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High-Velocity Development: Gene Therapy Vs. Small Molecule

By **Raul P. Lima**, inSeption Group

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While gene therapy has been around for decades, the field is not as mature as many might imagine. Additionally, the pace, structure, and funding dynamics for gene therapy development are unique among treatment modalities. Combined with the inherent difficulty of the chemistry behind creating a gene therapy, these factors undermine countless development efforts and, by extension, sink many biotechs.

In gene therapy, clinical tasks overlap and translational medicine digs deeper and takes longer. Rather than sequential development, many activities take place in parallel. That crunch on chemistry, manufacturing, and controls (CMC) personnel, as well as lab personnel, is difficult to navigate. The sponsor does not know how to make the drug and does not have full release on it. Nor does the sponsor have all the data it would like to have heading into the first-in-human patient study (Phase 1/2). Thus, a carefully plotted approach is required to minimize risk and maximize chances for success.

DIFFICULT SCIENCE WITH NO MARGIN FOR ERROR

Typical small molecule research proceeds through animal studies and in vitro work before moving on to proof of concept. After that, the molecule progresses into tox studies, then an IND. After that, a single ascending dose and a multiple ascending dose (SAD-MAD) study each would be conducted in healthy volunteers. Only then would you proceed to a Phase 2 study. This creates ample time to perfect CMC formulation and assays, as well as to contemplate scale-up. Throughout, the sponsor maintains an ongoing dialogue with regulators.

That luxury does not exist in gene therapy. To meet timeline goals and maintain funding, development typically moves on from the animal tox study at the three-month mark. The IND is submitted with three-month data and a regulator mandate to supplement that with nine month and/or one-year data after the IND is opened. In the meantime, the developer may begin starting up clinical sites, because the institutional review board (IRB) for your first clinical study can take up to six months.

The alternative is waiting a year for the animal study to finish, then several more months to complete the IND, plus several more for the IRB submission, putting the project at the two-year mark. That is not tenable. So, many development activities in gene therapy have to overlap. Further, developers should run their first-in-human study as if it could be registrational (either on great data or by just expanding that study to include more patients).

This is a key stumbling block for many developers: they tend not to think about Phase 3 endpoints and meticulous data collection for that first-in-human study. Or, they consider those elements, but the logistics of coordinating their experts, equipment, and facilities are inadequate. The result is lots of organizations trying to develop gene therapies and failing. Patients are too hard to find; process issues or quality problems occur. No registration endpoint is effectively determined. These delays impact the developers' clinical programs, which negatively impacts funding.

That said, the huge risk associated with moving directly into patients is not a unique problem. Oncology, for example, does the same. In the past two decades, though, oncology therapy development has become a more stable, regimented environment. The same cannot be said of gene therapy. Few sites dose gene therapies and the disorders being addressed typically are rare, making patients hard to find and recruit.

Even if the developer is able to produce the therapy consistently and gathers enough sites and patients, it is inherently difficult to answer questions of efficacy in gene therapy. Many rare monogenic diseases are degenerative, which means developers must prove reversal or lack of degeneration in a brief time window with a very small number of patients. There is no virus to measure, and we cannot measure patients' DNA. Biopsies are an imperfect vehicle that does not reveal the full picture of efficacy (in the unlikely event that patients would even enroll in a protocol that requires them to

undergo numerous biopsies). Clinical evaluations are often not sensitive enough to detect small changes.

So, the industry still lacks effective means to measure the therapy after it is in a patient's body, and we do not have effective ways to determine efficacy clinically on many of the targeted diseases. It is difficult to support either a biological argument or a clinical argument, even if the therapy is, in fact, working. That makes for exceedingly difficult translational medicine.

ADOPT A GENE THERAPY DEVELOPMENT MINDSET

The root of many gene therapy development challenges is companies retaining a small molecule mindset: they will advance through preclinical work and then pull clinical experts into the project. But gene therapy Phase 1 studies enroll actual patients (gene therapy is not used on healthy volunteers), so developers must be considering the full-scale clinical group well in advance.

They must build an adept, multifunctional team to survive, let alone succeed, in completing a single trial or advancing the field. Consider that many of the individuals involved do not know how to work with each other. They don't use the same language/terms and may manage timelines differently. And the skill sets of translational medicine experts and Phase 3 experts don't often overlap. Even in biotechs, this is a specialized experience.

To manage the chaos, developers typically hold regular, cross-functional, project team meetings, assembling the three vital pillars of necessary content experts. First is the preclinical team, which handles tasks including animal studies, proof of concept, and petri dish studies. Second is manufacturing, which sources raw materials and prepares the drug in whatever format is required at sites. Third is the clinical team, which includes doctors who determine

endpoints and clinical operations individuals who run the study and oversee monitoring.

