

PEPTIDE DRUG HUNTING



OUR CHRONICLE OF ENTREPRENEURIAL SCIENCE & INNOVATIVE TECHNOLOGIES
EMPOWERING BREAKTHROUGH MEDICINES

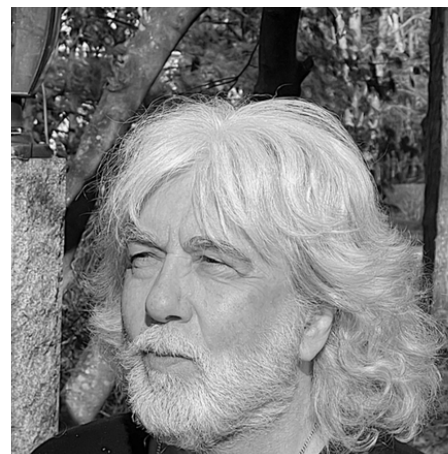
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A COMMENTARY BY THE EDITOR-IN-CHIEF

On behalf of the entire PDHC, especially those who have contributed as authors, editorial reviewers, and our publishing team, we enthusiastically welcome you, our readership, to our second issue of the PDHC Chronicle. We have several outstanding articles for you to enjoy, and our second issue reflects significant momentum for the PDHC. At the beginning of 2026, we welcomed new leadership under Charlie Johannes and Anthony Partridge as President and Vice-President, respectively, amongst others on the PDHC Leadership Team. Their bold vision, along with our PDHC entrepreneurial advisory board, entrepreneurial business network, and our outstanding PDHC sponsors, will enable a stronger modus operandi to impact PDHC's Initiatives as well as webinars and partnering with key conferences that promote peptide drug hunting worldwide!

The PDHC Chronicle Editorial Team has continued to reach out to peptide drug hunters to contribute to multiple topics that reflect upon the entrepreneurial multidisciplinary spirit of the PDHC. Four topics mirroring our PDHC Initiatives include: *De Novo Design, Synthesis Innovation, Translation into the Clinic, and Life of a Peptide*. Three topics highlighting the PDHC's core enterprise include: *Entrepreneurial Science, Innovative Technology, and Breakthrough Medicines*. Furthermore, several other high-level topics include *Leadership Insight, PDHC Vision, PDHC Spotlight, Peptide News, Peptide Fun Facts, Conference Highlights, and PDHC Upcoming Events*.



We will focus special efforts to build upon the first year of the PDHC Chronicle to play a key role in capturing the multidisciplinary spirit and science-business interface of peptide drug hunters from academia, biotech, pharma, R&D organizations, service providers, and investors!

Please let us know if you are interested in sharing your thoughts on any of the above topics of the PDHC Chronicle. We also welcome anyone who may wish to be involved with our publishing team.

Lastly, please see the accompanying article entitled Special Acknowledgments to Authors & Editorial Team for their contributions to this inaugural issue.

TOMI SAWYER,
Editor-in-Chief





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.**

ANTHONY PARTRIDGE

Vice President, PDHC

PDHC
AT AN



INFLECTION
POINT

BY CHARLES W. JOHANNES



PDHC AT AN INFLECTION POINT: A VISION FOR 2026 AND BEYOND

When the Peptide Drug Hunting Consortium (PDHC) was founded, it emerged from a simple but powerful idea: peptide drug discovery advances fastest when knowledge is openly shared and when experienced practitioners actively mentor the next generation of scientists. Progress accelerates when scientists, engineers, and innovators are connected across disciplines, organizations, and geographies. From the beginning, PDHC has been a community built on curiosity, generosity, and shared technical passion.

Today, PDHC stands at an inflection point.

We are fortunate to have an exceptional and deeply experienced membership across our Entrepreneurial Advisory Board (EAB), Executive Business Network (EBN), and Editorial Advisory Board. This breadth of expertise is one of PDHC's greatest strengths. As we move forward, the opportunity, and the need, is for these leaders to interact more intentionally across the EAB and EBN, collaborate around shared themes, and take ownership of their respective domains. The next phase of PDHC requires a shift from advisors to architects: individuals who not only offer insight, but help shape programs, content, and direction.

In 2025, execution necessarily relied on a small number of committed leadership team members. In 2026 and beyond, PDHC's impact will depend on broader engagement, shared responsibility, and collective ownership from across this community.

In 2025, we saw extraordinary grassroots engagement, from scientific discussions and

CHRONICLE ABSTRACT

The Peptide Drug Hunting Consortium (PDHC) enters 2026 at a dual inflection point: for the peptide field, as medicines and enabling technologies reach new levels of clinical and translational maturity; and for PDHC itself, as a growing organization. Built on a foundation of shared knowledge, mentorship, and community-driven exchange, PDHC has grown into a global network spanning academia, biotech, pharma, and emerging technology platforms. With this growth comes the opportunity, and the responsibility, to evolve from a volunteer-driven community into a durable platform with clear leadership, sustainable funding, and shared accountability.

In this President's Vision, Charles Johannes outlines how we will accelerate peptide drug discovery by leveraging the collective genius of the PDHC network and a deliberate integration of our diverse scientific, entrepreneurial, and translational expertise. Reflecting on lessons from 2025, including the transition to nonprofit status, the article defines priorities for 2026 focused on leadership engagement, high-quality programming, responsible funding, and clear pathways for contribution. Ultimately, PDHC's impact will be measured by the success of its members: advancing science, enabling entrepreneurship, and translating peptide innovation into better medicines.

educational content to global participation across academia, biotech, pharma, and emerging technology platforms. That momentum affirmed the original premise of PDHC. It also revealed an important truth: if PDHC is to reach its full potential, it must evolve from a volunteer-driven community into a durable platform with structure, resources, and shared accountability.

As I step into the role of President, I want to share my vision for PDHC in 2026 and beyond, and importantly, invite the community to help shape and build what comes next.

WHY PDHC MATTERS

Peptide drug hunting succeeds when the right biology is matched to the right modality and when translation is deliberately engineered. It requires tight integration of chemistry, biology, computation, and development, along with access to the people, resources, and capital needed to move discoveries from insight to impact. Progress in peptide drug hunting depends on collective genius: the deliberate integration of diverse expertise, perspectives, and experiences across the community to generate insights and solutions that no single laboratory, company, or discipline could achieve alone.

PDHC exists because the most meaningful advances in peptide therapeutics happen when ideas move freely, when technical lessons are shared honestly, and when emerging scientists learn not just what works, but why. Equally important, progress depends on entrepreneurial science, the ability to connect scientific insight with resources, capital, and pathways to translation. Our mission is to catalyze progress by connecting people, elevating knowledge, and accelerating translation. Thus we will link researchers with industry partners, venture capital, technology transfer offices, and other enablers of innovation, in service of better medicines.

This mission has defined PDHC since its inception. Our ability to deliver on it must now grow.

REFLECTIONS ON 2025

The past year demonstrated what a motivated community can accomplish. PDHC benefited from strong participation across industry and academia, a willingness of leaders to share hard-learned lessons, and a growing appetite for deeper technical discussions.

Beyond PDHC itself, 2025 was also a consequential year for peptide drug discovery. Advances across metabolic disease, oncology, and targeted delivery continued to validate peptides as medicines with differentiated engineered pharmacology. These developments underscored both the maturity of the field and the pace of innovation, reinforcing the value of timely knowledge exchange, mentorship, and cross-sector dialogue.

At the same time, 2025 revealed the limits of informal structure. Leadership bandwidth was stretched, and execution depended heavily on a small number of contributors. PDHC also undertook the essential transition to 501(c)(3) nonprofit status, a step critical for long-term credibility and impact, but one that temporarily constrained funding flexibility.

These are not failures; they are signals. They tell us that PDHC has reached a scale where enthusiasm alone is no longer sufficient. To amplify impact, we need clearer roles, better resourcing, and a more intentional operating model.

2026: FROM COMMUNITY TO PLATFORM

In 2026, PDHC will focus on building the infrastructure required to support long-term impact. This vision rests on four pillars.

1 Leadership with Clarity and Accountability

PDHC will continue to evolve its leadership structure to support the organization we are becoming. As our mission and activities expand, leadership roles will be clearly defined, purpose-driven, and aligned with strategic priorities. Authority and responsibility will be thoughtfully distributed to enable effective decision-making and sustained momentum.

Contributors will be invited to articulate how they would like to engage and where they can lead, support, or build. PDHC is strongest when individuals step into roles that reflect their strengths and interests, and when those strengths are intentionally integrated across the organization to unlock our collective genius.

2 Programs That Create Signal

PDHC will prioritize high-quality, technically meaningful programming. This includes flagship webinars featuring industry, academic, and technology leaders; structured discussion formats that encourage real exchange; and expanded PDHC Chronicle content. Accessible science summaries will be developed in part through community-

facing initiatives, such as the proposed Social Hour for Social Change, which emerged from leadership discussions around science communication and public engagement. These efforts will help members communicate peptide science to broader audiences, broaden engagement, and support PDHC's outreach and funding efforts.

Our goal is to make PDHC a trusted signal source, a place where the peptide community comes to learn, challenge assumptions, and stay current.

3 Funding the Mission Responsibly

To sustain and grow these efforts, PDHC must be financially supported. In 2026, PDHC will actively pursue funding aligned with its mission, including support from industry partners, philanthropic organizations, and family offices that value scientific education and translational impact. As PDHC professionalizes as a nonprofit organization, funding efforts will be anchored by clearly defined leadership roles, articulated goals, and shared accountability for outcomes.

Funding will enable scaled programming, including initiatives that translate peptide science for public audiences; improved infrastructure and communications; support for leadership and operations; and travel and engagement that broaden PDHC's reach. Transparency, independence, and community trust will guide all funding decisions.

4 Clear Paths to Contribute

PDHC's strength lies in participation. In 2026, we will make it easier for members to engage meaningfully, and we will ask members to explicitly define how their expertise, time, and perspective can contribute to PDHC's goals. Contribution may take many forms, including writing, organizing events, mentoring, fundraising, or leading new initiatives, but in all cases it will be grounded in clear ownership and intentional impact.

If PDHC matters to you, there will be a clear way to contribute.

WHAT SUCCESS LOOKS LIKE IN 2026

By the end of 2026, success for PDHC will be measured not by scale alone, but by substance and outcomes. We will have an engaged leadership team with clearly defined roles, regular interaction across the EAB and EBN, and shared ownership of programs and outcomes. For members of the Executive Business Network, success will include increased connectivity that leads to new business opportunities, partnerships, and informed strategic decisions. For entrepreneurs and startups, success will be reflected in clearer pathways to capital, more informed engagement with venture investors, and stronger connections to industry and technology transfer ecosystems. PDHC will deliver consistent, high-quality programming that informs and connects the peptide community, supported by sustainable funding and transparent governance. Most importantly, PDHC will function as a trusted platform where knowledge, experience, mentorship, and commercial insight actively flow between generations of peptide drug hunters. When PDHC members succeed, scientifically, professionally, or entrepreneurially, PDHC itself will have succeeded.

LOOKING AHEAD

PDHC is entering a new phase, one defined by intention, execution, and shared ownership. My role as President is to help create the conditions for collective genius to emerge, where knowledge, experience, and judgment are combined across the community to drive progress.

This is an invitation. To participate. To contribute. To help shape an organization that supports peptide drug hunting not just for today, but for the next generation.



CHARLES JOHANNES, PH.D.

President, Peptide Drug Hunting Consortium

[HTTPS://PEPTIDEDRUGHUNTING.ORG](https://peptidedrug hunting.org)

Rapid Cyclic Peptide Development Enabled by Artificial Intelligence

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Background

Cyclic peptides have emerged as an increasingly attractive therapeutic modality, occupying a distinctive space between small molecules and biologics. Their conformational rigidity, high binding affinity, and tunable physicochemical properties enable access to biological targets that are often challenging for conventional drug modalities^{1,2}. Yet, despite these advantages, the discovery of high-affinity cyclic peptides against predefined targets remains intrinsically difficult. A central limitation is not simply the size of sequence space, but the low information density of each optimization cycle once cyclization introduces strong conformational coupling. In cyclic peptides, local sequence changes frequently propagate global structural consequences, making structure–activity relationships (SAR) highly non-additive and difficult to extrapolate from standard medicinal chemistry logic^{2–4}.

The discovery of high-affinity cyclic peptides against predefined targets remains intrinsically difficult.. What slows progress is not only how many variants can be screened, but how efficiently each round of data is converted into the next round of design choices.

