Biospecimens: The Key to the Research that Leads to the Cure

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Translational Research Promises to Realize the Vision of Personalized Medicine

Molecular Data → Diagnosis / Therapy

PERSONALIZED CANCER CARE

Biospecimen Analysis → Biospecimen Collection

Biospecimen Processing and Banking
The Personalized Medicine Universe

Personalized Medicine: Individualized Medical Management Based on the Specific Biology of the Patient and His/Her Disease

> 1000 different genomic changes in various combination may be involved

= Each patient differs with respect to the molecular character of his/her cancer

Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg
Today

Tumor 1  Tumor 2  Tumor 3

Standard Therapy

Future

Tumor 1  Tumor 2  Tumor 3

More effective
Less toxic
Less costly

Molecular diagnosis

Therapy 1  Therapy 2  Therapy 3

In 2001, only one of three patients benefited from cancer drug treatment (Spear et al. (2001) Trends Molec. Med. 7, 201-203)

Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg

Biospecimens and Personalized Medicine

• Biospecimens are the basis of:
  – Molecular characterization of the disease
    • Molecular classification of tumor
    • Characterization of tumor heterogeneity/therapeutic targets
  – Molecular characterization of the host
    • Disease susceptibility
    • Treatment efficacy (e.g., pharmacogenomics)
  – Personalized medicine will depend on accurate, reproducible data derived from patient samples in the clinical setting
Biospecimen Quality Impacts Clinical and Research Outcomes

- **Effects on Clinical Outcomes**
  - Potential for incorrect diagnosis
    - Morphological/immunostaining artifact
    - Skewed clinical chemistry results
  - Potential for incorrect treatment
    - Therapy linked to a diagnostic test on a biospecimen (e.g., HER2 in breast cancer)
- **Effects on Research Outcomes**
  - Irreproducible results
    - Variations in gene expression data
    - Variations in post-translational modification data
  - Misinterpretation of artifacts as biomarkers

Powerful Tools: Powerful Risks

- The technological capacity exists to produce low-quality data from low-quality analytes with unprecedented efficiency
- We now have the ability to get the wrong answers with unprecedented speed
- Unraveling the massive matrix of misleading data is compromising progress in unprecedented ways
An Inconvenient Truth.....

Garbage in...

Diamonds in......

...Garbage out

Modified from Jerry Thomas

Market Research Conducted for OBBR by NCI’s Office of Market Research and Evaluation

<table>
<thead>
<tr>
<th>Methods</th>
<th>Time Frame</th>
<th>Respondents</th>
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</thead>
<tbody>
<tr>
<td>In-depth Interviews</td>
<td>July/August 2008</td>
<td>22 (30 invited)</td>
</tr>
<tr>
<td>Online Survey</td>
<td>October 2008</td>
<td>727 (~5000 invited)</td>
</tr>
</tbody>
</table>

Types of Respondents
- Academia, NCI grantees (the majority of respondents)
- Federal agencies (NCI, NIH, other)
- Cancer/clinical centers
- Foundations and advocacy groups
- Industry (pharma, biotechnology)

Themes of Questions
- Need for quality biospecimens
- Barriers to access
- Consequences of poor access to quality specimens
- Response to the concept of a central biorepository resource
Initial Survey Findings: Researchers Are Working in Silos

What percentage of your biospecimens come from each of these sources?

<table>
<thead>
<tr>
<th>Source</th>
<th>% Get any from source</th>
<th>Mean % from each</th>
</tr>
</thead>
<tbody>
<tr>
<td>My patients/volunteers</td>
<td>42%</td>
<td>25%</td>
</tr>
<tr>
<td>Other patients in my org</td>
<td>55%</td>
<td>31%</td>
</tr>
<tr>
<td>Other research institutions</td>
<td>41%</td>
<td>17%</td>
</tr>
<tr>
<td>Other medical care facilities</td>
<td>23%</td>
<td>8%</td>
</tr>
<tr>
<td>Commercial U.S. biobank</td>
<td>18%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-profit biobank</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>NCI CHTN</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Sources outside the U.S.</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Other sources</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

• Collaborative agreements are not widespread
  55% None/Few (0-25%)
  23% Some/Many (26-75%)
  22% Most/All (76-100%)

Can Investigators Get What They Need?

Ease of Acquiring the Quantity of Biospecimens Needed

- Very easy/Easy: 11%
- Somewhat easy: 20%
- Somewhat difficult: 31%
- Difficult/Very difficult: 39%

Ease of Acquiring the Quality of Biospecimens Needed

- Very easy/Easy: 8%
- Somewhat easy: 13%
- Somewhat difficult: 32%
- Difficult/Very difficult: 48%
Consequences for Investigators (and NCI): The Science Suffers

Question Their Data Because of the Quality of Biospecimens

- 40% 
- 40% 
- 20%

Limit Their Scope of Work Due to the Shortage of Quality Biospecimens

- 19% 
- 36% 
- 45%

Comments about Biospecimen Needs

- “While it remains an ideal goal at this point, I firmly believe that high quality specimens are required for all uses - mine specifically include: identification and validation of biomarkers, establishing clinical cut-offs for test values, establishing normative data for test values, determining predictive value of tests, validating test methods [new and modified], etc.”

- “We don’t know [if high-quality biospecimens are necessary or desirable] because we aren’t sure how variable our current specimens are and how much this is affecting our outcome.”

- “It would be great to always have ‘high quality biospecimens’, but we often have to make do with what we have.”

- “As basic researchers in a cancer center, we rely on others to obtain ANY samples, whether high quality or not. A centralized source for high-quality biospecimens (QA/QC SOPs established and monitored by NCI, for example) would be absolutely ideal.”
Why Is It Difficult to Acquire High-Quality Specimens and Data?

