Science Advancement & Outreach
A DIVISION OF PETA

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NCATS FY 2024–2029 Draft Strategic Plan Framework

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Science Advancement and Outreach

A division of People for the Ethical Treatment of Animals

We are writing on behalf of People for the Ethical Treatment of Animals—PETA entities have more than 9 million members and supporters globally—regarding the National Center for Advancing Translational Sciences' (NCATS') draft strategic plan framework. NCATS' strategic plan for the next five years prioritizes the improvement of diagnostic strategies and therapies, particularly for rare and intractable diseases, through fostering new alliances and enhancing both scientific and operational processes.

Overall, the draft strategic plan is commendable, and PETA supports NCATS' mission to provide health solutions for all using human-relevant innovative approaches that allow the translation from preclinical to clinical contexts. Below, we expand on recommendations for each priority listed in this request for public comment.

We have previously written to NCATS about our Research Modernization Deal, a plan of action with detailed recommendations for advancing biomedical research in the U.S. through non-animal methods, applicable across various research domains. This plan can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf and would be of use for NCATS to review in its planning process.

Given our knowledge about animal sentience and the significant failure of experiments on animals to translate to human health benefits, NCATS must shift research investments away from the experiments on animals it currently funds, including in its TARGETED Challenge, Antiviral

Program for Pandemics, Clinical Trial Readiness program, Bridging Interventional Development Gaps program, Bespoke Gene Therapy Consortium, and more. The only way to achieve NCATS' mission of more treatments for all and more quickly is by supporting the development of new technologies and research pipelines with modern human-based models, not ineffective experiments on animals.

Goal 1: Apply Approaches to Foster the Identification of, Development of, and Access to More Treatments

With only a few available treatments for thousands of known diseases and the long years required to bring a new drug to the market, therapeutic interventions remain very limited. NCATS' goal of developing new treatments by leveraging technologies and techniques across the translational science spectrum is therefore extremely necessary, particularly for rare diseases.

We agree that the current drug development framework is inefficient and slow. A primary reason is the reliance on animal models to predict efficacy and toxicity in humans,[1,2] contributing to the staggering 90-95% failure rate during clinical trials,[3] as noted in Objectives 1-3. We support NCATS' stated intentions to "increase the predictive value of research models by supporting the development and dissemination of more human, cell-based, physiologically relevant tissue and other nonanimal models," use "computational modeling and artificial intelligence (AI) and machine learning (ML)," and "make processes in drug development more rigorous, reproducible, data driven." **We urge the institute to go further in its mission to promote rigorous, reproducible, and data-driven research by refusing to fund experiments on animals for preclinical testing and screening, as well as drug development.**

Failures in clinical trials often happen due to unanticipated side effects that were not predicted during preclinical assays using animals. As a result, human population studies and data on existing drugs may be recycled when assessing safety for new therapeutic uses.[4] In this regard, provided it does not involve additional animal testing, drug repurposing is a worthy strategy to accelerate the discovery of new

[1] Atkins JT, George GC, Hess K, et al. Pre-clinical animal models are poor predictors of human toxicities in phase 1 oncology clinical trials. *Br J Cancer*. 2020;123(10):1496-1501.
[2] Lampreht Tratar U, Horvat S, Cemazar M. Transgenic Mouse Models in Cancer Research. *Front Oncol*. 2018;8:268.
[3] Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? *Acta Pharm Sin B*. 2022;12(7):3049-3062.; National Center for Advancing Translational Sciences (NCATS). New Therapeutic Uses. https://ncats.nih.gov/research/research-activities/ntu. Accessed February 2, 2024.
[4] Kulkarni VS, Alagarsamy V, Solomon VR, Jose PA, Murugesan S. Drug Repurposing: An Effective Tool in Modern Drug Discovery. *Russ J Bioorg Chem*. 2023;49(2):157-166.

treatments for rare diseases. Genomic screening and *in silico* pharmacokinetics assessment are great tools to find novel indications for drugs.[5]

NCATS should explore two venues in parallel to more quickly and efficiently achieve clinical benefits. First, NCATS must emphasize its investment in non-animal approaches with patient-derived cellular models to test available drugs. Combining these cellular models with current -omics technologies can leverage the relevance of the studies and identify new targets for genetic diseases. These new approaches relying on patients' data allow for a better correlation between genetics, phenotype, and environmental factors. Therefore, they open new opportunities for addressing conditions that are clinically undiagnosed and impossible to study with animal models.

