

ARTICLE

Application of a Dynamic Map for Learning, Communicating, Navigating, and Improving Therapeutic Development

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Drug discovery and development is commonly schematized as a “pipeline,” and, although appreciated by drug developers to be a useful oversimplification, this cartology may perpetuate inaccurate notions of straightforwardness and is of minimal utility for process engineering to improve efficiency. To create a more granular schema, a group of drug developers, researchers, patient advocates, and regulators developed a crowdsourced atlas of the steps involved in translating basic discoveries into health interventions, annotated with the steps that are particularly prone to difficulty or failure. This Drug Discovery, Development, and Deployment Map (4DM), provides a network view of the process, which will be useful for communication and education to those new to the field, orientation and navigation of individual projects, and prioritization of technology development and re-engineering endeavors to improve efficiency and effectiveness. The 4DM is freely available for utilization, modification, and further development by stakeholders across the translational ecosystem.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Developing therapeutics is not a linear pathway, yet this process is often represented by the unidirectional “chevron” map, which oversimplifies and overlooks the multidimensional integration of activity between different steps. This linear pathway, commonly described as a “pipeline,” is a misnomer that is inaccurate, misleading, and perpetuates unrealistic expectations among scientists, healthcare professionals, policy makers, and the public.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ Standardizing and bringing clarity to this complex network could help to set a vocabulary and allow more fluid dialogue among ecosystem participants to encourage further innovation.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The resulting 4DM facilitates ongoing discussion to help frame, map, and synergize ecosystem activities. Defining key terms, such as translational science and regulatory science, and locating complex activities within this landscape may help to articulate problem areas and provide opportunities to learn from local environments in which the system is efficient and well-integrated with other areas.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

✓ The 4DM provides a network view of this highly complex process that can be used as a tool to educate others and identify areas in greatest need for innovation.

Although the therapeutic development ecosystem is a dynamic network of activity, it is often represented by a linear “chevron” diagram (Figure 1). The experts view the chevron as a useful oversimplification, whereas nonexperts and those new to the field typically take the representation literally. The “pipeline” moniker is similarly misleading to the nonexpert, because it implies that drug development entails inevitably successful passage of material unchanged from start to finish limited only by time and gauge of the pipe. The lack of an accurate and commonly utilized representation of the therapeutic development process per-

petuates widespread public misperceptions¹ and impedes productive dialog about improving the process among scientists, healthcare professionals, policy makers, and the public. Baxter *et al.*¹ recently promulgated the idiosyncratic nature of the current state.^{1,2} Building on this and other efforts (e.g., refs. 3 and 4), a group of stakeholders from all parts of the therapeutic development ecosystem have crowdsourced a complete, accurate, and comprehensive diagram of the current drug development process, called the Drug Discovery, Development, and Deployment Map (4DM). We present distinct versions of the 4DM depicting small molecule

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Figure 1 Therapeutic development chevron diagram. Traditional chevron diagram representation of therapeutic development. Colors in this chevron correspond to the associated “neighborhoods” on the Drug Discovery, Development, and Deployment Map. FDA, US Food and Drug Administration.

development, biologics development, and the steps most prone to delay or failure. To facilitate understanding of the 4DM, we provide several case studies illustrating its utility. To maximize its current use and further development as a community resource, the 4DM is being made publicly available at <https://ncats.nih.gov/translation/maps> under a Creative Commons Attribution-ShareAlike 4.0 International (CC BY-SA version 4.0) license, and several directions for future development are explored.

METHODS

An “Action Collaborative” (collaborative) was established under the auspices of the Forum on Drug Discovery, Development, and Translation (the Forum) of the National Academies of Sciences, Engineering, and Medicine to create a map of the process of drug discovery, development, and deployment. The Forum provides a unique platform for dialogue and collaboration among thought leaders and stakeholders in government, academia, industry, foundations, and disease and patient advocacy with an interest in improving the system of drug discovery, development, and translation, and educating the policy community about issues in which biomedical science and policy intersect. Using the Navigating the Ecosystem of Translational Science (NETS) map^{1,2} and other published schema as a foundation, the Forum’s Collaborative members and additional experts (see Acknowledgments) engaged in an intense crowdsourcing process to identify and correctly order all steps in the development and deployment of a small molecule drug, group these steps into conceptual “neighborhoods” of activity, and indicate the feedback loops and connections among steps and neighborhoods. The same process was then followed to create an analogous map of biologics development. Methods used were primarily in person and virtual facilitated discussion.

