PEPTIDE DRUG HUNTING CONSORTIUM www.peptidedrughunting.org

PEPTIDE DRUG HUNTING

OUR CHRONICLE OF ENTREPRENEURIAL SCIENCE & INNOVATIVE TECHNOLOGIES EMPOWERING BREAKTHROUGH MEDICINES

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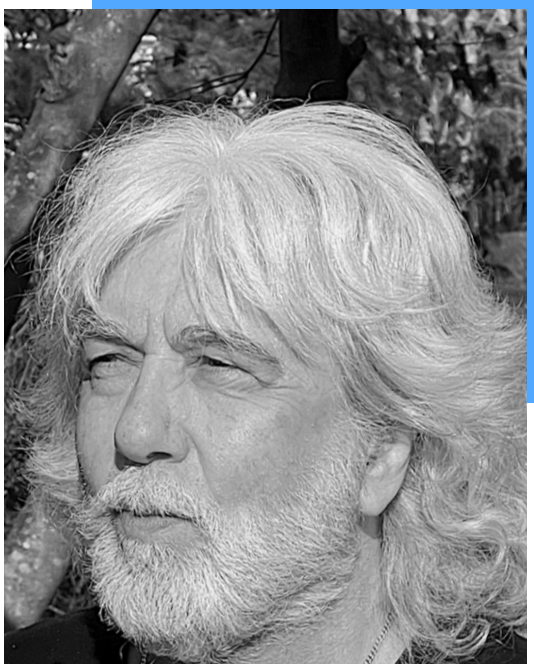
OUR INAUGURAL ISSUE OF THE PDHC CHRONICLE!

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 this inaugural issue of the PDHC Chronicle. We have several outstanding articles for you to enjoy, and this inaugural issue adds a special finale to a great year for the PDHC, including building the organizational infrastructure, partnering with conferences that highlight peptide drug hunting, establishing a first wave of founding sponsors, and recently achieving our 501(c)(3) non-profit status!



A Commentary by the Editor-in-Chief

The PDHC Chronicle editorial team has established an outstanding opportunity to future contributors with respect to 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. Other high-level topics include: Leadership Insight, PDHC Vision, PDHC Spotlight, Peptide News, Peptide Fun Facts, Conference Highlights, and PDHC Upcoming Events.

We wish the PDHC Chronicle to be special to all peptide drug hunters, including those from academia, biotech, pharma, R&D organizations, service providers, and investors!

Please let us know if you are interested to share 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 final article entitled Special Acknowledgements to Authors & Editorial Team for their contributions to this inaugural issue.

With warmest wishes,

Tomi Sawyer
Editor-in-Chief

PDHC

DECEMBER 2025 | ISSUE 1

LEADERSHIP

INSIGHT: LEADING FROM THE OUTSIDE

by **Charles W. Johannes**,
Co-Founder, VP, & Board Member, PDHC

Leadership is often associated with authority and control, but in consultancy it takes a different form — shaping outcomes without formal power.

Leadership in Consultancy

Consultancy relies on vision, influence, and the ability to empower others. At its best, consultancy is about defining clear objectives, aligning diverse expertise, and creating the conditions for others to succeed. The current scientific and business environment has only increased the demand for this type of leadership. Difficult science, shifting political priorities, and financial pressures have led many organizations to externalize talent. A cautious investment climate, an abundance of entrepreneurial ventures, and a relatively young talent pool have accelerated the use of consultants, CROs, and virtual company models. These approaches reduce infrastructure costs while delivering targeted expertise when needed.

Framework for Collaborating

In my own work, I have seen this across several dimensions. Through the Peptide Drug Hunting Consortium, we built a framework for collaboration that unites industry, academia, and entrepreneurs around shared challenges. In venture due diligence, I've balanced the perspectives of investors, biotech founders, and CRO partners to ensure risks are understood without overlooking opportunities. In advisory and fractional leadership roles, continuity has been key: setting up systems and processes that allow progress to continue even when I step back. Perhaps most rewarding has been mentoring younger teams, helping them navigate the complexities of translational science and organizational growth.

Consultancy as Catalysis

Yet consultancy is more than filling gaps. Done well, it acts as a catalyst — challenging assumptions, sharpening strategy, and connecting groups that might not otherwise align. Consultants build trust, balance competing stakeholder interests, and help teams make decisions under uncertainty. In this way, external leadership expands an organization's capacity to innovate.

Contributing & Enabling

In all these contexts, my role has been twofold: contributing specific scientific and experience-based insights, while also acting as an enabler — aligning people, creating momentum, and ensuring that progress continues. This dual contribution highlights the unique value of external leadership and its lasting impact on organizational success.

PEPTIDE DRUG HUNTING CHRONICLE

PDHC VISION

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WENDY J. HARTSOCK
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HIGHLIGHTS

In this inaugural article, we share our inspiration and founding vision for the Peptide Drug Hunting Consortium (PDHC) as a global initiative to champion entrepreneurial science and innovative technologies in peptide drug discovery.

For each of us, building the PDHC has been a memorable and rewarding journey uniting bold ideas, dedicated people, and a shared belief that peptides still have untapped medical applications.

For the broader community, we hope this marks the beginning of an adventure that is both inspiring and catalytic—a call to advance the multidisciplinary science, innovation, and strategy that will define the next generation of peptide therapeutics.

OUR MUSINGS OF BEGINNING THE PDHC

"First, I wish to share my warmest wishes to all who may be reading this inaugural article in our PDHC Chronicle Peptide Drug Hunting! After 40+ years as a (mostly) peptide drug hunter, I am pleased to share in the beginning of the Peptide Drug Hunting Consortium and envision how it may enable the science and business enterprise of peptide medicines for the benefit of humanity. My experience has been blessed with many opportunities to contribute to drug discovery campaigns, including those targeting GPCRs, proteases, intracellular protein-protein interactions and enzymes, as well as diverse peptide modalities, ranging from linear to macrocyclic and conjugates thereof. It has been my desire to create this consortium for the worldwide peptide drug hunting community and share my adventures, odyssey, and legacy in gratitude for the gift of being a scientist."

“There are moments in science when the right combination of curiosity, controversy, and collaboration ignites something bigger than the sum of its parts. For me, one of those moments came in 2015—what I’ve since come to think of as the third wave of peptide therapeutics.

At the time, I had the privilege of collaborating with Tomi, a humble visionary within Merck (MSD), on a project with A*STAR in Singapore. The literature was buzzing—sometimes antagonistically—with debates on what peptides could or couldn’t do. But beneath the noise, there was a quiet convergence happening: better chemistry, more predictive modeling, a renaissance of interest in intracellular targets long considered undruggable.

Tomi’s passion for the field was contagious. What began as a Merck initiative to explore peptides soon caught fire, spreading globally and influencing others—myself included. It planted the seed that would grow into the Peptide and Protein Society Singapore (P2S2) and later a national peptide engineering program. We were fortunate to build in an environment that encouraged bold thinking, including collaborators like Sir David Lane and Greg Verdine pushing the boundaries of what chemistry and biology could achieve together.

Years later, as I moved into my role at FOG Pharma, the momentum didn’t slow. The Helicon™ platform was born, and with it, novel peptide therapeutics like FOG-001. At the same time, I reconnected with Wendy at Aralez Bio, a rising biotech that was pushing the limits of biosynthetic amino acids. The landscape was evolving—but one thing was clear: even with growing commercial success (GLP-1s, GIPs, IL-23 antagonists), the peptide field was still missing something. Specifically, it lacked a community built to explore without the pressure to commercialize too early. It lacked a home for ideas that were too translational for academia, but too risky for venture. It lacked connective tissue between innovation and infrastructure.
That’s when the idea for the PDHC began to crystallize. Not as a company. Not as a lab. But as a mission-driven nonprofit—a place where scientists, entrepreneurs, and technologists could tackle the hardest problems in peptide drug discovery. A place built to de-risk, to dream, and to deliver.

I often wonder what the fourth wave of peptides will look like. Will it be shaped by AI? By noncanonical biology? By new delivery modalities? Or will it come from unexpected places—people and perspectives we haven't yet included? Whatever it is, I hope it will be collaborative, open, and unapologetically ambitious. Because the future of peptide therapeutics isn’t just about the next drug—it’s about the ecosystem we build to make the impossible, possible.”

“To me, the PDHC represents the ultimate collaboration model to realize ideas from inception to market and tackle barriers to the peptide drug discovery and development process. It is a tool to help every member of the peptide community from entrepreneurs to seasoned drug hunters connect with the right information (which could be in the form of a chronicle, website, network, 1:1 connections, and so many other possibilities).

As a non-profit, the PDHC is accessible to every member of the community so that they can participate in initiatives and gain benefit from shared knowledge and collective innovation. When Tomi approached me to help formally launch the PDHC, we shared the experience (Tomi to a few orders of magnitude above mine) of being asked the same questions repeatedly by different peptide drug hunters looking for answers for things as simple as the best technique to determine and remove trifluoroacetic acid to pathways of starting a company. And that is what the PDHC can offer, solutions that impact all aspects of the peptide drug hunter’s mission.”

VISION OF THE FUTURE PDHC

"Perhaps to look into the future is to imagine what may be and dedicate one's effort to make it happen. From a past interview discussing the role of a drug discovery scientist and addressing a question of what makes research important, I stated, "The most important impact of this research, whether my own or that of other biomedical scientists, is that of providing hope a reality — for some a cure and others a chance to alleviate some of the suffering they live with." Providing hope a reality has been my passion as a drug discovery scientist. It is also something which I seek to inspire in others, including peptide drug hunters; the peptide medicines we bring forth to humanity ought to provide hope a reality for those in need. I'm pleased to have an outstanding inaugural PDHC Leadership Team, Entrepreneurial Advisory Board, and Entrepreneurial Business Network, many PDHC Followers (>2,800), PDHC Media Partners, and PDHC Sponsors! Thank you, all, for your support to this laudable cause!"

"Sometimes I wonder: if we were to start over—today—how would we build a drug discovery ecosystem around peptides? Not just a company or a lab, but a true ecosystem. One that prioritizes the most impactful science. One that welcomes uncertainty. One that doesn't ask, "How fast can we get to market?" but instead, "What new capabilities are needed to unlock biology and medicines we can't currently touch?"

That's the spirit behind the PDHC. Not another incubator. Not another accelerator. But something different—a nonprofit, purpose-built to serve a translational void that many of us in science have felt for years.

The PDHC was born from the conviction that the next wave of peptide innovation won't come from any single lab, company, or investor, but from the space in between. It will require new chemistries, noncanonical thinking, AI models that learn from sparse data, and an openness to collaboration that goes beyond institutional boundaries.

So where are we going? We're setting our sights on three areas where progress has stalled:

- Predictive design and screening: tools to go beyond brute-force selection, and instead use smart, learnable models.
- Scalable, modular synthesis: platforms to make what we imagine, not just what's convenient.
- Integrated delivery systems: solving for intracellular targets, oral bioavailability, and stability in ways that aren't siloed by modality.

But beyond the tech, the structure matters. We chose to build PDHC as a nonprofit to keep the mission at the center: scientific advancement in service of patients, not shareholders. We think that's the kind of clarity that can attract both visionary talent and aligned capital—including venture partners who see value in early de-risking, not just in fast exits.

The question I keep coming back to is, "How do we build something durable? Not just flashy or fundable—but an institution that can move the needle for the next generation of peptide drug hunters?"

The answers won't come from any one of us. That's the point. But if you believe that peptides are more than a niche, if you believe there's untapped biology still waiting to be drugged, then the PDHC might be the experiment worth running.

Let's build the future—together, deliberately, and without compromise."

"As the collective genius grows and PDHC members drive the initiatives, new concepts arise and new philosophies are discovered. I believe we will witness a perpetuation of novel ideas and unique avenues of thinking about peptide therapeutics, from dynamic personalized polypharmacology to revolutionary methods for peptide synthesis across discovery and commercial scales to clinical trial design and biomarker identification. The future is rich and vast for peptide drug hunters and the PDHC will be there to connect them with one another, capture their input, and communicate their insights."

CONCLUDING REMARKS

"My special comments here are to acknowledge my two great friends and PDHC Co-Founders, Charlie and Wendy, who have taken so much of their time and energy to build the PDHC. As you read their musings, vision and concluding remarks, you will know how passionate and dedicated they each are. Their contributions, along with so many others, including my friends Danielle, our awesome PDHC Project & Operations Manager, and Jeff Geniesse, our amazing PDHC Website & Media Portal Designer, are highly appreciated. I'm truly humbled to work with everyone in our talented and ambitious PDHC team!

Please share this inaugural article with your colleagues and friends, and we invite you to join us as Peptide Drug Hunters!"

"As we close, one idea keeps surfacing: breakthroughs don't just come from solving problems, they come from choosing the right ones.

At the PDHC, we believe the future of peptide therapeutics depends on this kind of focus. It's not just about speed or scale—it's about picking the bottlenecks that matter, where progress unlocks new biology, new modalities, and new ways of thinking. But that's only part of the equation.

We also believe that what we build—whether it's tools, data, or insight—shouldn't stay siloed. Sharing knowledge is how early ideas become real impact. It's how we make discovery more accessible, and progress more durable.

We founded PDHC as a nonprofit to keep this mission front and center: Identify the right problems. Solve them collaboratively. Share what works. Because when we do that, we don't just push peptide science forward—we pull the whole field with us.

Thank you for being part of this. Let's keep building—deliberately, together!"

