NCI Innovative Molecular Analysis Technologies (IMAT) Program

Carolyn Compton, MD, PhD
Acting Director

12th Annual Principle Investigator's Retreat
Rockville, MD
November 14, 2011

NATIONAL CANCER INSTITUTE

Program Updates

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- **IMAT RFA Renewed!**
  - ➔ Hoping to announce receipt dates for new applications and resubmissions in early 2012
- **New central coordinator**
  - ➔ Tony Dickherber, PhD
  - ➔ Seeking advice on improving outcomes for IMAT program and its investigators
- **Collaborations available with the NCI Cancer Human Biobank (caHUB) for biospecimen science and platform validation**

Key Objectives of the PI Retreat

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1. **Progress updates and face-to-face time for program staff with PIs**
   - ➔ IMAT program goal is to assist in dissemination of supported technology development
   - ➔ Evolving NCI priorities require greater efforts in keeping up with your progress, generally

2. **Catalyzing new innovative ideas and opportunities for potentially transformative collaboration**
   - ➔ Many new awards for IMAT are granted out of novel collaborations among existing IMAT investigators
   - ➔ IMAT PI's are a unique network of highly innovative investigators

Sparking Novel Transformative Ideas: Our Own Provocative Questions Exercise?

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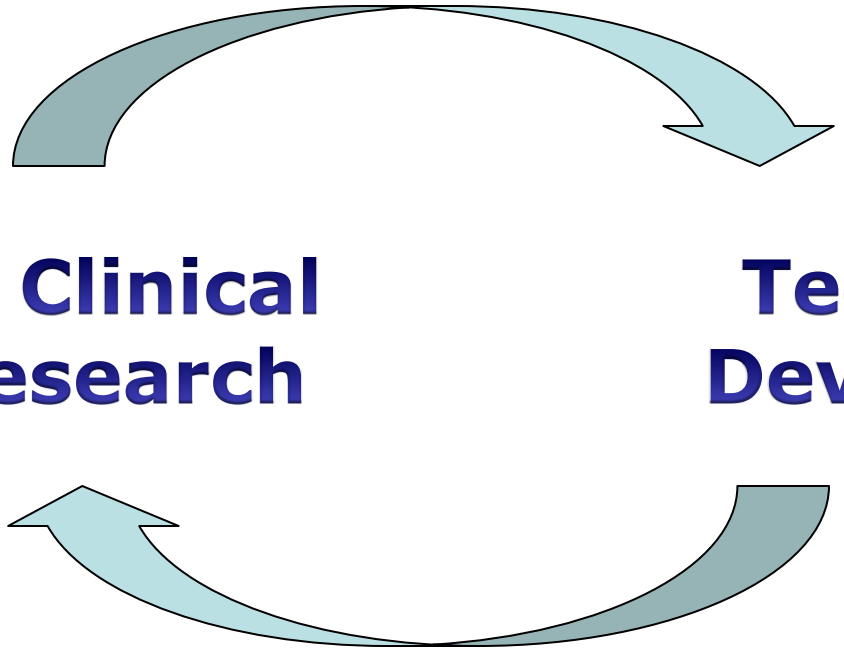

http://provocativequestions.nci.nih.gov/

PQ9: Can we identify mutations most critical to maintenance of oncogenic phenotype?

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- **What is the relationship between low frequency mutations and "driver" mutations? How to determine which mutations have key roles in tumor development?**
  - ➔ Can we establish methods that will determine which changes are important for tumor development and use these methods to study the functional roles of these mutations?
  - ➔ Appropriate mutation analyses will provide an important set of RNA and protein targets for therapy and yield key insights to cancer etiology

- **Technology opportunity:**
  - ➔ Tools to elucidate the relationship between individual and pathway-related mutations and tumor development
  - ➔ Tools to track order of mutation development and corresponding metastatic potential in models

PQ11: How do changes in RNA processing contribute to tumor development?

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- **Large number of unexpected tumor-specific alternative splicing and other changes in RNA processing events.**
  - ➔ Presumably some of the selected splicing events are beneficial for tumor development, but functional significance of these is poorly understood.
  - ➔ Other changes in RNA processing may alter protein levels or lead to changes in regulatory RNA molecules

- **Technology development opportunities:**
  - ➔ Tools to measure RNA regulation *en masse* and *in situ*?
  - ➔ Tools to monitor activity of protein products of targeted RNA transcripts

PQ14. Are there properties of benign lesions that predict invasive or metastatic disease?