To create versions of the maps that provided information on the differential difficulty of traversing the steps shown, 20 representatives of stakeholder groups that captured the full diversity of actors across the drug development spectrum participated in crowdsourcing sessions and were asked to indicate the three steps they and their organizations found particularly problematic with regard to time, resources, or success rate. The steps were indicated as dark red (receiving at least 35% of the votes), light red (receiving 20–35% of the votes), and yellow (receiving 10–20% of the votes) on the “traffic” version of the map, steps with few or no votes were left unannotated. Participants were explicitly asked to explore aspects of the map, whether in terms of priorities of level of difficulty, which differed according to the type of

organization (e.g., company, academic, or patient foundation); these can be conceptualized as “overlays” that provide constituency-selective perspectives on the map and directions for further development.

RESULTS

The 4DM provides an accurate, multiconstituency crowdsourced, freely available schema of the realities of therapeutic development, which will be useful for education, orientation, guidance, and process engineering. In presenting the drug development process in all its present complexity, the 4DM provides a template for efforts to reduce that complexity, or create mechanisms to overcome it with the goal of improving the pace and effectiveness of new drug development.

Creation of the 4DM by a crowdsourcing approach that included participants across the drug development spectrum was particularly effective in ensuring the accuracy of the map and incorporating viewpoints of many stakeholders simultaneously. Insights from participants about the critical differences between small molecule and biologic development led to the creation of distinct versions for small molecules⁵ and biologics, the latter using monoclonal antibodies as the representative modality (**Figure 2**). The major of the differences between the two maps are in neighborhoods (C) and (D), which diagrams therapeutic candidate identification and optimization, respectively. Compared with previous schemata,^{1,2} postmarketing activities (neighborhood G) now includes observations on safety, usage patterns, and effectiveness. A Medical landscape neighborhood (H) captures the increasingly critical issues of access and reimbursement. In the Clinical research and development neighborhood, (E) the critical importance of natural history studies, epidemiology, and patient input was emphasized. Finally, a target pharmacology and biomarker development neighborhood (B) was added, although it was recognized that biomarker development takes place over multiple stages of discovery and development rather than at a single time during the process.

With the maps complete, we realized that the 4DM would be much more useful if features could be added analogous to those in dynamic route-planning tools, such as Google Maps or Waze, which include features such as traffic, road conditions, tolls, and anticipated travel time. Therefore, we next crowdsourced the identification of steps in the 4DM that participants had found most problematic in time required, likelihood of failure, and/or cost. This exercise identified 18 steps felt to be most often burdensome; these are listed in **Table 1** in three levels of difficulty that mirror the dark red, light red,