"At the end of the day, therapeutics have one goal, to help patients. If we can elevate the peptide drug hunting community through networking and education, we can ultimately help more patients gain access to effective peptide medicines, particularly those that treat so-called undruggable diseases. To me, this is the fundamental reason to volunteer my time and ensure that the PDHC is successful long after I am gone. Though, I will admit, I also find deep joy in connecting with the community and spending time with my all-time peptide hero, Tomi Sawyer."

Breakthrough Medicines

Q&A

WITH TOM TUCKER

ON THE DISCOVERY OF MK-0616 (ENLICITIDE), A NOVEL ORAL MACROCYCLIC PEPTIDE PCSK9 INHIBITOR

I have recently retired from Merck & Co., Inc., Rahway, NJ, USA (hereinafter "MSD") and my comments are solely my own opinions and perceptions. I've tried to be frank and honest in my comments but also have purposefully and deliberately avoided anything proprietary that hasn't been previously published or presented at various external meetings. - Tom Tucker

For this issue of the PDHC Chronicle, we had the opportunity to speak with Mr. Tom Tucker, corresponding author on two landmark Journal of Medicinal Chemistry papers describing MK-0616. This investigational oral macrocyclic peptide represents a breakthrough in targeting PCSK9, a key regulator of LDL cholesterol. Remarkably, MK-0616 has now advanced to Phase 3 clinical development, underscoring both the scientific and translational impact of the program. In this conversation, Mr. Tucker reflects on the journey from concept to clinic, the challenges faced, and what this program means for the future of peptide drug discovery.

Why MK-0616 Matters

- **First-in-class oral macrocyclic peptide targeting PCSK9, a key regulator of LDL cholesterol.**
- **Now in Phase 3 clinical development, with potential to become the first oral alternative to PCSK9 antibodies and siRNA therapies.**
- **Demonstrates that oral peptide therapeutics can achieve drug-like PK/PD profiles, challenging the notion that peptides are limited to injectables.**
- **Built on a multidisciplinary platform approach combining mRNA display, medicinal chemistry, structural biology, and innovative assays.**
- **Could impact patient accessibility by enabling convenient daily oral dosing in cholesterol management.**
- **Serves as a proof-of-concept for expanding peptide drug hunting into other "undruggable" targets.**

Q **The development of MK-0616 was a tour de force effort involving a large multidisciplinary team and platform technologies. How did you each get involved in the project, and what role did you each play on the team?**

I became involved in the project from day one. At that time, MSD was just reentering the peptide space and beginning to rebuild its peptide capabilities. A member of my team at West Point (Chengwei Wu) who is an experienced peptide synthesis expert taught most of the chemists on the project at that time (who were historically small molecule chemists), how to do peptide synthesis, and the effort expanded from there. MSD has since hired many dedicated peptide synthesis specialists as well as continued to give small molecule chemists the opportunity to cross train and learn to do peptide synthesis. I think this blend of unique perspectives and experiences provides the opportunity for very novel solutions to difficult design and development problems.

Q **Looking back, what was the spark that convinced you and the team that PCSK9 could be drugged with an oral peptide, despite the conventional wisdom that this was nearly impossible?**

Oral bioavailability in this space was deemed to be a necessity from day one. I think early on we had some doubters as we began to make peptides and realized what the properties of these early hits were like – the molecules were poorly permeable, unstable, and had poor PK properties. But we continued to work hard, and I have to give a lot of credit to a scientist in our DMPK team by the name of Ken Koeplinger (who has since retired from MSD) who I worked very closely with. Ken was convinced based on what he had seen in the literature as well as in conversations with academic consultants that enhanced formulation based oral delivery of peptides was possible and practical. Ken convinced our chemistry team as well as our management that this could be done successfully and safely, and we worked together to demonstrate the feasibility in early animal experiments. We as Med Chemists realized that stability in the gut would be a key and necessary component of oral delivery, and we worked collaboratively with our DMPK colleagues to establish the assays needed to fully interrogate and solve these issues.

Q **What was the most difficult medicinal chemistry challenge on this program? How did you decide which scaffolds to prioritize, and what were the most informative assays?**

The biggest Med Chem challenge was solving the gut stability issue. We had four key amide bonds in our early leads that were all critical for interaction with PCSK9 that were being metabolized, and fixing these issues necessitated that we design some very complex scaffolds that required a lot of out of the box, non-conventional thinking. Interestingly, coming out of the early mRNA Display screening collaboration with Ra Pharma, we had found two distinct chemical lead series. The one that most of the team was following up showed some very good oral bioavailability when dosed with our enabled formulations on the front end, but after initially working on this we chose to pursue the other lead class. We just had a good feeling about these other hits and felt that they might be more optimizable than the prior series. Ultimately this second series led to the clinical compound. We also made a decision early on to take a valuable external collaboration with our IRBM colleagues for peptide design and synthesis. They focused on replacing the original dibenzyl xylene (dbx) linker in the molecules and it's two thioether moieties with alternative amino acid-based linkers. Interestingly, there were no metabolic nor other issues associated with the dbx linker, but ultimately when we found a chemical stability issue in the presence of specific permeation enhancers. We averted disaster by having a plug and play solution ready to go. In terms of assays, the key assay for us was our Target Engagement assay which allowed us to accurately relate PK and PD in plasma and help us to accurately predict our human doses. We worked closely with our DMPK colleagues to develop this assay using a biotinylated version of one of our inhibitors. The procedure is described in our publications. Amazing cross-disciplinary collaboration was a key part of this effort from end to end, and I can't say enough about the ability of this team to collectively solve each complex challenge that came along during this work.

MK-0616 in the Spotlight

- ***Featured as a "Molecule of the Month" by Drug Hunter, a leading resource for medicinal chemistry insights.***
- ***Voted 2023 Molecule of the Year by the Drug Hunter community, reflecting its impact and excitement across the global drug discovery field.***
- ***Celebrated not only for its therapeutic potential in lowering LDL cholesterol but also for demonstrating the feasibility of oral macrocyclic peptide medicines.***

Q **Can you comment on the research operating plan and share how the workflow was structured to keep the team moving forward?**

We had a well-defined ROP and we stuck to it methodically throughout the project. Fret assay on the front end to determine potency, followed by IV PK in rats and assessment of stability and metabolic ID. We also used ID /oral gavage dosing in rats to guide our progression of compounds forward to our target engagement assay and more advanced PK/PD studies in primates.

Q **If you had the chance to go back and change any decision that the team made, what would it be?**

I don't think I would change a thing. That's not to say we were perfect and didn't make mistakes because we made many. But the entire project worked out so well and found such exceptional chemical matter that in the end I

wouldn't change anything. I would readily admit that several very serendipitous events throughout the process fell the right way for the team, but as any experienced medicinal chemist knows serendipity is always a key and welcome component of any successful drug development program!

Q **Peptides often face hurdles in permeability and stability. What specific strategies proved most effective in overcoming these liabilities for MK-0616?**

In our case, since our molecules were targeting a circulating target in plasma, having poor intracellular permeability was an advantage and really helps to prevent our molecules from engaging other potential targets inside cells. In terms of gut permeability, we were able to show early on in our leads that gut permeability was low even with fully stabilized molecules. We knew early on that if we were going to get an orally bioavailable molecule, we would likely need to use an enabled formulation-based approach that focused on allowing our molecules to be absorbed via paracellular absorption through transient opening of the tight junctions in the gut. This enabled early commitment to and focus on this approach.

In terms of stability, this is critical. If you want to be orally bioavailable with a peptide therapeutic, stability in the gut is everything! We were able to assess stability to the key gut enzymes on our key molecule and were also able to take advantage of having access to metabolic ID studies early on. We were able to systematically identify the vulnerable spots on our peptides and develop specific synthetic strategies to block these metabolic sites and stabilize the molecules. We identified four major vulnerable amide bonds and guided by this data and structure- based design, we were able to design some complex cross linking strategies to modify the molecules that not only fully stabilized them to metabolism but also greatly increased the potency of the molecules, down to the picomolar level!

Q **What were the largest bottlenecks in the program, and are there any lessons learned that could help the broader field accelerate peptide medicines to the clinic?**

The largest bottlenecks throughout this project were related to the complex synthesis of our key molecules throughout the progress of the program. As I said in order to solve the metabolic issues as well as some off target issues, the amount of complexity that had to be built into the molecules was quite amazing. I still look at the structures in awe and amazement that we were able to turn these complex peptide molecules into drug candidates. Early on we used SPPS to build these complex structures and were able to adapt a lot of chemistry to both on and off-resin synthesis. Later, it became necessary to move to solution-based approaches to allow for more efficient scale up. The work done by our process chemistry group to improve the scaleup and synthesis of MK-0616 is world class and equally as impressive as the discovery effort. The development of biocatalytic approaches to most of the steps in this synthesis really enabled the clinical development. Our process team recently published this work in JACS, and I would encourage everyone to read this manuscript.

Q **Were there any unexpected PK/PD findings when moving from preclinical to clinical evaluation?**

Not really – our Target Engagement model was so robust that it was able to help us clearly build solid and predictable PK/PD correlations that carried over into the clinic. We were pleasantly surprised in the clinic as we were able to get sufficient exposures to reach the Target Engagement levels with the desired efficacy at doses that were even lower than our early human dose projections.

Q **MSD has a history of exploring macrocyclic peptides. How did MK-0616 build on prior internal knowledge, and how does it inform MSD's broader peptide platform strategy?**

In many ways, we were able to blend MSD's strong background in small molecule drug discovery with our growing expertise in peptide therapeutics to create complex structures for challenging biological targets. The demonstrated success with MK-0616 has allowed the cyclic peptide platform to become a key focus of novel therapeutic discovery efforts at MSD and has helped to solidify our "Modality Agnostic" approach to novel therapeutic discovery.

Q **Do you see PCSK9 inhibition via peptides as a unique case, or do you believe this program could catalyze a wave of peptide design across other undruggable targets?**

This has already happened at MSD and is happening across the pharmaceutical industry. Our internal peptide discovery efforts have clearly been bolstered, and cyclic peptides have become a key modality for ongoing and future drug discovery efforts at MSD. The rapid explosion of interest in this space across the industry catalyzed by the success of MK-0616 and other similar molecules from other pharma companies has been remarkable and I believe this revolution in peptide therapeutics will continue and will accelerate.

Q **The PDHC emphasizes the "Life of a Peptide"—from de novo design through translation into the clinic. Which stage of MK-00616's journey did each of you feel was most transformative, and why?**

Several stages were transformative. First of all, the early design of the peptides and the unique solutions discovered for the numerous issues we encountered were revolutionary to the field. From the design of multiple cross links to rigidify the molecules and block metabolism, to the use of the quaternary amine sidechain to help physical properties and also help eliminate several off target issues,to the development of our Target engagement assay, the early discovery and lead optimization parts of this program required novel, outside the box thinking and approaches. The other transformative stage was already mentioned – the incredible process chemistry work and the extensive use of biocatalysis to make the scaleup feasible and cost efficient.

Q **How important were external collaborations, or cross-disciplinary knowledge-sharing in making MK-0616 possible?**

As I mentioned earlier, we entered into a collaboration with Ra Pharma to apply their mRNA display screening capability to identify cyclic peptide starting points for our hit validation efforts. We also partnered with IRBM on the medicinal chemistry efforts across lead identification, lead optimization and finally candidate selection. Importantly, we were able to work closely with them to solve a key issue we had with the dbx crosslinker which came from the mRNA display post-translational macrocyclization chemistry. We did this work at risk and under pressure before we even knew this would be a problem. It was one of those experience/intuition things; there were no observed issues early on, but something told us there would be at some point and this was done in parallel, in anticipation of potential downstream issues. I'm a big believer in the intuition of experienced medicinal chemists, and I trust that immensely. In this case it paid off handsomely! Both Ra Pharma and IRBM proved to be an incredible collaborators, and they have demonstrated expertise and a proven track record of making important contributions to clinically advanced peptides.

Q **In your opinion, what does the peptide field need most right now—new synthetic methods, better predictive models, translational biomarkers, or something else?**

It's all of the above and more! Small Molecule drug discovery and antibody therapeutic discovery have been given huge investments by pharma in the past twenty years, however the "space in between" occupied by peptides and especially cyclic peptides has been largely ignored until more recently. In many ways, we are having to learn how to most efficiently design, develop, and market these unique molecules. I also think that in the past, peptide chemists had very limited views of how to make a peptide therapeutic based on their backgrounds and experiences. Technologies like mRNA display are revolutionizing peptide lead finding, and this has in turn fueled a revolution in the development of novel chemistry with the design and synthesis of non-natural amino acids. This revolution has just begun and I hope we will see it continue to amplify and expand. I also think that molecules like MK-0616 start to somewhat blur the line between peptides and small molecules, and I think that as more historically small molecule focused medicinal chemists begin to appreciate and work in the peptide therapeutic space, they will bring even more synthetic creativity and novel design concepts that I think have been on hold in the peptide space for a while. This has not been the fault of peptide chemists, but more the deemphasis of the peptide therapeutics space throughout the 1990s and the early 2000s by the pharma industry. New ways of thinking about molecular design and synthesis are expanding the pallet of tools available for novel peptide design and synthesis.

