

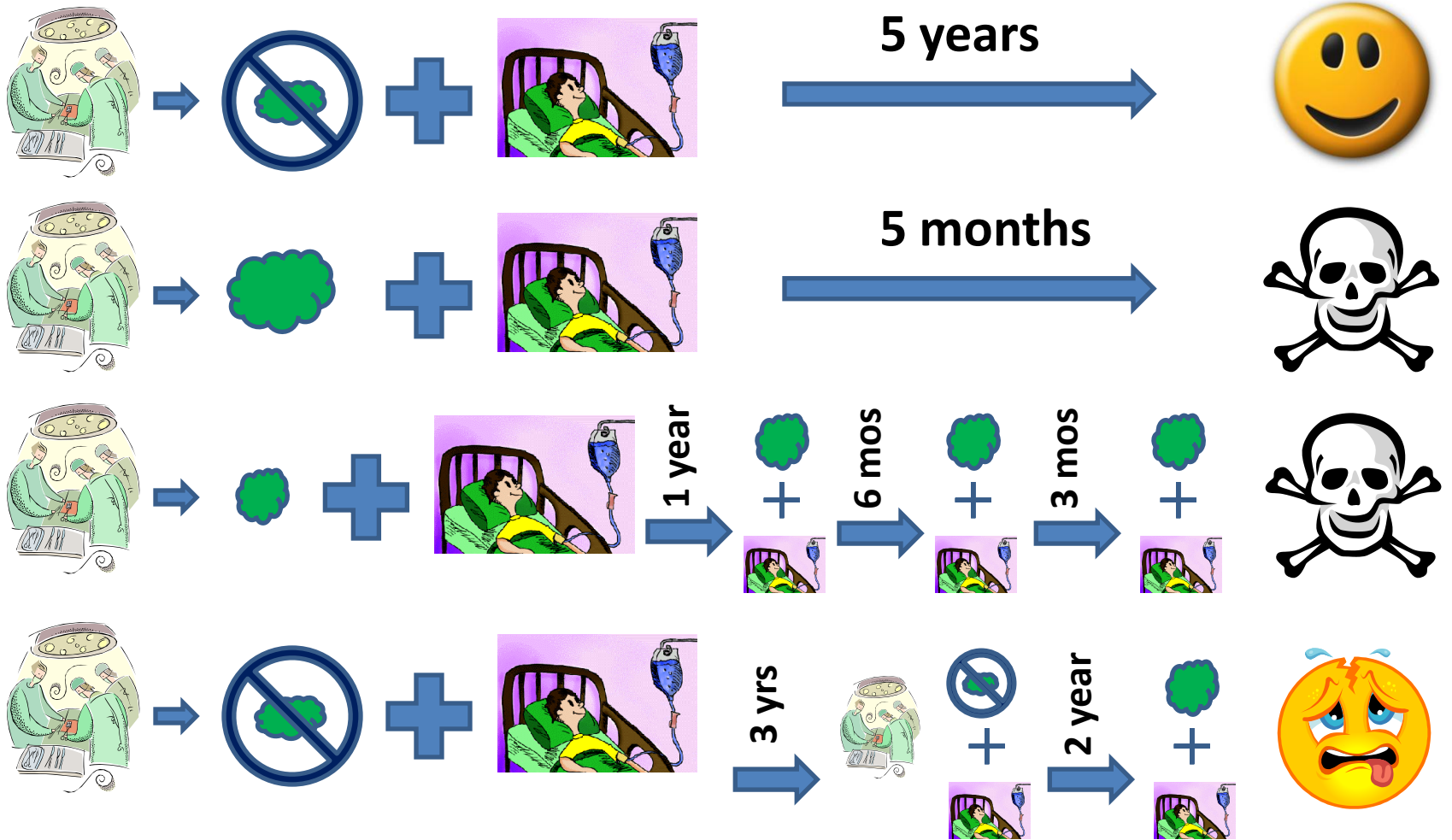
Validated Targets associated with Curatively Treated Advanced Serous Ovarian Carcinoma

