

**NATIONAL
CANCER
INSTITUTE**

Center for Cancer Research



Pediatric
ONCOLOGY BRANCH

The Applications of Microarrays and Artificial Neural Networks for Diagnosis, Prognosis and Selection of Therapeutic Targets

Oncogenomics Section

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NCAB-September 2006

Outline

1. Cancer Diagnosis using Gene Expression Profiling and Artificial Neural Networks (ANN)
2. Prognosis Prediction using ANNs
3. NCI-UMCP-NASA-NanoBioSensor Initiative

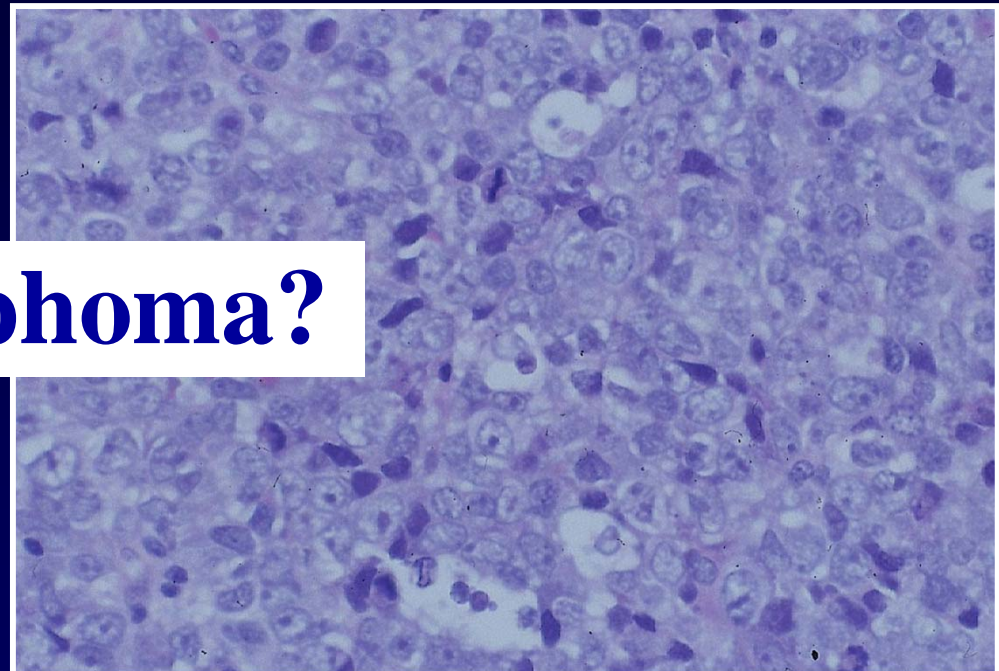
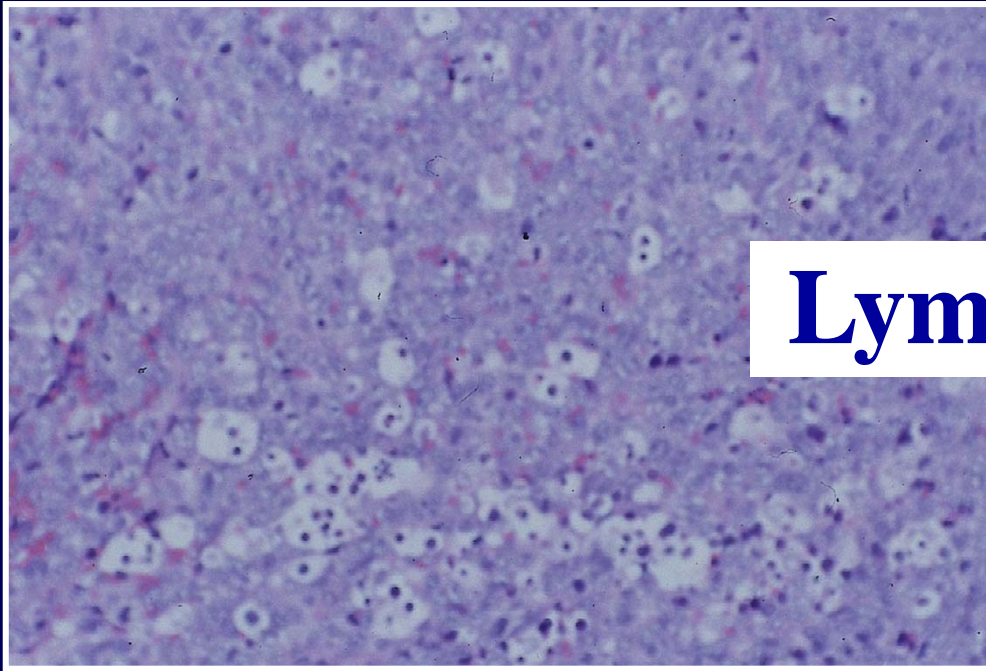
Why Artificial Neural Networks (ANNs)?

- Powerful pattern recognition algorithms
- Modeled on the human neuron/brain
- Learning from prior experience by error minimization
- Input any type of data, e.g. gene expression
- Output = 0-1, can be any given number of categories (≥ 1)
- Hidden Layers allows for non-linearity in data
- Allows for translation to the clinic

APPLICATIONS

- Defense
- Voice, handwriting, fingerprint recognition
- Diagnosis of Arrhythmias & Myocardial Infarcts
- Interpreting Mammograms, Radiographs/MRI

Despite availability of immunohistochemistry, cytogenetics and molecular techniques, in some cases incorrect diagnoses are made



Lymphoma?

