Barriers and Solutions to Developing Future Therapies for Pulmonary Hypertension

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Pulmonary hypertension (PH) and its subset, pulmonary arterial hypertension (PAH), are rare diseases with a significant unmet need. Between the 1980s and 2010s, the 5-year survival rate for PAH after diagnosis improved from 34% to 65%,[1,2] but remains unacceptably low. Since the introduction of vasodilator therapy,[3,4] important advances have been made in the understanding of the disease pathophysiology and development of targeted therapies. There are now 14 US Food and Drug Administration (FDA)-approved therapies that target 3 distinct pathways that contribute to PAH, and additional therapeutic targets are currently under investigation in phase 1, 2, and 3 clinical trials.[5] However, there have been major challenges in PH medication development to date, including: 1) only one medication approved for pediatric PAH; 2) focusing on vasodilator therapy rather than targeting the underlying pathogenesis of the disease; 3) no medications approved for PH World Health Organization (WHO) Groups 2, 3, and 5; and 4) several recent high-profile clinical failures after promising preclinical studies.

The focus and goal of the PH research community should be directed at identifying new options and solutions for patients. The field must ensure that the approaches used for clinical trials to develop orphan drugs maximize the scarce resources available for recruiting subjects, and are directed toward making safe and effective therapies available in a timely manner. Therefore, there is a critical need to coordinate and harmonize innovative approaches within the field, including strengthening translational research to deliver promising candidates and optimize the designs, endpoints, and biomarkers to conduct safe and efficient clinical trials.

WHO ARE THE STAKEHOLDERS IN PH DRUG DEVELOPMENT?

There are numerous participants in the development of new medications for PH, including industry, academia, patient advocacy groups, and federal agencies. Several of these perspectives were discussed at the 2018 Pulmonary Hypertension Association (PHA) International Conference by Dr Ramona Doyle of the University of California San Francisco, Dr Norman Stockbridge of the FDA, and Dr Sagar Lonial of Emory University. Dr Lonial recently published a summary on the experience of the multiple myeloma field (Figure 1).

In PH, academia includes physicians, scientists, nurses, research coordinators, and others who directly interact with patients with PH and/or who research PH-related topics at a basic, translational, or clinical level. Academic physicians and researchers have access to both patients and clinical data and can independently or through collaborations with industry perform single or multicenter observational or interventional studies. Some clinical trials are organized by academicians and are often focused on repurposed medications that are no longer on patent and thus less financially viable, as there will generally be cheaper versions of generics available on the market. Through the clinic contacts, biospecimens can be collected and analyzed to identify novel pathways that contribute to disease mechanisms, and thereby identify therapeutic interventions.

Industry groups have available resources to identify and optimize potential therapeutic agents through approaches including high-throughput screening and small-molecule optimization. They have expertise in scaling up production of medications to test in clinical trials and ultimately selling the medications after approval. Industry offers the capability to introduce a novel compound through preclinical studies, pharmacologic characterization, and phase 1, 2, and 3 clinical trials: in particular, phase 3 clinical trials of new PH compounds—which typically involve hundreds of patients across many international centers—can cost hundreds of millions of dollars to complete. Industry has the capacity to complete these studies with high fidelity, linking with investors willing to fund the development of promising compounds. Industry also includes people with expertise in obtaining regulatory approval of medications after clinical trials are completed.

Patient advocacy groups, such as PHA, bring together patients with a shared disease experience. These groups have the ability to set priorities for the development of new medications, identifying aspects of the disease that are most troubling and should be