Solving issues related to the oral delivery of peptides designed to reach intracellular targets remains a huge problem, and I believe a lot of focused work will need to go into solving this complex problem. How can we design

chameleonic properties into molecules from day one while also simultaneously retaining potent and specific biological activity and drug-like properties remains a massive challenge that will be difficult to solve and not something that can be easily adapted at this point to discovery technologies like mRNA Display. The use of AI/ML in the future may be able to provide insights and creative, outside the box solutions here, especially as computing capacity and capabilities continue to grow exponentially.

Q **If you imagine peptide therapeutics in 2030, what do you think will be the most striking differences compared to today?**

I really believe that there will be a continuing and expanding revolution in novel peptide design, synthesis, and development over the next five years. I believe more and more companies will jump back into the peptide therapeutics space and continue to fuel this revolution. I firmly believe that we will see a huge increase in the use of synthesized non-natural amino acids as a common route to solving multiple issues in peptide design and development. Structures like MK-0616 will become commonplace as companies become more willing to take on complex drug discovery problems that they would never have thought about taking on in the past. I also believe we will see a new revolution in peptide delivery and formulation that will make oral and other routes of delivery much more routine for peptidic molecules. Also, will the anticipated contributions of AI/ML come to fruition in the drug discovery space – this is a key question for the future?

Q **What advice would each of you give to young scientists and drug hunters who want to contribute to the next generation of peptide-based breakthrough medicines?**

First of all, learn about the peptide space and educate yourself through talking to those working in the field and immerse yourself in the peptide literature. Familiarize yourself with the key issues for drug discovery – potency, specificity, stability, PK, PD, formulation, and how these issues relate to design and development of peptides. Learn the fundamentals of peptide synthesis. But most of all, don't be afraid to jump into the field and contribute!

Q **Finally, do you view MK-0616 as primarily a proof-of-concept for oral peptides broadly, or as a case study in what it takes to industrialize such a modality?**

I view MK-0616 In both ways. First, it shows that the peptide modality is alive and well, and the once thought to be impossible goal of oral delivery of peptides is well within our grasp. Secondly, I think this work also clearly demonstrates the complexities associated with modern oral peptide therapeutics design and development and does indeed serve as a case study for future oral peptide therapeutics.

This project has been a crowning achievement for my career and as I just retired from MSD after 36+ years, I feel like I'm going out on a real positive, and I'm proud to have been a contributor to what I view as a game changer to peptide therapeutics. It was an amazing team effort and truly the highlight of my career at MSD.

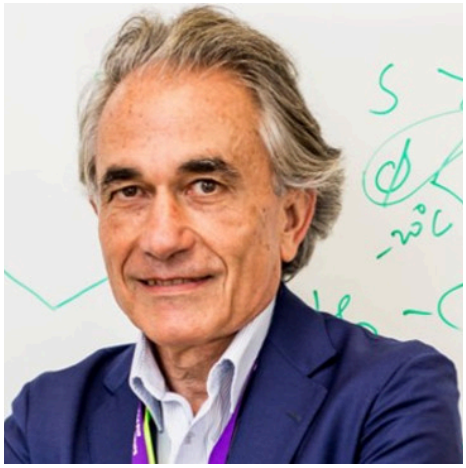
Closing Note

Mr. Tucker's reflections highlight not only the scientific ingenuity behind MK-0616, but also the collaborative spirit and persistence required to push the boundaries of peptide drug discovery. With the program now in Phase 3 clinical trials, MK-0616 stands, and how these properties relate are both a milestone and a springboard for future innovation in the peptide therapeutics field.

Synthesis Innovation

PEPTIDE SYNTHESIS: THE DRIVING FORCE OF THE PEPTIDE GOLDEN ERA

Fernando Albericio[1,2]



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[2]Department of Inorganic and Organic Chemistry, University of Barcelona, Barcelona, Spain

Abstract

Peptides have evolved from biochemical tools into a major class of therapeutic agents, propelled by the success of drugs such as semaglutide and tirzepatide. Their large-scale production has transformed peptide chemistry into an industrial discipline requiring multi-ton synthesis capacity and sustainable manufacturing solutions. Advances in solid-phase (SPPS), liquid-phase (LPPS), and hybrid synthesis, together with native chemical ligation (NCL), have enabled the efficient preparation of long and branched peptides. However, this rapid growth has revealed key challenges, including, the environmental impact of solvents and reagents, the need for greener synthetic strategies, sustainable methods for the large scale amounts demanded by the market, and limited availability of trained peptide chemists. Current efforts focus on developing low-swelling resins, alternative protecting groups to Fmoc, and solvent reduction strategies in line with Green Chemistry principles. Collaboration between academia, contract manufacturers, and pharmaceutical companies will be crucial to achieving sustainable, scalable peptide synthesis for future therapeutic demands.

Introduction

This synthesis-driven revolution now defines what many call the Peptide Golden Era—a convergence of science, industry, and sustainability that requires global collaboration. For many years, the use of the word “peptide” was confined to a strictly scientific context. However, a few years ago, with the discovery of semaglutide and later tirzepatide, peptides have become the new “rock stars”, frequently featured in mass media, television, newspapers, and social networks. The Peptide Drug Hunting Consortium (PDHC) has emphasized that sustainable peptide synthesis is not just a technical challenge but a community responsibility. By connecting academic innovators, CDMOs, and therapeutic developers, PDHC initiatives aim to accelerate scalable, green peptide manufacturing practices and to disseminate shared best practices across the ecosystem. Today, the pharmaceutical industry requires tons of these peptides each year. In the case of tirzepatide, production relies entirely on chemical synthesis, whereas semaglutide is obtained either through semi-synthesis—a combination of biotechnological and chemical methods—or through purely chemical synthesis.

In the middle of the last century, such a scenario would have been unimaginable. Peptides were regarded merely as biochemical tools that could be synthesized, but not on a scale suitable for mass consumption. Figure 1 shows the milestones Driving the Peptide Golden Era.

In 1954, Vincent du Vigneaud achieved the first chemical synthesis of an active peptide, oxytocin, a milestone that earned him the Nobel Prize in Chemistry in 1955.[1] Although this synthesis was a true breakthrough, it did not yet allow scientists to foresee the crucial role peptides would later play in the pharmaceutical field.

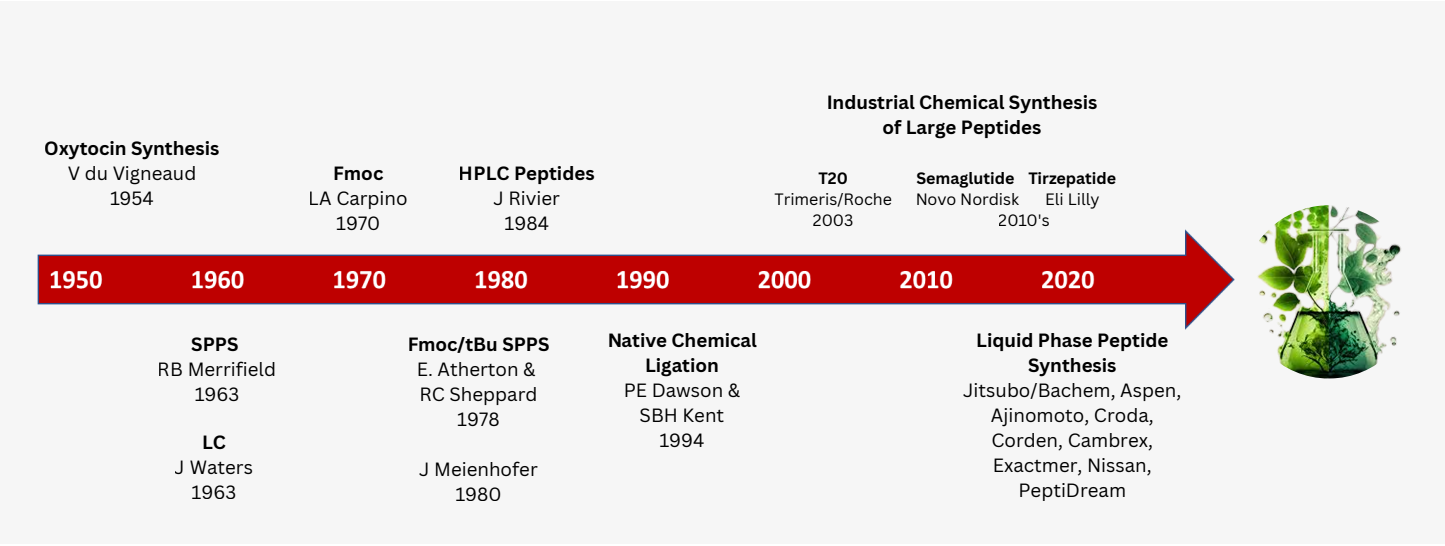

Figure 1. Milestones Driving the Peptide Golden Era: Key advances in chemical peptide synthesis.

In 1963, Bruce Merrifield introduced a revolutionary approach to peptide synthesis — the Solid Phase Peptide Synthesis (SPPS) method.[2] In this technique, the C-terminal of the growing peptide is anchored to an insoluble polymeric support, which allows the use of excess reagents to ensure good yields in each reaction step. The unreacted reagents and soluble by-products can then be removed simply by filtration and washing. Although SPPS initially faced significant criticism, particularly from European researchers,[3] it gradually became the method of choice for peptide synthesis. Merrifield's contribution was later recognized with the Nobel Prize in Chemistry in 1984.

In the 1970s, Lou Carpino introduced the fluorenyloxycarbonyl (Fmoc) group for α-amino protection,[4] likely without realizing how profoundly this innovation would influence the future of pharmaceutical peptides. The Fmoc group, which is removed by a β-elimination reaction in the presence of secondary amines, can be used in combination with tert-butyl (tBu) protecting groups for side chains, which are removable under mild acidic conditions such as trifluoroacetic acid (TFA). This Fmoc/tBu protection strategy replaced the earlier tert-butoxycarbonyl (Boc)/benzyl (Bzl) approach developed in Merrifield's laboratory, which required harsh reagents like hydrogen fluoride (HF) or trifluoromethanesulfonic acid (TFMSA) for deprotection. The adoption of the Fmoc/tBu system was strongly promoted by two research groups: one in Europe, led by Bob Sheppard and Eric Atherton,[5] and another in the United States at Hoffmann-La Roche, led by Johannes Meienhofer and Art Felix.[6] Hoffmann-La Roche was among the first pharmaceutical companies to recognize the therapeutic potential of peptides. Although the chemical synthesis of peptides was already established, a key factor in its consolidation occurred in the 1960s, when Jim Waters founded Waters Corporation, marking the beginning of modern chromatography. Later, Jean Rivier introduced reverse-phase chromatography for the industrial-scale purification of peptides, a major step toward large-scale peptide production.[7]

In 1994, Phil Dawson and Steve Kent developed the Native Chemical Ligation (NCL) method for the synthesis of large peptides and proteins.[8] Briefly, this strategy involves coupling unprotected peptide segments in aqueous media through a thioester-mediated reaction between an N-terminal cysteine-containing peptide and another C-terminal peptide thioester, followed by a rearrangement to form a native peptide (amide) bond. These unprotected peptide fragments are synthesized via SPPS, and because they lack protecting groups, they generally do not exhibit solubility issues in aqueous conditions.

Trimeris/Roche were the first to produce a large therapeutic peptide—the 36-amino-acid T20 (enfuvirtide)—on a multi-kilogram

scale for HIV treatment.[9] They employed a hybrid solid-phase/solution strategy, in which protected peptides synthesized on solid support were subsequently assembled in solution. The production of T20/enfuvirtide marked a kind of "democratization" of peptide manufacturing. For instance, CBL Patras, a small biotech company founded by the academic peptide chemist Kleominas Barlos in Patras, Greece, established within a year a facility capable of producing 2-chlorotrityl chloride (CTC) resin—essential for solid-phase peptide synthesis—on a multi-kilogram scale.[10] This development significantly lowered the prices of CTC resin and most Fmoc-protected amino acids, except Fmoc-Arg(Pbf)-OH, which remains challenging to synthesize and is absent from the T20/enfuvirtide sequence. The resulting cost reduction benefited both academic and industrial peptide research.

The same hybrid synthesis approach is now used for the production of tirzepatide, a 39-amino-acid peptide with a branched structure containing four moieties, developed by Eli Lilly.[11] Initially designed for the treatment of type 2 diabetes, tirzepatide is now also approved for obesity, requiring production volumes measured in tons. It acts as a dual agonist of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) receptors.

For the same therapeutic indications, semaglutide—a 31-amino-acid peptide with a branch containing two moieties—is produced by Novo Nordisk using a semi-synthetic strategy. In this approach, an unprotected linear peptide obtained biotechnologically is chemically modified by attaching the side-chain branch, followed by coupling of the C-terminal segment, which contains the non-proteinogenic amino acid Aib (α-aminoisobutyric acid). This strategy cannot be applied to tirzepatide because it contains an additional Aib residue within its linear sequence.

As the semaglutide patent nears expiration, numerous CDMOs (Contract Development and Manufacturing Organizations) and pharmaceutical companies are developing fully synthetic or hybrid manufacturing routes. The GLP-1 agonist field continues to expand rapidly, with several large peptides currently in advanced clinical trials, including retatrutide and mazdutide (Eli Lilly), cagrilintide (Novo Nordisk), survodutide (Boehringer Ingelheim), and pemvidutide (Altimmune), among others.

This situation represents a true earthquake in the peptide chemistry ecosystem, whose long-term repercussions are still difficult to predict. To meet the growing demand, Western CDMOs are doubling their production capacities; in China, CDMOs that traditionally focused on small molecules are launching peptide programs with reactors of several thousand liters; and in India, the Indian Peptide Society estimates that hundreds of CDMOs have already been established across the country.