As a result, traditional discovery workflows—large-scale screening followed by empirical, experience-driven refinement—often struggle to scale efficiently in rapid biotech settings. Bigger libraries may increase hit opportunities, but they do not automatically improve decision quality. What slows progress is not only how many variants can be screened, but how efficiently each round of data is converted into the next round of design choices. This is particularly relevant for cyclic peptides, where many experimental iterations can yield only incremental or low-value information. In this context, artificial intelligence (AI), when tightly integrated with high-throughput experimental technologies, offers a practical route to accelerate discovery by increasing the information extracted from each Design–Make–Test–Analyze (DMTA) cycle^{3,5}.

Technological Overview

This work illustrates an AI-enabled workflow for rapid, target-defined cyclic peptide development that integrates mRNA display-based library screening with AI-assisted sequence and structural optimization. Discovery begins with a predefined protein target, but the central objective is not simply to generate more candidates. Rather, it is to improve how efficiently experimental information is translated into design decisions. mRNA display provides access to ultra-large peptide libraries and supports rapid exploration of diverse sequence and cyclization architectures⁶. That experimental throughput is important, but experimental enrichment alone is often insufficient to resolve non-linear SAR or to identify which

optimization paths are truly worth pursuing^{3,6}.

A key distinction of this workflow is that AI is not positioned as a black-box affinity predictor. Instead, it combines sequence-level modeling, structure-aware ranking, and modification prioritization to identify variants most likely to improve affinity while preserving developability^{3,5}. In practical terms, AI is used to interpret emerging sequence-activity relationships from screening data, rank productive substitutions, and narrow the set of variants that need to be synthesized and tested. Its value lies in maximizing information gain per DMTA cycle rather than merely assigning a score to each sequence³.

AI-Enabled Cyclic Peptide Discovery as a Closed DMTA Cycle

The workflow can be usefully framed as a closed DMTA cycle tailored for cyclic peptide discovery (**Figure 1**). In the **Design** phase, AI-guided prioritization defines a feasible and information-rich modification space rather than attempting exhaustive enumeration. In the **Make** phase, high-throughput platforms such as mRNA display and rapid peptide synthesis enable parallel generation of diverse cyclic architectures⁶.

In the **Test** phase, quantitative assays including surface plasmon resonance (SPR), cellular uptake measurements, and in vivo studies provide readouts that are sufficiently consistent to guide iteration. In the **Analyze** phase, AI is used to interpret outcomes under non-linear SAR conditions, identifying patterns that would be difficult to capture heuristically from individual experiments alone. The practical advantage of this closed loop is not merely predictive accuracy; it is decision compression—shortening the path between one experimental round and the next^{3,4}.

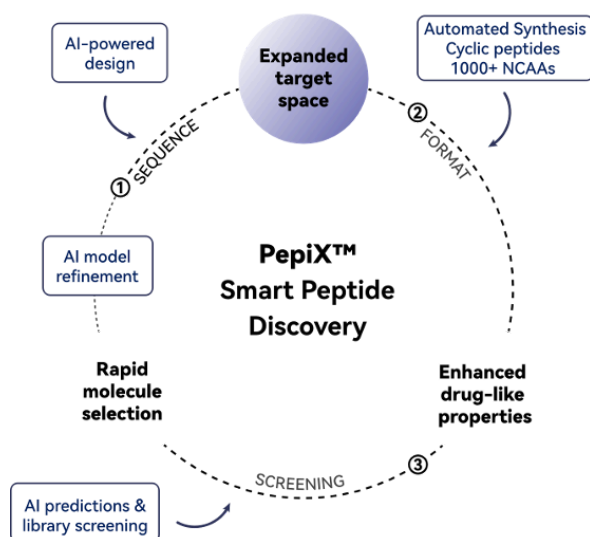


Figure 1. Closed DMTA cycle for AI-enabled cyclic peptide discovery.

Case Study 1: mRNA Display and AI-Assisted Optimization for High-Affinity Target Binders

The first case study illustrates how integrating AI-guided refinement with mRNA display screening changes optimization behavior across three distinct stages: previously reported sequence space, mRNA display-enriched hits, and AI-refined variants.

As an initial benchmark, peptides from this previously reported sequence set were evaluated by SPR and showed measurable target engagement, but with broad variability in affinity (**Table 1**). The median affinity for this group was approximately 49 nM, with the best binder reaching 4 nM, and 19% of candidates falling below the predefined activity threshold of 10 nM. Cyclic peptides identified through mRNA display screening improved both hit quality and hit rate:

the median affinity shifted to 5 nM, the best binder improved to 2 nM, and the proportion of candidates below the activity threshold increased to 67%.

When AI-guided sequence and structural refinement was applied to selected mRNA display hits, the optimized variants showed a further shift toward stronger and more uniform binding. The median affinity improved by approximately 2-fold relative to the mRNA display group and 24-fold relative to the previously reported sequence set, while the best binder reached 0.6 nM. The practical importance of this result is not simply that AI found a stronger binder, but that it reduced the number of unproductive optimization paths that had to be explored experimentally.

Table 1: Representative stage-wise comparison of discovery efficiency in Case Study 1

Stage	Sequence Source	Median Affinity	Best Affinity	Below Activity Threshold
Stage 1	Previously reported sequence space	49 nM	4 nM	19%
Stage 2	mRNA display-enriched hits	5 nM	2 nM	67%
Stage 3	AI-refined variants	2 nM	0.6 nM	75%

Case Study 2: AI-Guided Discovery of Cyclic Peptides for Blood-Brain Barrier Transport

Case Study 2 explores the use of AI-enabled cyclic peptide discovery in the context of blood-brain barrier (BBB) transport, a functional challenge that extends beyond conventional target binding. Efficient delivery of macromolecules to the brain remains a major limitation for many therapeutic strategies, as most biologics and large molecules cannot cross the BBB through passive diffusion⁵.

To address this challenge, cyclic peptides were identified as potential transport ligands capable of mediating receptor-driven BBB translocation. Initial hits were obtained through mRNA display screening of large peptide libraries against BBB-associated targets. These libraries contained both linear and cyclic peptide architectures, enabling exploration of diverse binding topologies. Following hit identification, AI-guided refinement was applied to improve binding performance and structural compatibility with receptor-mediated transport mechanisms.

Analysis confirmed measurable binding

interactions for optimized peptide candidates, with representative affinities in the sub-micromolar range. In addition, fluorescence imaging experiments indicated strong cellular uptake for selected peptides, suggesting efficient cell-penetrating properties (**Figure 2a**).

To evaluate functional transport *in vivo*, representative peptide candidates were assessed in mouse models following systemic administration. Brain imaging and tissue analysis demonstrated detectable peptide exposure within brain tissue at defined time points after dosing (**Figure 2b**).

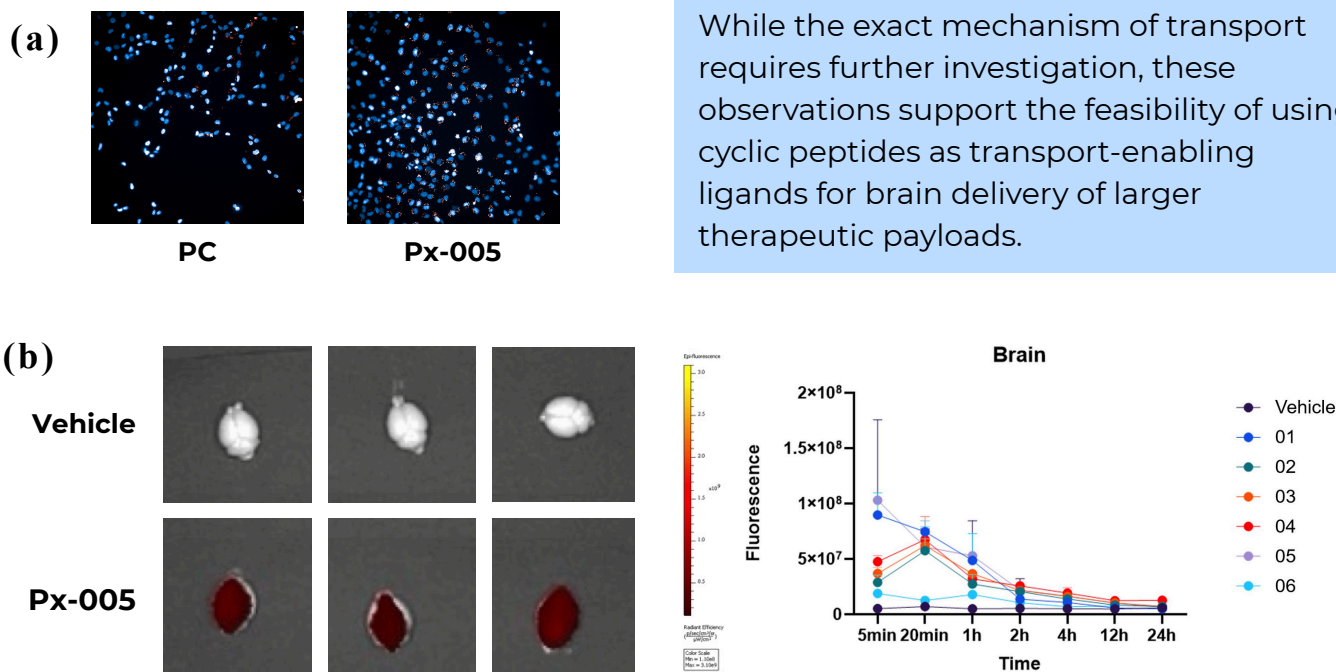


Figure 2. AI-enabled cyclic peptides supporting blood–brain barrier transport. (a) Fluorescence imaging showing cellular uptake of selected peptides. (b) *In vivo* imaging indicating peptide exposure in mouse brain.

This case illustrates an important distinction from affinity-focused discovery. For BBB transport, binding affinity alone is not sufficient to predict functional performance. Instead, molecular size, structural rigidity, receptor engagement, and systemic pharmacokinetics jointly determine delivery efficiency. The integration of AI-guided design with high-throughput experimental screening provides a practical way to navigate these competing requirements within a closed DMTA cycle.

Conclusion

Taken together, these examples show that rapid cyclic peptide discovery is not simply a matter of running larger libraries or generating more screening data. The more consequential shift comes from embedding AI within a closed DMTA cycle so that each round produces more useful design information. In Case Study 1, that translated into quantifiable gains in median affinity, reduced affinity dispersion, fewer low-performing outliers, and a measurable reduction in low-value optimization rounds. In Case Study 2, the same framework was extended to a more complex biological objective, demonstrating that the platform can move beyond binder discovery toward functionally relevant transport behavior at the blood–brain barrier.

From a platform perspective, the differentiated value lies in the combination of experimental throughput, flexible screening modalities, and an AI layer designed to improve decision quality rather than merely rank candidates. More broadly, this work suggests that the future of cyclic peptide discovery will be shaped not by library scale alone, but by tighter integration between computational design, experimental validation, and learning velocity across the DMTA cycle¹⁷. Platforms that can reliably reduce unproductive iterations or compress discovery to the same endpoint in fewer experimental cycles may define the next generation of peptide drug hunting.

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A Seven-Year Adventure in Peptide Drug Discovery!

Tomi Sawyer

Founder, Chief Drug Hunter & President

Thomas & Jonathon Sawyer

Heads, Structural Biology & Peptide Chemistry

The logo for Maestro Therapeutics. It features the word "MAESTRO" in large, bold, black capital letters, and "THERAPEUTICS" in smaller, black capital letters below it. To the right of the text is a stylized graphic of a star or a sunburst with multiple points.

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| Abstract

Peptide drug hunting is both fascinating and challenging! Maestro Therapeutics has evolved as a unique enterprise of R&D consulting, business advising, and mentoring over the past seven years. This PDHC Spotlight highlights the sustained impact of Maestro Therapeutics on peptide drug discovery through a significant number of biotech collaborations to advance proof-of-concept studies and drug development candidates. Beyond R&D focus, Maestro Therapeutics has supported many of its biotech portfolio in various business development goals, including realizing internal ambitions, interfacing with potential investors, connecting with prospective pharma partners, and overseeing work as liaison with service providers.

| Maestro Therapeutics R&D Collaborations

Since 2019, Maestro Therapeutics has worked with >40 biotechs (spinouts, early-to-late-stage, and public), venture firms, and pharma. From its inception, the focus of its efforts has been to support R&D objectives, especially preclinical peptide lead optimization and providing strong collaborative know-how throughout the drug discovery process. This has included peptide design (linear and macrocyclic modalities and conjugates thereof) and lead optimization to development candidates, structural biology, computational modeling, peptide chemistry, and translation of *in vitro* SAR data to *in vivo* efficacy, pharmacokinetic, safety, and drug delivery models. Several thousand peptide analogs have been advanced via Maestro Therapeutics' collaboration with several key biotechs.