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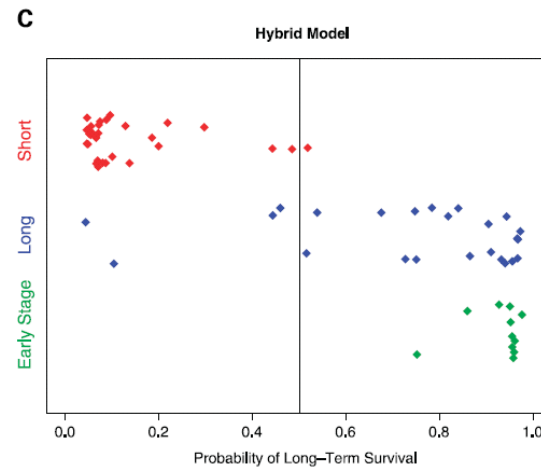
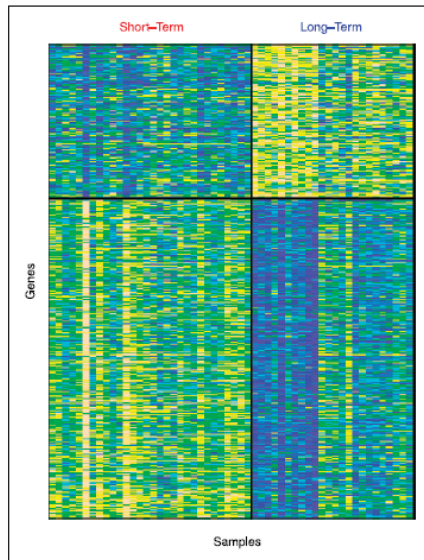
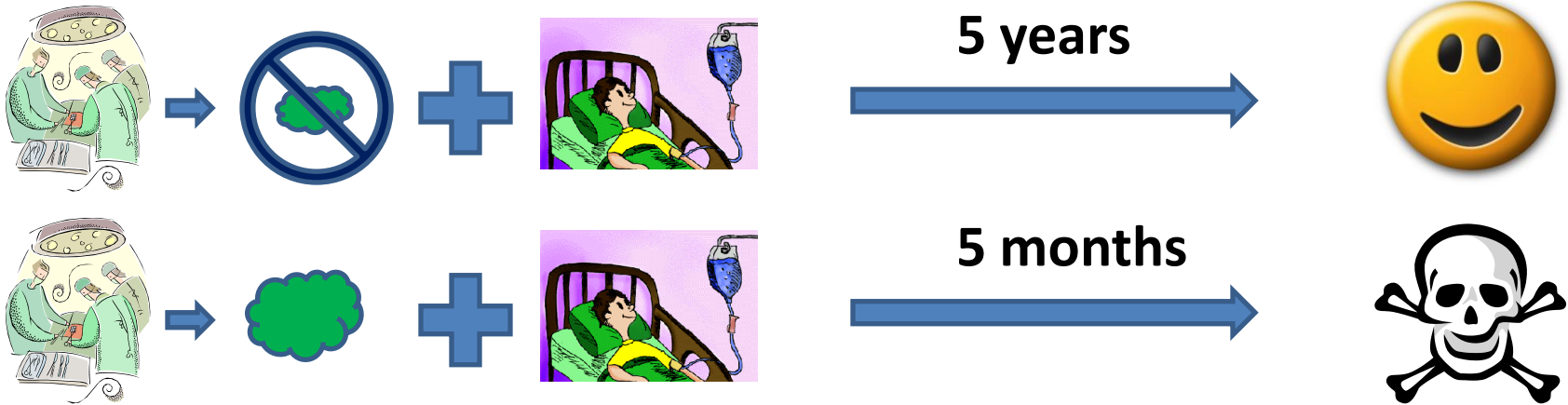
Cancer Genomics

