Innovative Genomics Institute

Re: Docket No. FDA-2023-N-3742 – Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies

November 20, 2023

Attn: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Therapeutic Products

Re: Docket No. FDA-2023-N-3742

Innovative Genomics Institute
2151 Berkeley Way
University of California
Berkeley, CA 94704
phone: (510) 664-7110

www.innovativegenomics.org

Please direct inquiries regarding this comment letter to:
Dr. Manar Zaghlula at
manar.zaghlula@berkeley.edu.

To whom it may concern,

The Innovative Genomics Institute (IGI), a public, academic research institute formed through a partnership between the University of California, Berkeley and the University of California, San Francisco, below submits comments to the request for information on Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies by the U.S. Food and Drug Administration. We applaud FDA for committing valuable resources to understanding how to best move forward with cell and gene therapies (CGTs) for N-of-1/Few patients.

To compile comprehensive and actionable suggestions to the agency, we relied on our extensive network of experts and practitioners. Given the IGI's research priorities, we primarily center discussions and examples on gene-editing therapies in our response, but emphasize that many comments are applicable to CGTs more generally. We believe a new framework for individualized CGT development is needed, and hence, in preparing this letter, not only interviewed researchers and clinicians in the field, but also regulatory and bioethics experts. While many suggestions were shared, we would like to emphasize that this is not a consensus document and that the ideas presented below may not fully reflect the views of any one contributor. A list of contributing experts can be found at the end of this letter.

We thank the FDA for engaging on this critical topic and hope our comments are helpful. The IGI and its experts stand ready to address any questions or provide further information as needed.

On behalf of the Innovative Genomics Institute,

Manar Zaghlula, Ph.D.
Policy & Engagement Manager
Innovative Genomics Institute

Innovative Genomics Institute

Overarching Comments – Developing a new Framework

Given the unique circumstances of individualized CGT development (as outlined by FDA in the RFI), treatments for N-of-1/Few patients should be governed by a novel framework. We propose that FDA develop such a framework through an extensive stakeholder engagement process. While we are very encouraged by this request for information, there are concerns that many academic researchers and clinicians are unaware of this opportunity to inform FDA. Thus, we hope there will be varied engagement opportunities in the future (e.g., workshops, FDA-academia exchanges) to help develop and concretize an adequate 'N-of-1 Framework'.

Individualized CGT treatment constitutes a paradigmatic shift from traditional small molecule interventions. An N-of-1 Framework should therefore consider development challenges from a range of perspectives, including scientific and regulatory, as well as incorporate economic limitations of (academic/non-profit) developers, build on bioethics research in the field, and rely on patient and caregiver voices. Importantly, unless individualized CGT development becomes of commercial interest (e.g., if platforms can be used to treat ultra-rare diseases in aggregate), academic developers will remain at the forefront of the fight against ultra-rare diseases.

First, FDA should define N-of-1/Few and ultra-rare diseases with commercial viability/interest in mind and, accordingly, ensure its guidances on this topic are not beyond what is feasible with respect to cost, labor, capacity, and time in the academic setting. Second, in order to learn from each N-of-1 treatment case, regardless of outcome, transparency expectations should be an integral part of the framework. We propose that transparency requirements go beyond publications, and, to support this, that FDA establish a public database wherein investigators submit detailed information about both successful and failed individualized CGT treatment cases as soon as available and continuously (e.g., long-term follow-up, autopsy results, etc.). Especially in academic settings, where investigators may have very limited knowledge about regulations, open channels of communication are key.

Importantly, an N-of-1 Framework should consider that for many progressive genetic diseases time is of the essence. As has been shown in animal models and clinically, the sooner an intervention is given, the more likely it is to have significant long-term therapeutic impact. For example, a CGT may halt the progression of a retinal or neuro-degenerative process, but cannot restore lost photoreceptors or neurons, underlining the imperative to reduce the time from diagnosis to treatment. Accordingly, the burden of preclinical data should generally enable timely treatment, rule out acute toxicities known to occur with a class of intervention (or at least identify them to evaluate the risk-benefit and implement a clinical action plan), and rely, as much as possible, on previous knowledge about the therapeutic class (i.e., the platform technology). For extremely urgent cases, a new form of expedited IND for CGTs could be developed with clear guidelines on what information about the patient and the drug product is needed to proceed with treatment within a short period of time.