Peptide drug hunting is both fascinating and challenging! Maestro Therapeutics has evolved as a unique enterprise of R&D consulting, business advising, and mentoring over the past seven years.

Maestro Therapeutics Funding & Partnering Liaison

Tomi's prior experience in biotech and pharma provides valuable insight and understanding of the cost of drug discovery especially for start-up and early-stage companies as well as effective ways to gain funding from venture capital firms and pharma (R&D, BD&L and/or venture groups). As a key opinion leader, he has influenced and promoted >\$500M in biotech funding via venture capital, pharma, and IPOs to support peptide drug discovery. Furthermore, Tomi's previous work contributed, in part, to >\$2B market cap growth (Ariad Pharma), a \$1.1B biotech-pharma strategic alliance (Aileron Therapeutics and Roche), and establishing the first pharma-based integrated Peptide Drug Hunter Network (Merck). In this spirit, Maestro Therapeutics has been building a deep interfacing network with many pharma, venture capital, contract R&D organizations, and service providers to support biotechs in terms of corporate business goals, including funding and partnering.

Maestro Therapeutics Multidisciplinary Expertise

7 YEARS AGO

Maestro Therapeutics was founded by Tomi Sawyer (1981 Ph.D., University of Arizona). Tomi did his graduate studies with Professor Victor Hruby, a legendary peptide chemist. He has surpassed four decades of driving drug discovery within several pharma and biotech companies as well as via Maestro Therapeutics (since 2019). Tomi's scientific and leadership experience includes Senior Vice President, Drug Discovery (Ariad Pharma [now Takeda]), Chief Scientific Officer (Aileron Therapeutics [now Rein Therapeutics]) and Distinguished Scientist (Merck). He is credited with >660 publications, patents and presentations.

4 YEARS AGO

Thomas Sawyer (2022 Ph.D., Molecular and Cellular Biology, University of Massachusetts) and Jonathon Sawyer (2022 Ph.D., Biochemistry, University of Arizona) were recruited to join and evolve Maestro Therapeutics. Beyond their respective graduate studies, Thomas and Jonathon did several internships with biotechs, and these experiences further ignited their entrepreneurial spirit to take on a non-conventional career path to bolster Maestro Therapeutics' support of peptide drug discovery R&D efforts.

The collective scientific expertise of the Maestro Therapeutics team exceeds six decades of multidisciplinary working knowledge on diverse peptide modalities, therapeutic targets, drug design and structural modeling applications, peptide chemistry and biology strategies, peptide pharmacokinetic, and drug delivery approaches. Although our ongoing R&D work with biotechs remains confidential, we have engaged in significant peptide drug discovery efforts to drive lead optimization on key therapeutics targets, including both extracellular receptors and intracellular targets. Typically, this has involved having co-structures (X-ray and/or cryo-EM) and the use of sophisticated computational modeling methods.

We seek robust collaborations with our biotech partners with regular project meetings, transparent idea and data sharing, real-time tracking of peptide chemistry and SAR, and driving lead optimization to *in vivo* proof-of-concept and promising development candidates. We have achieved success with several of our biotechs in terms of progressing peptide leads into late preclinical development.

Before Maestro Therapeutics, Tomi's track record for drug discovery includes peptide (linear and macrocyclic), small molecule, and natural product modalities. Some specific examples are ALRN-6924/Sulanemadlin (dual MDM2/MDMX antagonist), Iclusig® (Gleevec-resistant Bcr-Abl kinase inhibitor), Ridaforolimus (mTor inhibitor), AP23464 (Src kinase inhibitor), AP22408 (Src SH2 antagonist), U-81749 (HIV-1 protease inhibitor), Ditekiren (renin inhibitor), NDP-MSH/Scenesse® (MC1R superagonist), and cyclo[Cys^{4,10}]-MSH (MC1R superagonist).

Tour de Force for Good Medicines

Maestro Therapeutics is seeking to expand its future scientific and business *modus operandi* to include other entrepreneurs in peptide drug discovery. This will fortify its capabilities to meet the ever-changing needs of R&D consulting, business advising, and scientific scholarship. We have dubbed this endeavor our "Tour de Force for Good Medicines" and we look forward to engaging individuals in the future who may wish to share their expertise and talents with Maestro Therapeutics!

Professional & Entrepreneurial Mentoring

Professional and entrepreneurial mentorship has been a long-lasting prerogative of Tomi, and such has included >100 individuals (e.g., undergraduates, graduates, post-docs, scientists, directors, vice presidents, and C-level officers) across the academic, biotech, and pharma spectrum. Lastly, with similar inspiration for training, teaching, and transforming R&D teams, Maestro Therapeutics has been a founding partner and Magnum Sponsor for the Peptide Drug Hunting Consortium to support its vision and mission for entrepreneurial science and innovative technology enabling future peptide medicines.

Scientific Scholarship & Intellectual Property

Summarized here are several invited talks at key symposia/conferences and biotech/pharma seminars as well as published perspectives, reviews, articles, and patent filings credited to Maestro Therapeutics and its collaborators since 2019:

9 LECTURES

- Victor J. Hruby Symposium (2026)
- TIDES USA conferences (2026, 2020)
- Hanson Wade Summits (2026, 2024)
- CHI conferences (2021, 2020, 2020)
- Expert panels (CHI conference 2025; Hanson Wade Summit 2025).

17 SEMINARS

- Abbvie
- Abiologics
- Bicycle Therapeutics
- Biohaven Pharma
- Entrada Therapeutics
- EpiAxis Therapeutics
- Exeliris
- 48Hour Discovery
- Genentech
- GlaxoSmithKline
- J&J Innovative Medicine
- Ormoni Bio
- Pepticom
- Perpetual Medicines
- SyntheX
- Vivtex

12 PATENTS

- Courage Therapeutics
- Centessa Pharma
- Resolute Bio
- Merck
- Other biotechs (undisclosed)



14 PERSPECTIVES, REVIEWS, ARTICLES

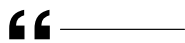
- Nature Communications
- Journal of Clinical Investigation
- Journal of Medicinal Chemistry
- Journal of the American Chemical Society
- ACS Chemical Biology
- ACS Medicinal Chemistry Letters
- Chemical Science
- Molecules
- Pharmaceutical Research
- Journal of Controlled Release
- International Journal of Toxicology

6 BOOK CHAPTERS

- ACS Symposium Series on *Approaching the Next Inflection in Peptide Therapeutics Attaining Cell Permeability*
- Royal Society Drug Discovery Series on *Peptide Therapeutics: Strategy and Tactics for Chemistry, Manufacturing, and Controls*
- Wiley & Sons' *Contemporary Accounts in Drug Discovery & Development*

Testimonials

The following biotechs were invited to share comments on their perspective of working with Maestro Therapeutics regarding impacts to their R&D pipeline, drug discovery platforms, and/or supporting their corporate business goals:



Aqur Biosciences

As Aqur Biosciences advances the development of our novel oral peptide-based cholesterol therapy, Tomi and the Maestro Therapeutics team have become invaluable scientific and strategic partners. Their exceptional expertise in peptide drug discovery, structural biology, computational modeling, medicinal chemistry, and translational development has significantly strengthened our R&D strategy and accelerated our program. Under Tomi's leadership, together with the outstanding contributions of Thomas and Jonathon, they have built and now lead the R&D team at Aqur Biosciences. Their commitment, scientific excellence, creativity, and collaborative approach have been instrumental as we work to accelerate our development program. We look forward to continuing this exciting journey together. – Michael Fole, CEO

BioAge Labs

Working with Tomi and the Maestro Therapeutics team has been a genuine pleasure and a big help to BioAge. Their deep expertise in peptide design, chemistry, computational modeling, and lead optimization has meaningfully strengthened our discovery efforts, while their engagement with external partners has provided valuable support for both our science and business objectives. We are grateful for the partnership and look forward to continued collaboration. – Kristen Fortney, CEO

Courage Therapeutics

Tomi is a recognized world-class peptide chemist known for his creativity and productive thought processes. As a leading chemist in the melanocortin peptide field, having designed both NDP-MSH and the first cyclic melanocortin peptides, we deliberately sought him out to embark on our mission together. Tomi's expertise has been invaluable for the development of best-in-class MC4R agonists at Courage Therapeutics. We also value having Thomas and Jonathon contributing their know-how in support of Tomi's chemistry leadership to advance our R&D efforts. – Giovanni Ferrara, CEO

Entrada Therapeutics

From Entrada's inception, the team at Maestro Therapeutics has been an integral part in our journey to push forward the boundaries of peptide therapeutics. Tomi is an institution in the peptide field and an exceptional thought partner, possessing an endless reservoir of knowledge paired with an uncanny ability to ask the right questions at the right time driving us to find solutions to advance our programs. Jonathon brings unbridled scientific curiosity and insight to the process, and Entrada benefited from his work both scientifically and operationally to compile and disseminate literature from across the peptide landscape. Their work, both at Maestro and at PDHC, has provided Entrada with a wealth of connections to a community of researchers advancing our field and is one we continue to benefit from every day. – Natarajan Sethuraman, CSO

EpiAxis Therapeutics

Maestro Therapeutics has been instrumental in supporting EpiAxis' strategic and scientific progress over a period of significant change. The deep, multidisciplinary experience that Tomi and the Maestro team have contributed to our discovery efforts have created significant value for our company. Maestro's dedication to bringing forth the transformative medicines of tomorrow through advancing the forefront of peptide science is genuinely inspiring. – Ben Buckley, CEO

48Hour Discovery

For several years, we have worked very closely with several members of the team at Maestro and we couldn't be happier with the results. The expertise that the Maestro Therapeutics Team has brought to 48Hour Discovery includes everything from tactical fixes to strategic direction. We consider that the support we've received from Tomi and his team has positively reset the trajectory for 48Hour Discovery over the past three years. – Rick Finnegan, *CEO*

Ladder Bio

Tomi has been a trusted scientific advisor and consultant to Ladder Bio for many years, bringing deep peptide drug discovery expertise, practical pharmaceutical development experience, and creative scientific insight. He recognized early the unique potential and differentiated capabilities to design and build Spiroligomers (ladder-shaped, peptide-like structures), and his guidance has helped us sharpen the platform, prioritize its most differentiated targets, and advance this new modular chemistry toward meaningful medicines. In addition to the technical expertise, Tomi is a great person, always responsive, and a pleasure to work with. – Eric Heil, *CEO*

Onca Bio

Whenever we have a question about peptide development—chemistries, targets, regulatory, assays, informatics, and everything in between—we know we can count on Tomi and the Maestro Therapeutics team. They not only provide us the right information but also the broader context: the people, companies, and programs that ultimately make new drugs. This has been invaluable for us in the early days at Onca Bio. Lastly, I'm grateful for the education, the ideas, the connections, and just the conversation with Tomi. Congratulations on seven years of helping grow the peptide field! – Tyler Stukenbroeker, *Co-Founder & CEO*

Pepticom

For Pepticom the work with Tomi and the Maestro Therapeutics team is a great source of knowledge, knowhow, and an outstanding perspective of the peptide drug field that enabled the streamlining of our platform as well as the creation of valuable business collaborations. – Immanuel Lerner, *CEO*

Receptor.AI

Maestro Therapeutics has been a valuable scientific and strategic partner to Receptor.AI. Tomi has brought deep expertise in peptide drug discovery, practical insight into translational development, and thoughtful guidance on how to position and advance collaborative programs. His support has helped us strengthen both the scientific framing of our peptide platform and our engagement with potential partners. – Alan Navfiev, *CEO*

Vivtex

Over the past three years, Tomi has been an invaluable scientific advisor to Vivtex. Across a remarkably wide range of topics — from deep scientific questions to business development and corporate strategy — he has consistently provided insightful, thoughtful, and highly valuable guidance that reflects both his profound expertise and his distinguished, longstanding career in the biotech and pharmaceutical industry. Beyond his technical acumen, Tomi is an outstanding communicator and a true pleasure to work with. We are grateful for his continued partnership and look forward to working with him for years to come. – Thomas Von Erlach, *CEO*

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A Perspective for the Peptide Drug Hunting Consortium

Synthetic Combinatorial Libraries: Four Decades of Peptide-Driven Innovation and the Road Ahead



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Abstract

Combinatorial chemistry has transformed the discovery of bioactive molecules by enabling the rapid generation and screening of large, structurally diverse chemical libraries. Since its emergence in the 1980s, the field has evolved from early peptide-based approaches—establishing a versatile chemical space bridging small molecules and biologics—to encompass a wide range of platforms, including one-bead-one-compound (OBOC) libraries, solution-phase mixture libraries, biological display technologies, and DNA-encoded libraries (DEL). These advances have dramatically expanded accessible chemical space and accelerated the identification of ligands for diverse biological targets. Notably, peptide and peptide-like modalities have played a central role in this evolution, serving as a bridge between small molecules and biologics in combinatorial discovery.