- 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

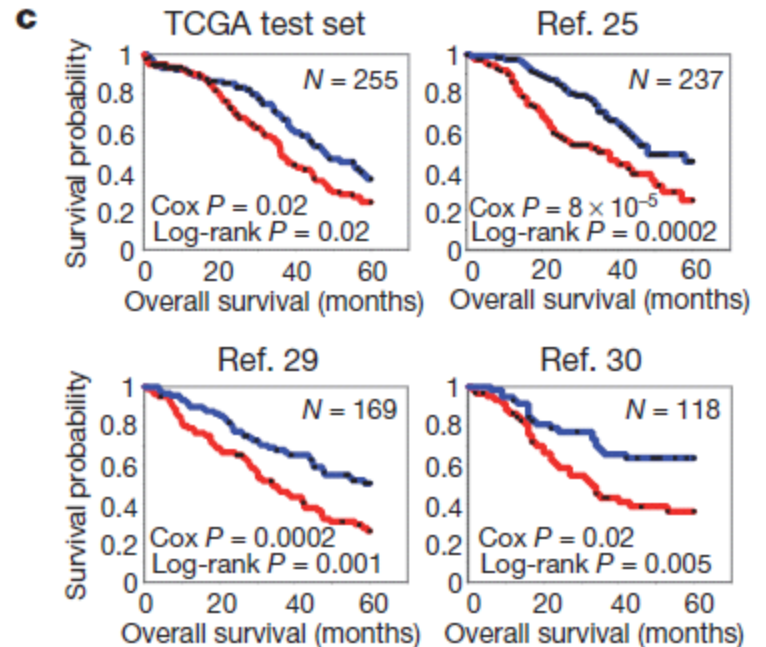
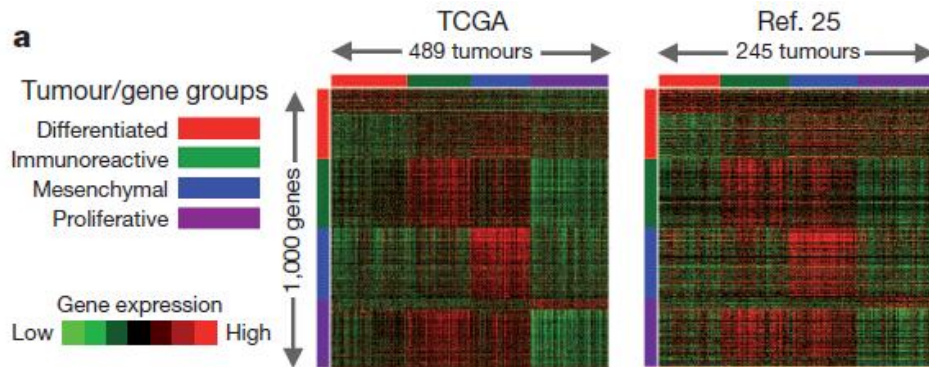
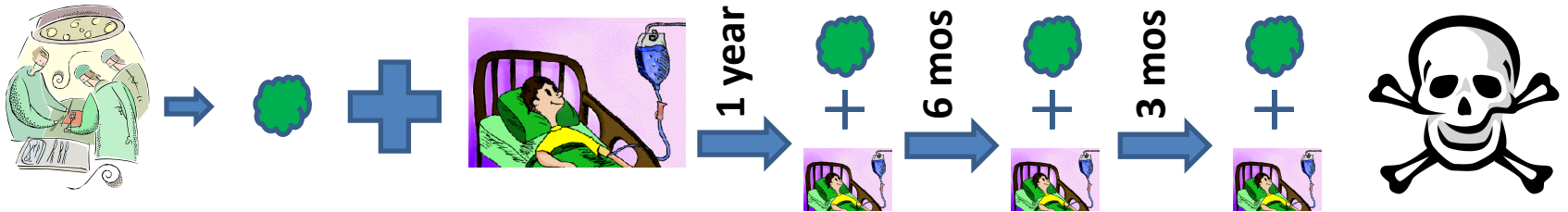
Ovarian Cancer