However, one of the most critical challenges remains the shortage of well-trained peptide chemists to support this rapidly expanding field. The PDHC aspires to develop mentorship and training opportunities and to connect CRO technologies through our EBN in process peptide chemistry to help close the gap.

The current momentum in peptide-based drugs for diabetes and obesity has coincided with another major global trend — sustainability — which has fuelled numerous initiatives inspired by Green Chemistry. As defined by Paul Anastas, Green Chemistry is "the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances."[12]

In parallel, PDHC is convening roundtables on green process metrics (PMI/E-factor), DMF alternatives, low-swelling resins, and one-pot SPPS cycles to accelerate adoption of pragmatic, scalable practices.

In addition to efforts aimed at identifying greener solvents for synthesis, non-solvents for work-up, bases for the removal of temporary protecting groups, and acids for final global deprotection and cleavage (topics that will be discussed later), recent years have also witnessed a revival of an older strategy originally proposed by Manfred Mutter and Ernst Bayer in the 1970s: the Liquid-Phase Peptide Synthesis (LPPS) method.[13]

LPPS, like SPPS, is a continuous process, but instead of anchoring the growing peptide to an insoluble solid support, it is attached to a soluble polymer. After each synthetic step, the peptide–polymer conjugate is separated from excess reagents and soluble by-products through precipitation and filtration or ultrafiltration. LPPS thus combines the advantages of both classical solution-phase synthesis and SPPS: the reactions occur in homogeneous solution, allowing the use of smaller reagent excesses, while maintaining simple and efficient purification

steps.
Over the years, the original concept of LPPS developed by Mutter and Bayer has evolved considerably, now involving hydrophobic soluble polymers or even small discrete hydrophobic molecules known as tags. In these modern variants, the growing peptide can be isolated either by precipitation or by liquid–liquid extraction in aqueous media.[14]
It is important to distinguish LPPS from classical solution-phase peptide synthesis, as employed by du Vigneaud for the synthesis of oxytocin. The term LPPS should be reserved for continuous processes where peptide elongation occurs on a soluble polymer or tag, following the same conceptual framework as SPPS.[15]
Beyond the large branched peptides such as semaglutide and tirzepatide, which incorporate fatty acid chains to substantially extend their half-lives in the human body, another emerging and highly significant class comprises mono-, bi- and tri-cyclic peptides of approximately 15 amino acids. Most of these molecules have been identified by PeptiDream, the Japanese company founded by Hiroaki Suga,[16] or through phage display technologies developed by Sir Gregory Winter,[17] who won the Nobel Prize in Chemistry in 2018 and whose work underpins the company Bicycle Therapeutics.
These condensed polycyclic peptides typically contain non-proteinogenic amino acids and synthetic chemical moieties such as thioethers, products of click chemistry (as developed, among others, by the 2022 Nobel Laureate in Chemistry, Morten Meldal,[18] himself an accomplished peptide chemist), as well as metathesis or cross-coupling reactions. The result is a rigid and highly stable scaffold, functionally and structurally approaching that of small molecules.
With this panorama — and a forecast predicting a GLP-1 market of USD 100–150 billion by 2030 and approximately 9% of the U.S. population using GLP-1 analogues by that year — the outlook for peptide therapeutics is extraordinary. While business leaders see billions of dollars in revenue, peptide chemists foresee multi-tons of resins/tags, Fmoc-amino acids, solvents, reagents, and inevitably, waste. The key question, therefore, is: what is the future of peptide synthesis?
At the research scale, SPPS remains the method of choice. A wide variety of high-performance resins are available, and together with an extensive range of peptide synthesizers—in which heating systems (conventional, microwave, or infrared) have been implemented for all synthetic steps—allow the preparation of peptides in milligram-to-gram scales with sufficient purity for early-stage drug discovery.
For larger peptides and small to medium-size proteins, Native Chemical Ligation (NCL) is the preferred technique. To extend the applicability of NCL, cysteine residues can be strategically placed at alanine positions in the target sequence, followed by desulfurization, thereby regenerating the native Ala residue.19 This desulfurization strategy has been extended to other β-thiol amino acids, which can serve as chemical precursors of proteinogenic residues, thereby expanding the ligation sites available for fragment coupling. Thus, in research environments and early drug discovery, peptide availability is no longer a bottleneck. However, the major challenge lies in industrial manufacturing.

α-Amino Protection

Since the introduction of the Fmoc protecting group by Lou Carpino[4] and its adoption in SPPS, the Fmoc/tBu strategy has been the standard due to its avoidance of strong acids. Nevertheless, Fmoc is far from ideal. It is not environmentally friendly, as it is derived from coal-based chemistry, and its bulky aromatic structure results in poor atom economy—only a small fraction of its atoms end up in the final peptide. For instance, the atom economy is 0.40 for Fmoc-Phe-OH and 0.19 for Fmoc-Gly-OH, the highest and lowest values, respectively, among all proteinogenic amino acids. Moreover, the aromatic, hydrophobic nature of Fmoc promotes π–π interactions—either between Fmoc groups on different peptide chains or between Fmoc and aromatic moieties within the peptide–resin complex. These interactions can lead to peptide aggregation, hindering both coupling efficiency and Fmoc removal, often resulting in deletion peptides.
To our knowledge, at least four academic–industrial collaborations have attempted to introduce alternative Nα-protecting groups: (i) Barany (in collaboration with Bioresearch, San Francisco) proposed Nα-dithiasuccinoyl (Dts), removable

in the presence of thiols;[20] (ii) Carpino, first with Waters-Millipore and later with CEM, developed 1,1-dioxobenzo[b] thiophene-2-ylmethyloxycarbonyl (Bsmoc), removable via Michael addition with secondary amines;[21] (iii) Hack-Joo Kim and Vladimir Sabirov in collaboration with Hyundai Pharm introduced 2-(4-nitrophenylsulfonyl)ethoxycarbonyl (Nsc), removable similarly to Fmoc through β-elimination in the presence of secondary amines;[22] (iv) Most recently, Harald Kolmar and Sulfotools proposed Smoc-amino acids (2,7-disulfo-9-fluorenylmethoxycarbonyl), which are bis-sulfonated Fmoc analogues.[23] The sulfonate groups impart water solubility to the Smoc-amino acids. The first three strategies, however, did not progress beyond early studies, and the Smoc approach still requires demonstration of its feasibility for large-scale peptide synthesis.

Although Fmoc is imperfect, its replacement poses formidable challenges. A new protecting group cannot be acid-labile, since acid treatment is reserved for side-chain deprotection and peptide cleavage from the resin in SPPS. Designing a group removable by basic conditions is also problematic, as it must coexist with the nucleophilic amino group, which itself could remove the protecting group from incoming monomers—leading to undesired dipeptide formation, as seen with free proline.

Alternative protecting groups such as Alloc (allyloxycarbonyl) or photolabile groups—used for Lys side chains—are associated with side reactions and are difficult to scale industrially for repetitive α-amino protection–deprotection cycles. Moreover, while developing a new solid support or coupling reagent involves a single molecule, a new α-amino protecting group requires hundreds to thousands of new derivatives, since the current commercial Fmoc-amino acid library contains over one thousand components. This represents a major obstacle to Fmoc replacement.

An underexplored alternative involves non-covalent masking of the amino group's nucleophilicity. The pioneering work of Paolo Mascagni,[24] who employed crown ethers for this purpose, deserves renewed attention. Such masking agents could, in principle, be recycled, as their use does not require bond formation or cleavage in the protection/deprotection cycle.

Side-chain Protecting Groups

There is broad consensus in the peptide community that side chains of trifunctional amino acids should be protected with acid-labile groups. For residues such as Lys, Cys, Asp, and Glu, protection is mandatory due to the intrinsic reactivity of their functional groups. In contrast, protection for Arg, His, Trp, Asn, and Gln can sometimes be omitted, though unprotected forms may lead to side reactions that limit their applicability in large-scale synthesis.[25,26,27] The development of transient protecting groups—able to temporarily mask reactive functions only during coupling—could be a promising direction.

On the other hand, the absence of certain protecting groups can enhance peptide solubility, which may be advantageous or detrimental depending on the synthetic strategy. In hybrid approaches (e.g., coupling of protected fragments in solution), partially deprotected peptides obtained after cleavage from the resin or soluble tag may exhibit improved solubility, facilitating fragment condensation and offering potential process benefits.

Solid Supports

Polystyrene (PS) resins remain the most widely used supports in Solid-Phase Peptide Synthesis (SPPS), both in research and industrial settings. These resins are mechanically robust, chemically stable, provide good loadings, and are available on the multi-kilogram scale at reasonable cost.

However, the synthesis of long or aggregation-prone peptides has encouraged the adoption of more hydrophilic resins. The first generation of such materials was polyethylene glycol (PEG)–grafted PS resins (Tentagel, HiCore, Octagel, PS-PEG are currently the only commercially available), which outperform PS alone.[28] Although PEGA[29] and ChemMatrix[30] (full-PEG resins) are no longer commercially available, they are still recognized as superior to both PS and PEG-PS resins in terms of performance.

The improved behavior of PEG-PS and PEG resins over PS is largely attributed to their greater swelling capacity. For many years, high swelling was regarded as a synonym for high resin quality. However, excessive swelling also

implies the need for larger solvent volumes, which, in large-scale peptide production, translates into larger reactor sizes for equivalent peptide output. This is technically inefficient and contrary to the principles of Green Chemistry, which advocate minimizing solvent use. Consequently, the use of more rigid resins is now being explored. These materials allow reduced solvent consumption during washings (from roughly 10 volumes per gram of resin down to 3–5), enable higher-concentration reactions, and permit the use of smaller reactors for equivalent peptide quantities.

Coupling Reagents

A wide range of coupling reagents is commercially available to meet the diverse requirements of SPPS.[31] Among these, derivatives of 1-hydroxy-7-azabenzotriazole (HOAt)[32] and Oxyma[33] are particularly efficient. It is important to note that, in most cases, low coupling yields arise not from the reagent's inefficiency but from aggregation of the growing peptide chain, a problem that cannot be solved simply by changing the coupling reagent.

With the emergence of LPPS in its liquid–liquid extraction format, further research should focus on traceless coupling reagents or those whose by-products are water-soluble. EDC remains an interesting candidate, although it is insoluble in most organic solvents and performs less efficiently than other carbodiimide-based reagents.

Solvents

Historically, dichloromethane (DCM) and later N,N-dimethylformamide (DMF) have been the solvents of choice in SPPS. The use of DCM is now prohibited in most countries, and the use of DMF and other amide-based solvents is increasingly restricted.[34]

To date, no single solvent has successfully replaced DMF. Mixtures of ethyl acetate (EtOAc) with N-butylpyrrolidone (NBP)[35] or with dimethyl sulfoxide (DMSO)[36] are currently the most widely adopted in large-scale synthesis. Further development of alternative solvent systems, particularly for PS-based resins, remains an important research priority.

Until now, most efforts have focused on identifying green solvents compatible with PS resins, but a more holistic approach is needed—one that develops new resins and new solvents in parallel, ensuring mutual compatibility within a sustainable framework.

Although water is often proposed as the ultimate green solvent, its use is not without controversy. While water is non-toxic and safe to handle, it is difficult and expensive to recycle or dispose of, and it remains a scarce resource in many parts of the world. Moreover, many Process Mass Intensity (PMI) analyses omit the contribution of water, leading to an unfair comparison with other solvents.

Liquid-Phase Peptide Synthesis (LPPS)

As discussed earlier, LPPS has recently emerged as a powerful strategy within the peptide field. However, a key limitation is the broad intellectual property coverage surrounding many tags and other proprietary reagents essential for efficient LPPS operation. In this sense, LPPS is still in its early developmental stage, and much research is required to develop: (i) new tags (both for precipitation and extraction modes); (ii) compatible green solvents; (iii) effective protecting-group removal reagents, and (iv) general strategies for process optimization. To de-risk adoption, PDHC is curating case studies and fostering open benchmarking templates (cycle time, solvent volume per residue, and waste streams) to enable apples-to-apples comparison between SPPS, LPPS, and hybrid routes.

While there is little doubt that LPPS offers great potential for the synthesis of small- and medium-size peptides—including protected intermediates used in hybrid SPPS/solution strategies—it remains necessary to validate LPPS for the multi-kilogram synthesis of large peptides under industrial conditions.

Two-Step vs. Four-Step Peptide Bond Formation

Traditionally, the SPPS peptide-bond formation cycle involves

four steps: (i) coupling; (ii) washing; (iii) α-amino deprotection, and (iv) washing again. To reduce both reaction time (particularly considering the time-consuming filtrations at scale) and solvent consumption, this cycle can be simplified to two steps: coupling, followed directly by addition of the deprotection reagent without intermediate washing, followed by a final washing step. This two-step approach was first implemented in CEM's microwave-assisted synthesizers[37] and later extended to other SPPS configurations.[38] Interestingly, this simplified approach is even more commonly applied in LPPS than in traditional SPPS, owing to the greater homogeneity of liquid-phase systems. Community SOPs that define guardrails (e.g., acceptable residual activator and base thresholds) would further standardize two-step cycles; PDHC is assembling these checklists from contributors across academia and CDMOs.