Recent progress has shifted the focus from library size alone toward increased molecular complexity, functional relevance, and integration with advanced screening technologies. Innovations in synthetic methodologies—including macrocycle construction, post-translational modification, and DNA-compatible chemistries—have enabled the generation of more diverse and drug-like compounds. In parallel, developments in high-throughput and high-content screening, microfluidics, and encoding strategies have enhanced both the efficiency and depth of library interrogation.

This article highlights the historical perspective and key advances in combinatorial library synthesis, screening, and encoding, with an emphasis on emerging technologies that bridge chemistry and biology. It further examines how the convergence of synthetic innovation, functional screening, and data-driven analysis is reshaping the field. Finally, future directions are outlined in which integrated, function-oriented, and information-rich approaches are expected to drive the next generation of therapeutic and materials discovery. These developments align with emerging community-driven efforts, such as the Peptide Drug Hunting Consortium (PDHC), to integrate chemistry, biology, and data science in next-generation discovery.



Introduction

Combinatorial chemistry involves the generation of large arrays of structurally diverse compounds—referred to as chemical libraries—through the systematic and repetitive covalent assembly of modular building blocks. Once constructed, these libraries can be screened in parallel to identify compounds that interact with biological targets of interest. Active compounds can then be identified either directly in addressable libraries or through decoding strategies that rely on genetic or chemical barcodes. Combinatorial chemistry has played a central role in drug discovery and lead optimization [1-4]. As summarized in **Figure 1**, most combinatorial platforms—including phage display, yeast and bacterial display, mRNA display, one-bead-one-compound (OBOC) libraries, DNA-encoded libraries (DEL), and solution phase mixture peptide libraries (e.g., SPCL, PC-SPCL)—are capable of generating libraries with enormous diversity (often exceeding 10^6 members) while supporting rapid, parallel screening against biological targets. In contrast, parallel synthesis and planar microarray approaches typically produce smaller, more focused libraries (hundreds to thousands of compounds) but offer advantages in structural definition and downstream optimization.

Planar microarrays have been particularly valuable in peptide research; however, other classes of compounds can also be synthesized *in situ* using microtiter arrays or droplet-based reactors in a high-throughput manner [5]. Each combinatorial technology possesses distinct strengths and limitations, and both the chemical nature of the library members and the screening modalities employed vary substantially across platforms (**Figure 1**). Phage-display and mRNA-display libraries are genetically constructed primarily from amino acids, yielding peptides and proteins that inherently reflect a biological bias. In contrast, synthetic libraries accommodate a far broader range of building blocks and are not subject to this biological constraint.

Within this landscape, peptides and peptide-derived modalities occupy a distinct middle ground, combining synthetic accessibility with biological relevance, and are therefore particularly well suited to combinatorial discovery.

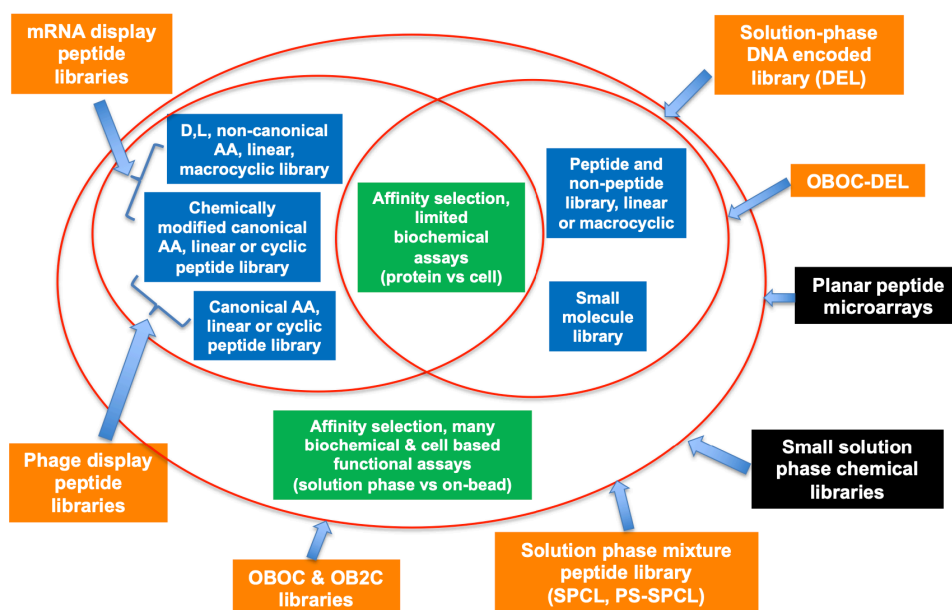


Figure 1. Overview of combinatorial technologies. The various combinatorial platforms are shown in orange (diverse and focused libraries) and black (focused small libraries), the chemical nature of library compounds is shown in blue, and the two broad groups of screening assays are shown in green. Depicted within the red ovals are the screening assays and nature of library compounds pertaining to each combinatorial platform. (Modified from Fig. 1 of Ref. 1).

In general, with some exceptions, affinity-based selection (binding assays) is the primary screening approach used for DEL, mRNA-display, and phage-display libraries. In contrast, OBOC libraries and solution-phase mixture libraries such as SPCL and PS-SPCL are compatible with a wide range of biochemical and cell-based functional assays in addition to binding assays. The diversity afforded by each method also differs substantially: OBOC libraries (90 μm beads) can achieve 10^6 – 10^7 diversity (and higher with smaller beads), PS-SPCL (10^8 – 10^{12}), phage-displayed peptide libraries (10^7 – 10^{11}), mRNA-displayed macrocyclic peptide libraries (10^{12} – 10^{14}), bead-based DEL (10^6 – 10^8), and solution-phase DEL (10^8 – 10^{11} for dual pharmacophore DEL). While DEL offers exceptional diversity, it is generally limited to small molecules, small macrocycles or short peptides with a restricted number of diversity points. In contrast, peptide and macrocyclic peptide libraries—particularly those derived from OBOC and mRNA display—enable access to higher-order structural complexity and functional diversity that

more closely approximates biologics while retaining synthetic control. It may sometimes be beneficial to combine different platforms, for example using DEL, mRNA display or phage display platforms to discover a lead compound and then utilizing OBOC cell-based screening platform to optimize the molecule with desirable cellular effects.

When integrated with computational approaches, focused libraries generated by parallel synthesis are particularly effective for structure-activity relationship (SAR) studies and lead refinement. Emerging computational tools—including AlphaFold-based structure prediction, artificial intelligence-driven design, and ADMET filtering—are increasingly incorporated into combinatorial library design, significantly accelerating the identification of viable drug candidates. Selected combinatorial approaches are highlighted in this mini review, with synthetic combinatorial libraries as the primary focus. Nucleic acid-based libraries (e.g., aptamers [6]) are beyond the scope of this article.

Historical Evolution of Combinatorial Libraries

The historical evolution of combinatorial library platforms is illustrated in [Figure 2](#). The foundations of combinatorial chemistry were established in the mid-1980s with Geysen's multi-pin technology [7] and Houghten's tea-bag method [8], both of which enabled parallel synthesis of defined but small peptide sets. These approaches were built upon the seminal solid-phase peptide synthesis method developed by Bruce Merrifield in 1963 [9].

These peptide-based innovations were not only foundational historically, but continue to define the trajectory of combinatorial discovery due to their modularity, synthetic tractability, and compatibility with both chemical and biological screening paradigms.

In 1991, we [10, 11] introduced the OBOC concept and demonstrated that millions of random peptides could be generated via solid-phase “split-mix synthesis” (also referred to as split-and-pool synthesis), screened, and decoded using automated Edman sequencing. Houghten [12] described solution

-phase mixture peptide libraries decoded through iterative screening, which later evolved into positional scanning synthetic combinatorial libraries (PS-SPCL) [13]. Fodor reported the synthesis and screening of 1,024 peptides in ten steps on a glass slide using photolithography and light-directed deprotection to create spatially addressable planar peptide microarrays [14]. Furka independently reported split-and-pool synthesis for solution-phase peptide mixtures, but the OBOC concept was not explicitly articulated [15]. Biological display technologies emerged alongside these chemical approaches. Smith introduced the phage display concept in 1985 [16] and demonstrated its application to peptide libraries in 1990 [17]. Positive binders were enriched through multiple rounds of bio-panning and identified by DNA sequencing.

The 12th American Peptide Symposium (Boston, June 1991) marked a pivotal moment in the combinatorial field. At this meeting, several foundational technologies were presented, including OBOC libraries [18], phage-display peptide libraries [19], photolithographic peptide microarrays [20], and solution-phase mixture libraries [21].

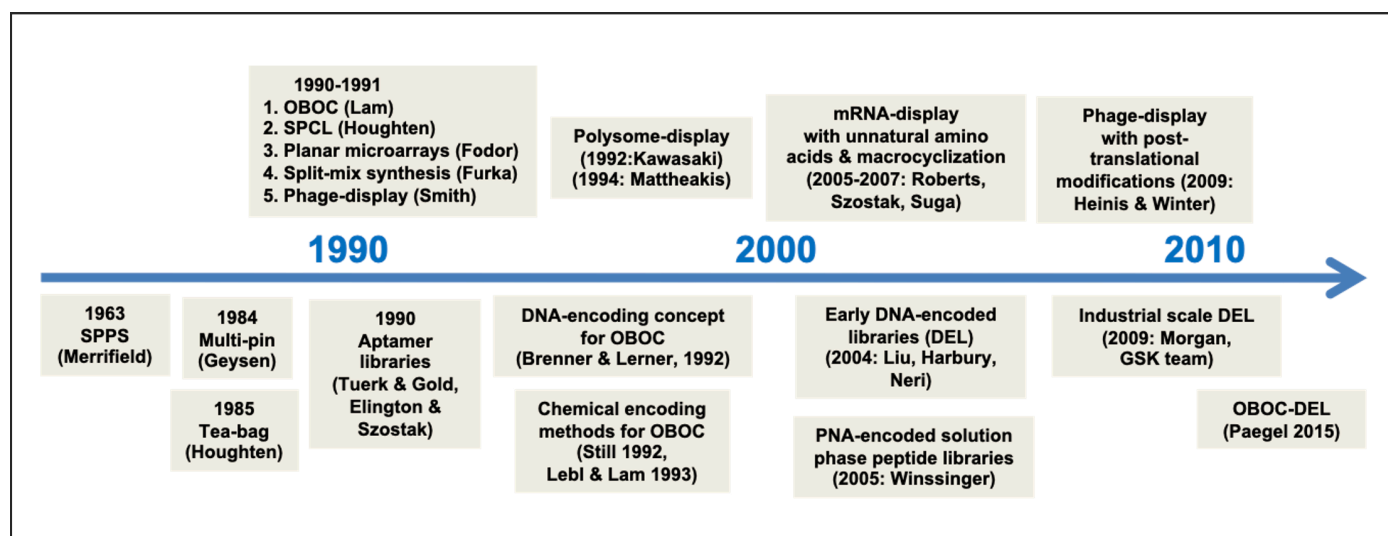


Figure 2. Historical development of combinatorial library platforms

Collectively, these advances established the conceptual and technical framework for modern combinatorial chemistry.

Early biological display systems—including phage, yeast, and polysome display—were initially limited to the 20 canonical amino acids and simple disulfide-mediated cyclization. This limitation was substantially overcome in the mid-2000s through advances in mRNA display and reprogrammed translation systems. Work by Frankel [22], Josephson [23], and Suga [24] demonstrated the incorporation of some non-canonical amino acids into macrocyclic peptide libraries. Subsequently, Heinis and Winter [25] introduced post-translational chemical modification strategies for phage display enabling access to conformationally constrained, proteolytically stable peptide scaffolds with expanded chemical diversity and improved drug-like properties.

Shortly after the introduction of the OBOC platform [10], Brenner and Lerner in 1992 proposed using DNA as an encoding element, leading to the concept of a DNA-encoded library (DEL) that could be prepared with a split-and-pool strategy on a solid support [26]. However, limitations in DNA sequencing technology initially restricted practical implementation. Approximately a decade later, Liu introduced DNA-templated organic synthesis [27], and in 2004 demonstrated a 65-member macrocycle library that could be decoded via PCR amplification [28].