The establishment of platforms is a critical component of advancing individualized CGTs. Based on our understanding of FDA's current thinking, platform designations will initially be limited to individual manufacturers who have at least one approved product and use the same constituent or process (i.e., platform building block) in the development of another product. For academic N-of-1 treatments, this would be too restrictive. Rather, FDA should work with academic investigators and manufacturing centers to establish platforms that can be used across individualized CGT products. Standard operating procedures should be established where feasible to streamline regulatory review processes. A transparent approach would ensure academic centers across the country follow standardized, FDA-approved protocols.

Therefore, to implement this framework, we propose that FDA establish an office within OTP dedicated to the development of CGTs for ultra-rare disorders in the academic/nonprofit setting. Such an office should be equipped to review investigator regulatory submissions for N-of-1 treatments in a timely manner. Its reviewers should be able to evaluate information about the rarity of the disease, diagnostic confidence in the genetic cause, whether the mutation is actionable with the proposed genetic intervention, and what the burden of evidence should be relative to the severity of disease (see below for further discussion). This office should also be given the operational authority to be flexible, advance regulatory innovation to first-in-human clinical trials, and to establish seamless intra-agency collaboration to maximize learnings. We emphasize that intra-agency collaboration between CBER and CDER are critical given that there is precedent for individualized treatment with another platformizable, genetic intervention: antisense oligonucleotides (ASOs). Learnings should also be expanded to areas where patients are rare and require urgent intervention, e.g., pediatric oncology.

Lastly, the N-of-1 Framework should be built upon a foundation of bioethics research (principles from the Belmont Report). The patient and their autonomy should be front and center. In order for this vulnerable population (both patients and caregivers) to make autonomous and well-informed decisions, they should be given adequate information about the interventions, potential risks and benefits, given an opportunity to ask questions, and understanding of the information should be checked. Patients and caregivers should also be made aware of any misconceptions (e.g., clearly understanding that the treatment is experimental and not a proven therapy) and gaps in knowledge (e.g., uncertainty about off-targets). Clinical care review teams (further discussed below) that include bioethicists further play an important role in ensuring that investigators avoid potential conflicts of interest (e.g., personal physician or scientist motivations driving care) and are themselves aware of gaps in knowledge. Given the experimental nature of N-of-1 interventions and unknown long-term effects, informed consent should be thorough and clear information about the purpose and frequency of long-term follow-up activities provided. Where long-term follow-up in pediatric patients is expected, the autonomy of these individuals should be respected as they become older.

Bioethical principles should also inform the risk-benefit calculus for individualized CGTs. It is important to consider that these treatments will not be marketed to the broader public, so the evidence standard should be proportional to the disease severity and patient population size. Where disease severity is not known, clinical predictions should be made based on the clinical history of the patient and, where applicable, related disorders. Importantly, a lack of natural history data should not preclude treatment.

For our specific comments and suggestions below to have greater impact, we suggest that they be implemented in the context of such an N-of-1 Framework.

Nonclinical Development

Diagnostic Challenges and Therapeutic Actionability. The first critical challenge for individualized treatments is diagnosis and classification of a genetic N-of-1/Few disease. Because determining the causal relationship between a mutation and pathogenicity can be arduous and not always straightforward, how actionable a mutation is using a genomic medicine should be tiered by supporting evidence and disease severity.

We propose that the FDA build a decision tree that establishes the diagnostic confidence threshold needed to enable intervention. Scores could be assigned based on evidence levels and disease severity to determine whether an individualized CGT should be approved and what the evidence standard for nonclinical studies should be.

