NATIONAL CANCER INSTITUTE

INNOVATIVE MOLECULAR ANALYSIS TECHNOLOGIES

Request for reissuance of four Request For Application (RFA) solicitations

December 2014

Motivation for Request for Reissuance

1. IMAT program continues to account for the majority of NCI's support for investigator-initiated technology development, addressing an area unmet by other FOAs

2. IMAT solicitations continue to receive a significant number of high-scoring applications that offer potential to address unmet clinical and basic research needs

3. Strong record of success, as supported by multiple external program outcome evaluations.

Presentation Overview

1. ***Overview of the program***

2. ***Evaluation of most recently completed IMAT projects***

3. ***RFA Reissuance request details***

4. ***BSA Subcommittee questions***

IMAT Program Overview

- ***Technology-focused***. Projects focused on pursuing biological hypothesis are barred from review.

- Emphasis on supporting development, testing, and validation of ***high-risk/high-impact*** multidisciplinary, cancer-relevant technologies for the molecular and cellular analysis of cancer

- ***100% Investigator initiated*** *r*esearch project grants, utilizing the R21 and R33 award mechanisms for phase-1 and phase-2 levels of support

- ***Trans-divisional***, cooperative initiative focused on technological innovation with specific inclusions to minimize overlap or duplication with other programs/initiatives

IMAT Core Program Team

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IMAT Program History

- Solicited applications every year since 1998, 3 rounds of receipt/yr
  - No solicitations in CY2011, and only 1 round received in 2004

- Total of **3914 applications** received
  - 3098 R21 & 847 R33
  - Ave ~300-350 applications/yr (~3.5:1 ratio R21:R33)
- Total of **478 new competitive awards**
  - 357 R21 and 121 R33
  - Ave ~30-40 awards/yr

- ~**70-100 active projects** any given time (97 as of Nov 2014)

Portfolio Evaluation

Outcomes from Recently Completed Projects

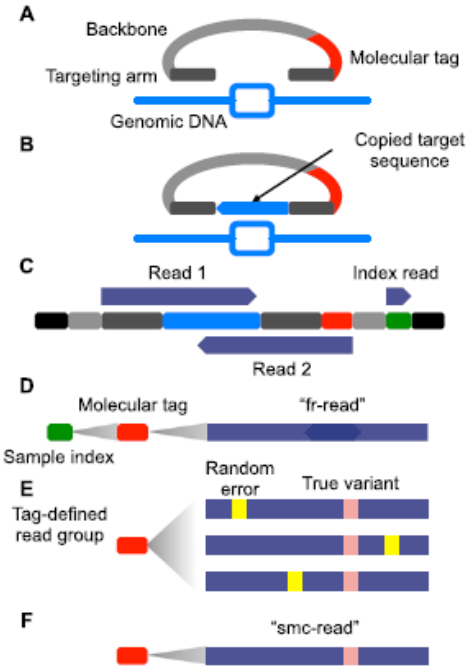
- **30 R21 grants (from 358 applications submitted in FY2010)**
  - 74 publications (6 of the projects accounting for over half of these)
  - 19 US patent applications submitted, plus 3 provisional patents filed and 7 awarded for supported platforms (5 of the projects account for nearly 67% of these)
    - 9 licensure agreements are in progress or completed
  - 31 new applications have since been submitted to NIH that indicate use of the technology developed under these R21s; of these 9 were awarded and 12 are still pending
    - 7 of these applications were submitted for IMAT R33 support and 1 application was for a new IMAT R21 that leverages findings from the original R21; 2 succeeded in winning R33 awards and many PIs indicated an intention to submit for R33 support

- **11 R33 grants (from 61 applications submitted in FY2010)**
  - 75 publications (4 of the projects accounting for roughly two thirds of these)
  - 15 US patent applications submitted plus 2 patents awarded (accounted for by 5 projects)
  - 1 product driving clinical profiling (OncoPanel) for thousands of patients at both Dana Farber Cancer Institute and Brigham & Women's Hospital in Boston, MA
  - 4 commercially available products, with several more licensing agreements in process
  - 22 new applications have since been submitted to NIH that indicated use of the technology developed under these R33s; of these 7 have received awards and 4 are still pending.