Ovarian Cancer – Short/Long



Overall Survival - Typical



One and Done – Pts doing well

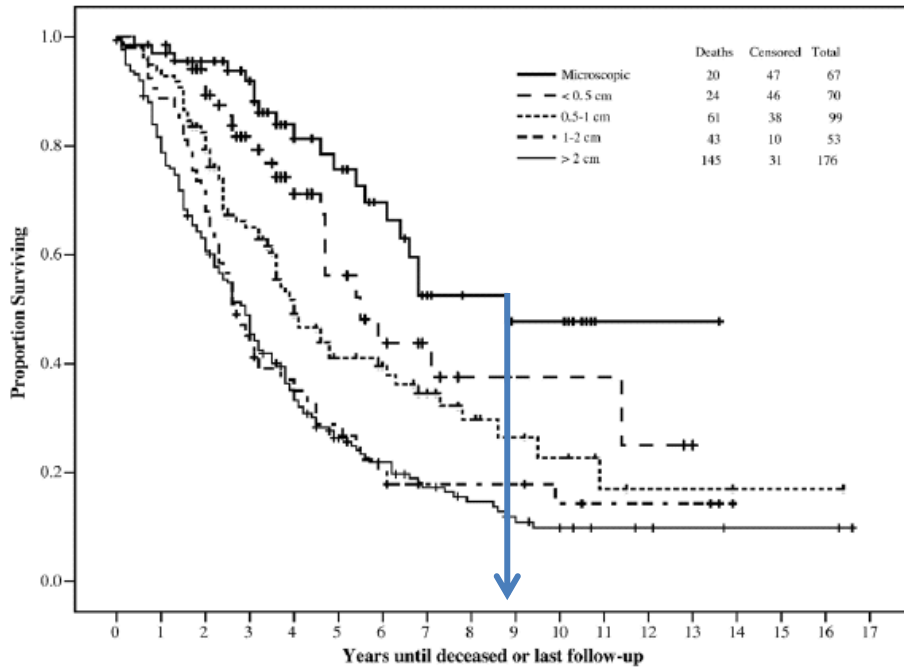
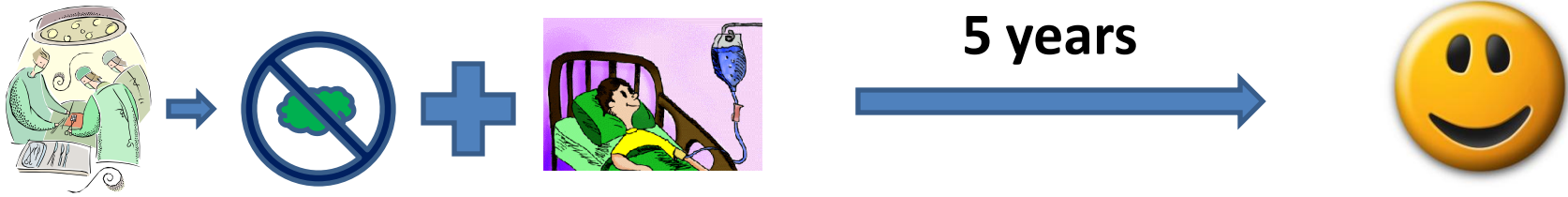
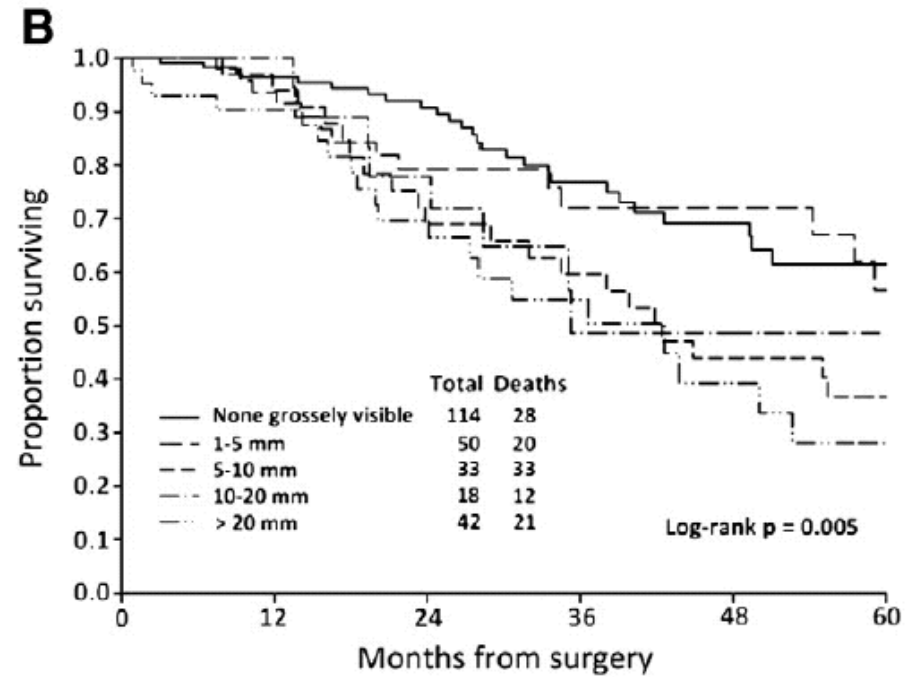


Fig. 1. Overall survival, stage IIIIC ovarian cancer, 1989–2003.



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

The screenshot shows the National Cancer Institute website. At the top, the logo and name of the National Cancer Institute are on the left, and the text "U.S. National Institutes of Health | www.cancer.gov" is on the right. Below this is a blue header with the text "Provocative Questions" in large white letters, followed by "Identifying Perplexing Problems to Drive Progress Against Cancer" in smaller white text. A navigation bar below the header contains links for "Home", "RFA Links and Provocative Questions", "Community Dialog", and "Workshops". Below the navigation bar, a breadcrumb trail reads "You are here: Home → RFA Links and Provocative Questions → Why are some disseminated cancers cured by chemotherapy alone?". A red banner below the breadcrumb contains the text "RFA Links and Provocative Questions" on the left and two search boxes labeled "Search RFA Questions" and "Search" on the right. Below the red banner are two blue buttons: "NIH Funding Announcement (RFA-CA-11-011)" and "NIH Funding Announcement (RFA-CA-11-012)". The main content area features a section titled "PQ - 19" with the question "Why are some disseminated cancers cured by chemotherapy alone?". Below the question are three paragraphs of text, each starting with a bolded label: "Background:", "Feasibility:", and "Implications of success:".

National Cancer Institute U.S. National Institutes of Health | www.cancer.gov

Provocative Questions

Identifying Perplexing Problems to Drive Progress Against Cancer

Home RFA Links and Provocative Questions Community Dialog Workshops

You are here: Home → RFA Links and Provocative Questions → Why are some disseminated cancers cured by chemotherapy alone?

