



OBBR

Office of Biorepositories
and Biospecimen Research

Biospecimen Research Network: Program Update

Helen M. Moore, Ph.D.

2010 BRN Symposium

“Advancing Cancer Research Through Biospecimen Science”

March 24, 2010

NATIONAL
CANCER
INSTITUTE



What is the Opportunity for Biospecimen Science?

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- To enable better, more reproducible cancer research
- To develop better products from that research
- To do so faster, better, more reliably
- To translate better research to better products for patients

Translational Research Promises to Advance Molecular Medicine for Cancer Patients

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Molecular Data

Diagnosis / Therapy

Translational Research

PERSONALIZED CANCER CARE

Biospecimen Distribution

Biospecimen Collection

Biospecimen Processing and Banking



Progress in Cancer Treatment and Research are Dependent on High Quality Human Specimens

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Identification of targets for drug development, treatment and prevention

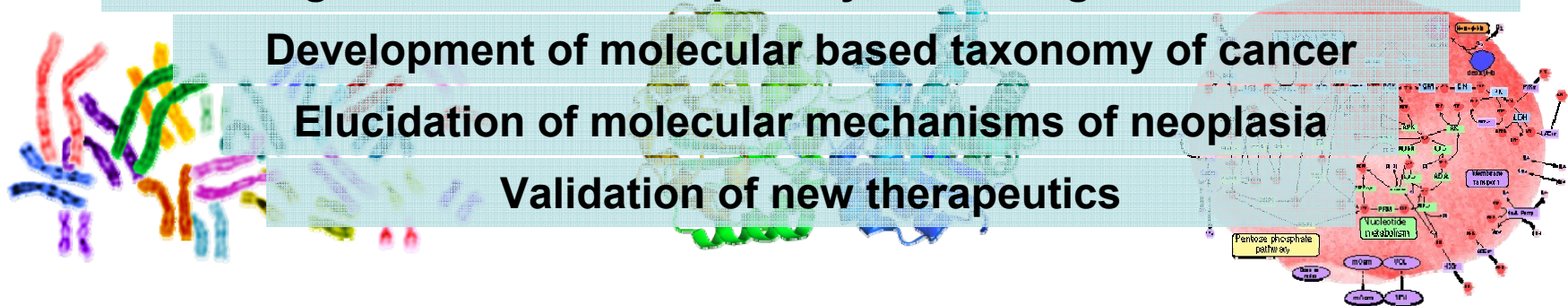
Identify biologic variations that determine drug efficacy and drug toxicity

Defining markers for susceptibility, screening and reoccurrence

Development of molecular based taxonomy of cancer

Elucidation of molecular mechanisms of neoplasia

Validation of new therapeutics



All Depend
On High-Quality, Annotated
Human Biospecimens



Biospecimen Collection in the U.S.

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- 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**



Biospecimens and Cancer R&D

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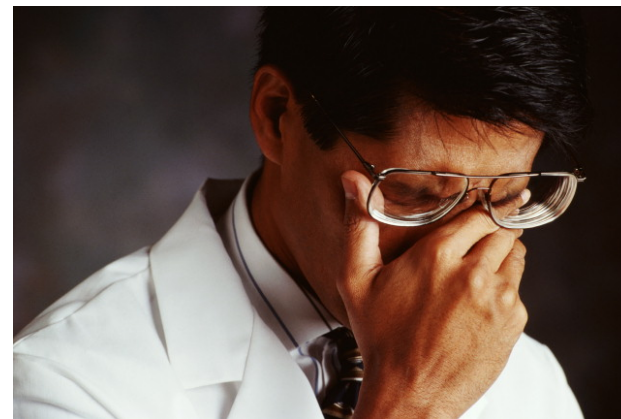
- **The lack of high-quality biospecimens is the number one obstacle for cancer research**
- **The accuracy of research data may be compromised when utilizing biospecimens of poor or unknown quality**
- **This issue must be addressed to move cancer R&D forward**
- **An issue for us all - academics, government, industry**



Molecular Research and Analyte Variation

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The lack of standardization of human biospecimens compromises the quality and the utility of molecular research and the advances in clinical medicine dependent on them.