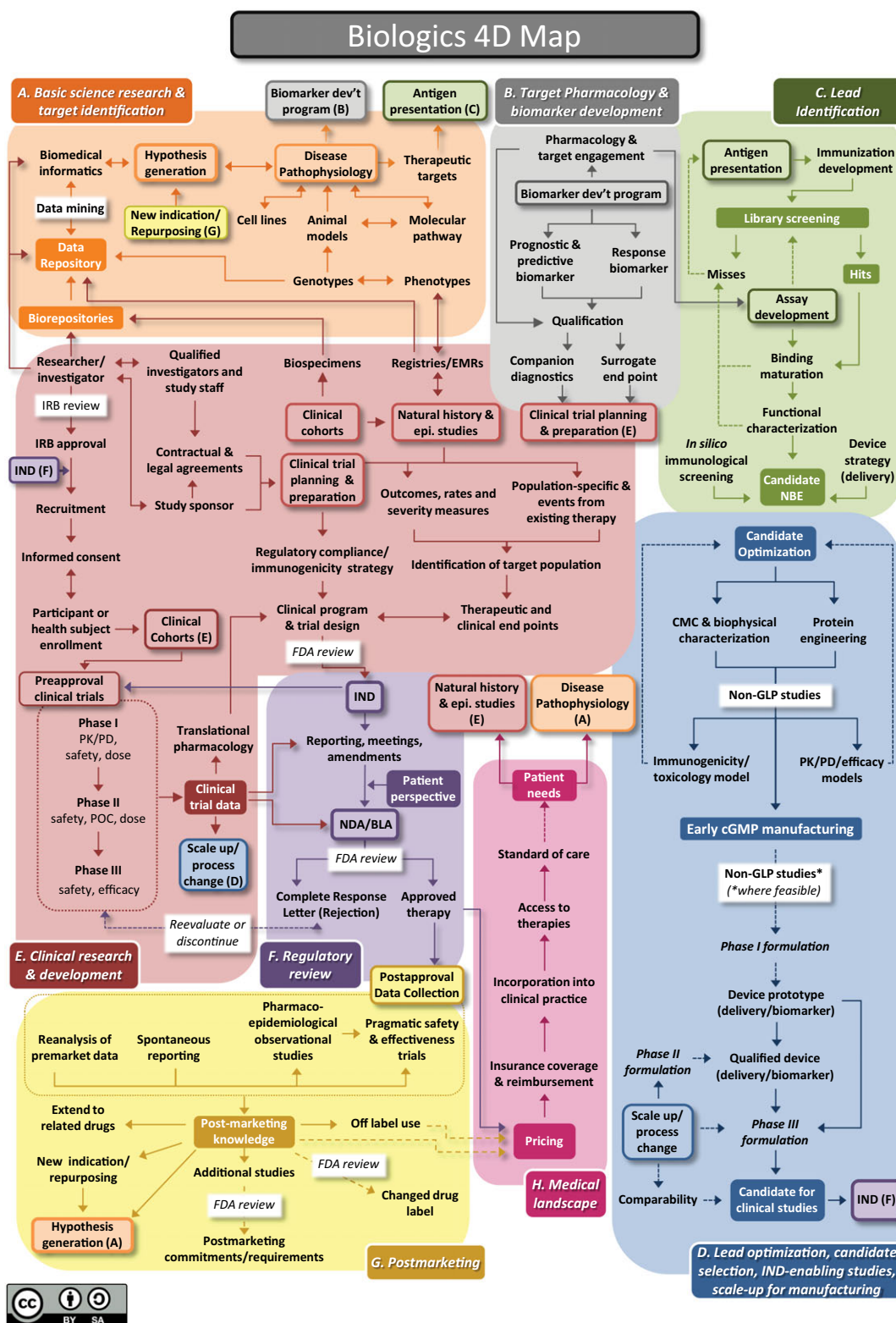


Figure 2 Drug Discovery, Development, and Deployment Map biologics map. The map comprises neighborhoods, each of which consists of a complex network of steps that interact with steps in other neighborhoods. The primary distinguishing steps between biologics and small molecules⁵ are in neighborhoods C (lead identification) and D (lead optimization). This file is licensed to the public under the Creative Commons Attribution-Share Alike 4.0 license, which allows use and adaptation as long as the user provides attribution and shares any adaptations back to the public under the same license, and is available to download at <https://ncats.nih.gov/translation/maps>. BLA, biologics license application; cGMP, current good manufacturing practice; GLP, good laboratory practices; IND, investigational new drug; IRB, institutional review board; NBE, new biological entities; NDA, new drug application; PK/PD, pharmacokinetic/pharmacodynamic.

Table 1 Heat map of bottlenecks identified by participants in the forum on Drug Discovery, Development, and Translation Action Collaborative

A. Basic science research and target identification	
Data mining (biomedical informatics, data repositories, biorepositories)	
Therapeutic targets	
B. Target pharmacology and biomarker development	
Biomarker development program: prognostic/predictive biomarkers	
Biomarker development program: response biomarkers	
Biomarker qualification: companion diagnostics, surrogate end points	
E. Clinical research and development	
IRB approval	
Recruitment and participant enrollment	
Contractual and legal agreements	
Collecting and using patient registries and EMRs	
Natural history and epidemiological studies (measurement of outcomes and severity, target population identification)	
Decision-making regarding therapeutic and clinical end points	
F. Regulatory review	
Incorporation of patient perspectives in NDA decision	
G. Postmarketing	
Pragmatic safety and efficacy trials (phase IV interventional)	
H. Medical landscape	
Insurance coverage and reimbursement	
Incorporation into clinical practice	
I. Layers	
Regulatory science	
Data sharing (clinical trial, failure data)	
FDA/regulatory review	
Business considerations/investment perspectives	
Rare disease/other accelerated pathways	
Patient perspectives	

EMRs, electronic medical records; FDA, US Food and Drug Administration; IRB, institutional review board; NDA, new drug application.

Bottlenecks identified by Action Collaborative participants during a 2016 survey were binned into related categories. Each bottleneck is colored according to the number of combined votes: from dark red, indicating a high number of votes, to yellow, for lower number of votes.

and yellow colors of a traffic map. Identification of these rate-limiting steps in the therapeutic development process will focus the systems engineering work of the Forum and other organizations on new approaches targeted to those steps most likely to produce overall improvement in productivity.

The 4DM can be used by therapeutic development organizations to retrospectively determine the reasons for translational failure, and prospectively anticipate likely difficult steps and ideally avoid them by devising mitigation strategies. For example, a user could examine how participant enrollment is affected by upstream inputs: the informed consent process, recruitment for a clinical trial, or institutional review board approval. Likewise, effects on downstream steps from partic-

ipant enrollment, clinical cohort formation, and preapproval clinical trials, could be evaluated. This analysis could identify actions that would lead to an improvement in participant enrollment and, thus, lead to more efficient and successful therapeutic development.

To illustrate use of the 4DM to retrospectively dissect project slowdown or failure, three case studies from Forum organizations are presented below. In these case studies, the text on the small molecule version of the map⁵ that corresponds to the action being described is indicated in [brackets]. For each case study, the relative ease and difficulty of completing each step is summarized in Figure 3.