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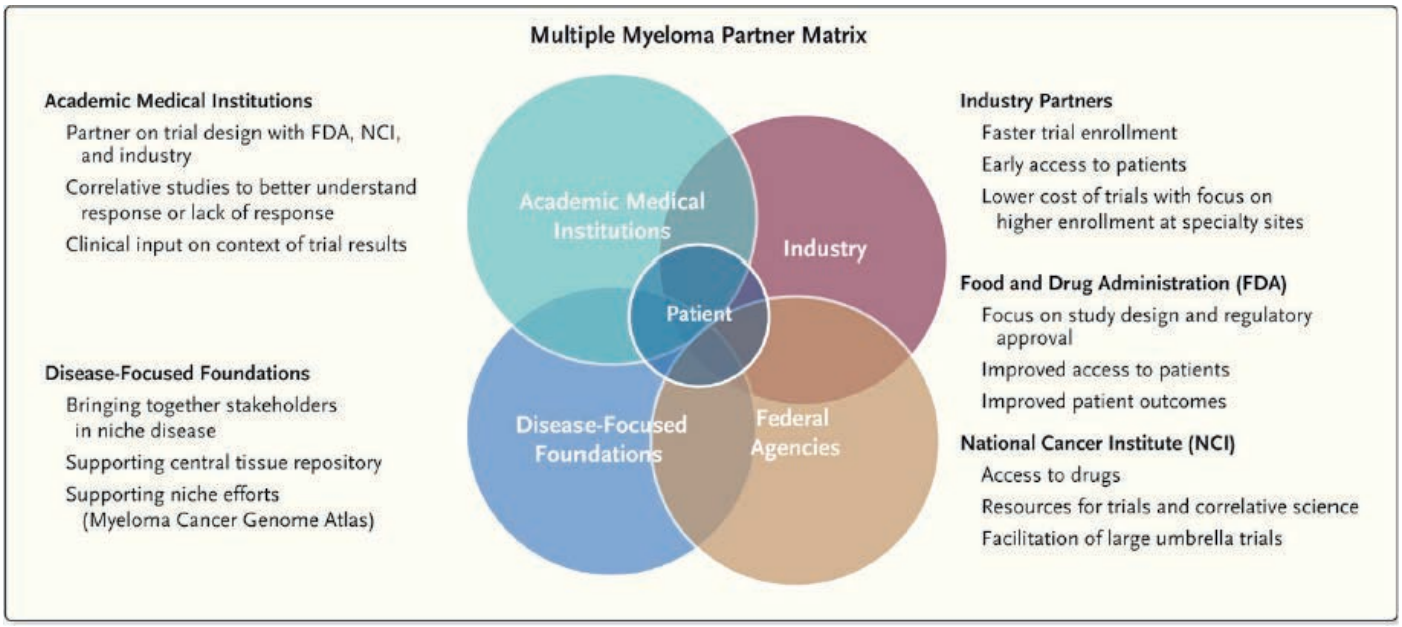

Figure 1: Example of a collaborative matrix from the experience of the multiple myeloma community in developing new medications. From Ramsey BW, Nepom GT, Lonial S. Academic, Foundation, and Industry Collaboration in Finding New Therapies. *N Engl J Med*. 2017;376(18):1762-1769. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

prioritized, or which medication side effects are acceptable or unacceptable. Patient advocacy groups can directly communicate with other groups, like academia or industry. They can also directly determine agendas through the creation of foundations to support research and grants specifically, particularly to academia, which may be targeted to specific identified priorities. Patient advocacy groups can have academic and industry councils, as the PHA has with the Scientific Leadership Council (SLC) and the Corporate Committee.

Federal agencies involved in PH medication development include the Office for Human Research Protections (within the Department of Health and Human Services), which confirms the safe conduct of clinical trials; the FDA, which aims to ensure that medications are safe and effective; and the National Institutes of Health, which provides grant funding for preclinical and clinical trials. Efficacy at the FDA is broadly defined as improving how patients feel or function and increasing longevity. In PH, the 6-minute walk distance (6MWD) has been a long-standing clinical trial outcome as an indicator of patient function.

These groups are all working to develop new treatments for PH and are aligned in this shared goal but offer different perspectives on the same topic. All must collaborate to identify and advance new medications for treating PH through the stages of development. We must optimize these interactions to accelerate drug discovery, reduce costs, and improve the lives of patients with PH.

The PH field will benefit from a forum to promote stronger partnerships between academia, industry, patient advocacy groups, and federal agencies.

We propose the optimal approach to achieving such a goal: stimulate early and continuous dialogue on innovative clinical and regulatory development strategies via a forum with open discussion between industry, academics, patient advocacy groups, and regulators worldwide. This will foster and facilitate the collection of thoughts and experiences on relevant information through organized workshops; to discuss, harmonize, and implement these innovative solutions in a productive and noncompetitive environment.

