Drug Development & Delivery

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The Science & Business of Pharmaceutical and Biological Drug Development

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Richter et al., Pharmaceutics 2024, 16, 1368.

Bioavailability & Solubility

"Improving the bioavailability and solubility of modern APIs remains one of the most persistent hurdles in drug development. As pipelines continue to shift toward highly lipophilic, poorly water-soluble molecules – particularly BCS Class II and IV compounds – formulators are turning to advanced materials, predictive tools, and mechanistic design approaches to ensure adequate bioavailability and therapeutic performance."

p.34

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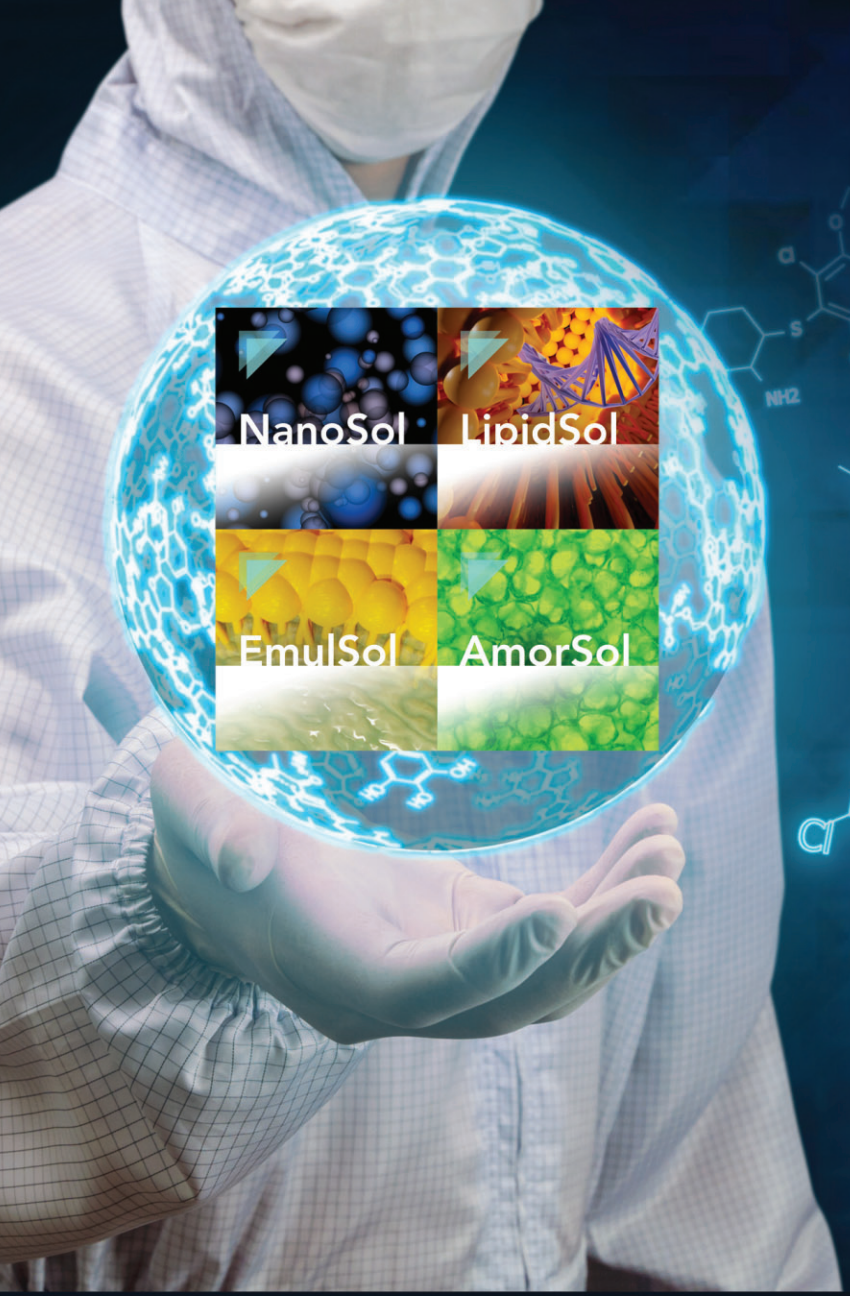

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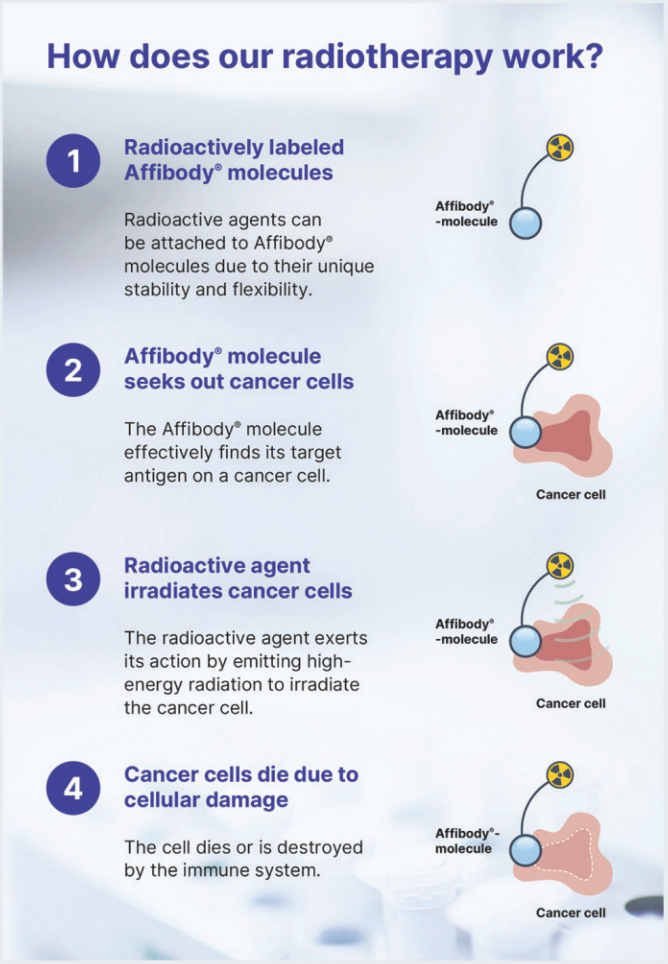
Radioligand Therapies

Following initial attempts to address radiopharma using full-size monoclonal antibodies (mAbs), recent advances in the radiopharma field have predominantly focused on peptides. These significantly smaller molecules can penetrate deep into solid tumors and allow more efficient internalization into cells. They also offer lower immunogenicity, easier chemical modification, speedier diagnostics, and changed non-target toxicity."

p.68



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PRISM ALS: New Stem Cell Models Could Transform Research Into Treatments for MND/ALS

A new global initiative launched today aims to close a critical gap in ALS/MND drug discovery – current cell models used for testing treatments do not currently reflect the diverse nature of the disease – that affects both researchers developing therapies and the people urgently waiting for them.

The ALS Therapy Development Institute (ALS TDI), LifeArc, and Axol Bioscience announced the launch of Patient induced pluripotent stem cell (iPSC)-based Research to Improve Sporadic ALS Modelling (PRISM), a collaborative effort to expand access to high-quality, patient-derived stem cell models that better reflect the biological complexity of amyotrophic lateral sclerosis (ALS).

ALS is a heterogeneous disease. While 10-15% of cases are linked to inherited mutations, nearly 85% are sporadic. Yet much of ALS drug discovery has relied on models representing a limited number of rare genetic subtypes. This mismatch has constrained target discovery, limited therapeutic testing across patient populations, and contributed to the high failure rate of clinical trials.

This unprecedented initiative will provide a reliable, high-quality, and accessible source of sporadic ALS/MND models for use in research. PRISM ALS aims to develop, evaluate, and make available a diverse panel of well-characterized, patient-derived induced pluripotent stem cell (iPSC) models that capture both genetic and sporadic forms of ALS.

For researchers and drug developers, those standardized, human-relevant models could allow them to better understand disease mechanisms, identify therapeutic targets, and evaluate treatments across distinct biological subtypes. For people living with ALS, it means therapies can be developed and tested in models that more closely mirror their own biology, increasing the likelihood that discoveries will translate into meaningful treatments.

The stem cells used in PRISM ALS are derived from samples contributed by people living with ALS through ALS TDI's ALS Research Collaborative (ARC) Study, the longest-running longitudinal patient study in ALS.

Over more than a decade, ALS TDI has built one of the most comprehensive collections of ALS-specific iPSCs available today. These cells come directly from people living with ALS, many of whom also contributed detailed clinical data, creating an unparalleled resource for understanding how the disease behaves and how it may respond to therapy.

This work is only possible because of the more than 1,800 people with ALS who have chosen to participate in the ARC Study and contribute samples and data to advance research.

By enabling standardized production at scale, the collaboration ensures quality, consistency, and reproducibility across laboratories. The goal is to accelerate progress across the ALS field by providing robust, human-relevant tools that better reflect the biological diversity and complexity of the disease.

By working together, the partners aim to ensure that these models become a widely accessible, high-quality resource for researchers in academia and industry who are committed to advancing ALS therapies.

Cyclerion Therapeutics & Korsana Biosciences Announce Merger Agreement

Cyclerion Therapeutics, Inc. and Korsana Biosciences, Inc. recently announced they have entered into a definitive merger agreement for an all-stock transaction. Upon completion of the transaction, the combined company plans to operate under the name Korsana Biosciences, Inc. and trade on Nasdaq under the ticker symbol KRSA.

In support of the proposed merger, Korsana has secured commitments for an oversubscribed private investment that is expected to result in total gross proceeds of approximately $380 million from a syndicate of investors led by Fairmount and Venrock Healthcare Capital Partners, with participation from General Atlantic, TCGX, Forbion, Wellington Management, Commodore Capital, RA Capital Management, RTW Investments, Vivo Capital, Janus Henderson Investors, Foresite Capital, J.P. Morgan Life Sciences Private Capital, SR One, Sanofi Ventures, Kalehua Capital, Spruce Street Capital, and other leading investment management firms. The financing includes common stock and pre-funded warrants exercisable for shares of Korsana common stock.

The financing is expected to close immediately prior to completion of the proposed merger. The combined company's cash and cash equivalents balance at closing, including the funds from the private placement, is anticipated to fund Korsana's operations into 2029 and provides runway through key clinical milestones. These include the advancement of KRSA-028 through Phase 1 healthy volunteer data expected in mid-2027 and interim proof of concept data measuring amyloid plaque clearance in Alzheimer's patients expected by the end of 2027.

Korsana is the seventh company to launch with assets discovered and developed by Paragon Therapeutics. Korsana's lead program is KRSA-028, a next-generation shuttled antibody targeting amyloid beta for the treatment of Alzheimer's disease, discovered in partnership with Paragon Therapeutics. KRSA-028 utilizes the proprietary Therapeutic Targeting (THETA™) platform, which incorporates clinically validated transferrin receptor (TfR1) and Fc engineering and is designed to improve brain delivery and solve limitations of other TfR1-based approaches. KRSA-028 was designed to increase amyloid plaque clearance, reduce the rate of amyloid-related imaging abnormalities (ARIA) and hematologic adverse events, and optimize convenience and compliance with a low-volume subcutaneous route of administration. Korsana is advancing a pipeline of innovative THETA-enabled therapies for other undisclosed, neurodegenerative diseases with high unmet need.

The transaction has received approval by the Board of Directors of both companies and is expected to close in the third quarter of 2026, subject to certain closing conditions, including, among others, approval by the stockholders of each company, the effectiveness of a registration statement to be filed with the U.S. Securities and Exchange Commission (the "SEC") to register the securities to be issued in connection with the proposed merger, expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the satisfaction of other customary closing conditions.

