Developing Common Biorepository Infrastructures

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IOM Workshop:
Developing Precompetitive Collaborations to Stimulate Genomics-Driven Drug Development
Washington, DC
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Getting to Personalized Medicine

Molecular Data → Biospecimen Collection → Biospecimen Processing and Banking → Quality Here → Personalized Cancer Care → Diagnosis / Therapy

Translational Research

Determines Quality Here

Quality Here

Office of Biorepositories and Biospecimen Research (OBBR)
The Demand for High Quality Human Specimens

Identification of targets for drug development, treatment and prevention

Elucidation of molecular mechanisms of neoplasia

Development and validation of new therapeutics

Development and validation of new diagnostics

Defining markers for susceptibility, screening and reoccurrence

Identify biologic variations that determine drug efficacy and drug toxicity

All Depend On High-Quality, Annotated Human Biospecimens
Quality Data Begins with Quality Analytes

Garbage in...

Diamonds in......

...Garbage out

Modified from Jerry Thomas
High-Quality Specimens Are Needed

The lack of high-quality, clinically annotated human specimens is the #1 limiting factor for translational cancer research.
Libraries of Flesh: The Sorry State of Human Tissue Storage

By Steve Silberman  May 24, 2010 | 12:00 pm | Wired June 2010

Of all the forms of woe that root in the human genome, the cancer called Glioblastoma multiforme is one of the most merciless. It can infiltrate the brain’s white matter for months before causing any symptoms. By the time memory loss and seizures reveal the presence of an invader, there’s often little to do but minimize the patient’s suffering. Most who are diagnosed with the disease—people like the late senator Edward Kennedy—are dead within two years.
The Question Is Not Just…

.... can I get existing biospecimens, but do I want them???

• Key Issues:
  • What is the quality/consistency of available samples data?
  • Do we even have the “yardstick of truth” by which to benchmark existing samples??

Sharing specimens and data of unknown, low, or variable quality is unlikely to accelerate progress.
Why Is It Difficult to Acquire High-Quality Human Biospecimens and Associated Data?

- Collection, procession, storage procedures differ
- Degree and type of data annotation varies
- Scope and type of patient consent differs
- Materials transfer agreement conditions differ
- Supporting IT structures differ in capacity and functionality
- Access policies are lacking or unknown to potential users

→ WIDE VARIATION IN QUALITY AND ACCESSIBILITY OF SPECIMENS AND DATA
Lessons Learned at the NCI in Acquiring Biospecimens For Strategic Initiatives (e.g., The Cancer Genome Atlas)

- Quality of existing samples is typically overestimated by biobanks
- Collection of normal control samples is not routine
- Clinical data on specimen donors is not readily available
- Histological quality does not guarantee molecular quality
- Other important factors that challenge the scientific project:
  - Consent, IRB, privacy law (HIPAA) issues
  - Material transfer agreement, intellectual property, authorship issues
  - Informatics issues (that make data access and sharing problematic)
    - Lack of compliance with IT standards
  - Costs
Stepwise Approach:

• Standards
  • The NCI’s Best Practices for Biospecimen Resources

• Biospecimen Science
  • NCI’s Biospecimen Research Network

• Specimens and Service
  • The Cancer Human Biobank
NCI’s Best Practices for Biospecimen Resources: Rules of the Road

- State-of-the-science baseline for operating standards on which to build as the state of the science evolves
- Unifying policies and procedures for biospecimen resources across the USA
- Web version 2009 capabilities:
  - Hyperlinks to outside resources and references
  - Internal links between various sections
  - Search functionality
- First step to improve the quality of human biospecimens used in cancer research
- Updated in 2009-10; release to Federal Register July 2010
NCI Best Practices include recommendations for:

- Technical, operational and safety best practices
- Quality assurance, quality control and quality management programs
- Implementation of enabling informatics systems
- Addressing ethical, legal, and policy issues
- Establishing reporting mechanisms
- Providing administration and management structure
- Defining of key terms
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Understanding the Biology of Biospecimens: The Goal of Biospecimen Science

Cancer Patient → Mini-Me Biospecimen → Disease Biology → Translational Research → Researcher

"Induced" Molecular Changes → Object of Investigation (NCI’s Biospecimen Research Programs) → Cured Patient

Biological Stress!

