Summary: Public Meeting on the Development of a Public-Private Partnership Developing Anti-Cancer Therapies for Ultra-Rare Tumor Indications

The Foundation for the National Institutes of Health (FNIH)
National Cancer Institute (NCI)
FDA Oncology Center of Excellence (FDA OCE)

On August 24, 2023, the Foundation for the National Institutes of Health (FNIH), the National Cancer Institute (NCI), and the U.S. Food and Drug Administration Oncology Center of Excellence (FDA OCE) conducted a virtual meeting to discuss plans for creating a public-private partnership (PPP) to guide and support the development of new treatments for patients with ultra-rare cancers. Many pediatric and adult ultra-rare cancers have actionable oncogenic drivers not present in more common cancers; however, there is limited economic incentive to encourage concerted and coordinated efforts to develop drugs for these ultra-rare cancers.

During this multi-stakeholder meeting, participants discussed options for a collaborative open-science, open-drug development process for targeted therapies for ultra-rare cancer indications. FNIH solicited feedback and suggestions from the ultra-rare cancer community on the proposed PPP plans and moderated a discussion to gauge interest and resources available for drug development in this arena.

Introduction, Agenda Review, and Meeting Objectives
Stacey Adam, FNIH

FNIH is helping to coordinate the proposed PPP with the NCI and the FDA OCE. FNIH is a congressionally mandated nonprofit formed in the mid-1990s, whose mission is to help the NIH build partnerships that connect private sector stakeholders and U.S. government (USG) partners to build bridges toward a breakthrough. Across all the partnerships that the FNIH has established, it has raised $1.5 billion in funds, and it currently has 122 active partnerships.

The meeting assembled a diverse group of stakeholders interested in ultra-rare cancers to explore the challenges and current state of ultra-rare cancer drug development and to review and discuss examples of existing resources that could contribute to a PPP. If the PPP is formed, it has no intention of competing with commercial pharma companies or other potential stakeholders, but rather to establish synergy with existing efforts and share working drug development paradigms for the community to utilize. In the longer term, the PPP intends to harness state-of-the-art technologies to target established, previously undruggable biological vulnerabilities to treat ultra-rare cancers.

Dr. Adam provided an overview of the day's agenda. As described in the following sumary, the meeting began with opening remarks and presentations from NCI and FDA OCE addressing the need for the proposed PPP, and then a series of experts gave presentations highlighting a sample of existing programs and resources that could potentially contribute to the PPP. Following these presentations, both industry and advocacy stakeholders provided their perspectives. Finally, Dr. Adam presented a strawman for the PPP governance and topics to be addressed to contextualize the roundtable panel and audience discussion about considerations, challenges, and necessities for the PPP.

Opening Remarks
Monica Bertagnolli, NCI
Marc Theoret, FDA OCE
Rick Pazdur, FDA OCE

Dr. Monica Bertagnolli, the NCI Director, discussed the critical need for the PPP, not only for the individuals and families affected by ultra-rare cancers but also because it presents opportunities to better address challenges for people with *all* cancers. President Biden has made progress against cancer a presidential priority, and the goal is to reduce cancer mortality by half in the next 25 years. Faster progress against common cancers is not enough—progress against the rarest of cancers, such as epithelioid sarcoma, pulmonary blastoma, certain pediatric cancers, and many more, is also needed to achieve this goal. A collaboration of professionals and stakeholders from within and outside the NCI will be paramount in achieving these Cancer Moonshot^{SM} goals through a National Cancer Plan. The PPP presents an opportunity for federal and industry partners to work together and develop concrete ideas to meet the challenge of effective care for those living with ultra-rare cancers and for preventing these cancers.

Two key challenges fundamental to the success of such an endeavor are (1) representation and participation in cancer research, and (2) the expansion and modernization of clinical trials. For ultra-rare cancers in particular, it is difficult to collect enough data to produce meaningful analyses that allow us to understand fundamental tumor biology, and then leverage that understanding to develop prevention, detection, and treatment approaches that work. There is a critical need for infrastructure to gather this data. NCI's Childhood Cancer Data Initiative (CCDI) has made great progress in providing childhood cancer data that has historically been challenging for researchers to access. The model, which emphasizes the importance of gathering data and learning from every child with cancer, can help inform the needs for ultra-rare cancers. Certain populations also face barriers to participation in clinical trials, which particularly effects trials for ultra-rare cancers, where the affected population is already small. To break the mold and take worthwhile risks, a dedicated team at the NCI has already begun collaboration with the FDA, industry partners, and other groups to approach clinical trials in an innovative way. This Clinical Trials Innovation Unit (CTIU) collaboration, launched at the beginning of 2023, selects high-priority

scientific questions that are amenable to new study designs and operational procedures and then works to move them forward through the National Clinical Trials Network.

Solving the challenges of ultra-rare cancers will come at a significant expense and require expertise and resources from multiple organizations. Partnership and collaboration will be critical to success.

Dr. Marc Theoret, Deputy Director of the FDA OCE, provided FDA's perspective on the potential PPP efforts. He shared that OCE was authorized by the 21st Century Cures Act as a result of the initial Cancer Moonshot℠ effort. As the FDA's first inter-center institute, the OCE was established to facilitate the development and clinical review of oncology products by uniting experts across the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health to conduct expedited review of oncology drugs, biologics and devices. OCE also leads research, policy, and educational and outreach programs to advance the development and regulation of medical products for patients with cancer. Under the direction of Dr. Richard Pazdur, the OCE has developed multiple cross-cutting programs under the overarching umbrella of modernizing data and evidence generation, as well as regulatory review of data, for a more efficient paradigm for oncology drug development.

