Request for Information:

Input on the NIH-Industry Program to Discover New Therapeutic Uses for Existing Molecules

Summary

June 12, 2012

National Center for Advancing Translational Sciences
National Institutes of Health
Department of Health and Human Services

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Introduction

On May 3, 2012, the National Center for Advancing Translational Sciences (NCATS) issued a *Request for Information (RFI): Input on the NIH-Industry Program to Discover New Therapeutic Uses for Existing Molecules*. In addition to identifying their main areas of research interests, respondents were asked to answer the following:

1. Partnerships with industry have been used throughout government and the biomedical research community to leverage each sector's expertise to speed scientific research and corresponding commercial development. We are interested in hearing about innovative strategies and practices that have proven successful to develop novel uses for discontinued Agents that have no known development limitations and are safe for use in humans. Your response can include your opinion of the most significant challenges for public-private partnerships that foster drug rescue between biomedical researchers and the pharmaceutical industry as well as your experiences with drug rescue or repurposing partnerships. Your input on options NCATS can consider which promise to nurture academic efforts to foster greater translation through projects such as the NIH-Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules. Your response can also include input on how NIH can identify partners that would like to provide drugs and biologics that are no longer being pursued internally to the NIH research community for investigation for new therapeutic uses.

2. Because this Program involves obtaining permission to use, and work with, privately owned Agents, exclusive patent or regulatory rights will likely be important incentives for the commercial success of the new therapeutic use for a drug candidate identified under the NIH-Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules. The ability to achieve an exclusive right to market a drug product, whether through a new use or other patentable subject matter related to the Agent, is likely to significantly affect the pharmaceutical partner's or other developer's incentive to commercialize rescued drugs or biologics based on new research results arising from the Program. NCATS understands that a significant impediment to government, academic, non-profit, and industry partnerships involved in discovering and commercializing new uses of Agents is the "transaction cost" of negotiating appropriate legal agreements on a case-by-case basis. Thus, to address this concern, a key feature of the Program is that template agreements will be offered as a means of implementing the partnership. We are interested in the views of potential academic and industry partners on the transaction cost of developing individual agreements as well as the desirability of using template agreements and incorporating them into this Program. We are interested in your comments on how the use of template CDAs and CRAs in general and the current CDA and CRA might affect your institution's participation in the therapeutics discovery program. Applicants will be able to access these agreements prior to submitting an NIH X02 pre-application. For more details, please see Notice NOT-TR-12-001.

3. Comments on how working with a Clinical and Translational Science Award site (CTSAs) could advance drug rescue research projects, particularly for rare and neglected diseases.

4. Comment on how working with NIH Intramural Research Program investigators (http://www.irp.nih.gov) and the NIH Clinical Center resources (http://www.cc.nih.gov/index.html) could advance your drug rescue research project.

5. Discuss whether the goals and incentives of the NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules are sufficient for biotechnology and pharmaceutical companies to participate in the Program. Your perspective on how success of the therapeutics discovery program would be defined.

6. Comment on the resources that a biotechnology or pharmaceutical company partner might realistically contribute to an NCATS program on therapeutics discovery in addition to the Agent and the associated data. You can also comment on the type of information about the molecules that you would be willing to disclose publicly.

7. Comment on the pharmacologic activity or biological target of the drug candidate that you need access to in order to test your biological hypothesis of disease intervention.

8. Any additional comments regarding this program.

Description of Responses

Twenty-nine responses were received by the June 1 closing date. Responses were received from a range of stakeholders including, individuals from academic institutions, groups of academic institutions, academic advocacy organizations, and industry. The following provides de-identified individual responses; however organizations are named in some instances. Answers have been moderately truncated to focus on the material that most directly answered the question. However, full responses are being reviewed by NCATS staff as they prepare the funding opportunity announcement and as NCATS further develops and expands the pilot program. For those organizations that chose to submit letters that did not match the web-based questions, they will be considered by NCATS staff in their entirety and will be represented where possible in the following report.

Characteristics and Areas of Research Interest

Please identify the nature of your interest in the area (e.g., are you a biomedical or clinical researcher, a pharmaceutical company partner interested in participating in this initiative, a member of an advocacy or community group, or other?):

- Public Private Partnership Key Function Committee, one of several committees designed to carry out work on behalf of the CTSA consortium.
- Consortium of Clinical and Translational Science Award (CTSA) institutions.
- Cancer Therapeutics and Immunology at the Drug Development Division of Southern Research.
- CTSA Principal Investigators
- Web-based drug discovery company
- Psychiatrist and biomedical researcher
- Company that has developed a computational platform to identify alternate sites of action of drugs.
- Biomedical researchers conducting in vitro, pre-clinical, and clinical research on therapeutics
- Biomedical Researcher trained in Pharmacology
- Academic dermatologist with a dermatology practice.
- Manufacturer
- Biomedical researcher
- Biomedical Researcher who runs a Core Small Molecule Screening Facility and runs a Therapeutic Discovery Interest Group
- Biomedical researcher who has been involved in the non-clinical drug development and toxicity.
- Pediatric endocrinologist working in the area of clinical trials for type 1 diabetes.
- Biomedical researcher (medicinal chemist) involved in academic drug discovery and development.
- Biomedical researcher interested in personalized/stratified medicine, use of biomarkers and companion diagnostics and human translational research.
- Biomedical researcher
- Biomedical researcher interested in molecules that mitigate oxidative injury. Also co-founder of a small, drug development company.
- Basic science researcher in academia.
- Clinical neurologist and neuropathologist; research physician

- Clinical specializing in cardiac ischemia-reperfusion injury
- An association representing a regional group of academic institutions
- Academic associations

Please indicate your main area of research interest:

- On behalf of the Public-Private Partnerships (PPP) Key Function Committee (KFC) of the Clinical and Translational Science Award (CTSAs) Consortium PPP has focused on how working with the Clinical and Translational Science Award (CTSA) Consortium (and in particular the PPP KFC) could advance drug rescue research projects, particularly for rare and neglected diseases
- As a contract research organization, we provide preclinical drug development and clinical trial support services to pharmaceutical and biotechnology companies on an outsourced basis.
- Our institute is involved in promoting translational research efforts in our region by enhancing and developing collaboration networks, providing educational programs to strengthen translational research at all levels of experience and supporting innovation and fostering a community that values translational research.
- The pilot program helps to advance public confidence in the effectiveness of principled partnerships between academic medical centers, industry, and Federal agencies to ensure continued advances in the prevention, diagnosis, and treatment of disease.
- Our organization provides cloud based (web based) software and services (SaaS, Software as a Service).
- Functional neuroimaging in combination with pharmacological manipulations to understand psychiatric pathophysiology and identify new therapeutic agents/targets.
- Our computational platform is general in that the identity of the alternative targets is not known beforehand, nor is the potential therapeutic use.
- Pathogenesis and treatment of viral diseases.
- Smooth muscle pharmacology.
- Dermatology and the use of topical agents for major skin problems.
- The Upright MRI allows us to study a new science.
- Drug treatments to treat addiction and enhance cognitive function.
- Working with small molecule interactions with a large variety of pathways and targets. Drug development for the treatment of Pneumocystis pneumonia.
- Type 1 Diabetes
- Neuroscience, especially Alzheimer's and ataxias. Inflammatory and autoimmune diseases, personalized medicine, biomarkers, drug repurposing.
- Cancer therapeutics
- Use of nanoparticles as drug delivery vehicles as well as their independent therapeutic effects. Cardiac ischemia-reperfusion injury (aka acute myocardial infarction, heart attack), and the development of cardioprotective drugs.
- Friedreich's ataxia; other hereditary ataxias.

Comments

1) **Partnerships with industry have been used throughout government and the biomedical research community to leverage each sector's expertise to speed scientific research and corresponding commercial development. We are interested in hearing about innovative strategies and practices that have proven successful to develop novel uses for discontinued Agents that have no known development limitations and are safe for use in humans. Your response can include your opinion of the most significant challenges for public-private partnerships that foster drug rescue between biomedical researchers and the pharmaceutical industry as well as your experiences with drug rescue or repurposing partnerships. Your input on options NCATS can consider which promise to nurture academic efforts to foster greater translation through projects such as the NIH-Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules. Your response can also include input on how NIH can identify partners that would like to provide drugs and biologics that are no longer being pursued internally to the NIH research community for investigation for new therapeutic uses.**

- One of the key criteria for developing successful partnerships through projects, such as the NIH-Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules, is having a flexible format for exploring repurposing opportunities. If there is preliminary data for an Agent that suggests utility for a new application, that particular Agent can be directed to studies to confirm utility. The challenge is having an appropriate investigator apply and be accepted into the program. Assuming such an investigator is awarded a grant, the partnership is a straightforward collaboration and license option arrangement. If there areno preliminary data for an Agent that suggests a utility for a new application, but an Investigator within the program identifies a particular Agent with structural similarity to other compounds and activity in a particular therapeutic model, then a successful interaction will be similar to the first situation. Another possibility is that there are no data for an Agent that suggests utility for a new application and an Investigator has no scientific basis to be able to a priori select an Agent for testing. In this case, the type of partnership that should be considered is to allow for screening all the available Agents within the program in *in vitro* models of a particular therapeutic application as a Stage 1 project. If a particular Agent is found to have activity in a particular model, a Stage 2 project could be considered for funding that would resemble the type of partnership outlined above.
- Stimulating the use of discontinued agents. There are several resourceful ways that our biomedical research community has already engaged with industry to foster research and commercialization of therapeutic agents. For example, the Cystic Fibrosis Therapeutics Development Network (TDN) provides industry rapid access to experts in drug development, clinical trial disease and conduct in CF and more broadly in the field of inhalation therapies. The TDN has also developed widely applicable tools such as standardized IRB applications, case report forms, study designs, outcome measures, etc. Industry has been very responsive and the TDN has worked successfully with over 60 companies of all sizes.
- Another model of a partnership between industry and academic medical centers is the Pfizer Centers for Therapeutics Innovation (CTI). In these CTIs, Pfizer not only provides therapeutic agents and background information, but also involves Pfizer scientists with drug development expertise to participate in development teams. Some of the key features of successful programs include dedicated support and expertise in drug development and protein sciences as well as

access to proprietary tools and technologies. The timing of funding and program milestones are established on a project-by-project basis which is usually 2-3 years for the preclinical stage.

- Conducting first-in-human drug trials at a university is difficult due to a lack of resources and reluctance on the part of investigators given the many regulatory hurdles. The pharmaceutical industry can help by opening up its regulatory files to investigators, such as files pertaining to FDA approval.
- One of the most difficult challenges of fostering public-private relationships is the need for researchers to have access to all available information about a drug molecule and the previous phases of research that it has undergone, including toxicology and adverse effects data. We have submitted proposals for CTSA supplements that have included drug repurposing for clinical trials. These proposals were not well received—not because of their quality but because the concept is not yet accepted by clinical investigators.
- The proposed program presents an opportunity for a novel interaction between NIH, industry, and academic partners, and will have maximum effect only if all partners are actively engaged throughout the process. NIH has recognized the unique experience that academic medical center investigators can bring to the discovery of new therapeutics, and asks that NIH ensure that the academic medical center partners are considered integral and equivalent partners in this pilot. Current successful collaborations between academic medical centers and industry have demonstrated many benefits from melding their comparative strengths and respective expertise.
- Drug repurposing partnerships face similar challenges as those faced by neglected disease drug discovery projects. In both cases, researchers must do more with less and synergy is key, particularly in areas underrepresented by market drivers. Often natural market-funded drug discovery projects do not always maximally benefit world health (antibiotics, tuberculosis, malaria, etc.) or address limited market opportunities in rare diseases. Pharma and Biotech necessarily focus on the bottom line, creating investor value, and have difficulty entering these markets alone. Complementary funded collaborative projects, whether publicly-funded from NIH, privately-funded (e.g., Bill and Melinda Gates Foundation), or corporate-sponsored, with the right collaborative infrastructure, can bear fruit. Technology is needed for capture and sharing of molecular structures and biodata and for compliance and communication. Thus, the NIH-Industry Pilot Program can fill a critical gap: to unearth the power of drugs which lie dormant in many pharma and biotech.
- The best way to identify pharmaceutical partners is to provide incentives to their participation in the form of development rights/some immediate compensation with possible larger future financial gain, that way they will identify themselves. The biggest challenges for public-private partnerships are lack of sufficient financial incentives to industry, difficulty negotiating intellectual property issues, and academic concerns about potential barriers to publishing.
- Some concerns that arose in our prior work have been on the level of safety that has been proved. Drugs that have proven to be safe for short term treatments might or might not be as safe if the alternative use is for treatment of a chronic illness, for which the drug needs to be administered continually over a long period of time. Even if an alternative biological site can be successfully identified, it is essential that existing safety and toxicity data are readily available from the outset to assess whether the cross-purpose use is indeed feasible.
- These collaborations present two major challenges. It is important to decide whether to charge the federal or corporate indirect cost rate when industry-academic partnerships are initiated. If the industry partner provides the compound directly to the investigator, then the corporate rate is charged. On the other hand, if the compound arrives as part of an NIH-sponsored project,

then the federal rate is charged. It is expected that the federal indirect costs will be charged to the NIH if pharmaceutical companies provide their existing molecules to investigators as part of this Pilot Program. A second challenge in collaborating with industry partners is building a team of scientists and administrators on both sides. It is essential for the investigator and laboratory technicians to develop relationships with key personnel at the company. Similarly, our Sponsored Programs officers need counterparts at the company to handle the financial and legal affairs.