The combined company plans to operate under the name Korsana Biosciences, Inc. and will be led by Dr. Violin, Korsana's current Chief Executive Officer. Korsana's existing Board of Directors will become directors of the combined company, chaired by Tomas Kiselak, Founding Partner at Fairmount, and including Andrew Gottesdiener, M.D., Partner at Venrock Healthcare Capital Partners, Nilesh Kumar, Ph.D., Head of Biotech Private Investments at Wellington Management, Michelle Pernice, Operating Partner at Fairmount, Nimish Shah, Partner at Venrock Healthcare Capital Partners, and Dr. Violin.

Adragos Pharma Finalizes the Acquisition of Commercial-Scale, Sterile Fill-Finish Manufacturing Site From Sanofi

Adragos Pharma recently announced it completed the acquisition of a commercial-scale sterile fill-finish facility in Maisons-Alfort, France, from Sanofi. The Maisons-Alfort site is one of Europe's largest manufacturing facilities for sterile injectables, with industrial-scale capacity for pre-filled syringes (PFS), as well as liquids and lyophilized vials.

The facility, located in the south-eastern suburbs of Paris, is regularly audited by international health authorities, including ANSM (France), NMPA (China), MFDS (South Korea), and ANVISA (Brazil), and supports the global supply of critical injectable medicines.

The Maisons-Alfort site employees are joining Adragos Pharma, bringing with them expertise in sterile manufacturing, ensuring full operational continuity while preserving the technical excellence built over the years. This complete talent integration represents a major strategic asset for the site's future.

This site significantly expands Adragos' sterile injectables network, adding high-volume pre-filled syringe manufacturing capabilities to its existing vial and ampoule filling operations in Jura, Switzerland, and Livron, France. The combined platform establishes Adragos as one of the leading sterile injectables CDMOs in Europe.

Dr. Andreas Raabe, Founder and CEO of Adragos Pharma, commented: "Maisons-Alfort is a landmark acquisition for Adragos and a defining step in our growth journey. We are adding one of Europe's leading sterile manufacturing sites to our network. Our ambition is clear: to invest, scale, and further develop the site into a top-tier fill-finish platform. This transaction is fully aligned with our strategy to secure and expand highly differentiated pharmaceutical manufacturing capacity in Europe."

Moritz Hafner, Partner at FSN Capital (investment advisor to FSN Capital VI), added: "This acquisition is a significant step in our strategy to build Adragos into a leading player in the European pharmaceutical CDMO market. The Maisons-Alfort site is a strong strategic fit – it enhances Adragos' sterile injectables capabilities and adds a highly experienced team that will further strengthen the Adragos platform. We are very proud of the trust that Sanofi places in Adragos to continue producing life-saving medicine. We look forward to the journey ahead with the Adragos management team as we continue to grow and serve the increasing customer demand for high-quality pharmaceutical products."

Philippe Charreau, Head of Manufacturing & Supply Sanofi France: "For decades, Maisons-Alfort has been a cornerstone of sterile manufacturing for Sanofi's most trusted products, built on deep expertise, advanced capabilities, and the unwavering commitment of its employees. We are confident that Adragos will carry forward the site's tradition of operational excellence, leveraging the exceptional talent and experience of these teams to continue serving patients and write a successful new chapter for this site."

Adragos Pharma is a global CDMO headquartered in Munich, Germany, focused on the development and manufacturing of pharmaceutical products. The company is building a differentiated international network across Europe and Japan, with a strong focus on sterile injectables and complex dosage forms. Adragos operates manufacturing sites in France, Germany, Switzerland, and Japan, as well as a development site in Greece, and is backed by FSN Capital and the Prange Family Office.

Amprion Grows Global Footprint With Australian Partnership & Expanded Research Collaborations

Amprion recently announced a series of strategic milestones that underscore the company's accelerating growth, expanding international footprint, and continued commitment to advancing earlier and more accurate diagnosis of neurodegenerative diseases.

Amprion will continue to work with The Michael J Fox Foundation for Parkinson's Research (MJFF) on multiple research initiatives in 2026. Ampiron's seed amplification assay (SAA) is an integral part of the inclusion criteria for the ongoing Parkinson's Progression Markers Initiative (PPMI) study which continues to help the scientific community further define and understand Parkinson's and its progression. Additional collaborative research efforts are exploring how SAA data may contribute to understanding disease progression and evaluating different sample types.

Amprion is also partnering with Macquarie University to establish clinical alpha-synuclein seed amplification testing in Australia. The collaboration will support both clinical and research initiatives to advance the understanding and detection of neurodegenerative diseases. The site is an Australian first and marks an important step toward expanding international access to seed amplification technology.

"Macquarie University's leadership in neurodegenerative disease research across Parkinson's, Alzheimer's, ALS/MND, and REM Sleep Behavior Disorder makes it a strong partner in advancing this technology," said Russ Lebovitz, MD, PhD, CEO and co-founder of Amprion. "Establishing Australia's first alpha-synuclein seed amplification testing site is an important step in expanding global access to more precise diagnostic tools."

As Amprion continues to expand internationally, the company is strengthening its global intellectual property portfolio. With the recent addition of China, Amprion now holds patents across all major regions of the world, reinforcing its leadership in SAA technology. The company is actively working to establish partnerships with leading hospital networks across Europe, South Korea, and China to further broaden access to its testing platform.

Amprion's seed amplification testing technology has demonstrated autopsy-confirmed diagnostic accuracy, providing clinicians and researchers with insights into the underlying pathology of synucleinopathies such as Parkinson's disease, Lewy body dementia, and related neurodegenerative disorders.

Demand for Amprion's SAAmplify-αSYN test has grown rapidly, leading to office space expansion and the identification of redundancy for manufacturing its substrate to support increased testing volume.

To learn more about Amprion's global initiatives and plans for 2026, stay connected on LinkedIn or book a meeting at one of their upcoming conferences. Amprion recently wrapped up a successful International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD).

Amprion's SAAmplify-αSYN test is a first-in-class qualitative Laboratory Developed Test and the only seed amplification assay available to aid the diagnosis of synucleinopathies such as Parkinson's disease, Lewy body dementia, and Alzheimer's disease with Lewy body co-pathology. The U.S. Food and Drug Administration granted Amprion a Breakthrough Device Designation in 2019 for use of the test as an aid in the diagnosis of Parkinson's disease. The test became commercially available in the United States in 2021.

Samsung Biologics Completes Acquisition of GSK's Manufacturing Facility

Samsung Biologics recently announced the completion of its acquisition of a manufacturing facility in Rockville, Maryland from GSK, establishing the company's first manufacturing presence in the United States. The Rockville site comprises two cGMP manufacturing plants with a combined 60,000-liter drug substance capacity, supporting both clinical and commercial biologics production across multiple manufacturing scales. With this addition, Samsung Biologics' total global manufacturing capacity increases to 845,000 liters.

Samsung Biologics will continue supplying the products previously manufactured at the site to GSK under the terms of the agreement, and the site will transition to serve additional contract manufacturing needs. Samsung Biologics also plans further investments to expand the site's capacity and upgrade technologies, reinforcing its long-term commitment to advancing a more resilient global supply chain and improving patient access to critical medicines.

"This represents a meaningful step in expanding our U.S. manufacturing footprint. The addition of the Rockville site strengthens our ability to operate a geographically diversified manufacturing network, and we are thrilled to officially welcome more than 500 colleagues at the site to the Samsung Biologics family," said John Rim, President and CEO of Samsung Biologics. "The Rockville team brings deep expertise and strong operational experience that will further strengthen the site as part of our global manufacturing network. As a CDMO, our mission is to help our partners bring important therapies to patients worldwide, and this site will play a pivotal role in that mission while ensuring continuity and upholding the high standards our clients expect."

The completion follows the previously announced agreement to acquire the facility on December 22, 2025.

Samsung Biologics (KRX: 207940.KS) is a leading contract development and manufacturing organization (CDMO), offering end-to-end integrated services that range from late discovery to commercial manufacturing. With a combined biomanufacturing capacity of 785,000 liters across Bio Campus I and II in Korea, and 60,000 from the acquisition of a manufacturing facility in Rockville, Maryland, U.S., Samsung Biologics holds total global manufacturing capacity of 845,000 liters. The company has also secured land for Bio Campus III, laying the groundwork for future capacity expansion to support next-generation therapies and emerging modalities. Samsung Biologics leverages cutting-edge technologies and expertise to advance diverse modalities, including multispecific antibodies, fusion proteins, antibody-drug conjugates, and mRNA therapeutics. By implementing the ExellenS™ framework across its manufacturing network with standardized designs, unified processes, and advanced digitalization, Samsung Biologics ensures plant equivalency and speed for manufacturing continuity.

Samsung Biologics' global manufacturing and commercial network spans Korea, the U.S., and Japan. Samsung Biologics America supports clients based in the U.S. and Europe, while its Tokyo sales office serves the APAC region. Samsung Biologics continues to invest in new capabilities to maximize operational and quality excellence, ensuring flexibility and agility for clients. The company is committed to the on-time, in-full delivery of safe, high-quality biomedicines, as well as to making sustainable business decisions for the betterment of society and global health.

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ARTIFICIAL INTELLIGENCE

The AI-Driven Path to Precision Therapeutics

By: Rotem Gura-Sadovsky, PhD, and Maayan Eilon-Ashkenazy, PhD

INTRODUCTION

For years, advances in biomolecular omics and robotic automation have steadily increased our data-generation capabilities. Now, breakthroughs in AI enable significant progress in drug discovery, conditioned on both generating the right data and deploying AI to the right applications. In this article, Rotem Gura-Sadovsky and Maayan Eilon-Ashkenazy explore the potential for AI to transform drug discovery, charting a path towards more targeted precision therapeutics.

The field of omics, which encompasses high dimensional biomolecular data such as genomics, transcriptomics, proteomics, metabolomics, and microbiome metagenomics, has grown rapidly, both in accessibility to the scientific community and in sensitivity. For example, single-cell RNA sequencing can now examine the gene activity of individual immune cells, showing how T cells, macrophages and B cells react to a drug or stimulus.

At the same time, automated robots have become more accessible and faster, able to perform thousands of tests daily, speeding up lab experiments that used to take weeks.

But the real potential game-changer is AI. While data and automation have not yet revolutionized drug discovery, as has been frequently promised, AI has the power to integrate with these advances and trigger transformative leaps.

THE NEW ERA OF SELF-SUPERVISED AI MODELS

In the last decade, the application of AI in personalized drug discovery has primarily focused on supervised learning models. These models are typically trained on clinical cohorts, labeled with outcomes such as patient response to a specific drug. While this approach has driven significant progress in personalized cancer diagnostics and treatment, its success has been limited in areas outside of oncology despite intensive attempts for over a decade.

However, the era of self-supervised models is upon us. These models employ vast computational power to extract complex pat-

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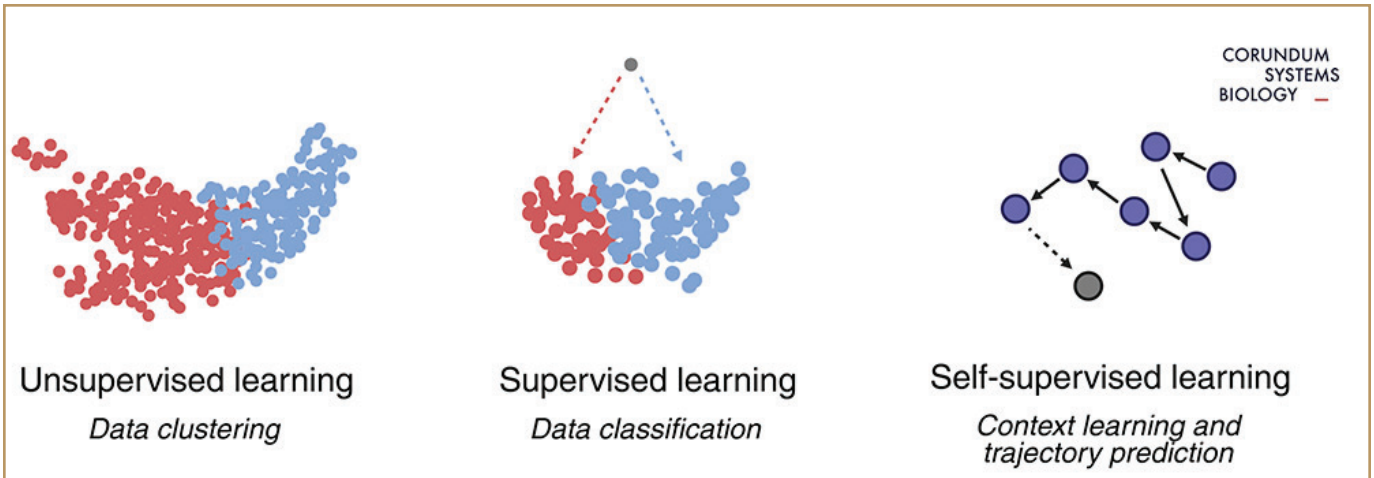


Biomarker measurements (left) feed into a disease-risk prediction model (center), stratifying patients into low (blue), medium (teal), and high (red) risk groups. Each risk tier then maps to a tailored intervention (right), illustrating how molecular data guide personalized treatment pathways. Created in BioRender. Eilon Ashkenazy, M. (2025) https://BioRender.com/up5m5hj

terns from unlabeled data, which is much more plentiful than labeled data. By applying these models to massive clinical data like omics and medical imaging datasets we can uncover subtle patterns, augment supervised models and advance personalized drug discovery.