Urgent Needs Being Addressed by OBBR

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- **BEST PRACTICES:** state-of-the-science guidance for biobanking to harmonize procedures for collection, processing, storage and distribution of biospecimens
 - *The NCI Best Practices for Biospecimen Resources*
- **RESEARCH** to better understand how pre-analytical variables affect the molecular integrity of the biospecimen
 - *The NCI Biospecimen Research Network*
- *and...all of this integrated into a national biobank to facilitate cancer research: **caHUB***

New Web-based Format of NCI Best Practices ...and Revised Version Coming

OBBR Office of Biorepositories
and Biospecimen Research

Home Page- OBBR Best Practices - Microsoft Internet Explorer

Address <http://biospecimens.cancer.gov/bestpractices/>

National Cancer Institute U.S. National Institutes of Health | www.cancer.gov

OBBR NCI Best Practices for Biospecimen Resources
Office of Biorepositories and Biospecimen Research

Visit the OBBR website

Home | Sign Up For Updates

Search NCI Best Practices GO

Sign Up For Best Practices Updates Please Provide Us Your Feedback Take Our Poll And See What Others Are Saying

Introduction

Scope, Applicability, Implementation

Technical and Operational Best Practices

Ethical, Legal, and Policy Best Practices

References

Web Resources

Glossary of Terms

Acronym List

Appendix 1: NCI Infrastructure to Support Informatics Best Practices

Appendix 2: Material Transfer Agreement (PDF)

NCI Best Practices for Biospecimen Resources (PDF)

One of the most widely recognized and significant roadblocks to progress in cancer research is the lack of standardized, high-quality biospecimens. The National Cancer Institute (NCI) developed the NCI Best Practices for Biospecimen Resources (NCI Best Practices) based on extensive research and expert input into the state of NCI-funded biospecimen resources and the quality of biospecimens used in cancer research. The NCI Best Practices outline the operational, technical, ethical, legal and policy best practices for NCI-supported biospecimen resources.

Scope, Applicability, Implementation

The NCI Best Practices incorporate key principles that

- define state-of-the-science biospecimen resource practices
- promote biospecimen and data quality
- support adherence to ethical and legal requirements

The NCI Best Practices define principles to guide procedures developed by biospecimen resources. They are intended to be adapted based on the mission and scientific needs of biospecimen resources. While adoption of the NCI Best Practices is voluntary, the NCI believes that these principles optimize biospecimens for cancer research. [Learn more](#)

Technical and Operational Best Practices

Although the specific mission of a biospecimen resource will define its collection and processing procedures, common principles apply to all biospecimen types. The best practices within this section are based on current, published information and will be revised periodically as new

See the poster by Nicole Lockhart for more information



The Cancer Human Biobank (caHUB)

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Envisioned as:

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.

Please join us for the caHUB session tomorrow afternoon



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- **Supporting the development of Best Practices for collection, annotation, processing, and storage, based on scientific evidence**
 - *What evidence is already available about how different biospecimen collection, processing and storage procedures affect biospecimen molecular integrity?*
 - *What new research is needed?*
 - *How do we accomplish that research?*
- **Evidence-based biospecimen practices will underpin the entire caHUB effort**



Multiple pre-analytical variables can affect the molecular integrity of the biospecimen