- A suggestion for this Pilot Program is to clearly designate the scientist and administrator at the pharmaceutical company who will take responsibility for interacting with their academic partners. A suggestion for identifying pharmaceutical partners to participate in this Pilot Program is to query the FDA for records of companies that began clinical trials but were halted at Phase III for lack of effectiveness for their intended disease.
- Directors of clinical trials, both in hospitals and pharmaceutical companies, are another group that may know of drugs that are safe but were abandoned. The professional societies for clinical trials directors, such as The Society for Clinical Trials (http://www.sctweb.org/) and the Association of Clinical Research Professionals (http://www.acrpnet.org/), would be another source. Lastly, trade journals for the pharmaceutical industry would likely accept articles or notices about this Pilot Program.
- There is a wonderful give-take from such a relationship. Having students involved in such a program would be particularly valuable.
- The combined efforts or our dermatological sciences can be very helpful toward the discovery of new uses.
- Include the compounds in compound screening libraries. If they hit a specific target, this would lead to new hypotheses on how the compounds could be used clinically. Test the compounds in a variety of established rodent models of disease, as well as in new academic animal (i.e. rodent) models of disease.
- NIH support of such niche endeavors is necessary for their survival. The companies desire to protect their drug, are not particularly interested in seeing it "repurposed. Using the power of the NIH to persuade them to partner would be ideal.
- Presumably the compounds made available to the program have human safety and pharmacology data. They may have failed to advance because the indication or the population of subjects in previous trials was not ideal for the mechanism of action of the drug and the drug's target. We are very interested in obtaining the list of available compounds and their mechanism of action/target prior to committing to specific therapeutic areas.
- These compounds likely did not have sufficient activity in humans for one of two principle reasons; 1) the drug did not effectively reach the target organ or 2) the compound targeted a single cellular pathway which by itself was not sufficient to mitigate a course in the disease. Combining these compounds with carrier molecules that have greater tissue biodistribution may be a useful approach as well as coupling the compounds with other molecules with different but complimentary actions.
- Biggest challenge is secrecy within the pharmaceutical industry. Even with confidentiality agreements in place, pharma will often not discuss their findings in a completely open manner. From an academic standpoint, there are certain things which we take for granted - knowing the structure of a molecule of interest for example - and if that stuff is hidden, it makes collaboration very difficult.
- Another issue is the simple act of trying to obtain material for conducting studies on approved drugs. In some cases, if the molecule is available from the Sigma catalog, it is either controlled

and so difficult to obtain in large enough quantities, or it is not available at all. In other cases, the molecule is simply not available at all. There needs to be a central repository of ALL approved drugs, easy for researchers to buy. A simple NIH-sponsored repository would sidestep this. It could be written into FDA approval rules - once your drug gets approved, you're legally required to make it available to researchers.

- In order to maximize the success of the collaborations, pharmaceutical companies must provide investigators with the Agent and all information relevant to the successful conduct of the collaborative project. Such information would include, but would not be limited to: binding kinetics, toxicity, study reports from all clinical trials, animal models, and information on relevant related molecules, as well as a description of why the company did not proceed with further development. In addition to the provision of all relevant written reports and data analyses, investigators would benefit significantly from consultations with experts from the company on study design and implementation. The extent of these consultations could be negotiated in the individual agreements, but an NIH-directed framework would help to streamline the process. To be a truly collaborative program, there must be a bi-directional flow of information between investigators and their industry partners.
- The development of the CTSA Pharmaceutical Assets Portal, supported by several NCRR administrative supplement awards, was undertaken to identify barriers for repurposing of discontinued drugs and to explore mechanisms to overcome such barriers. As part of this process, several barriers to collaboration were identified (see Marusina et al, Drug Discovery Today: Therapeutic Strategies, 2011; 8: 77-83). Of the listed barriers, several have been addressed in the present initiative but some remains. Examples include the reluctance of companies to release compounds and the difficulty in identifying collaborators and an area of mutual interest. Although 24 agents have been included in the exciting initiative, there are 100-fold more potentially available. The efforts to expand the program would serve to tap these resources. Further, the balance of private sector interest with an academic investigator focus area to identify a topic of mutual interest might present challenges, and on-line tools and/or informatics efforts might prove useful in mitigating such challenges and barriers.

2) **Because this Program involves obtaining permission to use, and work with, privately owned Agents, exclusive patent or regulatory rights will likely be important incentives for the commercial success of the new therapeutic use for a drug candidate identified under the NIH-Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules. The ability to achieve an exclusive right to market a drug product, whether through a new use or other patentable subject matter related to the Agent, is likely to significantly affect the pharmaceutical partner's or other developer's incentive to commercialize rescued drugs or biologics based on new research results arising from the Program. NCATS understands that a significant impediment to government, academic, non-profit, and industry partnerships involved in discovering and commercializing new uses of Agents is the "transaction cost" of negotiating appropriate legal agreements on a case-by-case basis. Thus, to address this concern, a key feature of the Program is that template agreements will be offered as a means of implementing the partnership. We are interested in the views of potential academic and industry partners on the transaction cost of developing individual agreements as well as the desirability of using template agreements and incorporating them into this Program. We are interested in your comments on how the use of template CDAs and CRAs in general and the current CDA and CRA might affect your institution's participation in the therapeutics discovery**

program. Applicants will be able to access these agreements prior to submitting an NIH X02 pre-application. For more details, please see Notice NOT-TR-12-002.

- We noted that all of the agreements provide that the university will serve as the sponsor and IND holder of any clinical trial under the program. Each agreement references an Investigator Initiated Research (IIR) Agreement, but no form is included.
    - 1) It would be important for many institutions to ensure they have ownership of all intellectual property rights (granting options for licenses to the company consistent with the main research agreement).
    - 2. In the Astra Zeneca agreement, there is a reference in 9.2.2 to set royalty rates, which we do not agree to up front due to tax exempt reasons.
    - 3. Related to issues of confidentiality, how will information in the proposals be treated (at both stages)? Will the participating companies be included in the initial review of proposals and if so, how will they handle the information provided in the proposals?
- This program will involve obtaining permission to use and work with privately owned Agents. The rights of each partner in such a collaborative program to any new intellectual property developed are a major incentive to each of the partners. The exclusive patent or regulatory rights are an important incentive for the commercial success of the new therapeutic use for a drug candidate identified under the NIH-Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules. The ability to achieve exclusive rights to market a drug product, whether through a new use or other patentable subject matter related to the Agent, affects the pharmaceutical partner's or other developer's incentive to commercialize rescued drugs or biologics based on new research results arising from the Program.
- An understanding of each participant's expectations regarding the commercialization of new intellectual property should be known up front. The use of template agreements will facilitate these expectations. The "transaction cost" of negotiating appropriate legal agreements between collaborative partners in a program such as this could be a significant impediment to government, academic, non-profit, and industry partnerships. In previous government-sponsored programs, using template agreements as a means of implementing partnerships, has been extremely beneficial. These templates can be altered to meet the specific needs of each partnership. We have participated in the establishment of template agreement as a member of several government-sponsored Testing Centers. After reviewing templates used in previous government sponsored programs, the MOU, CDA, and CRA, template agreements are useful for this program.
- Standardizing negotiations between industry and academic institutions. A major incentive for pharmaceutical partners to work with other entities is the ownership of exclusive marketing rights of the resulting therapeutic. The proposed use of CDA and CRA templates by NCATS is one way to eliminate time spent negotiating individual case agreements between entities. We do not identify any problems in using the CDA template but we do have some concerns regarding the CRA wording and would like to address them before the therapeutics discovery program becomes active. The current CRA template seems to be drafted as a master of very wide applicability, including preclinical development and clinical trials, which is confusing as they have different requirements.
- The indemnification is adequate although there is no coverage for injuries caused by the material. Both the CDA and CRA templates reference the terms of an additional IIA for clinical trials, but those terms are not included, so we cannot review them. It is difficult to determine if all studies would be considered investigator-initiated and what the corporate partner is responsible for. The companies waive all liability for infringements of third parties IP rights and a

disclaimer of warranties is provided for the corporate partner but not for the academic institution. It is unclear who the Project PI is for the institution, what studies they will fund with this grant funding and what the relationship is between the basic research investigators and the clinical protocol authors.

- We also note that the IP terms are not favorable to the institutions as the companies are allowed to drive the patent prosecution and licensing decisions on all joint inventions without consulting the Institution. The R&D licenses are acceptable but with the commercial licenses, all have arbitration clauses that favor industry. Given that the CRA template contract states that company confidential information may not be available for publication, any investigator considering these projects should carefully consider whether the anticipated publication of the proposed study and results would be seriously impacted by lack of access to the corporate information. Finally, given the lack of guaranteed access for commercialization purposes, it would be important for the institution and the NIH to consider including conditions under which the corporate partner would grant rights to the compound for the limited field of use (e.g. orphan diseases/small market).
- Template agreements and mechanisms for streamlining and expediting the legal processes involved in collaborating with pharmaceutical partners would be a tremendous help to university research teams and a benefit of NIH-coordinated efforts such as the Discovering New Therapeutic Uses for Existing Molecules program.
- One aspect of the proposed program that may produce benefits beyond the direct development of novel therapeutics is the proposed use of template agreements, which would expedite negotiation for partnerships in using these compounds and, as the Federal Register notice indicated, may lessen the "transaction costs" of negotiating collaborative research agreements and other arrangements de novo. The Association and other organizations have made past efforts to promote use of template agreements or provisions to facilitate collaborations, e.g., in sponsored research agreements, clinical trials, and in sharing of research materials. The development of reliable templates acceptable to all parties has been difficult to accomplish for various reasons, and that their use in this high-profile pilot program could be precedential. Past efforts to develop template agreements (or standard provisions) have revolved around otherwise commonplace collaborations where new agreements usually resemble previous agreements. On the sharing of compounds under the pilot program, the situation is in fact – as NIH noted in its announcement—new and not routine.
- It is unlikely that the template agreements in current form would be acceptable to university partners of research, and expect that further revision is needed. Indeed, for example, the current template agreements require academic partners to share data and other information with firms providing the compounds even where IP rights do not necessarily extend to that information. This advocacy organization agrees with these concerns and recognizes that the agreements will need to be revised with academic partners before they could serve as models or templates for other agreements. The fundamental principles are similar to the NIH's own 1994 guidance on developing sponsored research agreements, which also noted that, "The NIH recognizes that sponsored research agreements are unique, creative devices which reflect the needs and interests of the parties involved and require a delicate balance of risks and benefits to all of the parties." The template Memorandum of Understanding does reference "public health and academic research goals" stipulating that the company is expected to permit dissemination of research results and provide a non-exclusive research-use licenses to non-profit and government entities as provided under the agreements. This association certainly approves the inclusion of these provisions. While supportive of the use of the template agreements, the

current templates should be modified after involvement of academic partners in the research collaboration.

