Alliance of Glycobiologists

for Detection of Cancer

Manual of Operations

Version 3.0

Revision History

Version	Date	Change
1.0	8-14-07	Created Sections 1, 2, and 3
2.0	10/24/07	Revision 1
2.1	11/23/07	Revised after first teleconference
2.2	11/27/07	Revised after comments from BH and KK
2.3	1/22/08	Revised after discussion during December conference call
2.4	1/31/08	Section on Collaborative Resource Funds revised
2.5	5/28/08	Sections 3.1.3 and 3.1.6 revised on CR Funds priorities and review process
3.0	12/13/12	Revised to accommodate changes with second funding phase

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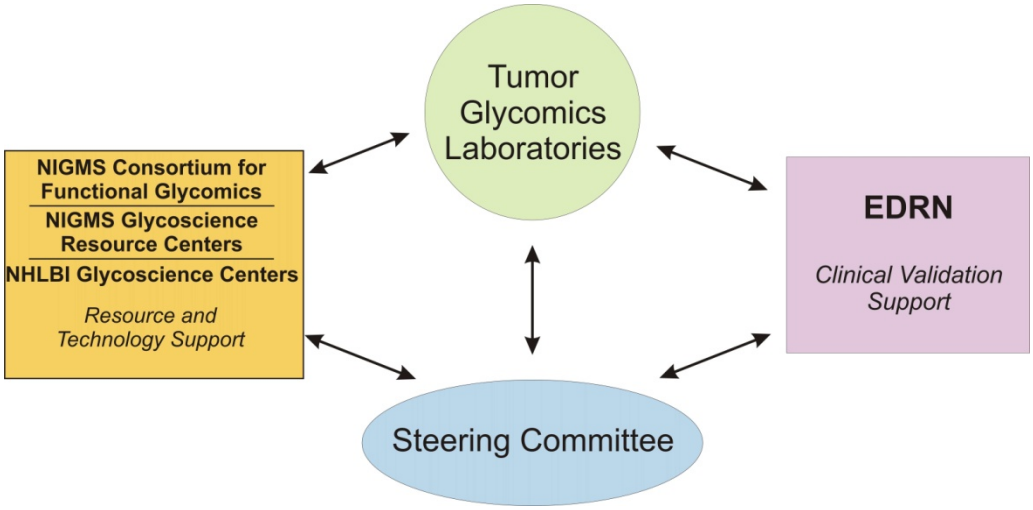
SECTION 1 ORGANIZATION AND DEVELOPMENT

The Division of Cancer Prevention in the National Cancer Institute created the Alliance of Glycobiologists for Detection of Cancer (the Alliance) for supporting investigator-initiated, collaborative research on glycomic-based biomarkers for cancer detection and risk assessment. The Alliance may also be denoted the Alliance of Tumor Glycomics Laboratories. A number of NCI programmatic review groups recommended that funding for this new consortium be established to support developments in this underexploited field of cancer research and translational development.

The Alliance includes three components to facilitate discovery, development and validation of cancer biomarkers:

- **Tumor Glycomics Laboratories** – These laboratories form the core component of the Alliance. They are responsible for discovery, characterization and development of new or refinement of existing glycan-based biomarkers. In response to RFA-CA-07-020 each tumor glycomics laboratory assembled four subcomponents essential to meet this task: 1) Biomarker Discovery Component; 2) Carbohydrate Analytical Component; 3) Clinical Specimen Component; 4) Statistical Support Component
- **Programs supported by other institutes:** The Consortium for Functional Glycomics (CFG) and Glycomics and Glycotechnology Resource Centers (formally administered by NCRR) are funded by the National Institute for General Medical Sciences (NIGMS) and are available to provide specialized reagents, services, and technology requirements for the unique needs of the tumor glycomics laboratories analyzing complex carbohydrate structures. The Programs of Excellence in Glycoscience (PEGs) supported by NHLBI are also developing various core resources that could be of interest to the Tumor Glycomics Laboratories, as well as providing training opportunities to educate students and investigators in glycoscience.
- **The Early Detection Research Network (EDRN)** – Funded by the NCI, the chief mission of EDRN is to promote advancement of biomarkers for early detection, diagnosis, or risk of cancer through clinical validation. The EDRN will participate with the Alliance to facilitate clinical validation of biomarkers developed by the Tumor Glycomics Laboratories. This unique collaboration should minimize the time necessary to see translation of diagnostic tests for clinical application.



The Alliance is governed by the Steering Committee, consisting of the Principal Investigators of the Tumor Glycomics Laboratories, representatives from the partnering programs, and NIH program staff from NCI, NHLBI, and NIGMS.

These procedures provide guidance for the administrative and operational activities of the Alliance and may be modified or revised by approval of the Steering Committee as experience and need dictates. Any member in good standing (i.e., a member who attends at least one Steering Committee meeting per year) may propose amendments to the procedures.