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

→ Wide variation in quality of specimens and data

Molecular Analysis and Human Analytes

Challenge for the NCI: Lack of standardization of human biospecimens compromises the quality and utility of molecular research dependent on them.

Consensus of the Broad Scientific Community: The lack of high-quality human specimens has become the limiting factor for post-genomic biomedical science.

- The #1 roadblock to translational research in cancer!!
NCI Best Practices for Biospecimen Resources: The State of the Science Guidebook

Objectives:

- Unify policies and procedures for NCI-supported biospecimen resources for cancer research
- Provide a baseline for operating standards on which to build as the state of the science evolves
- Update in progress: scheduled for completion December 2009

Parallel Challenge: Data-driven standard operating procedures

Understanding Biospecimens:
The Goal of Biospecimen Science

Cancer Patient → Mini-Me Biospecimen → Disease Biology → Real Biospecimen → Biological Stress! → Unique Biology! → Object of Investigation (NCI’s Biospecimen Research Programs)

Translational Research → Personalized Medicine → M.D. → Cured Patient

Researcher
Biospecimen Science

Time 0

Specimen is viable and biologically reactive
Molecular composition subject to further alteration/degradation

Patient Acquisition Handling/Processing Storage Distribution Scientific Analysis

Knowledge Base

Pre-acquisition Post-acquisition

Variables for Study

Pre-acquisition variables:
- Antibiotics
- Other drugs
- Type of anesthesia
- Duration of anesthesia
- Arterial clamp time
- Blood pressure variations
- Intra-op blood loss
- Intra-op blood administration
- Intra-op fluid administration
- Pre-existing medical conditions
- Patient gender

Post-acquisition variables:
- Time at room temperature
- Temperature of room
- Type of fixative
- Time in fixative
- Rate of freezing
- Size of aliquots
- Type of collection container
- Biomolecule extraction method
- Storage temperature
- Storage duration
- Storage in vacuum
Phosphoprotein Expression and Postsurgical Ischemia:
PpTyr100 Immunostaining (Ventana)

No clear trend of pTyr100 expression within 60 min of cold ischemia

Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg

Phosphoprotein Expression and Postsurgical Ischemia:
PpMAPK Immunostaining (Ventana)

Change of pMAPK expression after 10-20 min cold ischemia

Slide Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg
The Biospecimen Research Network: Supporting Collaborative Research

• Provide a forum for research results on how biospecimen variables affect molecular analysis:
  – The Biospecimen Research Database: Make existing and emerging biospecimen research data more accessible
  – Annual symposium: “Advancing Cancer Research through Biospecimen Science” March 16-19, 2009, MD

• Collaborate with other programs, e.g.:
  – Clinical Proteomics Technologies Assessment for Cancer (CPTAC)
  – The Cancer Genome Atlas (TCGA)

• Generate new research data:
  – IMAT Program – “Innovative and Applied Emerging Technologies in Biospecimen Science” (RFA)
  – New Extramural Research Programs

Biospecimen Research Network: Progress Report

- Extramural research program, "Biospecimen Research for Molecular Medicine"
  Program aims:
  (1) Develop innovative approaches to the control, monitoring and assessment of biospecimen quality.
  - RFP issued 10/08, award decisions have been made
  (2) Systematically define the impact of key pre-analytical variables in human biospecimens of specific type on downstream molecular data generated from specific molecular analysis platforms.
  - Responses to RFPs received; August review scheduled

- Challenge Grant Topics on Biospecimen Research and Biobanking
  - Sponsor, collaborate, and promote research on biospecimen science both intramurally and extramurally:
    - The Biospecimen Research Interest Group
OBBR’s Most Recent Undertaking

- Development of key infrastructure for translational research:

  The Cancer HUman Biobank (caHUB)

What Is caHUB?

A unique, centralized, non-profit public resource that will ensure the adequate and continuous supply of human biospecimens and associated data of measurable, high quality acquired within an ethical framework.
The Importance of Standardized Specimens and the Requirement for a National Biospecimen Resource Is Widely Cited

- Genomics and Personalized Medicine Act of 2007
- Dept. of Health and Human Services, Personalized Health Care Report, Sept. 2007
- President’s Council of Advisors on Science and Technology: Priorities for Personalized Medicine, Sept. 2008
- President’s Cancer Panel Report, Maximizing Our Nation’s Investment in Cancer, Sept. 2008
- Kennedy-Hutchinson Cancer Bill ("War on Cancer, Part II"), 2008
- The NCI By-Pass Budget for FY2010

8. Biobanks

By ALICE PARK

Folks at the National Cancer Institute (NCI) are heading up an effort to establish the U.S.’s first national biobank — a safe house for tissue samples, tumor cells, DNA and, yes, even blood — that would be used for research into new treatments for diseases…. By fall, the group hopes to have mapped out a plan for a national biobank; the recent stimulus showered on the government by the Obama Administration might even accelerate that timetable.
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 U.S. biospecimen resources

Linking Biobanks Through Common Standards

caHUB Creates Unique Benefits for the Advancement of Science and Medicine

- Builds on NCI’s experiences to date and NBN principles
- Links cancer institutions, researchers, and scientific initiatives
- Benefits (not competes with) other biobanking programs
- Facilitates rapid development and regulatory approval of medical products
- Facilitates standardization and medical implementation of approved products
- Allows direct performance comparisons of different technologies
- Increases efficiency of scientific innovation and knowledge maturation
On the Road to Molecular Medicine.....

“There is an opportunity for the NIH to be the ‘Statue of Liberty’ in creating a vision for how to collect, annotate, store and distribute samples in a standardized way.”

- Steve Gutman, FDA

Who Are We?
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