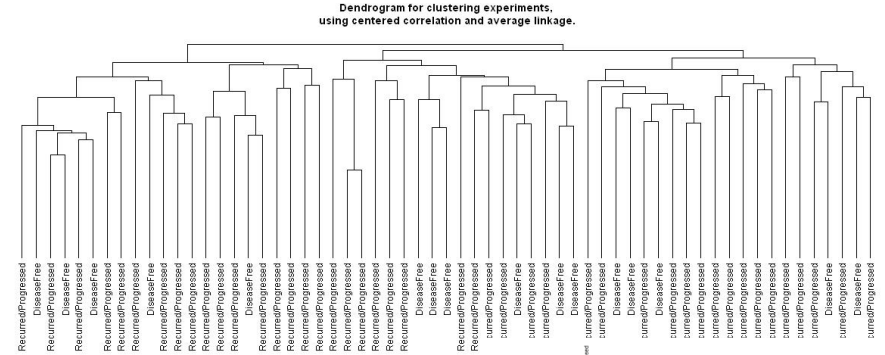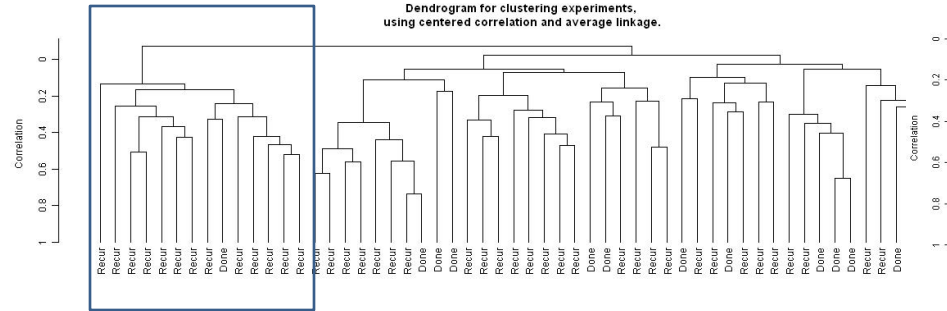
Data Set & Significance Threshold (P)		# Differentially Expressed Probe Sets	# Expected by Chance
TCGA	0.001	19	7
MSKCC	0.001	61	8
TCGA	0.01	158	72
MSKCC	0.01	285	76

- 7180 (TCGA) and 7645 (MSKCC) probe sets input into above analysis

Both datasets suffer from small sample size
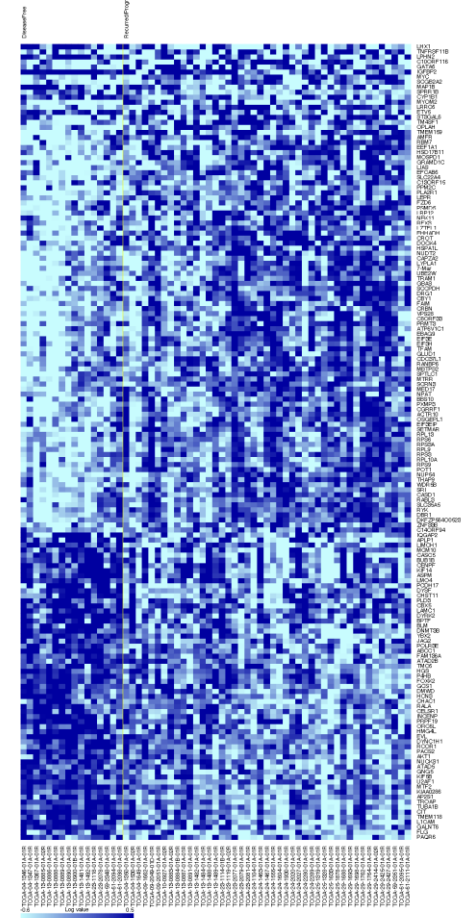
Pathway Analyses

