



LEADING INNOVATION

CREATING THE CONDITIONS FOR SCIENTIFIC BREAKTHROUGHS

by Anthony Partridge, Vice President, PDHC

Innovation is Situational

Most fundamental advances are not planned—they emerge when the conditions are right. When smaller steps forward are required, linear execution may be best: define a problem, develop a solution, and execute the plan. *However, the most innovative outcomes tend to come from projects that are genuinely exploratory. In those cases, progress rarely follows a straight line.*

Instead, it often unfolds through a series of twists, turns, and re-framings that lead to an outcome very different from the one originally envisioned—both in destination and in impact. My favorite example is how vacuum tubes, initially invented to amplify and transmit radio signals, were later repurposed as fast, general-purpose electronic switches and then, ultimately, reframed as a critical component of the first generation of computers.

Over time, I've come to believe that leadership in innovation is therefore situational. Some efforts require clarity on the destination and disciplined execution. Others—especially exploratory science—demand flexibility on outcomes, intellectual freedom, and the willingness to pivot as new insights emerge.

A Case Study: MSD Singapore

One personal experience that shaped my view on this subject took place while I was working at MSD Singapore, well before PDHC existed. Even then, the work was guided by leadership principles that continue to shape how we think about innovation today: investing in ambitious science, working across boundaries, and staying focused on long-term impact. The effort involved close collaboration with colleagues across Merck & Co., including Tomi Sawyer, who played a key role in helping enable partnerships with an international network of academic groups, such as Charlie Johannes's laboratory in Singapore at A*STAR. Our shared ambition was a familiar but challenging one: to drug the undruggable.

We began with macrocyclic peptides, drawn by their demonstrated ability to engage targets that small molecules had historically failed to address such as intracellular protein-protein interfaces, targets that are critical across disease areas. A central limitation of this modality, then and still today, was achieving efficient delivery into the cytosol, a grand challenge for the field.

Our initial strategy was to deliver high-affinity macrocyclic peptides with poor membrane permeability using diphtheria toxin, a system that had been shown to transport a range of biomolecular cargo into cells. We invested heavily in this approach, generating diphtheria toxin-peptide conjugates and testing them carefully in cellular systems. Despite the rigor of the work, the outcome was unambiguous: we observed no measurable activity.

Rather than abandoning the effort immediately, the team stepped back to reflect on why the approach might be failing. A key realization emerged: we were attempting to deliver stoichiometric inhibitors, and even successful delivery of small amounts of peptide per cell might simply not be sufficient to achieve functional inhibition at the cellular level. If that were true, better delivery alone would not solve the problem.

This led to our first major pivot.

Instead of focusing on inhibitor delivery, we began asking whether we should be delivering a catalytic payload. At the same time, interest in targeted protein degradation was growing, and several groups had shown that protein-based degraders—what we came to refer to as bioPROTACs—could be expressed intracellularly to drive efficient target degradation.

We reproduced key results from the literature and confirmed that bioPROTACs were highly effective when expressed in cells. As the work matured, it became clear

that this represented a new class of biomolecules capable of catalytically eliminating proteins of interest—highly valuable as biological tools, and with long-term potential as a novel therapeutic modality, albeit with substantial challenges remaining. *What had started as a delivery problem for macrocyclic peptides had now evolved into a fundamentally different approach for historically intractable targets.*

With renewed optimism, we returned once more to diphtheria toxin, this time aiming for intracellular delivery of bioPROTACs. The logic was straightforward: even modest intracellular delivery might be sufficient if the payload were catalytic. Yet again, the data surprised us. Despite extensive engineering and prior demonstrations that the system could deliver diverse proteins, we did not observe measurable degradation. The reasons remain unclear.

This led to our second major pivot.

At this point, the work had already diverged significantly from its original conception. The next pivot was prompted by a team member who challenged our assumptions about delivery altogether: rather than delivering the protein, why not deliver the mRNA encoding it?

This reframing proved decisive. Simple mRNA transfection led to robust bioPROTAC activity in cell-based assays. Working across Merck sites, we moved into delivery platforms with translational relevance, including lipid nanoparticles, to demonstrate effective delivery *in vitro*—

and well before mRNA became widely recognized as a therapeutic modality. We later extended this work further through additional academic collaborations to establish peptide coacervates as alternative delivery vehicles for both mRNA and cell-impermeable peptides, opening additional possibilities for *in vivo* biomolecule delivery.

By the end of this journey, the project bore little resemblance to where it had started. We began by trying to deliver cell-impermeable macrocyclic peptides using diphtheria toxin. We ended up exploring mRNA delivery of biodegraders using lipid nanoparticles and peptide-based coacervates. If someone had predicted that outcome at the outset, it would have been hard to believe.

What made this progress possible was not a perfectly designed plan, but a willingness to pivot—and a leadership culture that allowed those pivots to happen. Progress depended on trusting the scientists closest to the work, staying open to unexpected data, and keeping focus on the underlying goal rather than the original strategy.

From Lessons to Action

These lessons map closely to the mission of PDHC and the broader peptide drug hunting community. As a field, we have made meaningful progress—including significant advances in our understanding of how to engineer peptide permeability, both for oral bioavailability and cellular uptake.

Yet substantial challenges remain before we can routinely discover peptides that can both reach their targets and engage them with high affinity. Meeting these challenges will require not just technical advances, but a continued commitment—across PDHC and the broader community—to creating the conditions in which true scientific breakthroughs can emerge.

*For peptides to realize their full potential as a therapeutic modality, focused efforts will be required across this and other areas, including *de novo* design, peptide synthesis, and more enabled paths to the clinic—areas where PDHC seeks to catalyze progress through focused, collaborative initiatives ([see our website](#)). In some cases, progress will come through the cumulative effect of many smaller, well-executed, and planned steps. In others, particularly where true breakthroughs are needed, progress may require following a less predictable and more exploratory path.*

With this perspective, the question becomes less about prescribing a single path forward and more about creating environments in which innovation thrives. In practice, that means fostering cultures where curiosity is rewarded, assumptions are challenged, and scientists are trusted to follow the data—even when it leads somewhere unexpected. Innovation of this kind cannot be fully planned or tightly controlled. **But when the conditions are right, it has a way of taking us to places far more impactful than those we could have designed at the outset. If we, as a peptide drug hunting community, can foster this spirit, fundamental advances will follow.**