

Concept for RFA Reissuance  
(CA07-020)

**Alliance of Glycobiologists for  
Detection of Cancer:  
A Trans-NIH Program**

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*Division of Cancer Prevention*





# ALLIANCE of GLYCOBIOLOGISTS

For Detection of Cancer and Cancer Risk

## The Mission

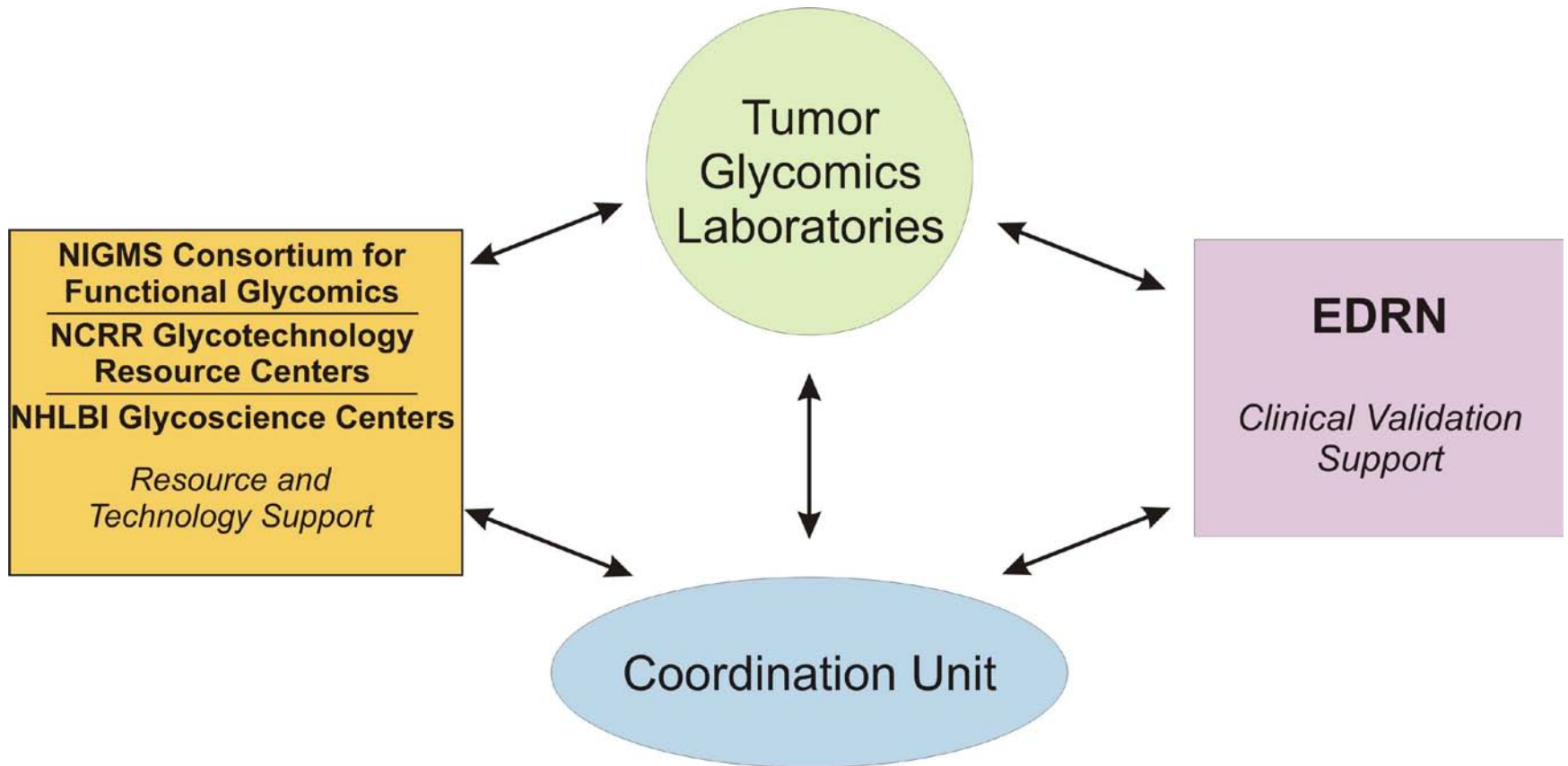
- Elucidate the structure and function of glycans that contribute to oncogenesis.
- Exploit aberrant glycosylation in cancer for the development of translational applications for cancer prevention, detection, and diagnosis.

