RFA Concept:
Glioblastoma Therapeutics Network (GTN)
Presentation to the NCI BSA

Based on Report & Recommendations, Glioblastoma Working Group

NCI Clinical Trials & Translational Research Advisory Committee (CTAC)

NIH NATIONAL CANCER INSTITUTE

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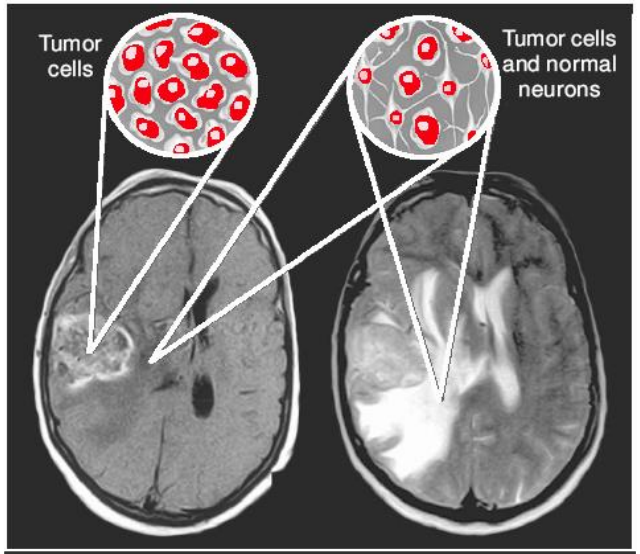
Glioblastoma (GBM)

- **Incidence: 13,000 new cases annually in US**
- **Standard Tx: Surgery, Radiation, and Temozolomide**
  - **Median overall survival ~15 months**
  - **5-year survival ≤ 5%**
  - **Tumor Treating Fields: +6m OS, selective use**
- **Pathophysiological challenges in developing effective GBM therapy:**
  - **Cannot resect adequately w/o neurological compromise**
  - **Radiation tolerance of normal brain limits RT dose**
  - **Blood-Brain Barrier limits adequate drug delivery**
  - **Genomic heterogeneity reduces target agents efficacy**
  - **Immunosuppressive microenvironment reduces immunotherapy effects**



- **T1 MRI (Left):** Resectable contrast enhancing (CE) part of GBM
- **T2 MRI (Right):** Malignant cells infiltrate far beyond resectable lesion into functional brain, non-contrast enhancing (NCE) GBM part

Therapeutics success is rare in GBM

- **Recent meetings by different stakeholders to address challenges:**
  - **National Brain Tumor Society Meeting – 2017**
  - **CTEP Strategies & Approaches to Optimizing GBM Therapy – 2017**
  - **Brain SPORE/Physical Science in Oncology (PSON) Retreat – 2018**
  - **US Brain Cancer Mission Roundtable Planning Summit – 2018**
- **Consensus: Urgent need to improve preclinical and early clinical qualification of agents for Phase 3 trials to increase success in GBM**

GBM Working Group: Major RFA Recommendations

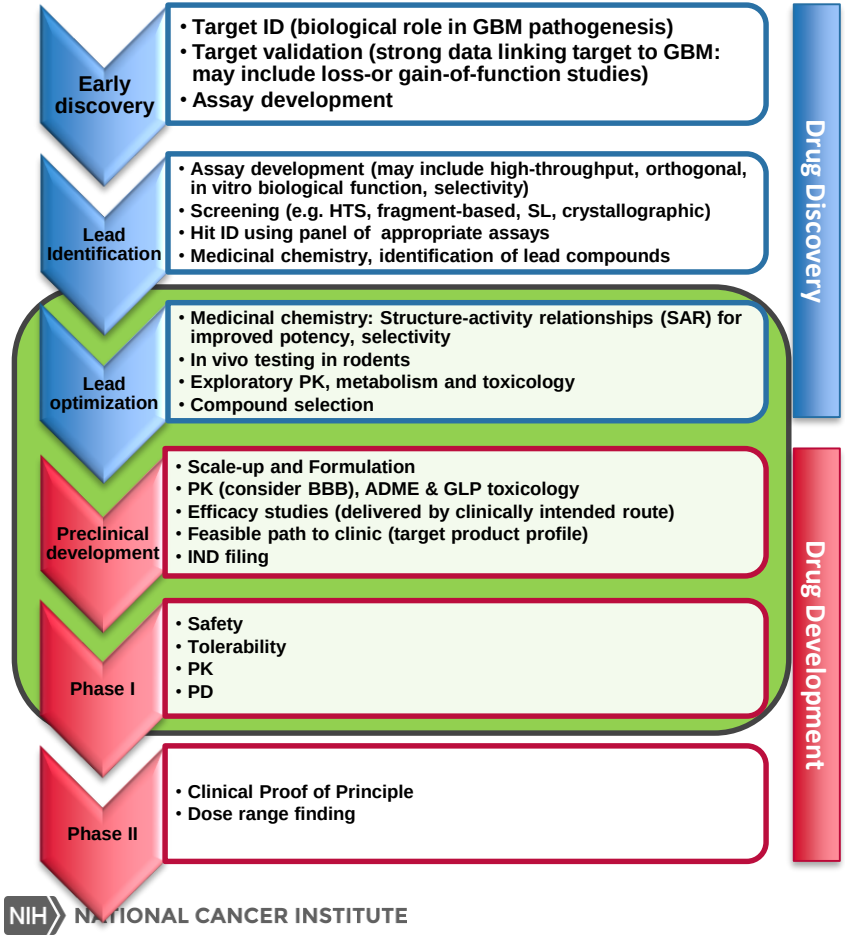
- Convened by CTAC to identify critical research gaps and define opportunities to improve therapy
- Overall recommendation (WG report, July 17, 2019):