To illustrate this tiering system in support of speedy decision-making, three main categories could include:

1. Is it a novel variant in a known disease-causing gene?
    a. Is the genetic mechanism of action of the mutation known (e.g., loss of function, gain of function, dominant negative, etc.)?
    b. Does the patient present similarly to other patients with more common disease-causing variants in the gene?
    c. Is there animal or human data supporting therapeutic benefit upon genetic correction?

        Example: A novel mutation in a gene known to cause an immunodeficiency; evidence of loss of function mechanism; patient presents similarly to others with the more common mutations in the same gene.

FDA action: This is clearly actionable and FDA should support product development for this N-of-1 patient in a timely manner and with nonclinical requirements that ensure safety yet are not cost-prohibitive or infeasible due to limitations of capacity and personnel.

2. Is it a novel variant in a coding or non-coding region unknown to cause disease, but with evidence of causal relationship?
    a. Is there human genetic data to support pathogenicity?
    b. Is there cellular and/or animal data to support pathogenicity?
    c. Is there computational data to inform pathogenicity of missense mutations?
    D. Is there cellular and/or animal data to support therapeutic benefit upon genetic correction?

        Example 1: A novel mutation in a gene thought to encode an ion channel; expressed in neurons; not seen in genetic databases of healthy individuals; patient has severe seizures; iPSC-derived neurons have abnormal firing which is corrected upon genetic correction in isogenic lines.

        Example 2: An intra-genic mutation in a region thought to act as an enhancer of a downstream gene critical for lysosomal storage; no animal data available; cellular modeling supports hypothesis of therapeutic benefit upon genetic correction; patient has had a rapid disease progression and is expected to succumb to the disease within 6-12 months.

FDA action: This is actionable. FDA should review the evidence for the specific case and work with investigators and the institutional review board to ensure appropriate informed consent that clearly lays out uncertainties. In example 2, the rapid progression of disease demands a shortened nonclinical evaluation, such as acute toxicity study of the proposed intervention.

3. Is it a novel variant either in a coding or non-coding region of the genome not known to cause disease and no clear causal link can be established?

    Example: Patient has a number of variants of unknown significance, one of which is suspected to be disease-causing and critical for neuronal axon development, but no confirmation. No cellular or animal data available. Patient presents with failure to thrive and is expected to succumb to the disease within 2 years. Disease mechanism not known.

FDA action: Unfortunately, this is likely not actionable.

In addition to diagnostic considerations, decisions about therapeutic actionability should consider how much is known about the safety and efficacy of the treatment modality, its likely benefits on patient health, and its side effects. Key questions in this category might include, for example:

1. Does the therapeutic intervention have the ability to halt or reverse (some features of) the disease?
2. Does the proposed approach effectively target organs/cell types affected by the disease process? Is biodistribution well understood?
3. To what extent are critical toxicities of the therapeutic approach understood (in humans or animals)? To what extent does the approach resemble or build upon other interventions with INDs or BLAs?
4. Might a focused targeting approach in one organ have systemic impacts (e.g., a liver treatment that removes a toxic metabolite from circulation, such as urea cycle disorders or organic acidemias)?
5. In complex disorders with multi-system involvement, is the therapeutic impact limited? If so, do the benefits of the intervention outweigh its risks?

Platform technologies. Establishment of an academic platform designation for modalities where prior knowledge about safety, dosing, adverse events, and pharmacology is available is essential. Such platforms should not be restricted to a single academic institution, as described above. When a platform technology is used, FDA should focus on nonclinical studies that provide evidence of therapeutic impact specific to the N-of-1 case. For example, if knowledge of the safety and biodistribution of a lipid nanoparticle (LNP) has been established previously, minimal such studies should be required to treat an N-of-1 case using the same LNP manufacturing process and excipients as the cargo is not expected to alter the characteristics of the delivery vehicle. Or, if a gene-editing approach is established for one (common) mutation within a gene and a new guide RNA is used to edit a specific novel mutation (causing the same disease), this should not be considered a new product that requires additional nonclinical toxicology and pharmacology data beyond an analytical pipeline for safety customized for the unmet medical need (an 'open IND' model).