CASE STUDY 1: DESIGNING CLINICAL TRIALS TO EVALUATE THERAPIES FOR POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD), the most common hereditary kidney disease, is characterized by progressive enlargement of the kidneys due to the formation and growth of cysts.⁶ Although there have been breakthroughs in the understanding of the pathophysiology underlying ADPKD, together with promising animal studies of potential drug therapy targets, the lack of acceptable clinical end points has stalled trials to establish the efficacy of a therapy intended to treat ADPKD [therapeutic and clinical end points].

Designing clinical trials for diseases that progress slowly—over decades—and with only small, sometimes indiscernible changes in standard measures is a challenge for drug developers [clinical trial planning and preparation].⁶ The clinical course of ADPKD starts at birth as cysts form, yet kidneys continue to function, as assessed by estimated glomerular filtration rate, until patients reach their 50s, at which time the irreversible fibrosis and distortion of kidneys results in end-stage renal disease. Biomarkers are essential for both selecting patients with ADPKD at high risk for a progressive decline in renal function for inclusion in interventional clinical trials (“prognostic biomarker”) and for evaluating efficacy (“surrogate biomarker”) [biomarker development program, qualification].

The Critical Path Institute’s Polycystic Kidney Disease Outcomes Consortium (PKDOC) identified total kidney volume (TKV) as a potential imaging biomarker for both patient enrichment in clinical trials and as a surrogate biomarker predicting decline of renal function [prognostic and predictive biomarker]. The consortium gathered longitudinal data from registries [registries/ electronic medical record (EMRs)] kept for decades at three research institutions as well as from two National Institutes of Health-sponsored observational studies [natural history and epidemiological studies]. These data sources used a variety of different imaging modalities (magnetic resonance imaging, computed tomography, and ultrasound), different methods/definitions, and different data-capture strategies. In order to pool data, first a Clinical Data Interchange Standards Consortium data standard was developed for ADPKD and then subject matter experts resolved methodologic differences between studies [data repository; data standards].⁷ Analysis of the pooled data revealed that baseline TKV, in combination with patient age and baseline estimated glomerular filtration rate, can accurately

	ADPKD/ PKDOC	FOP/ NCATS	NPY/ Biopharma
Animal models			
Assay Development			
Biomarker Development			
Biomarker Qualification			
Candidate compounds			
Clinical trial planning and preparation			
Compound libraries			
Data repository and Data standards			
Disease Pathophysiology			
Effectiveness and POC (nonclinical)			
Genotypes			
GLP preclinical studies			
HTS assay			
Hits, Unapproved compounds			
<i>In vitro</i> functional and safety screening			
<i>In vitro/in vivo</i> pharmacology			
IND			
Long term and reproductive toxicology			
Medicinal chemistry			
Therapeutic target			
Molecular pathways			
Natural history and epidemiological studies			
Participants or health subject enrollment			
Preapproval clinical trials, phase I			
Preapproval clinical trials, phase II			
Prognostic and predictive biomarker			
Recruitment			
Registries/EMRS			
Response biomarker			
Surrogate end points			
Therapeutic and clinical end points			

Figure 3 Heat map of relative ease and difficulty of steps in Drug Discovery, Development, and Deployment Map (4DM) case studies. The relative ease of the 4DM steps in different case-studies is shown in green to indicate relative ease and in magenta to indicate relative difficulty. ADPKD, autosomal dominant polycystic kidney disease; EMR, electronic medical record; FOP, fibrodysplasia ossificans progressiva; HTS, high-throughput screening; IND, investigational new drug; NCATS, National Center for Advancing Translational Sciences; NPY, neuropeptide Y; PKDOC, Polycystic Kidney Disease Outcomes Consortium.

predict the risk and cadence of disease progression in patients with ADPKD [prognostic and predictive biomarker].^{8,9} The US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) recently qualified TKV as a prognostic biomarker that can be used by drug developers in submissions of investigational new drug (IND) applications, new drug applications (NDAs), and biologics license applications without the relevant CDER review group reconsidering and reconfirming the suitability of the biomarker [biomarker qualification].¹⁰

Now the next phase can begin, in which companies conducting clinical trials of potential therapeutics can carry out TKV measurements during enrollment and conduct of the trial. If companies share that biomarker data with the consortium, PKDOC and the CDER review group can jointly deter-

mine whether there is sufficient data to support the use of TKV as a surrogate biomarker [surrogate end point].

