Report of the Biomedical Technology Research Resources External Review Committee May 2016

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Executive Summary

The NIGMS Biomedical Technology Research Resources (BTRR) program supports the development of novel technologies as well as collaboration support, training and dissemination of these technologies to NIH-funded researchers. This panel considered the collective outcomes of the current group of 33 BTRRs. From these data they ascertained the level of success and impact of the BTRR program and also made several recommendations for how the program could be improved.

In short, the panel was highly supportive of the BTRR program. It was felt that the BTRR centers have strong track records of success and that they have impacted a significant fraction of NIGMS funded research. Further, as technologies continue to become more advanced and complex, it was generally felt that the need for these types of national resources is only likely to increase. Together with this high level of enthusiasm, the panel did identify several areas for potential improvement of the BTRR program. Several of these suggestions are aimed at *increasing the turnover of BTRRs* and *allowing the introduction of new and more cutting-edge technologies*. Along these same lines, the panel felt *the application and review process should be altered*, and *more flexibility in BTRR program design should be allowed*. Finally, the panel *saw significant potential for better integration of the BTRR program into the overall technology development effort within NIGMS*, potentially through the introduction of companion grant mechanisms.

Introduction

The Biomedical Technology Research Resources (BTRR) program has existed for over 50 years, initially under the auspices of the National Center for Research Resources (NCRR). Its aim is to provide investigators with tools and environments that can facilitate biomedical research with the ultimate aim of detection, prevention and treatment of human diseases. NIGMS has administered the BTRR program since 2011, when NCRR was disaggregated and existing resources were transferred to NIGMS and to the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

The primary purpose of a BTRR is the development of new technologies. However, from the inception of the program, there has been a parallel imperative that each center be a resource for the biomedical research community and have a national impact. NIGMS convened a panel of experts to conduct an evaluation of the BTRR program; the panel met on December 2, 2015.

In order to assess the integration, function and success of BTRRs within NIGMS, the panel primarily focused on results and outcomes from 2007-2014. Data from this period was extracted, analyzed and summarized by the NIGMS Office of Program Planning, Analysis, and Evaluation (OPAE) and provided to the panel. All of these data were considered and discussed by the panel; much of it helped the panel members form opinions and draw conclusions, but only a small subset of the data is presented in this report.

The structure of the report that follows is based on the four key questions that were posed to the panel.

Success of the BTRR Program

The first question posed to the panel was, "*Has the BTRR program been successful in developing and distributing novel technologies of high utility to the biomedical research community?*" In addressing this question, the panel's conclusion was an unequivocal "yes." Technology development is a driving factor in science and plays an important role in supporting the hypothesis-driven R01 research in NIGMS. There were multiple factors that supported this conclusion, but one of the most compelling statistics was the fact that nearly 17 percent of NIGMS R01 grants cited support and/or use of P41 resources (see table). This rate of use was the highest among all the NIH institutes, and the panel felt it reflected significant value and benefit. Apart from impact in basic research, the BTRR program has been effective in developing and distributing technologies outside of academic boundaries. There have been a fair number of patent, patent citations, start-up companies, etc. that have arisen from BTRR activities (Appendix Figure 1).

Institute	% of Institute R01s Citing BTRRs
NIGMS	**16.6%**
NIAID	4.7%
NCI	2.9%
NINDS	2.5%
All other institutes are below 2.5%	