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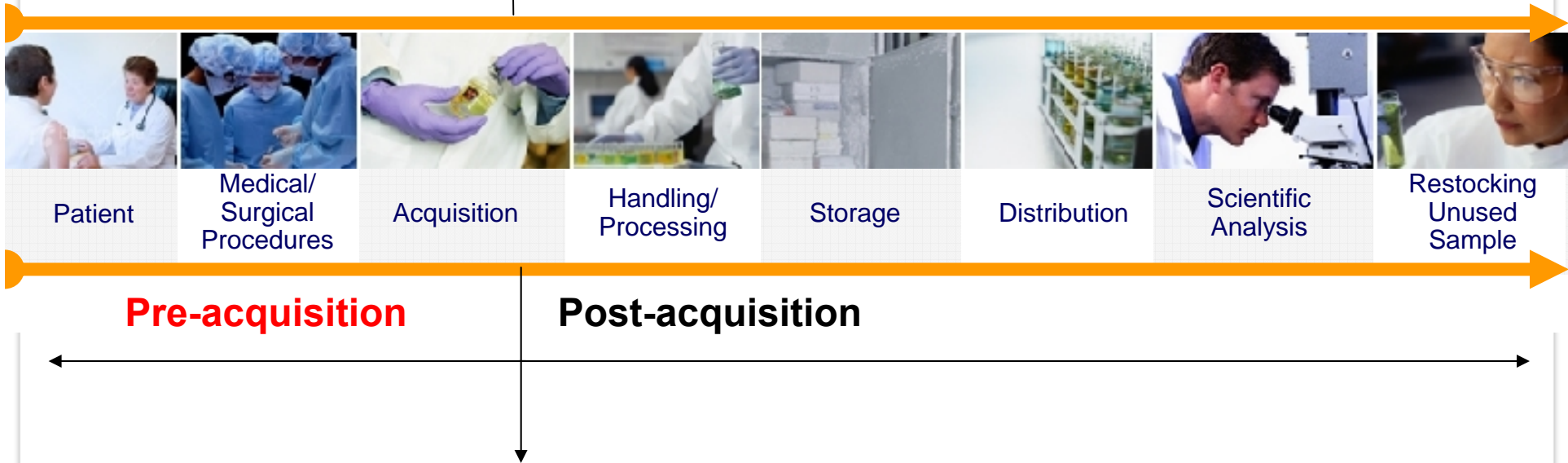
Variables (examples):

- 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



How Can Changes in Molecular Integrity of Biospecimens Affect Molecular Readout?

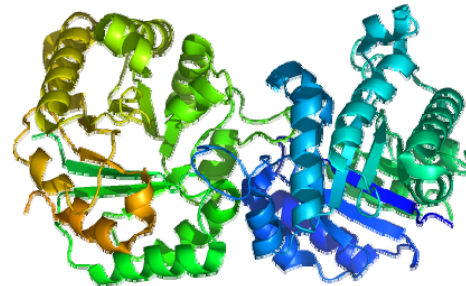
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Genomics



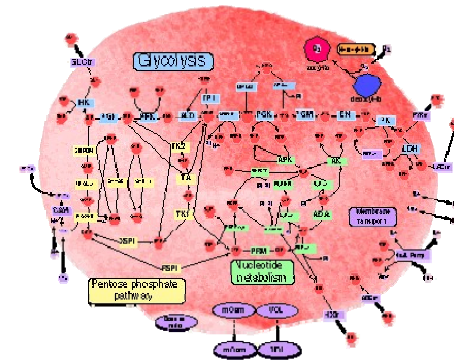
Changes in specific transcript levels based on ischemic time, not disease

Proteomics



- Lack of reproducibility of protein biomarkers in discovery research
- Inconsistent IHC results in Research and Clinical Labs

Metabolomics



Inconsistencies in small molecule readouts, yielding results that point to the wrong pathway



The Biospecimen Research Network: Supporting Collaborative Research

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- **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
 - This symposium: “Advancing Cancer Research through Biospecimen Science” <http://brnsymposium.com>
- **Generate new research data:**
 - Extramural Research Programs
 - IMAT Program – “Innovative and Applied Emerging Technologies in Biospecimen Science” (RFA)
- **Collaborate with other programs to facilitate biospecimen research and evidence-based biospecimen practices**



Launch NCI Best Practices for Biospecimen Resources

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- About OBBR
- About NCI Best Practices
- Biospecimen Research Network**
- caHUB
- News and Events
- Resources

PATIENT CORNER
Learn more

caHUB The Cancer Human Biobank
NCI caHUB Public Meetings
February/March 2010

2010 BIOSPECIMEN RESEARCH NETWORK SYMPOSIUM
MARCH 24 - 25, 2010 >>

OBBR Quick Links

- OBBR Toolbox
- Multi-Media
- Funding Opps

caHUB Acquisition of Normal Tissues RFPs

Preproposal Teleconference:
Feb. 26, 2010
Receipt Date: March 12, 2010

Proposals are requested by 4 p.m. on March 12, 2010, to collect normal human tissues for caHUB and the NIH Roadmap Project, GTEX. A preproposal teleconference was held on Feb. 26, 2010, from 1-3 p.m. EST, [Learn more](#)

- Overview
- Biospecimen Science
- BPM Symposia
- Biospecimen Research Database**
- Life Cycle of Biospecimens
- Funding Opportunities

OBBR's mission is to ensure that human research are of the highest quality.

ing a common biorepository infrastructure that science, in order to facilitate multi-institutional, studies.