That same year, several groups reported related advances. Harbury described a DNA-display peptide library generated through DNA-routing to identify ligands against anti-enkephalin antibody [29]. Neri introduced DNA-encoded self-assembling chemical libraries comprised of complementary DNA-tagged chemical fragments for small-molecule discovery [30]. Winssinger reported small PNA-encoded peptidic libraries synthesized via solid-phase methods and decoded with DNA microarrays [31]. With continued advances in next-generation sequencing (NGS), DEL technology has evolved rapidly. In 2009, through the concerted effort by a large team of investigators led by Morgan of GlaxoSmithKline, an 8×10^8 diversity small molecule solution-phase DEL was created from which inhibitors against Aurora A kinase and p38 MAP kinase were identified [32,33]. In 2015, Paegel reported the development of OBOC-DEL libraries using 10 μm beads, maintaining the original OBOC configuration while incorporating DNA encoding [33,34]. DEL is now widely adopted by many pharmaceutical companies [4]. Several drug candidates currently in clinical trials have been identified through DEL approaches [35-37]. Over the past five years, new encoding and screening strategies, expanded DNA-compatible chemistries, and machine learning-based data analysis have further accelerated the impact of DEL in drug discovery [4].

Preparation of Synthetic Combinatorial Libraries

Small synthetic combinatorial libraries (hundreds to a few thousand compounds) can be generated through parallel synthesis, either manually or using automated platforms, in solution or on solid support, with or without flow chemistry. These libraries offer broad flexibility in reaction chemistry and allow purification and full structural characterization of each member. Because the identity of each compound is predefined, such libraries are inherently addressable and well suited for systematic structure–activity relationship (SAR) studies.

In contrast, OBOC libraries are synthesized on microbeads using split-and-pool strategies, enabling the creation of much larger and more diverse libraries (thousands to tens of millions of compounds) [10]. Each bead displays a single compound species; however, these libraries are non-addressable. Therefore, active compounds identified during screening must be decoded, typically via direct chemical analysis of the library compound or through the introduction of chemical barcodes during synthesis. Unlike DELs, which use DNA barcodes that are unstable under harsh conditions, we encode OBOC libraries with chemical barcodes (e.g., peptide barcode for non-sequenceable polymers or small molecules [38]) that are compatible with a broad range of chemical reactions, including low pH, high pH, oxidizing conditions, and elevated temperatures.

For OBOC encoding, we developed topologically segregated bilayer beads, in which the library compound is displayed on the outer layer and the chemical barcode is embedded within the bead interior [39,40], thus minimizing potential interference of the barcodes with screening. The OBOC platform also allows the option of keeping library compounds tethered to the bead or releasing them into the vicinity of the bead for solution-phase assays. In addition to peptides, peptoids, peptidomimetics, and small molecules, we have successfully used glycosyltransferase enzymes to generate OBOC combinatorial peptide-glycan libraries (unpublished data). We have also developed strategies to convert OBOC peptide libraries into polyamine and small-molecule libraries

through global transformation [41]. SPLCs and PS-SPLCs are assembled on solid support via split-and-pool synthesis and subsequently cleaved into separate mixtures for screening in solution. Deconvolution strategies are then used to identify active components [12,13].

In 2004, when various DEL approaches were first developed, library synthesis was cumbersome and often impractical for generating high-diversity libraries. As the technology has evolved, DELs are now primarily prepared in solution using sticky-end enzymatic ligation strategies for DNA encoding, yielding solution-phase single pharmacophore DELs (diversity 10^6 – 10^9) and dual pharmacophore dynamic DELs (10^8 – 10^{11}). Typically, three to five cycles of coupling are performed to ensure encoding fidelity. This limits the construction of large macrocyclic structures or library compounds requiring more than six coupling cycles. Even though DEL synthesis is now primarily performed in solution, the original OBOC concept still applies because split-and-pool strategy is necessary to maintain the “one-DNA-one-compound” configuration.

Most pharmaceutical and academic investigators now use solution-phase DELs because of their enormous diversity. Nevertheless, bead-based OBOC-DELs remain very important, particularly due to their broader compatibility with assays beyond affinity selection. OBOC-DELs are prepared like solution-phase DELs, but $\sim 10\ \mu\text{m}$ beads are used as solid support [33,34].

Despite their potential for enormous diversity, DELs are constrained by the requirement for DNA-compatible chemistry. Reactions must typically proceed under mild, aqueous, near-neutral conditions to preserve DNA integrity, which limits the range of accessible chemical transformations and structural complexity. Nonetheless, there has been great progress in this area over the past five years [42]. In principle, PNA-encoded libraries could overcome many of these chemical limitations. However, it remains to be determined whether this approach can be translated to industrial scale, as has been achieved with standard solution-phase DELs.

Screening of Combinatorial Libraries

The choice of screening strategy is closely linked to library format and encoding methodology. Affinity-selection assays are the most widely used; however functional assays—including biochemical, enzymatic, and cell-based systems—provide critical complementary information. In particular, cell-based assays capture higher-order biological responses such as cytotoxicity, apoptosis, autophagy, receptor engagement, cell differentiation, cell motility, metabolism, and signaling pathway modulation, often using optical reporter systems (exogenous or engineered).

With few exceptions, affinity selection assays are the primary screening method for phage-display libraries, mRNA-display libraries, as well as solution-phase and bead-based DELs (Figure 1). Purified proteins are commonly used for affinity selection. In the case of cell surface receptors such as GPCRs, which are difficult to express in their native configuration, live cells or cell membranes may be used directly, with appropriate subtraction strategies. Screening methods beyond affinity selection, such as biochemical and cell-based assays, are actively being explored for solution-phase DEL; however, the literature in this area remains relatively sparse [43,44]. OBOC-DEL platform using small (~10 µm) beads has been shown to provide sufficient compound quantities per bead for biochemical assays when integrated with droplet-based microfluidic systems for automated functional screening at the picoliter scale [33,34]. These systems integrate compound release, assay incubation, fluorescence detection, and sorting into a continuous workflow, enabling highly efficient identification of active compounds.

Although the primary screening method for phage-display peptide libraries is biopanning with immobilized target proteins or intact cells, this platform also offers a powerful approach for identifying organ-targeting peptides through *in vivo* “panning,” which is very challenging with other combinatorial platforms. Phages recovered from specific organs following tail-vein administration in mice can be amplified in *E. coli* and subjected to repeated rounds of *in vivo* selection [45]. These canonical amino acid-containing organ-targeting

peptides can potentially be further optimized with non-canonical amino acid-containing OBOC libraries.

Addressable libraries generated by parallel synthesis or PS-SPCLs are in solution and are therefore well suited for manual or automated high-throughput screening (HTS) in multiwell plate formats (96-, 384-, and 1536-well). These formats are compatible with a wide range of binding, biochemical, and cell-based assays. In recent years, applications of PS-SPCLs have been largely concentrated in immunology, particularly in T-cell epitope mapping and vaccine development [46].

Among all combinatorial platforms, OBOC technology is the most versatile. It enables efficient screening across a wide range of targets, including soluble proteins, living cells, organoids, and even whole organisms such as bacteria, yeasts, and viruses. This versatility is particularly impactful for peptide and peptide-derived libraries, where functional screening can directly capture context-dependent biological activity, including cell penetration, receptor modulation, and tissue targeting. The historical development of methods for OBOC screening and encoding is shown in Figure 3. We typically use 90 µm TentaGel beads as solid support for OBOC library synthesis, which are significantly larger than mammalian cells (~10–20 µm in diameter). Each 90 µm bead can generate over 10 pmol of library compound. Compounds may remain tethered to the bead during screening [10] or be released into vicinity of the bead for solution-phase biochemical or cell-based functional assays [47,48]. For protein-binding assays, smaller beads (10–30 µm) may be used to increase library diversity within a given volume of beads, whereas 90 µm beads are preferred for cell-based functional assays.

For protein-binding detection, we have used enzyme-linked colorimetric assays for mapping B-cell epitopes [10], identifying MHC class I anchor residues [49], and discovering high-affinity peptides containing non-canonical amino acids against the SARS-CoV-2 spike protein [50].

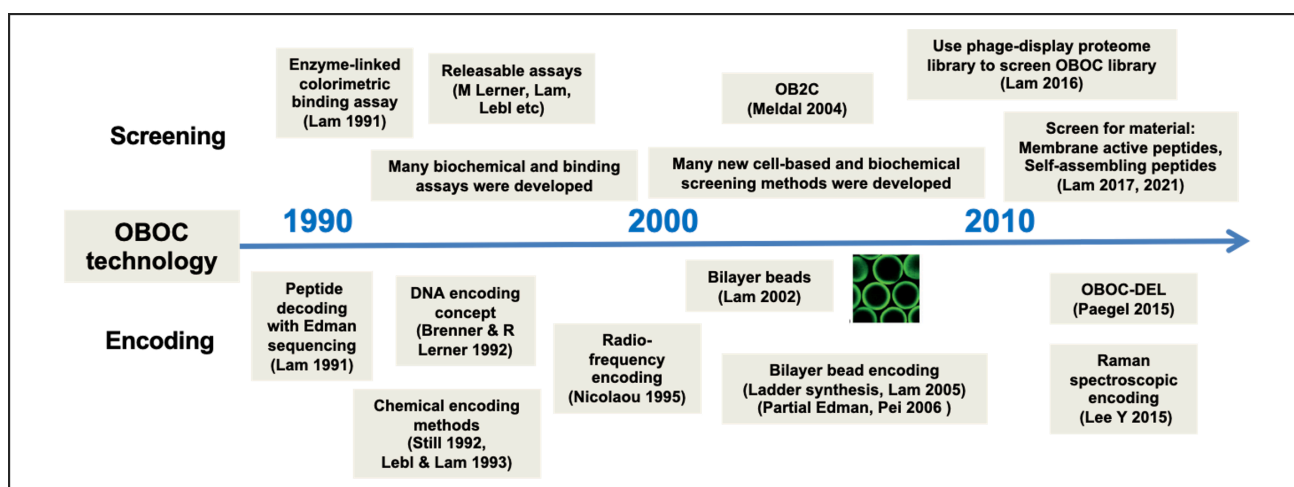


Figure 3. History of OBOC platform: screening and encoding

We have developed radiodetection assays to identify peptide substrate motifs for protein kinases [51,52] and sulfotransferases (unpublished work), as well as fluorescence quenching assays to identify protease substrate motifs [51,52]. We have also used [^3H]-strychnine and scintillation autoradiography to screen OBOC libraries for toxin-caging molecules (unpublished work). In addition, we developed a proximity ligation strategy to identify reactive affinity elements capable of site-specific ligation to immunoglobulins [53] and human serum albumin [54] for the development of drug carriers. We have used the OBOC platform to develop an illuminating peptide for instant detection of opioids in blood [55]. We employed a molecular rotor dye to screen OBOC

libraries for genetically encoded small illuminants [56]. For cell-based assays (Figure 4), we use live cancer cells as probes to screen OBOC libraries for cancer-targeting ligands [57-60]. We have also developed approaches to probe cellular functions, such as multiplexed intracellular staining with antibodies against signaling proteins. Alternatively, engineered cells incorporating optical reporter systems can be employed. Using these strategies, ligands capable of inducing osteogenic progenitor cell differentiation have been identified [61]. We have also utilized human brain endothelial cells to identify cell-penetrating peptides capable of crossing the blood-brain barrier *in vivo* (unpublished work).

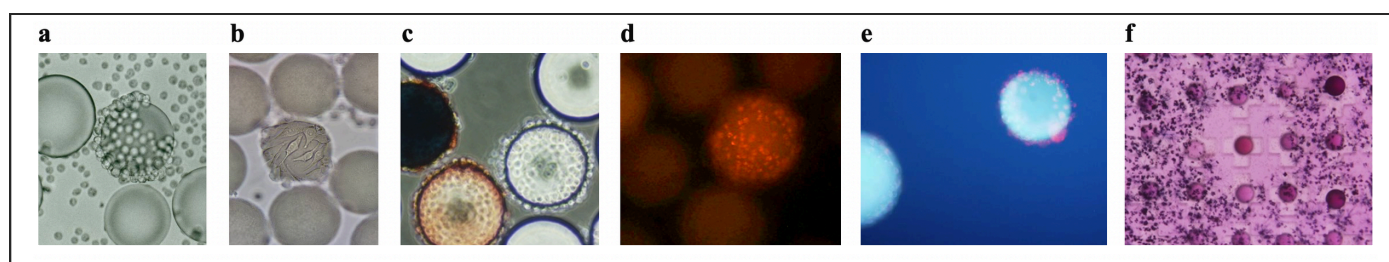


Figure 4. Various cell-based approaches to screen OBOC libraries: (a) cell binding assay, (b) cell binding and morphological changes, (c) cell-signaling assay; in-cell staining (brown) with anti-phospho-Erk antibody, (d) propidium iodide to stain cells on bead undergoing apoptosis, (e) cell-penetrating peptides delivered quantum dots inside brain endothelial cells coated on OB2C library beads, turning the cells pink, (f) library compounds released from immobilized OBOC bead, generating a cell-killing zone after addition of MTT.