RFA Links and Provocative Questions

Search RFA Questions Search

NIH Funding Announcement (RFA-CA-11-011) NIH Funding Announcement (RFA-CA-11-012)

PQ - 19
Why are some disseminated cancers cured by chemotherapy alone?

Background: Although chemotherapy is often effective, it is only rarely curative. However, it is well established that certain disseminated cancers can be completely cured with chemotherapy, even with drugs that are often of much less value in other settings. The tumors that can be cured include solid tumors (testicular carcinoma, choriocarcinoma, and Wilms' tumor) and hematological malignancies (ALL, Burkitt's lymphoma, and some diffuse large B-cell lymphoma). However, there is little understanding of the underlying mechanisms that might explain why these cancers can be completely cured with chemotherapy.

Feasibility: This question has largely been ignored since it was recognized, often decades ago, that such tumors could be cured by standard chemotherapeutic strategies. New methods are available for studying the biology of these "curable" cancers and for exploring the mechanisms by which the effective drugs work.

Implications of success: If we could identify the properties of cancers that render them susceptible to eradication by chemotherapy, we might better understand how certain therapies work, contemplate converting relatively insensitive tumors to highly sensitive ones, or develop new approaches to the treatment of intransigent malignancies.

Ovarian cancer disseminated? Yes.

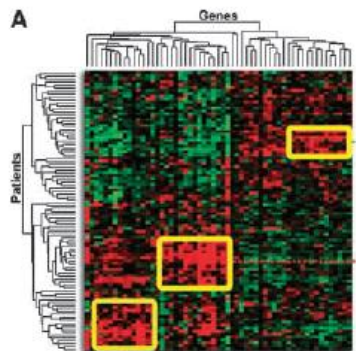
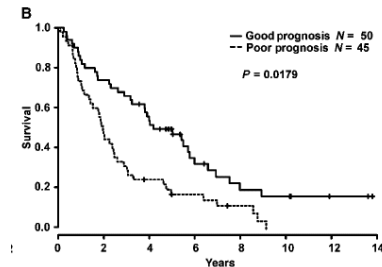
One and done cured by chemotherapy alone? Sort of.

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

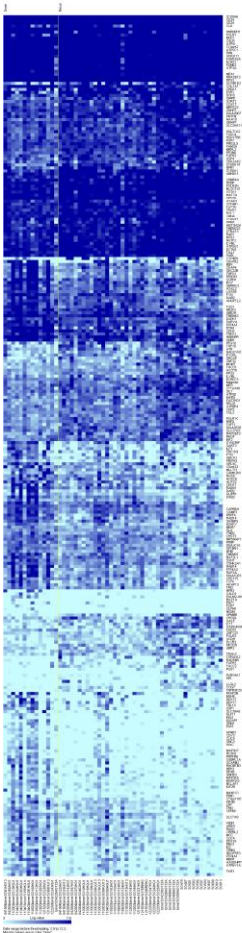
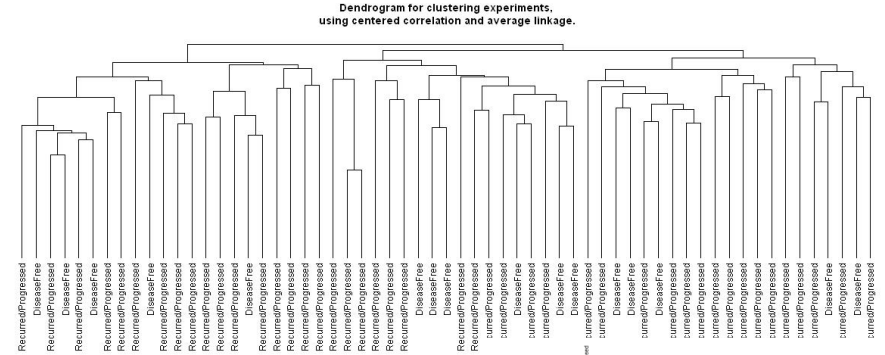
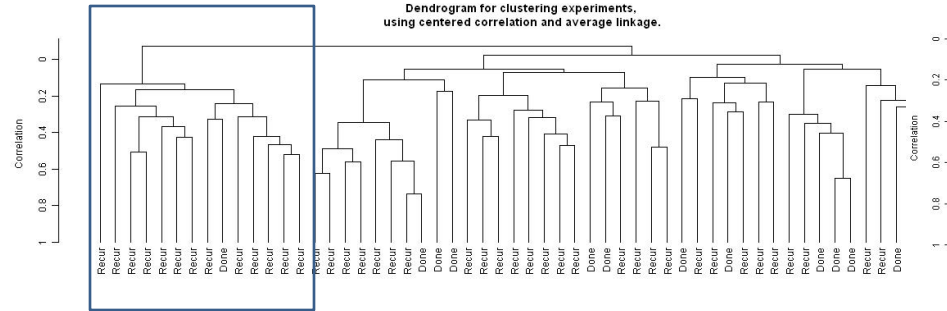
Patient Samples/Datasets