Native Chemical Ligation (NCL)

Given that both SPPS and LPPS become increasingly challenging as peptide length grows—and that hybrid methods (solution-phase coupling of protected peptide fragments obtained by SPPS or LPPS) often face solubility issues with protected intermediates—the ideal scenario would involve coupling unprotected peptide fragments. These fragments, which themselves can be synthesized via SPPS or LPPS, are joined directly in aqueous media through Native Chemical Ligation (NCL).

To date, and to the best of our knowledge, tirzepatide remains the only industrially produced large peptide obtained through an NCL-based approach.[39] There is no doubt that NCL will play an increasingly important role in the large-scale synthesis of long peptides in the near future. However, to fully realize this potential, fine-tuning will be required in three key areas: (i) the synthesis of unprotected thioester peptides; (ii) the selection and temporary protection of the N-terminal β-thiol amino acid in each fragment, and (iii) the optimization of desulfurization protocols to regenerate the native residues.

Given NCL's growing industrial relevance, PDHC is facilitating shared learnings on thioester access, temporary β-thiol installation/removal, and flow-enabled desulfurization to improve robustness at scale.

Enzymatic Coupling of Unprotected Peptide Fragments

A second promising approach for the ligation of unprotected fragments relies on enzymatic coupling methods. Considering that the assembly of a large peptide typically involves only three or four fragment couplings, this strategy is practically feasible at small scale, as demonstrated by technologies such as EnzyTag.[40]

The main limitation, however, lies in the preparation of unprotected peptide fragments bearing an activated ester at the C-terminal residue, which remains a major challenge for large-scale applications. Nevertheless, enzymatic coupling offers remarkable selectivity and mild reaction conditions, making it an attractive complement to chemical ligation strategies.

A community data room aggregating enzyme panels, substrate scope, and impurity profiles—hosted under PDHC—would accelerate method selection for specific fragment sets.

Biotechnological vs. Chemical Strategies

From a financial and environmental standpoint, biotechnological approaches are generally more favorable than purely chemical ones. However, they typically require longer development times, and by the time a biotechnological route becomes feasible, a chemical process is often already well-established.

Moreover, current trends in clinical and marketed peptide therapeutics show an increasing prevalence of non-proteinogenic amino acids in their sequences. This structural complexity limits the applicability of biotechnological methods, which rely on the proteinogenic amino acid repertoire. Thus, chemical synthesis remains indispensable for next-generation peptide drug candidates.

Working with our EBN and academic members the PDHC can help triage candidates early—matching sequence features (e.g., non-canonical load, macrocyclization, conjugations) to

the most viable manufacturing route

Final Considerations

The new demands of the pharmaceutical industry—namely, the production of large, branched, and cyclic peptides containing non-proteinogenic residues—are opening new directions for synthesis innovation. While SPPS remains the cornerstone of the field, the need to reduce solvent consumption and reactor footprint has accelerated the growth of LPPS and hybrid SPPS/solution strategies. One-pot (two-step) SPPS cycles, in which α-amino deprotection follows coupling without intermediate isolation, can substantially cut time and solvent use, aligning with Green Chemistry principles. In both SPPS and LPPS, low-swelling or rigid resins and traceless coupling reagents represent realistic near-term improvements. For large peptides, fragment coupling through NCL or enzymatic ligation continues to expand in scope, while efforts to minimize protecting-group use promise better atom economy and solubility management.

Amid these scientific and engineering challenges, the Peptide Drug Hunting Consortium (PDHC) can play a catalytic role by operationalizing collaboration. Through its triple-helix model—linking academia, CDMOs, and pharmaceutical developers—PDHC aims to:

- Standardize Green Synthesis metrics (PMI, solvent volume per residue, energy footprint) to benchmark SPPS, LPPS, and hybrid routes.
- Build a shared SOP Commons for one-pot SPPS and LPPS cycles, including impurity thresholds and resin/solvent compatibility maps.
- Curate NCL and enzymatic ligation playbooks, covering thioester preparation, β-thiol protection strategies, and desulfurization protocols.
- Create a route-triage framework to match sequence features—non-canonical load, conjugations, macrocyclization motifs—to optimal manufacturing approaches.
- Establish training and mentorship programs that address the global shortage of process-savvy peptide chemists.

By combining technical rigor with collective execution, PDHC transforms sustainability from a moral imperative into an innovation driver. Reducing solvent intensity, improving atom economy, and accelerating the validation of scalable synthetic routes are not only environmental gains—they are the foundation for sustaining the momentum of the Peptide Golden Era.

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Improving Solubility to Drive Clinical Translation

by Charles Johannes, Antoine Henninot & Wendy Hartsock

Potency is a key driver of therapeutic success, but even highly potent peptides often stumble at the clinic-translation step if their physicochemical properties, especially solubility and aggregation, are not adequately addressed. Low solubility limits dosing, bioavailability, and efficacy, and it also drags down manufacturing yields, complicates formulation/sterilization, and destabilizes the final products.[1] Moreover, poor physicochemical properties have been linked to increased risks of injection-site reactions and immune responses (immunogenicity). Hydrophobic or aromatic-rich sequences are particularly prone to aggregation, although such behavior can be difficult to predict.[2]

Solubility is one of the most critical developability factors as it determines whether a peptide can be reliably produced, formulated, and scaled for clinical and commercial use. A potential misstep in peptide discovery is focusing on biological activity while deferring solubility concerns to late-stage formulation. This reactive approach can compromise the original activity of the lead compound and add significant time, cost, and risk to development.

Promising fixes span both design and formulation. The most direct route is sequence engineering: for longer peptides, adjusting overall charge and isoelectric point (pI) is crucial; ideally targeting a pI<5 or >9 to enhance solubility near neutral pH. Modulating hydrophobicity, introducing cyclization, or incorporating non-canonical residues to balance physicochemical profiles are also common tactics. [3] Additional approaches have been reported in the literature, such as PEGylation, to boost aqueous behavior and exposure.[4] Increasingly, computational prediction tools; some capable of handling non-natural amino acids, allow more accurate assessment of intrinsic solubility by integrating sequence and structural features.[5]

Takeaway: solubility isn't a late-stage formulation cleanup, it's a core developability gate that should be optimized during lead optimization to de-risk translation and scale-up. The PDHC is interested in sharing knowledge on this important topic. How are you building solubility thinking into your peptide design or formulation workflows (screening rules, SAR knobs, platform excipients, or process parameters)?

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Invitation to Peptide Drug Development Experts!

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LIFE OF A PEPTIDE: PREAMBLE TO THE SERIES

A curated journey through the discovery, development, and delivery of peptide therapeutics, guided by voices shaping the future of biotech innovation.

By Charles Johannes

Peptides are transforming from the quiet workhorses of biology into the architects of a new therapeutic era. Once limited by questions of stability and delivery, these elegant molecules now stand at the crossroads of chemistry, biology, and digital science. They are redefining what medicines can achieve and inspiring a generation of innovators to explore the space between small molecules and biologics.

The rise of peptide therapeutics reflects more than scientific progress. It signals a change in how we think about discovery itself. Advances in automation, artificial intelligence, and high-throughput experimentation are shortening the distance between an idea, a drug candidate, and ultimately a final drug product. At the same time, the complexity of peptide development reminds us that success still depends on craftsmanship, collaboration, and a deep understanding of molecular behavior.

Life of a Peptide captures this unfolding story. Through concise perspectives and first-hand insights, the series follows peptides from concept to clinic, revealing the decisions, technologies, and people that shape each stage. Every article explores a pivotal moment in the development process, linking technical discovery to the broader vision of how peptide medicines reach patients.

Whether you're designing a new library, scaling a GMP campaign, or evaluating a platform for investment, we invite you to help illuminate the path from molecular design to human benefit. Join us as a contributor and share your perspective, case study, or insight into any stage of the peptide journey. Beyond the feature articles in the PDHC Chronicle, we've outlined the broader "Life of a Peptide" journey, and details of each stage will be available on the PDHC website.

Overcoming the Peptide Purification Bottleneck: The Evolution of Catch-and-Release Purification

By Dominik Sarma, Elizabeth Denton, Gordon Carlson, and Charles Johannes

1.0 The Persistent Challenge: Synthesis-Purification Mismatch

The field of peptide discovery and development faces a critical operational challenge; a profound mismatch between the high-throughput capacity of modern synthesis and the slower, more labor-intensive nature of traditional purification. Automated parallel synthesizers can produce hundreds of unique peptides in a single run. Yet, purification by Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC) typically processes samples one at a time. This disparity creates a bottleneck that slows the discovery-to-clinic timeline for peptide therapeutics.

In this life of a peptide update, we explore peptide purification using the catch-and-release strategy, featuring insights from Dominik Sarma, co-founder of Belyntic and now Product and Market Manager at Gyros Protein Technologies. Belyntic pioneered reductively cleavable linker systems, now commercially known as PurePep EasyClean (PEC™) for the broader peptide community.[1,2] We also highlight recent advances in this field, including Gyros Protein Technologies' newly launched PEC 2.0 technology, which represents the next evolution in catch-and-release, parallel peptide purification.

1.1 The HPLC Reality: Universal Access, Serial Constraints

RP-HPLC remains the gold standard for peptide purification, offering exceptional resolution and the ability to achieve ultra-high purity. Its universal presence in laboratories reflects decades of optimization and familiarity. However, HPLC is fundamentally a serial process. While state-of-the-art equipment can purify a single peptide in 15 minutes, conventional setups are typically limited to 3-4 runs per day, including preparation, method development for difficult peptides, fraction collection, and pooling. When laboratories need to purify 10 or more peptides for a validation study, this translates to several days of sequential processing. Additionally, certain peptide sequences present specific challenges for chromatography. Very hydrophobic peptides often won't dissolve in the water-acetonitrile mixtures required for HPLC injection—a

phenomenon familiar to any peptide chemist who has stared at an insoluble pellet. Very hydrophilic peptides present the opposite problem, flushing straight through RP columns with minimal retention. These edge cases often require extensive method development or entirely alternative approaches. When considering a panel of hundreds of molecules, synthesized in parallel, the probability exists that multiple molecules fall into these edge extremes, restricting the use of a “universal” plug-and-play HPLC protocol.

1.2 The Parallel Alternative: Catch-and-Release Fundamentals

Catch-and-release (c&r) purification, a concept introduced by Bruce Merrifield and co-workers,[1] offers a fundamentally different approach; one deliberately designed for parallel processing. Rather than separating peptides by their chromatographic properties, c&r systems use chemo-selective capture: the target peptide is specifically grabbed while impurities are washed away. This orthogonal separation mechanism enables simultaneous purification of multiple peptides using a single protocol.

The general workflow follows five key steps (Figure 1):

1. Tag installation: During solid-phase peptide synthesis (SPPS), a purification tag is selectively installed on the N-terminus of the full-length peptide. Using a capping step during synthesis ensures that truncated sequences do not contain this tag.

2. TFA cleavage and redissolution: The tagged peptide, along with capped truncations, is cleaved from the SPPS resin with TFA.

3. Immobilization (the "Catch"): The crude peptide mixture contacts a solid support (typically functionalized beads) that covalently reacts with the purification tag, immobilizing only the target peptide.

4. Washing: The solid support is thoroughly washed to remove non-tagged impurities, including truncated sequences, salts, and debris from protecting groups.

5. Cleavage (the "Release"): A specific chemical or physical stimulus cleaves the linker, liberating only the purified peptide from the solid support.

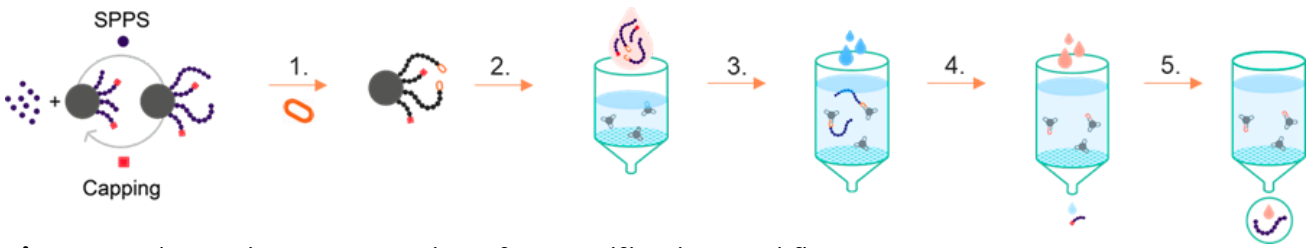

Figure 1. Schematic representation of c&r purification workflows.

This parallel processing capability represents a significant advantage. Where HPLC requires days to complete batch sizes of more than 10 peptides sequentially, c&r approaches can process them simultaneously in one day. Perhaps more importantly, the setup and preparation for a parallel purification approach is significantly less than that required for sequential, even minimally optimized, purification processes. The trade-off, though, is purity: c&r typically delivers what might be termed "fit-for-purpose" purity.

Table 1 gives an overview of purity recommendations for a selection of applications. In the most general sense, c&r can be expected to deliver an average purity of greater than 70%, which is sufficient for many discovery applications where throughput and speed are most critical, and not reliably reaching the 95% high-purity threshold is inconsequential.

Table 1. UV purity recommendations for a representative set of peptide-based applications.