We have developed a one-bead-two-compound (OB2C) configuration for cell-based assays, in which each bead displays both a fixed cell-capturing ligand and a random library compound on its surface. Upon incubation with live cells, each bead becomes coated with a monolayer of cells.

Cellular responses induced by interactions between tethered ligands and cell surface receptors can then be detected using imaging-based reporter systems [62,63]. This approach has enabled the discovery of pro-apoptotic ligands with anti-tumor activity in xenograft models prior to optimization [62,63].

Library compounds in OB2C or OBOC systems can also be released from the bead via cleavable linkers (e.g. disulfide bonds) to interact with cells bound to the bead surface or embedded within surrounding gel matrices [47,48]. For certain assays, photolithography has been used to fabricate PDMS microwell arrays for bead loading and screening [48] (Figure 4f).

In materials science, OBOC methods have been applied to discover membrane-active peptides [64, 65], some of which destabilize lipid bilayers or promote membrane fusion, while others exhibit antifungal activity [66]. OBOC approaches have also been used to identify self-assembling pentapeptides capable of forming nanoparticles, some of which can penetrate intact cells [67]. Methods have been developed to identify stealth peptides [68].

Many other groups have used OBOC approaches for basic research and drug discovery [2]. For example, Miller and others have used OBOC for the discovery of artificial enzymes [69,70]. Pei has successfully utilized OBOC to discover cell-penetrating cyclic peptides [71] and macrocyclic inhibitors against intracellular protein-protein interactions [72]. Meldal developed the OB2C method to display both substrate and library compounds on each bead, facilitating the discovery of protease inhibitors [73]. Heath [74] described an *in situ* click chemistry-based strategy for constructing multivalent protein capture agents directly on OBOC beads. This iterative process enables progressive affinity maturation, in which initial binders serve as templates for subsequent ligand assembly, leading to rapid improvements in affinity and specificity without prior knowledge of high-affinity ligands.

Magnetic and microfluidic devices have been used to increase the throughput of OBOC screening [75, 76]. A standard wide-field fluorescence microscope equipped with LED excitation and a CMOS camera has been shown to be highly efficient for OBOC screening [77]. Weller reported the use of bead arrays on microscope slide for efficient screening and mass spectrometry decoding of OBOC libraries [78].

mRNA-display and phage-display platforms enable ligand maturation through biological evolution via multiple sequential rounds of selection. In contrast, ligand maturation in OBOC and DEL platforms relies on iterative design of focused libraries combined with increasingly stringent screening conditions. Additional cycles of library design and screening can yield very high-affinity ligands. Common strategies to increase stringency include: (1) lowering target protein concentration, (2) increasing washing stringency, and (3) introducing competing ligands. For OBOC libraries, an additional useful parameter is reducing ligand density on the bead surface by down substituting the outer layer prior to library synthesis.

Overall, screening technologies are evolving toward greater integration of throughput, sensitivity, and functional relevance. The convergence of advanced imaging, microfluidics, chemical biology, and data-driven analysis is transforming combinatorial screening from a largely binding-centric process into a multidimensional platform capable of capturing complex biological responses. Continued innovation in this area will be essential for translating the expanding diversity of combinatorial libraries into meaningful therapeutic outcomes.

Encoding and Decoding of Synthetic Combinatorial Libraries

Efficient and high-fidelity encoding and decoding of library members are central to the utility of combinatorial chemistry, particularly for large, non-addressable libraries. For solution-phase mixture libraries, such as PS-SPCL, compound identity is determined through deconvolution. This iterative process involves testing defined sub-mixtures to progressively narrow down active components until the active structure is elucidated [12,13]. While

effective, deconvolution can be time-consuming, and the presence of multiple unrelated hits within the library can complicate interpretation.

Single-pharmacophore DEL utilizes covalently attached DNA barcodes to record synthetic history. Following affinity selection, bound library members are identified through PCR amplification and NGS of their associated DNA tags. Enriched sequences

are determined by comparing input library counts with post-selection counts. However, distinguishing true positives from background noise can be challenging. Emerging computational approaches, including artificial intelligence and active learning, are potential solutions to this challenge [79,80]. Dual-pharmacophore DEL evolved from the encoded self-assembling chemical (ESAC) library platform developed by Neri [30]. It affords dynamic screening and fragment based-drug discovery. Although dual-pharmacophore DEL provides substantially greater diversity, its screening and encoding processes are more complex than those of standard single-pharmacophore DEL [1-4].

Traditional OBOC libraries require external encoding strategies, as each bead carries a unique compound without intrinsic positional or genetic identifiers. In addition to DNA encoding, a variety of chemical and physical barcoding methods have been developed to address this challenge. Figure 3 shows the history on the development of OBOC encoding methods. Peptide or peptoid libraries can be directly decoded on-bead using automated Edman degradation sequencing [81], or compounds can be cleaved from

the bead for mass spectrometric (MS) analysis [78, 82,83]. For small-molecule OBOC libraries, we have used peptides as coding tags [38,39], while Still employed halophenol derivatives as tags decoded by gas chromatography [84]. Other decoding strategies include MS analysis of ladder sequences generated by partial Edman degradation [85], or ladder sequences formed during synthesis [86,87], Raman tag encoding [88-90], and colloidal barcoding [91].

Collectively, these encoding and decoding strategies reflect a broader trend toward increasing information density, speed, and compatibility with high-throughput screening platforms. DNA barcoding has enabled unprecedented scaling of library size, while advances in chemical and spectroscopic barcoding continue to enhance the practicality of bead-based systems. Looking forward, integration of encoding technologies with real-time screening, advanced imaging, and machine learning-driven analysis is likely to further streamline hit identification and accelerate the translation of combinatorial libraries into actionable chemical matter.

The Road Ahead: Future Opportunities for Combinatorial Libraries

The vast diversity and spatially segregated architectures enabled by OBOC combinatorial bead technology [10,92,93] and planar peptide microarrays [14], both emerging in the early 1990s, did more than introduce new experimental platforms—they reshaped how discovery is conceptualized. By enabling the simultaneous interrogation of thousands to hundreds of thousands of analytes, these technologies catalyzed a shift toward truly parallel experimentation. This “combinatorial mindset” rapidly extended beyond chemistry, influencing the development of DNA microarrays for high-throughput genomics [94-96] and bead-based multiplexed barcode platforms that underpin modern sequencing and diagnostic technologies [97-99]. In this sense, combinatorial thinking has evolved from a methodological innovation into a foundational framework for modern biology (Figure 5).

Proteomics has only begun to exploit this paradigm. OBOC peptide libraries can function as “compressive samplers” of proteomic complexity, selectively enriching subsets of proteins and reducing dynamic range—one of the central challenges in the field. Early demonstrations using gel-based [100] and mass spectrometric analytical approaches [101] highlight this potential, but a true inflection point will likely come from integration with artificial intelligence.

The convergence of combinatorial enrichment and machine learning-driven inference could transform biomarker discovery from a largely empirical process into a predictive, systems-level discipline.

Peptide and peptide-derived modalities are likely to play an increasingly central role in this evolution. Their ability to access extended binding surfaces, adopt defined secondary structures, and incorporate non-canonical chemistries positions them uniquely between small molecules and biologics. As combinatorial platforms become more integrated with machine learning and high-content screening, peptides provide a tractable and scalable modality for interrogating complex biological systems.

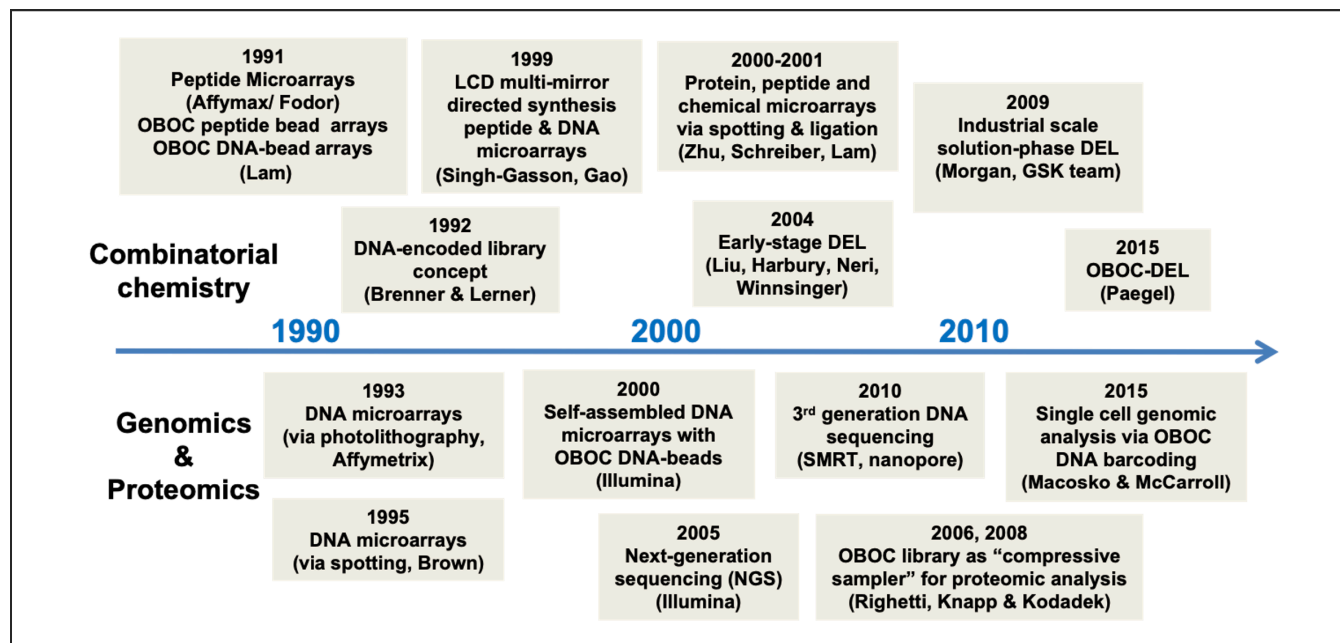


Figure 5. From combinatorial chemistry to genomics and proteomics

A broader frontier lies in the convergence of combinatorial chemistry with omics-scale interrogation. Rather than treating proteomes and cell lysates as passive outputs, they can be repurposed as active probes to map interactions across vast chemical spaces. For example, the use of phage-display proteome libraries to screen OBOC small-molecule libraries [102] begins to generate dense ligand–protein interaction networks. As these approaches scale, they will produce datasets whose complexity necessitates machine learning as an integral, rather than auxiliary, component of discovery.

In this context, OBOC and related platforms may serve as a critical bridge between experimental chemistry and data-driven biology.

One of the most underappreciated strengths of the OBOC platform is its intrinsic compatibility with functional screening. While many high-throughput platforms remain anchored to binding as a primary readout (i.e. affinity selection), OBOC enables direct

selection based on biological activity in live cells (Figure 4). This distinction is fundamental: it allows discovery to proceed at the level of phenotype rather than proxy. The identification of chemical compounds that mediate tumor targeting, cell penetration, blood-brain barrier traversal, cell differentiation, metabolic changes, or pathway modulation underscores this capability. Looking ahead, integration with high-content imaging, organoid systems, and immune system mimics using advanced microfluidics [103] will enable functional screening in increasingly physiologically relevant microenvironments, shifting combinatorial discovery from a target-centric to a systems-level paradigm.

Beyond biomedicine, the implications extend to materials science. Current materials discovery efforts remain constrained by relatively low-diversity, planar array screening approaches [104], leaving large regions of chemical space unexplored. OBOC platform offers an alternative paradigm: massively parallel synthesis and screening with built-in diversity and functional readouts.

Early studies on membrane-active peptides [64,65] and self-assembling peptides [67] suggest that such approaches can uncover emergent physicochemical properties of synthetic materials that are difficult to predict *a priori*. Extending this framework could enable the discovery of adaptive, bio-interfacing, and environmentally responsive materials.

OBOC platform also enables unconventional strategies in small-molecule discovery. Beyond identifying ligands, they can be used to discover compounds that sequester or neutralize other molecules. The identification of strychnine-binding “caging” agents, with demonstrated *in vivo* protection (unpublished work), highlights the potential of this concept. Such approaches suggest a complementary paradigm to classical pharmacology—one based on physical capture rather than biochemical antagonism—and could be extended to toxins, metabolites, and signaling molecules.