Investment in basic and translational science to understand the biological underpinnings of cancer and the host immune response to cancer has led to the development and approval of novel therapies for many cancer types in the past decade. However, there are untapped scientific discoveries for many rare cancer types where there is a low economic incentive for commercial development. Dr. Theoret introduced two programs at OCE that are working to build a collaborative scientific environment to advance the development of oncology products for ultra-rare cancers. The OCE's Project Catalyst, led by Dr. Jeff Summers, provides guidance and educational resources on regulatory aspects to academic incubators, accelerators, and small companies engaged in cancer therapy development. The Rare Cancers Program, led by Dr. Martha Donoghue, identifies opportunities and challenges in the development of new treatments for rare cancers by working with stakeholders to foster an efficient drug development environment. Challenges inherent in drug development for rare cancers are amplified for ultra-rare cancers by the small population of such patients and the lack of economic incentive for commercial drug development. A PPP of diverse stakeholders will bring together the expertise and resources to create a platform to develop novel treatments for ultra-rare cancers where the science is fit for development, and, through the principles of open science, provide a regulatory roadmap that could spark commercial development of treatments for patients with ultra-rare cancers.

Dr. Richard Pazdur, Director of the FDA OCE, also joined the meeting to represent FDA leadership support of the PPP. He highlighted three major issues with developing drugs for ultra-rare diseases: (1) the development and understanding of the basic underlying mechanisms of the disease, which in the past has transformed the management of several diseases; (2) a flexible regulatory framework to allow for the development of these drugs,

aiming not only for accelerated approval but for regular, traditional approval; and (3) the need for international collaboration to realize the potential of the drugs to help all patients and to also gain valuable international perspective with the availability of a small patient population.

The Challenge of Drug Development for Ultra-Rare Cancers
Karlyne Reilly, NCI CCR

A rare tumor in one part of the world may be a common tumor in a different part. In the U.S., the Orphan Drug Act defines a rare disease as one with fewer than 200,000 cases and the NCI defines a rare tumor as fewer than 15 cases per million individuals. These rare cancers account for 27 percent of diagnoses and 25 percent of cancer deaths. Historically, the study of rare tumors has been critical to understanding tumorigenesis mechanisms, so the study of rare tumors benefits all cancer patients.

Rare tumors present challenges for both patients and researchers. Due to a lack of familiarity with rare cancers at community hospitals, diagnoses of these cancers may be delayed, and patients may need to travel to find the expertise needed to help them. Clinical trials sometimes close due to insufficient accrual of target participants, and drug efficacy hypotheses may then go untested. Rare tumors also lack robust cell lines and animal models to support research to reflect the diversity of patient populations, and this makes rare tumor research difficult to fund. These issues are compounded for ultra-rare tumors. The proposed PPP aims to de-risk preclinical and clinical phases of ultra-rare tumor drug development by leveraging existing resources in cases where basic biology studies and development of models have provided insight into the mechanisms of tumorigenesis. While there is no agreed-upon definition of ultra-rare tumors, Orphanet and the Connective Tissue Oncology Society have used one case per million individuals to define the rarest tumor populations. Dr. Reilly estimates that there are about 75,000 people affected by ultra-rare tumors in the U.S. each year. More work is needed to obtain an accurate estimate of ultra-rare tumors in the U.S.

The NIH has several rare tumor programs and initiatives that could be leveraged for ultra-rare tumor drug development—for example, the National Center for Advancing Translational Sciences (NCATS) Genetic and Rare Diseases (GARD) Information Center and NCI extramural and intramural research programs, including the NCI Center for Cancer Research (CCR). The NCI CCR supports challenging and neglected cancer research that doesn't fall in the ambit of extramural grant mechanisms.

The CCR has developed the Rare Tumor Initiative (RTI) and the Rare Tumor Patient Engagement Network. Drugs for rare tumor indications have been successfully approved and existing infrastructure can be leveraged for testing in ultra-rare tumors. There are few examples of trials targeting molecular drivers of ultra-rare tumors, which will be the focus of this PPP. Valuable lessons learned in the CCR have indicated the importance of

understanding the natural history of the disease. The CCR has established the My Pediatric and Adult Rare Tumor Network (MyPART) as part of the Rare Tumor Patient Engagement Network to collect data for rare tumors to benefit future drug studies. MyPART was established to focus on rare solid tumors affecting young patients, and it operates via advocacy partnerships to engage with patients. With a central focus on natural history study, MyPART has the potential to provide foundational knowledge for different ultra-rare tumors that the PPP may want to leverage. More than 500 patients have been enrolled to date, of whom 43 percent have an ultra-rare tumor. A survey of rare tumor programs conducted by MyPART indicates that ultra-rare tumor researchers would be receptive to a transparent open-notebook approach for data sharing.

While research interest in rare tumors has rapidly expanded over the past 20 years—as evidenced by publication records—a major challenge is that drugs that may specifically work in ultra-rare tumors may not be tested due to a lack of economic incentive, and targets specific to ultra-rare tumors may not be adequately pursued. Therefore, there is an opportunity for the USG to de-risk projects for ultra-rare indications. Many existing NIH programs could be harnessed to support drug development in ultra-rare tumors. The NCI Chemical Biology Consortium (CBC) within the NCI Experimental Therapeutics (NeXT) program, the RAS initiative, the FusOnC2 consortium targeting fusion proteins in pediatric cancers, and the NCATS' Therapeutics for Rare and Neglected Diseases (TRND) programs are some of the resources available to support compound identification and molecular optimization. NeXT and TRND could also be leveraged to support preclinical optimization and testing together with programs like the Patient-Derived Models Repository (PDMR) and the NCI Pediatric Preclinical in Vivo Testing (PIVOT) program. For identifying patient populations, understanding clinical and molecular characteristics of ultra-rare tumors, and conducting small, exploratory clinical trials, the PPP could coordinate with programs like MyPART, Advancing RAS/RASopathy Therapies (ART), the Childhood Cancer Data Initiative (CCDI), NCI-Comprehensive Oncology Network Evaluating Rare CNS Tumors (NCI-CONNECT), and the Participant Engagement and Cancer Genome Sequencing (PE-CGS) Network. The Developmental Therapeutics Clinic (DTC) collaborates with the CCR Pediatric Oncology Branch and the NCI Experimental Therapeutics Clinical Trials Network to run clinical trials for pediatric and adult patients. Other available NCI clinical trials networks include the Pediatric Early Phase Clinical Trials Network (PEP-CTN) of the Children's Oncology Group (COG).

