IMAT
Innovative Molecular Analysis Technologies

Innovative Molecular Analysis Technologies (IMAT) for Cancer Program

Presentation to:

NCI National Cancer Advisory Board

September 7, 2006

Agenda

- **Greg Downing, D.O., Ph.D.**
  Director, Office of Technology and Industrial Relations
  "Overview of the Innovative Molecular Analysis Technologies (IMAT) for Cancer Program"

- **Stephen J. Kron, M.D., Ph.D.**
  Associate Professor, Molecular Genetics and Cell Biology, University of Chicago
  "Developing Tests for Bcr-Abl Activity and Gleevec Resistance in CML Patients"

- **Jan E. Schnitzer, M.D.**
  Scientific Director, Sidney Kimmel Cancer Center
  "Proteomic Mapping of Blood Vessel Surfaces and Caveolae In Vivo to Improve Antibody Penetration, Imaging and Therapy of Solid Tumors "

IMAT Mission and Goals

Mission:

To develop and apply new technologies that transform researchers' abilities to identify molecular changes that distinguish pre-cancerous and cancerous cells from normal cells.

Goals:

- To focus innovative technology development on cancer
- To solicit highly innovative technology development projects from the scientific and medical communities
- To accelerate the maturation of meritorious technologies from feasibility to development and/or commercialization.

Why the IMAT Program Was Initiated

- **Established in 1998 to encourage highly innovative cancer technology development projects that:**
  - Address the complexity of cancer, including myriad molecular and cellular processes
  - Understand relevant genes and roles of nucleic acids, proteins, and other cellular factors and modifications
- **Provides novel mechanisms, program, and review structures to:**
  - Support innovative cancer-relevant technology from inception
  - Support development of novel applications of those technologies that uniquely enable cancer biology research by R01 investigators
- **Ensures that resulting technologies are robust and appropriate for intended applications in basic, preclinical, and clinical settings**

Attributes of the IMAT Program

- **High-risk, high-impact**
- **Emphasis on technology development vs. hypothesis-driven research**
- **Milestone-based, with milestones that address quantitative measures of specificity, sensitivity, speed, and other performance parameters**
- **Staged process requiring quantitative evidence of progress before advancing to next stage**
- **Some IMAT funding opportunities directed at small businesses under SBIR and STTR; since inception, ~ 1/4 of applications and ~ 1/3 of awards for small businesses**

Life Cycle of an IMAT Technology Development Project

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Projects are staged from:

R21/Phase I

Mechanism:

Exploratory/pilot phase; requires innovative technology/approach; no preliminary data required

Requirements:

- Description of study
- Relevance to cancer
- Quantitative milestones
- Novel research tool, new detection methodology, or treatment technology
- Improvement over state-of-the-art

R33/Phase II

Mechanism:

Developmental phase; requires feasibility data

Requirements:

- Plan for developing the technology
- Description of potential impact
- Description of completed milestones or evidence of technical feasibility