Large Language Models (LLMs) are examples of self-supervised models applied to written languages, and they have already given rise to applications that boost drug discovery research. AI coding companions improve computational researchers' productivity, and natural-language interfaces broaden access to AI tools for non-coders. Using these models, researchers can, for example, generate novel protein sequences simply by describing desired functions. If deployed correctly, this accelerating force can reshape drug discovery, disease-prevention strategies and clinical trial design.

Companies are now working on integration of AI with high-throughput robotic screening platforms. By analyzing early assay readouts in real time and then triggering the next experiment autonomously, these systems can run screens 24/7. This delivers a boost in output, far beyond what robotics alone ever managed. All these lab-side innovations set the stage for the next frontier – analyzing and integrating pre-clinical lab data and patient-derived data at scale.

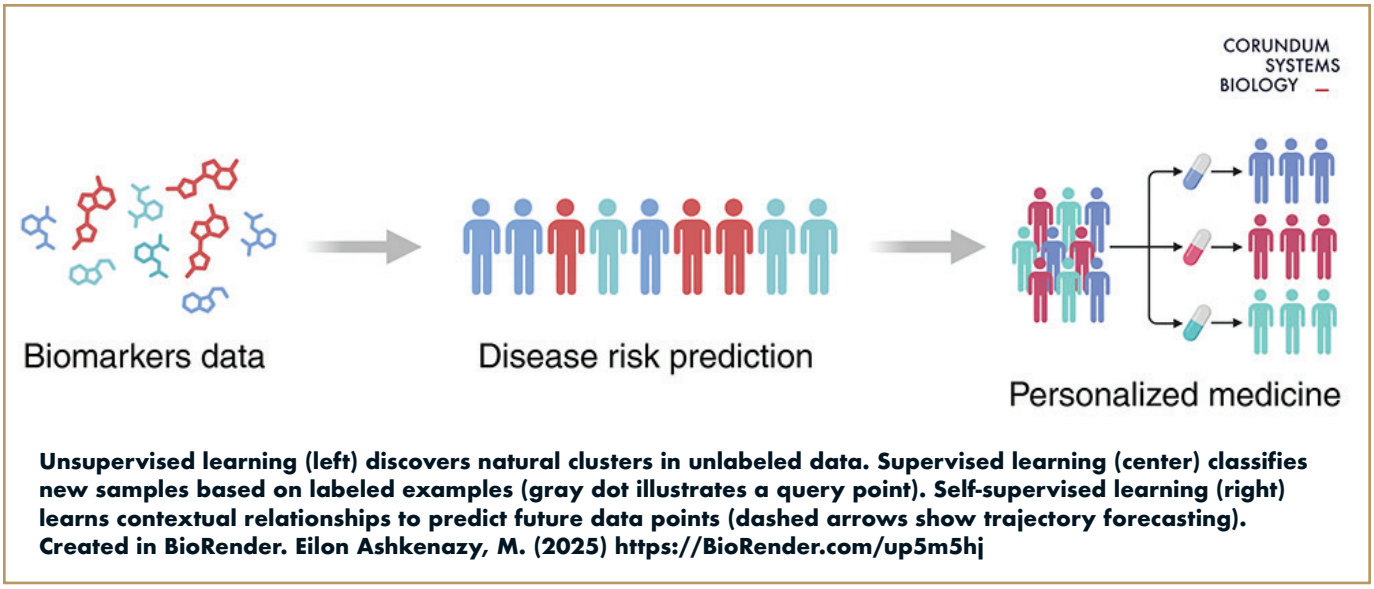
THE CONTINUOUS DATA IMPERATIVE

Today, most datasets are still falling short. Disease-specific cohorts often lack the sample sizes needed for AI training – a 10,000-person cohort sounds large, yet only a few hundred of those individuals may have a specific disease of interest, so the relevant sample size is much smaller. To increase cohort size, multiple cohorts could in principle be combined, but this is in fact very hard, because sample processing and data generation protocols vary across labs, which adds a lot of noise to the data.

Another challenge in clinical cohorts is that the biological samples often lack information about symptoms and medications taken by the patients. This lack of data labeling makes supervised algorithms less useful, as discussed above. Lastly, it is rare to find cohorts with multiple patient touchpoints, such as weekly blood samples that track macro-level health changes alongside molecular data, or trials that obtain paired pre- and post-treatment samples to pinpoint drivers of therapeutic response. These gaps limit the translational impact of even the most advanced algorithms.

Innovators are tackling these gaps. One company has built an at-home blood-collection platform, enabling frequent gene expression profiling without requiring clinical-site visits, which is key to data collection. Another initiative is collecting continuous data on blood glucose, diet, and sleep, along with comprehensive clinical phenotyping and multi-omics. Continuous data is valuable, it is especially compatible with training self-supervised models and enables us to see short-term responses to interventions like diet or medications.

Similarly, federated learning frameworks, which train models across multiple sites without sharing raw data, promise to harmonize distributed biobanks while preserving privacy. AI-driven calibration tools are in development to translate measure-



Unsupervised learning (left) discovers natural clusters in unlabeled data. Supervised learning (center) classifies new samples based on labeled examples (gray dot illustrates a query point). Self-supervised learning (right) learns contextual relationships to predict future data points (dashed arrows show trajectory forecasting). Created in BioRender. Eilon Ashkenazy, M. (2025) https://BioRender.com/up5m5hj

ments across disparate assay protocols. Finally, synthetic data generation offers a route to augment real-world datasets, balancing regulatory constraints with the need for comprehensive training inputs.

As frequently sampled longitudinal data accumulates over time and becomes widely accessible for research and AI deployment, we will see dramatic advances in our capabilities to predict health outcomes.

UNLOCKING OUR PREDICTIVE CAPABILITIES

The next generation of predictive models will integrate richly annotated, longitudinal patient data to detect disease before symptoms appear. Network-scale analyses will map interactions among proteins, RNAs, and metabolites, while simulation tools will forecast individual responses to pharmaceuticals, dietary changes or environmental exposures.

Yet, for even wider impact, we need to broaden our perspectives beyond the lab to consider how AI can streamline other critical areas of drug development.

STREAMLINING CLINICAL OPERATIONS

The high costs associated with drug development can be reduced by integrating AI into clinical development and operations. AI can optimize patient recruitment by fine-tuning inclusion and exclusion criteria to identify suitable participants and personalize patient engagement operations, mitigating two problems: competition for patients for clinical trials and patient attrition. In addition, AI technologies can streamline data reporting processes and timelines, enabling quicker and more accurate analysis of clinical trials.

There is significant potential for AI to advance drug discovery and development. It may boost our predictive capabilities, enabling us to treat diseases more effectively and even prevent them. Yet to make that promise real, the field must break through persistent data bottlenecks. We should prioritize frequent sample collection, acquire longitudinal data from these samples, and generate scientifically sound synthetic data to fill in the gaps. We should also continue introducing AI tools to standardize lab protocols and increase lab automation and streamline clinical trials. Doing this right will enable a future where we predict disease onset and mitigate it early, opening new paradigms of preventative medicine. ◆

BIOGRAPHIES

Dr. Rotem Gura Sadovsky is Senior Director, Head of Data Strategy at Corundum Systems Biology (CSB). He is an expert in systems biology, AI and machine learning, and big data analytics. Prior to joining CSB, Dr. Gura Sadovsky served as Director of Product at Enveda Biosciences, where he led a nascent platform utilizing multi-omics data to develop diagnostics. He earned a PhD in Computational Biology from MIT.

Dr. Maayan Eilon-Ashkenazy is Content Manager at Corundum Corporation. She is an expert in molecular biology, protein engineering, and structure-based drug development. She earned a PhD in Chemical and Structural Biology from the Weizmann Institute of Science.

BIOAVAILABILITY & SOLUBILITY

Formulation Strategies for Tackling Poor Oral Bioavailability

By: Richard Johnson, PhD

INTRODUCTION

Modern drug discovery techniques often lead to more complex and hydrophobic molecules that have difficulty dissolving and being absorbed by the body. As a result, oral bioavailability has emerged as one of the biggest hurdles in drug development. Indeed, many new chemical entities, (NCEs) fail in the development process not because they are suitable candidates to interact with the intended drug target, but because they cannot get absorbed when given orally.

Poor oral bioavailability usually results in insufficient systemic exposure and ultimately clinical failure – often in early phase trials where time, money, and resources are tight. Indeed, current figures suggest values of up to 90% of NCEs suffer from issues of poor solubility with concomitant poor bioavailability This often forces program termination despite promising preclinical activity.

Understanding the dissolution properties and subsequent bioavailability profile of an NCE is critical, and issues need to be addressed during preclinical or early formulation development. Relying on standard formulations without evaluating solubility and absorption challenges can result in program delay or potentially good drug candidates being abandoned. Both scenarios can be very costly.

Better characterisation of NCEs in the early stages of development and identifying solubility issues early offers the opportunity to address poor bioavailability using formulation techniques that deliver enhanced drug exposure – reducing risk, conserving resources, and increasing the chances of clinical success.

CATEGORIZING NCES BASED ON THEIR SOLUBILITY & PERMEABILITY: THE BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

Understanding and categorizing an NCE based on its likely solubility and subsequent permeability properties is an important part of drug product development. Indeed, overcoming poor solubility and permeability (with subsequent improved bioavailability) will ultimately improve the chances of success in the clinic.