[Learn more](#)

Moving Forward



Hear what important cancer community stakeholders from the patient, oncology, research and drug development communities have to say about the critical importance of high-quality biospecimens for cancer research and patient care.

[Learn more](#)

Paper and Study Details

2009 BIOSPECIMEN RESEARCH NETWORK SYMPOSIUM

March 16-18, 2009

[Home](#)

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[Experimental Factor Search](#)

[Curator Login](#)

PubMed ID: 16288005 

Lips Esther H, Dierrsen Jan WF, van Eijk Ronald, Oosting Jan, Eilers Paul HC, Tollenaar Rob AEM, de Graaf Eelco J, van't Slot Ruben, Wijmenga Cisca, Morreau Hans, van Wenzel Tom

Reliable high-throughput genotyping and loss-of-heterozygosity detection in formalin-fixed,paraffin-embedded (FFPE) tumors using single nucleotide polymorphism arrays.

Cancer Res, 2005, Vol. 22, Page 10188

Review Paper? No

Purpose of Paper: To determine if genomic DNA isolated from formalin fixed paraffin embedded (FFPE) tissue is applicable for genotype and loss of heterozygosity (LOH) analysis via single nucleotide polymorphism (SNP) arrays.



Conclusion of Paper: Results of SNP and LOH analyses were nearly identical among FFPE and frozen specimens. The authors conclude that genome wide genotyping using FFPE tissue is reliable, producing results that are reproducible with frozen specimens.

Studies

[Detail](#)

Specimen: Tissue / Colorectal / Formalin / Normal

Platform: DNA - SNP assay /

Findings : The occurrence of SNPs in FFPE and frozen matched controls were nearly identical (99.9%). Of the 8 LOH regions examined only 2 were not identical among FFPE and frozen specimens (located on chromosomes 3 and 8). Genotyping results were identical among the two SNP arrays (BeadArray and GeneChip).

[Detail](#)