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- **Not all cancers detected early are worth treating**
  - ➔ Genomic and proteomic technologies, coupled with microenvironment analysis, are capable of genotyping and phenotyping small collections of cells well, but remain limited in ability to assess the full tumor and deal with heterogeneity

- **Technology development opportunities:**
  - ➔ Tools that allow us to more effectively identify key differences between cell types, like non-malignant versus malignant cells in the same tissue type
  - ➔ Tools to characterize metastatic potential based on a multi-parameter screening assessment across larger volumes of tissue

PQ – 20 Can biomarkers or signatures be identified as predictors or surrogates of therapeutic efficacy for immunotherapy?

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- **There is increasing excitement about the use of immunotherapies in the treatment of cancer, but means of predicting or measuring efficacy are few.**
  - ➔ Sophistication of the immunology field may provide a particular advantage in the search for surrogates for therapeutic efficacy, and based on knowledge of immune responses, there may be clever approaches to identify useful markers.
  - ➔ The search for predictors of therapeutic efficacy also may rely on advances in molecular profiling.

- **Technology development opportunity**
  - ➔ Tools to facilitate the search for surrogate markers that predict or track immunotherapy efficacy

Direct Technology Development Targets from the PQs

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- **PQ 3. Are there ways to objectively ascertain exposure to cancer risk using modern measurement technologies?**
- **PQ17. Since current methods to assess potential cancer treatments are cumbersome, expensive, and often inaccurate, can we develop other methods to rapidly test interventions for cancer treatment or prevention?**
- **PQ18. Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?**
- **PQ24. Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?**

Technology Development
Provocative Questions Exercise

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- **Given the recent reassessment by the NCI leadership of priorities for scientific inquiry, are there fields in which technology development has yet to be applied?**
  - ➔ Mechanisms of metastases
    - Cell migration potential and pathways for migration (think CTCs, cancer stem cells, circulating tumor cell conglomerates vs. individual cells, epithelial-mesenchymal transformation)
    - Cancer cell physics (structural phenotyping and cell mechanics)
  - ➔ Biospecimen science
    - Fit-for-purpose sample processing and preservation
    - Quality assessment tools for targeted analytes
  - ➔ Biomarker science
  - ➔ “Missed” areas of proteomics and genomics?
  - ➔ Novel parameters for high-content screening platforms?

NCI caHUB Collaborative Agreements

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- **The NCI Cancer Human Biobank – a national center for biospecimen science and standards**
  - ➔ Goal: Investigate the impact of procedural and environmental variables on the quality of human biospecimens and data prior to downstream molecular analysis on various platforms (pre-analytical variation)
  - ➔ Seeking collaborative experimental design proposals that would result in evidence-based Standard Operating Procedures (SOPs)
  - ➔ Value proposition for IMAT investigators:
    - NCI is able to collect fit-for-purpose biospecimens and data of established quality according to strict SOPs to support technology development
    - NCI is able to collect specimens sets with systematically embedded pre-analytical variation for assessment by various molecular analysis platforms to determine required biospecimen quality

Assessing the Need for Biospecimen Science

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- Pre-analytical variation introduced during the process of collection, processing and storage of biospecimens can markedly skew the results of molecular analysis.
- Rigorous and sufficiently powered research studies are needed to understand the critical steps for standardization – and the caveats we accept when utilizing different SOPs.
- Opportunity to improve the accuracy of research and clinical data
- An issue for all of R&D --- and patients.