TCGA

MSKCC
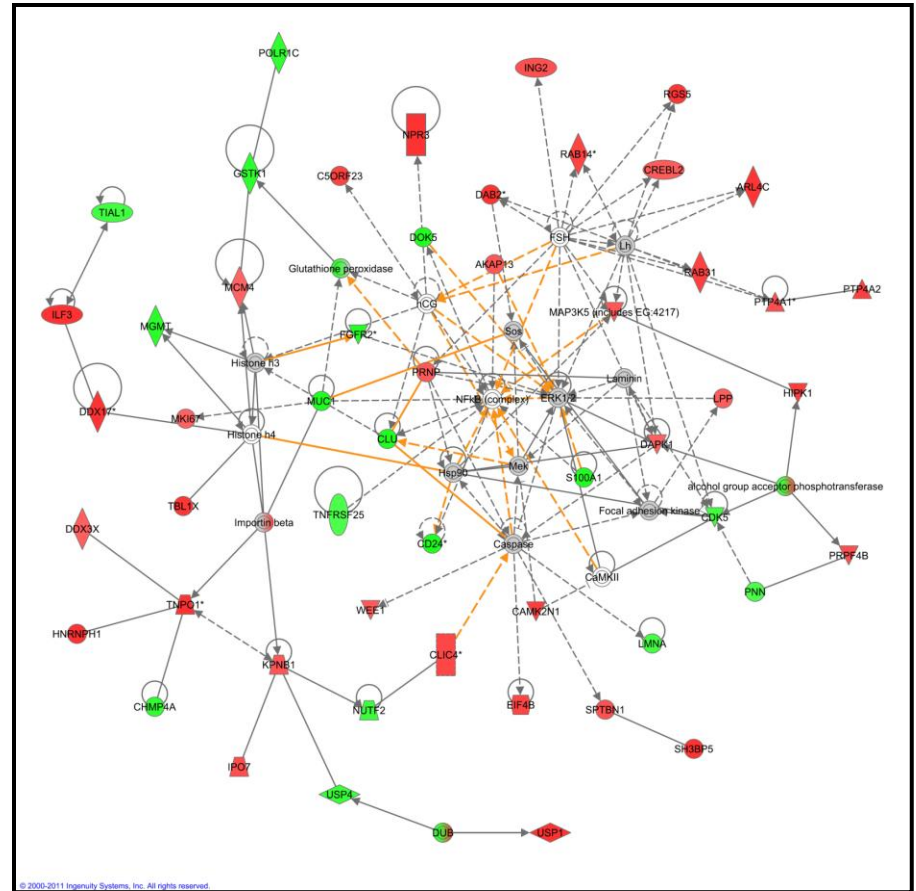
NFkB and ERK signaling over-represented

Technical Validation

- NanoString gene expression used to validate 86 targets from TCGA and MSKCC in residual frozen material
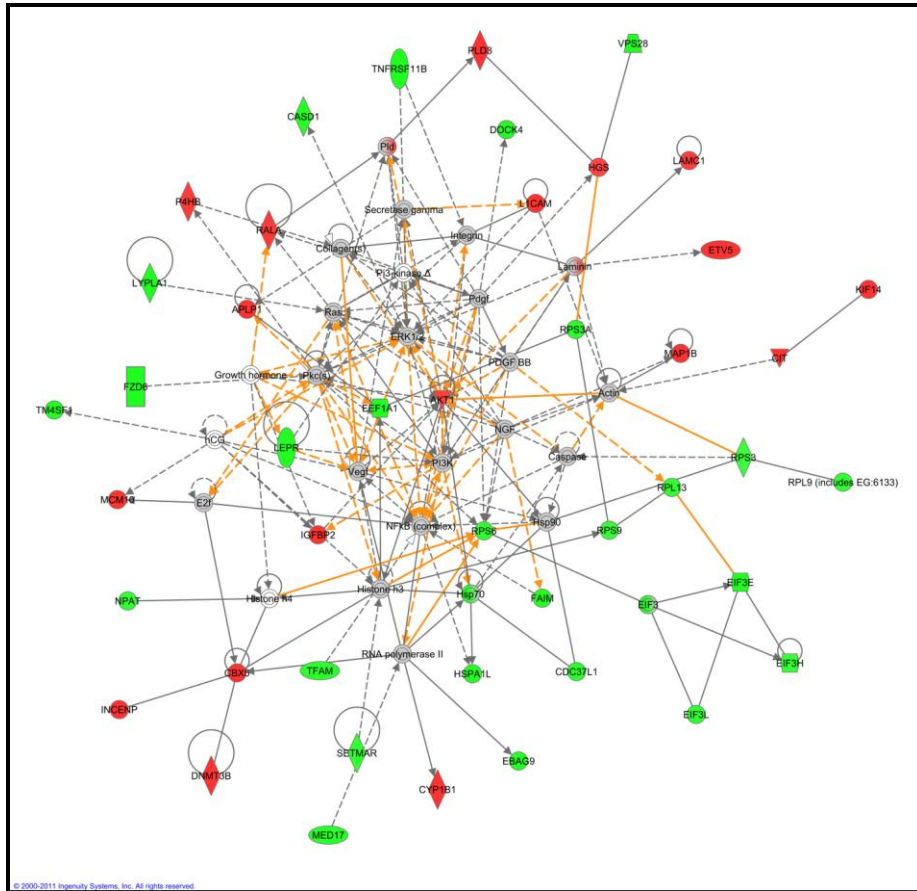   - 19 overlap genes from TCGA and MSKCC
    - 29 genes from NFkB pathway
    - 38 genes from ERK signaling pathway