# Background and History of the Alliance

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- Funding initiated in July 2007 to bolster research in an emerging area of research, not adequately supported by other funding mechanisms in NCI grants portfolio (<20 grants).
- NCI funded seven Tumor Glycomics Laboratories: \$3.2 M per year total costs.
- Leverage existing infrastructures of other NIH programs
  - Consortium for Functional Glycomics – NIGMS
  - Glycotechnology Resource Centers – NCRR
  - EDRN - NCI
- Collaborations among Alliance laboratories and with external investigators facilitate the pace of progress on glycan cancer targets.

# Structure of the Alliance



# Tumor Glycomics Laboratories

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William Hancock, Ph.D. – Northeastern Univ.

Michael Hollingsworth, Ph.D. – Univ. of Nebraska

Margaret Huflejt, Ph.D. – New York Univ.

Milos Novotny, Ph.D. – Indiana Univ.

J. Michael Pierce, Ph.D. – Univ. of Georgia

Ajit Varki, M.D., Ph.D. – Univ. of California, San Diego

Denong Wang, Ph.D. – SRI International

(Reissuance will be an open competition.)

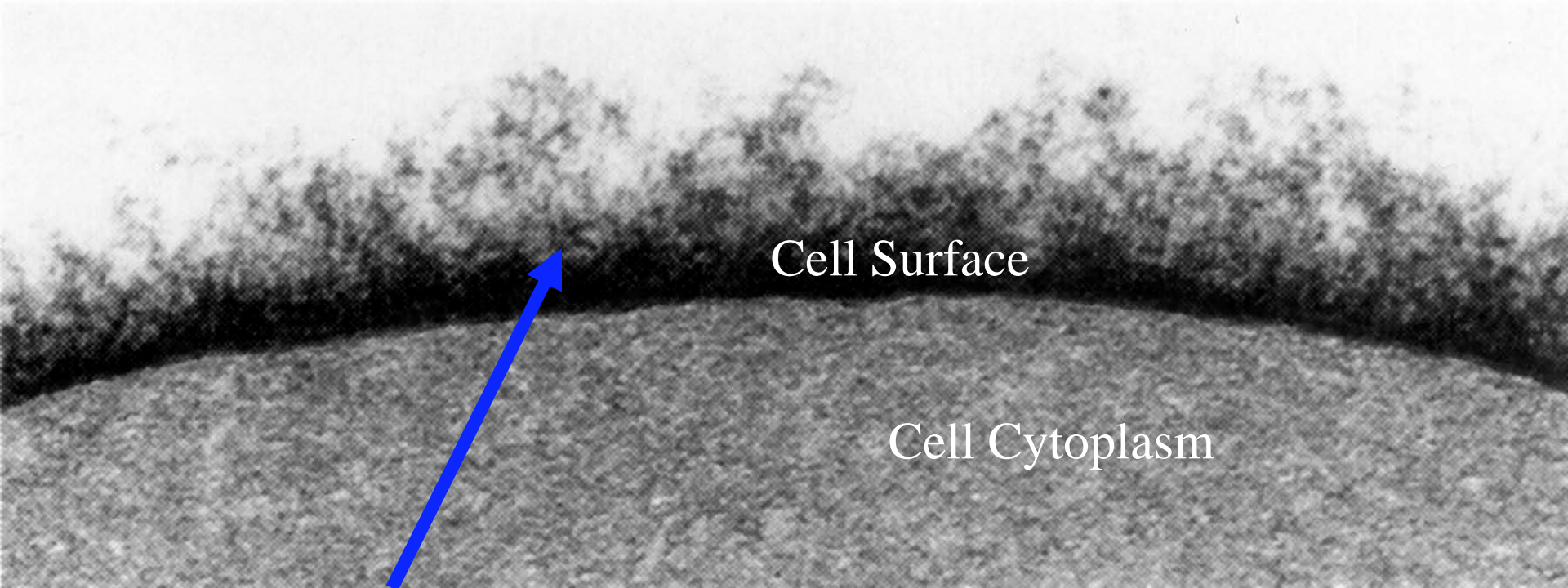
# Openly Available Tools and Reagents

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- High-quality synthetic glycan/glycopeptide arrays in various formats
- Bioinformatics tools for glycan microarray analysis
- Human chromosomal “glyco-genome map”
- Monospecific antibody for N-glycolyl sialic acid
- Automated platform to fractionate the human plasma glycoproteome
- Protocol to analyze N-glycan profiles from as little as 10 ul of serum
- Development of a bacterial protein to isolate GPI-anchored glycoproteins