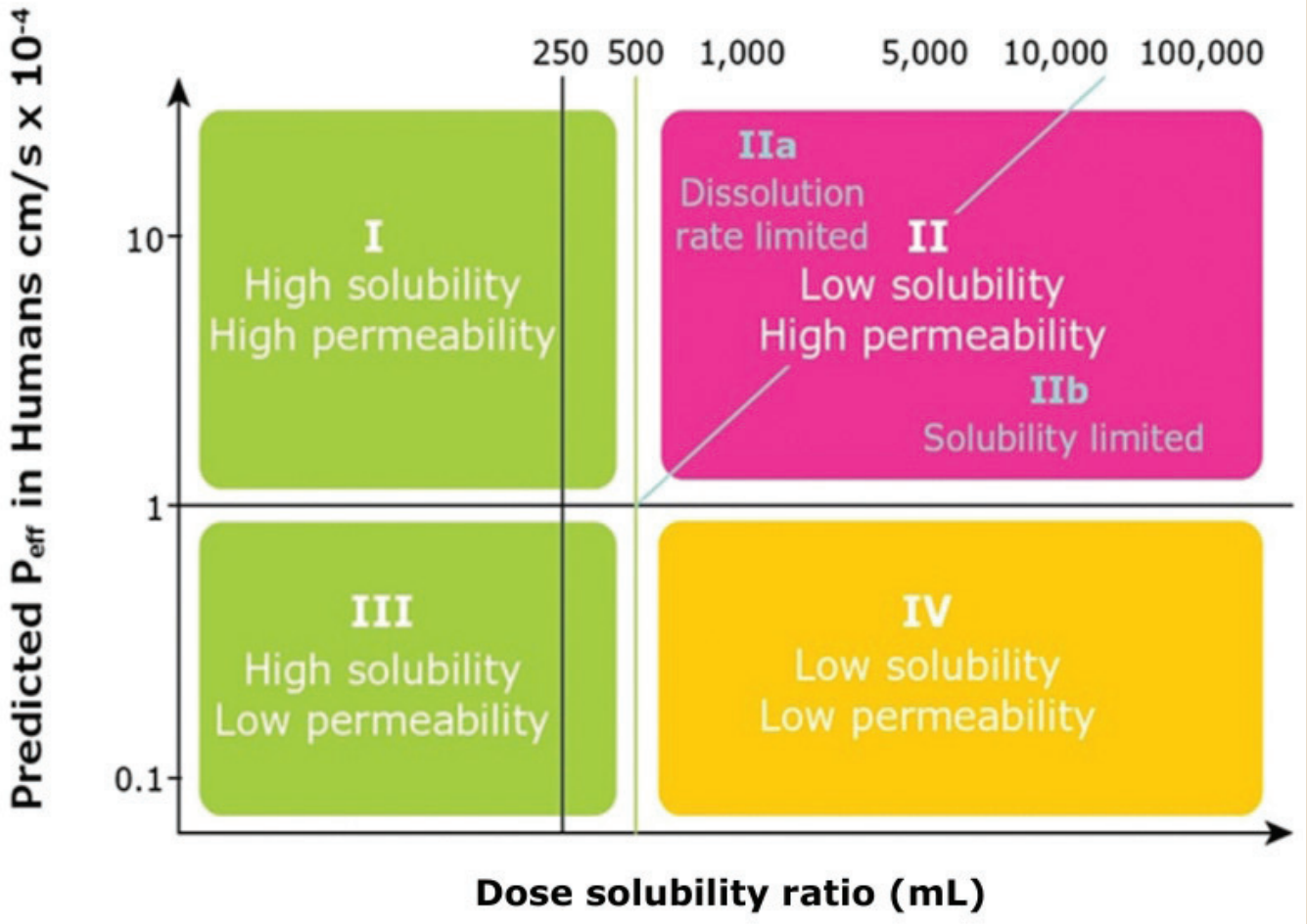
Typically, formulation scientists will turn to the established Biopharmaceutical Classification System (BCS) in the earliest stages of formulation development to help determine whether an NCE is likely to require enhanced formulation strategies to improve bioavailability.

The BCS places a given drug into one of four categories depending on its oral dosing solubility and permeability (Figure 1). A drug substance is considered "highly soluble" when the highest clinical dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1-7.5 at 37°C. A drug substance is considered to be "highly permeable" when the extent of the absorption (parent drug plus metabolites) in humans is determined to be I 90% of an administered dose, based on a mass balance determination or in comparison to an intravenous reference dose.

Clearly, solubility of an NCE is relatively easy to characterize using a standard dissolution testing apparatus in which the NCE can be added in increasing quantities until maximum solubility is reached.

Measuring membrane permeability is less straight forward. It can be determined a number of ways but is most often done using Caco-2 cell lines. In this test system, a monolayer of cells

FIGURE 1



Biopharmaceutical Classification System, a General Approach to Formulating Drugs Based on BCS Category

is grown, and drug permeation from the drug donor (apical side) to the acceptor (basolateral side) compartments is assessed, usually by direct UV or LC-MS assay.

Figure 1 shows a summary of the main classes in which NC's are categorized in the BCS system.

In its simples form, an ideal NCE should show high solubility and permeability, meaning either a simple formulation or even the unformulated crystalline drug can be used to assess the drug in the clinical setting.

An important factor to remember with the BCS is that it accounts for potency in that solubility and permeability are relative to clinical dose. Again, oral dosing is assumed in the testing design. So, for example, a compound that has poor absolute solubility might paradoxically be classified as "highly soluble" if it were a highly potent compound and the whole clinical dose was soluble in 250 mL.

A closer look at the four categories shows that ideal drug would fall into the BCS I category whilst the most challenging drugs are in the BCS class IV category.

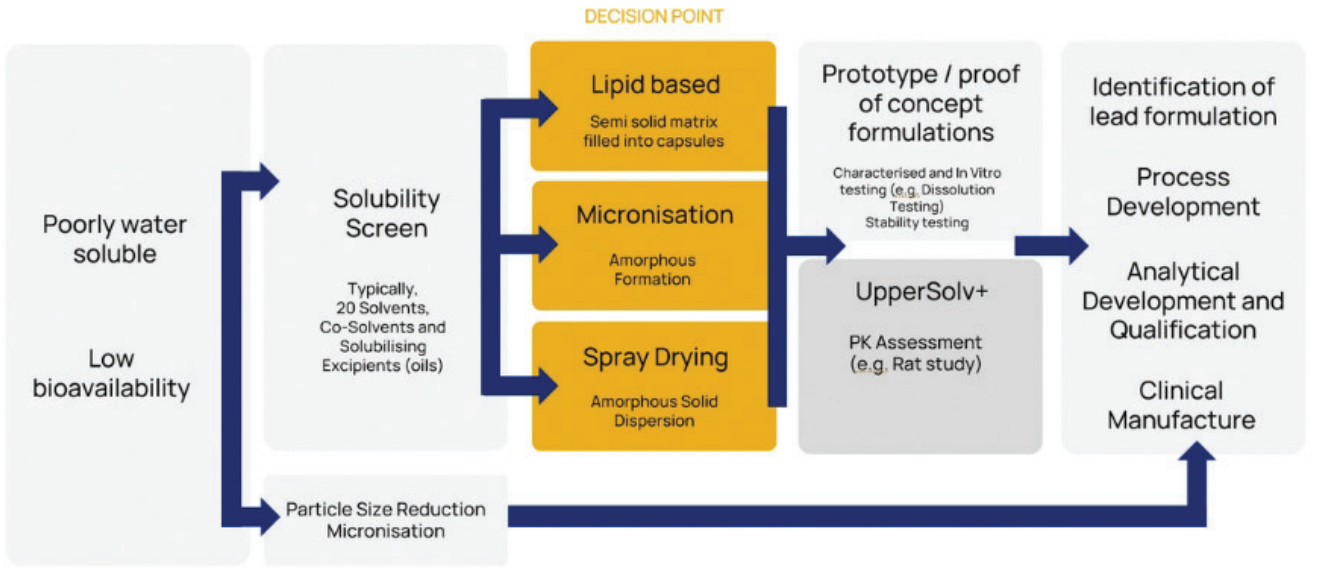
Once the BCS class has been determined, formulation screening can begin. However, this is a complex process with multiple variables. With this in mind, it is important to take a systematic approach using the solubility and permeability data obtained to take the most appropriate formulation approach needed for successful development. Taking a systematic approach ensures the following:

- **Data-led Selection:** *In vitro* and *in vivo* studies guide formulation choice.
- **Time Savings:** Testing several strategies in parallel, not in sequence.
- **API Efficiency:** Keeping API usage to a minimum to explore options.
- **Risk Reduction:** Taking the most appropriate approach to focus on what works.

Formulating BCS 1 APIs Into Oral Dosage Forms

Drugs that are freely soluble and show good permeability are more straight forward to formulate as they can be presented in simple tablet or capsules formulations with no need for solubility enhancement. In early clinical studies, the API can be delivered in its basic crystalline

FIGURE 2



UpperSolv Development Platform

form in a simple capsule fill (quick approach) or as a basic/standard tablet presentation that is suitable for scale up at a later date.

Formulating BCS II APIs Into Oral Dosage Forms

Drugs that fall into the BCS II category exhibit low aqueous solubility despite the fact that permeability of the soluble drug is relatively high. Because of this low solubility, the drug will show lower bioavailability because in oral dosing, the drug will tend to pass through the digestive tract with less than 100% less solubility, meaning it will be eliminated from the digestive tract before it can be absorbed.

For BCS II drugs, formulation solutions will be focussed on enhancing solubility of the API. However, to overcome the solubility issue, it is important to understand the root cause of API insolubility, which generally is of two types, which in turn can be overcome using the following different strategies:

Dissolution-Rate Limited (BCS Class IIa): APIs that fall into this category may dissolve poorly primarily due to the drug crystal size being too large or wetting is slow, which in turn will result in slower than required dissolution. Physical adjustment of particle size using micronization techniques can increases surface area and speed up dissolution.

Solubility-Rate Limited (BCS Class IIb): In this case, the chemical nature of the API itself limits how much can dissolve, regardless of particle size. Formulation strategies for this class of API will involve using enabling technologies, such as lipid systems, to dissolve the API into a lipidic carrier or creating amorphous solid dispersions (ASDs) to increase solubility.

Formulating BCS III APIs Into Oral Dosage Forms

This class of API exhibits satisfactory aqueous solubility, but its permeability is low. To overcome this, the API should be formulated with permeation enhancers to improve epithelial membrane transport.

Formulating BCS IV APIs Into Oral Dosage Forms

This class of API provides the most significant challenge because it exhibits satisfactory aqueous solubility, but its permeability is low. To overcome these issues will require the addition of solubility-enhancement (lipidic or ASDs) and the addition of excipients that can enhance permeability.

ENABLING TECHNOLOGIES DESIGNED TO ENHANCE SOLUBILITY

As explained earlier, enabling technologies that can overcome the barriers created by low solubility can eventually generate good bioavailability. Typical solubility-enhancement techniques that can be used to enhance the solubility of BCS class IIa/IIb and class IV APIs are summarized below.

Micronization

- Using high-energy particle size reduction techniques (such as jet milling) to reduce particle size to increase wettability and dissolution.
- Proven, low-risk technique, and often sufficient for dissolution-limited APIs.

Lipid-Based Systems (SMEDDS, SEDDS)

- Formulating lipophilic APIs by dissolving or suspending lipophilic drugs in oils, surfactants, and co-solvents.
- Improving dispersion and solubility in the digestive tract and improving solubility and absorption via lymphatic transport.

Amorphous Solid Dispersions (ASDs)

- Incorporate APIs into polymers via spray drying (or by co-milling with amorphous excipients).
- Increase solubility by maintaining the API in more stable, higher-energy forms (amorphous state rather than crystalline).
- Successfully used to enhance bioavailability of a large number of poorly soluble BCS Class II drugs.

A SYSTEMATIC, EARLY SCREENING PLATFORM DESIGNED TO SPEED UP DEVELOPMENT & REDUCE TIMELINES & COSTS

UpperSolv™ provides a structured way to evaluate formulation routes using minimal API (~5 g) in about 8 weeks. The following six steps are involved in this systematic process:

1. **Solubility Profiling:** Assess a range of solvents, co-solvents, and excipients to determine the BCS category the API falls into.

2. **Create Formulation Prototypes**
- Micronized powders
- Lipid systems in capsules
- Co-milled polymer blends
- Spray-dried dispersions in capsules/tablets

3. ***In Vitro* Testing:** Dissolution, stability, and solid-state analysis.

4. ***In Vivo* PK (UpperSolv+):** Small animal studies for comparative exposure.

5. **Data-Driven Decision:** Compare performance across prototypes.

6. **Scale-Up Readiness:** The chosen formulation is designed to translate into GMP manufacturing.

SUMMARY

The systematic evaluation of the solubility and permeability properties of an API is an essential part of early stage formulation development. Once the solubility and permeability properties of the API have been determined, any signs the molecule might exhibit poor bioavailability can be addressed.

By determining the BCS category of the API, it is possible to determine the rate-limiting aspects of the API and key features that control/limit bioavailability, such as dissolution rate, innate solubility, or permeability issues, with the API in question.