Second, as mentioned in Objectives 1-1 and 1-2, NCATS should support a national collaborative network to improve diagnoses and interventions. Approximately 95% of rare and orphan diseases have no pharmaceutical intervention and families are mostly guided by health professionals who provide palliative treatments to manage the challenges imposed by the health condition,[6] a standard of care which does not fully meet their needs. One obstacle to progress is the lack of funding for human-relevant studies on diseases affecting a small number of individuals.[7] Although the FDA provides opportunities for collaboration with institutions across the U.S.,[8] to achieve greater clinical benefits, NCATS should encourage and support multimodal and multicentric therapeutic approaches that do not involve preclinical testing on animals.

NCATS should not only support and leverage its existing networks, but also increase its support for the creation of new non-animal technologies hubs both within the NIH intramural system and at extramural research facilities. These could be hubs for the development and use of human cellular systems or for advanced computational methods. *In silico* technologies can be used as tools to advance clinical diagnoses and to model therapeutic protocols based on data obtained from molecular and genetic target profiles using patient-derived cellular models. To develop patient-relevant studies for the over 280 rare diseases addressed in Objective 1-2, new non-animal *in vitro* and *in silico* methods will be invaluable tools. They can be used as high throughput screenings platforms that will readily expand the knowledge about rare diseases which lack effective and reproducible models.

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[5] Demkow U. Next Generation Sequencing in Pharmacogenomics. In: Demkow U, Ptoski, R, eds. *Clinical Applications for Next-Generation Sequencing*. Academic Press; 2016:217-240. Accessed June 13, 2024.
[6] National Organization for Rare Disorders. Rare Disease Day: Frequently Asked Questions. RareDiseases.org. Accessed June 13, 2024. https://rarediseases.org/wp-content/uploads/2019/01/RDD-FAQ-2019.pdf
[7] Fu MP, Merrill SM, Sharma M, Gibson WT, Turvey SE, Kobor MS. Rare diseases of epigenetic origin: Challenges and opportunities. *Front Genet*. 2023;14:1113086.
[8] FDA. Funding Opportunities for Rare Diseases at FDA. Updated April 24, 2024. Accessed May 31, 2024. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/funding-opportunities-rare-diseases-fda.

Goal 2: Enable All People to Contribute to and Benefit from Translational Science

Objectives 2-1 to 2-3 focus on the inclusion and engagement of diverse individuals and communities in translational research, a goal which is also embraced by PETA. This priority will help facilitate equitable access, representation, and participation in translational science efforts. More than 80% of known rare diseases have a genetic origin.[9] In many cases, cultural background may be a barrier for inclusion, particularly when genomic assessment is required. Therefore, diverse ethnic groups would benefit from community leaders' engagement in public initiatives to develop trustworthy interactions tailored according to their narrative. Listening to families and their leaders is the best way to include the community and achieve NCATS' mission.

In 2019, a study on NIH funding revealed that Black/African American investigators were significantly more likely to submit grant applications that involve human subjects, not animals, and more likely to propose research at the community and population levels.[10] These topic choices among investigators contributed to lower funding rates. One step that NCATS can take to ensure more equitable funding and the cultivation of a "multifaceted, highly skilled, representative, and including translational scientific workforce" (Objective 2-4), which also provides a direct benefit to communities, is to place a higher priority on these kinds of projects and the training needed to conduct them.