CASE STUDY 2: THE DISCOVERY AND DEVELOPMENT OF DORSOMORPHIN DERIVATIVES FOR THE TREATMENT OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

In 2008, researchers at Massachusetts General Hospital and Harvard Medical School identified the first known small-molecule inhibitor of bone morphogenetic protein (BMP) signaling – dorsomorphin [Hits, unapproved compounds].¹¹ The BMP signaling family is a diverse subset of the transforming growth factor-beta superfamily, and dysregulation of this pathway is implicated in a variety of diseases, including primary pulmonary hypertension, hereditary hemorrhagic

telangiectasia syndrome, juvenile polyposis syndrome, and fibrodysplasia ossificans progressive (FOP).¹²

Dorsomorphin was identified through an *in vivo* phenotypic screen measuring the ability of compounds to perturb dorsoventral axis formation in zebrafish embryos [assay development].¹¹ The researchers selected this *in vivo* screen rather than a traditional high-throughput screening (HTS) screen in order to have the built-in means to assess specificity, efficacy, and toxicity in the context of whole live animals. In total, 7,570 compounds were screened, including synthetic screening compounds (Chembridge Corporation, 5,580 small molecules) and known bioactive compounds (Microsource Discovery Systems, 1,840 small molecules, and Sigma-Aldrich, 150 small molecules) [compound libraries].

Later that year, the researchers partnered with the Laboratory for Drug Discovery in Neurodegeneration at Brigham & Women's Hospital to complete a structure-activity relationship study to improve the inhibitory activity and metabolic stability of dorsomorphin (concentration of half inhibition = 0.5 μM) [*in vitro* functional and safety screening]. An optimized compound (LDN-193189) [candidate compounds] demonstrated higher potency of inhibition (concentration of half inhibition = 0.0049 μM), improved mouse liver microsome stability (terminal half-life = 82 min; intrinsic hepatic clearance = 16.9 $\mu\text{L}/\text{min}/\text{mg}$ protein), and moderate pharmacokinetic characteristics (plasma terminal half-life = 1.6 h) following intraperitoneal administration in mice [*in vitro/in vivo* pharmacology].¹³ Both microsomal stability and pharmacokinetic studies were performed by private contractors (Absorption Systems and Cyprotex, respectively).

The relationship between BMP receptor signaling and FOP was first demonstrated in 2006 by the discovery of a mutation involving a single amino acid substitution in the BMP type I receptor in a subset of five families exhibiting unambiguous features of FOP [genotypes].¹⁴ FOP is a rare, fatal, autosomal dominant genetic disorder marked by inappropriate growth of bone fragments within the muscles, ligaments, and other connective tissues, causing pain and progressive immobility.¹⁵ There are no disease-modifying therapies approved by the FDA. The researchers at Massachusetts General Hospital later showed that this activating mutation in the BMP receptor could be blocked *in vitro* with dorsomorphin treatment [molecular pathway, therapeutic targets]. However, these results were not able to be confirmed in an *in vivo* disease model as no suitable system reflecting the FOP phenotypes existed at the time [animal models].

By the end of 2008, an inducible mouse model of FOP expressing the mutant BMP receptor was created to test the derivatives of dorsomorphin identified through the structure-activity relationship study in an *in vivo* system [animal models].¹⁶ The lead molecule (LDN-193189) continued to show selective inhibition of BMP type I receptor signaling and amelioration of the FOP phenotype. Even with this promising result, the researchers noted that comprehensive and long-term toxicity studies in multiple species [long-term toxicology, reproductive toxicology, carcinogenesis, etc.], along with further drug refinement and optimization, would be necessary to ensure adequate safety and efficacy.

In 2011, the researchers at the Harvard-affiliated hospitals established a collaboration with the National Center for Advancing Translational Sciences (NCATS) Therapeutics for Rare and Neglected Diseases (TRND) program to utilize the expertise and resources of NCATS to advance the development of the dorsomorphin derivatives for the treatment of FOP and other diseases. TRND researchers are currently performing medicinal chemistry optimization to identify a derivative suitable for formal preclinical development [medicinal chemistry]. Once such a compound is identified, TRND researchers will conduct the necessary studies to support filing an IND with the FDA [GLP preclinical studies, IND].

Once a promising therapeutic candidate advances through preclinical testing and development, it faces two additional major scientific and operational hurdles. First, FOP is an ultra-rare disease with an estimated 3,000 affected individuals worldwide and ≈ 800 known patients. Simply identifying, recruiting, and retaining sufficient numbers of participants in a clinical trial for FOP is a very daunting task, one that has been made achievable through the efforts of the International FOP Association to create a global patient registry [participants or health subject enrollment, recruitment, clinical trial planning, and preparation].