An example of such a collaborative organization is the Multiple Myeloma Research Consortium (MMRC) (provided by Dr Lonial), the goal of which is to identify new medications for treating multiple myeloma. There is not presently a direct equivalent of the MMRC in the PH community, although there are some individual components such as the SLC within the PHA and the Pulmonary Hypertension Breakthrough Initiative (PHBI), which facilitates multicenter tissue accrual and distribution. The MMRC started as a component of the Multiple Myeloma Research Foundation (MMRF), a patient advocacy group, initially with just 4 sites but now expanded to more than 20. The MMRC integrates multiple functions, including those currently in the PH field: determining priorities for the field (such as by the PHA and SLC) and maintaining a shared tissue bank for distribution to investigators (such as by the PHBI). However, it also includes functions not present in the PH field, like facilitating clinical trial development and implementation by working with industry partners to improve access to patients and simplify the conduct of trials by working with a single organization (see additional characteristics of the MMRC in Figure 3 below).

Current phase 2 and 3 PH clinical trial designs and study endpoints are not conducive to this rare disease.

Randomized controlled trials are the gold standard for traditional drug

development and regulatory approvals globally. These studies generally rely on a broad patient population and large sample size with clinical outcome–driven endpoints. These potentially large clinical trials are, however, not conducive to rare diseases where there are few patients and limited resources available for recruiting subjects, requiring many years to complete enrollment. The traditional approach of conducting small phase 2 studies followed by large phase 3 designs, however, has been and is still being attempted to develop drugs in PH.

Phase 2 dose-ranging studies in rare diseases are generally underpopulated due to limited availability of subjects, and unfortunately may be terminated early for this reason. This challenge is amplified if a primary endpoint does not directly correlate to a clinical outcome, or if it is not acceptable for regulatory approval. Moreover, a successful early exploratory phase 2 study does not guarantee success in phase 3 trials. However, it is critical to clarify the optimal dose and dosing interval in phase 2 clinical trials before proceeding to larger phase 3 studies, as was seen with twice-daily dosing of oral treprostinil in the original FREEDOM trials as compared to 3 times daily dosing in the recently reported and successful (by preliminary results) FREEDOM-EV study.[7]

INNOVATIVE METHODOLOGIES FOR CLINICAL TRIAL DESIGN WILL ACCELERATE PH DRUG DISCOVERY

Adaptive designs and/or open-label studies to identify the most responsive subjects and innovative approaches to selecting a safe and effective dose should be considered in phase 2 trials.

A well-conducted phase 2 trial should be followed by one adequately powered phase 3 study in an "enriched population" that can provide a sufficient level of assurance to identify a safe and effective dose for regulatory approval and early access to patients. Surrogate markers, biomarkers, or patient-reported endpoints obtained from this enriched population should be considered acceptable to grant at least a conditional approval via an accelerated regulatory review pathway. Once on the market, post-approval case registry studies can be conducted to advance the understanding of the benefit vs risk assessment combined with clinical experiences.

More robust post-approval monitoring, such as phase 4 clinical trials and registries, can assist in the approval process.

The treatment and care of patients with rare diseases like PAH are generally confined to a smaller group of highly specialized physicians. These physicians effectively communicate, share, and compare their clinical experiences within the health care community, and continually monitor the safe and effective use of these medications. A greater reliance on this post-approval clinical monitoring should be supported by organizations like PHA through interactive and collaborative discussions.

Optimization of discussion with regulators and regulatory approaches.

Adaptive licensing is a pilot of the European Medicines Agency (EMA) to improve patient access to new medicines by approval in stages. The intent is to allow for early and progressive patient access to new medications. The FDA has a similar Breakthrough Therapy Designation program. Parallel to the EMA's adaptive licensing pilot, the organization's innovative Medicines Adaptive Pathway to Patients (MAPPs) aims to foster access to beneficial treatments for patients with unmet needs in a sustainable fashion. Regulatory discussions need to occur early in development, to ensure that the most appropriate design for a specific study is implemented. The FDA's Special Protocol Assessment (which states that an uncompleted phase 3 trial's design and endpoints are acceptable for FDA approval), the EMA's Scientific Advice Working Party, and the traditional regulatory phase gated meetings are recommended to ensure smooth development and regulatory approval. However, all parties (industry, academia, patient advocacy groups, and regulators) must embrace the common goal of distributing medicines to critically ill subjects in the rare disease space as early as possible with the best utilization of the scarce resources available. Use of novel clinical trial designs, as proposed here, should be discussed with regulatory agencies for agreement on the most acceptable approach.