Sampling of Successful Projects (IMT)

Single molecule Molecular Inversion Probes (smMIP)

More sensitive sequencing approach for detecting somatic mutations present at a frequency of 1 mutant copy among 100,000 wild type.



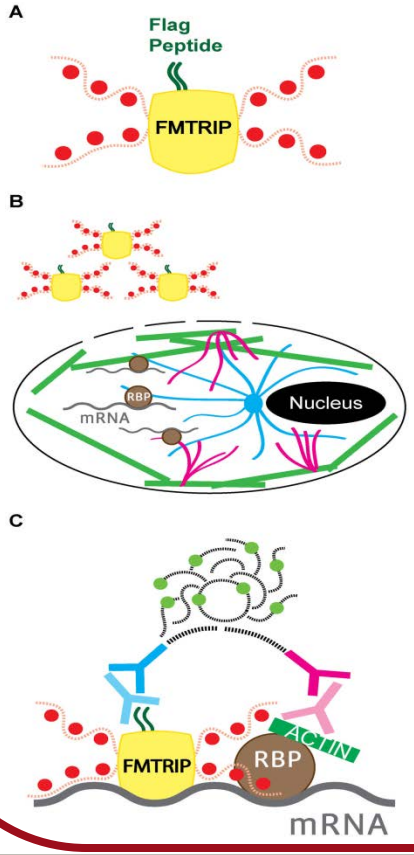
Jay Shendure, MD, PhD
Genome Sciences
University of Washington

Hiatt *et al*, Gen Res Feb 2013

FMTRIP-PLA

Novel binding probes for imaging RNA-protein bound complexes with single interaction sensitivity.

Georgia Tech | Wallace H. Coulter Department of Biomedical Engineering (Georgia Tech College of Engineering and Emory School of Medicine) | Emory University



FMTRIP-PLA:
Flag-tagged multiply-labeled tetravalent RNA imaging probes detected by proximity ligation assay

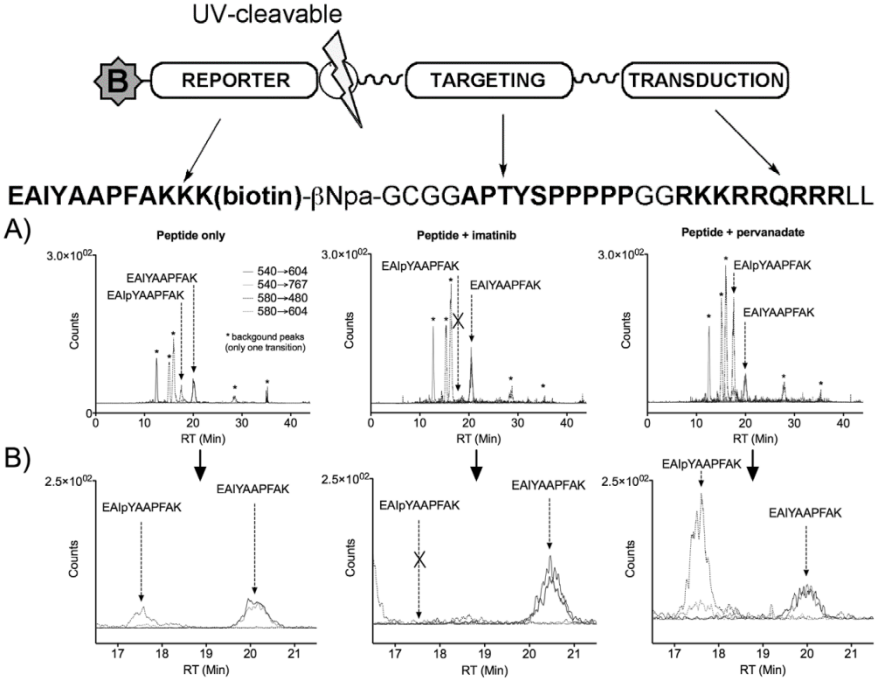
Philip Santangelo, PhD
Biomedical Engineering
Georgia Tech/Emory

Jung *et al*, PloS One, Sept 2013

Sampling of Successful Projects (EMT)

Kinase Activity Biosensors

Nano-scale sensors for detecting kinase activity in intact cells.