Second, the most characteristic symptom of FOP is heterotopic ossification (spurious bone formation in connective tissues), which occurs sporadically and with up to 1–2 years between flare-ups [therapeutic and clinical end points]. Even though the disease was first identified in the 17th century, it remains extremely difficult to predict the onset, duration, or severity of a flare-up. Such prolonged and unpredictable timelines for measuring primary clinical end points makes it very challenging to assess the efficacy of drug treatment and incentivize private investment. Much more clinical information on the clinical complexity of FOP is needed: the progressive developmental stages and evolving time course of each lesion; the various anatomic sites involved in the disease process; the variable clinical course of flare-ups even in the same individual; and the different individual responses to symptomatic measures over time [natural history and epidemiological studies]. The FOP community has recognized the need for qualified pharmacodynamic biomarkers that could be used to measure the biological effects (*i.e.*, target engagement) of a drug *in vivo*, and, hence, its potential as a therapeutic, on a much shorter timescale [biomarker development and qualification]. Such a biomarker would be used to relate BMP signaling modulation by the drug in humans at the tolerated exposure to the level of modulation required for efficacy in the mouse model. Biomarkers could be used to determine whether a more lengthy and expensive clinical trial measuring flare-ups as the primary end point would be warranted, and whether additional medicinal chemistry lead optimization is likely to be necessary to provide a drug with an improved therapeutic index.

CASE STUDY 3: ASSESSING AN INEFFECTIVE DRUG TARGETING NEUROPEPTIDE Y

The neuropeptide Y (NPY) pathway is a well-validated target for obesity treatment. Evidence supporting the role of NPY in appetite and obesity includes genetic, pharmacology, neurophysiology, and neuroanatomy^{17,18} [therapeutic targets,

disease pathophysiology, and molecular pathway]. In an effort to explore the NPY hypothesis, MK-0557, a potent, selective, and orally available NPY5R antagonist,¹⁹ was discovered and developed [lead identification (neighborhood C) and lead optimization (neighborhood D)]. In nonclinical proof-of-concept (POC) animal model studies, MK-0557 reduced body weight gain and hyperphagia in rodent models with pharmacologically and diet-induced obesity [animal model, effectiveness, and POC]. An NPY5R-selective positron emission tomography (PET) ligand, [¹¹C] MK-0233,²⁰ was developed and qualified in rhesus monkeys as a target engagement biomarker [response biomarker].

In early phase I studies, MK-0557 was found to be generally well-tolerated in single and multiple doses, with no dose-limiting side effects [preapproval clinical trials, phase I]. PET studies with [¹¹C] MK-0233 were performed to characterize receptor occupancy study in healthy subjects and found essentially complete receptor occupancy associated with low, once-daily doses of MK-0557¹⁷ [response biomarker].

A clinical POC/dose-ranging study revealed that MK-0557 induces modest weight loss in obese individuals over 12 weeks and is generally safe and well tolerated. Because there was no evidence of a plateau in the weight loss over the 12-week treatment period, it was hypothesized that continued weight loss might be observed over a longer treatment period and, therefore, a long-term, 52-week study with MK-0557 was initiated [preapproval clinical trials, phase II]. In this multicenter, randomized, double-blind, placebo-controlled trial involving 1,661 overweight and obese patients, a statistically significant, but not clinically important, weight loss was observed at 52 weeks, demonstrating a lack of POC for NPY5R antagonism¹⁷ [therapeutic and clinical end points].

This case study illustrates the bottlenecks of: (i) target validation and (ii) effectiveness and POC in nonclinical research. Despite rigorous target validation, nonclinical POC did not translate into clinically meaningful weight loss. That said, this case study also illustrates the successful strategic use of biomarkers [response biomarkers] that facilitated decision-making for MK-0557. The combination of robust target engagement and well-qualified disease-related biomarkers tied the mechanism of action together with the nonclinical POC experiments, allowed the assessment of target engagement, facilitated dose focusing, and improved decision-making quality. In the case of the MK-0557 example, the combination of robust target engagement, with PET imaging, and a well-qualified disease-related biomarker of weight loss provided the definitive assessment that MK-0557 adequately engaged the target NPY5 receptors; however, it did not achieve sufficient, clinically meaningful weight loss. Without a target engagement biomarker, even in the absence of clinical POC, there would have been doubt about whether the mechanism or the molecule failed to establish clinical POC.

DISCUSSION

The 4DM provides a freely publicly available resource that will advance drug development in several ways. First, it provides a common framework for discussing the therapeutic development process as well as for educating those who

are new to it. This has become increasingly important as the longstanding contributors in therapeutic development (e.g., biopharmaceutical companies and regulators) have been joined by participants from other sectors (e.g., academic investigators, patients, and nonprofit disease advocacy organizations). Although this newly diverse ecosystem has brought fresh dynamism and innovation to the process, varying degrees of experience and underlying knowledge among the ecosystem's members has the potential to lead to misunderstandings that could delay realization of the common goal of developing novel, more effective therapeutics for patients in need. Therefore, we view the maps as both useful and timely documents for education, helping all stakeholders understand, and have a common conceptualization of the current state of the therapeutic development process.