Adaptive randomized designs.

These include covariate-adaptive and response-adaptive randomization, or a combination of these 2. Covariate-adaptive design ensures the balance of key subject characteristics between different treatment groups, even when the sample size is relatively small. Response-adaptive design favors treatment groups with a better chance of success and increases the probability of patients being randomized to that group. Bayesian design integrates data from previous trials to create a larger evidence base.

Crossover design.

Crossover design, in which participants receive 2 or more treatments in random order and act as their own controls, must consider washout time and necessitates that the disease and patients' health status remain stable throughout the study. But this type of design is extremely valuable in rare diseases as it can reduce the number of subjects and can be used to compare 2 active treatments to either demonstrate superiority of or noninferiority of treatment. An example of such an adaptive crossover study design is the phase 3 study of treprostinil in patients with PH due to chronic obstructive pulmonary disease (COPD) (Figure 2). This ongoing study will use an assessment of retention prior to the crossover design phase of the study.

Randomized withdrawal designs.

In a randomized withdrawal design, patients receive a test treatment for a specified time (the enrichment phase) and those who demonstrate a favorable response (referred to as responders) are randomized to continue on the same treatment or to receive placebo. Clinically relevant differences in the group receiving treatment vs placebo would validate the effect seen in the enrichment phase. An early escape design gives patients the option to opt out or "escape" their assigned treatment if there

is no change or worsening of outcomes while on the placebo and encourages continued treatment in those who demonstrate a response. This design might improve outcome efficiency and statistical power, while limiting patients' exposure to ineffective treatments. If implemented in an enriched population, these studies can be extremely powerful in validating that the treatment effects are real and valid.

There is precedence of a randomized withdrawal design in a PAH population in a study on the transition of patients stable on intravenous (IV) epoprostenol therapy (an enriched population) who were randomized to transition to subcutaneous (SC) treprostinil or placebo in a 2:1 fashion and were monitored for clinical deterioration.[8] Patients with clinical deterioration were quickly transitioned back to IV epoprostenol. The study demonstrated, within a relatively short duration and with only 22 patients enrolled, that 7 of 8 subjects (88%) withdrawn to placebo had clinical deterioration compared to only 1 of 14 (7%) withdrawn to SC treprostinil (P=0.00023 based on treatment comparison of time to deterioration).[8]

The concept of running these types of enriched withdrawal studies as an efficient and ethical way of demonstrating persistent effects was introduced at the FDA's Center for Drug Evaluation and Research (CDER) Enrichment Webinar in March 2013 by Dr Robert J. Temple, and was presented as an option for studies in PAH subjects in July 2016 by Dr Ellis F. Unger at the Pulmonary Vascular Research Institute (PVRI) PAH meeting. Randomized withdrawal studies have been considered an acceptable study design for phase 3 studies by the FDA, with recent general acceptance at the 2018 PH World Congress in Nice. However, challenges exist in clinicians' adoption and patient and caregiver acceptance and education. There needs to be clinical equipoise in the specific question that will be tested, but approaches to patient/caregiver outreach efforts are also needed to better understand key reservations in adoption of randomized withdrawal studies.

Figure 2: Design of the ongoing study "A Phase 3 Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients With PH Due to COPD" by United Therapeutics (ClinicalTrials.gov identifier NCT03496623).

RETHINKING ENDPOINTS IN PH CLINICAL TRIALS

Traditional drug development with large sample sizes with clinical outcome–driven endpoints (ie, morbidity and mortality or time to clinical worsening) is not practical for rare diseases like PAH in adult and pediatric populations. The 6MWD, with all its limitations, has to date supported regulatory approval for the majority of PAH treatment options. This is a marker of function but is not ideal in predicting clinical outcomes. Dr Norman Stockbridge commented at the PHA meeting in Orlando in July 2018 that the FDA has been lenient in allowing use of this endpoint.