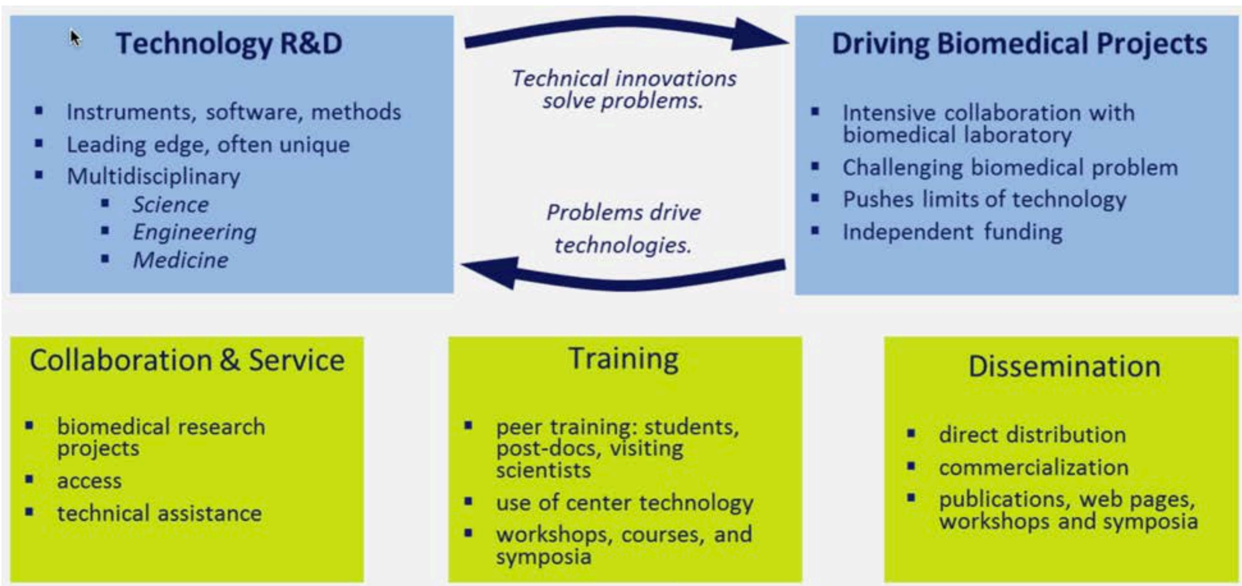
Issues and Improvements: Although the panel felt the BTRR program has been successful in its mission, there was broad agreement that it could nonetheless be improved.

- Duplication of Resources: It was generally felt that there might be some degree of duplication of resources among the current set of BTRRs (e.g., multiple sites that appear to provide similar resources for mass spectrometry or structural biology). Apart from evaluation of individual BTRRs, there should be more assessment of the overall portfolio (Appendix Tables 1-2).
- Missing Technologies: Related to the point above, it was felt that there were some missing technologies that would meet existing needs within the research community (e.g., there are no resources that provide nucleic acid technologies, etc.).
- Low Rate of Program Turnover: There was unanimity within the panel that the low rate of turnover within the BTRRs (approximately one per year) was a significant limitation. Since the overall size of the BTRR program is essentially fixed, this low rate of turnover prevents new technologies from being introduced (Appendix Figure 2).

- Better Documentation of BTRR Outcomes: The panel could assess some of the impact of technology on basic science, in part from the publication and citation information, however it was felt that more details of how novel technologies resulted in new science was needed. At the same time, it was determined there should be better documentation of patents, patent citations, and commercialization of technologies.
- Better Highlighting of BTRRs: Finally, the panel felt that the BTRRs would be better utilized if NIGMS did more to raise the visibility of the BTRR program by promotion and highlighting of their capabilities. Researchers with NIGMS R01s could avoid needless duplication of effort and perhaps save money by making use of existing expertise at these centers.

Synergies Between BTRR Components

The panel next considered the question of "*Do synergies exist between components in the current BTRR model, and if so, are they appropriate?*" As illustrated in the figure below, each BTRR is expected to have five separate yet synergistic components.



The driving force in each BTRR is the integration between the technology R&D (TRD) and driving biomedical projects (DBP) components, but these are supported by the remaining three parts: collaboration and service, training and dissemination. The panel opined that few BTRRs could truly achieve full integration of all five components. An early-stage BTRR would necessarily be focused on the TRD element, while a more established BTRR would likely have shifted to emphasize the DBP component. Similarly, components like training and dissemination would be present at different levels depending on the maturity of the technology within the TRD part.

Issues and Improvements: Although the panel thought the overall five-component structure for a BTRR was reasonable, they felt there should be flexibility and modularity in how these components are implemented.