Specimen: Tissue / Colorectal / Formalin / Normal

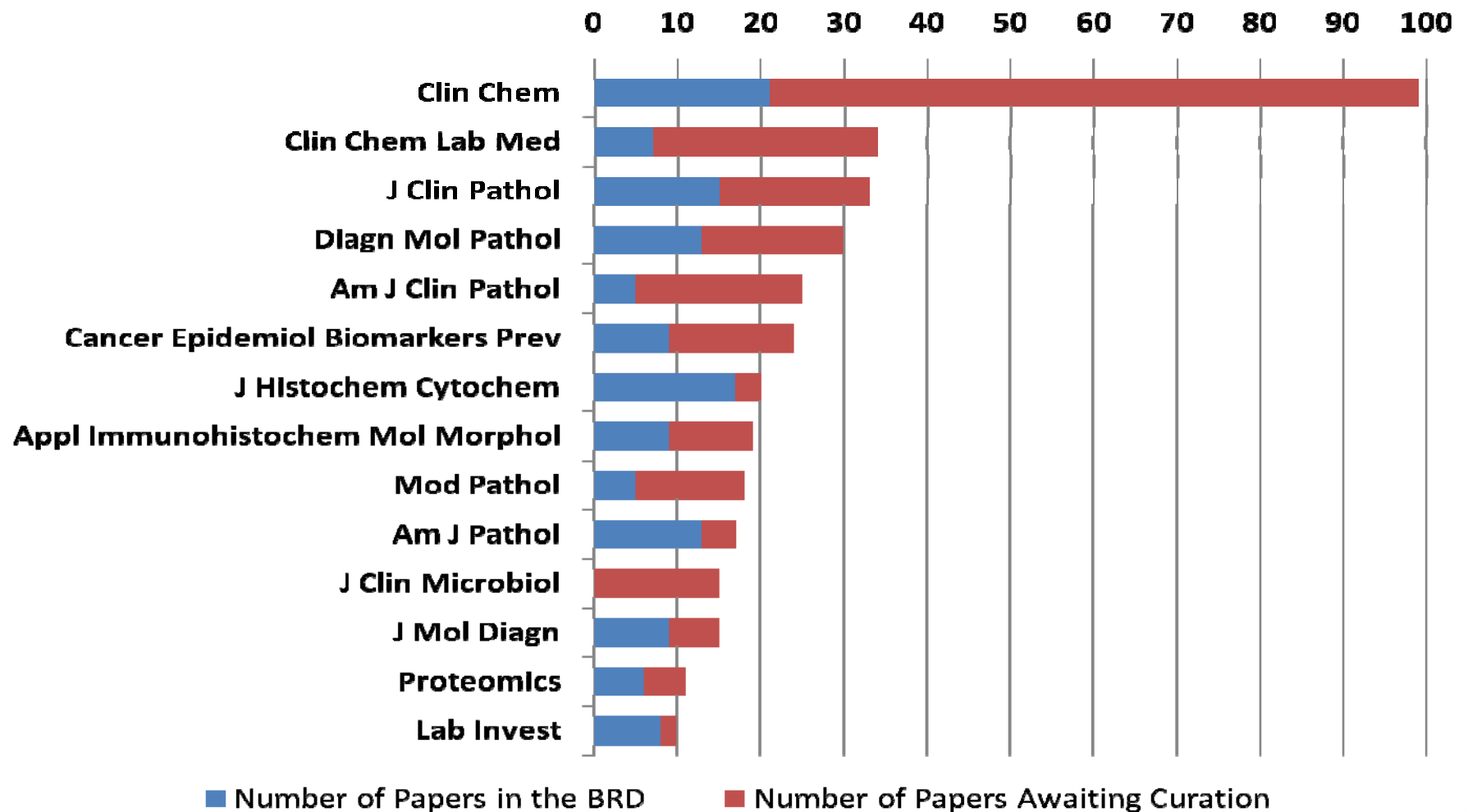
Platform: DNA - DNA Sequencing /

Findings : DNA sequence analysis confirmed SNP results.

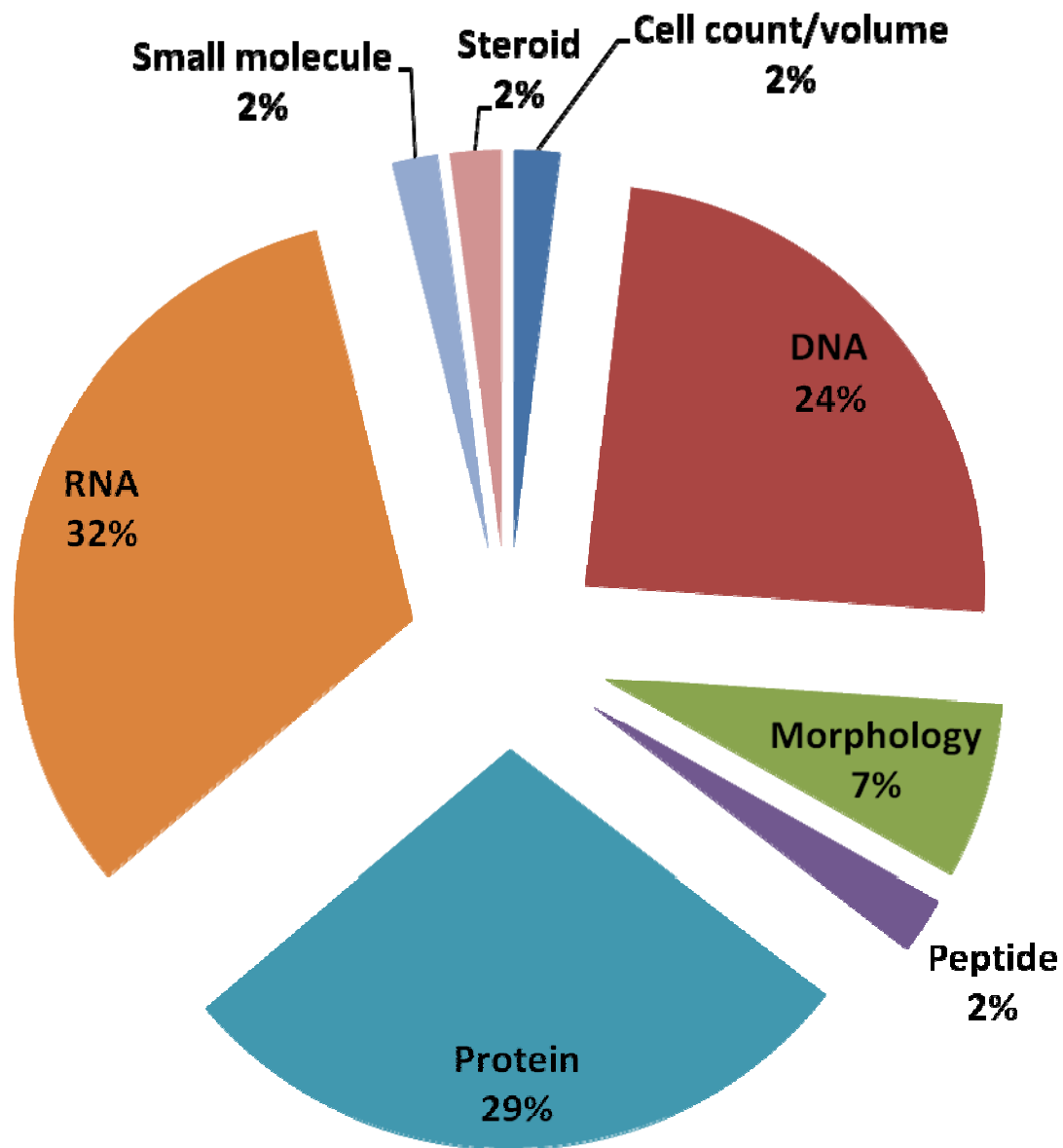
Biospecimen Research Database Update: 300 papers now curated