Typical UV-purity (210 nm)	Application
Crude purity	• Initial screening • Sequence optimization • Qualitative binding
Low purity (>70%)	• ELISA testing • Polycolonal antibody production • Peptide arrays
Medium purity (>85%)	• Epitope mapping • Semi-quantitative enzymatic assays • Ligands for affinity purification
High purity (>95%)	• *In vitro* biological assays • Quantitative binding studies • Quantitative inhibition studies
Very high purity (>98%)	• GMP production • Clinical trials • cosmetics

2.0 The Evolution of Linker Chemistry

The effectiveness of any catch-and-release system hinges on its linker chemistry. The ideal linker must satisfy stringent, sometimes contradictory requirements: survive harsh synthesis conditions, enable efficient capture, wash cleanly, and release the peptide under conditions that don't damage sensitive sequences or introduce contaminants. The evolution of linker technologies reflects the challenge of meeting all these criteria simultaneously.

2.1 First Generation: Base-Labile Systems and Their Limitations

Early catch-and-release systems often relied on base-labile linkers, which created a fundamental dilemma. The cleavage conditions—typically pH >11—could damage peptides through several well-documented side reactions such as oxazolidinone and Aspartimide formation (Figure 2)[2]:

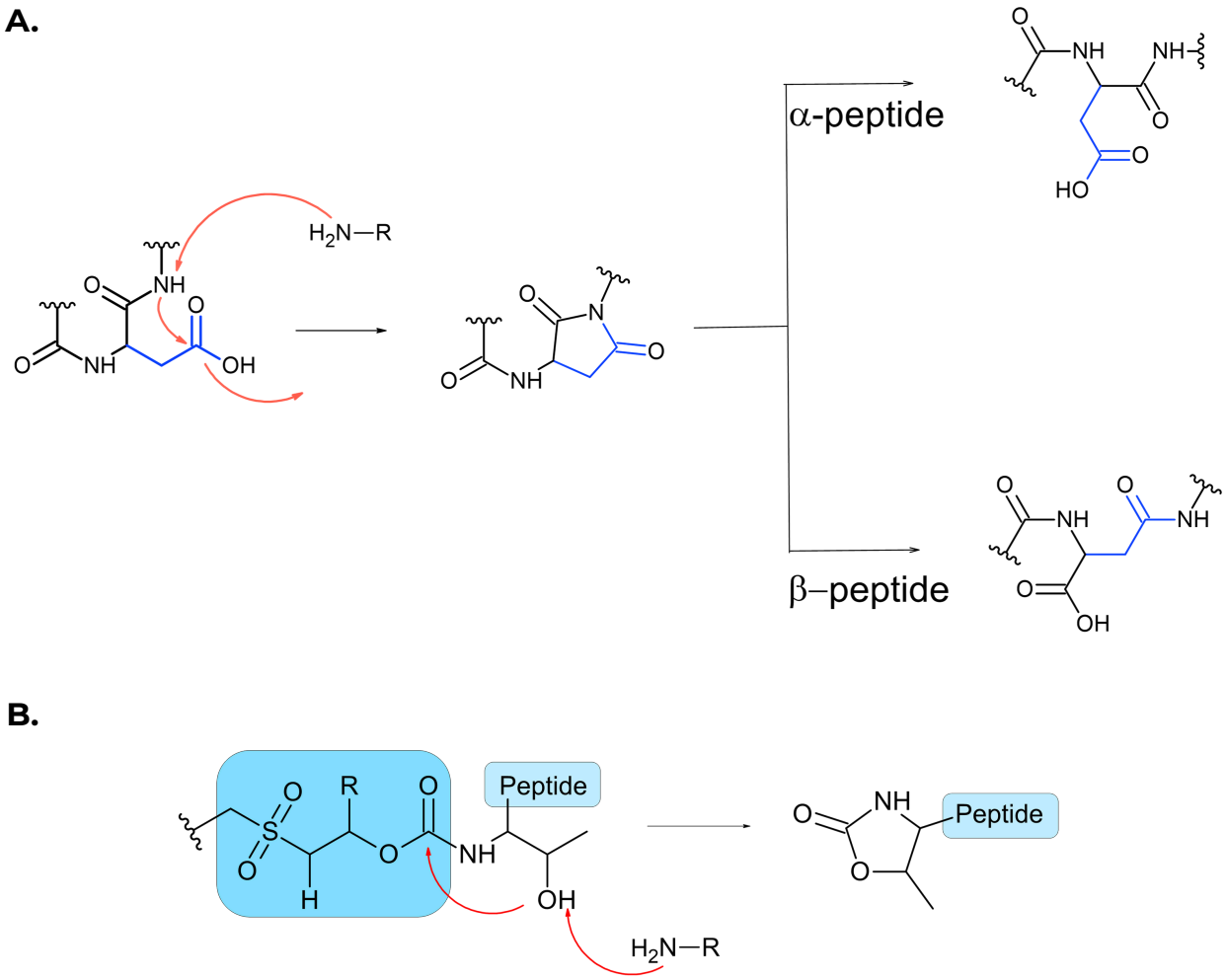

Figure 2. Common side-products using base-induced linker cleavage. A) Aspartimide formation B) Oxazolidinone formation

Chemists faced an un-winnable choice: use harsh conditions that risk damaging the peptide, or use milder conditions that leave the peptide contaminated with cleavage byproducts. Other early systems using nucleophile-induced cleavage introduced different contaminants that often necessitated a subsequent HPLC polishing step—defeating the purpose of parallel purification.

2.2 Reductive Cleavage: The Belyntic Innovation

Dominik Sarma and colleagues at Belyntic pioneered a breakthrough approach using reductive cleavage chemistry, which ultimately led to the invention of the PurePep EasyClean (PEC) technology.[3] Their linker (Figure 3) features a preactivated (grey box) para-azido-benzyl carbamate core (dark blue box) with a protected oxyamine catch tag for immobilization (light blue box). The key innovation lies in the release mechanism: reduction of the aryl azide to an aniline triggers a spontaneous 1,6-elimination cascade that cleaves the carbonate bond.

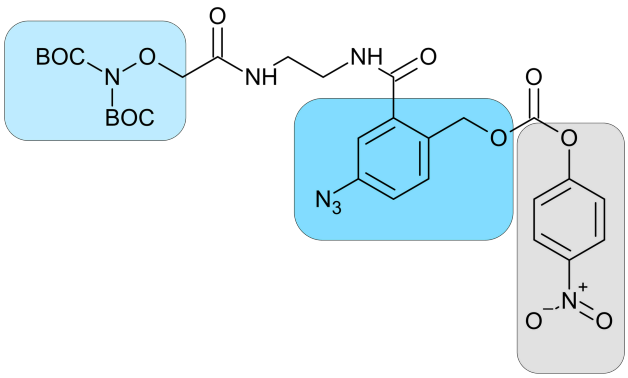

Figure 3. Molecular structure of the first-generation reductively cleavable PEC-Linker.

However, the first-generation linker revealed an unexpected vulnerability: instability in the TFA cleavage cocktail used during peptide deprotection. This instability caused premature linker loss and low peptide recovery, indicating that linker stability optimization was necessary.

2.3 Engineering Stability: The Brominated Linkers

To improve TFA stability while maintaining clean release, the Belyntic team introduced electron-withdrawing bromination.[3] The mono-bromo and di-bromo linkers showed dramatically improved acid stability—92% and 97% intact after 2 hours in TFA cleavage cocktail, respectively.

The mono-bromo PEC linker enabled an elegant "safety-release" mechanism (Figure 4). Using dithiothreitol (DTT), a non-hazardous reducing agent, the azide is reduced at pH 8, "arming" the linker. Crucially, the armed linker remains stably bound, allowing for the complete washout of DTT and its byproducts. An acid wash then triggers clean peptide release. This two-stage approach eliminates contamination from reducing agents while operating under universally compatible conditions. Critically, the carbamate moiety spontaneously decomposes into CO_2 and the free peptide, leaving no residual artifacts—a truly "traceless" release.

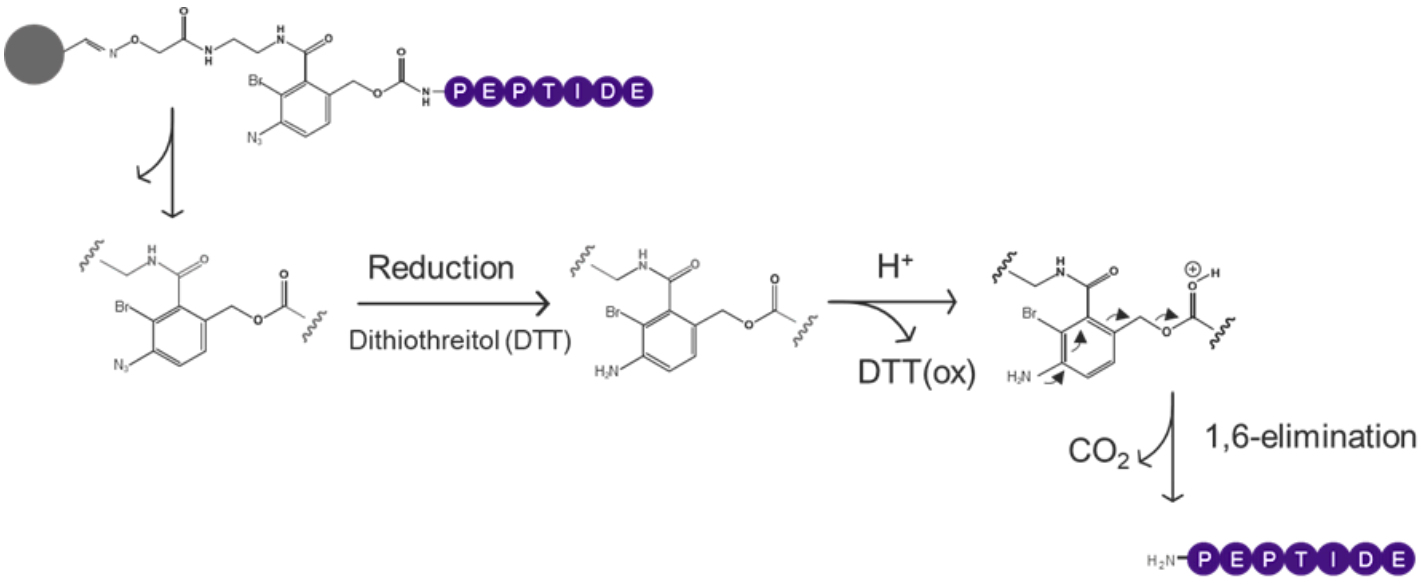

Figure 4. Schematic representation of the safety-release mechanism, enabled through bromination of the aryl-azide core.

The practical impact was demonstrated in a study on neoantigen vaccine manufacturing, where 20 distinct peptides were purified in parallel within 6 hours. One particularly challenging hydrophobic peptide was improved from 6% crude purity to 99% final purity —a result that would have been exceptionally difficult to achieve via traditional HPLC. Even with these impressive time and purity improvement results, it is critical to note that a modest level of purity improvement using c&r purification is required for neoantigen vaccine manufacturing. The presence of related, peptidic impurities, such as n-1 and n+1, in particular, renders many of these assays and products unusable and is among the most challenging impurities to remove via HPLC – a simple task for c&r purification, though.

2.4 PEC 2.0: Eliminating Workflow Steps (Engineering stability – choice of immobilization media)

On November 4, 2025, Gyros Protein Technologies launched PEC 2.0, a significant advance in catch-and-release purification.[4]

Where Belyntic's innovation focused on linker-chemistry optimization, Gyros Protein Technologies' further development of PEC addresses a critical workflow challenge. Former catch-and-release methods, as well as traditional HPLC, require an intermediate step: after TFA cleavage and side-chain deprotection, peptides are precipitated in ether, dried, and then redissolved before immobilization or injection. This redissolution step frequently failed with hydrophobic or aggregating sequences—creating a "success-or-failure" moment that limited downstream reliability.

PEC 2.0's innovation centers on TFA-stable beads (polymethacrylate, as opposed to the agarose used in the previous version) that enable direct immobilization from the TFA cleavage cocktail itself. The workflow simplifies significantly (Figure 5):

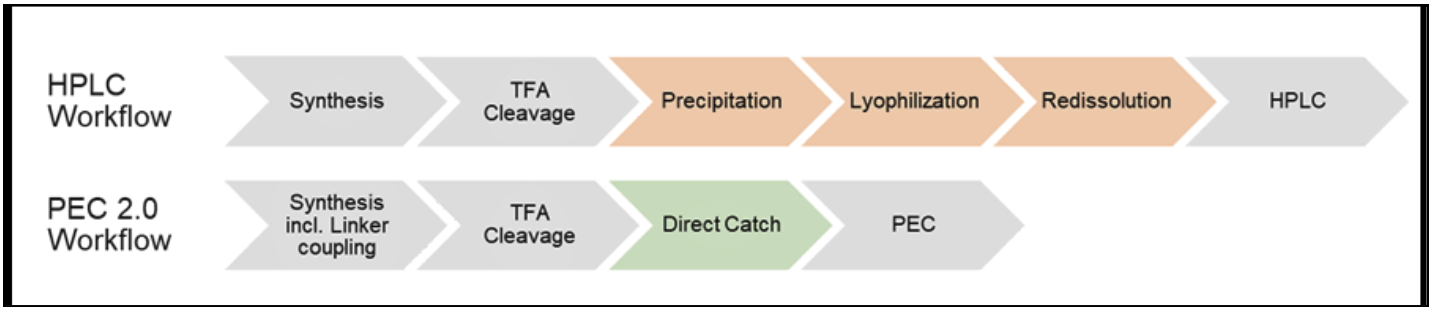

Figure 5. Comparison of conventional HPLC workflows in contrast to the precipitation- and redissolution-free workflow from synthesis to purification with PEC 2.0.