Despite all these existing federal resources, there is still a strong need for other stakeholders to contribute resources to help develop therapies for ultra-rare cancers. The proposed PPP would establish collaboration and intellectual property (IP) agreements across sectors to promote drug development and establish non-profit or for-profit mechanisms for sustained supply of drugs for patients. Given that a blending of public and private resources will be needed for success, the handling of IP issues and sometimes conflicting obligations to patients, taxpayers, funding agencies, stockholders, and other stakeholders are likely to determine the success of this PPP. Above all, with multiple stakeholders participating and with the plan to focus on a few tumors each year, the success of the PPP will require strong, transparent governance and nimble decision-making. This includes developing a clear

strategy for focusing the efforts of the PPP. Dr. Reilly proposed that the PPP would pick one to two ultra-rare tumors to pilot and build the PPP platform and then, in the following iterations, invite the stakeholder community to provide data supporting proposals to select subsequent tumors. In addition to the criteria of unmet need and well-defined molecular drivers, priority would be given to ultra-rare tumors with committed advocates who could act as liaisons to patient communities, clinician champions willing to lead early-phase clinical trials, and committed researchers with expertise in biological mechanisms or innovative approaches to targeting molecular drivers.

FDA Engagement in the Proposed Public-Private Partnership for Ultra-Rare Cancers
Martha Donoghue*, *FDA OCE

There is no universal definition of what constitutes a rare cancer. For the purpose of this PPP, ultra-rare cancer is considered to be diagnosed in approximately less than or equal to 300 patients in the U.S. annually (fewer than one in a million). The proposed PPP should focus on cancer types rare enough to render independent commercial development economically unattractive. Although there have been numerous approvals for orphan-designated drugs, very few new drugs have been approved for ultra-rare tumors. Successful drug development in ultra-rare cancers typically occurs for those that share targets with common cancers. Cooperative groups cannot shoulder the sole responsibility for drug development in all ultra-rare cancers. One of the biggest obstacles is a lack of financial incentives, particularly when the overall success rate for oncology drug development is estimated to be less than five percent. Other challenges include the difficulty of enrolling a sufficient number of patients for a meaningful evaluation of safety and efficacy. There may also be a limited understanding of the pathophysiology of the disease, and diagnostic delays can lead to a lack of timely enrollment and care for patients. An emerging pattern over the last decade points to risk-averse decision-making and a tendency to develop targets that have been shown to be active in other drug development programs. This trend is likely to disproportionately affect drug development for rare cancers with unique biological vulnerabilities not shared with more common cancers.

Orphan drug designation can provide economic incentives by providing tax credits for qualified clinical trials. The FDA's Office of Orphan Product Development typically offers 5 to 12 new clinical grants annually via a competitive process to develop orphan products. The Pediatric Rare Disease Priority Review Voucher program confers transferable priority review vouchers following the original approval of a new drug for a rare pediatric disease. The Best Pharmaceuticals for Children Act (BPCA) provides an additional incentive for drug development for pediatric cancers by conferring six months of additional exclusivity to the active moiety in return for reports of voluntary pediatric studies outlined in an FDA Written Request. Despite these incentives, there is a high unmet need for new drugs targeting ultra-rare cancers. The multiple existing NIH resources devoted to rare cancer drug development—along with FDA and other stakeholder resources—can be more fully utilized in a focused and coordinated fashion made feasible by the proposed PPP.

There are a variety of reasons for proposing the PPP at this time. First, there are examples of successful drug development targeting carefully selected oncogenic drivers, such as imatinib (targeting the BCR-ABL pathway), and more recently, the $KRAS^{G12C}$ inhibitors, sotorasib and adagrasib. Second, there are ultra-rare cancers that lack successful drug development efforts despite well-documented pathognomonic oncogenic drivers. Additionally, with emerging technologies it is becoming possible to render previously undruggable targets druggable, or in some cases, to disrupt fusion oncogenes using CRISPR technology. Emerging experience from other ongoing efforts, such as the Bespoke Gene Therapy Consortium (BGTC) and other FNIH partnerships, can benefit the PPP.

The proposed PPP offers a mechanism to leverage existing government and private sector resources and expertise to systematically and efficiently address challenges to drug development for ultra-rare cancers. It will also provide a way to help de-risk the development of new therapies and ultimately establish a dynamic process that can be refined and reutilized. The PPP is also an important avenue for stakeholders to learn more about drug development through open notebook processes to promote increased efficiency.

The staff at the FDA's OCE, in conjunction with other FDA centers active in oncology drug development, are a resource with extensive experience. This includes the experience needed to establish a first-in-human trial, as well as dosing and modern clinical trial design and analysis methods that can be applied to study new drugs for rare cancers. Investigators can engage with the OCE's Project Catalyst prior to the pre-IND stage of drug development by requesting an Accelerator Innovator Discussion (AID) meeting or through the Oncology Regulatory Expertise and Early Guidance (OREEG) program. The FDA's Real World Evidence (RWE) Program fosters regulatory science and collaboration to translate real-world data into evidence. The Patient-Focused Drug Development (PFDD) Program works with other FDA centers and external stakeholders involved in patient outcomes. The Pediatric Oncology Program facilitates expedited development of oncology drugs for children with cancer. Project Orbits provides a framework for concurrent submission and review of oncology products among international regulatory partners to facilitate earlier access to products for patients with cancer globally. Project Pragmatica integrates aspects of clinical trials into real-world routine clinical practice through the appropriate use of pragmatic design elements. Finally, the Rare Cancers Program leverages FDA resources and collaborates with stakeholders outside the FDA to promote the development of new, safe, and effective drugs for people with rare cancers.

