

FILLING GAPS IN DRUG DISCOVERY PIPELINES: FROM COMPOUND CANDIDATE TO CLINICAL REALITY

In the world of drug discovery, countless potential treatments languish in the proverbial “valley of death” that separates promising candidate compounds from clinical implementation. Investigators face high costs, lengthy timelines, and regulatory hurdles. Many experts outside the pharmaceutical industry lack access to tools, like high-throughput screening technology, that would let them pursue targets identified in the lab. Despite monumental investments of time, resources, and intellect, the journey from bench to bedside remains fraught with challenges.

Nowhere are these challenges more pronounced than with rare and under investigated conditions. Traditionally overlooked by pharmaceutical giants because of limited market potential, research into diseases affecting small patient populations often struggle to attract research funding and industry interest. Familiar drug development models, driven by profit motives and market forces, tend to ignore these conditions in favor of more lucrative opportunities, leaving patients and families with few treatment options and no clear path forward.

Fortunately, those models are not the only option. The US National Institutes of Health (NIH) recognized the chance to bring together government, academic, and industry resources through strategic initiatives that streamline processes and maximize benefits. With programs like the [Blueprint Neurotherapeutics Network \(BPN\)](#) and the [National Cancer Institute \(NCI\) Experimental Therapeutics \(NeXT\) program](#), pioneers in drug discovery collaborate with governmental specialists and industry advisers to propel their pipelines toward realization. These multiyear partnerships offer access not only to funding but also to deep and wide-ranging expertise, contract services, and cutting-edge technology that might otherwise be out of reach.

“As targets have become more clearly defined and cost-risk structure has shifted, it’s become easier—but by no means easy—to go after rare and

underserved diseases in drug discovery,” says James Doroshow, director of the NCI’s Division of Cancer Treatment and Diagnosis. “It’s not big pharma’s initial expectation that they’re going to get a billion-dollar drug on a disease with 150 patients per year. We see it as a major role for government organizations like the NCI.”



Reagent preparation for a bioactivity testing.

Credit: Curia Global

PROGRAMS DESIGNED TO CREATE PARTNERSHIPS

These NIH programs are structured to maximize collaboration and support that facilitates early-stage drug discovery projects, with the goal of moving basic research into human trials over the course of just a few years.

“Academics or biotech companies might have discovered a few molecules that look promising, but they need additional resources to continue along the research path and discover new medicines,” says Matthew Surman, associate director of medicinal chemistry at Curia Global, Inc (Curia). “Through these partnerships, innovators get access to services and expertise that help drive these programs forward and really develop them into more mature programs that get treatments into the clinic.”

From the moment a project is accepted, a dedicated team of NIH scientists and industry experts is assigned to work with the investigators. These teams stay with the project from start to finish, providing continuity and long-term insights. Regular check-ins and milestone reviews built into the program structure provide continuous guidance and help keep projects on track. This structure fosters accountability and allows for dynamic problem-solving and adaptation as a project evolves.

Another advantage of these research partnerships is the sharing of credit and the control of products and deliverables. Because the primary focus of these programs is expediting the development of new therapies, industry and government partners work alongside investigators without overshadowing their contributions. In most cases, investigators retain full intellectual property rights after their participation in an NIH program. Investigators who are successful can leave the NIH program to set up a company, obtain additional funding, or seek acquisition by a pharmaceutical firm. The ability of an investigator to advance a product through a pipeline while collecting extensive supporting data and retaining intellectual property make a drug program extremely attractive to outside investors.

Everyone who participates in these fully integrated programs has something to learn, according to Surman. “Each organization has a different approach to drug discovery and development—NIH experts go about it one way, and then contractors like Curia and other companies each bring yet another approach,” he says. “Combining that diverse pool of knowledge into one place is helpful for academics or biotech start-ups who don’t have quite as much experience. We’re not just contractors; we’re also consultants.”

PAIRING DEEP EXPERTISE WITH UNPARALLELED TECHNOLOGY ACCESS

Identifying a promising therapeutic target can feel paradoxical to some investigators: on one hand, the discovery is exciting, but on the other, it is frustrating to be unable to pursue that target without access to tools like high-throughput screening technology. Similar roadblocks can arise at other steps, from protein crystallography to formulation. Strategic government partnerships exist to help promising compounds overcome those hurdles.