Biomedical research has suffered from poor translation to human health benefits because of the fundamental gap between the human physiology and pathology and that of the animals used in preclinical experiments, as well as the past clinical trials based on these poorly predictive animal models.[1,2] To overcome this long-standing challenge, NCATS should foster and create collaborative research programs that prioritize patients throughout the entire process, building a sense of allegiance and care. The Trial Innovation Network is an important step towards more collaborative and meaningful research for rare diseases. We support NCATS' recognition of the necessity to incorporate patients' perspectives at all levels of the research and development process, including the preclinical phase.

To meet these goals, NCATS can reinforce access and information by educating primary health professionals, such as nurses, family physicians and social workers, about genetic counseling, since these providers are often the first to interact with affected individuals. Genetic counseling is critical for rare

[9] Fu MP, Merrill SM, Sharma M, Gibson WT, Turvey SE, Kobor MS. Rare diseases of epigenetic origin: Challenges and opportunities. *Front Genet*. 2023;14:1113086.
[10] Hoppe TA, Litovitz A, Willis KA, et al. Topic Choice Contributes to the Lower Rate of NIH Awards to African-American/Black Scientists. *Sci Adv*. 2019;5(10):eaaw7238.

diseases and many advocate that it should be extended beyond genetic experts.[11] By fostering an inclusive and informative environment within communities, NCATS can harness a wide range of perspectives to drive health innovative solutions for all who need it.

NCATS could develop mobile genomic clinics to provide health care access to vulnerable individuals, such as those in indigenous communities, in collaboration with local leaders to adapt to their social and cultural environment. Such a strategy may encourage patients to provide samples for preclinical studies and to support decentralized trials for rare diseases, as discussed in Goal 1. An interesting example of community engagement in research is the world's largest community-based genetics study, Genes & Health, from the British program Born in Bradford (BIB), where 100,000 Pakistani and Bangladeshi people provided salivary samples to investigate genetic heritage disorders and therapeutic opportunities.[12] By implementing these strategies, NCATS may move towards bridging the gap between scientific research and real-world health outcomes.

Goal 3: Accelerate Translation by Addressing Both Scientific and Operational Challenges

Removing barriers that slow down the process of diagnosis and hinder research advancement is crucial, otherwise it remains a challenge to improve human health and quality of life. Reducing the time required to translate early discoveries into clinical treatments is a key step towards a future with more effective outcomes. For example, therapeutic targets for fragile X syndrome (FXS) identified using mouse models have failed to show efficacy in clinical trials with teens and adults mostly due to species-specific distinctions in human and mouse brain development that provided misleading data.[13,14] It is commendable that NCATS is proposing to make great use of statistical and computational methods with available data and to explore human-based cell models, *in silico modeling*, and innovative patient-centric design, but **the institute needs to fully divest from failing animal models in order to free up the resources necessary for these laudable goals.**

Objective 3-3 draws a direct path to benefiting individuals with rare diseases as soon as possible by combining multiple approaches. Identifying unexplored causalities for hard-to-diagnose diseases could benefit from strategies that monitor families from early pregnancy or even prior to conception. Factors

[11] Rare Diseases International. Genomic technologies. RareDiseasesInternational.org. Accessed May 30, 2024. https://www.rarediseasesinternational.org/genomic-technologies/.
[12] Genes & Health. About the Study. GenesandHealth.org. Copyright 2024. Accessed June 3, 2024. https://www.genesandhealth.org/about-study.
[13] Hagerman RJ, Berry-Kravis E, Hazlett HC, et al. Fragile X syndrome. *Nat Rev Dis Primers*. 2017;3:17065.
[14] Berry-Kravis E, Des Portes V, Hagerman R, et al. Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials. *Sci Transl Med*. 2016;8(321):321ra5.

such as age,[15] lifestyle,[16] and genetic makeup[17] impact offspring but the underlying mechanisms explaining specific rare conditions are frequently overlooked or inaccessible.