**Alveolar Rhabdomyosarcoma
Small Round Blue Cell Tumor (SRBCT)
Lymphoma/RMS/EWS/NB**



Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks

**Lymphoma
(BL)**

**Ewing's
(EWS)**

6567 element cDNA Microarray

**Unknown n=25
Non-SRBCT n=5**

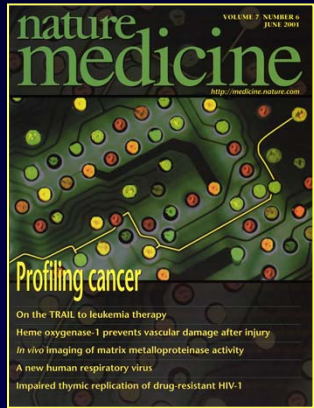
**Rhabdomyosarcoma
(RMS)**

**Neuroblastoma
(NB)**



Khan, Wei, Ringnér et al. Nat Med. 7: 673-9, 2001

Several Novel Features for Microarray Data Analysis



Khan et al., 7, 673-9, 2001

Microarray Data
(6567x88)

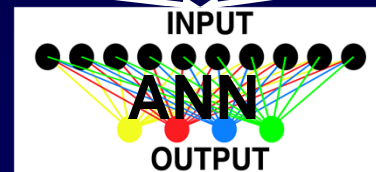
Quality Filter
(2308x88)

Principal Component
Analysis (10x88)

- Broad Applications
- “n” Categories
- Diagnosis
- Prognosis
- Elucidate Biology
- Molecular Targets

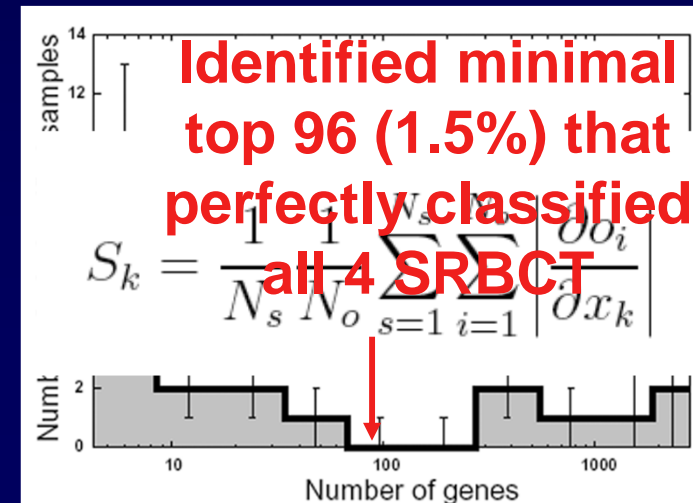
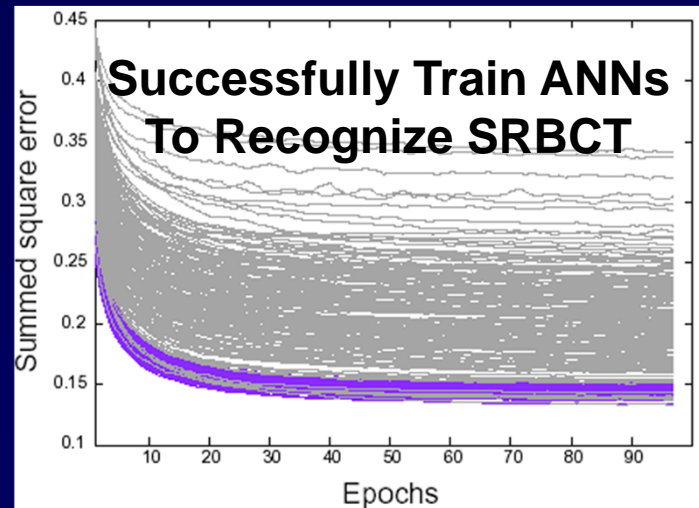
Training