To distinguish its role in the PPP from the official regulatory work it is mandated to perform, the FDA envisions its staff will participate in the PPP as liaisons providing strategic, regulatory, and scientific insights (including insights on target selection and chemistry, manufacturing and controls) as product development evolves. However, FDA staff liaisons participating in the PPP would not be part of FDA review teams responsible for sponsor interactions and decision-making related to any products developed by the PPP.

An open notebook approach to drug development is envisioned for the proposed PPP. In such an approach, publicly posted minutes and notes from Scientific Advisory Board and Steering Committee meetings, FDA meeting minutes, study protocols, and results would inform the evolving landscape of new drug development against a chosen target. There would be documented information regarding both the preclinical work that would take place and the exploration of mechanisms to ensure availability of subsequently approved drugs. There would be information about the challenges and course corrections that take place along the way.

The PPP would be an avenue for stakeholders to obtain insights that would help promote efficiency of future drug development efforts, both within the PPP and outside of it. The PPP is a unique and exciting opportunity to utilize collective scientific knowledge and expertise to overcome the many challenges it will likely encounter.

Compound Screening to Lead Compound
Jay Schneekloth*, *NCI CCR

The NCI Center for Cancer Research (CCR) has several investigators with deep expertise in cancer biology, disease biology, and fundamental biology. They have identified a variety of new targets, in particular for rare diseases. Resources to identify small-molecule hits also come from high throughput and computational efforts, where one can work with the NCATS. Chemistry technology resources within the NCI include a synthetic support group, a probe development group, and the NCI Experimental Therapeutics (NeXT) program. Other resources advance small-molecule therapeutics through the Drug Development Collaborative (DDC).

Hits from high-throughput screens are often not suitable for development as therapeutics, due to poor potency, off-targets, or other issues. The Medicinal Chemistry Accelerator (MCA) has the goal of enabling preclinical discoveries on new targets by developing novel small-molecule chemical probes that could advance toward novel therapeutics. The MCA goal would be achieved through a highly collaborative approach working with CCR investigators. The resources include synthetic organic chemistry, structure, activity, relationship-directed structural biology, biophysical analysis, *in vitro* profiling data analysis, and panel screening to help de-risk off-target activity and toxicity.

The work will be done via Contract Research Organizations (CROs). A steering committee has been established that includes professionals with diverse expertise within the NCI and technology transfer professionals to help the group understand IP and patient landscapes of any discoveries. Dr. Bill Moore, who is the first project lead, established blanket purchase agreements with a variety of CROs that the MCA would use to facilitate critical research activities. The MCA has developed an optimization and screening paradigm to take initial hits and optimize them again. The aim is to move initial hits of newly discovered compounds toward *in vivo* profiling. Within the first three months of operation, the MCA was able to

synthesize 250 new analogs and work on improving their properties, such as aqueous solubility, protein binding, permeability, and metabolic stability. The MCA hopes to have two to three projects ongoing by early fall, and projects that focus on rare cancers would be welcome.

Preclinical Testing Models for Rare Tumors
Malcolm Smith and Alice Chen, NCI CTEP

Dr. Malcolm Smith shared that there are enormous opportunities, as well as challenges, with prioritizing those cancer drugs that are likely to be most effective among the multitude of cancer drugs that could be studied in children. Preclinical testing can play a central role in addressing some of these challenges, as seen in the systematic approach to pediatric preclinical testing supported by NCI for approximately 20 years. The current iteration is the NCI Pediatric Preclinical *in Vivo* Testing (PIVOT) Program, which is funded through a cooperative agreement grant mechanism. The data generated by PIVOT research teams are published after sharing with collaborators. With regards to the PPP, the PIVOT program could potentially be able to help with *in vivo* testing and allow the PPP to save resources for other mission-critical activities. PIVOT *in vivo* testing is performed by seven highly qualified research programs. The PIVOT coordinating center is at the Jackson Laboratory, and the NCI has specific responsibilities in terms of scientific and technical assistance, and also in terms of negotiating material transfer agreements with collaborating companies. The PIVOT program has genomic datasets for more than 250 models that are accessible online at PedcBioPortal. With an ongoing second genomic characterization campaign, another approximately 500 models will be added, such that there will be about 800 to 1,000 genomically characterized models available for testing. With the proposed PPP, there is the potential for finding agents that can induce robust regressions, thereby leading to potential major impacts on patient outcome. With the availability of preclinical data for drug developers, clinical researchers, and regulators, there is hope for bringing agents to clinical testing in children with rare cancers. In addition to discussing the preclinical *in vivo* testing program, Dr. Smith also discussed the new RFA-CA-23-037 that was issued to solicit proposals for establishing next-generation chemistry centers for fusion oncoproteins, which are often drivers in rare pediatric cancers. This mechanism is intended to bring together teams that have the requisite expertise for drug development for these oncogenic drivers and could be another resource for synergy with the PPP.