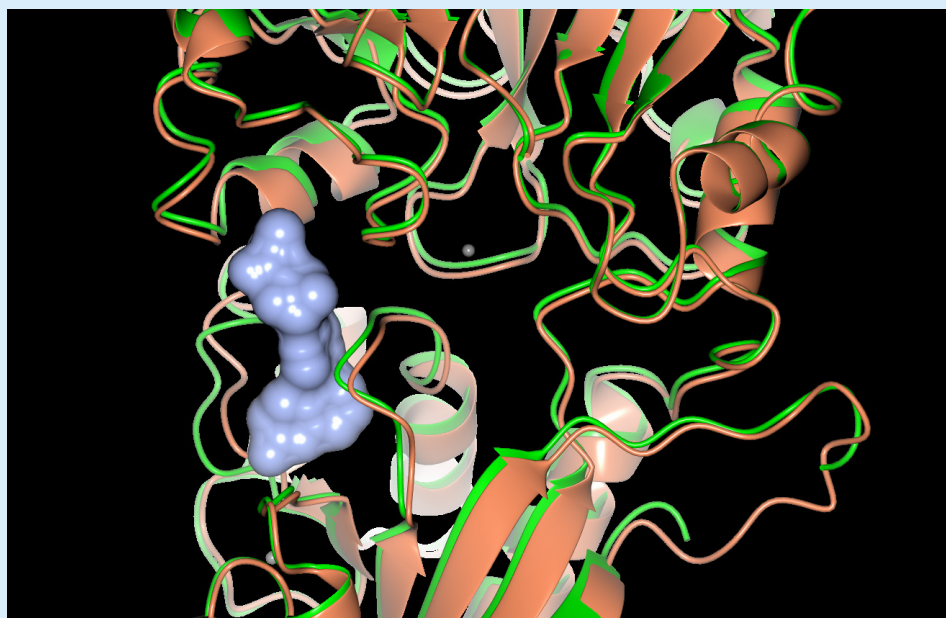
“These programs give academics access to resources they’d never be able to access anywhere else,” says Grant Carr, vice president and head of global R&D drug discovery at Curia.

“It’s not just expensive equipment; it’s also the expertise of contractors who can operate that equipment to obtain the best results for investigators who want to test whether their drug programs have legs. If they do, these resources can help drive them forward. Investigators may not know at the outset exactly what technology they’ll need to leverage, but if they find they need something along the way, one of the service providers almost certainly has it and can provide access right away.” The NIH supplements its own considerable resources with an extensive network of industry service providers recruited via a competitive process. At no additional cost, investigators can take advantage of services spanning medicinal chemistry, pharmacokinetics, toxicology, drug manufacturing, formulation, and Phase 1 clinical trials.

CASE STUDY: UNLOCKING THE ARTEMIS ENDONUCLEASE AS A THERAPEUTIC TARGET

A notable success story from the Chemical Biology Consortium (CBC) in the NCI Experimental Therapeutics (NeXT) Program involved the [characterization of the Artemis endonuclease](#), which plays a vital role in DNA repair. Artemis had been recognized as a potential drug target for over a decade, but scientists struggled for years to resolve its protein structure and conduct important cell-based assays.

When NCI partners reached out for help, Curia scientists stepped up to the challenge. An expert team produced highly purified protein, which allowed crystallographers to obtain high-resolution crystal structures of the endonuclease—not just in its isolated form but also bound to several compounds.



Co-crystallization and crystal soaking are used to identify structure-based drug design-enabled hits and unexpected ligand binding sites.

Credit: Curia Global

“It’s important to understand how compounds bind to the protein; that’s where we come in,” says Mary Rosenblum, a senior research scientist at Curia who worked on the fully integrated Artemis project. “We know investigators need to see where the bonds of the drug are and the features of how they interact and how that can be used to make a better, more interactive drug.”