- Multiphase Grant Mechanism: The panel envisioned a multiphase mechanism where an initial phase award could support higher risk technology development, a middle phase could fund continued TRD while developing the DBP and other components, and a final phase award could support BTRRs with established technologies where TRD is minimal or even absent and the DBP and other components are the focus of the center. *The three "phases" of support could result from different grant mechanisms*, perhaps something along the lines of the R21/R33 or SBIR/STTR pathways.
- Integration of Technology Programs: Although it is somewhat beyond the scope of this panel's mission, it was felt that BTRRs *could be more effectively integrated with existing technology-focused R01s within NIGMS.* Similarly, the introduction of a smaller technology development award mechanism could allow

for initial support for development of more novel and risky technologies ultimately leading to new BTTR formation. These ideas are built upon in the following section where we consider the integration of the BTRR program within NIGMS.

Role of BTRR within NIGMS

The panel considered the question, "*How does the BTRR program fit into the broader NIGMS strategy of technology development?*" The panel saw significant merit in the NIGMS BTRR program, as well as the technology-focused R01s in NIGMS. This enthusiasm primarily stemmed from the fact that these technological advances have direct impact on biological and biomedical problems relevant to the mission of NIGMS.

Issues and Improvements: Even with this enthusiasm, the panel had several ideas on how BTRRs and technology-based grants could be better integrated into NIGMS.

- <u>Using Technology R01s to Feed BTRRs:</u> There is a broad assortment of technology-based R01s, and this range of technologies could be surveyed to determine new techniques that might be developed into BTRRs. This relates to the integration of technology programs detailed above.
- <u>Coordination of Reviews:</u> The panel felt there should be better overall coordination in the review of P41s and technology-based R01s. This may include a common review panel or some other mechanism. A review group or groups focused on research resources and technology development grant applications, which by nature are less hypothesis-driven, would be more appropriate than research-oriented review groups.

Additional Suggestions for BTRR Program Changes

The final question posed to the panel was, "*Are there any program alterations that can potentially improve the impact of the BTRR program?*" Many suggestions from the panel are already detailed in the above sections, but listed below are additional suggestions and recommendations that were discussed and could be considered.

- <u>The Need for Comparative Reviews:</u> The current review mechanism was inherited from NCRR, but there is a clear need to modify the procedures so that most reviewers would see multiple P41 applications and over time participate in multiple site visits (perhaps a model similar to T32 reviews). Without comparative reviews, shortfalls in a given program may not be evident, which diminishes opportunity for positive program evolution and contributes to the observed low rate of turnover for BTRR programs (Appendix Figures 2-3).
- <u>Joint Review of NIGMS BTTR and NIBIB Biomedical Technology Resource Centers (BTRC) programs</u>: The objectives of the BTRR and BTRC programs are not identical, but are sufficiently similar that a single review panel might prove effective in evaluating the merit of the programs and enhancing coordination of the two programs and the range of centers they support.
- <u>Enhanced Program Flexibility:</u> The panel felt that allowing more flexibility in the BTRR requirements (e.g., the type and number of required projects) could again help in both turnover and the introduction of novel technologies. Similar flexibility in allowing proposal to address the five BTRR components in a more modular fashion could enhance the application process.
- <u>Recognizing Differences in BTRRs:</u> Related to the last two points, it should be acknowledged that there are fundamental differences in the technologies and their ability to be disseminated. Computational and software tools are eminently suited for distribution while resources such as beamlines and cryo-electron microscopy facilities are not.
- <u>Potential Merits of a BTRR Sunset:</u> One significant difference in the BTRC program is the 15-year sunset requirement for this NIBIB program. There was a lengthy discussion of the potential utility of such a sunset policy for the NIGMS BTRR program. Discontinuation of critical site-specific resources (e.g., synchrotron beamlines, electron microscopy facilities, etc.) could have deleterious effects on a user community pursuing outstanding science. The panel opinions were split on the potential merits of

a sunset policy. Given the range of additional changes that are proposed in this document, including a more comparative review mechanism, the panel ultimately concluded it would not be wise to introduce a sunset mechanism at this point. This issue can be revisited once the NIBIB program collects more data on its effectiveness for the BTRC programs.