Dr. Alice Chen shared ongoing efforts for drug development in rare adult cancers. Drug development is no longer histologically driven, as much as by the prospect of targeted therapy. The NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial is a tissue-agnostic study for infrequently studied rare tumors. The Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) study predominantly looks at ipilimumab and nivolumab in rare tumors. The NCI Division of Cancer Treatment and Diagnosis (DCTD) is screening rare tumors with investigational drugs in a systematic fashion, and to achieve that, patient-derived xenograft (PDX) models were developed in the rare tumor space. The DCTD has

generated more than 300 PDX models from rare cancers that are available to the public via the NCI Patient-Derived Models Repository (PDMR). Forty percent of all models in the repository have been developed from rare tumors. The repository also includes common tumors with a rare mutation or a molecular aberration that could potentially make them rare tumors. Before they are distributed to the research community, PDMR models go through extensive quality control and are fully characterized. The PDMR is currently running a pipeline to query fusions in available models, but fusions of interest would also be added to the repository. The PDMR has tissues for rare tumors, and common tumors with rare mutations, which are available to the public. Organoids, tumor cell cultures, and cancer-associated fibroblasts are also available from patients who have been willing to donate a part of their biological specimen for development. The DCTD has pulled 39 rare tumor models and is investigating them in 57 novel investigational therapeutic combinations. Any interesting synergistic combination is intended to be taken to the clinic.

Possible NCI SBIR Funding Mechanisms for Ultra-Rare Cancer Drug Development
William Bozza, NCI SBIR

The Small Business Innovation Research (SBIR) program, which is congressionally mandated, is one of the largest sources of early-stage nondiluted seed funding for small businesses trying to develop their technology toward a commercial product. The SBIR is a three-phase program, where Phase I is for proof-of-concept type studies, and Phase II is along the R&D pathway—the Phase IIB or the Bridge Award is the largest award for project periods of two to three years. Combining all phases, the funding comes to $7 million, with the goal that the companies will have reached a critical inflection point by then and be able to raise substantial capital from outside the federal government to drive the technology toward a commercial product.

The SBIR portfolio at the NCI currently has 450 active projects. For the purposes of the PPP, to qualify for the SBIR program, the awardee must be a small business, and predominantly owned and operated by U.S. employees. In the case of this PPP, the small business could be a therapeutic developer or a platform technology company. In the former case, the SBIR can fund any portion of the preclinical or clinical development of the therapeutic. The second case is more in alignment with the open science model proposed by this PPP, where the technology platform providers could be involved in a large number of steps during the preclinical development of the therapeutic. While in both cases the small business concern would retain the IP of their product or technology, they would still contribute to the preclinical development that would benefit all funded entities.

For SBIR Phase I, the funding amount is $400,000 for one to two year projects. The SBIR Phase II involves larger dollar awards of $2 million for two to three year projects—they are suited for IND-enabling studies, and portions of clinical trials could be funded using this mechanism. SBIR funding mechanisms occur through grants and contracts. The Small Business Concept Award mechanism aligns with some of the proposed PPP's goals. The

focus is on earlier-stage research with high risk and a high bar on innovation. No preliminary data is required for funding. Solicitations for this mechanism typically receive 100 white papers per fiscal year, which are used to triage some of the proposals. It would be feasible to have members of the proposed PPP serve as white paper reviewers, who are currently internal to the NIH. As an example of a success story, a small business called Immunomedics developed Trodelvy, an antibody-drug conjugate that is directed against Trop-2, a cell-surface protein expressed in many solid cancers. The SBIR program funded the first-in-human clinical trial of Trodelvy, after which the FDA approved it for treating triple-negative breast cancer. The company was subsequently purchased by Gilead.

Preclinical IND Enabling Studies at NIH
Liz Ottinger, NCATS TDB

The NCATS' Therapeutic Development Branch's (TDB) mission is to accelerate IND-enabling, first in-human, proof-of-concept studies through transformative teams- and technology-based strategies and platforms. The TDB addresses challenges in developing therapies for cancer and neglected diseases and fosters close collaborative interactions among clinicians, researchers, and patients. The NCATS portfolios are disease agnostic; they address a variety of therapeutic areas and work on different modalities such as small molecules, biologics, and gene therapy. Since its establishment, the TDB has participated in collaborations to move 52 INDs to help support clinical trials. The TDB de-risks projects by working with nonprofits and biotech companies at different stages of drug development and approaches therapeutic development taking a "team of teams" approach. Working with key interacting partners, the TDB provides project management support for preclinical drug development. Being an NIH intramural entity, the TDB does not sponsor grant mechanisms but provides resources to work with collaborators and drive the scientific and operational aspects of the project.

To translate a program through preclinical development, the TDB starts from the end of a target product profile by querying how the product can be utilized clinically to work for patients, and then working backward, to see how the preclinical program can support development through different stages needed in the IND-enabling phase. Some examples of case studies include the development of Parathyroid Hormone Inverse Agonist (PTH-IA) therapy for Janssen's Metaphyseal Chondrodysplasia (JMC) and the Platform Vector Gene Therapy (PaVe-GT) approach for organic acidemias and congenital myasthenic syndromes. The first investigational product of PaVe-GT is AAV9-hPCCA for Propionic Acidemia. Utilizing commonalities with clinical trials within the NIH, the TDB intends to make data publicly available, in alignment with goals for the proposed PPP.

Incentives and Challenges for Participation with Large Pharma
David Weinstock, Merck

The pharma ecosystem is complex; and each company has its own philosophy, strategy, and biases, some of which may be historical. Therefore, each company may have to be

approached individually when a partnership is intended. All cancer vulnerabilities may not always be the most reasonable targets to pursue from the lens of a pharma company. Although the proposed PPP focuses on targets that are currently not drugged, working with those targets for which there are already established therapeutics with opportunities to develop additional uses may make the pipeline more straightforward from an industry perspective. The complexity of drug development poses multiple risks throughout the pipeline, which starts with approximately 5,000 to 10,000 compounds at the drug discovery phase and narrows to one candidate being approved by the FDA over 10 to 14 years. Narrowing down that flow into a single, rare indication introduces additional challenges. Furthermore, even the most successful therapeutics tend to lead to incremental improvements in the overall outcome. Therefore, iterative development of therapeutics and combination therapies may take a long time.