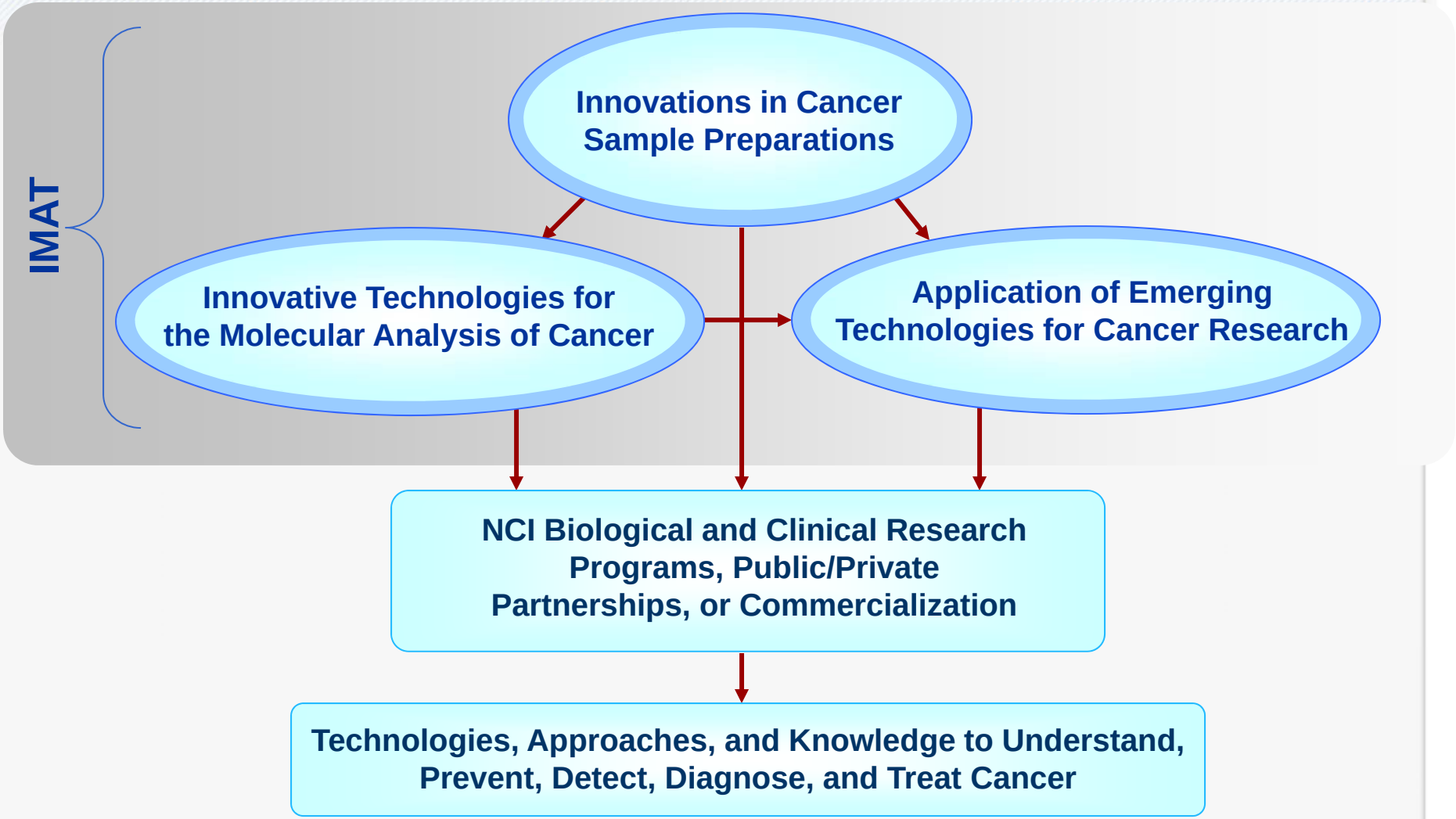
Technology Dissemination via:

- NCI Programs and Initiatives
- Collaboration
- Publication
- Licensing
- Commercialization

Technology Tools for Researchers:

- Gene expression arrays
- Clinical specimen preservation
- Ultra-high-throughput molecular detection
- Multi-dimensional protein identification
- Photo-stable labels

IMAT Development Pathway



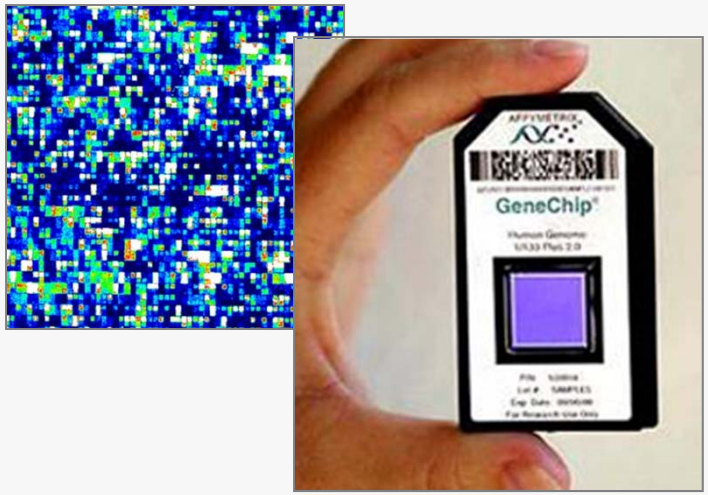
IMAT Review Process

- **Focus on technology development vs. hypothesis-driven research**
- **Milestones reviewed and improvements recommended**
- **Focus on whether technology is an improvement over state-of-the-art**
- **Review continuity by using previous IMAT panel members and IMAT grantees**