- 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

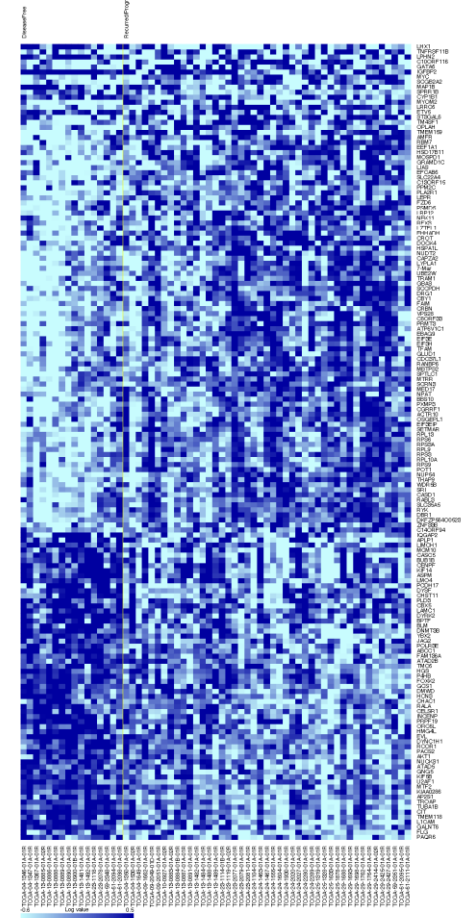
MSKCC



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

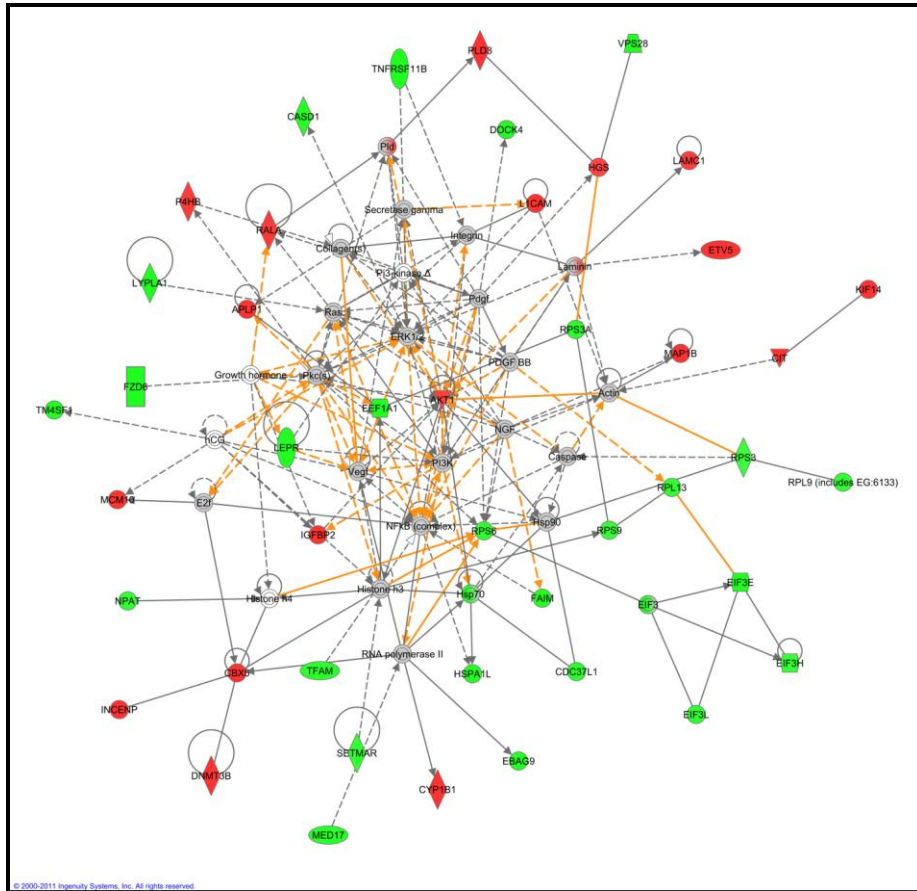
- 7180 (TCGA) and 7645 (MSKCC) probe sets input into above analysis