The need for rapid responses to emerging infectious diseases further underscores the value of combinatorial approaches. OBOC and DEL platforms enable direct screening against microbial targets ranging from isolated proteins to intact pathogens. The rapid identification of SARS-CoV-2 spike protein binding peptides that supported diagnostic development [50] illustrates this capability. More broadly, combinatorial platforms can function as front-line discovery engines, generating ligands for diagnostics, targeting, and therapeutic intervention of global outbreaks under compressed timelines.

A parallel challenge lies in accessing structurally complex chemical space. Many of the most potent natural products are large macrocycles and non-peptidic, yet they remain difficult to translate into combinatorial formats. Overcoming this limitation will require new synthetic strategies that render complex architectures modular and “combinatorially accessible.” At the same time, naturally occurring scaffolds such as cyclotides [105,106] provide highly stable frameworks that can be diversified through sequence grafting, genetically [107] or chemically [108], enabling libraries that combine structural precision with functional diversity.

Taken together, these developments point to a broader conclusion: OBOC, DEL, and related combinatorial technologies should not be viewed merely as tools for generating molecular diversity, but as platforms for interrogating—and ultimately engineering—complex biological and chemical systems. Their greatest impact will emerge at the interfaces: between chemistry and biology, experiment and computation, and molecules and systems. In this context, the true promise of combinatorial chemistry lies not only in accelerating discovery, but also in redefining how discovery itself is conducted. Community-driven efforts such as the Peptide Drug Hunting Consortium (PDHC) are helping to formalize this convergence by integrating advances in peptide design, synthesis, screening, and data science into a cohesive discovery framework.

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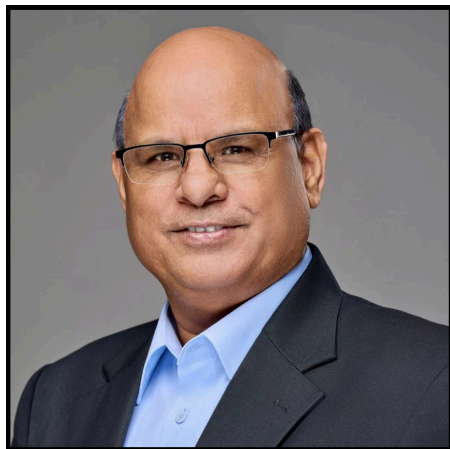
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**Synthetic Combinatorial Libraries:
Four Decades of Peptide-Driven Innovation
and the Road Ahead**

A Perspective for the Peptide Drug Hunting Consortium



PEPTIDE NEWS

PDHC CHRONICLE
JAN - JUNE 2026

VED SRIVASTAVA

SUMMARY

Recent **clinical and regulatory advances** underscore a rapidly accelerating peptide therapeutics landscape, driven by transformative efficacy in obesity and by expanding innovation in macrocyclic modalities. Leaders such as Eli Lilly, AbbVie, Roche, and Novo Nordisk are advancing next-generation incretin and non-incretin (e.g., amylin-based) therapies, while innovators including Aktis Oncology are extending peptides into radioligand therapy (RLT).

On the **business front**, ecosystem consolidation and partnering are accelerating, with CordenPharma's acquisition of AmbioPharm and collaborations spanning Regeneron Pharmaceuticals, Novartis, Parabilis, and Unnatural Products, alongside capital deployment by Full-Life Technologies, Syneron Bio, and licensing from ZonsenPepLib highlighting strong momentum in macrocyclics, radiotherapeutics,

and AI-driven discovery. Meanwhile, China continues to scale innovation hubs and global manufacturing, with its peptide market projected to reach ~¥1.42 trillion (~\$200B), driven primarily by surging demand for metabolic disease treatments.

BREAKING NEWS

June 9, 2026 | Perpetual Medicines and Third Rock Ventures announced a development candidate delivered in under 18 months, validating their computational physics and AI-driven drug discovery platform. By combining rigorous physics-based modeling with predictive AI, the approach bypasses traditional iterative bottlenecks of empirical drug design. This triggers a milestone payment and highlights accelerated R&D productivity. A second program is already progressing through lead optimization. [Read more](#)

June 4, 2026 | Peptide biotech Parabilis Medicines has unveiled plans for an IPO on Nasdaq under the ticker PBL5. It could

raise up to \$476.4 million, following a recent partnership with Regeneron. The company plans to offer 25 million shares at the midpoint price of \$18 per share, with proceeds primarily funding the advancement of its lead candidate, zolucateotide, into Phase 3 trials for desmoid tumors. Formerly known as FogPharma, Parabilis intends to list on Nasdaq under the ticker PBL5. [Read more](#)

CLINICAL AND TECHNOLOGY ADVANCEMENT

May 21, 2026 | Eli Lilly and Company reported strong Phase 3 TRIUMPH-1 results for its triple-agonist retatrutide, demonstrating substantial and clinically meaningful weight loss across all doses in adults with obesity or overweight without

diabetes. At 80 weeks, patients receiving the 12 mg dose achieved an average weight reduction of 70.3 lbs (28.3%), with 45.3% losing at least 30% of body weight, levels typically associated with bariatric surgery, while those on 9 mg and 4 mg lost 64.4 lbs (25.9%) and 47.2 lbs (19.0%), respectively. In an extension study, individuals with baseline BMI ≥ 35 on the 12 mg dose reached up to 85.0 lbs (30.3%) weight loss at 104 weeks. [Read more](#)

May 04, 2026 | Aktis Oncology announced initiation of a Phase 1b clinical trial of AKY-2519, a B7-H3-targeted miniprotein radioconjugate, in patients with metastatic castration-resistant prostate cancer (mCRPC), including both PLUVICTO®-naïve and experienced cohorts,

as part of a broader two-trial strategy that also includes a planned basket study in lung, colorectal, and other high B7-H3-expressing solid tumors; preliminary results expected in 2027. AKY-2519 is its second clinical-stage miniprotein radioconjugate alongside AKY-1189, which is also in Phase 1b development. [Read more](#)

April 28, 2026 | Zealand Pharma announced that Boehringer Ingelheim's glucagon/GLP-1 dual agonist survodutide delivered compelling Phase 3 results in the SYNCHRONIZE-1 trial, achieving up to 16.6% mean weight loss (≈ 39.2 lb / 17.8 kg) over 76 weeks in adults with obesity or overweight without type 2 diabetes, significantly outperforming placebo (3.2%; $p < 0.0001$). [Read more](#)

April 16, 2026 | A major [FDA](#) peptide policy shift was underway. The FDA is actively reviewing the lifting of regulatory restrictions on several peptides, including Melanotan II (MT-II), BPC-157 (osteogenesis and bone healing), and MOTS-C (anti-aging), with a major advisory decision expected at the Pharmacy Compounding Advisory Committee (PCAC) meeting in July 2026. Up to approximately 14 previously restricted peptides could be reintroduced under regulated compounding pathways, though not as fully approved drugs. This development signals a potential reopening of clinical and commercial pathways for certain non-approved peptides. Please feel free to raise any concerns about this policy shift. [Read more](#)

March 26, 2026 | U.S. Food and Drug Administration has approved Awiqli (insulin icodec- abae), injection 700 units/mL, the first and only once-weekly, long-acting basal insulin, from Novo Nordisk, marking the first and only once-weekly basal insulin for adults with Type 2 Diabetes. Awiqli® offers a more convenient alternative that may better align with patient preferences and adherence. [Read more](#)

March 18, 2026 | Protagonist Therapeutics announced that Johnson & Johnson has received U.S. FDA approval for ICOTYDE™ (icotrokinra), the first and only oral IL-23 receptor-targeted peptide for treating moderate-to-severe plaque psoriasis in adults and adolescents (≥ 12 years, ≥ 40 kg) eligible for systemic therapy or phototherapy. The once-daily therapy demonstrated complete skin clearance and a favorable safety profile across four Phase 3 trials involving over 2,500 patients. Under their longstanding collaboration with Janssen Biotech, Johnson & Johnson will commercialize ICOTYDE, while Protagonist receives a \$50 million milestone payment and remains eligible for up to \$580 million in additional milestones plus tiered royalties of 6–10% on global net sales, with the top royalty tier of 10% applying to sales above \$4 billion. [Read more](#)

March 9, 2026 | Regeneron Pharmaceuticals reported positive topline Phase 3 results of Olatorepatide, a dual GLP-1/GIP receptor agonist, in adults with obesity or overweight, where once-weekly treatment led to

statistically significant weight reduction versus placebo and up to 19% mean body-weight loss at 48 weeks, with up to 97% of participants achieving at least 5% weight loss. The randomized, double-blind study enrolled 604 patients across 33 sites and met both co-primary endpoints across 5 mg, 10 mg, and 15 mg doses, while also showing a favorable gastrointestinal tolerability profile, with low rates of nausea ($< 10\%$) and vomiting ($< 5\%$) and fewer discontinuations than comparable dual incretin trials. Olatorepatide from Hansoh Pharma and trials are conducted in China. Regeneron holds ex-China rights under its licensing agreement, while Hansoh retains Greater China rights, and the company plans to initiate its global registrational program later this year. [Read more](#)

Mar 09, 2026 | AbbVie announced positive topline results from a Phase 1 multiple ascending dose study of ABBV-295, a long-acting amylin analog, demonstrating clinically meaningful, dose-dependent weight loss of approximately 7.8% to 9.8% over 12–13 weeks across weekly, biweekly, and monthly dosing regimens, compared to negligible changes with placebo. The therapy was generally well tolerated at all dose levels, with no serious adverse events reported and mostly mild, transient gastrointestinal side effects occurring early in treatment. These findings support continued development of ABBV-295 as a potentially differentiated, non-incretin-based therapy for chronic weight management. [Read more](#)

March 04, 2026 | Roche reported positive Phase II results from the ZUPREME-1 trial of petrelintide, an investigational once-weekly amylin analog for overweight and obesity, demonstrating statistically significant and clinically meaningful weight loss across all five dose arms versus placebo in 493 participants (mean BMI 37 kg/m²). Weight reduction reached up to 10.7% at week 42 compared to 1.7% with placebo (p<0.001), with effects sustained beyond the 28-week primary endpoint. The data support further development of petrelintide as both a mono-therapy and a combination agent for chronic weight management, with female participants exhibiting greater weight loss than male participants. [Read more](#)

Feb 27, 2026 | The FDA approved once-weekly YUWIWEL® (navepegritide) by Ascendis Pharma for children aged 2 years and older with achondroplasia, making it the first and only therapy designed to provide continuous systemic exposure to C-type natriuretic peptide (CNP) over a weekly dosing interval to increase linear growth in this population under the Accelerated Approval Program. The therapy, a once-weekly prodrug of CNP, targets overactive FGFR3 signaling underlying achondroplasia and is expected to become commercially available in early Q2 2026.