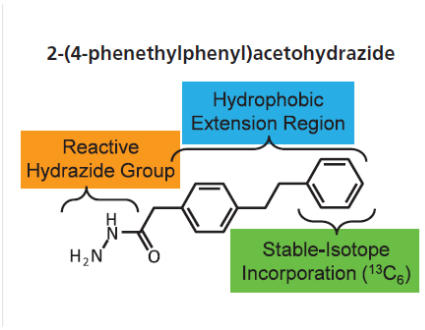


Yang *et al*, PloS One, Feb 2013

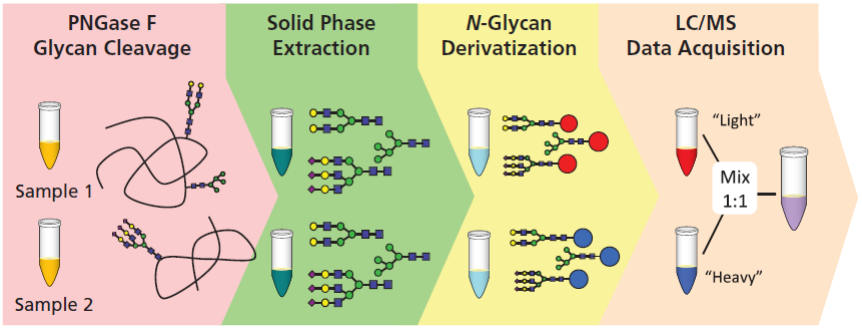
Laurie L Parker, PhD
Medical Chemistry & Pharmacology
Purdue University

INLIGHT™

Novel tags to facilitate quantitative mass spectrometric analysis of N-linked glycans with improved limits-of-detection.



David Muddiman, PhD
Chemistry
NC State University

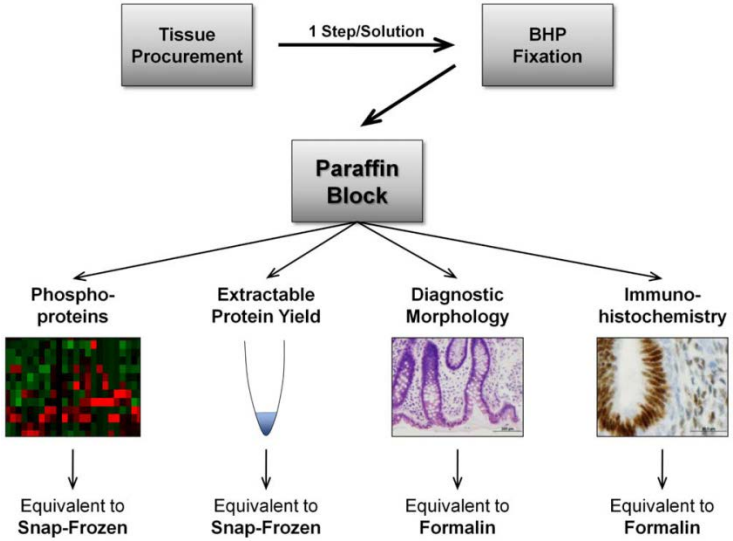


http://www.stableisotope.com/userfiles

Sampling of Successful Projects (BSP)

Biomarker & Histology Preservative (BHP)

Validation of a novel tissue fixative as a replacement for formalin fixation, especially for the ability to preserve phosphoproteins.