- Mechanisms for support adjustments over time: This would take into account evolution and maturation of technologies and BTTR functions and also relates to the sunset discussion above. Transition to other support mechanisms is appropriate for mature technologies and critical site-specific resources so that essential resource service and training would be provided once the technology development goals are achieved. Where possible and appropriate, transition to fee-for-service or private sector support for some resources could be cost-effective options.

APPENDIX: Figures 1-3 and Tables 1-2.

Figure 1: BTRR-supported patents awarded. Each point represents the patents awarded to an individual BTRR, with boxes representing the interquartile range of patents awarded across the program. Two timeframes are shown: 1996-2014 (all available data) and 2007-2014 (evaluation window). Of the 58 patents, 3 were identified with subsequent commercialization activity.

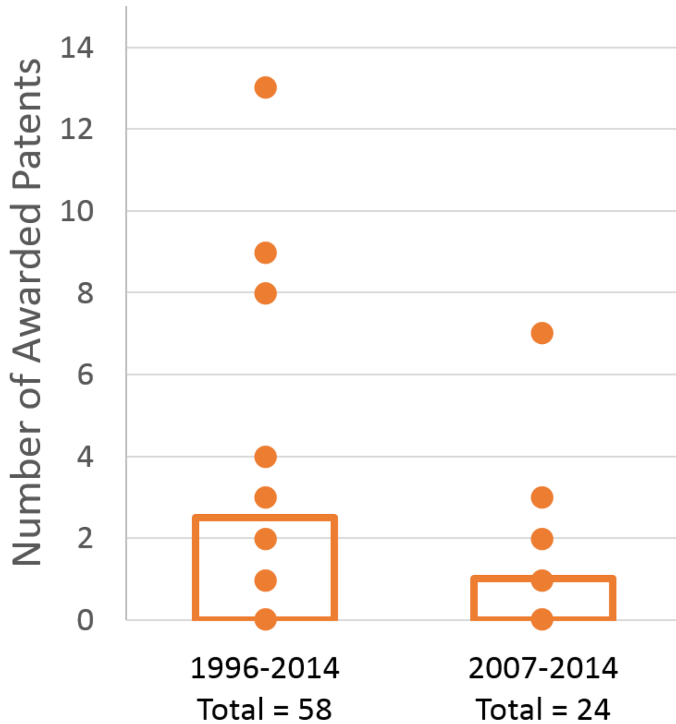


Table 1: Broad categorization of BTRRs with information on number and age of resources. Age is defined based on the number of years since initial award. Category of resource is an exclusive categorization system with descriptions for each group below

Broad Category	Mean Age	Median Age	Number of Resources
Computing and Informatics	17	17	8
Molecular and Cellular Imaging	23	26	5
Structural Biology	24	26	10
Systems Biology	21	19	11
Grand Total	21	19	34

Description of Categories (taken from http://www.btrportal.org/about):

Computing and Informatics Technology Centers: These centers develop advanced methods and technologies for biomedical computing and informatics. This includes high-performance computing systems as well as software for complex data visualization and analysis, simulation and modeling of biological systems. The centers make their computing infrastructure and software freely available.

Molecular and Cellular Imaging Technology Centers: These centers develop advanced imaging and associated analytical and computational technologies for the anatomic and functional analysis of organelles, cells and tissues. The technologies include a complementary variety of microscopies using electrons or X-rays as the source for tomography and correlative approaches. Mass spectrometry imaging is available to visualize the spatial distribution of compounds, biomarkers, metabolites, peptides or proteins by their molecular masses. Sample preparation is an important component of each of these centers.

Structural Biology Technology Centers: These centers develop technologies including spectroscopic techniques, synchrotron radiation and macromolecular microscopy for studying the structures of biomolecules predominantly ranging in size from peptides to very large macromolecular complexes. Detection, data analysis and automation are important components of most of these centers.

Systems Biology Technology Centers: These centers support the continued development of advanced biomedical, analytical and computational technologies capable of high throughput and applicable to complex samples and their integration into comprehensive interdisciplinary approaches to various aspects of systems biology.