Personalized Medicine
Pre-analytical Variables Can Affect Molecular Composition and Integrity

Variables (examples):
- Antibiotics
- Other drugs
- Type of anesthesia
- Duration of anesthesia
- Arterial clamp time

Time 0

Variables (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
Intrasurgical Ischemia (Time from Artery Ligation to Tumor Resection)
Affects Gene Expression In Colon Cancer

Indivumed-NCI Study
Ischemia regulated genes c-fos, HIF-alpha and HO-1

Tissue ischemia and gene expression profiling
(Comparison Affymetrix data and real-time RT-PCR)

Sprüssel et al, BioTechniques 2004
Common colorectal tumor markers *CEA* and cytokeratin *CK20*

**Tissue ischemia and gene expression profiling**
*(Comparison Affymetrix data and real-time RT-PCR)*

Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg
Phosphoprotein Expression and Postsurgical Ischemia:
pMAPK Immunostaining (Ventana)

<table>
<thead>
<tr>
<th></th>
<th>Case A</th>
<th>Case B</th>
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<tbody>
<tr>
<td>10 min</td>
<td><img src="10_min_case_a" alt="Image" /></td>
<td><img src="10_min_case_b" alt="Image" /></td>
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<tr>
<td>20 min</td>
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<td><img src="20_min_case_b" alt="Image" /></td>
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<tr>
<td>60 min</td>
<td><img src="60_min_case_a" alt="Image" /></td>
<td><img src="60_min_case_b" alt="Image" /></td>
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</tbody>
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Change of pMAPK expression after 10-20 min cold ischemia

Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg
# Plasma Biomarkers: Collection Protocol

## Variations with Known Effects on Analyte Assays

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venipuncture</td>
<td>Needle gauge, Priming volumes</td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>Patient position (seated /reclining), Tourniquet time, Tube orders, Venipuncture sites</td>
</tr>
<tr>
<td>Collection device</td>
<td>Tube types</td>
</tr>
<tr>
<td>Blood derivatives and processing</td>
<td>Anticoagulant types, Temperatures, Centrifugation speeds, Processing time</td>
</tr>
<tr>
<td>Time between collection and storage</td>
<td>Variable or unknown times</td>
</tr>
<tr>
<td>Storage and shipping</td>
<td>Temperature, Duration</td>
</tr>
</tbody>
</table>
How Can Changes in Biospecimens Affect Molecular Readout?

<table>
<thead>
<tr>
<th>Genomics</th>
<th>Proteomics</th>
<th>Metabolomics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in specific transcript levels based on handling variables, not disease</td>
<td>Lack of reproducibility of protein biomarkers in discovery research</td>
<td>Inconsistencies in small molecule readouts that may point to the wrong pathways</td>
</tr>
<tr>
<td>Changes in RNA levels with frozen storage time or freeze-thaw cycles</td>
<td>Inconsistent IHC results in research and clinical labs</td>
<td></td>
</tr>
</tbody>
</table>
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Providing Resources for the Research Community: The Cancer Human Biobank (caHUB)

The vision:

- unique, centralized, non-profit public resource
- source of adequate and continuous supplies of human biospecimens and associated data of *measurable, high quality* acquired within an ethical framework
- source of high-quality biobanking services for the community
caHUB Key Concepts

- Scientifically designed collection strategies (including rare diseases)
- Multiple aliquots of every specimen
- Standardized, annotated collection, processing of all specimens
- Centralized QC and pathology analysis of every specimen
- Rich, standardized data profile for each sample
- Centralized source of normal human specimens
- Provision of tools, resources, training for biospecimen resources
caHUB Collection Design: Informed by User Need