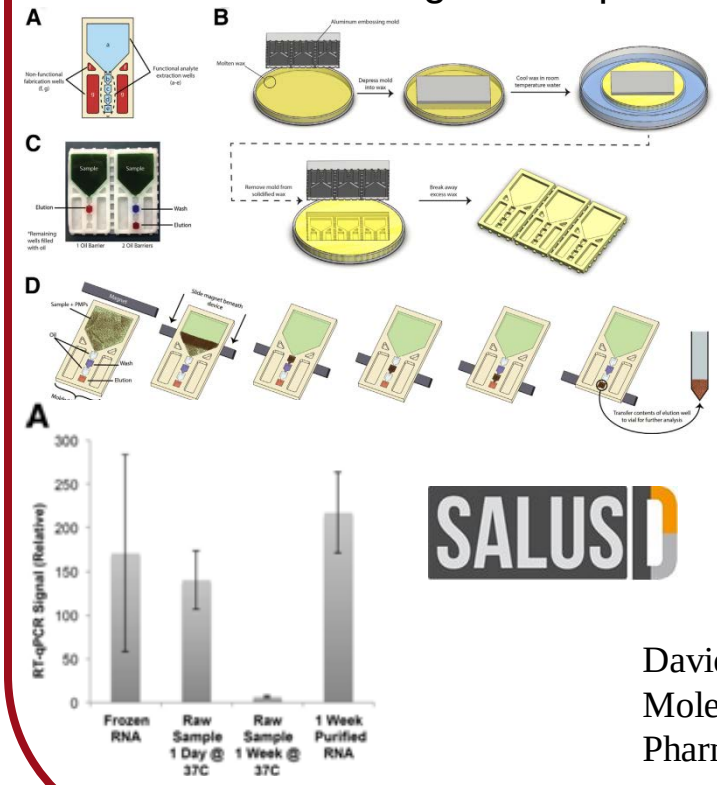


Mueller *et al*, PloS One, Aug 2011

Lance Liotta, MD, PhD
Center for Applied Proteomics and Molecular Medicine

Exclusion-based Sample Prep (ESP)

A seamless nucleic acid purification and amplification capability directly in line with a co-culture platform to examine intercellular interactions in heterogeneous patient specimens.



Berry *et al*, J Mol Diag, May 2014

David Beebe, PhD
Molecular & Cellular Pharmacology

Sampling of successful IMAT Technologies

Genomics

- Multi-photon Intravital Imaging (MPIVI) (Condeelis, awarded 2001)
- Pyrophosphorolysis Activated Polymerization (PAP) (Sommer, awarded 2002)
- Pair-end Sequencing, developed initially to screen structural rearrangements (Collins, awarded 2003)
- COLD-PCR (Makrigiorgos, awarded 2005)
- Digital Transcriptome Subtraction (Moore, awarded 2007)
- Integrated Genomics Viewer (IGV) (Hahn, 2007)

Proteomics

- Multi-Dimensional Protein Identification Technology (MuDPIT) (Yates, awarded 1999)
- Gateway ORF Cloning Tool (Vidal, awarded 2000)
- Isotope-Coded Affinity Tags (ICAT) (Aebersold, awarded 2000)
- Synchrotron Footprinting (Chance, awarded 2000)
- Deuterium exchange Mass Spectrometry (DXMS) (Woods, awarded 2003)
- Nucleic Acid Programmable Protein Array (NAPPA) (LaBaer, awarded 2003)
- Pressure-assisted Protein Extraction (Fowler, awarded 2009)
- High Pressure-High Resolution Separation with Intelligent Selection and Multiplexing (PRISM) (Tang, 2011)

Epigenomics

- Differential Methylation Hybridization (DMH) (Huang, awarded 2003)
- Chromatin Immunoprecipitation with next gen Sequencing (ChIP-Seq) (Ren, awarded 2004)
- Zinc Finger Nucleases for targeted double-strand breaks (Porteus, awarded 2006)
- Methylated CpG island amplification followed by sequencing (MCA-Seq) (Shen, awarded 2009)