Understanding the Biology of Biospecimens: The Goal of Biospecimen Science

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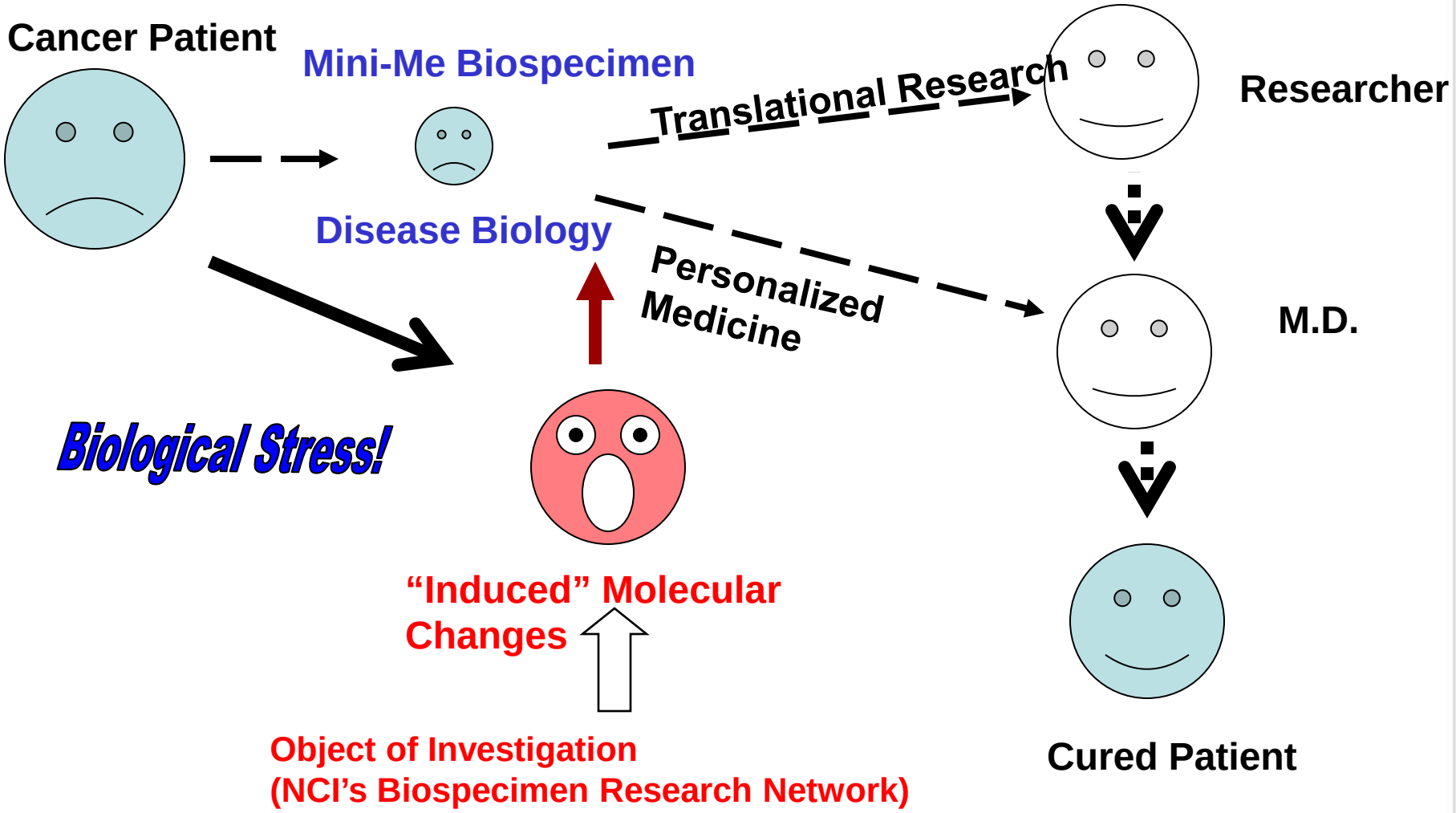

Biospecimen Lifecycle: Pre-analytical Factors Affect Molecular Composition and Integrity

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Specimen is viable and biologically reactive

Factors (examples):

- Antibiotics
- Other drugs
- Type of anesthesia
- Duration of anesthesia
- Arterial clamp time

Time 0

Molecular composition subject to further alteration/degradation

Factors (examples):

- Time at room temperature
- Temperature of room
- Type of fixative
- Time in fixative
- Rate of freezing
- Size of aliquots

Patient | Medical/ Surgical Procedures | Acquisition | Handling / Processing | Storage | Distribution | Scientific Analysis | Restocking Unused Sample