The therapeutic index of a drug, which is the difference between the amount at which a drug is effective or toxic, can largely determine which cancer vulnerabilities are good targets for developing therapeutics. The toxicity of a drug candidate jeopardizes the likelihood that patients are going to be able to take the drug for as long as they need to get maximum benefits from it. Finding a drug candidate for a rare cancer imposes greater challenges on this scenario. The drug belzutifan is a small molecule that blocks the interaction between a transcription factor called HIF-2α and its partners. It was well tolerated and effective in patients with Von-Hippel Landau Disease, and it had multiple uses that applied to other rare diseases. Therefore, focusing on a rare disease—where there is also an indication for opportunities in a larger population—could be a good pathway for engaging pharma.

Patient Advocate Perspective on the Need for Partnership
Jim Palma, TargetCancer Foundation

TargetCancer Foundation was founded by Paul Poth, who was diagnosed with cholangiocarcinoma in his late 30s. Cholangiocarcinoma was rare, with little research being carried out; therefore, few treatment options were available to Mr. Poth. He started TargetCancer Foundation while being treated, and his mission has continued since his death in 2009. Challenges faced by patients and researchers of rare cancers are unique but consistent across other rare cancer types. TargetCancer Foundation works directly to effectively alleviate these challenges by acting as conveners to bring together different stakeholders. An example is the TCF-001 Target Rare Cancer Knowledge (TRACK) study, a prospective clinical study enrolling 400 patients with rare cancers and cancers of unknown primary. TargetCancer Foundation has developed TRACK to have a simultaneous impact on patients and research. TRACK is a completely remote, decentralized trial that expands geographical reach and encompasses patient populations in community settings. To alleviate the cost barrier to genomic testing, patients enrolled in TRACK receive genomic testing of tissue and blood at no cost. Testing results are returned to patients and to treating physicians.

To address another challenge—having patient test results correctly interpreted—TRACK has assembled a virtual molecular tumor board that meets weekly to evaluate patient genomic reports and medical histories. The virtual molecular tumor board provides treatment recommendations that are transmitted back to the patients and their treating physicians. The patients are followed for a year after the initial steps, during which time there may be repeated testing. TRACK has enrolled more than 150 patients representing 41 states in the U.S., for 40 different types of rare cancer. To reach patients, TRACK has built collaborations across stakeholders throughout the rare cancer universe. TRACK has also developed partnerships with industry collaborators to understand challenges in drug development for rare cancers.

Operating fully remotely, TRACK utilizes advocacy partnerships to recruit patients. These advocacy organizations are specific to rare cancers, and they communicate with patient communities that they represent to provide information on TRACK and why it may be of interest. TRACK utilizes external vendors to run technological aspects of the project, such as e-consenting and running the technology platform to support the virtual molecular tumor board. Most importantly, TRACK is partnering with patients who choose to participate in the trial at difficult points in their treatment to contribute to greater knowledge about their cancer.

Summarized Strawman for PPP
Stacey Adam, FNIH

The proposed PPP will consist of three stages and is currently in the first stage, which is the landscape evaluation and stakeholder assessments of the potential PPP. The second stage will be the Biology Interrogation and Drug Platform Conferences (BIDPC), in which the PPP intends to evaluate data on potential ultra-rare cancers to be selected for treatment development. Discussions coming out of this phase will allow for the selection of one or two ultra-rare cancers and molecular targets to investigate, as well as drug platforms best suited to address the selected molecular targets. Stage three will involve the development of the PPP governance and execution of pilot partnerships to perform end-to-end drug development for selected ultra-rare cancers and molecular targets. The selection of the first two pilot projects is intended to be an internal PPP process, consulting with experts from the USG, industry, and nonprofits about top candidates for development and resources that may be utilized. A strong biological rationale would be needed for selecting a particular candidate and a particular molecular target. There will also be a preliminary rationale for selecting the drug platform. A detailed partnership execution plan will be developed during these discussions. The FNIH and the USG will then work to secure funding and resource allocation agreements to launch the pilot projects, including the appropriate partners necessary to operationalize the PPP.

A strong coordinating entity, such as FNIH, and a reasonable amount of governance would be needed in order to move in an expedited fashion and without conflicts of interest. The proposed PPP governance framework is one that FNIH has used variations on for most of its

major partnerships. The governance will have three primary committees, including an executive committee under which there would be a scientific advisory board and a steering committee. The scientific advisory board will be composed of critical knowledge leaders in the field being studied, pulling from government academics, regulators, patients, and companies in advisory capacities to provide strategic scientific counsel and recommendations. The group should have a broad composition to allow for all necessary expert discussions and avoidance of potential conflicts of interest. The steering committee would comprise USG, private sector resource contributors, and patient advocates to help make tactical decisions about the resources contributing to the PPP. The executive committee would be comprised of senior members of the USG and senior representatives of the partner organizations. This entity is intended to provide executive guidance to the PPP, as well as mediate conflicts that may arise if the scientific advisory board and the steering committee are not in agreement. Supporting the steering committee will be a number of working groups tackling key topics and issues needed to operationalize the PPP.

According to a pre-meeting survey sent out to the participant sector, advocacy groups and pharmaceutical companies have a high interest in the PPP, as do a wide range of other participating entities, such as academics, researchers, regulatory bodies, and professional associations. Respondents who do not work in rare cancers expressed interest, as well. Most respondents thought that the PPP would help address the gaps in drug development for ultra-rare cancers. Finally, since the intention of the PPP is not to compete with the private sector or nonprofit partners but to find a synergy in facilitating and expediting the development of those drugs for which there may not exist economic feasibility for development via other avenues, the respondents to the survey provided thoughts on efforts and resources that should be factored into planning to ensure synergies.