Both datasets suffer from small sample size

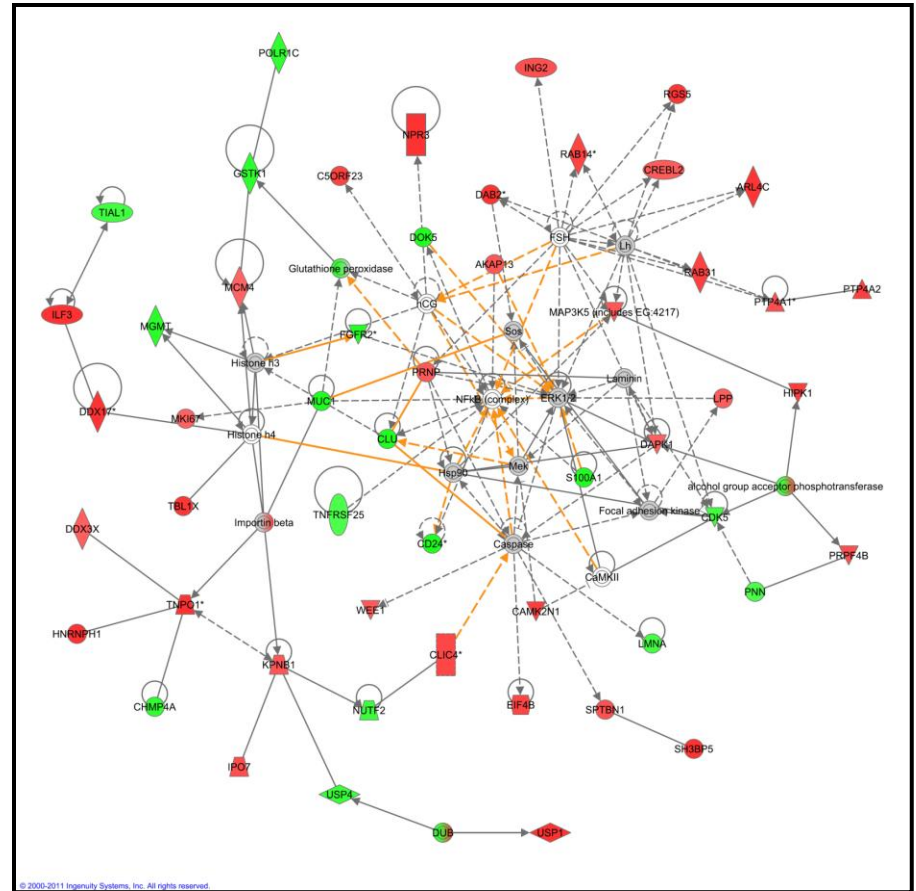


Pathway Analyses

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

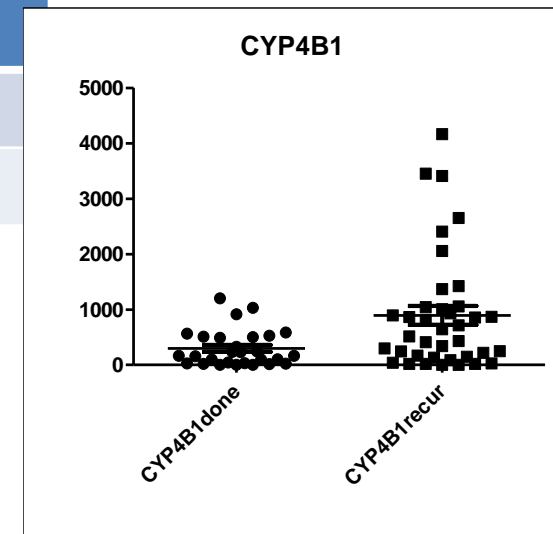
Gene	Source
HRAS	ERK
MLLT11	overlap
NRAS	ERK
E2F1	ERK
PIK3CB	overlap
MARCKS	overlap
FOS	NFkB
CEPT1	overlap
MAPK1	ERK
CYP4B1	overlap
MAPK6	ERK
CDK4	ERK
RIPK1	NFkB
CHMP4A	overlap
KRAS	ERK

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



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.