Validation



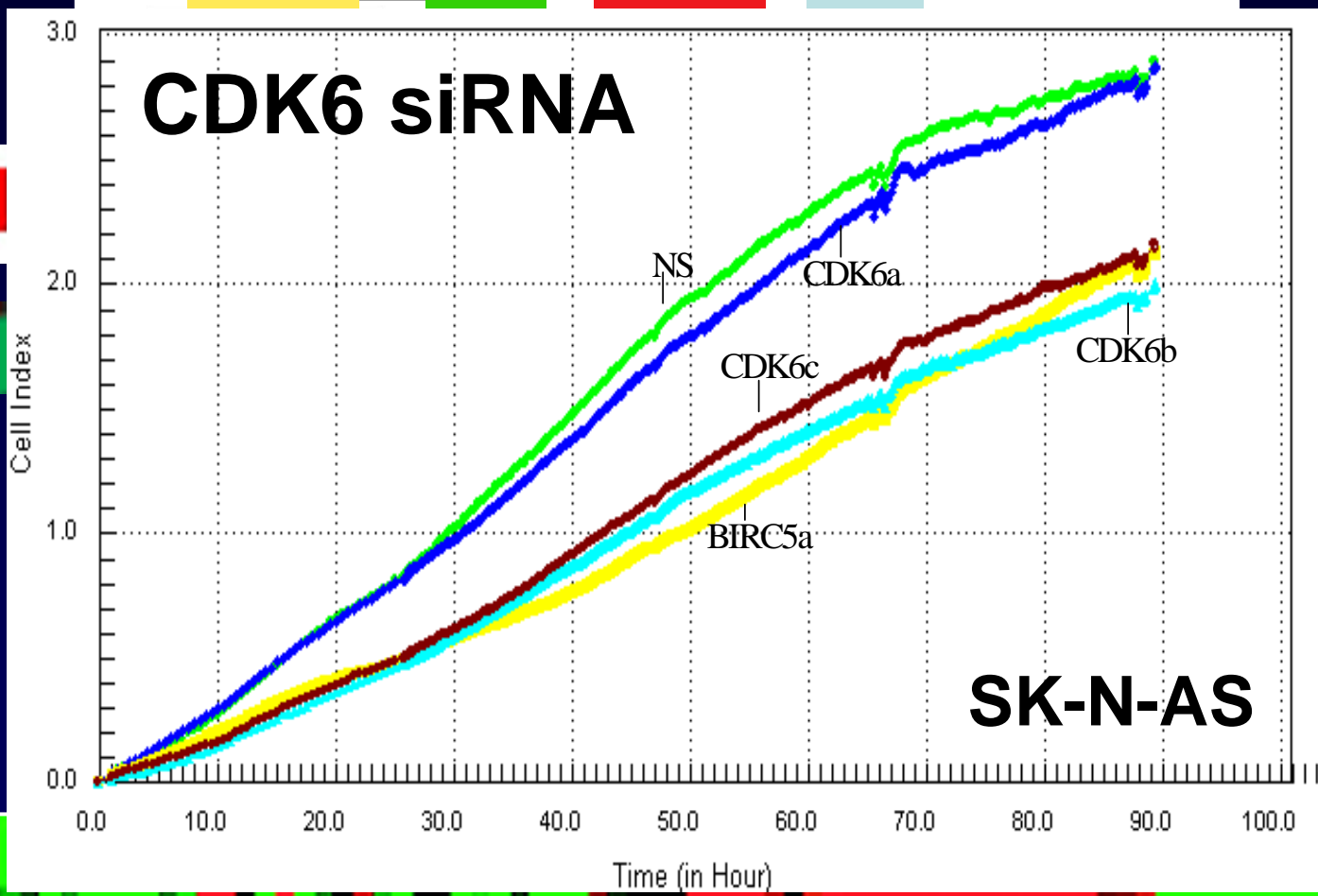
Novel Gene
Ranking Algorithm

Gene
Minimization



ANN Identified 96 genes/6567 that Resulted in “Perfect” Hierarchical Clustering

EWS — **NB** — **RMS** — **BL**



1435862 MIC2

295985 EST

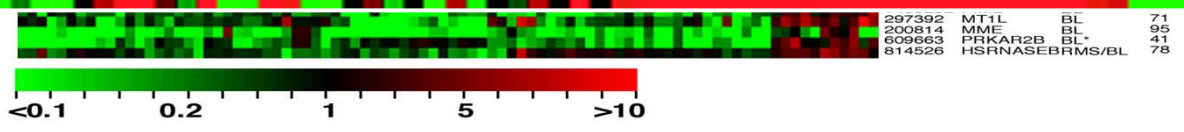
↑

CDK6

784224 FGFR4

296448 IGF2

207274 IGF2

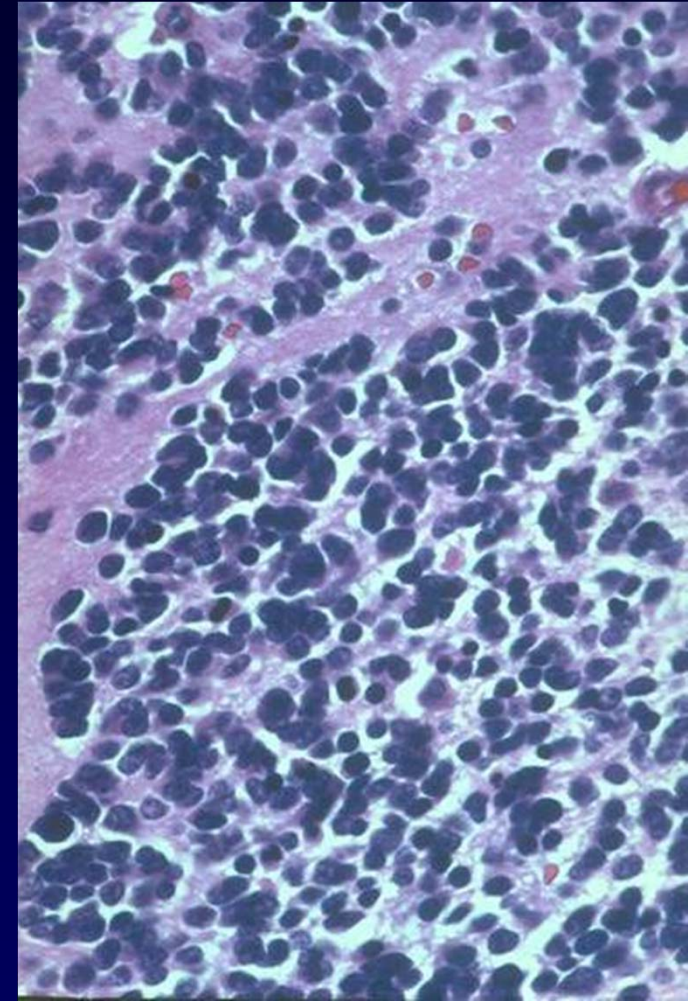
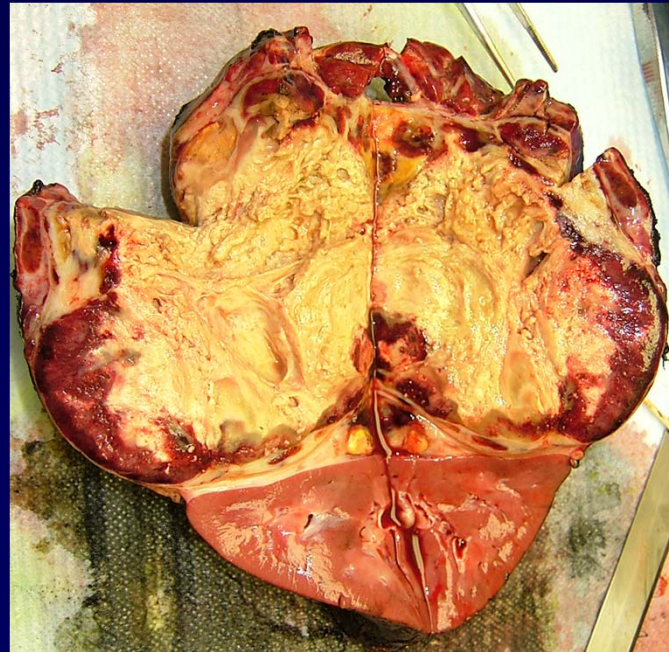
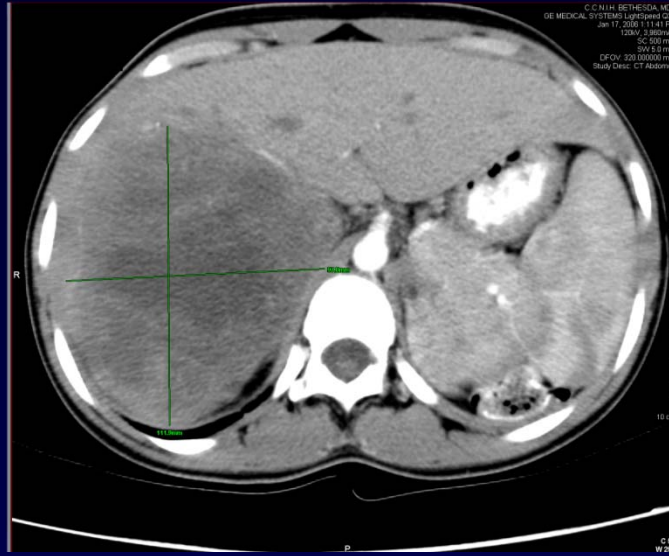