Jan 05, 2026 | Novo Nordisk's announced Wegovy® pill, the first oral GLP-1 medicine for weight loss in adults, is broadly available across the United States following FDA approval in

December 2025. In the OASIS 4 trial, the tablet demonstrated an average weight loss of about 17% if patients remained on treatment (and ~14% regardless of discontinuation), compared with ~2–3% for placebo, when used alongside diet and exercise. The once-daily pill is offered at an introductory self-pay price of \$149 per month for the 1.5 mg starting dose and is being distributed through 70,000+ pharmacies nationwide, including CVS and Costco, as well as telehealth platforms. [Read more](#)

BUSINESS AND COLLABORATIONS

May 27, 2026 | Basel-based CordenPharma agreed to acquire AmbioPharm, a U.S.-headquartered peptide CDMO with facilities in South Carolina and Shanghai, strengthening its global manufacturing footprint. By integrating AmbioPharm's assets, CordenPharma improves supply flexibility, scale-up pathways, and regional manufacturing options for customers, positioning itself to better meet surging demand—particularly from GLP-1 therapeutics. [Read more](#)

May 18, 2026 | Parabilis Medicines entered a strategic multi-target collaboration with Regeneron Pharmaceuticals to develop novel Antibody-Helicon™ Conjugates (AHCs), combining Parabilis's cell-penetrant Helicon™ peptide platform with Regeneron's antibody expertise to address historically “undruggable” intracellular targets. The agreement includes \$125 million

up front to Parabilis along with up to ~\$2.2 billion in potential milestone payments and tiered royalties on future sales. Regeneron will lead development, manufacturing, and commercialization, positioning the collaboration to advance a new class of targeted therapeutics across multiple disease areas. Parabilis plans an IPO to fund tumor drug's phase 3 push. [Read more](#)

May 18, 2026 | Full-Life Technologies announced the closing of a \$150 million financing package led by Vivo Capital, with participation from SK Biopharmaceuticals and multiple existing investors, to accelerate its evolution into a fully integrated global radiotherapeutics company. Proceeds will advance key clinical-stage assets, including the potentially best-in-class [²²⁵Ac]-FL-020 for prostate cancer and the first-in-class [²²⁵Ac]-FL-261 for solid tumors, while supporting the expansion of its UniRDC™-derived pipeline, which is expected to reach three differentiated clinical programs by year-end 2026. [Read more](#)

March 31, 2026 | Syneron Bio, a Beijing-based intelligent platform-driven macrocyclic peptide drug discovery company, announced the successful close of a \$150 million Series B financing led by an international life sciences fund and others to support further advancement of Syneron's proprietary Synova™ macrocyclic peptide discovery platform and accelerate its diversified pipeline toward clinical development. [Read more](#)

Feb 18, 2026 | Unnatural Products, Inc. (UNP) announced a research collaboration and licensing agreement with Novartis to develop macrocyclic peptide therapeutics against historically “undruggable” targets, initially focused on cardiovascular disease. The partnership combines UNP’s AI-enabled macrocycle discovery platform—integrating computational design, high-throughput synthesis, and direct-to-biology screening—with Novartis’ global development and commercialization capabilities. Under the terms, UNP is eligible for up to \$100 million in upfront and pre-IND milestones, up to \$1.7 billion in development, regulatory, and commercial milestones, and tiered royalties ranging from mid-single to low double percentages on net sales. [Read more](#)

Jan 13, 2026 | Zonsen PepLib, a China and Boston-based biotech, announced a worldwide license agreement with Novartis for an undisclosed internally developed peptide-based radioligand therapy (RLT) asset, under which Novartis gains exclusive global rights and will lead all development and commercialization activities. The partnership leverages Novartis’ established leadership in RLTs to advance the program into its next stage, with the asset expected to complement its existing oncology portfolio and potentially deliver a new targeted treatment option for patients worldwide. Under the terms, PepLib will receive a \$50 million upfront payment and is eligible for additional development, regulatory, and sales milestone payments, as well as tiered royalties on future global net sales.

Jan 06, 2026 | AstraZeneca is investing up to \$18.5bn (including \$1.2bn upfront) in a major collaboration with CSPC Pharmaceutical Group to access sustained-release delivery technology and AI-enabled peptide drug discovery capabilities aimed at accelerating its weight management strategy. The deal grants AstraZeneca exclusive global rights to eight preclinical obesity assets, including SYH2082, a long-acting GLP-1/GIP receptor agonist with potential once-monthly dosing. The partnership marks one of the largest transactions in the obesity and metabolic disease space, underscoring the growing strategic importance of next-generation peptide therapeutics and long-acting incretin-based therapies. [Read more](#)

KEY STRATEGIC TAKEAWAY FOR 2026

Mid-2026 represents a regulatory and strategic inflection point for peptide therapeutics in the U.S., with forthcoming FDA decisions poised to reshape the competitive landscape. While GLP-1-based therapies remain the dominant commercial anchor, the field is rapidly expanding beyond metabolic disease into cardiovascular, CNS, inflammatory, and oncology indications. In parallel, high-value modalities, including macrocyclic and oral peptides, are gaining clinical and partnership validation, reinforcing their translational potential. Concurrently, the AI-driven drug discovery ecosystem is becoming more structured, spanning pure AI-peptide startups and broader AI-first peptide-based drug discovery companies such as Peptilogics, Ardigen, Syneron Bio and Perpetual Medicines, Tandem AI, Absci, and Isomorphic Labs, just to name a few.

Strategically, large pharmaceutical companies are leveraging GLP-1-driven cash flows to build diversified, multi-modality pipelines. Industry leaders continue to set benchmarks in efficacy and delivery, while emerging players differentiate through novel biology and platform innovation. At the same time, major incumbents are expanding through partnerships and portfolio optimization to access high-growth segments.

China is rapidly consolidating its role as both a manufacturing powerhouse and fast-follower innovator, particularly in oncology and GLP-1 generics following patent expiration.

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SPECIAL ACKNOWLEDGMENTS TO AUTHORS, SPONSORS & EDITORIAL TEAM

FIRST, I WISH TO ACKNOWLEDGE THE AUTHORS CONTRIBUTING TO OUR SECOND ISSUE! THANK YOU!!!

Charlie's "PDHC at an Inflection Point: A Vision for 2026 and Beyond" article brings both hope and confidence to me that, without question, the PDHC has a new great President, as I stepped down to be President-Emeritus and focus on other PDHC priorities (e.g., the PDHC Chronicle)! There are many things that Charlie has noted within the scope of both a near-term and future vision, and, as many of you may know him, whatever is shared in his article is the tip of the iceberg! As captured in the abstract, Charlie "outlines how we will accelerate peptide drug discovery by leveraging the collective genius of the PDHC network and a deliberate integration of our diverse scientific, entrepreneurial, and translational expertise." His vision should reflect all of our (PDHC and beyond) shared vision as Peptide Drug Hunters and the collective genius that the PDHC was designed to enable through its modus operandi. Indeed, as Charlie states in the subsection entitled "2026: From Community to Platform" and the transition from a prior organizational building mode, PDHC's current focus is defining roles, resources, and infrastructure by way of four pillars: (1) Leadership with clarity and accountability; (2) Programs that create signal; (3) Funding the mission responsibly; and (4) Clearing paths for contribution. Charlie's PDHC vision will be fulfilled by engaged responses to his invitation and individual contributions. Please contact Charlie and the PDHC Leadership Team to become involved in shaping the future of peptide drug discovery through science, innovation, entrepreneurship and the development of breakthrough peptide medicines!

Anthony's Leadership Insight article "Leading Innovation: Creating the Condition for Scientific Breakthroughs" is a very well-articulated and expert testimony to achieving innovation in exploratory science, sharing the wisdom that it may not be a simple, straightforward path. This article shares insights from Anthony's days at Merck (MSD Singapore) alongside his colleagues and collaborators (A*STAR), including Charlie and myself, to leverage all know-how in an ambitious effort to 'drug the undruggable' with a focus on optimizing cell-permeable macrocyclic peptides. Pivoting and perseverance were key attributes toward making significant progress, and exemplifying this was innovation focused on intracellular delivery of bioPROTACS as well as mRNA encoding protein-based degraders of a specific target using lipid nanoparticles and peptide-based coacervates. Noteworthy, a supportive leadership culture to the scientific team throughout made the difference, especially during times of need and even pivoting in response to unexpected data. I wish to echo Anthony's concluding remarks, *"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."*

Kit Lam's perspective “Synthetic Combinatorial Libraries: Four Decades of Peptide-Driven Innovation and the Road Ahead” is an outstanding reflection of the many advances in diverse platforms (e.g., OBOC and DEL) that have greatly contributed to peptide drug discovery. Having known Kit since his pioneering work at the University of Arizona that led to what now exists within the scope of synthetic combinatorial libraries, it was an added pleasure that he accepted our invitation to author this expert perspective! I hope the readership will learn about the historical breakthroughs and development of new technologies that have been achieved, as well as the integration of the screening and data science that is now being exploited by synthetic combinatorial libraries.

XtalPi's team of Doudou Qin, Genwei Zhang, Weijia Wei, Yanwei Ding, Hongfei Dai, Nan Jing, Qingxia Zhang, Kuo Yu & Lipeng Lai wrote a wonderful PDHC spotlight article on “Rapid Cyclic Peptide Development Enabled by Artificial Intelligence” that highlights their successful efforts to build an AI-enabled workflow for rapid, target-defined cyclic peptide development that further integrates mRNA display-based library screening with AI-assisted sequence and structural optimization. Ultimately, the strategic goal of this work is to not only generate more candidates but also to improve the overall process of translating experimental data into design decision-making, and especially for ultra-large peptide libraries of various sequences and cyclization architectures. The XtalPi team's perspectives certainly resonate with many other peptide drug hunters, and I appreciated their specific comment, *“In practical terms, AI is used to interpret emerging sequence–activity relationships from screening data, rank productive substitutions, and narrow the set of variants that need to be synthesized and tested. Its value lies in maximizing information gain per DMTA (Design-Make-Test-Analyze) cycle rather than merely assigning a score to each sequence.”*

Maestro Therapeutics' team, including myself and my sons Thomas & Jonathon, recently shared a special PDHC Spotlight article on “A Seven-Year Adventure in Peptide Drug Discovery” that highlights our scientific consulting business, professional and entrepreneurial mentoring, and public outreach. As a key opinion leader in peptide drug discovery, I've supported many biotech, pharma, and venture capital companies to advance their R&D efforts from early stage to into-the-clinic, partnering, mergers, and IPOs. Over the last four years, Thomas & Jonathon expanded the impact of Maestro Therapeutics on the R&D programs of several biotechs, and transformed it into a unique family business venture. We appreciate the testimonials given by the CEOs of Aqur Biosciences, BioAge Labs, Courage Therapeutics, Entrada Therapeutics, EpiAxis Therapeutics, 48Hour Discovery, Ladder Bio, Onca Bio, Pepticom, Receptor.AI, and Vivtex in this PDHC Spotlight. We are quite fortunate to work with such outstanding scientific teams and partners to advance peptide drug discovery and future peptide medicines.

Ved's Peptide News for January-June 2026 shares a synopsis of recent clinical and regulatory advances in a rapidly accelerating peptide therapeutics landscape, with an emphasis on transformative and evolving drugs for obesity. Unquestionably, there are many pharma and biotechs engaged in such efforts, including Eli Lilly, AbbVie, Roche, and Novo Nordisk.

Moreover, we are witnessing advancements in both next-generation incretin and non-incretin (e.g., amylin-based) therapies. Beyond obesity, there are noteworthy innovative R&D efforts in peptide-based radioligand therapy (RLT) by many biotechs, including Aktis Oncology, as well as a record-breaking \$670 million initial public offering by Parabilis Medicines (PBLS, Nasdaq) in June. Specifically, the Parabilis Medicines IPO marks the largest venture-backed biotech IPO in history, eclipsing previous IPOs. The PDHC Chronicle will be inviting all of these biotech and pharma companies to share their stories in future articles! Business-wise, the worldwide peptide R&D ecosystem reflects ongoing consolidation and partnering, such as CordenPharma's acquisition of AmbioPharm and collaborations spanning Regeneron Pharmaceuticals, Novartis, Parabilis Medicines, and Unnatural Products as well as capital deployment by Full-Life Technologies, Syneron Bio, and licensing from ZonsenPepLib. Lastly, peptide R&D continues to gain more momentum in macrocyclics, radiotherapeutics, and AI-driven discovery. Notably, Ved points out that China continues to build innovation hubs and global manufacturing, expecting to reach ~¥1.42 trillion (~\$200B) in its peptide market projections to meet surging demand for metabolic disease treatments. We appreciate Ved's many roles within the PDHC, and thank him for compiling a great list of accomplishments through the first half of 2026 by peptide drug hunters.

SECOND, WE WISH TO ACKNOWLEDGE THE EDITORIAL REVIEWERS AND PUBLISHING TEAM FOR THEIR MANY CONTRIBUTIONS TO LAUNCH THIS ISSUE.

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THIRD, NONE OF THIS WOULD BE POSSIBLE WITHOUT THE GENEROUS SUPPORT OF OUR SPONSORS. WE ARE GRATEFUL FOR THEIR CONTINUED SUPPORT OF THE PDHC CHRONICLE AND LOOK FORWARD TO PARTNERING WITH THEM IN FUTURE ISSUES.

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Quality Peptides and Services

康龙化成
PHARMARON

VIVTEX

COURAGE
THERAPEUTICS

PeptiLand
安澜泰业

X-CHEM

PeptiFinder
BIOTECH

PolyPeptide

Schrödinger

RECEPTOR.AI

Excellerate
Bioscience

constructive.bio
Life, reimagined.

LASTLY, WE EXTEND A WELCOME TO OUR READERSHIP TO COMMUNICATE WITH US ABOUT OPPORTUNITIES TO PUBLISH IN OUR H2 2026 ISSUE. PLEASE REACH OUT TO US (INCLUDING DANIELLE) IF YOU ARE INTERESTED!

With warmest wishes,

Tomi Sawyer, Editor-in-Chief

On behalf of the PDHC Editorial Team

Charlie Johannes, Executive Editor

Ved Srivastava, Executive Editor

Thomas Sawyer, Managing Editor

Jonathon Sawyer, Editor-at-Large