- Another association of academic institutions has considerable experience working with pharma and biotech companies, including the three companies that are participating in the pilot. In fact, a number of their institutions have template agreements in place with such companies. While template agreements can reduce transaction costs, it is vitally important that they contain terms acceptable to all parties. They note that while the university community was represented in the NIH-Industry Roundtable mentioned under "Background" in the RFI, to our knowledge university representatives were not invited to participate in the actual development and negotiation of these templates. Their additional comments follow:

    - The companies are providing drugs but not funding, yet the terms NCATS has presented in the templates go beyond what academic institutions typically agree to for investigator-initiated studies that are fully funded by a company. Some of these terms are likely to present significant problems for our institutions. Moreover, it appears that federal officials have negotiated these templates "on behalf" of the academic community, which places the recipient institutions in a difficult position when negotiating institution-specific requirements. We believe it is relatively unprecedented for federal agencies to pre-negotiate the terms of contracts between two private entities. While it is certainly appropriate for the NIH to point out where provisions in the contracts must be consistent with the requirements of federal funding, we are deeply concerned that NIH's involvement in negotiating terms such as those related to indemnification, compensation for subject harm, or details of publication is an unwarranted intrusion into the rights of universities and research organizations to manage such matters themselves.
    - The subject RFI requests comments on how the current Confidential Disclosure Agreements (CDAS) and Collaborative Research Agreements (CRAs) might affect participation in the program. Unfortunately there are a number of provisions in the CRAs that in may be potential "dealbreakers" for many of our institutions. One is the broad scope of rights to "Technical Developments" which is common to the CRAs with all three participating companies. These rights are overly broad, and not likely to be acceptable to many institutions. Another is the Indemnification provisions in all three agreements. Acceptability of indemnification provisions is highly institution-specific, particularly for public institutions, and does not easily lend itself to a template approach. In some cases, state laws or board of trustee policies may strictly limit indemnity for specific institutions.
    - While we have identified some specific issues with the indemnification terms in the CRAs, institutions may have additional concerns with the terms that will prevent them from agreeing to them. Other provisions that potentially are very problematic include those on the ownership of intellectual property, publication, and choice of law and jurisdiction. Finally, for a program that has a stated intent to quickly move compounds into the clinic, the agreements are oddly devoid of necessary terms related to representation that compounds will be manufactured and labeled to cGMP standards, and that companies will permit appropriate cross reference of their Master Drug Files.
    - This advocacy organization has chosen to comment mostly on the potential "deal breaking" provisions that would likely prevent many research universities, especially the publics, from participating in these exciting new NCATS programs. We also note a number of other potentially problematic term as follows:

- "**Technical Developments"** - All three CRAs define this term as including any invention, discovery, composition, enhancement, technology, advancement, know-how, process, data, device, machine, material, software or any other information arising from the Program (including any such development protectable by patent, copyright, or other protection under the law in which a Party has an ownership interest). The agreements give the company exclusive commercial option rights to such Technical Developments in which a collaborating academic institution has rights and interests and a royalty-free nonexclusive research license. This definition is overly broad, particularly to the extent it includes non-patentable inventions, know-how and data "arising from" the Program. As worded, it appears to cover raw data and other original source material, and could include data related to the program but collected independently. Non-patentable information such as data and know-how cannot generally be licensed. The broad definition also raises issues regarding student theses, faculty publications etc. The license rights should be limited to patentable inventions conceived and reduced to practice in the direct performance of the study. In particular, exclusive access to unpatentable research results is only possible by withholding the results from publication, which is antithetical to the academic mission of dissemination of new knowledge. To the extent that the language can be read as claiming rights in copyrightable results of the research, this provision could prevent faculty from signing the necessary copyright assignments to have their work published in peer reviewed journals. We have additional concerns about the provision that ownership of technical developments shall be determined according to their "origin" in all three agreements (7.2 Lilly, 8.2 Pfizer and AstraZeneca). This is extremely vague and could lead to assertions that all data and other technical developments originated from the company (since the compound is owned by the company) and are therefore owned by it. This language goes beyond what is reasonable or necessary to protect the companies who are participating in this taxpayer funded program.

- **Intellectual Property Ownership** - All three CRAs have provisions requiring institutions to have policies and procedures in place to cause all personnel to vest all Technical Developments and Patents created by the personnel in the institution. This requirement again should be limited to patentable inventions. As written it would include vesting of all data, knowhow, copyrighted material and other information arising from the Program, which is inconsistent with the policies and practices of most academic institutions and raises serious issues with regard to scholarly publication rights and original data. To the extent that the broad definition of Technical Developments can be viewed to encompass human subject data or samples generated in the course of the research, many institutions may see ethical issues with granting the rights requested to the compound providers.
    - The terms also require collaborating institutions to grant, at the outset of the project, future rights to both a non-exclusive research license and an option to an exclusive commercial license to their rights in Technical Developments. This creates problems for institutions that need to track the grant of licenses carefully to ensure non-conflicting obligations. It creates a further problem given the scope of "Technical Developments" – it goes beyond the scope of patentable inventions conceived and reduced to practice in the direct performance of the research, making the need to track the grant of these

licenses to ensure institutions do not breach their obligations here, or with other parties, such as the federal government. Given that institutions do not typically have rights that the companies seek to the broad spectrum of research results (other than to statutorily protectable intellectual property, and certain narrow categories of other rights), one wonders what such a requirement accomplishes. If the participating companies are primarily concerned that they will be "blocked" from further developing the compounds, this goal could be met by more tailored language, in which the academic partner agrees not to assert certain rights against the participating company.

- **Indemnification and Representations and Warranties** - Acceptability of indemnification provisions varies widely among institutions, and the terms usually are specific to the institution, especially for public institutions. For this reason they do not lend themselves to a standardized template approach. In the case of these agreements, the carveouts to company liability are too broad, and should apply only "to the extent" the claim arises from the institution's negligence. In addition, the agreement should provide that the companies cannot admit fault or wrongdoing of the institution without its prior written consent, and that the institution has the right to participate in defense at its own cost and expense. It also would be advisable to add a provision addressing the company's obligation to compensate for injuries to subjects in the case of company-sponsored protocols. Quite frankly, the determination of the appropriate division of the risks of third party claims between private parties is not a matter that a federal agency should negotiate on behalf of those private parties. In addition, all three agreements contain representations and warranties that go beyond what many institutions can or will agree to for research projects. In particular, the AstraZeneca agreement contains an additional provision for indemnification by the institution from breach of the agreement or any representation or warranty. This is unlikely to be acceptable to most institutions. We question why it is included in this agreement and not the other CRAs.

- **Publication** - The AstraZeneca and Pfizer CRAs give the companies the right to "revise" manuscripts to ensure protection of the company's confidential information and to delay publication for any invention owned by the institution. It is critical to academic institutions that companies not have the right to "revise;" they should be entitled to review the manuscript for confidential information and the institution should be required to remove any confidential information that may have been included.

- **Choice of Law** - While the choice of governing law is properly left to individual agreements in the CRAs, in two of the CDAs (Lilly and AstraZeneca) it is subject to the laws of the state of Delaware and the jurisdiction of the federal courts (and state courts in the case of AstraZeneca) for Delaware. This is unlikely to be acceptable to some institutions, especially public institutions, and may raise issues of sovereign immunity. The following provisions also are problematic, but may be less likely to affect the willingness of institutions to participate in the Program.

- "**Confidential Information**" - The CDAs vary in their definition but all provide that the definition includes information marked or declared by the company to be confidential. However the Lilly agreement specifies that "confidential information" also includes information about the "discovery, development and properties of compounds to be

discussed, as well as clinical trial design and execution." All three CDAs should limit the definition of "Confidential Information" to include the information as specified in the Eli Lilly agreement, and be further limited to include only that information which the company provides to the institution for the purpose of evaluating whether to conduct a study with the company's compound. A core value of academic institutions is the ability to freely disseminate information; exceptions should depend on the purpose and nature of information provided, rather than a third party designation.

- The CRAs also vary in their definition. Two (Lilly and Pfizer, 2.6) include the concept of know how or other information communicated by the company. The other (Astra Zeneca) does not specifically include know-how, but expansively defines the covered information. These definitions are too broad. To the extent data, notes, etc. are included they raise issues of openness and the ability to publish research findings, notwithstanding the acknowledgment of the importance of publication in the CRAs. The CRA definition should be clearly limited to proprietary information embodying the company's technology, produces, business information or objectives. In addition, all three agreements provide that their terms and conditions shall be considered confidential. This may pose a problem for public institutions, which may be requiredto disclose agreement terms pursuant to state public or open records laws and whose routine practices do not accommodate the treatment of a research agreement as confidential. Finally, the CDAs do not reference the CRAs, all of which address Confidentiality. The terms of the CDAs are two years, with varying terms for the termination of the receiving party's obligations (three years in the case of Pfizer and Lily; five years in Astra Zeneca). This leaves ambiguous which agreement governs once a CRA is entered into. We believe the CRA provisions should supersede the CDA, and the agreements should so state.

- **Patent Prosecution for Joint Inventions** - Normally institutions prefer to take the lead in the patent prosecution process, including with regard to responding to opposition and other proceedings. This may become even more important with the implementation of the America Invents Act with its provisions for supplemental examinations, post grant review, etc. Yet the agreements give the companies sole responsibility for these actions (Lilly 7.6.1; Pfizer and AstraZeneca 8.6.1). We suggest that institutions should have at least the right of consultation in these matters and that the companies give good faith consideration to university input. At a minimum, this should include a robust right to review and comment not only on the initial drafting of the patent application but also on responses to questions raised during patent examination, approval of claims abandonment, etc. If nothing else, this gives the academic institution the ability to preserve its interests should the company abandon the application later.

- **Option Periods and Pricing** - We note that these vary among the CRAs. For the most part these terms, with the provisions for designation of Senior Negotiators and arbitration in the case of failure to reach agreement, appear reasonable. However, in the Astra Zeneca agreement, for institution inventions where the company does not obtain an exclusive license, the institution may never offer anyone else more favorable terms (9.2.4). This should be time-limited e.g. 6 months. Another issue unique to the AstraZeneca CRA is the pricing provisions (9.2.2). Inclusion of prenegotiated royalty

terms in research agreements is problematic for universities, and raises potential tax and other issues. These terms should be deleted.

- **IIR Agreement** - The CRAs reference an "IIR Agreement" which will be entered into should the parties conduct a clinical trial. They state that the IIR Agreement will be in the "form set out in Exhibit B", yet no terms are included in Exhibit B. Obviously these terms should be made available if the intent is that they also are to provide a template. At a minimum, such an agreement must contain appropriate language regarding: cGMP manufacture of materials provided by industry, rights to cross reference the industry partner's Drug Master File, and compensation for subject harm resulting from the trial.
  - Given the intent of this program is for NCATS to fund academic institutions to partner with companies, it is vitally important that template agreements reflect the input of all participants. If in the future NCATS plans to develop additional templates of this kind, we urge NCATS to include university representatives in the discussions. Higher education institution associations provide a mechanism to broadly reach academic institutions. NCATS may wish to consider this in developing future programs

- A regional group of universities collaborated on their response as follows. The group supports the use of template Confidential Disclosure Agreements (CDAs) and Collaborative Research Agreements (CRAs) and believe that the use of template agreements can reduce the transaction cost to academic medical centers' (AMCs) participation in the Program. In fact, this system of institutions heavily relies on master and template agreements with pharmaceutical and device companies in its clinical research. We currently have eight master CDAs, 19 master clinical trial agreements, and are in the process of negotiating clinical trial agreements with ten additional companies. Although AMCs like us have vast experience in working with pharmaceutical companies through the use of master research agreements, it appears that the academic community was not invited to participate in the development of these template agreements and, as such, the proposed template CDAs and CRAs contain problematic terms for public institutions. Also question the appropriateness of NIH negotiating the terms of agreements to be executed by two non –NIH entities, particularly in matters of critical importance to the academic medical community --indemnification and compensation to injured subjects participating in research, and the dissemination of research results. Many of the terms of these agreements will prevent this group of institutions from participating in the Program if included in the final templates. In the comments that follow, we address these problematic terms that either contravene our mission as a public institution or impose unmanageable burdens, and, where possible, also suggest terms more palatable for Academic Medical Centers. This group urges NCATS to revise the template agreements as and to include the academic community in the process of revising these agreements.