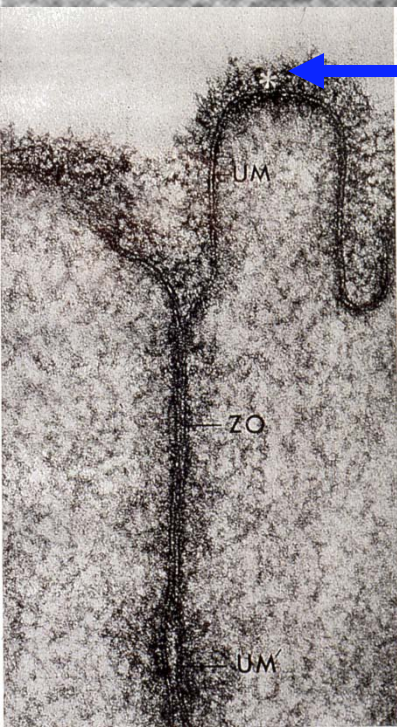
# Scientific Rationale

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Cell Surface

Cell Cytoplasm



## Glycocalyx

- All cells are “**sugar-coated.**”
- Proteins can recognize and bind to specific glycan structures.
- Some key functions mediated by glycans include:
  - Cell-cell & cell-matrix interactions
  - Protein/receptor regulation (e.g. Her2, Notch)
  - Proper protein folding & maturation during translation



# Why promote glycoscience for cancer research?

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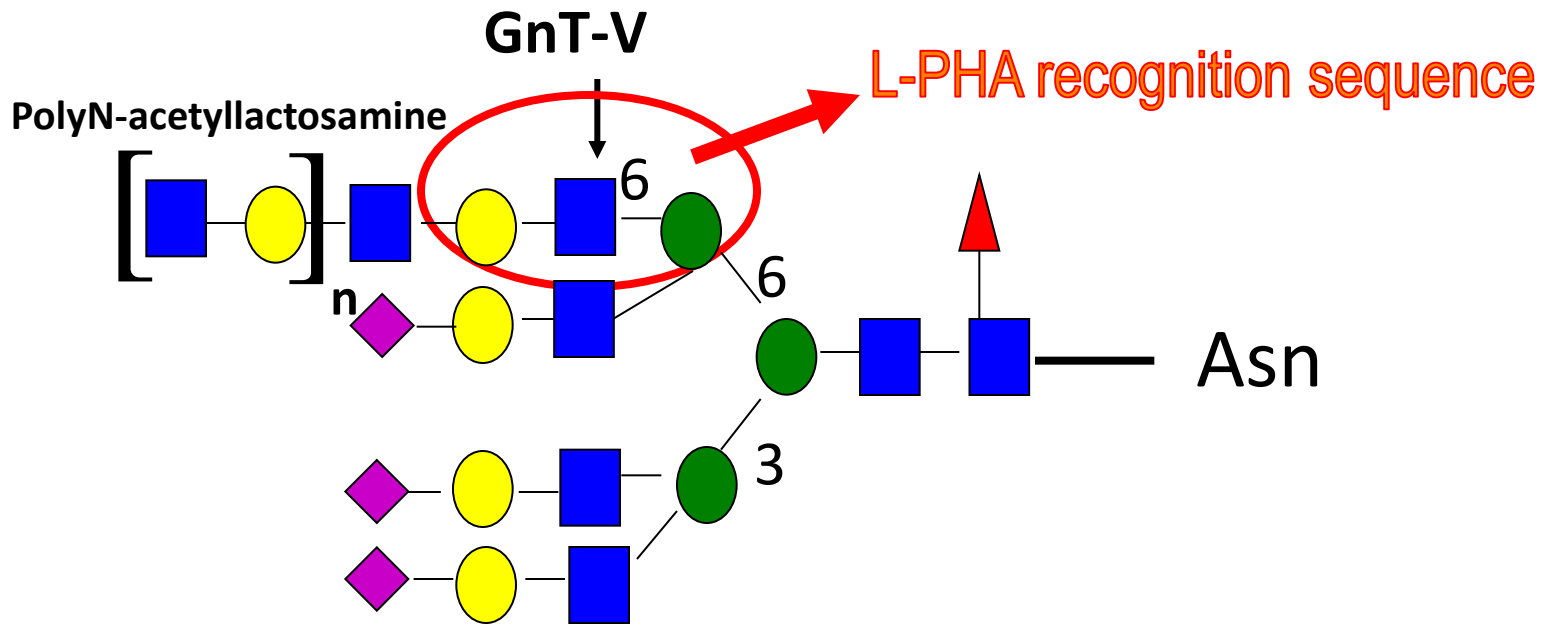
- Altered complex carbohydrate expression occurs during oncogenic transformation and contributes to growth, invasive and malignant cellular properties.
- Glycans represent a fertile area for diagnostic and therapeutic applications that remains largely untapped. *Most FDA-approved cancer biomarkers are glycoproteins, but little is known on how their glycan structures are altered in cancer where diagnostic performance could be greatly improved.*
- Attract a special cadre of scientists to exploit fundamental aspects of cancer biology.