This "redissolution-free workflow from synthesis to purification" eliminates the step where many difficult peptides previously failed. Hydrophobic sequences that won't dissolve, aggregating peptides, and long modified sequences all bypass the redissolution challenge entirely. It's worth noting that a final precipitation is still required after PEC purification for lyophilization—the innovation specifically targets the pre-purification redissolution struggle.

In a recent presentation at the Boulder Peptide Symposium,[5] Dominik Sarma shared results from a case study with T-Therapeutics, a UK-based biotechnology company, showing how PEC 2.0 was used to successfully purify extremely hydrophobic peptides with high Eisenberg values >5 to deliver a set of epitopes for T-cell validation studies – in contrast to the previous vendor that failed to provide all peptides.

3.0 Practical Considerations and Complementary Approaches

The evolution of catch-and-release technologies has not eliminated HPLC—nor should it. Each approach offers distinct advantages that complement different phases of the drug discovery funnel effectively. Many laboratories find value in using both strategically, either as independent purification strategies or in combination.

3.1 When to Choose PEC

Catch-and-release excels in specific contexts:

- Eliminating HPLC bottlenecks via parallel processing: PEC shines when your workflow requires multiple peptides purified at once. Its parallel operation allows you to complete, in a single day, what traditional HPLC would stretch over several days — removing throughput constraints without adding extra HPLC systems.

- Difficult peptides: Very hydrophobic sequences that won't dissolve for HPLC injection, very hydrophilic peptides that flush through RP columns, and long or heavily modified sequences benefit from PEC's orthogonal separation mechanism.

- Discovery-stage applications: Where fit-for-purpose or PEC-grade purity (validated in functional assays) suffices, PEC delivers results faster with less solvent consumption — typically 12x less per run.

3.2 When HPLC Remains Essential

HPLC maintains clear advantages:

- Ultra-high purity requirements: When you need a purity of greater than 95%, particularly for late-stage development or regulatory submissions, HPLC's resolution is typically necessary.

- Established workflows: When current HPLC methods work well and meet timeline requirements, there's limited incentive to change.

- Universal compatibility: HPLC is compatible regardless of the N-terminal modification status. PEC typically requires a free N-terminus for linker coupling (though alternative coupling sites may be developed for specific cases).

3.3 Hybrid Strategies: The Best of Both Worlds

Increasingly, laboratories employ both technologies strategically. Because PEC and HPLC use orthogonal separation mechanisms—chemo-selective capture vs. hydrophobicity-based separation—they complement each other effectively. One study showed that peptides purified by PEC alone achieved a 79% mean purity, but when followed by HPLC polishing, the combination reached a 94% mean purity across a set of very difficult peptides.[6] The PEC step removed synthesis-related impurities efficiently, improved handling (solubility, etc.) of the semi-purified sample, which then simplified HPLC for final purity refinement.

This orthogonal approach appears particularly promising for peptides advancing through development stages. Early discovery work can use PEC alone for speed and throughput. As peptides advance through a discovery pipeline, the number of molecules decreases, while the quantity per molecule increases, along with final purity requirements. HPLC polishing can then be added to the workflow. This staged approach optimizes both speed and final quality.

3.4 Solvent Reduction: A Practical Benefit

PEC offers substantial reductions in solvent consumption. Traditional preparative HPLC can use several hundred milliliters of organic solvent per purification, depending on the flow rate, run time, and gradient, consuming primarily acetonitrile for the mobile phase and column maintenance. PEC's catch-and-release mechanism uses approximately 50 mL of solvent per peptide, representing a significant reduction, even with highly optimized, short HPLC runs.

This difference scales meaningfully in routine use. Laboratories purifying multiple peptides weekly find that reduced solvent consumption eases both waste disposal logistics and associated costs. For organizations with sustainability commitments or facing regulatory pressure around solvent use, this represents a measurable environmental benefit alongside operational advantages.

4.0 Looking Forward: Continued Evolution

The peptide purification landscape continues to evolve rapidly. Several trends suggest where innovation may focus next:

- Expanded chemistry: Developing linker systems compatible with N-terminally modified peptides would broaden the applicability of PEC. Alternative coupling sites and custom linker development may address this limitation.

- Scale and automation: As peptide therapeutics advance through development, scaling PEC methods to millimolar quantities and integrating them with automated workflows becomes increasingly essential. The fundamental principles that enable parallel processing at discovery scale should translate to manufacturing scales.

- Application-specific optimization: Different therapeutic modalities—from screening libraries to personalized neoantigen vaccines to GLP-1 analogs—may benefit from tailored purification approaches. The field will likely see continued specialization.

- Quality standards: As PEC methods become more widespread, establishing clear quality frameworks for "PEC-grade" purity across different applications will enable researchers to make informed decisions about when each method is most suitable.

5.0 Conclusion: Complementary Tools for Modern Peptide Discovery

The evolution of catch-and-release purification—from the early reductively cleavable linkers to Gyros Protein Technologies' workflow simplifications in PEC 2.0—demonstrates how focused innovation addresses specific technical challenges. These advances haven't replaced HPLC; instead, they've expanded the toolkit available to peptide chemists, offering alternative approaches for situations where traditional methods struggle.

The synthesis-purification bottleneck that Sarma and his team identified remains relevant; however, researchers now have more options for addressing it strategically. For parallel processing needs, for challenging peptides that defy traditional chromatography, and for discovery applications where fit-for-purpose purity is sufficient, catch-and-release offers a validated pathway. When ultra-high purity is essential or when current HPLC workflows serve well, chromatography remains the standard. And increasingly, hybrid approaches leverage the complementary strengths of both technologies. (Figure 6)

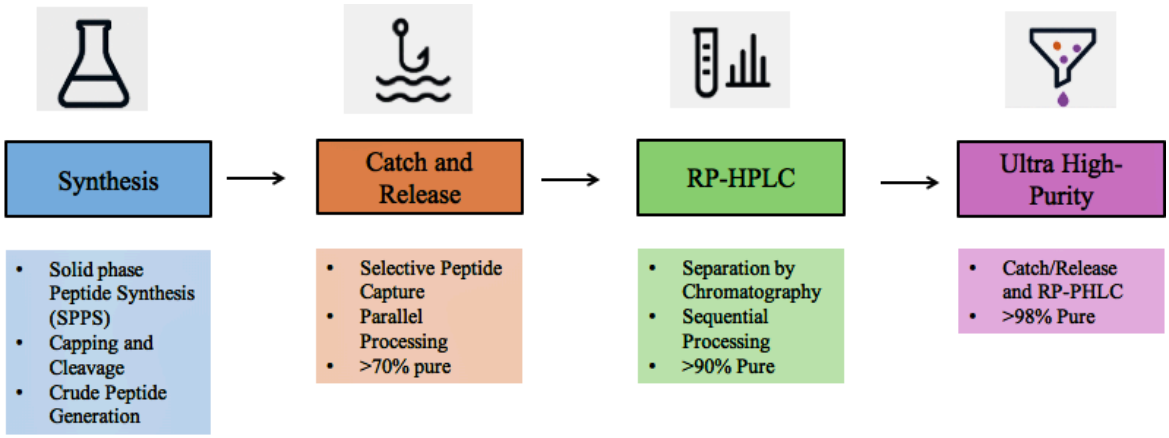

Figure 6. Complementary purification pathways and their roles across the peptide discovery workflow. Peptide synthesis can be followed by parallel catch-and-release purification for speed and throughput (>70% purity), by RP-HPLC when ultra-high purity is required (>90–95%), or by hybrid workflows that combine both approaches to reach >98% purity. This illustrates how PEC and HPLC together address the synthesis-purification bottleneck and support different stages of discovery and development.

As peptide therapeutics continue to achieve clinical success, the field's manufacturing infrastructure must keep pace. The continued innovation in purification technologies, alongside advances in synthesis, analytics, and delivery, ensures that promising peptide candidates can move from concept to clinic with increasing speed and reliability. The next chapter of this story will likely feature further workflow integration, expanded chemical compatibility, and new applications we haven't yet imagined.

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With the Subject: Life of a Peptide

PDHC

4Q 2025

PEPTIDE NEWS

By Ved Srivastava

SUMMARY

In 2025, the peptide field continued to accelerate across multiple vectors, including strategic corporate deals and licensing of platforms, as well as a stream of clinical advances, most notably in long-acting metabolic peptides and next-generation peptide biologics. It has sharpened the scientific advances in the peptide therapeutics field with sophisticated AI/ML frameworks for de novo peptide design and optimization. Key highlights are discussed below.

BREAKING NEWS

On Nov. 24, 2025, Dayra Therapeutics, a new biotech launched by Versant Ventures, is developing oral macrocyclic peptide drugs for immunological diseases and has formed a research partnership with Biogen. Biogen will provide a $50 million upfront payment. Dayra also secured a $20 million equity commitment from Versant.

On Nov. 13, 2025, Pfizer announced the successful completion of its acquisition of Metsera, Inc., valuing the deal at approximately $7.0 billion and adding a robust peptide portfolio of obesity and cardiometabolic drug candidates to its Internal Medicine pipeline. The acquisition brings MET-097i, a weekly and monthly injectable GLP-1 receptor agonist entering Phase 3, MET-233i, a monthly amylin analog in Phase 1 being evaluated alone and with MET-097i, as well as an oral GLP-1 RA in Phase 1; and additional preclinical nutrient-stimulated hormone therapeutics.

In October 2025:

Novartis announced the acquisition of Avidity Biosciences, a company focused on a new class of therapeutics enabling RNA delivery to muscle. The acquisition will strengthen Novartis's late-stage neuroscience pipeline, and Avidity will expand early-stage precision cardiology programs, possibly as a separate entity.

Rani Therapeutics announced a $1.085 billion collaboration and license agreement with Chugai Pharmaceutical to develop and commercialize an oral biologic using its RaniPill® platform with Chugai's rare and immunologic diseases.

The clinical-stage biotechnology company Peptilogics announced the completion of an $78 million Series B2 financing round. The funding will support the company's Phase 2/3 pivotal trial of Zaloganan (PLG0206), a first-in-class investigational treatment for prosthetic joint infections (PJI).

Johnson & Johnson (J&J) entered discussions to acquire Protagonist Therapeutics, prompting a more than 30% surge in Protagonist's share price on the day. The company's lead candidate, Icotrokinra (JNJ-2113), a hit from mRNA display, 8 non-canonical amino acids, 1.90 kDa, Alog P -0.11, an oral peptide targeting immune-mediated diseases such as plaque psoriasis and ulcerative colitis, is in late-stage clinical development. Protagonist, with a market capitalization of approximately $4.2 billion, is collaborating with J&J, which holds exclusive commercialization rights to Icotrokinra. The negotiations are preliminary, and no definitive agreement has been reached yet.

BUSINESS & COLLABORATION DEALS

The recent surge in strategic alliances and financing underscores growing investor and pharmaceutical confidence in next-generation biologics and peptide discovery. The deal marks a catalyst for 'Investment in Peptide Platforms and Validation of Oral Peptide Therapeutics', which has traditionally been a significant barrier in peptide therapeutics.

In October 2025, Halozyme announced plans to buy Elektrofi (up to $900 million), largely to bolster its drug delivery capabilities (e.g. biologics and peptide therapeutics) using Elektrofi's "Hypercon" platform.

In September 2025, PepGen announced the pricing of a $100 million public offering of 31.25 million shares at $3.20 per share, to advance its FREEDOM-DM1 and FREEDOM2-DM1 clinical trials and next-generation oligonucleotide therapeutic programs.

In August 2025, BioMed X and Novo Nordisk launched a project focused on oral formulations of peptide drugs such as GLP-1 mimetics, specifically designing systems that prolong retention in the lower small intestine to boost absorption.

In July 2025, Unnatural Products, Inc. (UNP), announced a multi-target research and licensing agreement with Argenx that could exceed $1.5 billion in potential research, development and commercial milestones, in addition to an upfront payment and future royalties. The collaboration positions the non-canonical amino acid-driven platform to discover and develop orally available macrocyclic peptide drug candidates for several "undruggable" targets.

In June 2025, Novo Nordisk struck a licensing deal worth up to $812 million with Deep Apple Therapeutics to co-develop drugs targeting cardiometabolic and obesity indications. While Deep Apple's platform is not purely peptide, this is relevant in the broader peptide and metabolic therapeutics space.

In March 2025, Roche and Zealand Pharma signed a $5.3 billion deal for an amylin-based peptide, Petrelintide, 4.2 kDa, comprising 3 non-canonical amino acids, aimed at obesity/weight-loss indications.

In January 2025, AbbVie completed the acquisition of Nimble Therapeutics, a company with an oral peptide IL-23 receptor (IL23R) inhibitor in preclinical development, and proprietary peptide synthesis/optimization platforms. This builds AbbVie a foothold in oral peptide therapeutics for immunology/ autoimmune (e.g. psoriasis) space.

FDA APPROVALS

Regulatory bodies are refining guidance on peptides and continue to approve peptide-based drugs for addressing unmet medical needs.

In October 2025, Wegovy (semaglutide) gained a new indication: accelerated approval in the US for treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH).

In September 2025, the synthetic tetrapeptide (D-Arg-Dmt-Lys-Phe-NH2) Elamipretide (Forzinity) was approved by the FDA to improve muscle strength in people with Barth syndrome (for those weighing ≥ 30 kg). It's a mitochondrial cardiolipin peptide binder.