Second, the 4DM will help to orient those in the midst of a step in the drug development process as to their progress and what is needed next, and will assist those planning to initiate a drug development project to anticipating needs and potential roadblocks. Both will, we hope, decrease occurrences of failure due to unanticipated resource requirements, and backtracking due to unanticipated requirements downstream in the process.

Third, the 4DM will help translational science organizations focus their systems engineering efforts on catalyzing improvements in the steps of the drug development process that are most limiting to translational efficiency.

There are several limitations of the 4DM in its current forms. Although our crowdsourcing methodology for creation of the maps and designation of bottlenecks gathered input from over 50 experts from a broad diversity of organizations involved in drug development, it was not a scientific sampling. Future development of the 4DM will benefit from additional input and viewpoints. The maps are currently not easily customizable to reflect (e.g., global regulatory requirements or pediatric development); they lack zoom in/out capacity with varying detail; they do not allow an individual user to locate the stage of a project on the map (i.e., they lack a "GPS" feature); and each step is represented essentially identically with no quantitation of required time or cost, which varies considerably across stages of the maps.

In order to facilitate as many organizations as possible using and further developing the 4DM for their own purposes, it is being made available under a Creative Commons Attribution-ShareAlike version 4.0 International (CC BY-SA 4.0) license and available to download at <https://ncats.nih.gov/translation/maps>. Several of the authors' organizations will make improvements in an ongoing basis and add features to the 4DM, making these available via their websites. Areas for future development may include:

Versions reflecting differential challenges among stakeholders

Crowdsourced development of the 4DM revealed that different stakeholders in the therapeutic development process experience many different roadblocks. For example, companies or academic institutions may find patient recruitment for clinical trials very challenging, but disease advocacy organizations may not. Therefore, creating "traffic" maps

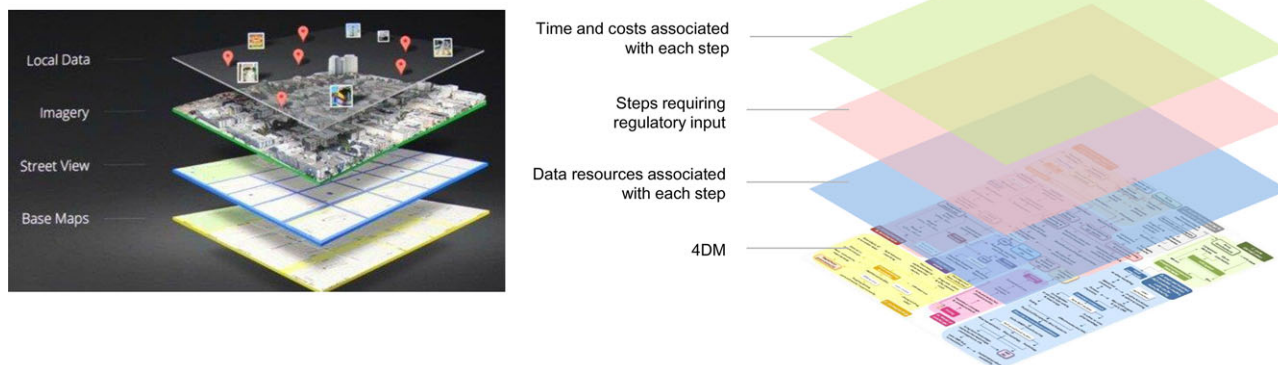


Figure 4 Potential “layers” of the Drug Discovery, Development, and Deployment Map (4DM). Similar to the layers found on Google Maps, we propose that the 4DM could contain layers of information that could be toggled on or off the user depending on the question being asked.

customized to sector will be important and the differences among them illuminating.

Engaging additional stakeholders

Further input from experts at large and small biopharmaceutical companies, academic institutions, patient and disease advocacy groups, government agencies, and others will enhance the utility of the maps.

Time and cost

Although the bottlenecks qualitatively indicate the degree of difficulty associated with a step, the 4DM does not currently capture the vastly different amount of time and cost of the steps required. Notating the map for unit and total cost and time, and expected success rate per iteration, will greatly increase its utility.

Magnification/feature toggling/layers

As with a traffic map, the 4DM will be most useful if users can view it with more or less detail depending on the question being asked. A layer, or perspective overlay, is similar to a Google Maps layer organized by geographical position (**Figure 4**). We envision layers, or features, such as time, cost, degree of difficulty, steps requiring regulatory input, sources of data or resources to assist with various steps, rare disease, and other stratified or accelerated pathways, manufacturing/supply considerations, areas impacted in a learning health system, such as the medical landscape and postmarketing neighborhoods, and other stakeholder-specific layers as being toggled on or off by the user.