Gene	Source
HRAS	ERK
MLLT11	overlap
NRAS	ERK
E2F1	ERK
PIK3CB	overlap
MARCKS	overlap
FOS	NFkB
CEPT1	overlap
MAPK1	ERK
CYP4B1	overlap
MAPK6	ERK
CDK4	ERK
RIPK1	NFkB
CHMP4A	overlap
KRAS	ERK

External validation

- 57 independent archival FFPE specimens
  - Frozen exhausted
- Serous ovarian cancer
- NanoString - 15 genes

Group	Samples
One 'n Done	25
Long-term Surv	32

Gene	CYP4B1	CEPT1	CHMP4A	MAPK1	PIK3CB
Source	overlap	overlap	overlap	ERK	overlap
P	0.008	0.019	0.048	0.070	0.057
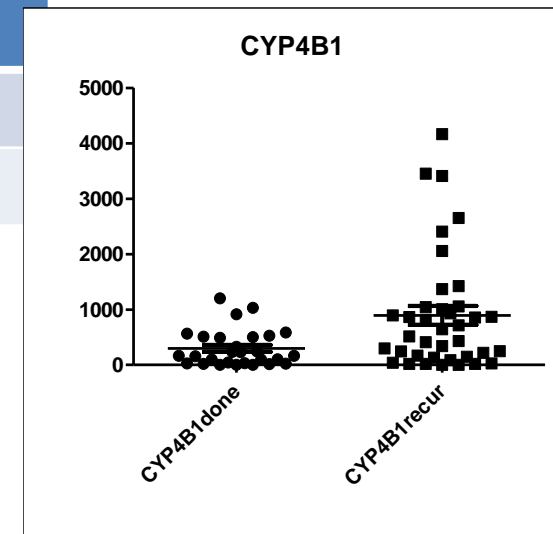
CYP4B1