  1. Confidential Disclosure Agreements

  In each of the CDAs, "Confidential Information" includes "any and all information or material…concerning a Disclosing Party's Subject Matter" which is designated by the disclosing party as "confidential." The scope of "Confidential Information" is overly broad, and includes information that is not necessarily confidential or proprietary information of either party, yet enables such information to be treated as "confidential" if so designated by the disclosing party. Public institutions serve the mission of disseminating information for the public benefit. Holding information as "confidential" merely because a third party has made such a designation, rather than due to the

nature of the information disclosed, contravenes this group's mission. Although the Eli Lilly template includes the problematic language cited above, this template also specifies that "Confidential Information" of Eli Lilly includes information about the "discovery, development and properties of compounds to be discussed, as well as clinical trial design and execution." Such information is likely to be confidential and proprietary information in this early stage of communication between the parties; therefore, this group recommends that the scope of "Confidential Information" be limited solely to "confidential or proprietary information about the discovery, development and properties of compounds to be discussed, as well as clinical trial design and execution" and which is designated by the disclosing party to be confidential. In addition, all three CDAs contemplate that information provided by the AMC to the company may be confidential. Public universities generate little, if any, information which they may seek to be protected as confidential. The templates should consider that AMCs may not have any information which they seek to treat as confidential. None of the CDAs contemplate the parties entering into a Collaborative Research Agreement and the resulting effect this would have on the obligations of confidentiality should that occur. This group of institutions encourages that the following language or similar language we added to the Term section of the CDAs: "Notwithstanding the foregoing, if the Parties enter into an agreement to conduct a project supported by NCATs for the discovery of a new therapeutic use for Company's compounds, then any disclosure of Confidential Information under this Agreement shall be governed by the confidentiality provisions of the applicable Collaborative Research Agreement." By including this language, the confidentiality obligations of each party will be clearer and subject to less ambiguity, whether or not the parties enter into a CRA.
group could subject the AMC to the cost of defending litigation far from any of the parties involved. This group recommends that the choice of law provision be removed from the templates.

2. Collaborative Research Agreements

As stated above, one regional group of institutions supports the use of template agreements, and many of the terms of the template CRAs are consistent with the research and publication missions of public universities. However, some of the terms are problematic for this group and run afoul of its mission as a public academic institution to advance science for the public good, violate laws applicable to this group, and would impose financial and operational burdens on the University. Specifically, this group addresses concerns relating to: (a) confidential information; (b) Materials; (c) the use of commercially reasonable efforts; (d) Technical Developments; (e) present grant of a license; (f) the option to obtain an exclusive license; (g) form of the IIR Agreement; (h) disclosure of protected health information; (i) filing patent applications; (j) indemnification obligations; (k) review of confidential and patentable information for publication; and (l) monitoring and auditing.

a. Confidential Information

The scope of Confidential Information as defined in the CRAs extends beyond confidential or proprietary information that may be disclosed for the purpose of conducting collaborative research. The definition should not include "know how

or other information" and should solely be limited to confidential and proprietary information pertaining to the Party's technology, products, and business information that is communicated to the other Party for the purpose of conducting research on the Company's compound. As a public institution, the group is obligated under law to disclose non-confidential information in its possession upon request. Moreover, consistent with this group's mission, the University, as other AMCs, requires openness in the publication of research results. However, pursuant to the terms of the CRAs, publication may be edited to remove Confidential Information. If Confidential Information were to include AMCs' data or results, this would impose a restriction on AMCs' ability to publish. A public research institution cannot and will not agree to any such restriction. Accordingly, the scope of the Confidential Information section of the CRA should be narrowed.

The CRAs should enable AMCs to disclose Confidential Information only to the extent required to provide medical care to subjects participating in any study of the Company's compound. AMCs must have the ability to disclose Confidential Information, such as information about the compound, or study protocol procedures, if the disclosure of such information would have a bearing on the type of medical care a subject should receive.

Pursuant to the CRAs, the terms and conditions of the agreement are also considered confidential information. This group is required by the California Public Records Act, Cal. Govt. Code § 6250, to disclose its public records, which would include the terms and conditions of the agreements to which it is a party. Moreover, in furtherance of this state law, the University maintains a readily accessible database of its proposals and awards, which include information such as the sponsor providing the funding, funding amount, project title and project type. Thus, the group would require that the terms and conditions of the CRA not be considered confidential. Other laws may similarly require other AMCs to make the terms and conditions of its agreements available.

b. Materials

This organization is concerned about the definition of "Materials" in the CRAs and its potential impact on the ability of AMCs to publish research results. "Materials" is defined to include the "Company compound, and other compounds, materials, biological samples, and other physical property" and must be treated as "Confidential Information." Pursuant to the Publication terms of the agreements, Companies may revise proposed publications to protect Confidential Information. By treating Materials as confidential, the terms of the CRAs could prohibit AMCs from publishing scientifically meaningful information that refer or rely upon these Materials, such as information contained in biological samples. The group highlights that tangible products such as "Materials" are not traditionally regarded as confidential in research agreements for this reason. Furthermore, it is not always meaningful to apply concepts that are relevant for "information" to tangible products; The group usually addresses *disclosure* of information and *transfer* of materials. In addition, the compounds at issue in these CRAs have already been disclosed and

patented – information relating to these compounds is publicly available. UC urges NCATS to remove language that treats "Materials" as "Confidential Information."

c. Commercially Reasonable Efforts

The agreements use the phrase "commercially reasonable efforts" to describe the effort a party must expend in order to accomplish an objective under the CRA, with such efforts being those normally used by the party to accomplish a similar objective under similar circumstances. The group and many other AMCs are not "commercial" entities; accordingly, the group is concerned that this language would obligate the group to a standard it does not practice in its ordinary course of business.

d. Technical Developments

The agreements contemplate the disclosure of a large and overbroad category of intellectual property and information to the Companies – "Technical Developments." The definition of these Technical Developments confers rights to the Companies in intellectual property and information that should be solely owned by the AMCs, the entities gathering and developing such information. Thus, for the reasons explained in further detail below, the group urges NCATS to limit the concept of "Technical Developments" to include only inventions subject to patent laws.

"Technical Developments" include non-patentable information, such as know-how, advancements and "data," and includes all such information "arising from the Program." Pursuant to the terms of the CRAs, the Companies are entitled to a non-exclusive royalty-free license under AMCs' rights to all Technical Developments. The scope of Technical Developments and the resulting rights conferred to the Companies not only create unmanageable obligations (as "know-how" cannot be licensed), but it also provides the Companies with the raw data generated by AMCs. This information, even if not collected pursuant to the Program, but collected in pursuit of the AMC's wholly independent research efforts, would be required to be provided to the Companies. For example, if the AMC were to collect data from study participants that do not need to be collected for the Program, but is collected for independent research, perhaps well after the study is complete or collected for medical care, the AMC would be required to provide these raw data to the Companies, as arguably, it is "data" that "arises from the Program." Companies have no right to these data.
In addition, the ownership of Technical Developments which are not "inventions" is determined according to the "origin" of the Technical Development, lending further confusion to the scope of the phrase.

A concern is that a company could argue that any data from the Program which are generated and collected by the AMC "originate" from the Company, as the compound originates from the Company. This language, therefore, could give the Company ownership rights to any and all data created by the AMC, which is generally unacceptable to academic institutions.

The myriad of problems with the phrase “Technical Developments” are best solved by removing the use of the phrase throughout the agreements and instead, giving the Companies rights to AMC Inventions and Patents covering such AMC Inventions. In the alternative, the scope of “Technical Developments” should be limited to patentable information which is made in the direct performance of the Program, with ownership of the “Technical Development” determined in accordance with U.S. patent law.

Finally, with respect to the intellectual property rights provided to the Companies in these agreements, whether ownership or the provision of an exclusive or non-exclusive license, this group notes that the Companies receive far greater rights than they would otherwise receive in conducting research with this group, particularly given that these agreements contemplate that the Companies are only providing the compounds, and no funding for the Program. In research where a company provides a compound only, the group traditionally only provides the company with a time-limited option to a license to inventions having a nexus with the study drug. This narrow provision of intellectual property serves to ensure that the group meets is mission of making scientific advancements available for the public benefit and to promote the open dissemination of research results, while providing the company with an appropriate benefit in return for making its compound available for research.

e. Present Grant of a License

The CRA template agreements require AMCs to presently grant a non-exclusive, world-wide, royalty-free and fully paid-up license to AMC’s rights in Technical Developments for internal research and development purposes. Because of the vast array of research the group conducts with third parties, including the federal government, the present grant of a license, particularly to intellectual property that extends beyond that which is conceived and reduced to practice in the direct performance of the research at issue in a given agreement (which is the case in these CRAs), creates a burdensome and potentially unmanageable obligation for the group. The present grant of a license, in conjunction with a broad license to intellectual property extending beyond the scope of patentable intellectual property created in furtherance of certain research with a third party, could put the group and other AMCs in the position of agreeing to conflicting intellectual property obligations, or providing intellectual property rights to a recipient not entitled to such a license. As sponsors have been requesting that the group presently assign or grant intellectual property as a result of the *Stanford v. Roche* decision, the group has been able to meet the concerns of such companies by affirming that its investigators have presently assigned their rights to any patentable intellectual property to the University. To relieve AMCs similar to the group of the potentially unmanageable burden of tracking the broad obligations at issue in this Program, the group urges NCATS to allow AMCs to agree to grant a license to Companies in the future, when the intellectual property actually exists, and provide an assurance that the AMCs have the full right to grant such a license to the Companies.

f. Option to Obtain an Exclusive License

All three CRAs provide the Companies with an option to obtain an exclusive license to AMC Technical Developments. Again, the group illustrates the problematic definition of "Technical Developments": an exclusive license to non-statutorily protected intellectual property (such as "know-how", "information," or "advancements") effectively prohibits AMCs from disseminating any information related to the research which could be regarded as "Technical Developments," a restriction that could wholly bar publication. It is for this reason that the group only provides an exclusive license to statutorily-protected information.
In Section 9.2.1, the Pfizer CRA provides Pfizer with the option to take over the AMC's investigational drug application (IND Application). Such a transfer would be required to take place *after* the AMC has conducted the trial and monitored the study, and *after* NIH or another funder has borne all of the trial's costs. A more equitable option for the AMC and funders of the study would be to provide Pfizer with a right of reference or use to the AMC's IND Application, which would enable Pfizer to rely upon the AMC's information so that Pfizer could commercialize any inventions.

In addition, the AstraZeneca CRA provides that AMCs grant to AstraZeneca the exclusive option to acquire the exclusive option to acquire a license in AMC Technical Developments. Should the Company not obtain an exclusive license to any AMC Invention or AMC Technical Development, the CRA states that the AMC may exclusively license its interest in such AMC Inventions or AMC Technical Development, provided that the terms of the license are not more favorable than those offered to AstraZeneca. There is no time restriction on this requirement; rather, the AMC is barred from ever providing more favorable terms. Changing business considerations and the advancement of science may cause the terms of these licenses to change. Thus, in the interest of promoting commercialization of any AMC Inventions or AMC Technical Developments, the group recommends that NCATS revise the language to provide that the AMC shall not provide more favorable terms to another party for six months following the end of the Option period, or other short and definite time period. This group also notes that the licensing terms in the AstraZeneca CRA calls for pre-pricing of licensed intellectual property. Given the unknown scope of intellectual property that could be generated in performance of this Program, the group recommends that this Section be removed, enabling the parties to negotiate licensing terms specific to the intellectual property ultimately created.

g. Form of IIR Agreement

The CRAs each reference an "IIR Agreement" which will be entered into should the parties agree to conduct a clinical trial and further state that the IIR Agreement will be in the "form set out in Exhibit B," yet there are no contemplated terms in that exhibit. Just as a template CDA and CRA will reduce the transaction cost of participation of this program, a template IIR Agreement would also greatly assist AMCs and reduce the burden and cost of participation.