This breakthrough resulted in a series of publications and unlocked a path forward for this therapeutic target. Exciting [proof-of-concept research](#) indicated that drugs targeting Artemis preferentially kill cancerous acute lymphoblastic leukemia B cells rather than normal human B cells, paving the way for new treatment approaches for leukemia and potentially other diseases.

REALIZING TRUE POTENTIAL

Strategic partnerships can help investigators save time and resources by identifying programs with a low probability of success, but they can also provide the resources to persist in drug development when setbacks might otherwise shut down a promising program. This can lead to unexpected innovations and discoveries.

“Industry contractors know what failed programs look like,” Carr says. “Sometimes it’s important to kill a project quickly and save funds. But on the other hand, sometimes the consultant team can help provide the intestinal fortitude to say, ‘We’ve got something here; let’s invest more.’”

Doroshow recalled an instance when investing NIH resources in sticking with a good idea paid off. An investigator approached the NCI with a proposal to target lactate dehydrogenase (LDH) for tumor treatment. This enzyme is important for cancer metabolism, and hypoxic signaling in tumor cells is often driven by mitochondrial signaling through LDH. But the investigator’s lead compound was a decades-old LDH inhibitor that was initially developed to fight malaria transmission and whose toxicity made it unsuitable for mammalian use. “The team had to start from scratch,” Doroshow says.

Over 8 years, collaborators painstakingly worked on [developing](#) and [optimizing](#) LDH inhibitors that would be tolerated at a therapeutic dose for oncology applications. Despite their efforts, they struggled to achieve a therapeutic effect in most tumors without causing severe side effects.

Just as the project was about to be shelved, a fortuitous discovery changed its course. A researcher at a team meeting mentioned a colleague at the University of Alabama at Birmingham studying hereditary hyperoxaluria, a rare disease caused by the inability to block oxalate buildup in the liver. Remarkably, one of the LDH inhibitor compounds developed by the NCI NeXT team effectively blocked LDH in the liver at one-tenth the concentration required for cancer treatment, indicating that it was a potential cure for the condition. The NCI NeXT team out licensed the LDH inhibitor portfolio to Chinook Therapeutics, which initiated [clinical trials of a promising candidate molecule](#) in 2022.

“This compound, which we couldn’t find a way to formulate safely for cancer, is now in clinical trials for treating this rare disease that until recently required kidney transplantation,” Doroshow says. “It took government investment in really rare diseases for that to happen.”

A LAUNCHPAD FOR CLINICAL SUCCESS

The benefits of strategic government partnerships can last far beyond the duration of an NIH program. For example, investigators can streamline their drug development by continuing to work with contract partners like Curia for manufacturing, formulation services, and much more as they build on their successes.



Biosafety level 2 (BSL-2) facilities for mammalian, insect, yeast and prokaryotic cell culture are used for cell line development, cellular testing and recombinant protein production.

Credit: Curia Global

“There’s a distinct benefit to continuing to work with the same company: it smooths the transitions between each stage,” Surman says. “Even within the scope of an NIH program—for example, if a drug goes from medicinal chemistry to chemical development—it helps to have the free flow of information that comes with making an internal transition from Curia scientists to other Curia scientists. It allows us to provide a greater degree of consultancy as the project continues. The first scientists who work on a given drug will go to new locations and help with tech transfer.”

Tapping into the extensive US-based network of experts and services ensures that hands-on support is available in adjacent time zones. Avoiding logistical hurdles or miscommunication can accelerate drug commercialization. But the importance of these partnerships lies not only in logistical ease but in the shared commitment to achieving breakthrough results for patients.

“We participate in these programs because we enjoy making a difference,” Carr says. “People love the science and want to help develop the next drug patients need.”

Explore [Curia’s strategic partnerships](#) with US government agencies to advance drug research. [Contact Curia Global](#).



ABOUT CURIA

Based in Albany, NY, Curia is a global contract development and manufacturing organization (CDMO) with 26 integrated sites. For more than 30 years, Curia has successfully partnered with biotech and pharmaceutical companies, government agencies, and therapeutic-specific institutes worldwide to drive the discovery and development of new medicines. We mitigate common challenges and regulatory risks associated with the offshoring of research programs. To learn more, visit us at curiaglobal.com.