Correlative Science Directed CALGB Lung Cancer Studies

(Part 2 of 3)

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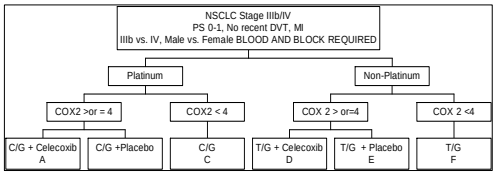
University of Minnesota

CALGB CRA Continuing Education Workshop, June 2007

CALGB 307XX



C/G = carboplatin AUC =5 d1, gemcitabine = 1000 mg/m2 d 1,8
T/G = paclitaxel 200 mg/m2 d1, gemcitabine = 1000 mg/m2 d1,8
Celecoxib 400 mg po bid

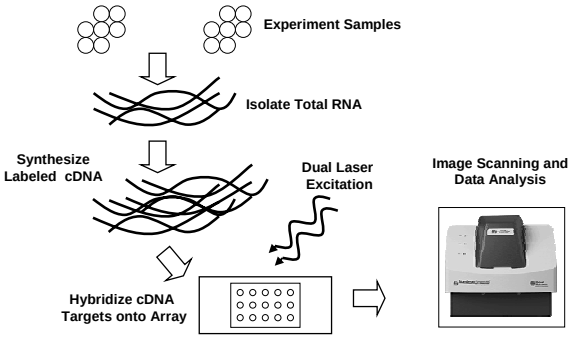
Objectives

- Primary:
  - 1. Determine if the addition of celecoxib to standard chemotherapy will increase one year survival.
  - 2. Determine if ERCC1 germline polymorphisms predict for response or survival with platinum based chemotherapy.
- Secondary:
  - Confirm the prognostic value of COX-2 expression.
  - Correlate germline polymorphisms for ERCC1 etc. with tumor expression.
  - Determine if platinum and non-platinum therapy are equivalent in patients who do not overexpress COX-2.

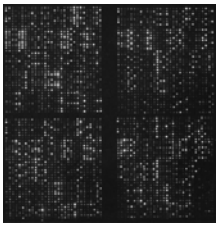
cDNA Array directed studies of NSCLC in CALGB

- Objective
  - Use current cDNA microarray based analysis to guide use of adjuvant therapy in early stage NSCLC as well as in stage 4 NSCLC
- Plan
  - Devise a study for resected NSCLC where the tumor will be sent to a central lab for analysis and therapeutic decisions will be made based on laboratory studies done in real time (<2 week turnaround)

cDNA Microarray Principles



Microarray Interpretation



Relative Transcript Abundance

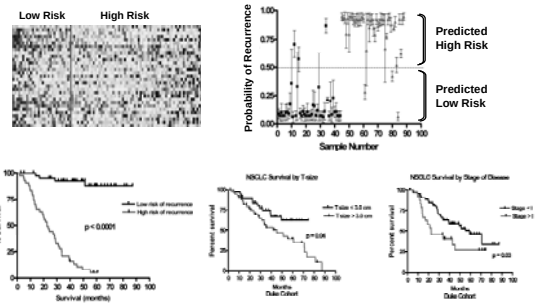
- ◯ **Tumor >> Normal**
- ◯ **Normal >> Tumor**
- ◯ **Tumor = Normal**
- ◯ **No Hybridization**

Catalog of Genes on Array

Gene Functional Categories	# Array Genes in Category
Inhibitors	18
Ligases	44
Receptors	65
Cytokines and Growth Factors	20
Isomerases	24
Oxido-reductases	72
Post-translational modifications	340
Other transport proteins	55
DNA or RNA associated proteins	272
Transferases	164
Hormones and active peptides	14
Structural proteins	96
Protein secretion and chaperones	22
Domains	352
Hydrolases	157
Electron transport proteins	39
Lysases	24
Others	136

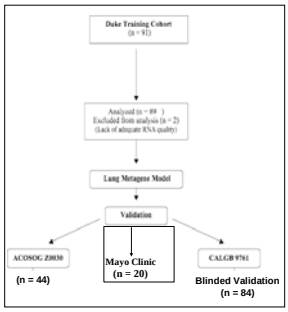
Validating an array based prognostic test in NSCLC (overview)