(The operating procedures were initially approved November 2007 by the Coordination Unit (Steering Committee as it was called at that time).

1.1 Statement of Objectives

- To support and facilitate a broad spectrum of research activities that identify cancer-related abnormalities associated with glycans and glycoconjugates having the potential to serve as cancer biomarkers. These research activities will involve a progression typified by: (a) the use of a variety of platforms and technologies for discovery of specific glycans or characteristics of glycan profiles that correlate with defined cancers; (b) the performance evaluation in terms of sensitivity and specificity of these biomarker candidates in case versus control clinical specimens; and (c) culmination in translational efforts to test the most promising biomarker candidates in clinical validation studies.
- To place highest priority on biomarkers for early detection and primary prevention of cancer, however, markers for diagnostic clinical testing of cancer or stratification of cancer risk also fulfill the mission of the Alliance. It is possible that markers for prognosis or prediction of response to therapy may arise from this research, and where appropriate, these additional biomarker applications may be explored.
- To function as a highly collaborative consortium facilitating cancer glycan biomarker discovery and development. Collaboration will be fostered through open discussion of research developments and discussions of strategies to most efficiently interrogate complex carbohydrates of clinical significance.
- To contribute to the development of glycan structural databases maintained by the Consortium for Functional Glycomics (CFG). All new structures elucidated from efforts supported by Alliance funding will be deposited into the CFG database maintained at the Massachusetts Institute of Technology.
- To promote collaboration and communication with other relevant programs at the NCI, other Institutes within NIH, and academic and industrial leaders where the research interests coincide with the mission of the Alliance.

SECTION 2 STEERING COMMITTEE

2.1 Overview

The Steering Committee (SC) has major scientific management, oversight, and responsibility for developing and implementing a collaborative research program within the Alliance. The Committee consists of a Chair, Co-Chair, the Principal Investigators of the Tumor Glycomics Laboratories, a designee from each of the partnering programs, and Program Coordinators from NCI, NHLBI, and NIGMS.

Members of the SC review data for supporting studies leading to validation studies, offer recommendations on strategies to expedite biomarker progression to validation status, determine when specific biomarker studies are ready for larger scale clinical validation, and monitor study results of these validation studies as they progress. The SC members also determine the rules by which the Alliance will govern itself, appropriate use of Collaborative Resource Funds for defined purposes, and propose collaborations with external scientists whose research interest or technology platforms are in line with the mission of the Alliance. Each Principal Investigator and the NCI Program Officer has one vote. The remaining SC participants act as *ex officio* members and provide valuable guidance concerning issues involving their areas of responsibility.

According to the requirements of the Cooperative Agreement, each Principal Investigator (PI) should attend the annual SC business meeting and one scientific workshop each year. In cases where the Principal Investigator cannot attend a SC meeting at least one representative from that Cooperative Agreement must be present. Additional meetings may be called as needed. The time and site for SC business meetings are determined by SC members. The minutes of the SC meetings are prepared by a specified party as a matter of record and distributed to the members of the SC for approval at the next meeting. NCI reserves the right to terminate a grant for failure to attend or have representation at SC meetings. Each PI may use her/his discretion in choosing to attend a scientific workshop covering the topics of glycobiology or biomarkers (such as EDRN-sponsored workshops).

Every PI will serve as a voting member of the Steering Committee, will attend the initial Planning Meeting for the Alliance, and will attend subsequent SC meetings or specify a senior investigator to represent the Tumor Glycomics Laboratory. The SC will also convene by conference calls throughout the year on a schedule to be decided by consensus and majority vote by the SC. The attendance of the PI at SC meetings and at least two-thirds of the scheduled conference calls is considered an essential part of the grant. Applicants must budget for travel and per diem expenses for SC meetings. In the first year, applicants should plan for two investigators, the Principal Investigator and an additional senior investigator, to attend a Planning Meeting, SC meeting, and one appropriate scientific workshop. In the second and subsequent years, applicants should plan for the PI or senior investigator to attend the SC meeting and one workshop per year.

SC conference calls are vital to keep abreast of recent developments within the Alliance, provide opportunities for sharing of ideas, strategizing experimental approaches for biomarker discovery, and allows time do address administrative responsibilities of the Alliance such as approvals to spend Collaborative Resource Funds. All coinvestigators from the Tumor Glycomics Laboratories may attend conference calls. Scientists from outside the Alliance can be invited to attend individual conference calls as agreed upon by a majority of

the SC. For each conference call every Tumor Glycomics Laboratory must be represented by at least one attendee, and PIs are required to attend a minimum of two-thirds of these calls.