Where appropriate and necessary, flexibility should be applied to critical experiments as the case requires. For example, if a patient urgently requires treatment, in a situation with appropriate benefit/risk, a 6-week acute toxicity study could be performed, instead of a 6-month-long experiment. We urge the FDA to work with academic institutions to establish platform technologies that support the treatment of ultra-rare disorders, working iteratively and openly to develop standards of nonclinical, manufacturing, and clinical parameters across different platform technologies and institutions. *De facto* restriction of such a designation to commercial manufacturers (e.g., by requiring an existing BLA based on the same platform) would be hugely limiting for access to transformative therapies.

Cell-based alternatives to animal models. Cell-based assays are a critical alternative to animal models, both in cases where models that recapitulate the disease are unavailable and where extensive *in vivo* experiments would be too time-consuming (such as *de novo* generation of a mutation-specific disease animal model). FDA should be flexible in its requirements and evaluate patients on a case-by-case basis. With cellular assays, functional readouts are key. Differentiated cells obtained from patient-derived induced pluripotent stem cells (iPSCs) can provide an excellent model to demonstrate that genetic correction with the proposed intervention have functional impacts predicted to ameliorate disease phenotype. In some cases, iPSCs or differentiated cells may not be as informative, or differentiation protocols too time-consuming or inefficient; then, cell lines with the mutation and a functional assay may be more suitable. Where disease modeling in cells is not feasible and no clear functional signal can be obtained, animal studies will likely be necessary. As with diagnosis, here too a decision tree would be helpful to determine what the evidence threshold should be to proceed.

Off-target analysis. For gene editing techniques, off-target analysis could be based on an agreed-ipon combination of *in silico* and experimental prediction methods. If a patient-derived cell is used for nonclinical studies, it may be most informative for off-target testing. Safe harbor methods, where only a transgenic insert is changed, but not the guide RNA, is another potential platform technology that would reduce the risk of off-targets and should therefore require only minimal such analysis upon adequate

initial assessment. Additionally, when enzymes that do not cut DNA are used (e.g., epigenetic editors), alternatives to traditional off-target analysis that are more informative in the context of the specific therapeutic modality should be employed to determine downstream unintended consequences, e.g., RNA-sequencing to assess 'off-target' changes in gene expression upon epigenetic editing.

Importantly, off-target risk should be viewed in the context of benefit/risk; specifically, the expected harm of the natural disease course versus the predicted functional impact of a potential off target. For example, if a predicted off-target affects an oncogene, how relevant is the risk of developing cancer in 5 years in an individual expected to survive only 1 year? How might routine cancer screening affect the risk calculus in such situations?

Burden of testing. There are critical experiments that should be performed to provide preclinical information about toxicities and dosing. For N-of-1 treatments, however, the scale of such experiments should be more limited than in preparation for an IND with bigger patient populations. For example, we recognize the importance of studying toxicity of a transgene delivered via AAV. However, rather than performing extensive animal studies, smaller N animal studies could be complemented with cell-based assays to evaluate the toxicity of overexpression of a gene. Similarly, other pharmacological and toxicological studies that typically require large animal cohorts and call for the evaluation of an array of organs and tissues should be more limited in scope. Specifics should be determined on a case-by-case basis.

It is essential that each requested study has a clear rationale and provides key pieces of information without unduly delaying patient treatment. For example, a study of a human T cell product in an immunocompetent rat model is not reasonable or informative if the cells are predicted to be rejected by the host immune response. Or, a serial transplant experiment that is expected to take 12 months may not be feasible for patients with rapidly progressing disease. Ultimately, clear guidance from FDA and ample opportunity to engage with the agency as these decisions are made is critical.

Manufacturing

Expectations of quality control. Quality control (QC) assays require a large amount of material (e.g., sterility testing), and could be simplified and accelerated by non-compendial methods. However, in order to establish these within the limitations of an academic center (cost and capacity), FDA should work with investigators to validate such assays. Additionally, QC tests should always have a strong rationale and be informative. For example, for an individualized product, a long-term stability assay may not be relevant. Similarly, innovative ways to assess potency could reduce development time and cost and may result in more appropriate correlates of potency than, for example, *in vitro* cell killing assays. FDA should also establish comparability requirements that are appropriate for individualized products and enable the use of platforms.