# Highlights of Progress Since 2007

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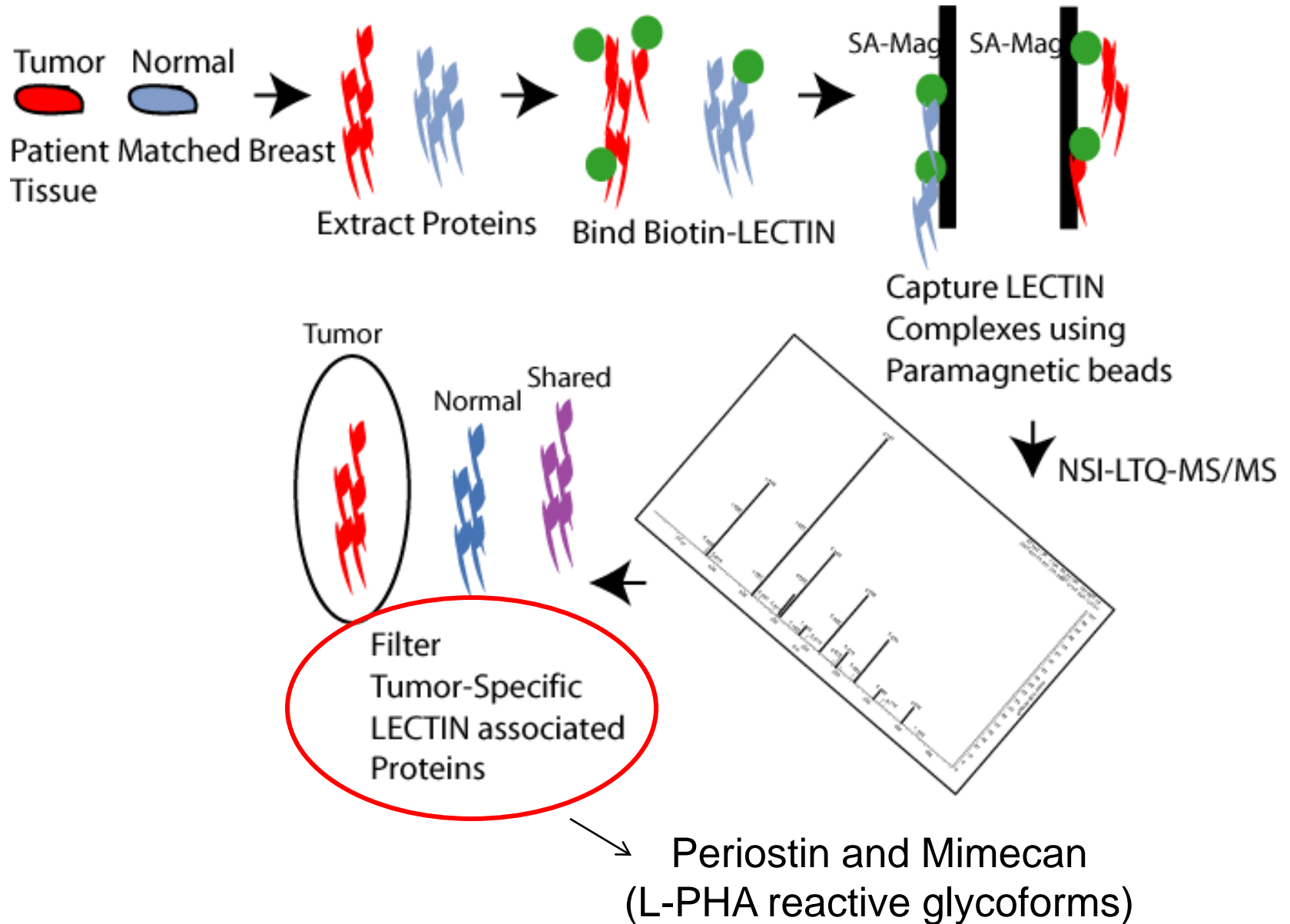
- Nine novel glycan structures associated with cancer identified on glycoproteins or glycolipids.
- Over twelve tumor-derived glycoproteins with altered glycans have been identified. Verification studies are planned.
- Discrete N-glycan profiles identified in sera from breast, prostate, esophageal, and liver cancers.
- Aberrant under O-glycosylation of mucins results in the appearance of anti-mucin IgG profiles of cancer patients.
- Specific anti-glycan antibody profiles found in cancer patients.