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Journals with 10 or More Papers Identified for BRD Inclusion



Analyte Distribution of BRD Paper Entries



Analytes Studied in < 2% of Papers	%
Carbohydrate	0.7%
Electrolyte/Metal	1.0%
Gas	0.0%
Glycoprotein	1.7%
Lipid	0.7%
Lipoprotein	0.3%

Kelly Engel



Test-Driving the Biospecimen Research Database: FFPE

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BRD Experimental Factor Classifications

Preacquisition

Acquisition

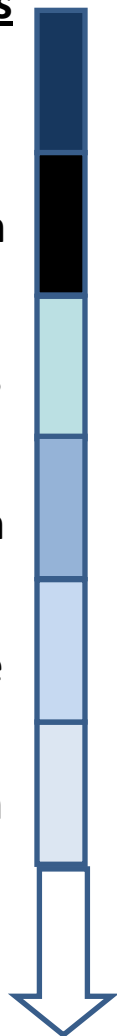
Biospecimen Aliquots & Components

Biospecimen Preservation

Storage

Analyte Extraction & Purification

Platform-specific Methodology



Fixation Parameters Investigated

Room temperature delay pre-fixation

Size of biospecimen

Temperature of fixation

Method of fixative delivery

Time in fixative

Duration of biospecimen archival

Kelly Engel

Conclusions supported by 3 or more papers populating the BRD

Analyte	No. of BRD Papers	Consensus
<i>Fixation Parameter: Biospecimen size</i>		
DNA	3	PCR results of small biospecimens (2-10 mm diameter) were favorable to larger biospecimens.
<i>Fixation parameter: Time in fixative</i>		
DNA	6	PCR analysis was optimal in biospecimens fixed for 2-48 h, with adverse effects reported after fixation for ≥ 72 h.
RNA	3	Evidence of RNA degradation was observed in specimens fixed for 1-72 h.
	3	mRNA transcript stability was analyte-specific, with fixation thresholds potentially influenced by platform sensitivity and amplicon length. Quantified analytes included: COX-1, beta-actin, MART, MMP-1, VEGF, p21, EGFR, C-BCR.
Protein	5	Protein immunoreactivity was stable in biospecimens fixed for 6 h-8 d. The antigens investigated included: p27Kip1, ER, PR, AR, c-erb-B2, HER/neu, EGFR, MMR-1, VEGF, p53, PCNA, Ki-67.
<i>Fixation parameter: Archival of formalin-fixed paraffin tissue blocks</i>		
DNA	4	PCR success and efficiency (of 90-435 bp fragments) were not impacted by paraffin block archival at room temperature for 1 wk-8 y.
RNA	3	RNA degradation was more extensive in blocks stored for 3.5-17 y compared to those stored for 1 y or less.
	3	RT-PCR success rate decreased by 0-20% after 1-10 y, 30-50% after 10-30 y, and 60% after 40 y of paraffin block archival compared to fresh blocks, although amplicon length also influenced RT-PCR success. The analytes investigated included hepatitis C, beta-actin, C-BCR.
	3	Real-time qRT-PCR analysis of paraffin blocks archived for 1-8 y was successful; while analysis was impaired for blocks stored for 11 y or longer. The analytes investigated included LDHA, RPL32, beta-actin, RPL13A, RPLO, CYP1, GUS, TBP, TFRC
<i>Fixation parameter: Archival of formalin-fixed, paraffin-embedded, slide-mounted sections</i>		
Protein	3	Immunostaining was altered in slides stored for 3 mon-3 y at room temperature compared to freshly cut sections. Alterations in immunostaining intensity and duration threshold were antigen-specific. The antigens investigated included ER, PR, HER-2, Chromagranin, CD3, Vimentin, EGFR.