For example, severe combined immunodeficiency (SCID) is a rare condition with unknown prevalence. Without the right diagnosis and treatment, life expectancy of children with this condition is only two years.[18] However, SCID can now be identified by prenatal genetic screening for X-linked and autosomal recessive mutations, rather than postnatal lymphopenia characterization. The implementation of newborn screening programs with genetic analysis, such the Newborn Genomes Program in the United Kingdom,[19] could potentially accelerate diagnosis of rare conditions and speed access to adequate treatment, currently taking over five years in most countries.[20] While genetic screening of newborns is available in the U.S., each state manages its screening program independently,[21] leading to variability in tests performed and potential delays in diagnosis. NCATS could improve the uniformity of screening tests across the U.S. and advance policies a step further with complementary genetic analysis of parents, i.e. genome sequencing, and the creation of databases, similar to the Orphanet portal in Europe, which would provide genealogic background research, currently nonexistent in North America.[22]

Concerning the automation of laboratory operations with enhanced rigor and reproducibility, NCATS must first prioritize and invest in technologies allowing for high-throughput analysis that can streamline research operations. As stated in the presented strategic plan, traditional models relying on animals lack human relevance, reproducibility, and robustness, failing to accurately predict drug efficacy and safety.[23] In this regard, advanced 3D human cellular systems offer a unique ability to standardize the manipulation of cellular composition and biochemical factors.[24] For instance, organs-on-chips have been developed for

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[15] Demko ZP, Simon AL, McCoy RC, Petrov DA, Rabinowitz M. Effects of maternal age on euploidy rates in a large cohort of embryos analyzed with 24-chromosome single-nucleotide polymorphism-based preimplantation genetic screening. *Fertil Steril*. 2016;105(5):1307-1313.
[16] Dhana K, Haines J, Liu G, et al. Association between maternal adherence to healthy lifestyle practices and risk of obesity in offspring: Results from two prospective cohort studies of mother-child pairs in the United States. *BMJ*. 2018;362:k2486.
[17] Feofanova EV, Brown MR, Alkis T, et al. Whole-Genome Sequencing Analysis of Human Metabolome in Multi-Ethnic Populations. *Nat Commun*. 2023;14(1):3111.
[18] Orphanet. Severe combined immunodeficiency. Orpha.net. Updated February 2013. Accessed May 29, 2024. https://www.orpha.net/en/disease/detail/183660.
[19] Genomics England. Newborn Genomes Programme. Copyright 2024. Accessed June 13, 2024. https://www.genomicsengland.co.uk/initiatives/newborns.
[20] Marwaha, S., Knowles, J.W. & Ashley, E.A. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. *Genome Med*. 2022;14(1):23.
[21] Expecting Health. Conditions Screened By State. BabysFirstTest.org. Copyright 2024. Accessed June 13, 2024. https://www.babysfirsttest.org/newborn-screening/states.
[22] Canadian Paediatric Society. Genetic testing and screening in children. CPS.ca. Posted February 12, 2022. Accessed June 11, 2024. https://cps.ca/documents/position/genetic-testing.
[23] Fan H, Demirci U, Chen P. Emerging organoid models: leaping forward in cancer research. *J Hematol Oncol*. 2019;12(1):142.
[24] Maulana TI, Kromidas E, Wallstabe L, et al. Immunocompetent cancer-on-chip models to assess immuno-oncology therapy. *Adv Drug Deliv Rev*. 2021;173:281-305.

the cultivation of patient-derived cancer cells, allowing the investigation of angiogenesis,[25] chemotherapy regimen toxicity,[26,27] and the recreation of 3D real scale models of brain tumors,[28] conditions which are both physiologically and technically difficult to study using animal models.[29] Therefore, NCATS should propel research with models that faithfully replicate the human body for faster diagnostic approaches and more personalized therapy.