ANN Diagnostic Classification

Cancer	Sensitivity (%)	Specificity (%)
EWS	93	100
BL	100	100
NB	100	100
RMS	96	100

The expression profile of 96 genes can predict the diagnosis of SRBCT using ANNs

Neuroblastoma Enigmatic Lethal Tumor: Stage 4 >18 months



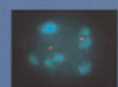
Survival <30%
Can we Predict Outcome?

Prediction of Clinical Outcome Using Gene Expression Profiling and Artificial Neural Networks for Patients with Neuroblastoma

Jun S. Wei,¹ Braden T. Greer,¹ Frank Westermann,² Seth M. Steinberg,³ Chang-Gue Son,^{1,4} Qing-Rong Chen,¹ Craig C. Whiteford,¹ Sven Bilke,¹ Alexei L. Krasnoselsky,¹ Nicola Cenacchi,¹ Daniel Catchpoole,⁵ Frank Berthold,⁶ Manfred Schwab,² and Javed Khan¹

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Cancer Research

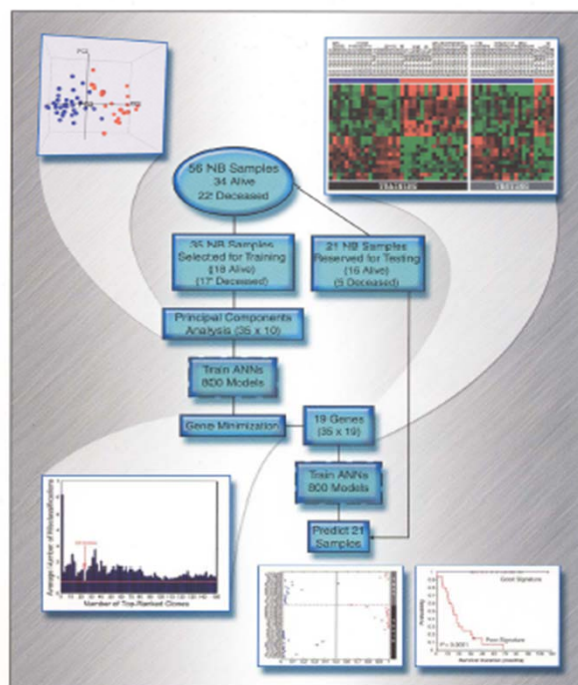


Men I-Mediated Tumorigenesis in the Absence of Chromosome Instability

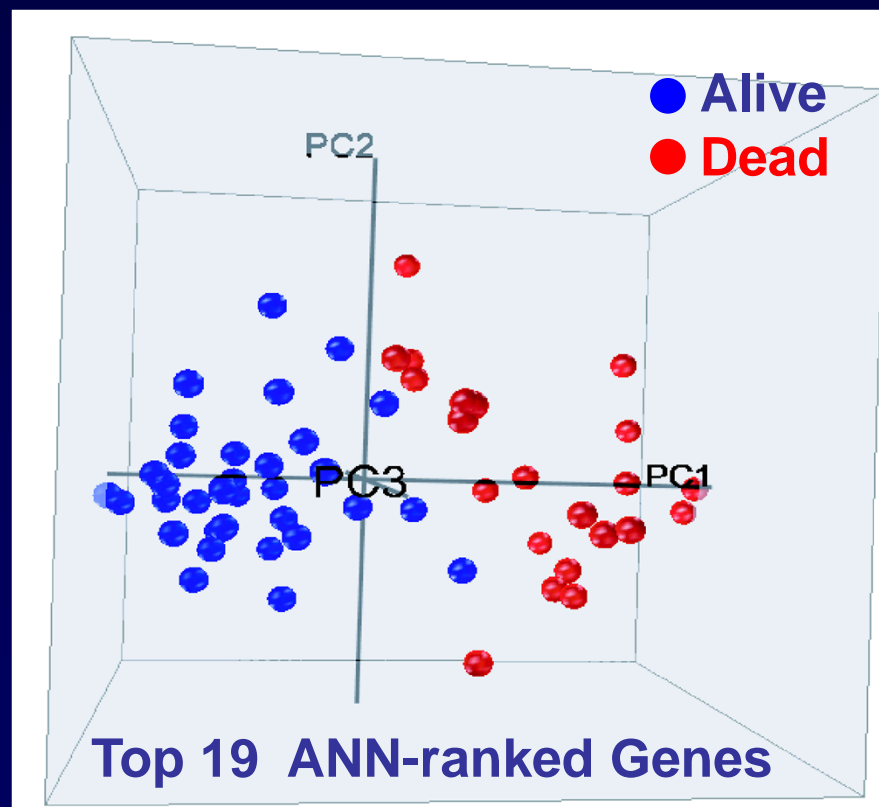


Control of Bleomycin-Induced Fibrosis by H2-Ea

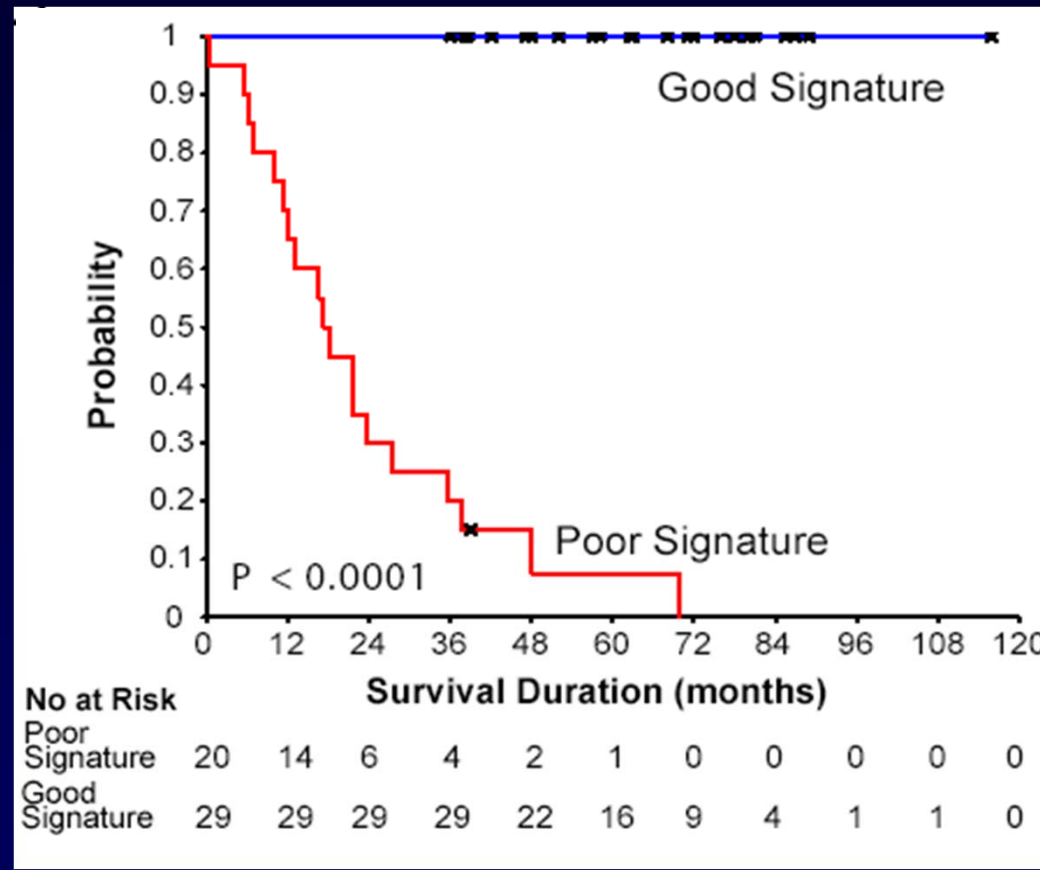
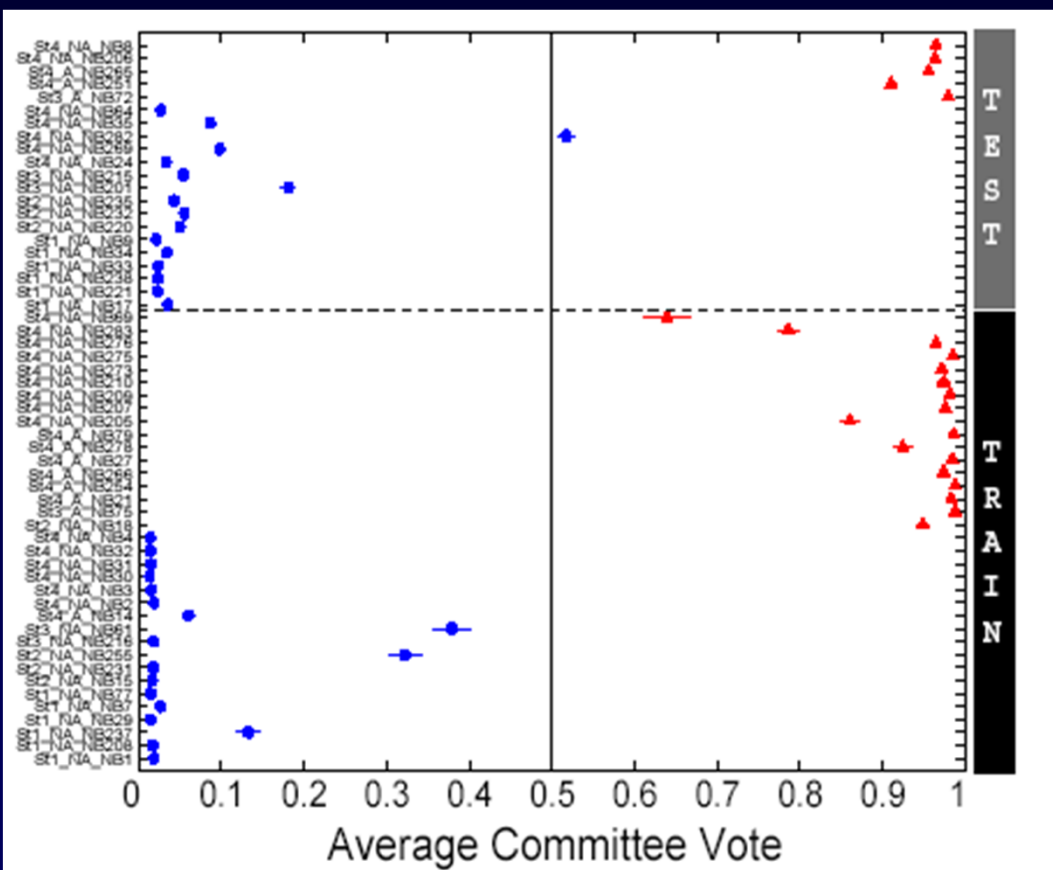
Predicting Prognosis With Artificial Neural Networks