Pathway selected genes did not validate
Poor tool or poor usage

CYP4B1

- Cytochrome P450 enzyme
- Not well studied
- Participates in drug metabolism in the liver
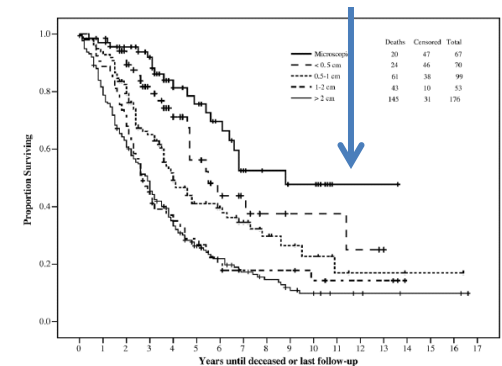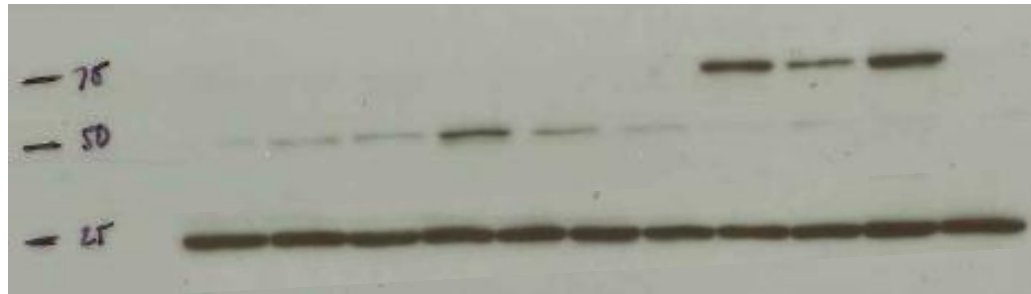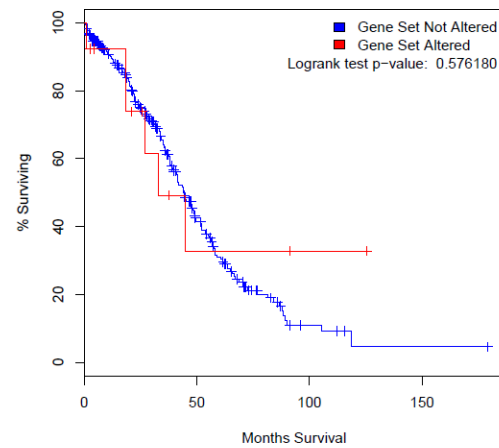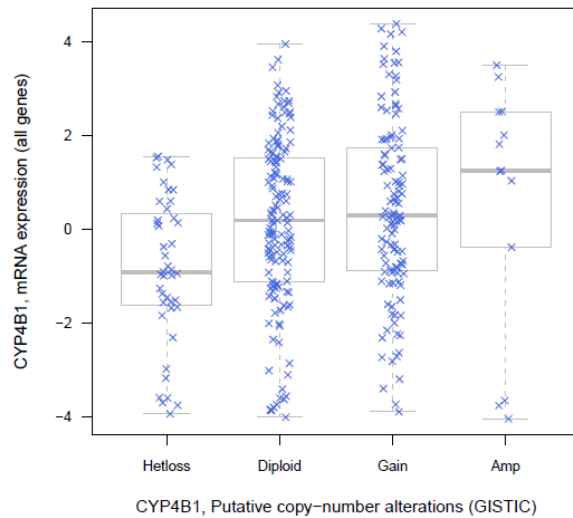- Taxol metabolized in liver by better known CYP3's and 2's.
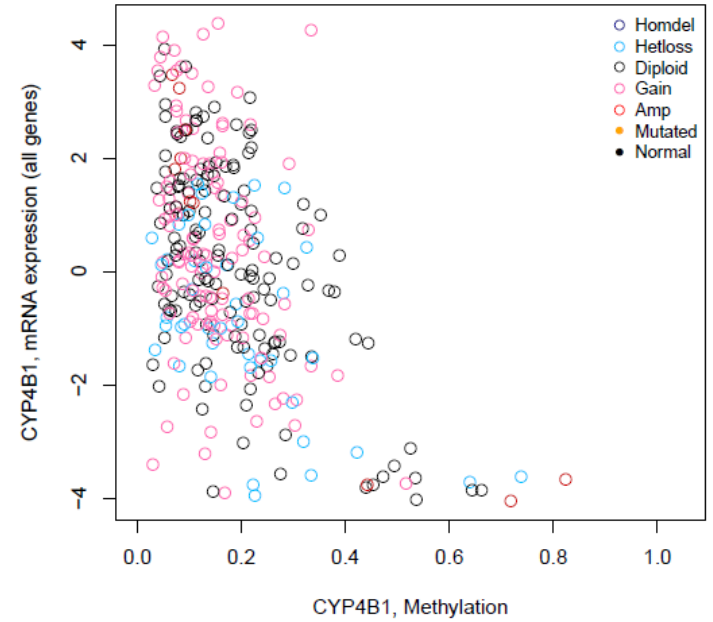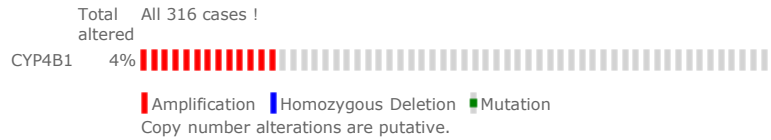

Fig. 1. Overall survival, stage IIIC ovarian cancer, 1989–2003.

CYP4B1 in TCGA OV

OncoPrint::Results

Case Set: All Complete Tumors: All tumor samples that have mRNA, CNA, methylation and se
samples)

Altered in 13 (4%) of cases.

Total   All 316 cases !
altered

CYP4B1   4%

Amplification ▌Homozygous Deletion ▌Mutation
Copy number alterations are putative.

cBio, MSKCC

Summary

- CYP4B1 overexpressed in curatively treated serous ovarian cancer patients
- Discovered through integration of TCGA and non-TCGA data
- Validated with orthogonal methods and external samples
- Biologic studies in progress
- Integration of TCGA data with external datasets for increased power
- TCGA well suited for applied cancer genomics

Thanks to TCGA, NCI, NHGRI

Generous Patients