# The $\beta(1,6)$ branched N-linked glycan synthesized by GnT-V



- ▲ Fucose
- Galactose
- Mannose
- N-Acetylglucosamine
- ◆ Sialic acid

# Targeted Glycoproteomics for Breast Carcinoma



# Future Directions for the Alliance

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- Validation of candidate glycan markers.
- Integrate recent developments of basic cancer biology to guide the search for glycan targets.
  - Cancer genome sequencing reveals tumor suppressor genes, e.g. *GALNT12* (Markowitz & Vogelstein).
  - Signaling pathways alter the glycotranscriptome.
  - Potential collaborations with TCGA.
- Continue to exploit immune system responses to cancer-specific glycans providing new leads to prevention.
  - Autoantibodies as early detection markers.
  - Immune tolerance mediated by glycan-binding proteins.
  - Contribution of glycans to chronic inflammation and progression.

# Program Relevance

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- This fully integrated initiative develops glycans with significant implications for effective prevention, diagnosis, and treatment research.
- Alliance maximizes use of limited resources and stabilizes investments in research over the long term by leveraging collaborations with other ICs and international scientists.
- The Alliance engages critical scientific disciplines (chemical sciences) to study an important spectrum of research opportunities in cancer detection.

# Why Renew this Initiative?

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- Enable follow-up and verification of promising targets.
- The overall NIH portfolio of grants and contracts for glycoscience continue to be low necessitating other ICs to issue new targeted RFAs (NHLBI, NCRR, NIGMS).
- There is little evidence of overlap with traditional funding mechanisms because the Alliance is more involved with “translatable discovery”.

# How does having a network add value?

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- Provide access to scientific expertise and resources beyond the scope of their individual laboratories.
- Alliance is based on sharing reagents, technologies, and resources to develop translatable products.
- Alliance makes experimental data publically available through the NIGMS-supported glycans database at MIT.
- Provides a setting for the testing and evaluation of innovative “high risk” research that may be difficult to fund through traditional mechanisms of support.



# Rationale for Coordinated Glycan Research

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- While studies conducted by individual investigators have been useful in advancing our understanding of cancer glycobiology, the systematic application of glycans in preclinical tumor development, early evaluation of new techniques, and their clinical application has lagged behind.
- As a consequence, much work in this area has been fragmented into numerous small and disconnected studies without complete evaluation. Usually, the results of these studies cannot be generalized to the population as a whole.

# Funding Mechanism: U01 (Cooperative Agreement)

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- Coordinate interactions and collaborations among the Tumor Glycomics Laboratories. (They become colleagues rather than competitors.)
- Ensure access to state-of-the-art resources, quality clinical specimens, or epidemiological expertise through other participating NIH programs.
- Facilitate collaborations with other scientists having relevant research projects or technology platforms.

# Why are set-asides needed to fund this type of research?

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- Need incentives to attract the leading glycobiology experts to do cancer research with defined clinical goals. Traditional funding mechanisms are not suited for an emerging field.
- Set-asides will ensure that a critical mass of quality researchers will be achieved to attain the synergy and integration needed for an important program.
- Establish a core of integrated glycobiologists to facilitate the development of cancer glycobiology for prevention and diagnostic applications. Separate contributions from independent R01s will not be easily integrated and not generalizable.