Discussion and Q&A

Roundtable Participants and Audience

Dr. Adam asked the panel to comment on whether approaches to treatments that do not focus on specific targets would be welcome in the PPP. Dr. Donoghue reiterated that the meeting is intended to get input and feedback about structuring the partnership and is at a stage for taking a flexible view of the mechanisms for developing therapies for ultra-rare cancers. Dr. Lyn Jones (Dana-Farber Cancer Insitute/ Harvard Medical School) said the PPP approach at this time could focus on linking the modality to the target and the patient. Alignment of these factors could help take an agnostic approach moving forward.

Meeting attendee Dr. Gary Schwartz (Case Western Reserve University) mentioned that NCI's NeXT program, which was discussed earlier in the meeting, consists of a panel of academic/industry leaders, and asked how the proposed PPP would differ from NeXT, and how the initiative compares to other initiatives. Dr. Adam indicated that NeXT is entirely an NIH-driven program, and while the private sector provides consultation, it doesn't bring in investments. The proposed PPP will leverage resources as well as investments from private and government sectors. Dr. Schwartz asked, from the perspective of an investigator

applying to a program, what would drive the decision to choose one program over another. Dr. Adam clarified that the proposed PPP would welcome collaborations, given the PPP would potentially look for cancers rarer than those the NeXT program may consider. Dr. Chen added that while the NeXT program focuses on drug development, the PPP would first pick an ultra-rare cancer and then approach therapeutics, subsequently taking them toward approval. Collaborating with the NeXT program could be a complementary opportunity for the PPP. Dr. Reilly said several groups within the NCI are aligned with these ideas, with the FusOnC2 Consortium being one of them. Each of them may work with a different process, so it is worthwhile assessing each group's strengths to determine where the PPP could fill potential gaps.

Dr. Adam posed a question from the audience asking how the PPP can help speed the development of therapeutics and incentivize it. In other words, how would the collaborating entities work to accelerate drug development most effectively for ultra-rare cancers? Dr. Brigette Widemann (NCI Center for Cancer Research) additionally asked how to recruit industry involvement in the PPP, as their expertise would be critical in helping speed the process of therapeutic development, providing context for realistic timelines and parameters for success. Dr. John Zhang (American Association for Cancer Research) indicated that two years may not be sufficient for a drug development pipeline, and five years may be more realistic, specifically when the target drug is not a common target present in more common diseases. Dr. Adam clarified that repurposed drugs are on the table for this conversation. As another attendee had mentioned in the chat, these are examples of out-licensing and that would be one potential avenue. Dr. Jones added that platform-based biotech companies involved in target discovery could be leveraged. The PPP could give structure, support, and a path forward to the companies with these assets that are currently not moving forward.

Dr. Anne Pariser (Alltrna) suggested areas where the target development process proposed by the PPP may become more attractive from the industry standpoint. She also noted that two years may be an aggressive timeline and that meeting that timeline would require seamless communication between drug developers and regulatory agencies. Therefore, involving regulatory agencies earlier in the process would help with decision-making. Their advice could potentially be recycled to move other programs. Dr. Lou Stancato (Eli Lilly) corroborated Dr. Pariser's suggestion, adding that for the PPP's purposes, discussions with regulatory authorities early in the therapeutic development process could also ultimately change the way clinical development of therapeutics for rare diseases is approached by industry. Therefore, the PPP would have benefits for diseases not represented in the PPP. From an industry perspective, these efforts could be made more timely by choosing the most tractable of the intractable diseases or disease-state targets. Selecting the easiest of the most difficult projects could be used as a proof-of-concept. In addition, Dr. Stancato noted that charging a few people with the decision-making process would likely be advantageous to cut the time required to attain a consensus from a larger decision-making body. Finally, he suggested that eliminating IP concerns from the beginning would be helpful to streamline the process as well, though that may be challenging to get partners to concede to.

Dr. Sarah Glass (n-Lorem) said that a key component to success is to start with the patient and then use a well-understood platform. She added that a two year timeline from drug discovery to the clinic is a very aggressive timeline, especially without the fundamental knowledge of the target or the modality. A wide experience combined with broad partnerships and synergy across methods would help move projects quickly, rather than a linear process. Dr. Angela Shen (Massachusetts General Brigham) indicated that the two year timeline is aggressive but doable if funding and IP concerns are clarified from the start and there is available expertise, seamless discussion with health authorities, a nimble team, and a simple, centralized decision-making structure. Dr. Schneekloth mentioned that it may be challenging to do preclinical research with any kind of IP, which is compounded by the fact that clinical research can be particularly expensive for rare diseases where it is difficult to find a reasonably sized patient population. He welcomed thoughts from the group on how to resolve IP issues early in the process. Dr. Pariser agreed and suggested drawing from the experiences of other consortia that have resolved IP issues early on.

Dr. Ottinger raised concerns about how sustainability would be offered to patients when product development is not commercially viable. Dr. Andrew Lo (Massachusetts Institute of Techonology) said that there are two aspects of commercial viability and incentives. One is developing the drug, and the second is delivering the drug to patients consistently. From examples of commercial models, combining drug development for ultra-rare conditions into a portfolio reduces risks, particularly if there are shared resources to develop multiple drugs together. He cited the example of BridgeBio Pharma, a company he co-founded, where the distributor withdrew a drug for cholangiocarcinoma despite it getting FDA approval because it was too expensive to run the confirmatory trials needed for distribution. He said that it is important to look at both sides of the commercial angle to create a sustainable business model. Dr. Reilly agreed and cited another example of a drug being approved previously and then being discontinued because of a lack of patients. She asked if the government could devise a nonprofit model not reliant on market forces when supply-and-demand logistics do not match up. Mr. Jimmy Rosen (Rapidly Emerging Antiviral Drug Development Initiative) said that an entrepreneurial approach—even though it has roots in government—will require building a small and nimble team and then going in a certain direction. He said that the government stepping up to take the initial steps forward would then garner interest from foundations and industry, who would prefer to enter the alliance at a stage where they can assess the opportunity based on the progress already made. He agreed with Dr. Lo on pursuing the project in a portfolio manner to attract industry participation. Finally, he noted that partnering with advocacy groups would be one way to garner some funding to aid in building the consortium.