Once the rate-limiting factors have been identified, formulation development techniques can be implemented to address poor oral bioavailability early. This is best achieved using a systematic approach to overcome these factors. Indeed, tried and tested screening tools like UpperSolv allows formulators to test multiple formulation routes with minimal API and time investment.

The outcome is data that will guide the formulator in choosing the most appropriate enabling technology needed to improve oral bioavailability and in doing so, save both time and money. ◆

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BIOGRAPHY

Dr. Richard Johnson is the Founding Director and Chief Scientific Officer of Upperton Pharma Solutions, a UK-based Contract, Development and Manufacturing Organization. Graduating from Warwick University with a PhD Biochemistry, he was employed as a protein chemist at Delta Biotechnology. In 1994, he was part of a management buy-out team that founded Andaris Ltd, a research and development company exploiting the use of spray drying technology in the fields of diagnostic imaging and drug delivery. In 1999, he founded Upperton and has overseen significant growth and expansion over the past 25 years.

CML ADVANCES

To Improve Upon a Miracle Drug: Overcoming Drug Resistance & Intolerance in CML

By: Ben Hohl

INTRODUCTION

May 10, 2001 was an otherwise unremarkable day. Bridget Jones' Diary was usurped by The Mummy Returns at the box office, while It's All for You by Janet Jackson was in the middle of a seven-week streak at the top of the Billboard 100. That afternoon, the FDA also announced the approval of imatinib (Gleevec).

The news garnered tremendous attention as it was the first targeted therapy that inhibits a specific genetic abnormality in cancer cells to be approved by the FDA. Even back then, it was hailed as a "miracle drug" that would usher in a new era for cancer therapy. In many ways, they were right. Gleevec, sold by Novartis, hit peak annual sales of over $4 billion until it became generic in 2016. Imatinib effectively turned chronic myeloid leukemia, or CML, into a long-term condition. Before imatinib, the 10-year survival rate for patients with CML was less than 20%; today, it is over 80%.[1]

Yet, almost a quarter of a century after imatinib's landmark approval, a growing number of patients, oncologists, and drug developers, including Enliven Therapeutics, are still seeking to provide people living with CML a better treatment option. While imatinib and other tyrosine kinase inhibitors, or TKIs, have undoubtedly positively impacted the lives of many people living with CML, thousands of patients are still looking for drugs that provide better efficacy, tolerability and convenience.

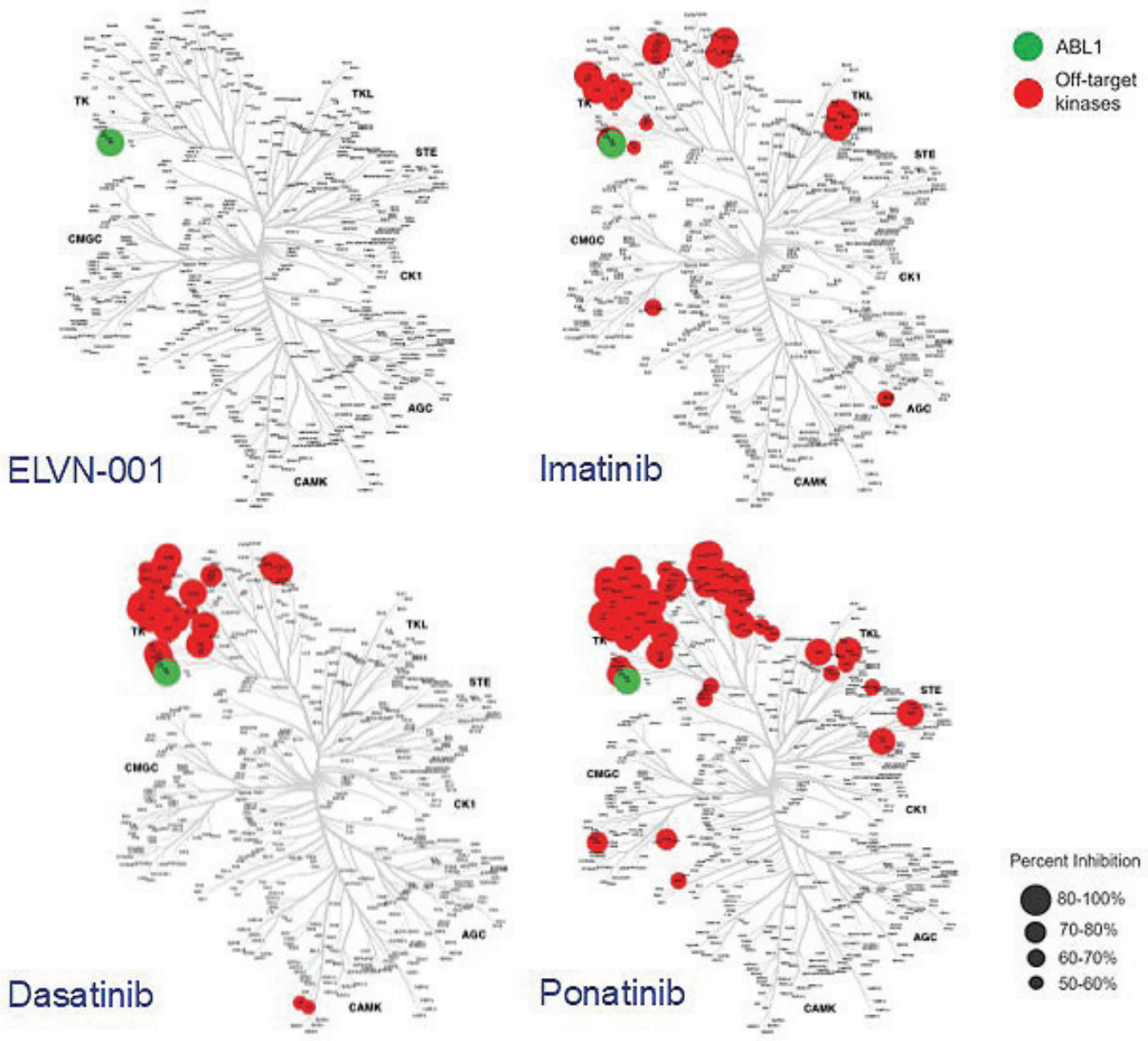
THE SILVER BULLET

In retrospect, the simplicity in the messaging around imatinib probably played a non-trivial role in the public misconception that it was a "silver bullet" for patients with CML, and for cancer in general. This blood cancer, which occurs in approximately 1 out of 500 people, is caused by a gene translocation in chromosomes 9 and 22 that creates a fusion gene and an aberrant protein called BCR::ABL1.[2] This new protein is also an oncoprotein and highly active tyrosine kinase that drives uncontrolled cell division of leukocytes that leads to CML. Imatinib is a small molecule inhibitor of this particular tyrosine kinase, and preclinical studies consistently showed its impact on blocking kinase activity mediated by BCR::ABL1. When clinical trials demonstrated that imatinib had a significant impact on hematologic (peripheral blood counts normalizing) and cytogenetic (bone marrow) response rates, the FDA granted Novartis an accelerated approval to market the drug. Subsequent trials proved the drug also led to a meaningful survival benefit.

In the following decade, the FDA approved the use of dasatinib and nilotinib. In fact, today there are six approved TKIs with the addition of bosutinib, ponatinib, and the most recently approved drug, asciminib. These newer TKIs drive deeper and faster molecular responses, while also addressing resistance mutations that emerged from the previously approved drugs. Each of the approved ATP-competitive TKIs has a distinct profile, which has allowed all of them to become an important part of the arsenal of available therapies that have transformed CML from a fatal disease into a chronic condition, with life expectancy in the decades for many patients.

Other patients, however, are not as lucky. Over time, CML can develop resistance to TKIs and in some cases patients must eventually switch therapies. In fact, around 65% of patients switch therapies due to a lack or loss of response to their prior therapy.[3] One reason why patients lose response is due to the emergence of point mutations in the BCR::ABL1 protein. Most of the available TKIs are susceptible to such resistance mutations and can gradually lose efficacy, at which point patients with CML no longer respond to the drug. Since the current standard of care in CML

FIGURE 1



ELVN-001 is a highly selective ATP-competitive inhibitor of BCR:ABL1, unlike the past generations of ATP-competitive inhibitors that hit off-target kinases. This lack of selectivity has led to undesirable tolerability profile for long term treatment. Reference: Company data on file.

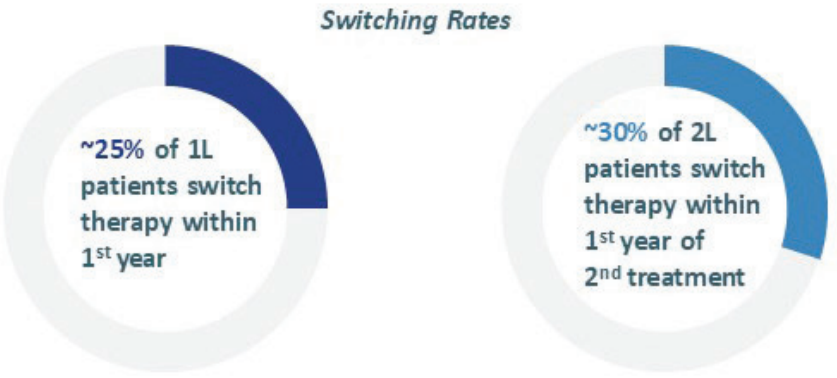
continues to be life-long treatment with TKIs, the emergence of drug resistance is an area of high unmet need in patients.

However, unlike many other cancer indications where there is a clear first-line therapy, second-line therapy and so on, CML is different. All of the drugs are used interchangeably throughout lines of therapy. Every patient is different, and because all available options have different mutational and tolerability profiles, doctors and patients are continuously searching for the therapy that will best serve each individual patient.

Historically, the most prevalent and problematic mutation in CML has been T315I.[4] This mutation alone renders four of the six currently available TKIs completely powerless to prevent disease progression. Only ponatinib and asciminib are approved for use in patients with CML that harbor T315I mutations. These drugs are able to largely overcome resistance borne from T315I mutations because of how or where they bind to the BCR::ABL1 protein. However, that difference can also lead to other significant issues.

For example, ponatinib's ability to overcome multiple BCR::ABL1 mutations also allows it to bind to other protein kinases, conferring unintended, off-target side effects. In fact, ponatinib's label comes with a black box warning for poten-

FIGURE 2



The switching dynamics in CML are unlike other cancer indications and highlight the significant need for better treatment options. Patients switch therapies due to lack or loss of response, intolerance, DDIs, and other reasons as they search for the drug that serves their needs best. Reference: Atallah EL, et al. J Health Econ Outcomes Res. 2022 Aug 4;9(2):19-29.

tial arterial occlusive events, heart failure, venous thromboembolism, and hepatotoxicity.

NEW DRUG MECHANISM LEADS TO NEW RESISTANCE MUTATIONS

Asciminib, on the other hand, uses a completely different binding mechanism to the other five TKIs approved in CML. It is an allosteric inhibitor that binds to the myristoyl pocket of the ABL1 protein instead of directly to the ATP-binding site. When asciminib binds, the BCR::ABL1 protein undergoes a conformational change that closes the ATP-binding site and switches off its kinase activity. Asciminib was approved in 2021 for the third-line and later settings but gained further approvals across all lines of therapy in 2024, and can now be used as a first-line treatment after a pivotal Phase 3 study called ASC4FIRST showed it offered better efficacy and safety than prior generation TKIs.

Interestingly, data from ASC4FIRST as well as other emerging literature suggests that, compared to other TKIs, resistance mutations can occur more quickly and frequently with asciminib. In fact, there is now a growing list of new mutations. These new mutations are due to the fact that asciminib is an allosteric inhibitor, whereas all of the other previously approved drugs are ATP-competitive TKIs. For these emerging mutations, there is a very high concordance between *in vitro* resistance to asciminib and other allosteric inhibitors, implying a class-like effect.