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 - IMAT Program – “Innovative and Applied Emerging Technologies in Biospecimen Science” (RFA)
- **Collaborate with other programs to facilitate biospecimen research and evidence-based biospecimen practices**



Central Themes for BRN Research

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- “Bridging the gap” between existing clinical practice for biospecimens and emerging technologies for personalized diagnostics and therapies
 - Tissue preservation variables and their impact on downstream applications (e.g., HER2)
 - Robotic surgery vs. manual surgery for prostate – are tissues harvested from robotic surgery suitable for advanced biomarker detection?
- Defining the most significant variables for prospective collection of tissues, blood, and body fluids
 - Effects of pre-acquisition variables and biomolecule extraction methods on biomolecule analysis results in blood
- Developing evidence-based biospecimen quality indicators for specific analytical platforms
 - How to assess whether a banked specimen is suitable for a specific molecular analysis approach?



BRN Research Funding Program: "Biospecimen Research for Molecular Medicine"

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- **Program aims:**

- (1) Develop innovative approaches to the control, monitoring and assessment of biospecimen quality

- *Investigator-driven Contract Research*
 - *"Biospecimen Molecular Integrity" RFP issued 10/08, four research contracts awarded, research is in progress*
 - *Second issue under ARRA funds, proposals were due 12/09, contracts in negotiation*

- (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

- *Program-directed Research: Contracts in negotiation*



Biospecimen Molecular Integrity: Program Approach

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- **Encourage the best research from the field**
 - RFP modeled on a Broad Agency Announcement
 - The “right” solutions to the many research problems out there are many
 - Different technology platforms may be applied
 - They do not all cost the same
- **This can be very challenging research to perform**
 - Biospecimen collection and molecular analysis procedures must be known and reproducible
 - Annotation and Quality Control are paramount



Biospecimen Molecular Integrity: Research Contracts

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- **“Investigations into the Effects of Blood Specimen Handling Procedures on Protein Integrity”**
 - Chris Becker, PhD, PPD Biomarker Discovery Sciences
- **“Credentialing Plasma and Serum Biospecimen Banks for Proteomics Analyses”**
 - Katy Williams, PhD, University of California San Francisco
- **“Intrinsic and Extrinsic controls for FFPE tissue”**
 - David Rimm, MD, PhD, Yale
- **“Effects of Biospecimen Integrity, Intratumoral Heterogeneity, and Analytical Variance on Microarray-Based Pharmacogenomics Tests of Breast Cancer”**
 - W. Fraser Symmans, MD, MD Anderson (PI), Christos Hatzis, PhD, Nuvera Biosciences (Co-PI)
 - *More to be announced soon*



BRN Research Funding Program: "Biospecimen Research for Molecular Medicine"

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- **Program aims:**

(1) Develop innovative approaches to the control, monitoring and assessment of biospecimen quality.

(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.