The group urges NCATS to develop a template IIR Agreement and to make the terms of this template agreement available for public comment.

h. Disclosure of Protected Health Information

The CRAs contemplate different levels of participation of the Companies in each study; in some, the Companies may act solely as the provider of the compound and will not play a role in developing the protocol or study design. In others, the Companies may work with the AMC to develop the protocol. Depending on the role of the Company in study design, the need for the Company to have access to protected health information of study participants accordingly varies. Further, state laws such as the California Confidentiality of Medical Information Act (Cal. Civ. Code 56 § *et seq*.) prohibit the disclosure of identifiable information of study participants to entities such as the Companies, if the Companies are not FDA-regulated "sponsors" charged with the duty to audit and monitor the study. The clauses should make clear that AMCs shall only provide protected health information of patients or study subjects to the Companies to the extent required and allowed by HIPAA, applicable state laws and regulations.

i. Patent Applications

The agreements require the AMCs to give the Companies written notice of any intent to file patent applications covering any AMC Invention, and further require the AMCs to give the Companies the right to review all patent applications on such inventions and enable the Companies to provide comments to such patent applications. Indeed, the agreements contain four long paragraphs on the terms of patent applications covering AMC Inventions, detailing the obligations the AMC has to the Company, and rights the Company has to patent applications covering AMC Inventions. These agreements give the Company the ability to control patent prosecution of inventions owned by the AMC. If an invention is owned by an AMC, the AMC should control prosecution. In fact, the Companies have full control of patent applications covering Company Inventions; the same rights should be given to AMCs with respect to AMC Inventions. Further, a Company should have input on the prosecution of a patent claiming a sole AMC Invention only so long as it has an exclusive option or license to the invention; if the option is declined, the Company should have no further input.

With respect to Joint Inventions, the Companies have full control over patent prosecution as well. At a minimum, AMCs should have the right to participate in patent prosecution, reviewing and providing comments during the patent examination process, and Companies should accommodate such AMC input unless they have a reasonable objection.

This group also notes that the CRAs require AMCs to give the Companies at least 45 days' notice of intent to file a patent application. AMCs usually have one day's notice of any anticipated patent filing, and would therefore not be able to comply with such a requirement.

j. Indemnification and Subject Injury

The CRA templates create overbroad carve outs of the Companies' indemnification obligations and do not adequately protect AMCs or study participants from financial burdens imposed by participation in the Program. Specifically, the CRA templates provide that the Companies are not obligated to indemnify if the claim is based upon the negligence, recklessness or willful misconduct of the AMC. This language creates a mechanism for Companies to assert that any claim for indemnification is based upon such negligence. Companies should be obligated to indemnify for all claims arising out of their use of information or material received from the AMC, and the carve out should be limited "to the extent" such claims were the result of negligence of the AMC. In addition, the indemnification obligations are limited to the Companies' or Companies' authorized third parties' use, sale or disposition of information or materials received from the AMC. The purpose of indemnification is to make the other party whole, or to compensate the other party, for losses attributable to the actions or omissions of the indemnifying party. Thus, Companies should also be required to indemnify for any claims to the extent they arise from the Companies' study design and the Companies' decided use of the compound. Further, to the extent that Companies make decisions regarding study design and guide the use of the compound in a given study, Companies should be obligated to compensate AMCs for any injuries that directly result from such study design and use.

Also, Companies should not have the ability to admit any fault or wrongdoing on the part of the AMC when settling or resolving any claim, without the prior written approval of the AMC. The AMC should also have the ability to participate in the resolution or defense of any claims to which the Company may indemnify, at its own cost and expense. This group urges that language providing these assurances to AMCs be added to the templates. Finally, the AstraZeneca CRA contains a provision that requires the AMC to indemnify AstraZeneca for any breach of the agreement by either party or any representation or warranty made by the AMC. This language would not be acceptable to AMCs, as it imposes financial risks on the AMC which it should not bear. For example, should the group breach the agreement, the law entitles the Company to seek contractual remedies owed to the Company. Should the Company breach, the group should not be obligated to pay for claims for losses attributable to the Company's actions or omissions. The group highly recommends that this section be removed.

k. Review of Confidential and Patentable Information for Publication

This group supports the goals of the publication clause of the CRAs – to promote and ensure timely publication of results and inventions, while protecting patent rights and Confidential Information. However, the clause as written does not adequately meet these goals. The publication clause gives the Company the right, with the AMC, to "revise" the manuscript to ensure protection of Confidential Information. AMCs aim for the highest degree of openness in its research, and in doing so, provides the companies with which it engages in research to *comment* on proposed publications and ensure that this group will

remove the company's confidential information from publications. Giving companies the ability to "revise" these manuscripts creates a mechanism for information, such as potentially negative research results, to be edited or removed from publication. Even if it is not the intent of the Companies to remove such information, contractual language that gives Companies the right to "revise" manuscripts could call into question the accuracy and validity of the published information by the scientific community and organizations such as the International Committee of Medical Journal Editors. To ensure that any resulting publications are not met with skepticism, UC urges NCATS to give AMCs the sole control to revise proposed publications to ensure that the Company's Confidential Information is removed. In addition, here, the scope of "Confidential Information" is also important, as the defined phrase should cover only the confidential and proprietary information of the Company, and should not reach to the research results generated by the AMC. AMCs should have the rights to openly publish its results, as discussed above.

Finally, the group notes that in the Publication section, the agreements use the term "results" (see, e.g., Pfizer CRA at Section 11.1), even though the term "Results" is defined. This is merely one example of the inconsistent use of defined and undefined terms throughout these agreements, which creates ambiguity, and therefore, increases the likelihood of dispute among the parties in the future.

l. Monitoring and Auditing

The CRAs also provide that upon reasonable notice and during regular business hours, the AMC shall permit the Company to monitor the study. Because the CRAs contemplate different levels of involvement on the part of the Companies in developing the studies, the agreements should state that the right of the Company to monitor the study and conduct inspections of the pertinent facilities and records is limited to that which is required by law. For example, the Companies have no reason to monitor studies for which they do not take over the IND. Finally, this group notes that it negotiates contracts to conduct research with *each* of the three companies currently set to participate in this program. This group's fruitful relationships with these companies and other biomedical companies exemplifies that the Program's CDAs and CRAs can be revised to better reflect the missions and realities of AMCs, while keeping the interests of the Companies in mind. To meet this goal, this group encourages NCATS to work with both AMC and Company representatives to revise these agreements.

- As stated in the RFI, there is a significant amount of "transaction cost" involved in negotiating individual agreements. This may prove to prevent the participation of many interested investigators. Nonetheless, it will be necessary to carefully construct the agreements between investigators and pharmaceutical companies as each relationship will be unique. For example, the nature of each partnership will depend on the applicability and usefulness of the initial data and information provided for each Agent. As these new collaborations may lead to the successful repurposing of existing molecules for new indications, assignment of intellectual property will need to be negotiated in advance. Moreover, as many of the Agents will already be off-patent or nearing patent expiration, the industry partner's ability to secure exclusive rights

to eventually market the Agent will need to be addressed. To that end, we recommend that NIH, at a minimum, provide a standard set of guidelines that can later be modified within the context of new partnerships.

- The use of template agreements will be crucial, and NIH should set non-negotiable parameters around the major issues so that individual agreements require very limited (preferably none) further academic-pharmaceutical negotiation. This may initially limit the number of willing participants, but will set the essential framework for future progress and dramatically expand the number of academic investigators who are motivated and able to participate - they in turn will pressure their university administrations to address institutional barriers. All of the financial rights should go to the pharmaceutical company to provide maximal incentives. In return they should be required to provide full access to information about the drug and its preclinical and clinical results to investigators. The template must include language that gives complete control over publication decisions and rights to the academic investigators, and it would probably be best to include language that actually requires the academic investigators to make results public, so that no conflicts of interest can lead to suppression of "undesirable" results. Any proprietary information about the drug and its preclinical/clinical history necessary for interpreting the study results should also be fully publically disclosed. Companies should also be required to keep an agent accessible under the same terms, so that they cannot re-exert "information control" over that specific agent once initial promising information becomes available. Broadly, a "deal" where the companies get control of the economic value, and the government/academics get control of the information. An attractive alternative would be to have NIH get a fixed small percentage of future earnings, or some lump sum from any future earnings above some large threshold, so that NIH can build an "endowment" to expand the program.
- A large concern regarding public/private partnerships is liability for adverse events that occur in the course of clinical trials. If complications arise in the course a patient's participation in a clinical trial using one of the molecules pursued through this program, it must be established *a priori* where the responsibility for patient protection lies. Pharmaceutical companies may not want or be able to indemnify investigators or institutions in such trials, while many investigators or institutions do not hold sufficient insurance to indemnify such claims. Whatever the terms of the contract, concerns about liability may limit participation and/or create a funding bias for investigators at institutions that are willing to assume liability. The NIH may wish to consider a scheme for pooled indemnification to support this initiative – potentially with contributions from industry, the NIH, and sponsoring institutions.
- Runaway legal fees can sometimes match or exceed the R & D costs; agreements need to be worked out beforehand or what works in a technological sense can be stymied by difficulties during business negotiations. This is particularly difficult when the ultimate result is unknown at the outset. Adequate definition, of typical, realistic expected 'milestones' beforehand has been a hold-up in agreements. Agreements are typically sketched out by business people with inflated expectations, many of whom rely on consultants for their technical expertise. Having a set of negotiating guidelines will be a plus.
- Template agreements could either encourage or discourage the participation of our institution depending on how they are crafted.
- Template agreements would be a good way to go. Universities need to know that they can't have exclusive rights to discoveries in this area. Pharma companies need to know that they can't have exclusive rights to what is discovered in academia, and that rescue of their compounds is a valuable use of work they have already sunk a lot of money into.

- Template agreements are a great idea, and will remove a lot of the gray area that might allow companies to exploit inexperienced researchers in academia.
- Should be straightforward for an existing drug that may be repurposed.
- The need to protect IP and yet to collaborate is one major reason why the CDD Vault technology is so critical. It allows scientists/project team members from different organizations and geographical locations to communicate and collaborate effectively while selectively shielding potentially sensitive intellectual property (use, composition of matter). CDD has not needed to offer any legal services or agreements, for effective collaborations over 8 years. The CDD Vault technology can be used before or after the collaborating parties agree upon their legal and IP terms and start to actively work together on a project. CDD has worked with Creative Commons to prototype community based IP agreements, given our capabilities for handling the underlying data. CDD can consider how to aid integration of agreement terms into a project workflow, to streamline the formalization of terms for data sharing, ownership and disclosure.
- We do not anticipate any obstacles to industry-academic partnerships because we have experience with relationships like this already. The active clinical research projects among the four local academic medical institutions have resulted in excellent, productive relationships with pharmaceutical companies and a streamlined, timely process on the front end when dealing with executing clinical agreements.

3) Comments on how working with a Clinical and Translational Science Award site (CTSAs) could advance drug rescue research projects, particularly for rare and neglected diseases.