Pre-acquisition **Post-acquisition**

A Fit-for-Purpose Framework for Biospecimen Science

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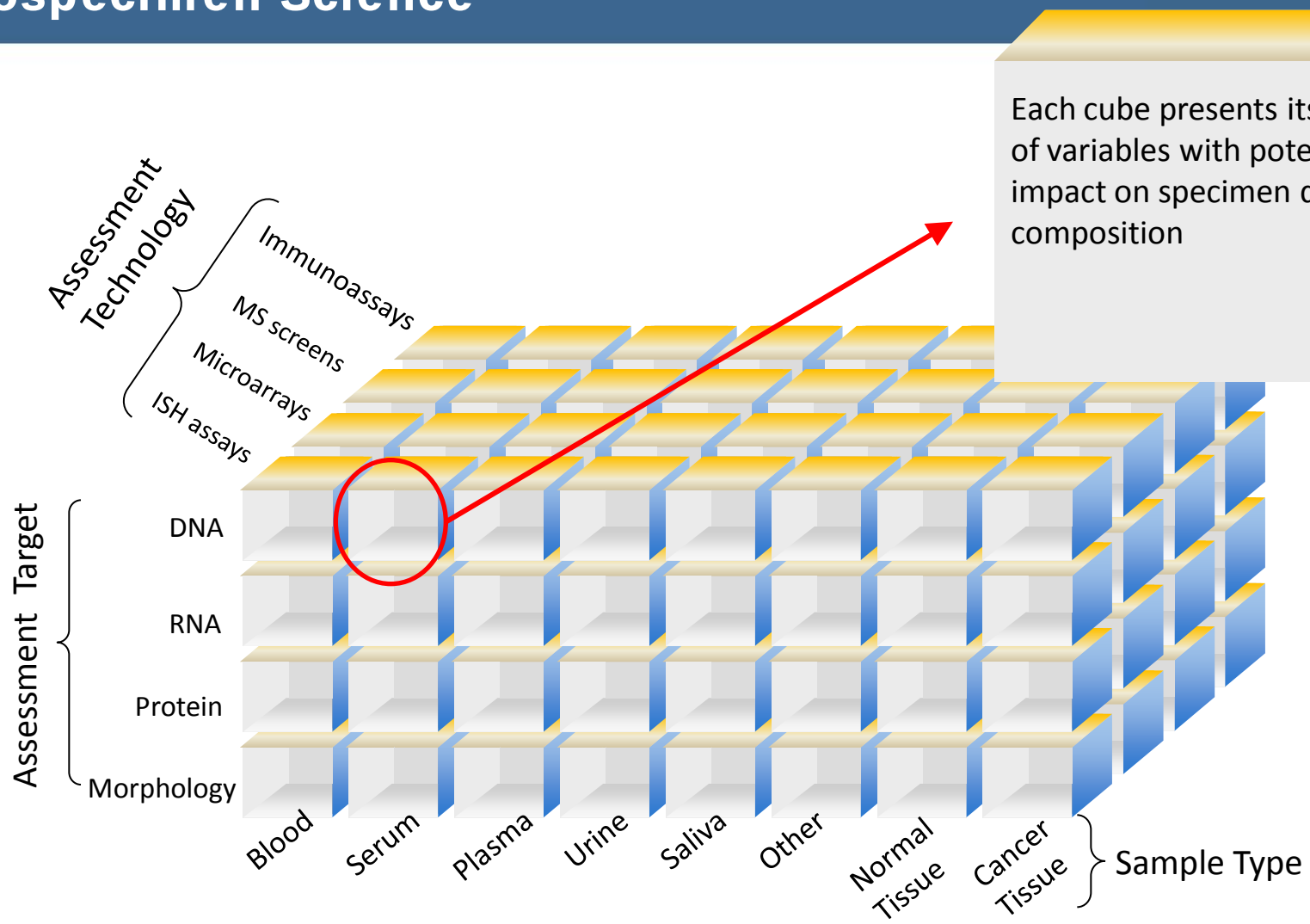


Defining Cubes

- ❑ **Specimen type: Plasma**
- ❑ **Molecule class: Protein**
- ❑ **Analysis platform: spec**

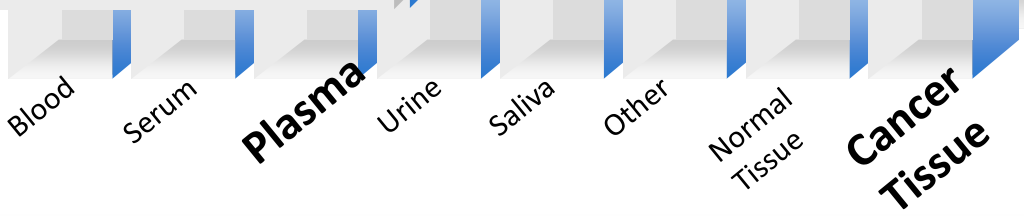
Pre-acquisition factors:
- Needle bore size
- Drugs administered
- Tourniquet time

Post-acquisition factors :
- Collection tube type
- Storage temperature
- Storage duration

- ❑ **Specimen type: Breast cancer tissue**
- ❑ **Molecule class: RNA**
- ❑ **Analysis platform: Affy Chips**