Clinical Diagnostics

- Protease-activatable near IR probes for *in vivo* diagnostics (Tung, awarded 2001)
- MicroSOL IEF, available from Invitrogen as Zoom IEF Fractionator (Speicher, 2001)
- Paramagnetic chemical exchange saturation transfer (ParaCEST) (Sherry, awarded 2002)
- Microfluidic Genetic Analysis (MGA) chip (Landers, awarded 2006)
- Oncomap, also known as OncoPanel (Garraway, awarded 2007)
- Oligonucleotide-selective Sequencing (OS-Seq) (Ji, 2010)

Sample preparation

- Magnetic Cell Sorting, now available from Ikotech (Chalmers, awarded 1999)
- Dielectrophoresis Field Flow Fractionation (DEP-FFF) available as ApoStream™ system from ApoCell (Gascoyne, awarded 2001)
- Cryopreservation followed by culturing of CML cells (Sims, awarded 2004)
- RainDance Oil Droplet Microfluidics (Link, awarded 2007)
- NanoTrap (Liotta, awarded 2009)
- NanoVelcro (Tseng, awarded 2010)

Drug Screening or Delivery

- One Bead One Compound (OBOC) (Lam, awarded 2000)
- CellASICs ONIX, available from EMD Millipore (Lee, awarded 2006)
- Genetically modified T-cells for acute lymphoblastic leukemia treatment (Cooper, awarded 2007)
- IUVO chemotaxis assays, available from Thermo Fisher (Beebe, 2009)

Reissuance Request

Request to reissue 4 RFAs

1. Early-Stage Innovative Molecular Analysis Technology Development for Cancer Research (IMT R21)
2. Advanced Development and Validation of Emerging Molecular Analysis Technologies for Cancer Research (EMT R33)
3. Early-Stage Innovative Technologies for Cancer Biospecimen Sciences (BSP R21)
4. Advanced Development and Validation of Emerging Technologies for Cancer Biospecimen Sciences (BSP R33)

History of applications and awards for each FOA

RFA Series	IMT R21		EMT R33		BSP R21		BSP R33	
	Apps	Awards	Apps	Awards	Apps	Awards	Apps	Awards
CA05	102	17	36	5	33	4	6	1
CA06	144	9	27	3	32	4	2	0
CA07	248	29	57	6	65	8	13	1
CA08	125	16	42	3	24	5	7	0
CA09	174	14	34	4	33	4	8	1
CA10	223	16	51	9	30	3	10	2
CA12	276	19	100	11	44	3	12	3
CA13	177	21	80	7	28	5	14	4
Total	**1469**	**141**	**427**	**48**	**489**	**36**	**72**	**12**

Need for the RFA Mechanism

- Assurance of NCI interest in technology development
  - Designed to address a specific need that other initiatives are not currently meeting.
  - Investigators at every stage of their career, but especially young investigators, do not consider the NIH and NCI as interested in supporting technology development research.

- Control over responsiveness and review
  - Administrative responsiveness determination, controlling the locus of review, and ability to work with DEA Scientific Review Officers seen as critical to managing the program.
  - Without the RFA mechanism, use of these elements are at the discretion of NIH/CSR.

Summary of Reissuance Request

Innovative and emerging molecular and cellular analysis technologies for cancer		
R21	~18-20 new awards per year	~$5M 1st year Total Cost
R33	~10-12 new awards per year	~$4M 1st year Total Cost
Innovative and emerging biospecimen science technologies for cancer		
R21	~4-5 new awards per year	~$1.2M 1st year Total Cost
R33	~2 new awards per year	~$0.8M 1st year Total Cost

Total: 34-39 new awards per year; ~$11M 1st year Total Costs

Selected Questions from BSA Subcommittee

- From a historical perspective, what has this program accomplished in terms of technological advances?
- How has this initiative advanced cancer research?
- Would the newly developed technologies have occurred without this initiative?
- Why is the number of applications decreasing?