Table 2: Types of work pursued at BTRRs. Each resource can pursue multiple areas of work, which cover both tools/techniques and fields of study (e.g. Mass Spectrometry and Structural Biology). Data taken from http://www.btrportal.org/centers#nigms – resources self-identify with each area of work.

Area of Work Pursued at Resource	Number of Resources
Structural Biology	19
Computing and Informatics	17
Mass Spectrometry	12
Data Integration and Visualization	11
Modeling and Simulation	10
Proteomics	10
Imaging	6
Synchrotron	6
Macromolecular Crystallography	5
Microscopy	5
Spectroscopy	5
Carbohydrate Structure and Function	4
Correlated Microscopy	4
Tomography	4
Cryo Electron Microscopy (Cryo-EM)	3
Glycomics	3
Small Angle X-ray Scattering (SAXS)	3
Electron Microscopy (EM)	2

Figure 2: Histogram of NIGMS BTRR support length for awards active in fiscal year 2014. Support year is defined as the cumulative years of grant support provided to the project at time of award.

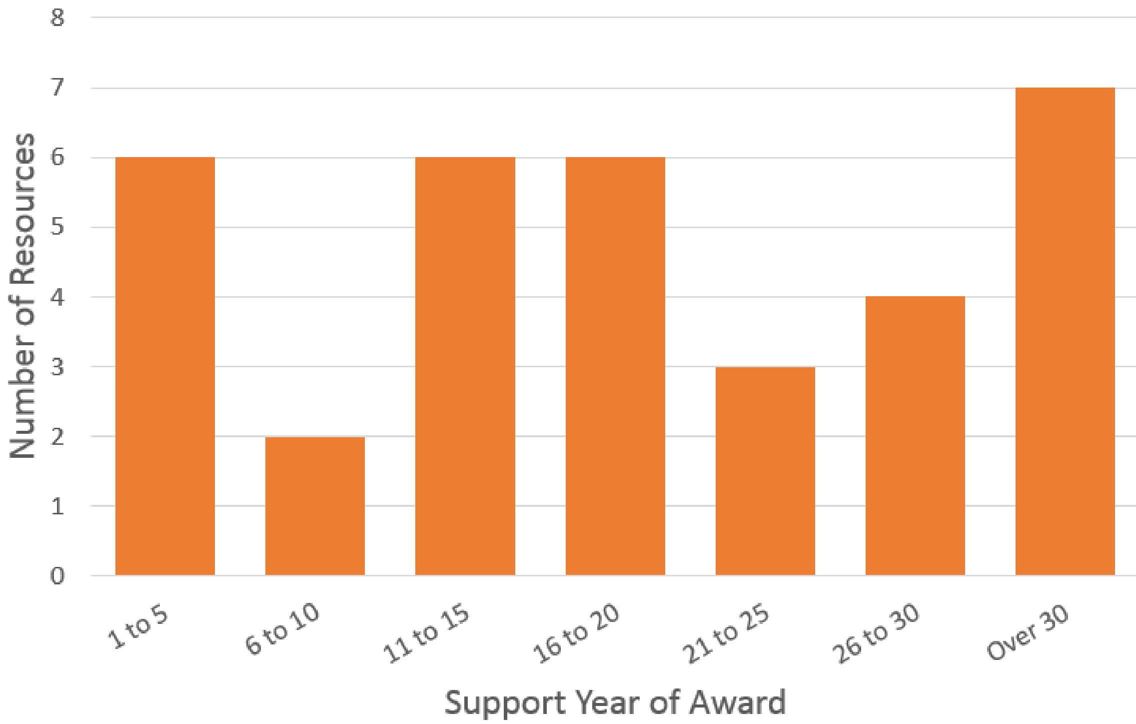


Figure 3: Success rates for P41 applications by year and application type. Success rate is defined as the number of awarded applications over the total number of applications in a given fiscal year. Total numbers of new (N) and renewal (R) applications are provided below each bar. Approximately 80 percent of renewal applications (types 2 and 9) were awarded, while 25 precent of new applications (type 1) were awarded over the same time period. This holds true across all fiscal years, with an increase in new applications and a decrease in renewal applications in the last 5 years.