- 42, 000 cDNA Microarray
- 49 Patients:
(19 Dead of Disease, 30 disease free >3yrs)



Performance of the top 19 ANN-ranked genes signature for predicting survival



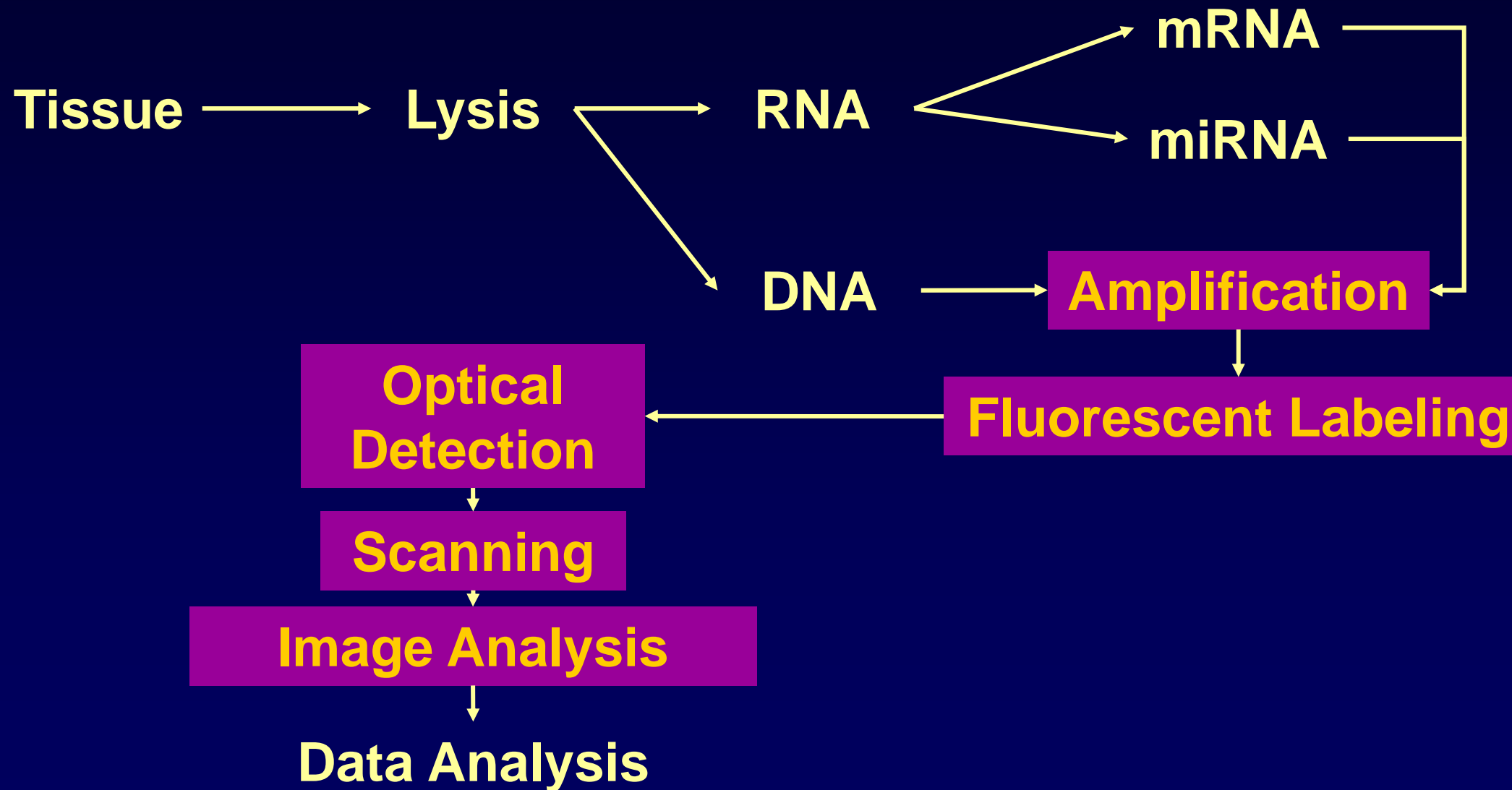
Possible to predict outcome of patients based on the gene expression profiles of the top 19 ANN-ranked genes of pre-treatment tumors alone