Pre-acquisition factors :
- Type of anesthesia
- Resection method

Post-acquisition factors :
- Time at room temperature before stabilization
- Type of fixative
- Time in fixative
- Rate of freezing



Biospecimens and the Molecular Diagnostic Development Pipeline

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Marker discovery → **Assay Development** → **Assay Validation** → **Clinical Trials**

SPECIMEN VARIABILITY

- Failure to control collection and processing variables
- Lack of evidence supporting biobanking practices
- Inadequate quality control metrics for biospecimens
- Failure to prioritize collection in pathology work flow

LOGISTICAL BARRIERS

- Matched samples unavailable
- Metastatic tumor tissue unavailable
- Clinical practice complicates/precludes tissue collection
- Informed consent standards inconsistent
- Lack of financial support for specimen collection

Differential analyte stability

Fewer samples available for R&D

Specimens of poor quality

Specimens that do not represent biology

Sample bias

THEN YOU CANNOT…

Identify biomarkers

Develop and validate assays

Perform bridging studies / Compare existing studies

Accrue meaningful samples during clinical trials

Perform retrospective studies use samples from clinical trials

Meet requirements for regulatory approval

Biospecimen Science Needs Technology Tools

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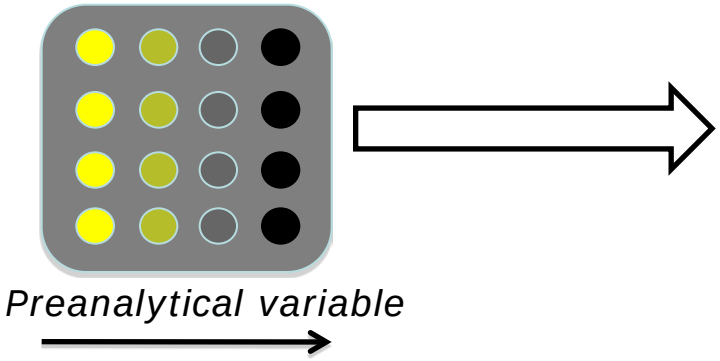

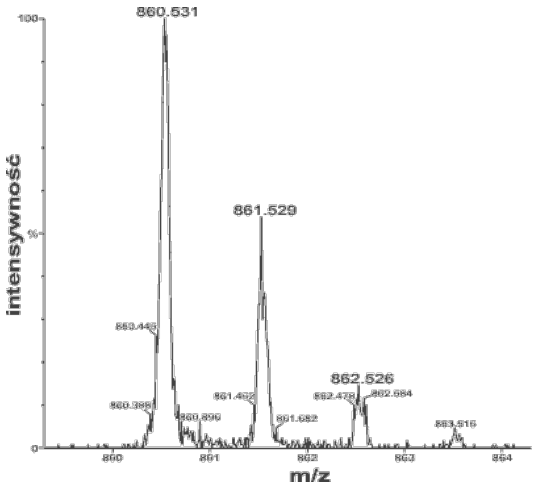

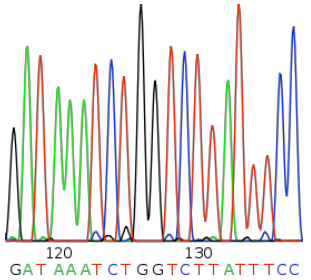

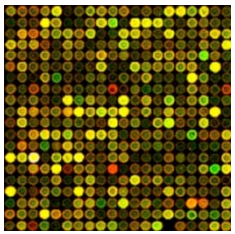

- What happens to known analytes as pre-analytical factors are varied?
- Is there a molecular signature that identifies particular sample handling variables?
- Is there a molecular signature that can provide a read-out of biospecimen quality?

Arnold Beckman: Beckman Instruments, Inc.

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“ I have done more for science in general by making instruments available for thousands to use than what I could do in my own laboratory by myself.”

Arnold Beckman: Beckman Instruments, Inc.

“ Inventors, by and large, are a bit goofy.”

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National Biospecimen Resource: caHUB

OBBR Office of Biorepositories and Biospecimen Research

A unique, centralized, non-profit resource that will provide high-quality well-annotated human biospecimens in support of biospecimen research.

- **High-quality** samples and associated data
- **Prospective** scientific design of collection strategies
- **Standardized** processing and annotation of all specimens
- **Centralized** operations for QC, pathology analysis, storage
- **Transparent** access policies
- **Cutting-edge**: leadership for biospecimen resources (biobanking tools, biospecimen science, training and education)