# Partnering Institutions

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National Institute of General Medical Sciences – *Consortium for Functional Glycomics* (Pamela Marino, Ph.D., Program Director)

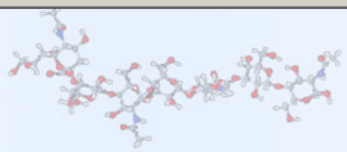
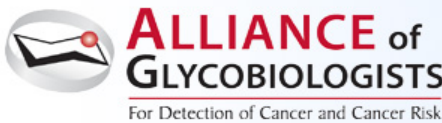
synthetic glycan standards & reagents, multiple glycan arrays

National Center for Research Resources – *Glycomics and Glycotechnology Centers* (Douglas Sheeley, Ph.D., Program Director)

MS platforms, analytical technologies, glycotranscriptomics

National Heart, Lung, and Blood Institute – (tentative) *Programs of Excellence in Glycoscience* (Rita Sarkar, Ph.D., Program Director)

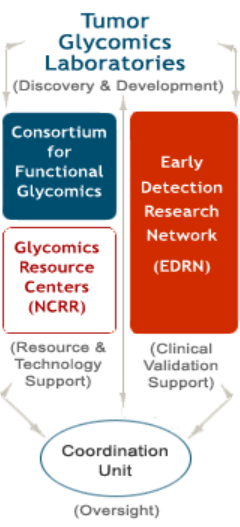
resources for glycoconjugate analysis, glycan synthesis, and analysis of protein/glycan interactions



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### STRUCTURE of the ALLIANCE of GLYCOBIOLOGISTS

For Detection of Cancer and Cancer Risk



- Partners
- CFG nature functionalglycomicsgateway Learn more
  - National Center for Research Resources Learn more
  - Early Detection Research Network (EDRN) Learn more

## Welcome

Welcome to the website for the Alliance of Glycobiologists for Detection of Cancer and Cancer Risk, a consortium of seven Tumor Glycomics Laboratories and research partners. The Alliance is working to reveal the cancer-related dynamics of complex carbohydrates, and to develop new validated, clinical biomarkers for early cancer detection and risk assessment.

By combining resources and expertise, the Alliance brings an unrivaled strength to this emerging field. Here you will find [publications](#), recent [news and media](#) coverage, upcoming [meetings and events](#), [contact information](#) and scientific [resources](#) from Alliance [members](#).

### Mission

The mission of the Alliance is to study structure and function of glycans in relation to cancer development towards developing clinically useful biomarkers for the early detection of cancer by using a variety of approaches and technologies. This charge also requires extensive collaborations across institutions with different skills and facilities to accelerate glycan-based biomarkers to the forefront of NCI's efforts to detect and diagnose cancer at early stages.

The unique needs of the laboratories for technologies embracing carbohydrate chemistry are further supported by the [Consortium for Functional Glycomics \(CFG\)](#) through the National Institute of General Medical Sciences (NIGMS), and the Glycomics and Glycotechnology Resource Centers through the [National Center for Research Resources \(NCRR\)](#). The Alliance will closely work with the NCI's [Early Detection Research Network \(EDRN\)](#) to validate promising glycans for clinical use.