Translation of Genomics to the Clinic

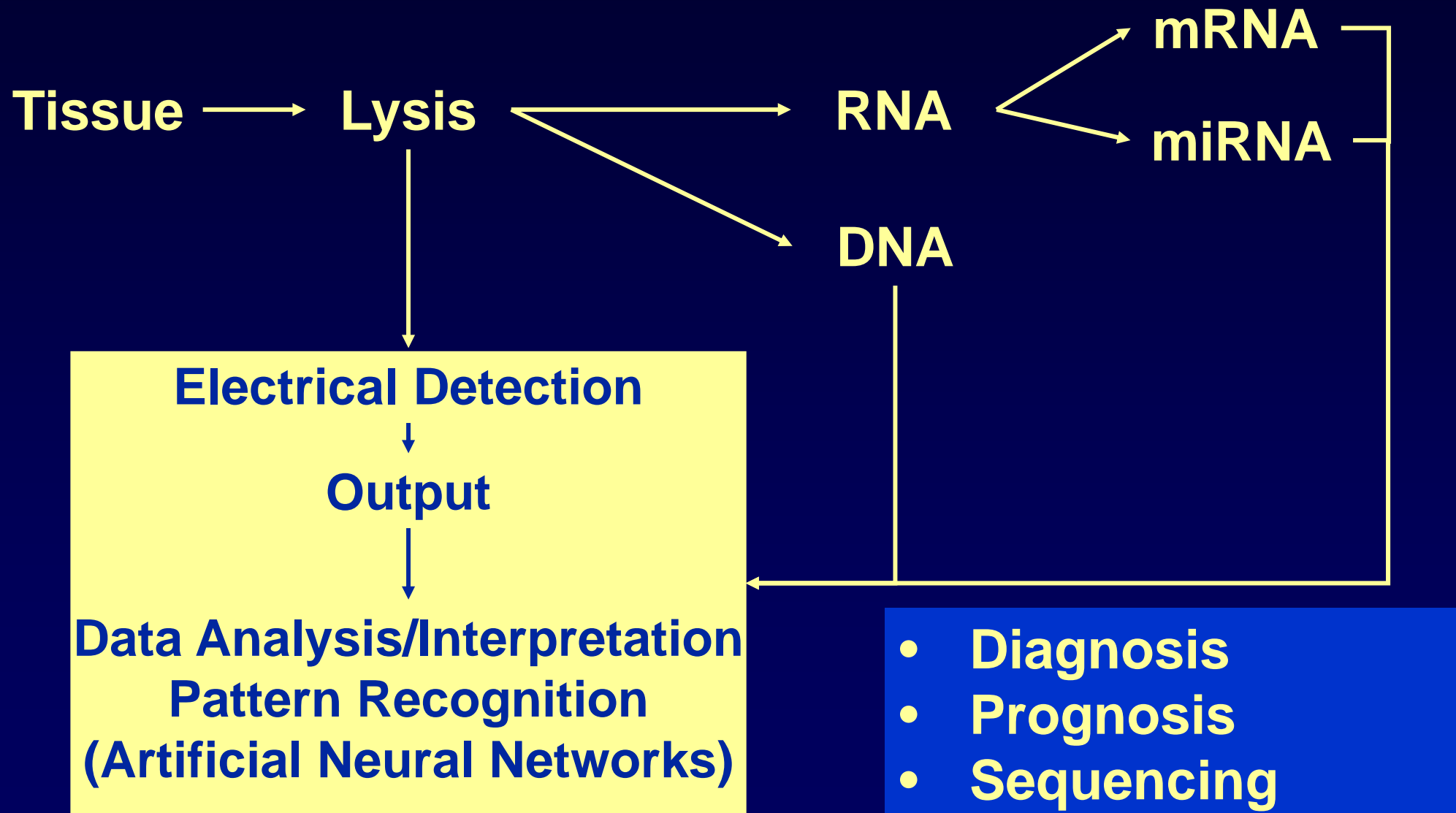


NCI-UMCP-NASA-NanoBioSensor Initiative

Current Microarray Technology

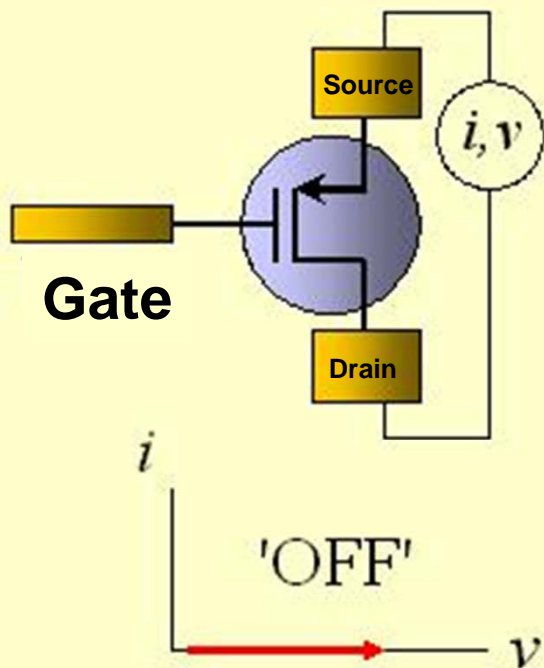


NCI-UMCP-NASA-NanoBioSensor Proposal



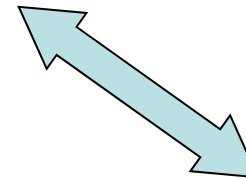
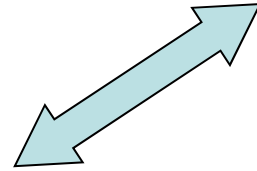
Principle of Electronic Hybridization Sensing using Field Effect Transistors