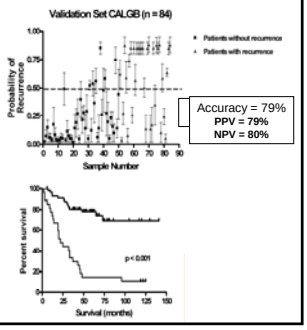
A Metagene Predictor of Recurrence



N Engl J Med. 2006 Aug 10;355(6):570-80

Independent Validation





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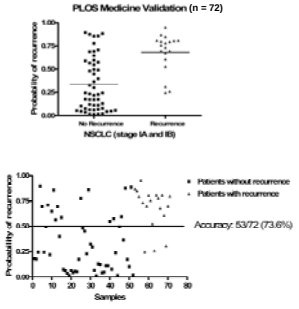
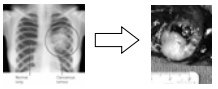
Independent Validation of the Metagene Recurrence Predictor

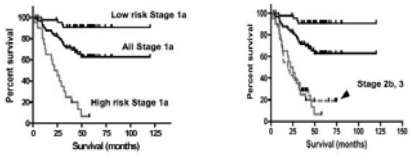


An Opportunity to Improve Prognosis in Lung Cancer



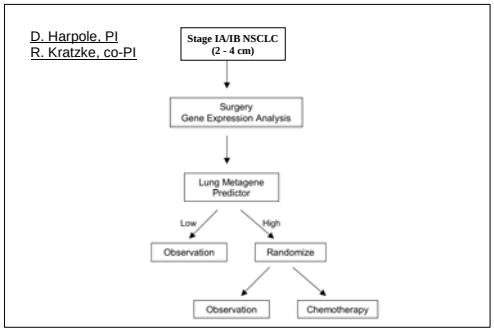
Stage Ia: Observation

Stage Ib-III: Adjuvant Therapy



CALGB 30506 - A Phase III Trial

D. Harpole, PI
R. Kratzke, co-PI



A Gene Expression Signature Predicts Survival of Patients with Stage I Non-Small Cell Lung Cancer

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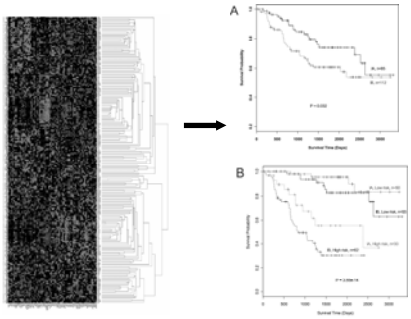
64 gene predictor



PLoS Med. 2006 Dec;3(12):e467

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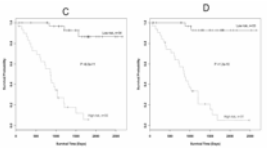
Characteristics	Measurements	Dataset 1	Dataset 2	Dataset 3	Dataset 4	Dataset 5	Dataset 6	Dataset 7
Total samples	n	36	18	67	4	72	63	64
Mean age (range)	Years	66 (48–81)	70 (59–80)	64 (41–85)	76 (61–88)	64 (33–88)	65 (40–82)	ND
Sex	Male	20	10	25	2	29	27	ND
	Female	16	8	42	2	43	36	ND
Mean follow-up (days)	Total overall survival	1,369	1,301	1,310	303	1,403	1,387	1,139
	Total alive	1,570	1,813	1,430	303	1,805	1,441	1,414
	Total dead	665	660	924	ND	901	1,064	785
Stage	IA	0	7	44	1	33	25	30
	IB	36	11	23	3	39	38	27
Histological type	ADC	14	0	67	3	72	63	31
	SCC	18	18	0	1	0	0	33
	Other	4	0	0	0	0	0	0

External validation In Duke Data (n = 64)

64 gene predictor



Beer 50 gene predictor

Summary

- **Multiple prognostic genomic predictors with variable accuracies (70% - 79%).**
- **Two predictors (Metagene and Wash U) have been validated in more than 250 patients !**
- **Overlap in genes is usually minimal.**
  - Not really an issue as long as models are fixed prior to testing and validation.
- **The importance of the first to define the strategy to test this prospectively**
  - CALGB 30506 as described in the NEJM paper.

After prognosis, how about prediction of response ?