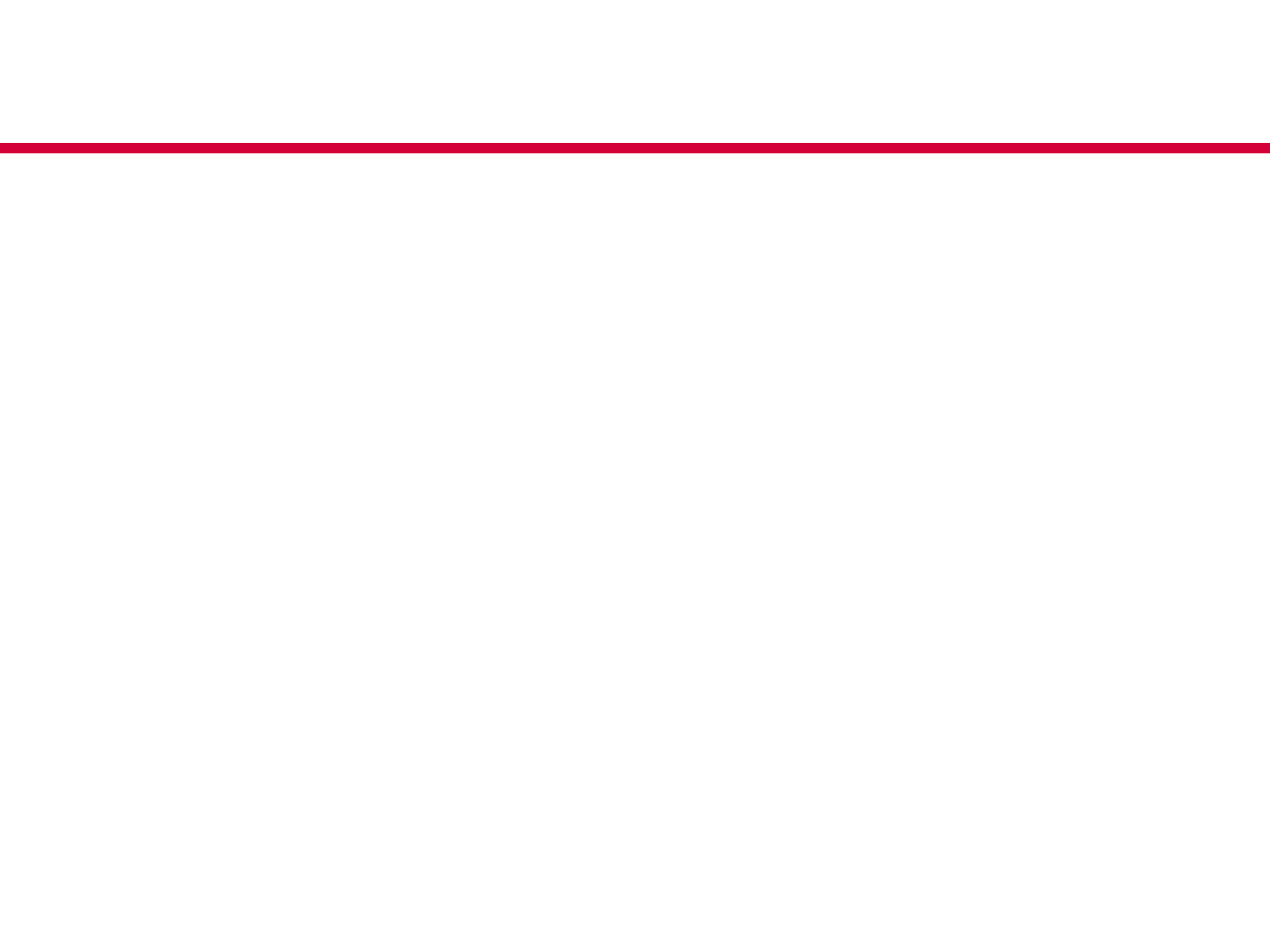
A Coordination Unit (CU) representing seven Tumor Glycomics Laboratories, CFG and EDRN, and program staff from NCI, NIGMS and NCRR integrates the activities of the Alliance.

#### In Focus

[Specific posttranslational modification regulates early events in mammary carcinoma formation.](#)

Proc. Natl. Acad. Sci. USA, 2010, Nov 15

[More news](#)



# Think-Tank On Post-Translational Modifications

## Onco-Glycomics

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- DCP sponsored a Post-Translational Protein Modification (PTM) Workshop. Recommendations were published in *Molecular and Cellular Proteomics* 5(10): 1799-1810, 2006.
- Concerted efforts are required to answer some intriguing questions:
  - To what degree does altered protein glycosylation during oncogenesis drive or potentiate the formation and progression of different types of cancer?
  - How does the immune system recognize and respond to tumor-associated glycans? Understanding of “self/non-self” discrimination of the tumor-derived glycans by the immune system will lead to identification of targets for detection, prevention and treatment
- PTMs are receiving increased attention by AACR, AACCC, and the Institute of Medicine (IOM) which is considering a workshop on Glycomics in collaboration with many ICs.

# Implementation of Recommendations

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- Alliance of Glycobiologists was started in July 2007.
- Model of collaboration is unique because the Alliance is leveraged through ongoing programs, such as the Consortium for Functional Glycomics (NIGMS) and Centers for Glycomics and Glycotechnology (NCRR).
- Alliance is built on basic science discoveries emanating from years of investments by NIH ICs.
- Alliance is focused on onco-glycomics as it relates to discovering targets for prevention, early detection and treatment.