Where feasible, QC testing should be performed on the class of reagent. For example, a well-designed study could establish the stability, sterility, and purity of lyophilized DNA oligonucleotides at -80°C over a period of time. Changes in nucleotide sequence are not expected to significantly alter these parameters and should therefore not be required of every new oligo. Additionally, new rapid methods using sequence-based technologies or flow cytometry should be developed in conjunction with FDA for rapid release testing. Lastly, when a treatment has been shown to be safe and effective in the first patient, and no major manufacturing changes have been introduced, QC data requirements for a new batch should be extremely limited in scope for individualized CGT products. The cost of QC data may prevent patients from receiving safe and effective therapies, and that risk should be weighed against the risk of a lack of batch-specific QC data.

Distributed manufacturing. Models of distributed manufacturing (DM) have been explored extensively, including, encouragingly, by the FDA. We urge the speedy establishment of pilot studies of DM in the academic setting, ideally within an N-of-1 Framework.

Expectations of grade. FDA should work closely with academic investigators to determine the extent to which GMP-grade material and processes are necessary and feasible. Cost of and time to obtain GMP-grade materials are the biggest bottlenecks to treatment and a patient should not be denied access to a potentially transformative intervention simply because the cost of goods at GMP standards is too high. Where research-grade or GMP-like material provides reasonable assurance of product safety, it should be allowed in the individualized setting. Where disease severity and progression are less concerning, requirements can be made more stringent, within the limits of affordability. Such steps would vastly expand the ability to manufacture individualized CGTs.

Clinical Development

Basket trials. We encourage FDA to apply learnings from basket trials in oncology to the N-of-1 clinical challenges. Basket trials, where small, non-responding patient populations are given experimental treatments based on the molecular profile of their cancers rather than tumor type or location, can serve as models for studying N-of-1 interventions in aggregate. For example, the safety of specific types of CGT intervention could be tested in the individualized setting, irrespective of the particular genetic mutation. Alternatively, patients could be stratified by disease types (e.g., severe combined immunodeficiencies) and the basket trial designed such that an outcome of immune function is evaluated. Established platforms, again, are crucial to implementing such a strategy effectively and maximizing learnings for future patients.

Clinical Advisory Boards. Within treating Centers of Excellence, enrollment/treatment advisory boards could serve to make informed, collective decisions about whether a patient has an actionable mutation, should be treated with an individualized CGT, and what specific approach is best. Such boards should be multi-disciplinary and strive to ensure that undue risk is not taken where it is not necessary and can inform investigators about, or respond to, potential adverse events. An advisory board should also include a bioethicist that ensures informed consent procedures are clear about the risks and uncertainties associated with the proposed individualized product, as well as any long-term follow-up procedures. These advisory boards, in collaboration with FDA, could potentially enable independent oversight of CGT-specific administration in an ‘open-IND’ setting at a high level of granularity, ensuring rigor and quality of oversight.

Measures of disease modification. Information about disease modulation should be collected at various levels. Where feasible, non-invasive target engagement measures and biomarkers should be developed that correlate with clinical outcomes. For example, an editing strategy that affects a liver enzyme may increase serum levels of the enzyme (target engagement), resulting in lower levels of a downstream metabolic marker (biomarker), and ultimately improve another organ’s function impacted by the buildup of a toxic metabolite (clinical outcome).

Patient-reported outcome measures. Because ultra-rare diseases present in heterogeneous ways for which we have little stratified natural history and outcomes data, traditional outcome measures are sometimes ill-suited to evaluate treatment benefit. Rather, patient-reported outcomes (PROs) should be developed by the patient/caregiver, physician team, and FDA and used either as the sole outcome measure or in combination with others, as feasible (e.g., performance testing, neurological outcomes, measures of immune function, metabolic output). Traditional outcome measures may also not capture priorities for the patient/caregiver, who may focus on day-to-day functioning, such as improved sleep or greater seizure control.