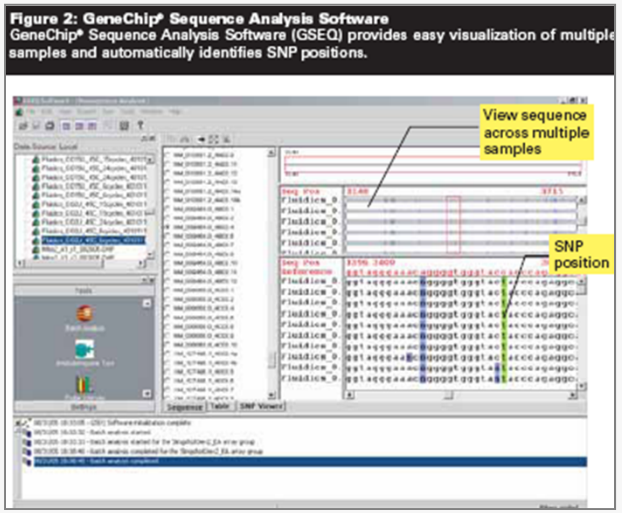
Case Studies

Jonathan D. Oliner, Ph.D., *Affymetrix*

- **IMAT Award:** Reverse-Engineering Signal Transduction Networks *(1998)*
- **Impact:** Gene expression arrays allow researchers to follow the downstream effects of perturbations to biochemical pathways or networks by highlighting changes in gene expression



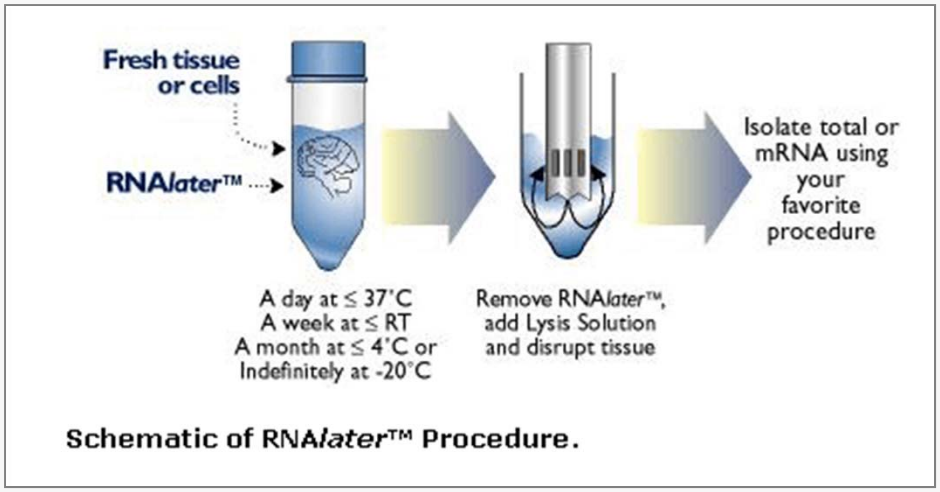
GeneChip® CustomSeq® Resequencing Arrays



Case Studies

Gary Latham, Ph.D., *Ambion, Inc.*

- **IMAT Award:** Enzymatic Tools for Degrading Tissue and Preserving RNA *(2001)*
- **Impact:** Researchers can store tissue samples without significant loss of RNA integrity