Establish a national infrastructure to enhance support for discovery and development of GBM therapies, with five areas of research capability:

1. **Preclinical qualification of new agents**
2. **Clinical trials driven by molecular pharmacodynamics (PD) and imaging**
3. Immunotherapy
4. Improving radiation therapy efficacy
5. Improving the quality of life of patients

Purpose of the RFA: Improve the treatment of adult GBM by developing novel effective agents and testing them in the clinic.

Key Guidelines for FOA



- Focus on late Drug Discovery through Phase I clinical studies (green area in pipeline diagram)
- Possible agents include small molecules, biologics, and/or radiotherapy
- Testing in animal models that closely mimic human adult GBM
  - Extensive model development is outside scope
  - Models should include assessment of passage through BBB and ideally allow for repeated testing of tumors over the course of treatment
- Aim for early-phase proof-of-mechanism clinical trials that include PK, PD and imaging; and include multiple clinical centers
  - Phase II and beyond is outside scope

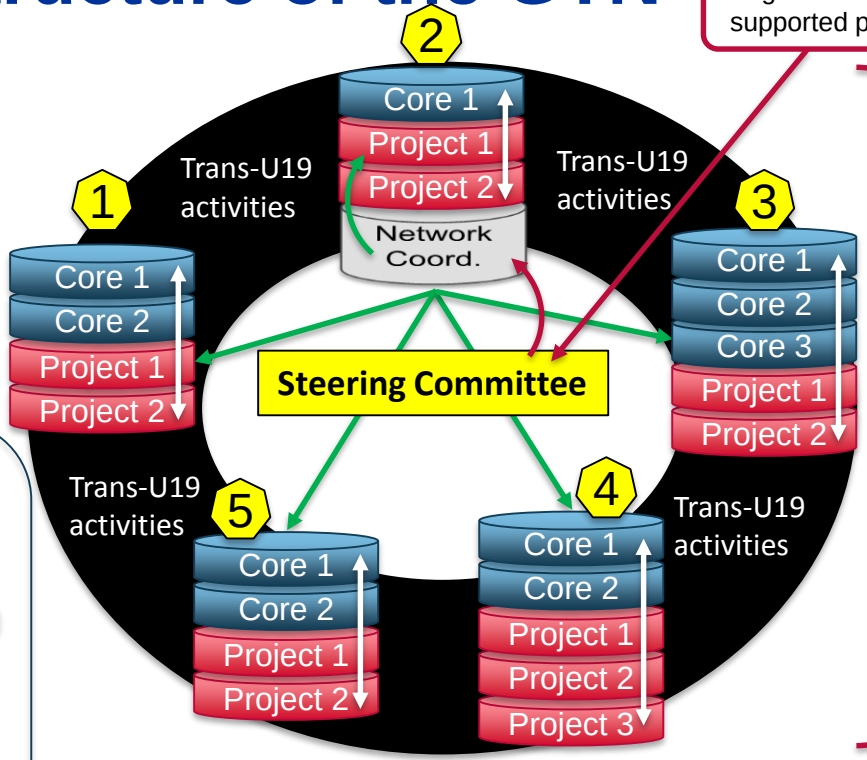
Implementation Plan

- **Create a national GBM Therapeutics Network (GTN) of cross-cutting teams using the U19 mechanism**, each team capable of:
  - Driving novel agents from the development stage through IND studies and into pilot clinical studies in humans, or;
  - Repurposing and testing approved agents and/or combinations* that appear to be efficacious in GBM.
  - Conducting PD-driven clinical trials.