The FDA, academia, and industry should raise the bar and choose a more discerning, validated, and clinically meaningful endpoint. Although there are 14 treatment options available, the characteristics of the disease and the key factors that manage or predict disease progression and survival are unclear. The 6MWD may no longer be able to detect any additional benefit over and above baseline therapy, especially if subjects are already on 2 or more PAH medications. Furthermore, the 6MWD is not very predictive of clinical outcomes or prognosis in both short-term and long-term trials, and there is no prospectively validated goal distance (only retrospective: 33 m[9]), which may result in statistically significant but not clinically significant outcomes. This leaves clinicians and regulators to make difficult choices that are often unguided or based on clinical experience, due to the limitations of relying on the limited clinical trial outcomes alone. Therefore, we should explore biomarkers, composite endpoints, patient-reported outcomes, and risk scores that are aimed at treating early stages of disease and advancing toward a cure rather than symptomatic benefits alone.

We need to learn from the experience and data generated from the 14 PAH treatment options and develop a disease model for both adult and pediatric PAH that provides insight into the defining characteristics and attributes of the disease with regard to its progression, severity, and risk factors. We could utilize a database of all PAH-related clinical trials submitted to date to collectively amplify and elucidate the biomarkers and endpoints used as secondary or exploratory endpoints to provide relevant evidence of effectiveness. Using machine learning, this could be used to derive a collection of submodels, better predict trial outcomes, and inform and extrapolate clinical trial designs and endpoints. This could be developed further in collaboration with FDA, academia, industry, and patient advocacy groups. Participation could be expanded to include other databases being developed by academia and other regulatory groups outside the US.

The probability of success is increased by clearer linking of disease mechanisms with individual phenotypes.

The PH field has achieved some success in identifying the 3 standard classes of medications in current use but has faced recent difficulty in expanding studies to novel targets. Recent unsuccessful clinical studies in PAH include imatinib, ubinemex, ASK-1 inhibition, and inhaled nitric oxide. The development of all of these medications was grounded in solid preclinical data,[10-13] elevating existing concerns about the reliability of preclinical models in widespread use to predict subsequent clinical success. This has introduced the idea that medications should show benefit in at least 2 preclinical models: the theory being

that this would increase the likelihood of subsequent success. Unfortunately, using multiple orthogonal models has not been clearly demonstrated as successful.

A major concern as the field moves toward more precise targeting of pathogenic signaling pathways is that the heterogeneity of clinical disease is not reflected by the homogeneity of inbred animals. We need to identify the patients that have increased likelihood of responding to the proposed therapy, an overall approach that falls under the umbrella term of "personalized medicine." In this regard, the PH field is at a disadvantage compared to the oncology field, where sampling the tissue and identification of genetic abnormalities is the norm, and treatment approaches can be tailored to each patient. In contrast, in PH lung specimens are not obtained routinely, largely because the disease itself places patients at increased risk from the biopsy procedure. Furthermore, there may be heterogeneity in the pathophysiology present between lesions within a single patient. It is also unclear how well peripheral blood specimens, inducible pluripotent stem cells, and even peripheral blood outgrowth endothelial cells[14] are reflective of the pathology present in the lung vasculature.

The PH field needs to move toward clearer linking of pathophysiology with treatment approaches. Identification of biomarkers that can be more readily assessed, such as through imaging or peripheral blood analysis, and that have real mechanistic relevance to disease pathophysiology will be critical. An example of this approach would be predictively enriching patients in clinical trials that increase bone morphogenetic protein receptor II (*BMPR2*) pathway signaling by specifically enrolling those with known *BMPR2* mutations on genotyping, or who have evidence of suppressed *BMPR2* expression or downstream signaling on peripheral blood specimens. These are the patients that are more likely to respond to a biologic effect of increasing *BMPR2* signaling, whereas patients with relatively normal *BMPR2* signaling are less likely to benefit from this intervention.

Table 1. Examples of barriers encountered and potential solutions to overcoming the barriers in PH.