Tissue Acquisition Variables Project



Tissue Acquisition Variables Project: Directed Research

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- **Aimed at understanding the variability introduced by different tissue fixation and processing procedures**
- **Multi-site study:**
 - Establish the state of practice in cancer tissue collection, processing and storage
 - Study the effect of different such practices on biospecimen molecular integrity
 - Hone in on the procedural variations that cause the most significant variations in molecular integrity
 - Use this data to inform the development of evidence-based Standard Operating Procedures (SOPs)



Tissue Acquisition Variables Project: Directed Research

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- **Contracts with Tissue Source Sites are in negotiation**
- **Additional funding opportunities to be announced**
 - To propose robust ways of analyzing the tissues to reveal the molecular readout induced by preanalytical variables such as time to fixation, fixation time, and different processing parameters



Funding Overview

Find Funding

Receipt Dates

Notices

About Funding

Past Funding Opportunities

New: SBIR Bridge Award



[Click here to learn about the](#)

Find Funding

Contract Topics

257 Biopsy Instruments and Devices that Preserve Molecular Profiles in Tumors

Number of anticipated awards: 2

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$250,000;
Phase II: \$2,000,000

(Note: It is strongly suggested that Proposals adhere to the above budget amounts. Proposals with budgets exceeding the above amounts may not be funded. Phase I project periods may last a maximum of 9 months.)

The deadline for receipt of all contract proposals submitted in response to this solicitation is: **November 9, 2009.**

Summary:

Molecular medicine holds much promise for advancing cancer diagnosis and

Contract Topics

Grant Topics

Phase II Bridge Award

Omnibus Solicitation

Innovative Molecular Analysis Technologies (IMAT)



Funding Overview

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Receipt Dates

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About Funding

Past Funding Opportunities

New: SBIR Bridge Award



[Click here to learn about the](#)

Find Funding

Contract Topics

284 Alternative Biospecimen Stabilization and Storage Solutions

Number of anticipated awards: 2

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget (total costs): Phase I: \$150,000;
Phase II: \$1,000,000

(Note: It is strongly suggested that Proposals adhere to the above budget amounts. Proposals with budgets exceeding the above amounts may not be funded. Phase I project periods may last a maximum of 9 months.)

The deadline for receipt of all contract proposals submitted in response to this solicitation is: **November 9, 2009.**

Contract Topics

Grant Topics

Phase II Bridge Award

Omnibus Solicitation

Innovative Molecular Analysis Technologies (IMAT)



How do we change the landscape of research through Biospecimen Science?

OBBR Office of Biorepositories
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- **Through building a new knowledge base in biospecimen science**
 - New research
 - Communication of research through publications, meetings, and the Biospecimen Research Database
- **Through changing how research using human biospecimens is published**
 - Hear Scott Jewell's talk later today about "Biospecimen Reporting for Improved Study Quality (BRISQ),"
 - Effort grew out of a workshop held at this symposium last year
 - The basic idea is that researchers need to say more in their publications about where the biospecimens forming the base of their study came from and how they were treated
 - Potentially huge impact on making research results more reproducible
- **Through this meeting and all of you who are passionate about this area**



A Few Program Notes

OBBR Office of Biorepositories
and Biospecimen Research

- **Thank you for joining us here today!**
- **Please sign up for “Meet the Experts” lunch tables**
 - See sign up sheets outside and flyers in your program book
 - Thank you to all the “Experts” leading these tables!
- **Please join us tonight for a poster session and reception starting at 5:15**
- **Have a great meeting!**



Thanks to...

OBBR Office of Biorepositories
and Biospecimen Research

- **The 2010 BRN Symposium planning team:**
 - Sherilyn Sawyer, Jim Vaught, Andrea Kelly, Renate Myles, Frank Bajowski, Jennifer Kostiuk
- **The two fellows who helped to get this symposium off the ground 2 years ago:**
 - Asha Collins and Mark Lim
- **The Biospecimen Research Database core team:**
 - Kelly Engel, Andrew Breycheck, Ian Fore
- **All of our incredible OBBR team, past and present**
- **Our extended team at SAIC-Frederick who work with us to develop and manage research contracts**
- **Carolyn Compton – our fearless leader!**

National Cancer Institute

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

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3RD ANNUAL BIOSPECIMEN RESEARCH NETWORK SYMPOSIUM

ADVANCING CANCER RESEARCH THROUGH BIOSPECIMEN SCIENCE

March 24-25, 2010

Bethesda North Marriott Hotel & Conference Center
Bethesda, Maryland

<http://www.brnsymposium.com>

For symposium updates, please send your contact information to
biospecimens@mail.nih.gov





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Helen M. Moore, Ph.D.

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