*Combinations of new or repurposed agents with: targeted agents, immunotherapy, and/or standard-of-care (temozolomide and radiation)

Possible Structure of the GTN

One U19 has a **network coordination center** (gray) with scientific and administrative coordination roles for the GTN (green arrows); up to $500K TC/year allowed for the coordination center



Drugs from other NIH-supported programs

- Up to 5 U19s (yellow numbers)
- Each U19 has 2 or more projects (red) and associated core(s) (blue)

Trans-U19 activities (black circle) include:

- Sharing of know-how and reagents
- Specific projects established between U19s after award ($50K DC/year)
- Participation as primary and secondary sites in clinical trials: U19- and NIH-supported agents

A Steering Committee will be formed, composed of representatives from each U19 team, NCI staff (extra-, intramural), funded GBM investigators, NINDS staff

Current NCI Portfolio Analysis in GBM: No dedicated extensive early drug development program

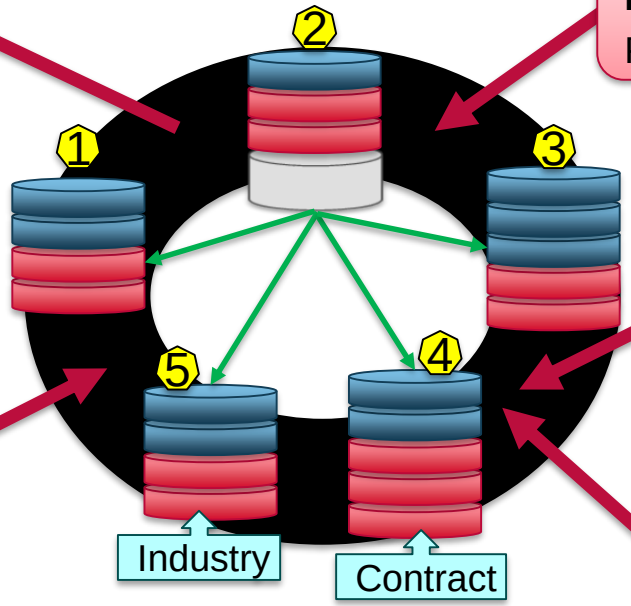
Mechanism	#	Description
R01	172	16 include interventional or imaging trial
R21	31	Exploratory Grants: None include a GBM clinical trial
R35	5	Outstanding Investigator Awards: 1 includes a clinical trial
P01	8	4 include imaging, 5 include clinical trials
P50 / SPORE	6	Drug development is not the primary focus
UM1	1	Adult Brain Tumor Consortium: Limited capacity to conduct small phase 1 & 2 trials, without preclinical drug development or correlative studies
U54 with U01 projects	6 & 2	Physical Sciences – Oncology Network: Basic/Translational for complex GBM research questions; but some grants will be phased out

NCI or NINDS grantees would be eligible to apply for a non-overlapping GTN U19

Current NCI Portfolio Analysis in GBM: Existing support to help new Glioblastoma Therapeutics Network

NCI Experimental Therapeutics Program (NExT)

NCI PDM Repository:
PDX models



PRE-medical Cancer Immunotherapy Network
PRECINCT Canine Trials

DCTD Resources:
- Formulary
- DCTD Clinical Pharmacodynamic Biomarkers Program
- DTP consultation services

Physical Sciences – Oncology WG:
- BBB structure
- Heterogeneity
- Drug distribution

Note: the Adult Brain Tumors Consortium will be ending April 2021

Justification for RFA and U Mechanisms

RFA

- Narrow scope in area of urgent need
- Recommendation of GBM WG
- Need concurrent start of funding across U19 teams to facilitate drug development and clinical trial activities
- A single receipt date is requested

"U" Cooperative Agreement

- Includes Steering Committee for transition of agents to clinic
- Incorporates trans-U19 collaborations, established post-award
- Includes monthly GTN teleconferences facilitated by Network Coordination Center

Budget Considerations

- Up to 5 U19 Awards
- Project Period: 5 years
- Total costs each year:
  - Each award $1.1 M
  - 1 Network Coordination Center $0.5 M
- RFA set-aside year 1: $6 M
- Total 5 year cost: $30 M

Evaluation: Criteria for Success

Overall goal: to develop novel agents for treatment of GBM and test in human pilot PD studies

- **Success of GTN at the end of a 5-year grant term must include trans-U19 clinical testing of one or more novel or repurposed agents. Agents may come from within the GTN or from outside (via the Steering Committee).**
- In addition, successful outcomes may include:
  - Promotion of one or more agents to IND stage, with plans for clinical testing after 5-year grant period
  - Preclinical development of one or more novel agents for GBM based on Steering Committee criteria for advancement to clinic; plans for IND submission after 5-year grant period
  - Preclinical development of combinations of novel agent(s) and standard-of-care therapy for GBM

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Rationale for choice of the U19 mechanism

NIH Guideline for U19s	Plans for this RFA
Multiple projects directed toward a specific major objective, basic theme or program goal	• Teams will have a minimum of two scientific projects and at least one core whose functions synergize toward a common set of goals • Projects and cores will vary depending on type and maturity of agent(s)
Requires a broadly based, multidisciplinary and often long-term approach	Multi-disciplinary, multi-PI projects that span multiple sites are anticipated
Can provide support for certain basic shared resources, including clinical components, which facilitate the total research effort	• Areas of expertise for success are likely to include medicinal chemistry, pre-IND in vivo modeling, drug development (drug formulation, scale-up, ADMET, PK/PD, imaging), and clinical trials development and execution • Projects may include existing NCI resources, expertise from contract research laboratories, or through public-private partnerships