I**n August 2025**, the calcitonin gene-related peptide antagonist Ajovy (fremanezumab-vfrm) got its indication expanded. It is now approved for pediatric episodic migraine in a younger population (4 to < 30 kg).

TECHNOLOGY PLATFORM ADVANCEMENT

AI has moved from hype to practical integration in peptide design workflows.

In October 2025, AstraZeneca entered into a licensing agreement with Algen Biotechnologies to develop gene therapies using Algen's proprietary AI-powered gene-editing platform for targeting immune system-related disorders. The deal is valued at up to $555 million, including upfront and milestone payments.

AstraZeneca also invested in artificial intelligence for drug discovery, following its $5.3 billion partnership with China's CSPC Pharmaceutical, announced in June.

Peer-reviewed studies and industry collaborations published in 2025 demonstrate the application of deep learning, reinforcement learning, and hybrid evolutionary strategies, including the Integration of large language models (LLMs) to design peptides with tunable properties (binding, stability, and aggregation tendency).

In September 2025, the Nature Journal reported "Artificial intelligence-driven approaches for the rational design of peptides with predictable aggregation propensity". This is an example of how ML is now addressing subtle developability issues important for peptide drugs.

OUTLOOK

Deal activities in 2025 show two clear themes: (1) platform consolidation to enable better peptide/biologics drug development and (2) large pharma doubling down on acquisition of peptide biotech and on AI-enabled discovery partnerships.

This year, the U.S. Food and Drug Administration (FDA) continues to intensify oversight of supply-chain integrity and compounding practices involving GLP-1 receptor agonists and other high-demand peptide therapeutics. The FDA addressed shortages, unauthorized imports, and misuse of GLP-1 ingredients in compounding. The FDA's evolving stance reinforces the need for proactive regulatory alignment and supply security in the peptide therapeutics sector.

Looking ahead, we anticipate a marked increase in clinical readouts and impactful peptide-related advancements, coupled with the integration of experimental flow-synthesis and AI-driven design loops into development pipelines by 2026.

FUN FACT

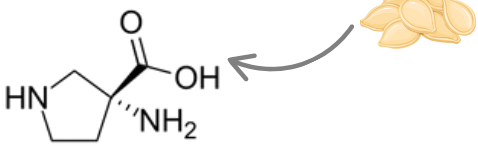
by **Charles W. Johannes**,
Co-Founder & VP, PDHC

Pumpkins have long been valued not only as a staple of fall traditions but also for their **medicinal seeds**, which were used for centuries as natural remedies against parasites. Modern research has revealed that pumpkin seeds are more than folklore—they are a rich source of **bioactive peptides** that bridge nutrition, medicine, and therapeutics.

Traditional roots

Pumpkin seeds were used for their anthelmintic activity, with compounds like **cucurbitin** playing a role in expelling intestinal parasites. This is a great example of a **non-canonical natural amino acid**.[1]

SNHANQLDFHP
PVQVLASAYR

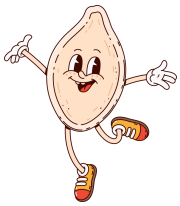


Modern bioactive science

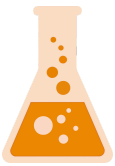
Enzymatic digestion of pumpkin seed proteins liberates short-chain peptides with antioxidant, antimicrobial, hypoglycemic, and antihypertensive properties.[2–4]

Standout discovery

From pumpkin seed meal, researchers recently isolated two **peptides**—**SNHANQLDFHP** and **PVQVLASAYR**—with strong angiotensin-converting enzyme (ACE) inhibitory activity, making them promising leads for blood pressure regulation and cardiovascular health.[5]



Future promise:



Antioxidant-rich pumpkin peptide hydrolysates also show excellent functional properties—such as emulsifying, foaming, and stability—which supports their use in functional foods and nutraceutical formulations. Their radical scavenging capacity is linked to enrichment in hydrophobic and aromatic residues such as Tyr, Phe, and Pro, explaining their potency.[4]

THE PUMPKIN'S STORY RUNS FROM AUTUMN DECORATIONS TO THE PEPTIDE LAB BENCH, EMBODYING THE PDHC SPIRIT OF CONNECTING TRADITION, INNOVATION, AND TRANSLATION.

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Join us for Peptide Drug Hunting 101 a symposium for all drug hunters, especially those focused on proteins and other biologics looking to renew or deepen their understanding of peptide drug discovery. Trace the life of a peptide through its full development cycle from initial discovery and design to optimization, validation, and therapeutic advancement highlighting how cross-disciplinary collaboration accelerates drug discovery. Explore emerging and established therapeutics targets for peptide modalities, modern drug design strategies, and how peptide tools contribute to proof-of-concept and unlock future peptide medicines. Whether you're re-visiting peptides or exploring them with new interest, this is an outstanding opportunity to gain practical insights and connect with experts shaping the future of peptide drugs.

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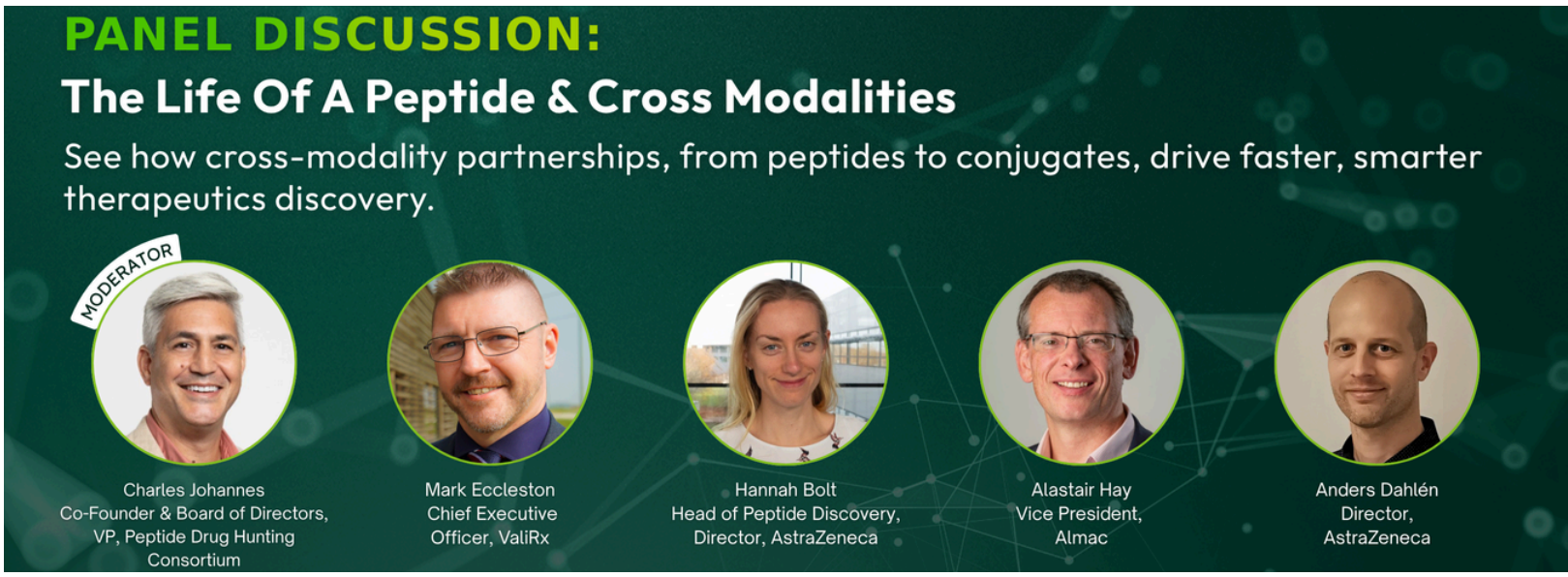

THANK YOU TO OUR SPONSORS

The **Peptide Drug Hunting Consortium (PDHC)** is a global, 501(c)(3) non-profit organization **dedicated to advancing multidisciplinary peptide drug hunting through collaboration** across academia, biotech, and pharma worldwide. PDHC Sponsors will enable PDHC programs, initiatives and operations to drive innovation, share learnings, and fortify the science/business interface **in one of the most impactful therapeutic modalities — peptides!**

Our **sponsorship tiers provide all organizations** (e.g., biotech, pharma, contract R&D organizations, service providers and venture capital) and benefactors (e.g., individuals, family offices and foundations) the opportunity to support PDHC's vision for empowering peptide drug hunters worldwide and engage directly with PDHC's leadership and members as well as gain **visibility through PDHC webinars, events, and publications** (e.g., PDHC Chronicle). PDHC Sponsors will have a unique role in **being part of a multifaceted enterprise** involving diverse modalities of peptides and therapeutic target space to integrate innovation, learnings and the science/business interface for **empowering breakthrough medicines!**

Whether as a **Founding, Executive, or Legacy Sponsor**, your support will enable the PDHC to **build a sustainable, collaborative worldwide enterprise that accelerates peptide science and technology innovations** from concept to the clinic and ultimately patients across a wide-ranging therapeutic landscape.

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SPECIAL ACKNOWLEDGMENTS TO AUTHORS & EDITORIAL TEAM

FIRST, we wish to acknowledge the authors contributing to our inaugural issue!

Charlie's Leadership Insight article "*Leading from the Outside*" as a consultant well articulates the challenges and opportunities of being an external member of an R&D team. We hope that it will be helpful to both current and future consultants where special expertise has a significant impact.

In the *PDHC Vision* article by Charlie, Wendy, and myself, we share our personal motivations for founding the PDHC. and give gratitude to our Leadership Team, Entrepreneurial Advisory Board, Entrepreneurial Business Network, Sponsors, our >3,200 PDHC Followers (LinkedIn) and our PDHC Media Partners. Above and beyond, we are very indebted to Danielle for her outstanding efforts to handle virtually everything that comes her way and to enable our PDHC vision to become reality.

Fernando's Synthesis Innovation article "*Peptide Synthesis: The Driving Force of the Peptide Golden Era*" exemplifies his deep expertise, genuine enthusiasm and legacy as one of the great peptide synthetic chemists worldwide. He wrote this article with a personal aspiration to share his knowledge and insights to peptide synthesis as the driving force at this long-awaited time in peptide science, technology and medicine — indeed the "Peptide Golden Era".

In the Life of a Peptide articles "*Overcoming the Peptide Purification Bottleneck: The Evolution of Catch-and-Release Purification*" by Dominik, Elizabeth, Gordon and Charlie and the "*Life of a Peptide: Preamble to the Series*" by Charlie share the first of a series that will integrate all aspects of scientific and technical progress that will continue to propel the multidisciplinary discovery and development of peptide medicines. This first article provides a focus on improving peptide synthesis efficiency relative to purification through catch-and-release methodology.

In the Translation into the Clinic article "*Improving Solubility to Improve Clinical Translation*" by Charlie, Antoine and Wendy, it states that optimizing physicochemical properties, especially solubility, is one of the most critical developability factors. The good news is that there is hope through both design and formulation. They strongly recommend addressing solubility as a core developability gate earlier within lead optimization rather than late-stage formulation.

Tom's Breakthrough Medicine article "*Q&A on the Discovery of MK-0616 (Enlicitide), a Novel Oral Macrocyclic Peptide PCSK9 Inhibitor*" provides a very special and in-depth perspective from one of Merck's outstanding medicinal chemists and a member of the PCSK project team. It describes the many facets of the discovery and development of a breakthrough orally bioavailable, tricyclic peptide MK-0616. We appreciate Merck's willingness to support our invitation to Tom and being able to share his responses to many questions about his experience, and we wish Merck good luck with its ongoing Phase 3 clinical development of Enlicitide!

Ved's *Peptide News* for 2025 shares a synopsis of an increasing momentum of peptide drug development and FDA approvals, business and collaboration deals, and an outlook with respect to future peptide technology platform consolidation, biotech acquisitions, and AI-enabled peptide drug discovery partnerships. 2026 should be a great year for peptide drug hunters!

Charlie's *Fun Fact* article was a Halloween treat and a scientific tribute to pumpkin seeds and the identification of biologically active non-canonical amino acids (e.g., cucurbitin) and peptides (e.g., SNHANQLDFHP and PVQVLASAYR) within them. Looking forward to future Fun Facts!

SECOND, we wish to acknowledge the editorial reviewers, and publishing team for their many contributions to launch this inaugural issue. All the above individuals supported the editorial and publishing process, along with Danielle (orchestrating the entire effort), Thomas (Managing Editor), Wendy (Member at Large advisor), Abbas Walji (special liaison), Jonathon Sawyer and Matt Naylor (contributing reviewers), and Jeff Geniesse (web version of the PDHC Chronicle). Thank you, team!

THIRD, please find a listing of our PDHC Editorial Advisory Board on the following page. We look forward to their support of the PDHC Chronicle in future issues.

LASTLY, we extend a welcome to our readership to communicate with us about opportunities to publish in our 1Q 2026 issue as well as to our Sponsors to consider our recently revised services as related to the PDHC Chronicle. Please reach out to us (including Danielle) if you are interested!

With warmest wishes,

Tomi Sawyer
Editor-in-Chief

Charles Johannes
Executive Editor

Ved Srivastava
Executive Editor

PDHC

thank you

LISTING OF OUR PDHC CHRONICLE EDITORIAL TEAM

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