To achieve such automatization and accelerate the transition to streamlined research and clinics, NCATS must also invest in education and training of professionals to maintain standards, as well as the development of thorough guidelines and computational tools[30] for implementation across the U.S. In parallel, NCATS must increase financial support for stakeholders to encourage the adoption of new non-animal methods with the potential for large scale and industrial applications.

Finally, NCATS should support non-animal methods that allow for the identification of molecular and clinical markers, ideally using clinical samples, especially in the context of rare diseases or vulnerable populations, where samples are scarce. For example, Zafarullah & Tassone[31] discussed new biomarkers for FXS identified with mouse models that are on their way to clinical trials. However, as mentioned earlier in this goal, mouse models have previously led to unsuccessful clinical trials based on inaccurate information. While we hope for their success, it is doubtful considering the past failures.

Goal 4: Advance Research and Operations that Cut Across Translational Science

In this goal, NCATS addresses the expanding scientific boundaries to reach a higher impact. Importantly, NCATS recognizes that challenges in translational science are interrelated. Building a multidisciplinary team, as NCATS has done, is an excellent way to unite forces and expertise to overcome roadblocks. As mentioned in Objective 4-4, not everyone is aware of the meaning of translational science which can impair the involvement of different stakeholders in developing studies. Families living with relatives who have rare diseases or ethnic communities possess unique value for research due to their genetic

[25] Miller CP, Tsuchida C, Zheng Y, Himmelfarb J, Akilesh S. A 3D Human Renal Cell Carcinoma-on-a-Chip for the Study of Tumor Angiogenesis. *Neoplasia*. 2018;20(6):610-620.
[26] McAleer CW, Long CJ, Elbrecht D, et al. Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics. *Sci Transl Med*. 2019;11(497):eaav1386.
[27] Abreu S, Silva F, Mendes R, et al. Patient-derived ovarian cancer explants: preserved viability and histopathological features in long-term agitation-based cultures. *Sci Rep*. 2020;10(1):19462.
[28] Tricinci O, De Pasquale D, Marino A, Battaglini M, Pucci C, Ciofani G. A 3D Biohybrid Real-Scale Model of the Brain Cancer Microenvironment for Advanced In Vitro Testing. *Adv Mater Technol*. 2020;5(10):2000540.
[29] Zitter R, Chugh RM, Saha S. Patient Derived Ex-Vivo Cancer Models in Drug Development, Personalized Medicine, and Radiotherapy. *Cancers (Basel)*. 2022;14(12):3006.
[30] Zhu J, Ji L, Chen Y, et al. Organoids and organs-on-chips: insights into predicting the efficacy of systemic treatment in colorectal cancer. *Cell Death Discov*. 2023;9(1):72.
[31] Zafarullah M, Tassone F. Molecular Biomarkers in Fragile X Syndrome. *Brain Sci*. 2019;9(5):96.

background, which is impossible and unethical to recreate using other species. However, lack of public support and information make individuals in these communities vulnerable and less open to collaboration. It is necessary to build trust within these communities beyond scientific communication. Therefore, NCATS must focus on education, outreach, and trust-building to effectively deliver information about the importance of patients in advancing translational science.

The development of programs that support local centers and specific contexts while ensuring data protection and social follow-up can encourage families to get involved in research programs. In the U.K. BIB is the largest longitudinal program studying different aspects of human life over the years, from genetics to ethnicity, involving entire families, schools, and local communities.[32] BIB has created a network to improve healthcare through studying humans in their environment, an important component since environment plays an important role in human development. Additionally, NCATS should engage with associations for rare diseases to provide ethical and proactive space for discussions, panels, and workshops with families and professionals.