Step 1. Bare transistor



NCI-UMCP-NASA-NanoBioSensor Initiative

Translational Biology

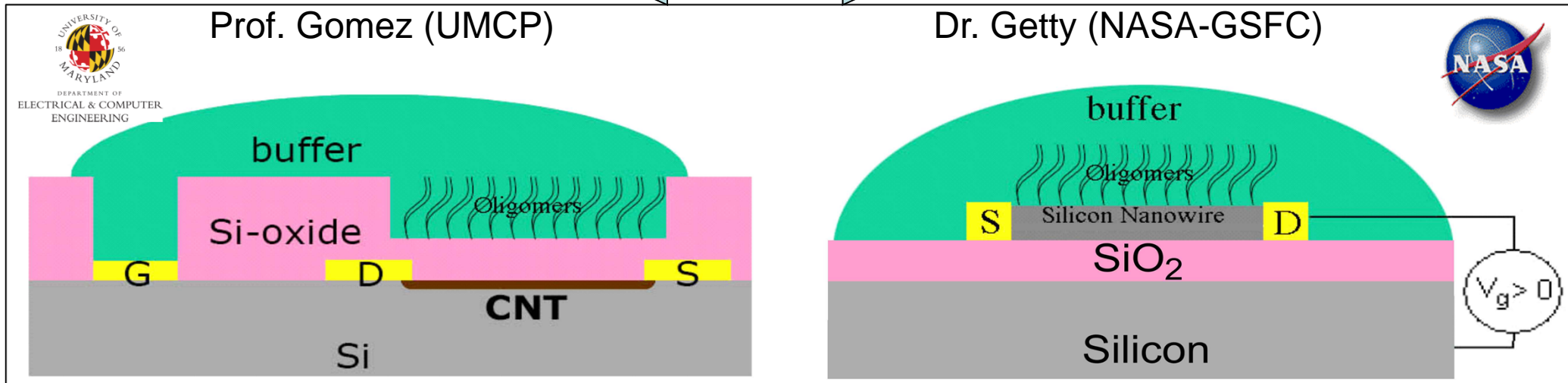


Carbon Nanotubes

Silicon Nanowires

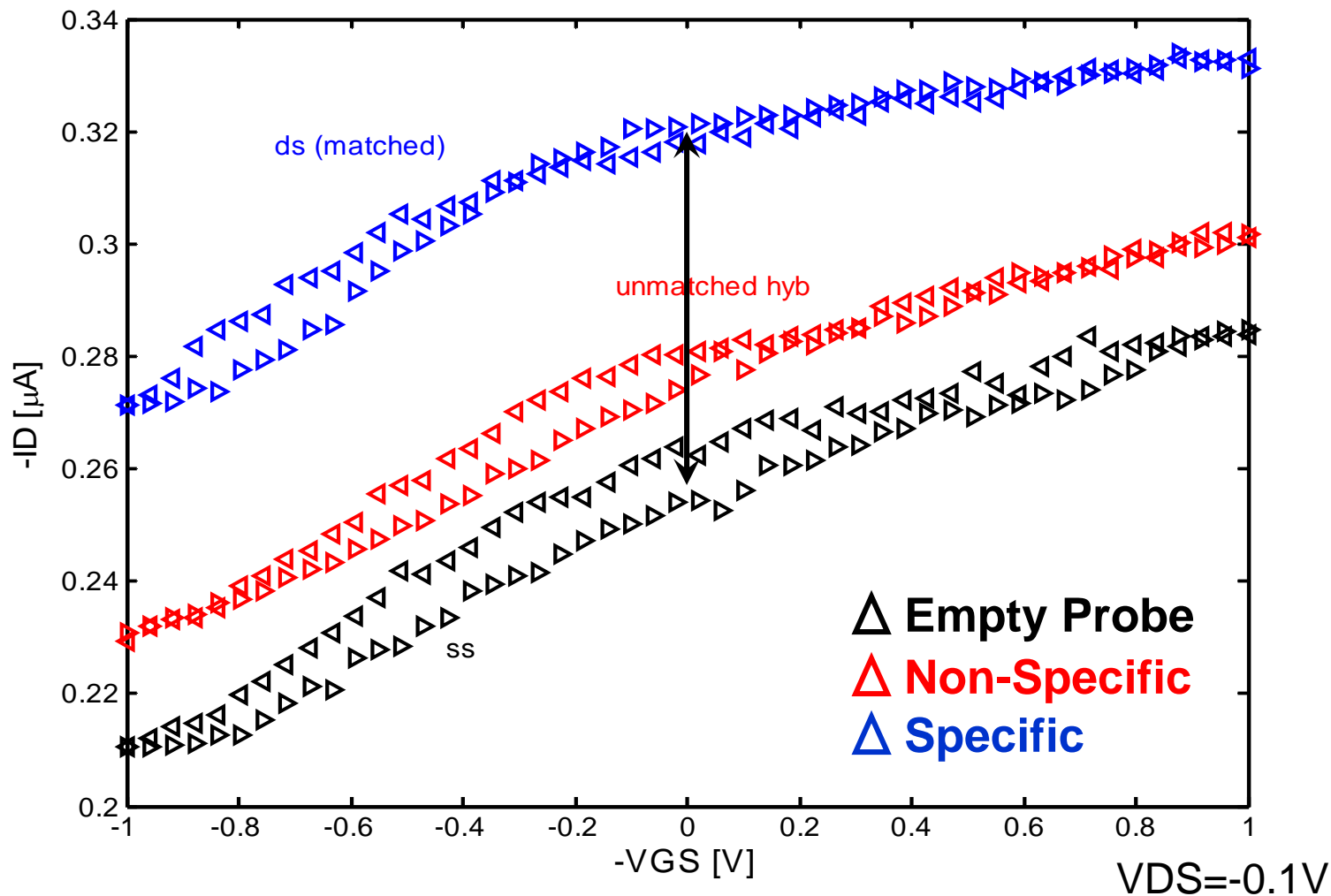
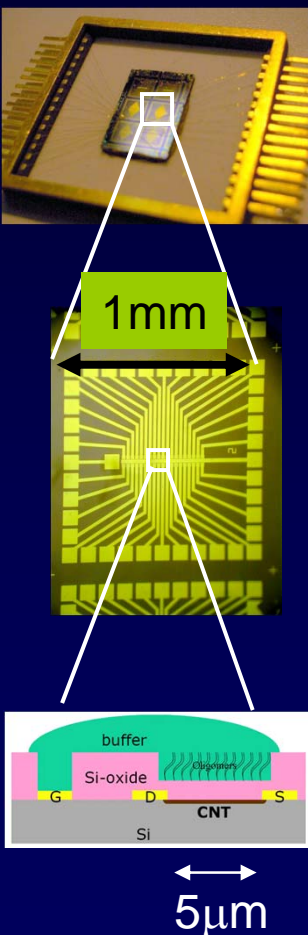
Prof. Gomez (UMCP)

Dr. Getty (NASA-GSFC)



Parallel Approach

Preliminary Data: Carbon Nanotubes (UMCP) Detection of Specific DNA-DNA Hybridization



Summary

- **Power of Genomics and Machine Learning Algorithms (ANN) for Diagnosis, Predicting Prognosis & Identifying Targets**
- **Interagency/ Local Academic Institute Collaboration Leveraging CCR Resources and Local Expertise and Resources**
- **Collaborative Initiative Involving Physicians/ Biologists/ Biochemists/ Bioinformaticians/ Electrical Engineers/ Physicists to Translate Genomics to the Clinic and “Think Outside of the Box”**
- **High-risk yet High-Yield Research (mRNA, miRNA, DNA, SNP, Sequencing, Aptamer; Drug, Protein)**