- CTSAs will provide valuable resources for investigators participating in the program through access to integrated translational science capabilities. Researchers at CTSA sites will also benefit from access to research tools to help design and implement clinical trials through the resources provided by their CTSA. It is critical, however, to preserve funding and capacity at these sites for fundamental research devoted to identifying new drug targets and disease processes in order to maintain input into the drug discovery pipeline. That is, implementation of the new program in the context of CTSAs should not come at the expense of the sites' other activities.
- Specific Public Private Partnership Key Function Committee roles, activities and potential value in future NCATS initiatives:
    - The Public Private Partnership (PPP) Key Function Committee has played a key role in the development of current demonstration projects such as the CTSA Pharmaceutical Assets Portal (http://www.ctsapharmaportal.org/) and the CTSA Intellectual Property (CTSA-IP) Initiative (http://www.ctsaip.org/). The Pharmaceutical Assets Portal project aims to facilitate the match between CTSA-affiliated investigators and the pharmaceutical industry with the aim of developing research partnerships based on compounds shelved at the clinical stage. Like the proposed Discovering New Therapeutic Uses for Existing Molecules Program, the Pharmaceutical Assets Portal represents an earlier stage effort to partner with the pharmaceutical industry, but lacks the critical funding to support studies with these agents. The Pharmaceutical Assets Portal provides compounds for scientific and medical investigation, including for new therapeutic uses, from Pfizer and other pharmaceutical companies. We are ready and willing to assist NCATS with this very exciting NIH funded initiative with the pharmaceutical industry.
    - CTSA-IP was created to aggregate and market technologies from CTSA institutions as well as those of the National Institutes of Health, with the goal of enhancing research activity and private partnerships across the CTSA consortium. CTSA-IP now has 24 CTSA

institutions and the NIH providing over 10,000 technologies. The CTSA-IP continues to evolve as a collaboration tool, partnering with other tools designed to aggregate research resources, researcher profiles and technologies. These programs could be expanded to include additional academic, industry, and government partners.

- The PPP Key Function Committee worked closely with NCRR in planning and leading the program for the "CTSA Industry Forum: Promoting Efficient and Effective Collaborations Academia, Government and Industry" held February 17-18, 2010 at the NIH. A meeting summary and several white papers from the meeting appeared in Science Translational Medicine in December, 2010 (http://stm.sciencemag.org/content/2/63).
- The PPP KFC can be utilized as a vehicle to engage the broader CTSA Consortium of 60 institutions to develop PPPs in key areas:
  - CTSAs are increasingly closely associated with their institutional office of technology management/transfer and clinical research office, ensuring coordinated program management between scientific, legal/IP, and regulatory personnel. This is a critical feature in forming partnerships and implementing studies.
  - The PPP KFC could provide a method to help develop common agreement templates between industry partners and the members of the CTSA Consortium. There are ongoing efforts in the PPP KFC focused on pre-competitive space initiatives. Specifically, the PPP KFC is currently exploring a pilot project to develop processes and procedures for industry to more easily access resources and initiate research collaborations with the network of CTSA institutions. This type of PPP initiative could be important in identifying new therapeutic uses for existing molecules. CTSA consortium in general can provide:
    - The ability to rapidly form project teams to identify and recruit patients with rare diseases.
    - Consortium cataloging efforts (such as the SGC5 effort led by the CTSA Consortium Coordinating Center and eagle-i) identify unique resources, expertise and facilities across the consortium that can be used for studies.

- The CTSA Consortium can form additional partnerships with NCATS to serve as a critical network of leading institutions to advance these and similar efforts. One of the unique opportunities available with the CTSA program is to more actively serve as a Consortium, functioning as a network to pilot and implement programs. This has occurred in several areas related to public-private partnerships, including the CTSA Pharmaceutical Assets Portal (http://www.ctsapharmaportal.org/), the CTSA Intellectual Property (CTSA-IP) Initiative (http://www.ctsaip.com/), and other projects. These types of collaborations have been facilitated through Consortium-wide groups such as the CTSA Public-Private Partnerships Key Function Committee and the Strategic Goal Committee #3, which is focusing on approaches to enable Consortium-wide collaborations. These groups could be further utilized to streamline the process to develop, pilot and implement processes and procedures for these and similar programs.
- The CTSAs are already working towards advancing drug rescue research projects by linking themselves to rare disease networks through the CTSA Consortium Child Health Oversight Committee. This effort has resulted in the sharing of best practices and tools between CTSAs. The most innovative program was a 2010 RFA supported by NICHD to support the development of better outcome measures and to enhance FDA approval of new therapies. Despite a lack of

funding for the actual support of rare disease networks, the CTSAs could help researchers by waiving costs for use of clinical units or clinical research staff for rare disease studies.

- Another tool for researchers has been the development of easy and cheap data management software such as REDCap, which allows research staff to self-manage data from multiple studies and case report forms. Many CTSAs are currently using ResearchMatch, a national research volunteer database, to identify patients for clinical studies across the country. The CTSA program should also think about whether it wants to establish a more active role as a coordinating center for multi-center studies in rare diseases Currently, there is no structure for coordinating studies but there are several good disease specific models exist such as Children's Oncology group.
- There are a number of advantages to working with CTSA sites to advance drug rescue research projects. The institutional emphasis on translational research has the potential to move research more quickly, and more cost effectively, from the pre-clinical to clinical testing phases. Infrastructure is already in place at CTSAs to conduct research that is focused on moving new discoveries into patient care and health outcomes.
- CTSAs may also provide access to populations historically difficult to access for clinical trials, which could be especially beneficial for rare or previously neglected diseases. That there are already established structures for collaboration between CTSAs is another advantage. Multiple CTSAs could leverage resources to conduct large research projects more effectively and efficiently. A multi-institutional clinical study between CTSAs could facilitate patient recruitment between or across geographic regions, resulting in larger study populations.
- Collaboration could also make access to medical informatics necessary for evaluation purposes, which would make the drug repurposing research more valuable. Infrastructure is already in place at CTSAs to mobilize research around a specific molecule or disease. Screening molecular libraries at multiple CTSA sites would rapidly identify drug candidates for rescue or repurposing. The focus of CTSAs on training and study designs that streamline scientific discovery provides additional benefits to drug rescue research projects.
- CTSAs are in a unique position to provide industry partners and other potential collaborators with expertise in trial design, especially adaptive design. NIH is resistant to providing molecular libraries to CTSA sites with screening centers. Providing molecular libraries directly to CTSA sites would be of great benefit to accelerate screening for drug repurposing efforts.
- When drug candidates emerge from laboratory research for potential translation into the clinic there is often a disconnect between the lab scientists and the clinical/medical staff. CTSA programs have the potential to play an important role in the translation of laboratory discoveries into treatments for patients, to engage communities in clinical research efforts, and to train a new generation of clinical and translational researchers. The program awards in our opinion should foster and reward collaborative work at the T1 translational level, and be framed as awards to self-forming translational consortia that view collaboration as a game changer and which include both Scientific and Clinical Key Opinion Leader (KOL) groups in a consortium proposal.
- This would be useful but I would prefer not to limit the ability to participate in this program to institutions with CTSAs.
- The greatest research expense, in terms of time, was setting up and validating the diversity of pre-clinical tests needed to test the identified new site of action. Since the new sites of action for our case were unknown at the outset, obtaining the required proteins in sufficiently pure form and the reagents for testing took much time. What is needed for CTSA sites for repurposing is such a general adaptability and flexibility to handle diverse problems. This is a

contrast to how most scientists usually work, namely as specialists for one particular area of study or class of proteins of interest. Focus is good once the new drug targets are established, but too much focus too soon will deter or prevent success.

- The quickest approach that will bring new medications to market is to examine all the clinical uses and reports of benefits in the literature and the side effects. Funding is needed to screen these drugs for additional indications.
- It is a great concept that could further drug development.
- Most TrialNet centers are affiliated with CTSAs but are currently sitting idle with NO intervention study to offer newly diagnosed type 1 patients. This has occurred to do a perceived lack of funding related to the cost of the agents for the ATG/GCSF combo in particular. However, the structure of TrialNet is already so well established that these trials could easily move forward with new partnerships.
- The CSTAs could do a better job of getting out into the University and "mining" the research for potential opportunities for rescue or repurposing. We have discovered that many faculty members are too busy to respond to emails or surveys. What is needed is more active involvement of some organization within the unde voiversity to connect with researchers in a 1:1 relationship. Currently, that role is played by our Institute. One researcher sat on an Alzheimer's researcher's group meeting for about 4 years before spotting a new therapeutic target. The CTSAs should be the ones going out into the early Discovery realm.
- We would work with any site that has suitable access to patients and appropriate supporting resources for our program providing intellectual property considerations are addressed. Working with a CTSA site may provide for some cost savings and clinical trial efficiencies.
- Can only see CTSA involvement really occurring at a later stage, clinical trial planning and conductance, and not really being involved in early basic science studies aimed at testing candidates in animal models etc.
- The NIH initiative of establishing the National Center for Advancing Translational Sciences (NCATS) is pivotal in generating innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of diseases and conditions. The new center’s activities will complement translational research being carried out at the NIH and elsewhere in the public and private sectors.
- The CTSA institutions provide an environment that maximizes sharing of information and serves as a catalyst to spark innovative research proposals and interactions. By the involvement of the CTSAs, academic researchers at partnership schools and colleges, such as Veterinary Medicine and Engineering can augment human-based research and development efforts in ways not accessible to most drug developers. Similarly, specialized animal model programs that include essential intellectual infrastructure, such as the National Primate Research Centers and other large animal facilities, can advance the use of compounds from discovery to IND-enabling studies to accelerate the pathway to clinical trials. • The availability of research imaging facilities has previously proven very useful in detecting unanticipated tissue localization or kinetic properties that might explain unexpected toxicities or reveal significant barriers for future advancement. Through the networking ability and research core facilities made available by CTSAs, as well as by the involvement of faculty with specialized competencies, such resources could be mobilized to reach critical go/no go decisions. • Biomarkers can be found in body fluids, tissues or amenable to imaging strategies—the CTSAs can contribute to involve key competencies in pathology and radiology.

4) **Comment on how working with NIH Intramural Research Program investigators (http://www.irp.nih.gov) and the NIH Clinical Center resources (http://www.cc.nih.gov/index.html) could advance your drug rescue research project.**

- The NCATs program offers an excellent opportunity to liaise and collaborate with intramural members of the NIH. As the steward of medical and behavioral research for the nation, the mission of the NIH is science in pursuit of fundamental knowledge about living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability throughout the world. The mission aligns itself seamlessly with those of the participating institutions and will serve to enhance existing collaborations and interactions with the NIH.
- Rather than focus on being competitive with universities, it would be of great benefit if intramural programs provide services to universities. A challenge with intramural program activity is that there is currently not an incentive for the intramural program to work effectively with universities. One possibility would be to develop clear opportunities for CTSAs to work with these entities in order to advance drug rescue research projects. There must also be mechanisms for investigator-initiated studies that originate in CTSAs to move studies forward and leverage resources from the intramural centers without transferring the project to the intramural program. An incentive for CTSA consortia would be to establish a collaborative structure where the NIH Intramural Program focuses on GLP and GMP animal studies and provides this at a lower cost, so that CTSAs could focus on the clinical trials.
- Compiling information and company data, especially some of the early discovery research in the files and looking at a variety of mechanisms from these medications is a key opportunity to review. Because these products already are safe for humans, it is easier to work with the medications. Funding for studies, supplies of drugs and background information.
- If the appropriate expertise exists within the intramural research programs at NIH this is clearly possible providing intellectual property considerations are addressed.
- Need to identify researchers that are experts AND understand the process of drug development. Often times the most difficult task is identifying the appropriate system in which to examine the effects of your drug.
- Have good working relationships with a couple of NIH intramural groups already (with NHLBI), so can only see the opportunity to work with them more closely as an advantage.
- Whereas having a broad pool of researchers with many areas of focus is useful, having a small cadre of more adaptable researchers would also be of benefit, since the ultimate useful targets found are likely to be outside of the particular areas of focus of any of the individual researchers. In theory, there may be someone with nearly an overlapping interest; in practice, researchers may be more interested in particular aspects of science. While there may be exceptions, it is expected that researchers will pay only nominal interest in advancing drug development if it is in an area somewhat outside of their direct area of focus.