In parallel to community inclusion, it is imperative to train researchers and health specialists in new, cutting-edge technologies and non-animal methods relying on human samples. **Building a solid foundation is the key to the long-term success of translational scientists. NCATS has an important place in the U.S. scientific landscape with an innovative vision on how to advance science for the benefit of society. PETA, sharing this vision with NCATS, has included in the Research Modernization Deal suggestions for the training and education of research teams as another step towards more human relevant discoveries. For more details, please visit: https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf.**

It is important to partner with experts beyond the U.S. borders, which can be facilitated by creating shared funding for non-animal research between countries and institutions who hold complementary knowledge. Furthermore, NCATS must proactively break barriers that slow down science translation at the preclinical and clinical levels. The bottom line to achieve this is by promoting human-relevant, non-animal approaches and fostering discussions with pioneering countries and institutions. **PETA's multi-national team of scientists with diverse expertise including many areas of biomedical science, toxicology, and medical training is available for consultation on this matter.**

[32] Born in Bradford. About Bradford. BorninBradford.nhs.uk. Copyright 2024. Accessed June 13, 2024. https://borninbradford.nhs.uk/.

Goal 5: Work Together as Stewards for Advancing Translational Science

NCATS' commitment to ethical and transparent resource management is both crucial and inspirational. It will ensure that science is conducted with rigor and responsible planning. To optimize research structure and quickly identify new challenges over the five-year period of this strategic plan, NCATS should provide continuous assessment of research data involving multiple stakeholders. Therefore, unmet needs can be addressed and adapted to the context in a timely manner.

Additionally, NCATS should expand its partnership with regulatory agencies, like the FDA, to reduce barriers in the process from clinical trials to translation, thereby speeding up the development of therapies for rare diseases. The creation of a national record for rare diseases, where all diagnosed conditions and individuals are listed, could facilitate bureaucratic and operational procedures, providing exclusive protocols for therapeutic approach access across the U.S. A similar procedure has been established by the Brazilian agency Anvisa, known as Resolution RDC 205/2017 (special procedure for rare diseases), for easy patient enrollment into clinical trials and access to drugs.[33,34] In the U.S. the Rare Diseases Register Program (RaDaR), maintained by NCATS, could benefit from a centralization strategy by automated registration of patients from hospitals and clinics, along with addition of genetic background as suggested in Goal 3.

NCATS can introduce non-animal methods for preclinical assessment of drug discovery and repurposing, as noted in Goal 1, as validation tools for further clinical trials. Similarly, implementing a robust data-sharing platform with international institutions aligned with FAIR principles would ensure that research findings are accessible and reusable, especially in the case of rare diseases. Such networks and operational strategies can enhance the overall efficiency and impact of their translational science efforts.

In the short term, including a mandatory validation step with patient-derived models for biomarkers and drug candidates identified in past animal-based studies would provide essential data on the translational potential of preclinical findings. A recent study by Kang, et al. compared the effects of the loss of FXP-related protein, known as FMRP, in mouse model and 3D forebrain organoids generated from FXS patient-derived induced pluripotent stem cells (iPSCs).[35] Genetic analysis concluded that human brain organoids were superior in mimicking FXS-associated phenotype in absence of FMRP and identified a

[33] Anvisa. Legislação: Resolução da Diretoria Colegiada - RDC nº 205 de 27/12/2017. Updated May 29, 2024. Accessed May 30, 2024. https://antigo.anvisa.gov.br/legislacao#/visualizar/364439.
[34] Anvisa. Drugs. https://www.gov.br/anvisa/pt-br/english/regulation-of-products/drugs. Updated March 15, 2024. Accessed May 30, 2024.
[35] Kang Y, Zhou Y, Li Y, et al. A human forebrain organoid model of fragile X syndrome exhibits altered neurogenesis and highlights new treatment strategies. *Nat Neurosci*. 2021;24(10):1377-1391.

human-specific target of FMRP not common to mouse models. This study underscores the potential of 3D patient-derived models to investigate rare diseases.

Finally, NCATS should engage in regulatory policies aimed at phasing out animal use for research on human-related diseases and implementing animal-free research methods, following the example of the international scientific community. This would go further in encouraging scientists in the U.S. to adopt non-animal methods.