Dr. Adam selected a question from the audience asking how the PPP feasibly translates into collaborative efforts with patient organizations. Dr. Palma responded that in the ultra-rare space, advocacy organizations will likely be the most unified network of not only patients, but also specialists, centers of excellence, and researchers. Therefore, it is critical to have key stakeholders at the outset. Having patients involved in protocol consent development and

choosing endpoints will be valuable in terms of advice based on their experience while driving key parameters of the trial. If at any point a drug is pulled after approval, patients need to be at the table as well to offer their perspectives.

Dr. Reilly reiterated the invaluable contributions of advocacy organizations that help set the stage for developing collaborations, accruing patients, and collecting funding for basic research to identify the drivers. Applying government funding would propel the project toward the finish line. Dr. David Drewry (UNC/Structural Genomics Consortium) added an example of the Chordoma Foundation, which has created cell-line models and patient registries—where a difficult target can be approached by pulling resources from interested parties, then assembling a team to take the basic discoveries that have been made to a pharmaceutical-level drug discovery program that brings compounds into the clinic. Dr. Chen highlighted the importance of avoiding duplicate efforts and establishing the finish-line definition. Was it getting a drug approved or ensuring continued availability to patients over time? Dr. Glass said that collecting natural history data would be important for patients, and it would also inform the platform choice for collecting data to enable access to patients in a meaningful way.

Dr. Rachel Harding (University of Toronto/Structural Genomics Consortium) touched on data sharing and communications and noted that laying out a summary accompanying each experimental dataset not only helps foster good community practice but also facilitates connection with physicians and individuals in the global network. Dr. Widemann said that the Childhood Cancer Data Initiative (CCDI) is developing a national strategy to study rare tumors, which will lead to a registry with common data elements and therefore engage different advocacy groups. This effort would provide the infrastructure to simultaneously allow for the investigation of multiple rare diseases and could potentially be a mechanism to help obtain natural history data when a trial is ready.

From the audience, Dr. Susan Weiner (Children's Cancer Cause), who represents the pediatric oncology parent community, said that it is essential that parents are involved in the decision-making, as parents provide consent for their children's participation in research. Parents' early input on trial design and protocol development is critical because they know how protocols can or cannot be implemented in children with life-threatening diseases. Access to and coverage of new agents is also essential to parents, and should be thought about in the planning of the PPP from the beginning. Finally, from the PPP perspective, an early win is an important fundraising tool to sell a novel approach.

Meeting participant Mr. Jeff Kramer (Chondrosarcoma CS Foundation) asked, in its conception of rare cancers, whether the PPP would address cancer subtypes that are rare. Dr. Pariser responded that looking at the tumor in totality may introduce more complexities. If speed is a goal, taking a focused approach might be more helpful. Dr. Reilly mentioned there could be programs where it may make sense to target all sarcomas as a group, rather than select molecularly defined subtypes. That approach could potentially expand the patient population to draw upon. If the focus is on a molecularly defined subtype, the same

drug may not necessarily target all subtypes. There may be different ways to attack the tumors—directed to different NCI or extramural programs—where the focus is on one molecular driver at a time. Dr. Donoghue added that the science would lead us to decisions regarding whether biomarker selection of sarcoma subtypes for the drug development program is warranted.

Meeting participant Mr. Josh Sommer (Chordoma Foundation) said that his foundation is adopting an agnostic approach at this time. He asked how the PPP aims to prioritize potential modalities. Would it utilize a portfolio-based approach and then narrow it down? Dr. Widemann responded that aiming for a win, she would do a deep analysis of where there could be success, especially when applicable to potentially more than one tumor type. Dr. Reilly added the approach could be to pick one or two ultra-rare tumors that look promising and then invite individuals using different technologies to weigh in on the best way to target them, discuss the strengths/weaknesses of the approaches, and narrow them down. Dr. Jones agreed and suggested the PPP look carefully at what a steady state may look like and pick low-hanging fruit to begin with but not do that perpetually. In the longer term, the idea should be to choose targets.

Dr. Bozza presented three scenarios: either a therapeutic exists but it is not known whether it hits the target, a therapeutic exists that is known to hit the target, or no therapeutic exists. There is an opportunity to explore more flexible IP positions for some of these scenarios depending on the resources used. Dr. Stancato said that rather than brainstorming therapeutic modalities at the outset, a rubric could guide the PPP to which disease the PPP may want to focus on, optimizing time to the clinic. He advised on identifying the best opportunity, with the caveat that therapeutic modality is only one piece of a series of questions to address. A potential output from this exercise might be to put on paper what a rubric would look like.

Dr. Peter Marks (FDA Center for Biologics Evaluation and Research) reiterated the opportunities to leverage regulatory pathways and collaborations to move the PPP forward. Dr. Marks also stated that making use of the best available science to move through expedited clinical trials and regulatory processes would facilitate the process. He emphasized that a program with a small target population should account for a different benefit-risk calculation and that the PPP would benefit from its position to be able to work with the combined perspective of regulatory, scientific, and other stakeholders.

Dr. Adam closed the meeting by providing a summary of the next steps and thanking the speakers, panelists, and attendees. She then adjourned the meeting.