Barriers Encountered in PH	Potential Solutions to Overcoming Barriers in PH
Limited clinical trial enrollment due to small patient population	• Identify and use endpoints that maximize statistical power for a limited number of subjects • Use an adaptive trial design to quickly move on from compounds that do not look promising • Organization of trials to share a single placebo group for multiple simultaneous trials, to maximize the number of patients receiving active treatment • Encouragement of factorial trial design to test multiple compounds simultaneously, particularly those that share a common targeted pathway • Support public awareness of both PH as well as the need to develop new treatments for PH
Success in preclinical studies do not predict clinical trial success	• Development of large animal models that may have a pathophysiology closer to human disease • Ensuring that preclinical studies are anchored by clinical analysis including biospecimens • More rigorous approaches to preclinical studies[15]
Limited access to human biospecimens to validate preclinical studies	• Use a consortium to support clinical trials, which links the collection of biospecimens to well-phenotyped subjects participating in the clinical studies • Encourage PH patients to donate specimens at the time of transplant or death, to support future research • Standardization of protocols to ensure high-quality sampling, phenotyping, and maintenance of biospecimens • Encourage sharing of specimens between centers, and with a diverse array of researchers such as with a research consortium
Expensive infrastructure for drug development, resulting in high costs of new approved agents to target this disease	• Organization of centers to increase the volume of patients accessible to trials without duplicating resources and reinventing approaches • Encourage repurposing of existing medications by supporting investigator-initiated studies • Encouragement of cost-benefit analysis studies
Need to develop treatments for pediatric PH patients	• Encourage pediatric PH drug development and study medications approved for adults in pediatric populations • Identify shared endpoints that are relevant in pediatric PH • Use a pediatric-specific research consortium to facilitate trials in pediatric patients with PH

SUMMARY OF IDENTIFIED BARRIERS AND POTENTIAL SOLUTIONS TO PH THERAPY DEVELOPMENT

In a recent editorial in the *New England Journal of Medicine*, authors from the cystic fibrosis, multiple myeloma, and type 1 diabetes mellitus fields listed their fields' respective barriers and the solutions by which they overcame these barriers (Figure 3).[6] Many similar and even identical barriers are also present in the PH field: examples of these barriers and potential solutions are listed in Table 1.

CONCLUSION

Despite the challenges unique to the rare disease of PH, remarkable progress has been made in just a few decades in the understanding of this disease, development of therapies, and impact on patients' quality of life and survival. There is great promise in the ongoing collaborations between academia, industry, patient advocacy groups, and federal agencies. Systematic identification of barriers and solutions can accelerate the pace of drug discovery. We propose that PH therapy development will ideally proceed in a forum where open, free,

Table 1. Approaches to Partnerships among Researchers, Patient Groups, and Industry in Three Diseases.