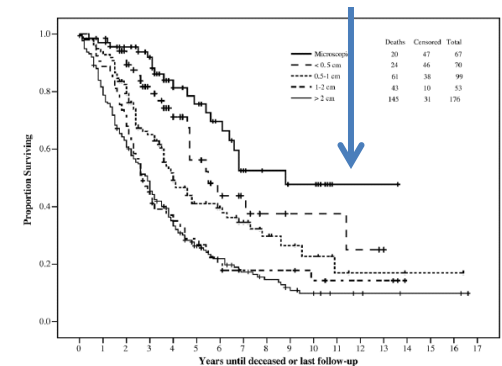
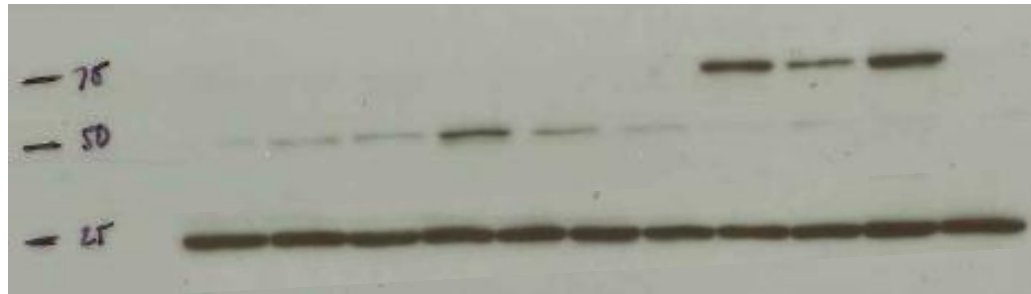


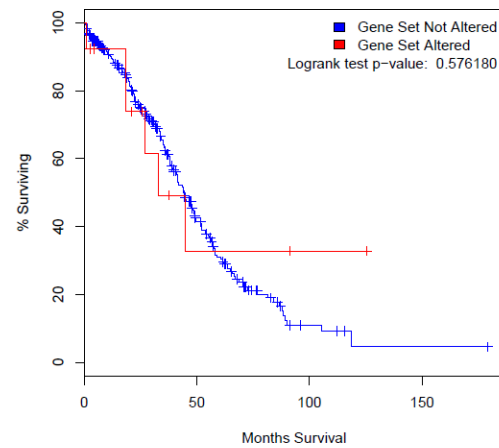
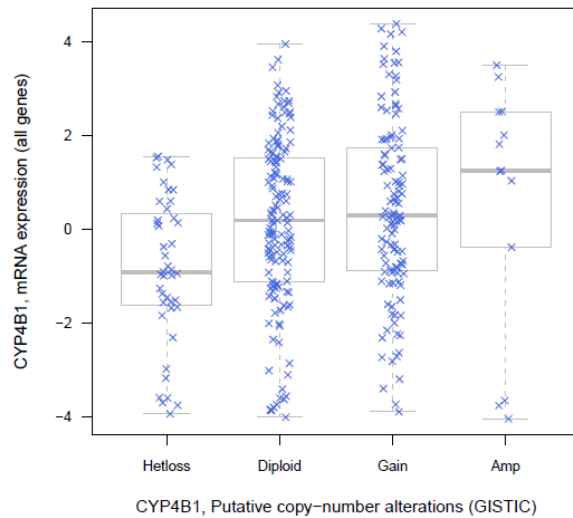
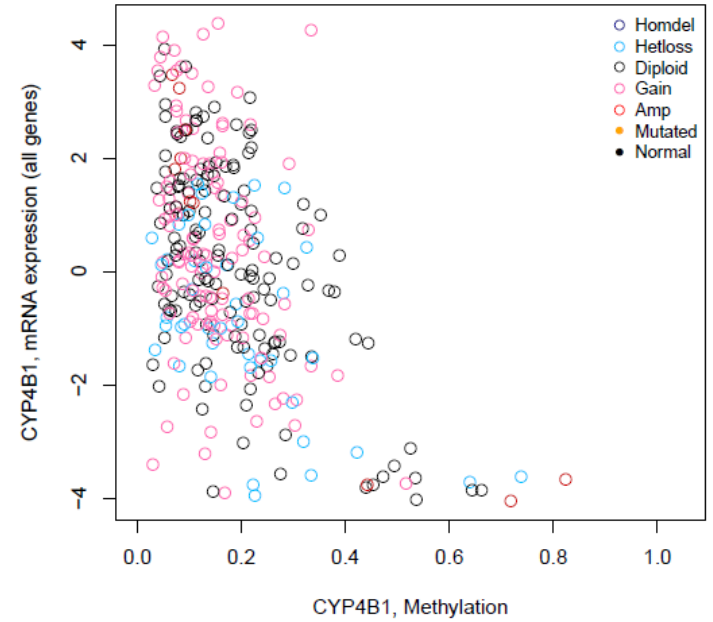
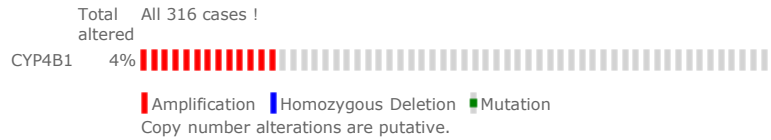
Fig. 1. Overall survival, stage IIIc ovarian cancer, 1989-2003.

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.



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