Mutations associated with asciminib resistance can occur outside of the myristoyl pocket, and throughout the BCR::ABL1 protein.[5] There now appear to be at least 20 distinct mutations that confer resistance to asciminib, although only a handful are in the myristoyl pocket. These mutations outside of the myristoyl pocket still allow asciminib to retain moderate to high binding affinity, but the mutations cause the allosteric mechanism to "break," rendering asciminib ineffective. Because asciminib was only recently approved, it is highly likely that more mutations will be identified that not just block drug binding, but alter kinase structure and activity in a way that disrupts allostery and confers resistance to asciminib and other allosteric TKIs.

OVERCOMING RESISTANCE WITH CHEMISTRY

Despite the promise of asciminib and allosteric TKIs, it is also increasingly apparent that there is a need for more treatment options, especially for patients that become resistant to asciminib. Enliven Therapeutics is developing ELVN-001, a potential best-in-class ATP-competitive TKI. Unlike other currently available ATP-competitive inhibitors whose issues stem primarily from a lack of selectivity, a key differentiator of ELVN-001 is that it is significantly more selective than the prior generation of ATP-competitive TKIs. Furthermore, its structure potentially allows it to have broad activity against not just T315I, but emerging mutations that confer resistance to allosteric TKIs, like asciminib. Both preclinical and clinical data show ELVN-001 is potentially a best-in-class therapy not only for the general CML patient population, but also for a broad range of mutations including the emerging category of allosteric mutations.

ELVN-001 targets the P-loop in the unique "folded-in" active conformation of BCR::ABL1, unlike some other TKIs that bind to the more common P-loop "extended" conformation, which makes them more promiscuous. Moreover, its unique structure helps it avoid a steric clash with the isoleucine in T315I mutations that most other ATP-competitive TKIs suffer from. Its favorable properties also mean it is not a substrate for common drug efflux transporters, like P-gp and BCRP, which are also thought to play a role in drug resistance.

Enliven is now evaluating ELVN-001 in the ongoing Phase 1 ENABLE study in patients with previously treated CML, with plans to begin a pivotal Phase 3 clinical trial next year. At the European Hematol-

ogy Association 2025 Congress, Enliven reported a cumulative major molecular response, or MMR, rate of 47% by 24 weeks on ELVN-001, with 32% of patients achieving MMR by 24 weeks, which compares favorably to precedent Phase 1 trials of the approved BCR::ABL1 TKIs. The ENABLE trial also enrolled patients that were significantly more heavily pretreated than previous Phase 1 clinical trials in CML; 67% of patients in the ENABLE study have had three or more unique TKIs (26% have had 5 or more), including receiving either ponatinib, asciminib, or both.

THE SEARCH FOR NOT ONLY BETTER EFFICACY, BUT ALSO BETTER TOLERABILITY & CONVENIENCE

While TKIs have transformed CML into a chronic disease, these patients still must take daily therapy for decades. During that time many patients are forced to switch therapies not only because of a lack or loss of response, but also because of drug intolerance. Of patients who switch therapy, around 30% do so due to intolerance.[6] A patient population that requires daily therapy to manage a chronic disease will naturally seek drugs that are more convenient and tolerable; when they must take a drug every day for decades, everything matters. Although edemas, nausea, diarrhea and headaches may seem like trivial side effects for most cancers, in CML these issues matter to patients and is why drug intolerance is one of the main reasons patients switch TKIs. Many of the drug intolerance issues stem from the lack of selectivity of previously approved ATP-competitive TKIs. In contrast, the data reported to date has suggested that ELVN-001 is well tolerated, consistent with its high selectivity for BCR:ABL1.

Data have also so far demonstrated that ELVN-001 has a low potential for drug-drug interactions, or DDIs. This is important as most currently available TKIs have risk of DDI with CYP inhibitors or inducers, a class of drug commonly taken to manage high cholesterol or blood pressure. The average age of first CML diagnosis is around 66 years, and over 50% of patients present with a comorbidity, often cardiovascular or metabolic conditions.[7] In fact, the average CML patient takes approximately five concurrent medications, meaning DDIs are top of mind for both patients and physicians.[8]

For example, many statins that are used to manage cholesterol can reach toxic levels due to DDIs with the existing drugs. Certain foods such as grapefruit or Seville oranges must be avoided with some of the existing anti-CML drugs due to DDI. As patients age on therapy the DDI issues associated with the approved TKIs may become difficult to manage.

As people with CML live longer, new challenges are emerging — tolerability, resistance, and long-term disease management. That is why Enliven Therapeutics is developing ELVN-001, a highly selective ATP-competitive TKI designed to address the unmet needs in the evolving CML treatment paradigm and could represent a new option for long-term disease control.

Thanks to the pioneering work of researchers advancing our knowledge of basic science and cancer, the field has been able to transform the lives of millions of patients with CML. But challenges remain, and everyone in the industry strives to improve upon the "miracle drug" imatinib, that was approved almost 25 years ago. I am grateful every day to the people working at Enliven Therapeutics that are all dedicated, like I am, to improving the standard of care as well as the quality of life for all patients suffering from CML.◆

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BIOGRAPHY

Ben Hohl is the Chief Financial Officer, and Head of Corporate Development at Enliven Therapeutics. Prior to joining Enliven, Ben was a Healthcare Investment Banker at Goldman Sachs, where he worked for nearly a decade. While at Goldman Sachs, he established himself as a senior leader in the healthcare group, advising biopharmaceutical and life sciences management teams and boards and executing a broad range of strategic and financing transactions. Ben successfully executed over 50 deals, including over $75 billion in M&A, equity and debt financings. Ben earned a B.A. in Business Economics and Accounting from the University of California, Los Angeles.

COMBINATION PRODUCTS

Early Decisions to De-Risk the Transition to Combination Products

By: Mike Ulman

INTRODUCTION

The combination product market has seen a significant amount of growth, driven primarily by the rise in chronic disease indications, the demands for self-administered therapies, and technological advancements. The use of combination products simplifies the process of drug administration for the patient and/or the caregiver and, in some cases, allows the patient to receive treatment at home rather than having to travel to a medical facility. However, there are many challenges that need to be navigated as one considers the transition from a vial system to a needle-based combination product.

The US FDA defines a combination product as comprising two or more constituents and classifies them into the following four types:

- Drug + Device
- Biologic + Device
- Drug + Biologic
- Drug + Biologic + Device

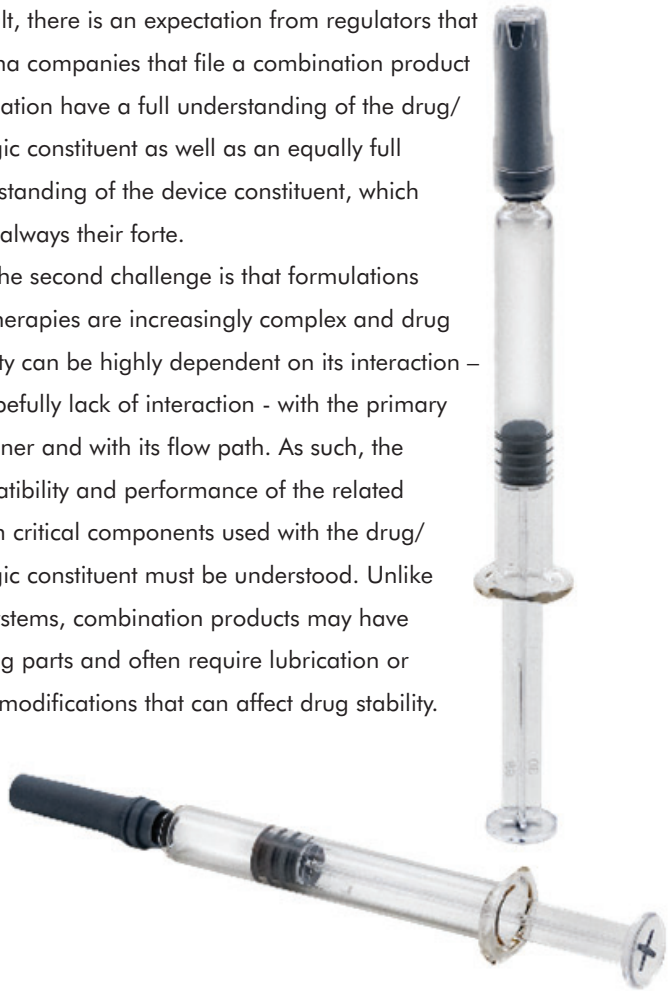
Each constituent retains its regulatory status. For example, a combination product comprised of a drug or biologic, and a device must meet the regulatory requirements of both the drug or biologic and the device, with the filing center being based on the primary mode of action of the combination product, either CDER/CBER or CDRH.

In the EU, a combination product can also be a medicinal substance with an integral or non-integral (co-packaged or referenced) medical device and the regulatory filing must include both the medicinal substance filing and the device filing.

COMBINATION PRODUCT DEVELOPMENT CHALLENGES

An important part of combination product development is compiling the regulatory submission. Without approval from regulatory bodies, products do not make it into regulated markets. The regulatory landscape is ever-changing within the combination product development space and regulators now have a lot of direct combination product subject matter expertise. As a result, there is an expectation from regulators that pharma companies that file a combination product application have a full understanding of the drug/biologic constituent as well as an equally full understanding of the device constituent, which is not always their forte.

The second challenge is that formulations and therapies are increasingly complex and drug stability can be highly dependent on its interaction – or hopefully lack of interaction - with the primary container and with its flow path. As such, the compatibility and performance of the related system critical components used with the drug/biologic constituent must be understood. Unlike vial systems, combination products may have moving parts and often require lubrication or other modifications that can affect drug stability.



Thirdly, there is the challenge of delivering great patient experience. The growing preference for self- or home-administration means that more medications are integrated with devices. The challenge is that devices must be easy for the patient to use and empower them to receive medication at their convenience, while simultaneously addressing costs associated with therapy administration. However, devices must be easy to use and empower patients to receive medication at their convenience while simultaneously addressing costs associated with therapy administration.

Finally, with more competition among drugs treating the same disease, as well as the growth of generics and biosimilars, there is a greater need for product differentiation, which can be achieved through an improved drug delivery system. A focused approach to moving from a vial format to a device driven combination product is recommended with three critical de-risk factors which include: the Plan, the Product, and the Patient Experience.