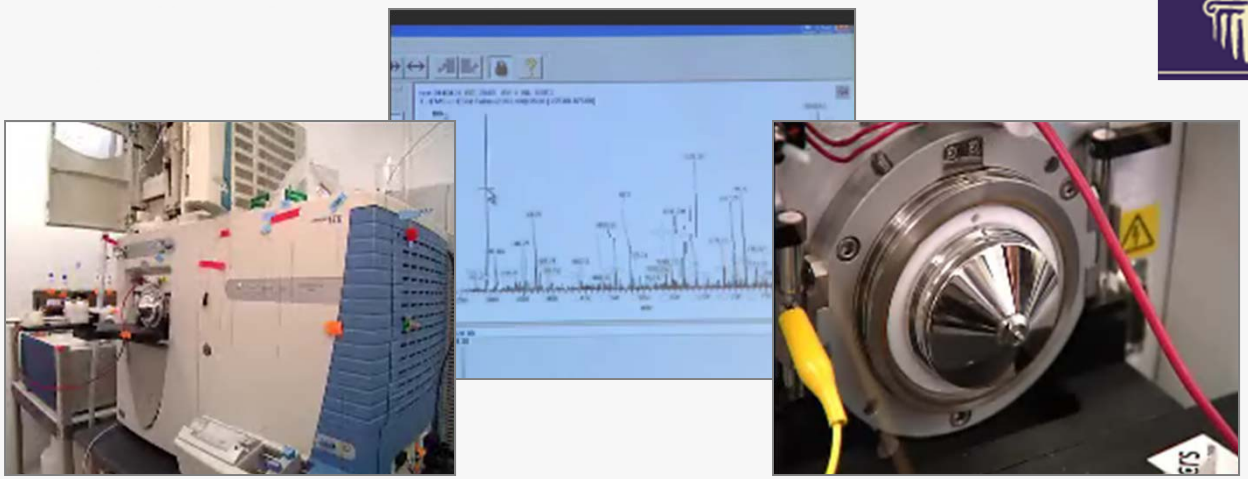


Schematic of RNA*later*™ Procedure.

Case Studies

John R. Yates, Ph.D., *University of Washington/Scripps*

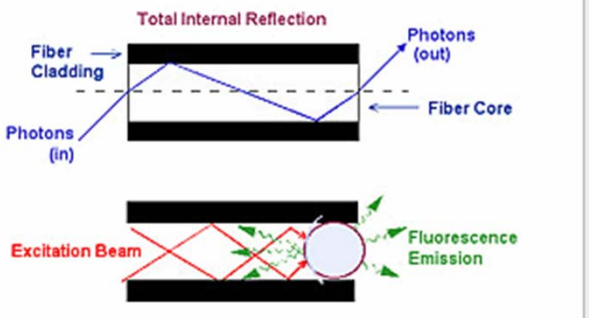
- **IMAT Award:** Direct MS Analysis of Complex Protein Mixtures *(1999)*
- **Impact:** The MudPit (multi-dimensional protein identification technology) platform marks the transition from traditional 2-D gel electrophoresis to 2-D liquid chromatography



Case Studies

Mark Chee, Ph.D., *Illumina, Inc.*

- **IMAT Awards:**
  - Gene Expression Analysis on Randomly Ordered DNA Arrays *(1998)*
  - Parallel Array Processor *(1998)*
  - Protein Profiling Arrays *(1999)*
- **Impact:** The ultra-high-throughput Illumina bead platform allows researchers to simultaneously assay over 100,000 points for gene expression, alternative splice detection, and protein expression



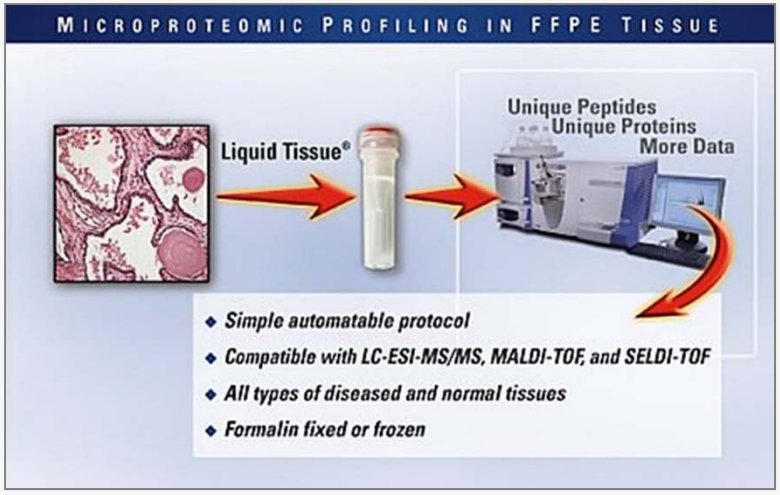
Individual fibers conduct light to enable data acquisition and quantitation of signal emitted by each bead.