2.2 Responsibilities and Privileges

- Develop guidelines for operation of the Alliance.
- Coordinate the research program and foster collaboration within the Alliance by establishing or refining policies and procedures for collaborative projects, protocols, and Alliance-defined projects.
- Develop criteria for reviewing progress of the Alliance and establish policies for reviewing changes in projects not showing translational significance at the request of the laboratories/centers.
- Establish and track realistic milestones.
- Develop and implement rules for sharing data and resources.
- Establish procedures for submission of requests and policies for allocations of Collaborative Resource Funds.
- Develop criteria for including external scientists to participate with in Alliance activities and establishing policies for them to request Collaborative Resource Funds.
- Develop “decision criteria” for promoting promising biomarkers for clinical validation studies and determine their clinical utility such as testing early detection markers, or as risk factors.
- Develop and approve protocols to be followed in validation studies.

2.3 Chairs

The Chair and Co-Chair are elected by the full SC. Any member of the SC can offer nominations for the Chair and Co-Chair. The term of office for the Chair and Co-Chair is five years with eligibility for re-election for one additional term (for a total of 10 yrs) if funding of the Alliance is continued for another round. The Chair and Co-Chair will, if possible, alternate yearly the primary Chair duties.

2.3.1. Duties of the Chair

- Preside at all meetings of the full SC when present.
- Appoint ad-hoc committees as needed or recommended by the SC and designate special assignments within these groups as needed.
- Invite consultants as needed for particular Alliance activities.
- Submit annual Progress Reports on the Alliance to NCI.
- Prepare the agenda for SC meetings with assistance from NIH program staff.

2.3.2. Duties of the Co-Chair

- Serve as acting Chair at SC meetings/conference calls where the Chair is absent. The Co-Chair will assume the primary duties of the Chair on alternate years (years 2 and 4).

2.4 Quorum

For holding meetings, including conference calls, a quorum is defined as the presence of the majority of SC members. If a quorum is not present, voting on any issues cannot occur.

2.5 Rules of Conducting Meetings

Robert's Rules of Order will govern the conduct of meetings of the Alliance

SECTION 3 POLICIES AND PROCEDURES

3.1 Funds

3.1.1. Definitions

There are two sources of additional funds available to the Alliance investigators: Collaborative Resource Funds and EDRN Core Funds.

Collaborative Resource Funds (CR Funds) are provided through set-aside funds built into each U01 award. These funds are reserved for various post-award necessities of the Alliance to encourage collaborations between Alliance investigators or outside investigators.

EDRN Core Funds can only be used for supporting validation studies of biomarkers developed by Tumor Glycomics Laboratories. Application and access to these funds is described in the EDRN Manual of Operations.

3.1.2. Use of Collaborative Resource Funds

CR Funds are reserved to establish collaborative research projects with other members of the Alliance or with outside investigators to facilitate research that meets the objectives of the Alliance for early detection or prevention of cancer. Specific uses of CR Funds include:

- CR Funds may support collaborative research projects between Tumor Glycomics Laboratories. This will likely involve sharing specific technologies between laboratories to synergize their research efforts.
- CR Funds may be used to partner with an investigator outside the Alliance who is willing to share a particular technology platform or to advance biomarkers provided the collaboration meets the objectives of the Alliance. In this context, CR Funds may support “pilot projects” that evaluate an interesting finding or reagent, such as an antibody or lectin that is of particular interest to the Alliance.
- CR Funds can be used for access to special resources or procurement of unique reagents available through Alliance partnering programs, such as the Consortium for Functional Glycomics, NIGMS Glycoscience Resource Centers, Programs of Excellence in Glycoscience (PEGs), or the Early Detection Research Network (EDRN).
- CR Funds can be used to support clinical validation studies of biomarkers developed within a Tumor Glycomics Laboratory. These funds may support tests needed to analyze large numbers of blinded samples from EDRN reference sets or enable procurement of existing clinical specimens for the validation trial if appropriate specimens do not exist.

3.1.3. Policies and Procedures for Release of the Set-Aside Collaborative Resource Funds

The request for release of CR Funds must be single-spaced and follow NIH Format, as used in PHS Form 398. It should be organized and submitted as follows:

1. Title Page (page 1 of the PHS Form 398). Description (Abstract), Performance Site(s) including, if applicable, the site providing the required resources/services. The application must be signed by the grantee institution's business office.

2. Scientific Proposal (maximum of 5 pages), may be organized as you feel appropriate for the following categories.

   A. *Intra-Alliance Collaboration* – Collaborations between two or more Tumor Glycomics Laboratories may take different forms but should capitalize on the strengths of the different labs. Specific details should be included that describe the roles and responsibilities of each Laboratory and how this collaboration will enhance the current project(s). Budget allocations (see below) by each Laboratory can only be requested within the set aside amount specified in their U01 Notice of Award.