DE-RISKING THE PLAN

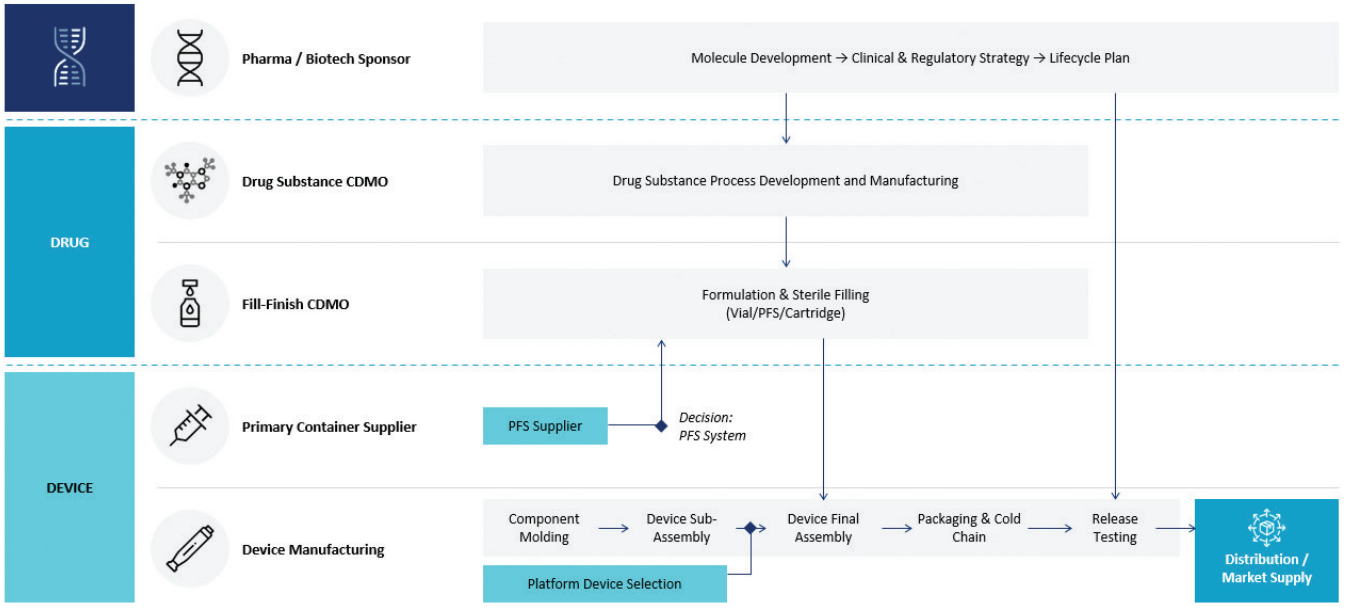
Key Considerations

- Effective lifecycle management
- Shelf-life study history (accelerated/real-time)
- Supplier regulatory submission support
- Simplified data package availability
- Subject matter expert support
- Direct risk assessment linkages
- Combination product testing support

Fundamentally, drug developers want to avoid introducing risk as they journey from clinical-milestone to clinical-milestone. There is a lot of uncertainty around combination products, and companies' common reaction to this uncertainty is to go to market with a simple, known, off-the-shelf delivery format not tailored to the molecule or to patient needs. However, simply avoiding complex product development is not patient-solution driven and will result in missed opportunities. A better approach is to begin with the end in mind and focus on the plan beginning with Lifecycle Management.

Starting with a simple delivery format and delaying Lifecycle Management until after commercial success is risky because companies often realize too late that their drug is at a competitive disadvantage and begin Lifecycle Management efforts only when it is too late. The results are higher overall costs, unfulfilled market potential, and, possibly, losing the momentum of being the first on the market. Biosimilar and Generic companies might underestimate the relentlessness of the originators to protect their brands. Thus, they are surprised to see that by the time they get their approval to launch the biosimilar or generic, the originator already converted the market to an advanced presentation and the biosimilar or generic is left chasing-the-innovator.

Partnering with suppliers that have component and system shelf-life testing history and knowledge, and with a proven track record in successful regulatory submissions, will help minimize surprises. When evaluating partners, make sure you understand the partner's credentials in the field. Is your drug going to be the partner's first to make the entire journey to regulatory submission and to commercialization or did the partner do this already for another drug. Does the partner have mean-



ingful platform data that could be leveraged into your development to save time and resources? If the supplier already has component extractables and device performance data packages, you can hit the ground running with application-specific testing, like leachables and drug delivery.

It is critical to partner with industry subject matter experts to establish risk-assessment-linkages from components to the combination product. When these linkages are established, it is easier to avoid surprises, shorten timelines, improve operational efficiencies that reduce costs, and increase the probability of regulatory success. Finally, you want a device partner who can also provide performance testing support for the final drug-device combination.

All of this means that the combination product can get to the patient faster with a competitive advantage, serve diverse market needs and most importantly, deliver a better patient experience, which also, naturally, leads to improved adherence to the drug regimen.

DE-RISKING THE PRODUCT

Key Considerations

- Patient and drug requirements
- Component knowledge
- Material, chemical, physical interactions
- Proper component selection
- System integration
- Suitability assessments
- Risk management
- Robust supply chain
- Experienced partner(s)

De-risking the product requires a thorough understanding of user requirements to know exactly what the product needs to do. By leveraging in-depth component knowledge from manufacturers – particularly regarding materials' chemical and physical interactions - system integrators can navigate proper-component selection to develop an optimal device design. These resources within the supply chain must possess the knowledge and expertise to assess suitability from the component level all the way through to the whole device constituent part of the combination product. They must also have established risk management expertise to connect component level assessments to higher level risk assessments of the complete combination product.

DE-RISKING THE PATIENT EXPERIENCE

Key Considerations

- Self-administration
- Ease-of-use
- IFU simplicity
- Minimize potential misuse
- Dose delivery optimization
- Pain threshold
- Adherence to therapy
- Direct component impact

A proactive approach to obtaining first-pass regulatory approvals must de-risk the patient. For example, as therapies become more complex and shift towards home administration, pharma companies are under pressure to bring more intricate devices to market that are also easy for patients to use.

But this isn't easy to do with constantly changing regulations and expectations that place more responsibility on pharma companies to prove that not only is their drug constituent safe and effective (which is their expertise), but to also show that the device constituent is safe, effective, reliable and with adequately designed-in human factors consideration, which are not aspects that are typical pharma company areas of expertise.

Such systems intended for home use need to require minimal thought from the user. If instructions are unclear or confusing, or if the system has not been thoroughly tested for real-world administration – including potential misuse – this can result in a poor patient experience, patient

pain, adherence challenges, compromise the therapy and reduced overall market acceptance – possibly even leading to product recall. Some of these factors can be a direct result of the component selection discussed earlier.

SUMMARY

In summary, when transitioning from a vial to a combination product system, the best approach is to have a holistic de-risk strategy with an intentional focus on the Plan, the Product and the Patient Experience. It is vital to select partners with in-depth understanding of the evolving regulatory landscape, that have a systems mindset, that have industry partnerships and that have subject matter expertise in areas required to establish drug-device suitability. With this approach, it is easier to avoid surprises, shorten timelines, improve operational efficiencies that reduce costs, increase the probability of regulatory success, and ultimately reduce risk to the patient. This approach will get the combination product launched and into the market faster while delivering a safe, effective, and positive patient experience.

When it comes to transitioning pharmaceutical products into a combination product system, West Vantage™ offers contract manufacturing solutions that enable customers to select the right combination product and facilitate design, system integration, analytical testing, manufacturing, filling and assembly. Additionally, West Vantage™ offers services to assist in regulatory dossier compilation and filing, as well as analytical testing via laboratories in Exton, PA and Waterford, Ireland to support the design verification and release testing of combination products. Supported by West's century-long leadership in containment systems, West Vantage™ offers the capacity, technical discipline, and operational excellence required to assemble and prepare complex delivery systems for clinical and commercial distribution. To learn more, visit WestPharma.com/Services. ◆

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BIOGRAPHY

Dr. Mike Ulman has over 17 years of experience in the pharmaceutical industry. For the past year, he has worked in Regulatory Affairs, focusing on how chemical and environmental regulations affect the pharmaceutical packaging business, while for the previous three years, he spearheaded the development of performance testing methodologies for combination products as the Technology Manager for Packaging and Delivery Systems, both at West. Prior to joining West, he spent 13 years at Piramal Critical Care, holding various technical roles in inhalation anesthetics, and nine years as a chemist at Air Products. He holds a PhD in Chemistry.

Drug Development
EXECUTIVE

Joseph Sinkule, PhD
Founder & CEO
Klotho Neurosciences

Klotho Neurosciences: Focused on Neurodegenerative & Age-Related Disorders

Neurodegenerative diseases, such as ALS, Alzheimer's disease, and Parkinson's disease, remain some of the most challenging disorders to treat. Despite decades of research, current therapies mostly manage symptoms rather than halt or reverse disease progression. Patients, families, and clinicians alike are seeking solutions that go beyond slowing decline, interventions that preserve function and potentially modify the course of disease.

Klotho Neurosciences, Inc. (NASDAQ: KLTO) is pioneering a gene therapy approach by leveraging the human Klotho gene, often referred to as the "anti-aging" gene, to create and develop novel gene and cell therapies. By delivering the secreted form of the Klotho protein (s-KL) directly to neurons, Klotho Neurosciences aims to protect, restore, and regenerate neuronal networks while addressing key biological drivers of aging and neurodegeneration.

Drug Development & Delivery recently interviewed Dr. Joseph Sinkule, Founder & CEO of Klotho Neurosciences, to discuss the company, its therapies, the human Klotho gene, and longevity.

Q: Can you tell us a little bit about Klotho Neurosciences and how your therapies work?

A: Klotho Neurosciences is a biogenetics company focused on pioneering the development of innovative, disease-modifying gene therapies using a patented, secreted form of the human Klotho gene, known as s-KL. This "anti-aging" gene was

first identified in 1997 by Dr. Makoto Kuro-o, who showed that mice lacking the Klotho gene and the protein transcribed by the gene showed accelerated aging across multiple systems, including brain functions, muscle and bone loss, and vasculature calcification. The discovery was transformative and the Klotho gene emerged as a master regulator of aging, influencing neuronal protection and survival, oxidative stress, mitochondrial function, autophagy, and neuroinflammation.

Our therapies at Klotho are designed to leverage these protective mechanisms. By delivering the Klotho protein via genetic or cell therapy, we aim to restore neuronal health, clear toxic protein aggregates, such as beta-amyloid and TDP-43, reduce chronic inflammation, and stimulate neurogenesis and myelin production on axons that traverse from the brain down the spinal cord and ending at the neuromuscular junction. Importantly, our lead program, KLTO-202, is targeting ALS, a disease where motor neurons at the neuromuscular junction progressively degenerate and die, leading to muscle wasting and loss of voluntary and involuntary muscle movement. In preclinical models, our Klotho-based interventions preserved motor neuron function, strengthened muscle movement and electrophysiology endpoints, delayed disease onset, and improved survival.

Beyond ALS, we also see potential applications in Alzheimer's disease, Parkinson's disease, Huntington's disease, and other neurodegenerative or age-related conditions. The Klotho protein is naturally produced by neurons throughout the central nervous system, but its levels decline with age and low levels are found in disease states. By supplementing this essential protein therapeutically, we hope not only to slow disease progression but also to improve overall neuronal resilience, muscle, and bone strength, and healthy aging.

Q: What is the significance of the Klotho gene, and where did its name come from?

A: The Klotho gene is one of the most important discoveries in aging and neurodegeneration research. In 1997, Dr. Makoto Kuro-o demonstrated that knocking out this gene in mice caused significantly shortened lifespans and accelerated aging across multiple systems — including muscles, bone, blood vessels, heart, kidneys, and the central nervous system. In the brain, mice lacking Klotho expression exhibited memory deficits, hippocampal degeneration, reduced numbers of synapses, impaired axonal transport, severe neuroinflammation, and defects in CNS-protective myelin production.

Kuro-o named the gene "Klotho" after the Greek goddess Clotho, one of the Fates, who "spins the thread of life." This gave rise to the gene's enduring nickname, the "anti-aging gene."

The Klotho gene actually produces two proteins. The membrane-bound form, m-KL, regulates phosphate and calcium balance in the kidneys by interacting with FGF-21 and FGF-23. The secreted form, s-KL, is particularly exciting for neurodegenerative diseases. It is produced mainly in the human brain and protects neurons from oxidative stress, enhances mitochondrial energy functions, reduces inflammation, enhances autophagy or the clearance of senescent cellular debris, improves synaptic plasticity and axonal transport, stimulates neurogenesis, and promotes myelination of axons in the spinal cord. These combined effects translate into better cognition, memory, and motor function in preclinical models.

Q: How do you see Klotho Neurosciences addressing the underlying biology of ALS and other neurodegenerative diseases?

A: Aging is the largest risk factor for neurodegeneration. As we age, DNA damage accumulates, mitochondrial function declines, autophagy slows, and inflammation becomes chronic. These processes drive neuronal death and synaptic dysfunction. As noted, Klotho acts at multiple points along these pathological pathways. It protects neurons from oxidative stress, enhances autophagic clearance of toxic proteins, stimulates neurogenesis, and modulates inflammatory signaling. In ALS, for example, Klotho preserves motor neurons, helps to generate new motor neurons, and facilitates the flow of neurochemicals across the neuromuscular junction, which is critical for muscle function. By intervening early, our therapies could restore or maintain neuronal signaling and slow ALS disease-associated pathologies and progression.