This collaboration and communication is vital because, in translational medicine, both the successes and failures of one of these three teams can introduce risk for one or more of the others. They need to quickly communicate any variances because their endpoint is somebody else's beginning point, and that's where things often fall apart. Almost every development task creates ripples upstream and downstream.

For example, if manufacturing talks about releasing product on a given day, clinical may interpret that statement as the product is ready for them to use. However, "release" has a specific meaning in manufacturing parlance. Acquiring the certificate of analysis (CoA) may take two or three weeks from the "release" date, followed by another six weeks for packaging the drug. The clinical people may not think to ask for clarification, and the manufacturing people don't necessarily think to elaborate because "release" holds clear meaning for them.

Thus, in those cross-functional meetings, it often is necessary to expend extra time and energy to ask a lot of clarifying questions and to ensure terms and language are aligned. Project managers, in particular, have a responsibility to ask those nuts-and-bolts questions. Cross-functional challenges that you don't anticipate will occur, because gene therapy is unlike most other therapeutic areas. The importance of checking ego at the door, and understanding that vast experience in small molecule does not translate to gene therapy knowledge, cannot be overstated.

HOW DOES GENE THERAPY MOVE FORWARD?

Regulatory guidances discussing gene therapy exist, but they do not tell you how to function as a business, just what you need to submit to the agency. In fact, the FDA established the hectic pace of gene therapy development the first time it approved an

IND with limited toxicology data. Precedent was set on the abbreviated timeline and a CMC crunch as development activities occur in parallel. But how to achieve that timeline has not spread as easily, because that is very human dependent.

Not having to wait for nine more months changed the development dynamic. Developers rush to IND approval because they may be able to raise money based on the fact that they cleared IND. They can create news flow (buzz that is valued by the business people), but it makes execution much harder. That fact is underappreciated, but it is preposterous to believe we can return to sequential development tasks in gene therapy now that the Agency has essentially codified completing those tasks in parallel.

The answer is obvious to state but complex to execute: coordination and communication between internal groups must be designed into the clinical development plan, far more than is typical in small molecule. Arrogance ("I already know this."), indifference ("Not my job; not my problem."), and territoriality ("This is my baby. I want my due credit.") all must take a back seat to grace and curiosity. As humans, we lean toward territoriality. So, the organization must actively create an environment of curiosity and thoughtfulness. Show interest in the work of others and be inquisitive. Done the wrong way, this can feel like micromanagement. But, done the right way, it sets a base expectation of collaboration and curiosity, versus self-preservation and one-upmanship.

Some developers consider partnering with a consultancy that deals in gene therapy, but your problems may not be the same as that consultancy's previous clients. Other developers will hire a chief medical officer, which has been fruitful as many CMOs recognize the need for a clinical operations team answering tough questions up front. Bringing clinical into the process early — not just doctors, but a person who knows how to deliver these studies — since they understand that what makes good science is not necessarily practical, and practicality must be injected into programs as early as possible.

A more profound step forward will be increased sharing of experiences and knowledge transfer between gene therapy companies. While this occurs to some extent at conferences, many of those events focus solely on the science, overlooking logistics. Conversely, logistical conferences may discuss a few aspects of gene therapy, but it is not covered broadly.

Consider that gene therapy was an industry darling just a few years ago. But it has proven extremely difficult, and it is not achieving on its promise at the rate people believe it should. Numerous gene therapy companies have emerged, but their efforts have resulted in only two approved drugs (as of Nov. 2023). The market has gotten tighter and, with interest rates where they currently sit, high-risk/high-reward propositions are less attractive to investors.

As a result, funding seems to be cooling down, at least until somebody makes a breakthrough to answer the science or logistical questions in ways that will help the promise pay off, in which case the money will come flowing back. The science of gene therapy is not stopping. But the development of it is likely to dial back, at least in the short term.

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Raul P. Lima is Executive Vice President of Clinical Operations at inSeption Group. He is a proven leader in clinical operations with over 20 years of strategic, tactical, and hands-on experience in the management of global, multi-center clinical trials. He has extensive experience with timeline, clinical trial budget, and people management, and has successfully led cross-functional teams, including at CROs. Raul has repeatedly executed strategies ensuring that clinical operations activities supporting clinical trial management are conducted effectively and efficiently, are quality-driven, and comply with all applicable regulations. He possesses an uncanny vision and expertise in communicating that vision to influence strategies that progress cross-functional projects, as well as an unwavering passion for championing development.

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