   B. *Collaboration with External Investigators* – Provide rationale and background of the proposed platform or biomarker to be investigated in conjunction with your laboratory. As appropriate, include preliminary data or enlarge any unique technology describing how the Alliance will benefit.

   C. *Resource Needs for a Tumor Glycomics Laboratory* – Provide a detailed description of the reagents, resources, or services needed with a justification for why they cannot be obtained through standard sources.

   D. *Clinical Validation Studies* – Provide data on the biomarkers demonstrating their readiness to be tested in a blinded validation study. Indicate the clinical context for which the biomarker is being tested (early detection of prevalent cancer in a defined population, determination of indolent vs. aggressive disease, etc). Provide details on the specimens to be tested, including numbers, pathological details on the cancers, matching of controls to cancers, and where these specimens will be obtained from. Note that this type of information is available for all EDRN reference sets. Since you will be blinded to the specimen status before and during testing, specify who will receive your data to analyze the biomarker(s) performance and at what point will unblinding occur.

   E. *Multiyear Projects* – If justified by the scope of the proposed project, it is possible to request funds for more than one year. Consideration of funding subsequent years is discussed below under the section on Review Process.

3. Budget Page - (final page unless an Appendix section is included). Use page 4 of the PHS Form 398. Adequate budget justification for direct costs is required. For multi-year projects use page 5 for budgets on subsequent years.

4. Appendix (optional).

5. One electronic copy (in PDF form) of the proposal should be submitted to the NCI Alliance Program Officer and your assigned Program Director. The application must be signed by the grantee institution's business office. Applications must be received within 90 days after the award renewal date (e.g. for a July 1 renewal date applications must be received by October 1).

All projects must comply with institutional regulations on research involving human subjects, children, minority groups, gender, animals, recombinant DNA, and hazardous materials. Appropriate approvals from the relevant committees, including approval from institutional review boards, must be submitted to your assigned Program Director before funds can be provided for successful applications.

3.1.4. Review Criteria

Review criteria for CR Funds are based on the following principles, as relevant, for the different request categories described above:

- Scientific merit
    - potential to discover and/or develop new glycan-based biomarkers or to significantly facilitate the development of glycan-based biomarkers currently under study
    - collaborative potential to draw on complementary features of both labs
    - compatibility with Alliance objectives
    - potential to develop new tools or technologies
- Well-defined needs of one or more laboratories in the Alliance requiring resources or services from labs of the partnering programs.

3.1.5 Review Process

The NCI Program Director will choose primary and secondary reviewers from the PIs and co-PIs of the Tumor Glycomics Laboratories. An NCI Program Director will also be assigned to review the proposal. An external *ad hoc* reviewer may be brought in to help evaluate a proposal that requires expertise that is not available within the Alliance. Each member of the review panel will independently review the proposal and submit a written review prior to a conference call to discuss the proposal. A brief summary of the panel's assessment of the proposal will be written by the NCI Program Director who will then forward this statement to the Alliance SC. The application will then be discussed by the entire SC during one of its monthly conference calls. Alliance PIs involved in a particular application will not participate in the discussion of that application.

Recommendations by the SC may be in four categories: 1) Not recommended for funding; 2) Resubmission of a revised proposal requested; 3) Conditional approval (where relatively minor changes or clarifications are requested for NCI Program to approve funding); 4) Recommended for funding. Applications recommended for funding will be forwarded by the NCI Program Director to NCI's Office of Grants Administration for release of the restricted set aside funds. Release of these funds will occur via a revised Notice of Grant Award.

For multi-year projects, release of funds for the second or subsequent years will require the submission of a progress report for this project included within the standard progress report for the award due 60 days before the renewal date of the U01 award. For example, for a July 1 renewal date, progress reports are due by May 1 and these should include reports of the original project(s) and a report for the collaborative research project, whether it is single year or multi-year. NCI program will assess the progress and determine whether continuation and release of the next year funds is justified for multi-year projects.

3.2. Confidentiality

The Alliance will be considered as “one” laboratory using “one electronic notebook” for all Alliance-supported efforts – so unless the public is invited – the SC meetings, including phone or video conferences, are considered ‘lab meetings.” All data (including that which has not yet been made public) are available through the electronic notebook to members of the Alliance and must be held confidential by all members of the Alliance until it is published or filed for patent. Confidentiality extends to data shared via non-public areas of the Alliance website. A blanket Confidentiality Disclosure Agreement will be signed by the respective institution(s) of each Tumor Glycomics Laboratory to cover all meetings of the Alliance and any participation within EDRN meetings. If a non-member of the Alliance is to participate in a meeting of the Alliance, including phone and video conferences, a non-disclosure agreement must be signed by the participant(s) in advance of the meeting if confidential information from Alliance investigators will be disclosed.