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)
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.

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.

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

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

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

NCI PDM Repository: PDX models

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

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<th>NIH Guideline for U19s</th>
<th>Plans for this RFA</th>
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| 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 |