5) **Discuss whether the goals and incentives of the NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules are sufficient for biotechnology and pharmaceutical companies and the biomedical research community to participate in the Program. Discuss the most important steps NCATS should take to promote and facilitate partnerships for therapeutics discovery between industry and the biomedical research community. Your perspective on how success of the therapeutics discovery program would be defined.**

- The goal of the *NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules* is an excellent idea that opens an avenue for testing drugs that have failed the rigorous criteria required for approval to treat a particular disease but may have potential to test other diseases. Due to the financial and regulatory constraints that apply to drug discovery and development it, is not always possible to test drugs on a wide variety of diseases.
- Drugs that are known to interrupt a specific signaling pathway and tested in a specific disease state may not be exclusive to that disease. Most cancers are caused by a multitude of complex interacting genetic and environmental factors and therefore have many targets that could potentially be further explored.
- The most important steps for NCATS are as follows: 1) **Motivation for Program participation**. In order to ensure that biotechnology and pharmaceutical companies participate in the Program, an incentive such as licensing may be necessary. For example, the partner academic institution or the NIH may need to consider an option to license the background IP from the company (i.e. the compound) in the event that a company chooses not to develop the compound. In this way, the company still benefits through a royalty-sharing agreement, without assuming the risk and costs of future clinical development. 2) **Promotion of joint discovery**. Existing disease networks or collaborations between CTSA organizations could facilitate the conduct of proof-of-concept clinical trials in rare and neglected diseases. However, this may be insufficient motivation to take the compound through development, given the potentially small market size. The biotechnology and pharmaceutical companies may need additional financial incentives or risk-sharing mechanisms before agreeing to develop their product for a rare or neglected disease.
- The main incentives for industry to provide their molecules to academic labs are that a patent for a new application would restart the clock and that commercialization could be accelerated using existing FDA applications. Having more than a decade to exclusively market an existing molecule for a new disease would make it very attractive. There would also be an indirect benefit in the knowledge that their previous efforts to develop the molecule were not wasted.
- The measures of success of this Pilot Program could include the following:
    - a. Patents filed for new applications of existing molecules
    - b. Acceleration of clinical trials based on previous data
    - c. Commercialization of an abandoned compound d. New treatment approved for an orphan disease (may not be profitable) e. Identification of a novel target for further drug development
- One of the things the biomedical community will need is to know that the process was fair and as inclusive as possible. It is virtually impossible to separate out the importance of a drug and disease. It would be useful to give examples of diseases that have been particularly challenging to control as ones for which success would be defined as identifying a drug, repurposed, that is useful in therapy of said disease.
- The goals are valid because of the existing uses already determine safety of the agents. Finding new mechanisms of actions and other clinical benefits is a common direction that is not a concerted direction most companies have historically taken. It has strong validity because it can give enough clinical potential for benefits. Dermatology is even more sure of success. New delivery of the medications and new diseases of treatments can be unique way for producing a whole host of new treatments.
- Access to test drugs, background data and funding to make possible behavioral pharmacology studies in animal models.

- The NIH should put out a call for biomedical researchers to advertise their services using a standard, electronic submission format. These would then be placed in a searchable database that would serve as the first step in matching the Pharm groups with testing/discovery labs.
- Develop a comprehensive, secure database of "rescuable" compounds that could be searched in a confidential manner for activity against known and novel targets (virtual screening). This could then connect academic researchers with the appropriate pharma contacts.
- Success should initially be defined on the number of academic/industry partnerships or collaborations established. Don't limit it to new therapeutics discovered. That's too high a bar. NCATs/CTSAs can best make a "splash" by showing that it can lead to (or mediate) more applied research between the "ivory tower" and industry.
- The goals of this program are sufficient for participation of many types of companies ranging from small biotech and pharma companies, to diagnostics companies, Clinical Research Organizations and technology providers. Success will depend on the quality of the compounds given to the program and the intellectual property constraints. It makes sense for the program to have a proof of concept endpoint and then clear paths for further development and commercialization.
- Access to both materials and intellectual expertise; Identification of appropriate biologic test beds; clear milestones and the costs both in terms of time and money needed to reach those milestones; and an understanding of the obstacles/costs associated preclinical and clinical development in particular the expectations for additional studies required for FDA approval.
- Goal-wise, all looks good. Incentives are a difficult matter. The inclusion of more than 24 drugs would make this a little more attractive. As an academic, one gets the impression that 24 is a bit of a small number. A much bigger number of agents needs to be included in the program.
- As far as the financial industry is concerned, the only measure of success is to have an FDA approved, marketed drug.
- Success could initially be based on the number of companies and investigators participating, the number of agents or targets available through the program, the number of projects funded. In the long term, the ability to bring these drugs to market is obviously important, but it is likely that critical knowledge will be obtained even from drugs that do not make it to market.
- The ultimate desired outcome of the projects supported through this program will be the progression of drug treatments through Phase III clinical trials and onto the marketplace. However, as drug discovery is challenging, other benchmarks (metrics) should be used to measure success of the program. It is likely that only a minority of molecules will progress quickly or fully through clinical trials. It is important that success be measured by accomplishments at several levels, including executing early phase studies, demonstrating (or disproving) proof of concept for a mechanism or target, successfully defining and validating surrogate or Phase III endpoints, training of highly qualified personnel, etc. Such measures reflect the success of the program as well as of the participating investigators. Of course, information and new knowledge generated from these partnerships will only be valuable if accessible to the broader scientific community. Indeed, as the work will be publicly-funded, the results rightly belong within the public domain. We, therefore, strongly encourage NIH to work with industry partners to devise standard agreements to ensure the ability of investigators to publish the results of the work emerging from these collaborative projects in a timely and relatively unrestricted fashion.
- This broad and deep question cannot be answered without ultimately knowing the members of the research community. However, it may require more than just “awards” and monetary stimulus. Project management and professional contract partners with industry experience

could be needed ingredients. One could run the project as a virtual pharma company outside NIH, or as done effectively for the NIH Neuroscience Blueprint, where NIH staff is augmented by experts with deep CNS drug discovery pharmaceutical experience. The Collaborative Drug Discovery (CDD) technology today supports many virtual pharma and drug discovery projects that can provide the scientific IT/IS project management side.

- An effective project would:
  - Develop a common interface/platform so that government, academic researchers and biotech/pharma project personnel can find each other for collaboration.
  - Promote an environment such as the GSK Commitment to Open Innovation to allow sharing of previously sequestered compound and bioassay data.
  - Guarantee secure access to data within a project after a collaborative relationship has been established.
  - Guarantee user sharing of results, beyond just the raw data. Therapeutic discovery program key milestones could include:
  - Lead compounds which could be advanced into preclinical small animal testing, perhaps that could be advanced into large animal studies or directly into humans, depending on the disease.
  - Provisional patent application data which could secure the use of the compound in a new application.
  - Identification of potential clinician-sponsored IND site.
  - Identification of potential licensing partner (e.g., small biotech or pharma). • Number of disease areas represented in the project portfolio
  - Projects successfully gaining match funding.

The success of the Pilot Program could be determined in 6 years by the number of compounds successfully out-licensed to private corporations for preclinical/clinical development. If one or more compounds has entered the clinic, since the program is focused on repurposing existing off-patent drugs, the program would be a success.

- Success of this program will depend on the incentives provided to the commercial partner and to the academic investigator. Important incentives for the commercial partner include access to new data generated by the academic investigator regarding the agent of interest. An additional incentive would be right of first refusal to any intellectual property generated with respect to the agent.
- Incentives for the academic investigator include full freedom to publish with minimal delay for patent filings, willingness of the commercial partner to cover patent expenses for filings related to the academic investigator's work, and willingness of the commercial partner to provide milestone payments and royalties to the academic institution. A major roadblock for the program is that commercial partners may not be willing to move forward with commercial development even if the academic investigator is successful in generating proof-of-principle data suggesting a new clinical application. It is critical that a contract be developed in which the commercial partner indicates an understanding that the objective of the program is to advance the agent of interest to commercialization and that the commercial partner is bound to use its best efforts to pursue development if there are reasonable chances of commercialization. The commercial partner should indicate that they acknowledge that adequate intellectual property protection is a use patent, formulation patent, trade secret or know-how; composition of matter protection is not required. Provisions should be made for independent replication of the research results of the academic investigator. Costs of replication could be borne by the commercial sponsor or by NIH.
- Success would be outcomes that demonstrate a productive collaboration between the private sector and academic institutions, including increased opportunities for translational researchers and

the increased capacity for drugs to be developed that may not be seen by industry to be commercially viable. A positive outcome would be if this model of collaboration resulted in testing and development of efficacy of a drug in a population where it would not otherwise be tested—for example, because of the affected population's location, small population size, etc.

- There is the additional benefit to pharmaceutical companies that university researchers may uncover new markets from regionally-specific patient sub-populations that may be difficult to access or that companies would not otherwise pursue. In order to do so, molecular libraries would need to be provided to CTSA sites with screening centers. Data related to screening should be broadly distributed, and CTSAs should be encouraged to form multi-center clinical trials to test drugs for potential rescue or repurposing.
- Necessary resources for NCATS program partnership. To ensure a successful partnership between a biotechnology or pharmaceutical company and the CTSA organizations, academic investigators would require access to extensive pre-clinical data from the companies such as the intended use and target of the therapeutic, pre-clinical and clinical trials results and the factors that halted development. Other useful information would be profiles of off-target activities, any alternative formulations, toxicology results as well as biomarker and pharmacokinetic profiles. Availability of support from the commercial partner would facilitate rapid completion of any additional necessary studies such as bioanalytical assays. Confidence in the therapeutics discovery process would be enhanced if the academic partner could interact directly with the development team. This open channel of communication would allow the scientific teams to discuss data and results, saving time and increasing both the efficiency and the output of the NCATS program.
- It is critical that the biotechnology or pharmaceutical company provide full disclosure of any and all scientific data that is available related to the agent of interest. If investigator brochures are available regarding the agent, these should be made available. In certain circumstances provisions could be made for maintaining portions of the dossier confidential and by mutual signature on confidentiality agreements.
- It is possible that many of the failed drugs may act through mechanisms not originally intended. An example of this is recent insights into stroma-cancer feedback pathways that are sensitive to metformin, quercetin and chloroquine. Basic science researchers at academic institutions would need to be informed by probably proprietary data on drug on- and off- (original) target effects to maximize the chance of connecting biology with successful repurposing

6) Comment on the resources that a biotechnology or pharmaceutical company partner might realistically contribute to an NCATS program on therapeutics discovery in addition to the Agent and the associated data. You can also comment on the type of information about the molecules that you would be willing to disclose publicly.

- Pharmaceutical companies that participate in the program should provide all the available information of the drug candidate in a database that is available to all researchers at universities. Researchers should have access to the previous studies and associated data. One anticipated problem with the pilot program as it has been introduced so far is that universities will need access to data that is mineable; information will need to be made available in a coherent database. Many CTSA sites have strong drug screening capabilities, and limiting molecular libraries in NIH intramural programs does not use the capabilities that exist in the universities nationally.
- Small pharmaceutical businesses are integral in bringing innovative medical products to the US marketplace. A properly defined partnership with pharma and the NIH could ensure a supply of

compounds that have undergone rigorous testing for treating a particular disease and found to be ineffective, but might still hold promise in other disease states. By incorporating a pharma partner, we anticipate being able to rapidly and efficiently test compounds using clinically relevant test systems to determine therapeutic potential. Furthermore, compounds with promising efficacy could be rapidly moved into IND. To ensure a successful partnership between a biotechnology or pharmaceutical company and the CTSA organizations, academic investigators would require access to extensive pre-clinical data from the companies, such as the intended use and target of the therapeutic, pre-clinical and clinical trials results and the factors that halted development.