In high demand and short supply:

- Benchmark samples
  - Collected through standardized methods with strict QC and metrics
  - Data associated with process variables
- Cases with multiple aliquots
  - Confirmation of prior studies
  - Opportunity to extend prior studies based on new technologies / analyses
- Statistically valid numbers of biospecimen sets
- Fully defined “patient case sets”
  - Tumor
  - Adjacent normal tissue
  - Tumor periphery (invasive border)
  - Pre- and post operative blood samples
  - Urine
  - Rich clinical data and outcome information for patients
- Non-surgical samples: normal tissues; metastases; pre-malignancy
caHUB: High-Quality Specimens and Data from Patients Who Receive High-Quality Care

Centralized Resource: Cost and Quality Control Efficiencies

- NCDB
- Tumor Specimens and Data from Patients in COC-Approved Institutions
- Normal Specimens and Data from Rapid Autopsy and OPO Programs

caHUB
High Quality Specimens
High Quality Data
From patients who receive High Quality Care

National Biospecimen Resource
BioSpecimen Access
Pathology Reference
Training & Education
Consulting Services

- NCI / NIH
- Other Government
- Academia
- Advocacy
- Industry

caBIG®
The caHUB as a Resource for Users

- Data available through the system:
  - Specimen type, amount, diagnosis, pathological characteristics, macro- and microscopic appearance
  - Collection, processing, storage, distribution
  - Quality control metrics
  - Clinical information about patient at multiple time-points
  - Molecular analysis results from different platforms

- The comprehensive data base may, with maturation over time, become more useful to the scientific community than the specimens themselves (in silico research)

- caHUB’s policies and procedures will be publicly available and may serve as standards for the biobanking community
Products for Patients: Developing Drugs with High-Quality Biospecimens

- Analysis of Molecular Features: Hypothesis Generation
- Demonstration of Linkage: Marker of Disease/Disease Feature
- Biomarker Validation
  
  **Milestone: Confirmation of Disease Biomarker**
- Product Development
  - Diagnostic test (clinical, pathologic)
  - Therapeutic drug
  - Molecular imaging tool
- Product Validation

Any association with specific features: subtype, stage, grade, outcome?

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**Investment of time and money**
Developing Drugs with Biospecimens of Unknown Quality

- Analysis of Molecular Features
- Identification: Marker of Disease/Disease Feature
- Biomarker Validation
  - Milestone: Confirmation of Disease Biomarker
- Product Development
  - Diagnostic test (clinical, pathologic)
  - Therapeutic drug
  - Molecular imaging tool
- Product Validation

CANNOT REPRODUCE ORIGINAL RESULTS

Investment of time and money

STOP

Pre-analytical artifact? Incorrect identification? Incorrect characterization? Poor product design?

DO NOT ENTER
“If you don’t have the time (or money) to do it right, when will you have the time (money) to do it over?”

- John Wooden, Coach Extraordinaire
Standards Are Required If Biospecimen Sharing Is to Enable Success

1. What are the unique issues in sharing biospecimens (and data) that need to be considered in a sharing framework?

   Standards are lacking that ensure comparability and fitness for specific use.
   New types of data (about the specimen) are required.

2. What have you learned from your initiative that could be used to define 'best practices' for specimen and data sharing?

   Best practices need to be data-driven and standardized but are not.

3. What should motivate industry stakeholders to share specimens and data with each other and with the broader investigator community?

   Positive: huge opportunity for exposing unfit samples, promoting quality samples and increasing product development efficiency
   Negative: things will stay the same -$1.2 billion and 10 years per drug

4. What incentives should or need to be in place to encourage sharing of biospecimens and data?

   Government requirement to do so if public funds contribute to creation of either/both.

5. What key structures and/or rules do you think are required for a framework of sharing biospecimens and data?

   A national biobank that can set the standards (with FDA and NIST) and supply benchmark samples for QA of specimens from any source
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