Illumina's BeadStation 500 enables you to process Sentrix® Arrays at high resolution.

Case Studies

Dave Krizman, Ph.D., *Expression Pathology*

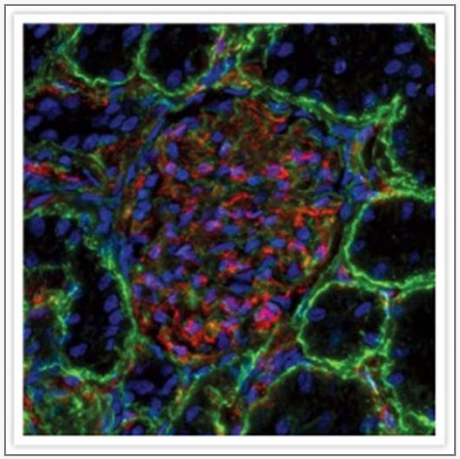
- **IMAT Award:** Protein Arrays for Molecular Analysis of Cancer Tissue *(2002)*
- **Impact:** New technology that permits effective, high-throughput discovery and analysis of protein biomarkers in formalin fixed paraffin embedded (FFPE) tissue

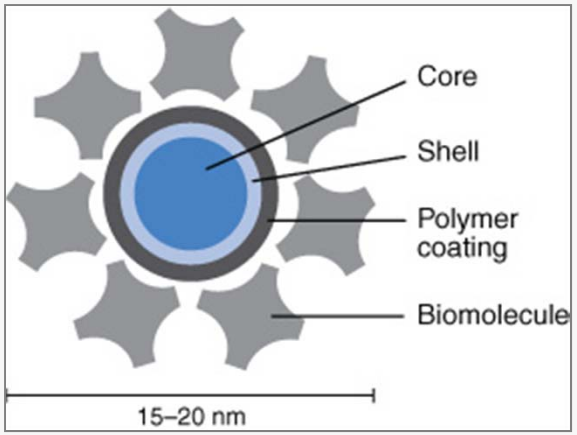


Case Studies

Robert H. Daniels, Ph.D., *Quantum Dot Corp. (Invitrogen)*

- **IMAT Award:** Sensitive, Multiplexed Analysis of Breast Cancer Markers *(1999)*
- **Impact:** Quantum dots (semi-conductor nanocrystals) are photostable labels that emit extremely bright light in a range of colors enabling researchers to monitor complex interactions within living cells or *in situ* on tissue microarrays





Next-Generation Technology: Overcoming Technical Barriers to Research Productivity

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Nucleic Acid

- Micro RNAs
- RNAi
- Epigenomics
- Alternative Splicing
- Genomic Regulatory Factors
- Mutation Detection

Protein

- Localization
- Fractionation and Quantitation
- Identification of Low Abundance and Transient Proteins
- Small Molecule Interactions
- Protein/Protein Interactions
- Structure/Function Modifications

Paradigm Shift

- Increased Sensitivity
- Improved Labeling Tools
- Increased Throughput
- Reduced Cost
- More Quantitative
- Single Molecule/Cell
- Reduced Sample Size
- Rare Entity Isolation
- Parallel Processing

Molecular Interactions

- Pathways and Networks
- Transient Complexes
- Real-time Macro Molecular Interactions
- Metabolite Detection/Quantification

Molecular Device/Chemistry

- Nanotechnology
- Microfluidics
- Surface Chemistries
- Sensors
- Platform Integration

Program Management Team

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Program Managers:

- Office of Technology and Industrial Relations:
  Greg Downing, D.O., Ph.D., *Program Director*
  Richard Aragon, Ph.D., *Project Manager*
- Division of Cancer Biology:
  Jennifer Couch, Ph.D.
  J. Randy Knowlton, Ph.D.
- Division of Cancer Prevention:
  Paul Wagner, Ph.D.
  Sudhir Srivastava, Ph.D., M.P.H.
- Division of Cancer Treatment and Diagnosis:
  Jim Jacobson, Ph.D.
  Rebecca Huppi, Ph.D.
  Avraham Rasooly, Ph.D.
- Division of Cancer Control and Population Sciences:
  Carol Kasten, M.D.

http://imat.cancer.gov