- Other useful information would be profiles of off-target activities, any alternative formulations, toxicology results as well as biomarker and pharmacokinetic profiles. Availability of support from the commercial partner would facilitate rapid completion of any additional necessary studies such as bioanalytical assays. Confidence in the therapeutics discovery process would be enhanced if the academic partner could interact directly with the development team. This open channel of communication would allow the scientific teams to discuss data and results, saving time and increasing both the efficiency and the output of the NCATS program.
- There are many ways that a company can foster the efforts of this Pilot Program. Foremost, they can provide an adequate supply of the compound, made under GMP, to perform the studies. The scientific resources could extend to unpublished background studies (pre-clinical and clinical) and special methods for using the compound. For instance, high-throughput assays could most easily be performed at the company using their robotics.
- Other analytical procedures such as High Performance Liquid Chromatography and quality control might already be in place at the company. A company may also provide specialized reagents to study the compound, including transgenic mice, monoclonal antibodies, cell lines, plasmids, recombinant bacteria or viruses, crystal structures, and more.
- Want to take several products that will block and decrease the effects of collagenase for epidermolysis bullosa. Want to look at the anti-inflammatory effects of statins and other agents for specific uses in psoriasis and rosacea. Have a list of dermatological conditions that could benefit.
- Testing drug candidates for tests of attention, learning and memory in rats and zebrafish and the effect of drug treatments limiting self-administration of nicotine, alcohol and other drugs of abuse in rat models.
- As a testing lab, information on solubility and any toxicity would be most welcome.
- Other screening and selectivity data on the compounds. This is especially true in the "rescue" arena.
- All resources necessary to take a compound with phase I safety, PK and pharmacology information to the conclusion of a proof of concept study in a new indication could be made available by partnering with companies such as biotech and pharma companies but also with CROs, biotechnology and systems biology companies. Selection of the new and best indication and subject population will be critical.
- Structure activity relationship capabilities - i.e. medicinal chemistry to enhance efficacy or weed out tox', if a new use is discovered. Pharma is simply much better/faster at generating structural variants, due to the organic synthesis capabilities they have on tap.
- Make pregabalin available at no or reduced cost.
- Having all available information about the known in vivo behavior of any of the compounds can prevent unproductive lines of investigation. Whereas some of these features may be able to be

modified through altered drug delivery, it is useful to know the starting parameters to assess the feasibility for new sites of action.

- The most important steps for NCATS are as follows: Motivation for Program participation. In order to ensure that biotechnology and pharmaceutical companies participate in the Program, an incentive such as licensing may be necessary. For example, the partner academic institution or the NIH may need to consider an option to license the background IP from the company (i.e. the compound) in the event that a company chooses not to develop the compound. In this way, the company still benefits through a royalty-sharing agreement, without assuming the risk and costs of future clinical development. Promotion of joint discovery. Existing disease networks or collaborations between CTSA organizations could facilitate the conduct of proof-of-concept clinical trials in rare and neglected diseases. However, this may be insufficient motivation to take the compound through development, given the potentially small market size. The biotechnology and pharmaceutical companies may need additional financial incentives or risk-sharing mechanisms before agreeing to develop their product for a rare or neglected disease.

7) Comment on the pharmacologic activity or biological target of the drug candidate that you need access to in order to test your biological hypothesis of disease intervention.

- There are a number of critical items that will be required for the initial development of the proposal to conduct the studies. One question will be to understand under what criteria these Agents were determined to have failed and been discontinued. What data will be available at the X02 stage (pre-CDA)? Overall, two key elements include: 1) providing any available publications, mechanism of action, state of pre-clinical and toxicology data; 2) knowledge of further access to the Agent, manufacturing capability, availability of matching placebo. It would helpful if participating companies allow the cross-referencing of existing INDs, if appropriate.
- One example of a drug that could be tested in our model is Bortezomib. Bortezomib is a highly selective, reversible inhibitor of the 26S proteasome. It has been shown to have anti-tumor activity in B cell malignancies. It is also recommended for single-agent use in the treatment of patients with multiple myeloma who have received at least two prior therapies and are progressing on their most recent therapy. We are interested in compounds that inhibit pathways essential for virus replication. These include functions that are unique to the virus or that are induced in infected host cells. a. Kinases: cell signaling, cell cycle, proliferation, inflammation, apoptosis Cyclin dependent kinases Extracellular regulated kinases (MEK1/2, ERK1/2) NFkB family cJun N-terminal kinase (JNK or SAPK) b. Nucleoside analogs c. Lipid bilayer fusion inhibitors d. Autophagy pathway e. Activators of interferon pathways.
- The process would be jump-started more effectively by disseminating a list of available compounds so that potential academic partners can consider their expertise and disease focus to determine whether a fit might exist.
- Key would be affinity (target and off-target) and any known agonist or antagonist or enzymatic activity this drug might have. Structure would be important, too.
- Statins for psoriasis based on the calcium channel effects and the anti-inflammatory effects that have been reported. Also modulation of fast growing cells to see if skin cancers can be controlled in the skin. Clinical testing will need to be done based on the NDA and the right for physicians within standard of care to test and use medications for unapproved uses if it is within normal clinical parameters.
- Drugs acting of nicotinic, serotonergic, dopaminergic, noradrenergic, glutamate, GABA, histamine and ryanodine receptors.
- Organism or disease specific, e.g. IC50 for infectious agents.

- Pegylated Granulocyte Colony Stimulating Factor.
- Selective and potent PKA inhibitor that is brain penetrant. These may have been made on drug discovery projects targeting Akt, ROCK, MSK, PKC, etc.
- We are quite flexible with respect to the type of disease intervention and will select that based on the pharmacologic activity and target of the drug candidates available and the one we select to progress.
- Drugs that either function as exogenous antioxidants, down-regulate inflammatory pathways or up-regulate endogenous free radical scavenging mechanisms (enzymatic or non-enzymatic).
- The pharmacologic activity would be a drug that improves the post-ischemic function of the heart (greater contractile function, and less myocardial infarct size) in animal models of heart attack. Although traditionally focused on the role that mitochondria play in ischemic injury and protection, we are "mechanism agnostic" for this project. If the drug protects the heart, we will figure out the mechanism later, from a well-studied list of targets we have in the lab (e.g. mitochondrial potassium channels, the mitochondrial PT pore).
- The precise mechanism by which pregabalin reduces cortical irritability is unknown.
- The more compounds that are available from the outset the more likely it is that a new use will be found for one of them. Also, the hits found are more likely to be unique ones if the compound is not very small. If it is known from pharmacokinetics that the compound is rapidly metabolized to another one, this information about these metabolites should be made available, since the structures of the quickly formed metabolites may be more pertinent to finding a new mode of action.
- There is a broad range of CNS agents that would be very useful. Agents targeting specific dopaminergic, gabaergic, adrenergic, serotonergic, glutamatergic etc CNS receptors, and neuropeptide receptors (eg, oxytocin).
- Examples of attributes desired for drug development: o Standard SAR parameters o Formula, 2D SMILES structure o pKa o Topological Polar Surface Area (TPSA) o Toxicity o Derek o hERG (the human Ether-à-go-go-Related Gene) o Promiscuity score o Artifact features - Assays vary based on the type of disease, but defined protein targets are very useful for advancing therapeutics. For infectious diseases, whole cell assay protocols and measurements of phenotypic changes can be employed in compound selection.
- Pharmaceutical companies that participate in the program should provide all the available information of the drug candidate in a database that is available to all researchers at universities. Researchers should have access to the previous studies and associated data.
- One anticipated problem with the pilot program as it has been introduced so far is that universities will need access to data that are mineable; information will need to be made available in a coherent database. Many CTSA sites have strong drug screening capabilities, and limiting molecular libraries in NIH intramural programs does not use the capabilities that exist in the universities nationally.
- Success for us would be outcomes that demonstrate a productive collaboration between the private sector and academic institutions, including increased opportunities for translational researchers and the increased capacity for drugs to be developed that may not be seen by industry to be commercially viable. A positive outcome would be if this model of collaboration resulted in testing and development of efficacy of a drug in a population where it would not otherwise be tested—for example, because of the affected population's location, small population size, etc. There is the additional benefit to pharmaceutical companies that university researchers may uncover new markets from regionally-specific patient sub-populations that may be difficult to access or that companies would not otherwise pursue. In order to do so,

molecular libraries would need to be provided to CTSA sites with screening centers. Data related to screening should be broadly distributed, and CTSAs should be encouraged to form multi-center clinical trials to test drugs for potential rescue or repurposing.

- The primary focus of this program needs to be better defined in the RFA. One approach would be to encourage “off target” use of discontinued drugs in other disease population where a rational strategy can be devised. This approach could include animal models and phase 1 and 2 clinical trials. The time frame of 3 years proposed could feasibly be achieved for this approach. The second approach is more structure driven where compound X looks like the structure of Y group of agents and pre-clinical screening and modeling would then be supported. We have concerns that the time frame of 3 years and the funding allocated is not sufficient for this approach.
- We are interested in compounds that inhibit pathways essential for virus replication. These include functions that are unique to the virus or that are induced in infected host cells. a. Kinases: cell signaling, cell cycle, proliferation, inflammation, apoptosis Cyclin dependent kinases Extracellular regulated kinases (MEK1/2, ERK1/2) NFkB family cJun N-terminal kinase (JNK or SAPK) b. Nucleoside analogs c. Lipid bilayer fusion inhibitors d. Autophagy pathway e. Activators of interferon pathways.

8) Please provide any additional comments regarding this program.

- The process would be jump-started more effectively by disseminating a list of available compounds so that potential academic partners can consider their expertise and disease focus to determine whether a fit might exist.
- The primary focus of this program needs to be better defined in the RFA. One approach would be to encourage “off target” use of discontinued drugs in other disease population where a rational strategy can be devised. This approach could include animal models and phase 1 and 2 clinical trials. The time frame of 3 years proposed could feasibly be achieved for this approach. The second approach is more structure driven where compound X looks like the structure of Y group of agents and pre-clinical screening and modeling would then be supported. We have concerns that the time frame of 3 years and the funding allocated is not sufficient for this approach.
- The IDIQ mechanism currently employed by NIH is clumsy and artificial for use by academic and biomedical institutions. There needs to be a better administered mechanism and an easier one to use. The volume of information needed to apply is ridiculous and daunting.
- This will be an effective program, especially at academic institutions that have ex-pharma employees that speak both from an industrial and academic perspective. Academic researchers sometime don't even realize that their ideas can be translated into new therapies. Starting from a "rescued" or “repositioned” compound would be so much easier than doing HTS and lead-optimization. Some targets still require this approach. But for established therapeutic targets where compounds were discarded by industry for off-target activity, the NCATS approach greatly accelerates the discovery process.
- Try to keep the management to a minimum. Realize that academic labs can't function like CROs. We need longer term contracts so we can maintain our trained technical staff. Realize that academics may not be interested in the development of their ideas...they just want to get back in their labs and do science.
- Some information about the nature of the compounds available will accelerate the start of this program.

- Would like to see the list of 24 compounds in advance, as that could help a lot in drafting a proposal. Without knowing what the chemicals are, it could be very difficult to draft an accurate proposal.
- "Repurposing" differs from "rescue," and the RFI is unclear on NCATS preference(s).
- This program is a great idea. It should not be structured in a way that limits participation to large companies and large academic centers but extends more broadly to smaller companies that create new agents but have limited resources to develop them, and to individual investigators with the resources to test agents but not the institutional resources to negotiate complex financial-legal agreements with pharma.
- The bottom line is that collaborative informatics infrastructure and effective support services can be a game-changer and the key to successful collaborations. The technologies can, and when appropriately adopted do, reframe the problem.
- The proposed pilot program has significant promise. To make a well-reasoned decision about whether to move forward with this program in a broader effort after the pilot, NIH will need to implement a robust evaluation process. NIH is urged to consider what a successful result would look like and how it could be measured, and to formalize this evaluation early in the pilot's launch. Establishing evaluation measures prior to beginning the pilot is far preferable to trying to develop a method to evaluate these elements after the project has been completed. A process evaluation would also help aid in understanding how collaborations succeed, and give a better chance of replicating such success in future. One advocacy organization summarized the following: 1. Supports the use of the template agreements, but the current templates should be modified after involvement of academic partners in the research collaboration. 2. Urges NIH to imbed within the pilot program a process and outcome evaluation to help guide later implementation and improvement of the resource-sharing program. 3. Due to the importance of full collaboration to realize the potential of this program, urges that academic and other research institutions be fully engaged as equal partners in these collaborations.