Disease and Barriers Encountered	Solutions to Overcome Barriers
Cystic fibrosis	
Lack of industry partners	In 1999, the Cystic Fibrosis Foundation (CFF) adopted a "venture philanthropy" approach to share costs of early drug development.
Lack of clinical-trial expertise and infrastructure to conduct clinical trials	The CFF established the Therapeutic Development Program and clinical-trial networks in the United States, which now has 82 sites; the European Cystic Fibrosis Society Clinical Trial Network hosts 43 sites in 15 countries.
Limited efficacy outcome measures in young and minimally affected patients	Partner-supported efforts developed better physiological techniques (e.g., multiple breath washout) and imaging techniques (e.g., magnetic resonance imaging) to identify early lung disease.
Lack of patient and family input in clinical research process	CFF established patient and family advisory groups at care centers worldwide and developed initiatives — such as "I Am the Key" (www.cff.org/Research/Developing-New-Treatments/Clinical-Trials/I-Am-the-Key/) — to help educate patients and their families about clinical research and participation in clinical trials.
Lack of attention to the expectations of patients and their families	The CFF developed Web-based educational programs for patients and their families at www.cff.org.
Limited clinical-trial enrollment because of small patient population	The CFF formed a partnership with the Food and Drug Administration (FDA) to develop more efficient study designs that minimize study populations while ensuring patient safety; the Therapeutics Development Network (TDN) created a process for international study review and prioritization, in which research staff and patient representatives ensure that patients have access to the most effective trials.
Suboptimal study conduct that places patients at risk and that has a negative effect on drug development	The CFF established a continuous, transparent assessment of study metrics at all TDN and Clinical Trials Network sites, including times for study initiation and enrollment and deviations from protocol; the foundation also established a data and safety monitoring board to review all TDN therapeutic trials.
Expensive infrastructure for the drug-development and clinical-trial networks, resulting in high drug costs	Drug manufacturers adopted prices that reflect the clinical benefit and size of the market relative to development costs (e.g., approximately $300,000 annually for ivacaftor), with drug revenues fueling further investment in the development of multiple new treatments; eligible patients can access approved drugs through public and private programs that provide copayment assistance for insured patients and free medication for the uninsured.
Multiple myeloma	
Lack of collaboration among academic groups with expertise in clinical management and conduct of clinical trials	In 2004, the Multiple Myeloma Research Consortium (MMRC) was established as an outgrowth of the Multiple Myeloma Research Foundation; the MMRC now has 22 sites.
Lack of a centralized, annotated tissue repository necessary for preclinical and correlative studies	The MMRC established a central tissue bank that now contains more than 3400 samples, with clinical follow-up leading to the genome sequencing of myeloma samples and other correlative study opportunities.
Need for more validated clinical targets developed from correlative studies	The MMRC developed clinical targets with support from trials conducted by the cooperative groups, including the Eastern Cooperative Oncology Group, the Southwest Oncology Group, and the Cancer and Leukemia Group B (now called the Alliance).
Prolonged start-up times for multicenter trials	All the academic centers in the MMRC agreed on a standard contract that leads to a 30% reduction in start time for trials conducted through the consortium.
Lack of communication among partners with the FDA about the most effective study designs and end points	The MMRC established a team-based approach with partners and the FDA to design more efficient study protocols and speed the development process.
Lack of common area for discussion and team-based global advances in this disease	The International Myeloma Foundation and the International Myeloma Working Group established global collaborations on guidelines.
High cost of sustaining infrastructure for therapeutic development	Drug manufacturers continue to seek a sustainable funding model for drug development.
Rising costs of new approved agents to target this disease	The MMRC and its partners encouraged a design for new trials with end points that do not lead to continuous therapy regimens; studies must show substantial clinical benefit to support drug approval and justify the additional costs to patients.
Type 1 diabetes mellitus	
Lack of industry initiatives for immunologic therapies for this disease	In the 1990s, groups that are sponsored by the National Institutes of Health (NIH) — particularly, the Immune Tolerance Network (ITN) and T1D TrialNet — began to design, fund, and conduct proof-of-concept clinical trials of agents from partner pharmaceutical companies to catalyze clinical development.
Limited public awareness of this disease as an immunologic condition, distinct from type 2 diabetes, with opportunities for different therapies	Private nonprofit organizations (e.g., the Juvenile Diabetes Research Foundation, the Helmsley Charitable Trust, and the American Diabetes Association) began to play an important role in public education and in bringing the experiences of patients and their families into the therapeutic development process.
Lack of sufficiently useful measures of efficacy as clinical end points	Academic networks and the NIH sponsored studies to improve the measurement of cellular, metabolic, and immunologic correlates of clinical benefit.
Need for combination therapy owing to the immunologic complexity in the disease mechanism	Drug manufacturers began to provide access to investigational drugs for use in T1D trials.
Requirement for thoughtful regulatory oversight for the testing of new drugs in children (the preferred target group in this disease)	Advocacy groups and T1D research networks began to push for changes in the policies of regulatory agencies that require proof of therapeutic benefit in adults before testing in children.
Need for data and sample sharing	Efforts by research networks and the NIH led to the development of accessible repositories and data portals, such as the ITN TrialShare resource at www.itntrialshare.org.
Higher costs for short-term biologic therapies than for insulin-replacement therapy	Advocacy groups and their partners began to encourage a cost–benefit analysis that includes financial savings associated with disease remission and the avoidance of long-term complications of diabetes.

Figure 3: Barriers and solutions identified by the cystic fibrosis, multiple myeloma, and type 1 diabetes mellitus communities in the development of new medications. From Ramsey BW, Nepom GT, Lonial S. Academic, Foundation, and Industry Collaboration in Finding New Therapies. *N Engl J Med*. 2017;376(18):1762-1769. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

and continuous dialogue between all stakeholders can take place, facilitating the sharing of innovative clinical and regulatory development strategies in a productive and noncompetitive environment.

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