Patient history. Where feasible, natural history from related disorders may be informative (though not a substitute). Patient history and baseline measures from clinical visits along with tools such as disease diaries (e.g., seizure diaries) and wearable devices (e.g., sleep trackers) can be used to chart an initial trajectory. These can then be complemented with information from related disorders to estimate disease trajectory. For example, a patient who lacks B and T cells as a result of a unique genetic mutation may have similarities with other severe combined immunodeficiencies. Such an estimation may not always be feasible, especially where disease severity is variable. Critically, however, lack of a clear understanding of the natural history should not be a reason to halt development of an individualized CGT product. Rather, the above decision trees, clinical advisory boards, and informed consent procedures should be leveraged to make case determinations.

Conclusion

Of the approximately 7,000 rare diseases, 40% are estimated to affect 50 individuals or less. Under the current business model, many of these diseases will not be of commercial interest and will therefore not benefit from scientific advances in cell and gene therapy development. FDA should leverage the platform nature of these technologies along with scientific and technical expertise in academic settings to enable individualized CGT development and treatment. We propose a new framework for N-of-1 CGT development that re-envisions nonclinical, clinical, manufacturing, regulatory, and bioethical aspects of drug development and increases patient access. Transparent sharing of outcomes from these trials could move this field from a disparate set of isolated clinical interventions with *ad hoc* reporting of successes and failures to a robust mode of true scientific knowledge production with a powerful set of platform technologies.

We look forward to continued engagement from the agency on this topic and opportunities for expert practitioners to help develop an implementable framework that ensures N-of-1/Few diseases benefit from the scientific leaps in cell and gene therapies.

Contributors

We would like to thank the following contributors for their time and expertise reflecting on the questions presented by the FDA.

Mehrdad Abedi, M.D.
Professor of Medicine
University of California, Davis

Lauren Black, Ph.D.
Distinguished Professor
Charles River Laboratories

Emma Canepa, MS, CCRP
Program Manager, Surgery
University of California, San Francisco

Stephanie Cherqui, Ph.D.
Professor, Department of Pediatrics
University of California, San Diego

Mark DeWitt, Ph.D.
Senior Scientist
Mammoth Biosciences

Jonathan Esensten, M.D, Ph.D.
Director, Advanced Biotherapy Center
Sheba Medical Center, Tel Hashomer, Israel

Petros Giannikopoulos, M.D.
Director, IGI Interventional Genomics Unit & IGI Clinical Laboratory
Innovative Genomics Institute
Assistant Adjunct Professor
University of California, San Francisco

Deborah Gouveia
Senior Vice President, Development Operations
EveryONE Medicines

Michelle Hermiston. M.D., Ph.D.
Professor of Pediatrics
University of California, San Francisco

Matthew Kan, M.D., Ph.D.
Assistant Adjunct Professor of Pediatrics
University of California, San Francisco

Billie Lianoglou, MS, LCGC
Genetic Counselor
University of California, San Francisco

Sharon O'Hara, DrPH, MPH, MS
Lecturer
University of California, Berkeley

Krishanu Saha, Ph.D.
Associate Professor
Director, NIH CRISPR Vision Program
Testbed Lead, NSF Center for Cell Manufacturing Technologies
University of Wisconsin-Madison

Blythe Sather, Ph.D.
Vice President, Head of Research
Tune Therapeutics

Brian Shy, M.D., Ph.D.
Assistant Professor of Laboratory Medicine
University of California, San Francisco

Rich Stoner, Ph.D.
Chief Executive Officer
Exthymic

Fyodor Urnov, Ph.D.
Professor of Molecular Therapeutics
University of California, Berkeley
Director of Technology & Translation
Innovative Genomics Institute

Mark Walters, M.D.
Professor of Pediatrics
University of California, San Francisco

Ross Wilson, Ph.D.
Director of Therapeutic Delivery
Innovative Genomics Institute

Winston Yan, M.D., Ph.D.
Founding President, N=1 Collaborative
Co-Founder & Head of Translational Strategy, Arbor Biotechnologies

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