Curation and access

All of these features, and the overall usability, of the 4DM will require creation of an electronic and mobile application version of the map, which will require access, maintenance, and curation. Members of the therapeutic development community will need to be able to add their perspectives and experiences to enrich the map via an open-source wiki mechanism, which is why we have licensed it under the Creative Commons license (see **Figure 2**).

Given the rapidly changing environment for drug development, and the increased focus on the process for medical and policy reasons, we hope that the 4DM will serve as a common reference for discussion, education, and communication, both for experts and for those who are interested in therapeutic development but have never personally experienced it. With this shared view of the drug development world, we look forward to the 4DM catalyzing efforts to improve the process, and thus advancing the universal goal of efficient and effective development of therapies for patients in need.

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1. Baxter, K. et al. An end to the myth: there is no drug development pipeline. *Sci. Transl. Med.* 5, 171cm1 (2013).
2. Navigating the Ecosystem of Translational Science. <http://www.geneticalliance.org/programs/biotrust/nets/fullview>.
3. The Drug Development Process. <https://www.fda.gov/ForPatients/Approvals/Drugs/default.htm>.

- Pritchard, J.F., Jurima-Romet, M., Reimer, M.L., Mortimer, E., Rolfe, B. & Cayen, M.N. Making better drugs: decision gates in non-clinical drug development. *Nat. Rev. Drug Discov.* **2**, 542–553 (2003).
- Wagner, J. et al. A dynamic map for learning, communicating, navigating, and improving therapeutic development. *Nat. Rev. Drug Disc.* (2017). <https://doi.org/10.1038/nrd.2017.217>
- Torres, V.E., Harris, P.C. & Pirson, Y. Autosomal dominant polycystic kidney disease. *Lancet.* **369**, 1287–1301 (2007).
- Perrone, R.D. et al. Therapeutic area data standards for autosomal dominant polycystic kidney disease: a report from the Polycystic Kidney Disease Outcomes Consortium (PKDOC). *Am. J. Kidney Dis.* **66**, 583–590 (2015).
- Perrone, R.D. et al. A drug development tool for trial enrichment in patients with autosomal dominant polycystic kidney disease. *Kidney Int. Rep.* **2**, 451–460 (2017).
- Perrone, R.D. et al. Total kidney volume is a prognostic biomarker of renal function decline and progression to end-stage renal disease in patients with autosomal dominant polycystic kidney disease. *Kidney Int. Rep.* **2**, 442–450 (2017).
- Food and Drug Administration. Qualification of biomarker—total kidney volume in studies for treatment of autosomal dominant polycystic kidney disease, guidance for industry. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf> (2016).
- Yu, P.B. et al. Dorsomorphin inhibits BMP signals required for embryogenesis and iron metabolism. *Nat. Chem. Biol.* **4**, 33–41 (2008).
- Salazar, V.S., Gamer, L.W. & Rosen, V. BMP signalling in skeletal development, disease and repair. *Nat. Rev. Endocrinol.* **12**, 203–221 (2016).
- Cuny, G.D. et al. Structure-activity relationship study of bone morphogenetic protein (BMP) signaling inhibitors. *Bioorg. Med. Chem. Lett.* **18**, 4388–4392 (2008).
- Kaplan, F.S., Fiori, J., de la Peña, L.S., Ahn, J., Billings, P.C. & Shore, E.M. Dysregulation of the BMP-4 signaling pathway in fibrodysplasia ossificans progressiva. *Ann. NY Acad. Sci.* **1068**, 54–65 (2006).
- Shore, E.M. & Kaplan, F.S. Insights from a rare genetic disorder of extra-skeletal bone formation, fibrodysplasia ossificans progressiva (FOP). *Bone* **43**, 427–433 (2008).
- Yu, P.B. et al. BMP type I receptor inhibition reduces heterotopic ossification. *Nat. Med.* **14**, 1363–1369 (2008).
- Erondu, N. et al. Neuropeptide Y5 receptor antagonism does not induce clinically meaningful weight loss in overweight and obese adults. *Cell Metab.* **4**, 275–282 (2006).
- Fichtner, M. et al. Discovery and evaluation of spirocyclic derivatives as antagonists of the neuropeptide Y5 receptor. *Bioorg. Med. Chem. Lett.* **22**, 2738–2743 (2012).
- Kealey, S. et al. Microfluidic reactions using [¹¹C]carbon monoxide solutions for the synthesis of a positron emission tomography radiotracer. *Org. Biomol. Chem.* **9**, 3313–3319 (2011).
- Zhang, L., Bijker, M.S. & Herzog, H. The neuropeptide Y system: pathophysiological and therapeutic implications in obesity and cancer. *Pharmacol. Ther.* **131**, 91–113 (2011).

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