Our approach allows us to bridge the gap between the abstract concept of healthy "longevity" and the tangible clinical outcomes patients care about that include stable or improved motor function, muscle contraction, cognitive preservation in the brain, and an extended quality of life.

Q: KLTO-202 has received Orphan Drug Designation for ALS. What are the next milestones in your clinical and regulatory pathway?

A: KLTO-202 is our lead candidate, and we're progressing toward Phase 1B/2A trials in early ALS patients. Our immediate milestones include completing manufacturing and IND-enabling studies this year, followed by filing the IND in Q4 2026 or Q1 2027. Once the IND is approved to begin clinical trials, the adaptive design clinical trial will leverage Fast Track designation and Breakthrough designation to accelerate development.

We're also advancing KLTO-101 for delivery of the gene to the brain to treat Alzheimer's, Parkinson's, and other neurodegenerative indications, with IND submission planned in mid-2027 and initiation of the trial later that year. Meanwhile, KLTO-301, a Klotho gene variant that makes a full-length m-KL protein, will target cardiovascular and chronic kidney diseases, which illustrate the broader potential of Klotho across multiple organ systems.

These programs are supported by strategic partnerships with leading contract manufacturing and adeno-associated virus (AAV) delivery organizations to ensure high-quality production and tissue-targeted delivery. Our goal is to move efficiently from preclinical success to human trials while maintaining rigorous safety and efficacy standards.

Q: The Klotho gene influences multiple biological systems. Do you see it more as a systemic longevity factor or for targeted disease-specific applications?

A: Both perspectives are valid, but from a clinical development standpoint, we focus on targeted applications first. If we can effectively treat several "diseases of aging", we will effectively promote a longer, healthy lifespan. Trying to prove claims of improving longevity or life-span extension in humans is extremely challenging as such studies would need to track thousands of participants over decades of time, which is not feasible for development and regulatory approval and commercialization.

That said, the Klotho gene does impact multiple tissues like the brain, kidneys, cardiovascular system, muscles, and more, so the therapeutic effects we see in one disease could translate to broader benefits. Our primary aim right now is to treat neurodegenerative ALS, Alzheimer's disease, and Parkinson's disease, where the unmet need is critical and where preclinical efficacy is strongest. The endpoints for market approval by the regulatory authorities are also well established for these diseases. As we gather more clinical data, we anticipate exploring additional age-associated conditions. In this way, Klotho Neurosciences could eventually serve both as a disease-specific therapy and as a systemic enhancer of healthspan.

Q: Klotho research is rapidly expanding. How do you anticipate its role in the broader longevity or geroscience field in the next decade?

A: Klotho is already recognized as a key longevity factor, and research is growing exponentially with over 4,000 publications on Klotho biology since 1997. In the next 10 years, I hope the scientific community will fully appreciate its role as a "master gene" regulating multiple pathways that influence aging and diseases of aging.

From a therapeutic standpoint, we envision Klotho-based treatments not only for specific diseases, but also as tools to enhance biological resilience in aging populations. Our epigenetic blood test, which measures the Klotho promoter's methylation status, could allow personalized interventions based on an individual's epigenetic biological age, and with a single intravenous infusion of a long-active gene therapy, potentially slow the rate of age-related decline.

Ultimately, our goal is to transform the treatment paradigm for neurodegenerative diseases while laying the foundation for broader applications in longevity medicine. ◆

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Special Feature

Bioavailability & Solubility: Experimental Techniques Combined with Computational Decision-Making Rapidly ID the Most Viable Enhancement Pathway

By: Cindy H. Dubin, Special Features Editor

Improving the bioavailability and solubility of modern APIs remains one of the most persistent hurdles in drug development. As pipelines continue to shift toward highly lipophilic, poorly water-soluble molecules – particularly BCS Class II and IV compounds – formulators are turning to advanced materials, predictive tools, and mechanistic design approaches to ensure adequate bioavailability and therapeutic performance, explains Gloria Ho, PharmD, RPh, Global Technical Marketing Manager, Pharma Solutions, BASF.

Advances in automation and technology, such as small-scale preparative techniques of solid forms and formulation screening strategies, coupled with evaluation of performance through automated online platforms, is imperative for success in early development, says Craig Grant, Vice President and General Manager, Cambridge, Veranova. "Using these in parallel to one another enables the measurement of critical solubility and dissolution properties, confronting potential developability issues earlier on, saving substantial time and resources."

Perhaps one of the more contemporary uses of automation and advanced technology is for improving oral GLP-1 bioavailabilty and solubility, protecting these delicate peptides from degradation and facilitating intestinal absorption. "Formulation strategies

Veranova's solid form and particle engineering scientists in Cambridge, UK.

increasingly rely on permeability enhancers, local pH modulation, and protective excipients to overcome low solubility and permeability, says Sanjay Konagurthu, PhD, Senior Director, Science and Innovation, Thermo Fisher Scientific Pharma Services. "These, combined with model-informed approaches, help quantify expected oral performance and guide rational excipient selection," he says.

This annual *Drug Development & Delivery* report highlights other ways formulators are relying on automation, such as Artificial Intelligence and Machine Learning, and how these tools are being combined with experimental confirmation to identify the most promising development strategies.

Ardena: AI-Driven Insights Focus on the Most Promising Development Strategies

At Ardena, improving bioavailability starts with understanding the physicochemical properties of a drug candidate. Poor aqueous solubility remains one of the most common challenges in drug development, particularly as modern small molecules tend to be more lipophilic and structurally complex. Ardena, therefore, follows a structured, science-driven roadmap that begins with characterization of key parameters such as solubility, ionization behavior, lipophilicity (logP), melting point, and solid-state properties. Laure Descamps, Formulation Scientist, Ardena, says these insights guide the selection of the most appropriate enabling formulation strategy for each compound.

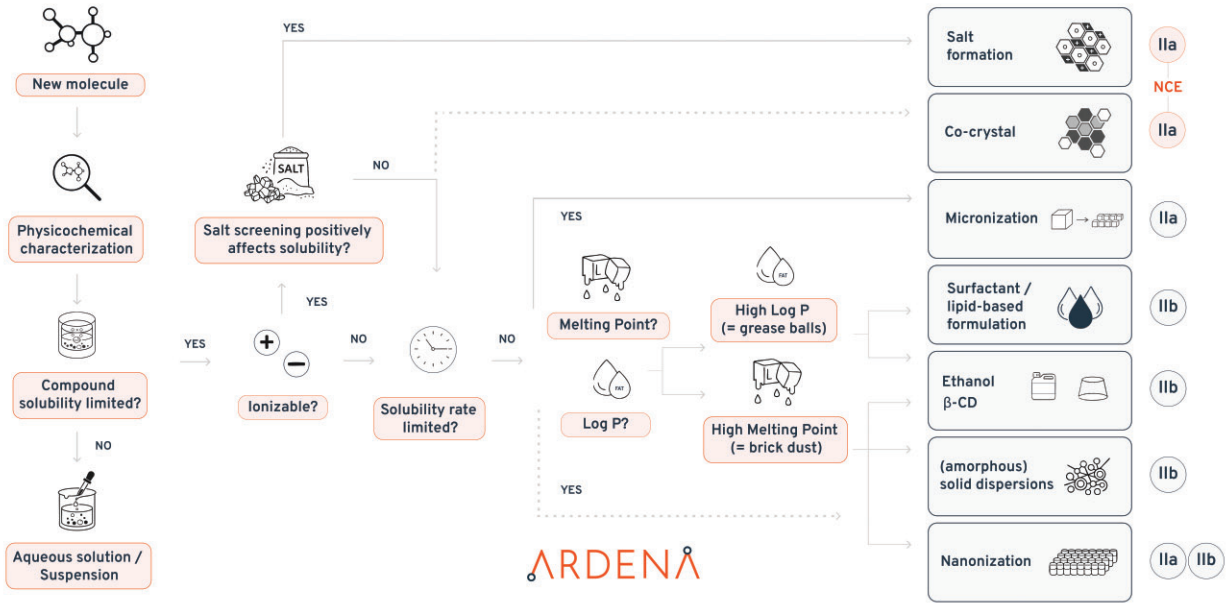
When a molecule is ionizable, Ardena typically evaluates salt formation first. "Salt screening can significantly improve solubility and dissolution while maintaining a relatively straightforward development pathway," says Timothy Pas, PhD, Director, Formulation Development and Production, Ardena. "If salt formation is not viable, alternative enabling technologies are considered based on the compound's limitations."

Particle size reduction is commonly used for compounds with dissolution-limited absorption. Techniques such as micronization or nanonization increase surface area and improve dissolution rates. In particular, nanosuspensions, where the API is reduced to nanometer-scale particles stabilized with surfactants or polymers, can significantly enhance dissolution and systemic exposure for poorly soluble molecules, explains Ms. Descamps. "At Ardena, nanosuspensions are also attractive in early development because the stabilized particles can be incorporated into multiple dosage forms, including suspensions, capsules, tablets, or parenteral formulations," she says.

For highly lipophilic molecules, Ardena often explores lipid-based formulations such as self-emulsifying drug delivery systems (SEDDS or SMEDDS), which form fine emulsions in the gastrointestinal tract and help maintain the drug in a dissolved state.

Compounds with strong crystal lattice energy and limited solubility, often referred to as "brick dust" molecules, are frequently addressed through amorphous solid dispersions. In these systems, the API

Ardena's Roadmap for Formulating Poorly Water-Soluble Drug Candidates



is dispersed in a polymeric matrix that inhibits recrystallization and enhances apparent solubility and dissolution kinetics.

Dr. Pas shares that Artificial Intelligence is increasingly supporting the prediction and optimization of solubility and bioavailability in drug development. Machine Learning models can analyze chemical datasets and identify relationships between molecular structure and physicochemical parameters such as solubility, pKa or lipophilicity. "These insights help scientists identify potential solubility risks earlier and guide formulation strategies more efficiently," he says.

AI tools can also assist formulation development by predicting how excipients, formulation approaches or processing parameters may influence drug dissolution and absorption. Ms. Descamps says: "By narrowing the experimental design space and prioritizing promising strategies, these tools can reduce the number of laboratory experiments required during early development. Within a CDMO environment, such as Ardena, the application of AI must be balanced with strict data governance and intellectual property requirements. Client-owned molecular structures cannot easily be shared with external AI platforms, and robust models require large datasets that are often difficult to assemble under confidentiality constraints."

For this reason, at Ardena, AI is viewed as a complementary tool that supports scientific decision making rather than replacing formulation expertise. Predictions generated by computational models still require experimental confirmation, as bioavailability and solubility depend on complex interactions between molecular properties, formulation design, and physiological conditions, Dr. Pas explains. "Combining AI-driven insights with formulation expertise and targeted laboratory experiments allows Ardena to focus on the most promising development strategies while maintaining scientific rigor."

Ascendia: Adapting New Technologies & Excipients to Expedite Drug Development

In recent years, drug manufacturers looking for appropriate technologies to bring new chemical entities (NCEs) to clinic faster are adapting novel excipients or technologies to expedite the development. Such strategies, aligned with formulation technologies, do pose some risks, but have led to the advancement of drug candidates across all modalities for oncology, anti-inflammatory, antiviral, CNS, and rare diseases. Soluplus®, for example, a polymer for amorphous dispersions, has helped the advancement of many drug candidates from early-phase screening of molecules to clinical phases, and launch, says Shaukat Ali, PhD, Senior Director Scientific Affairs & Technical Marketing, Ascendia. In addition to novel excipients, there is much interest in co-processed excipients comprised of polymers and solubilizers to address the poor solubility of new drug candidates.

Poor solubility stems from higher melting and logP, meaning the molecules bearing high melting are highly crystalline or have the higher partition coefficient in organic phase. "These attributes create a bottleneck in the industry as more than 80% new molecules coming out of discovery possess high melting and logP, yielding poor solubility," he says.

Fortunately, the pharma industry is open to adapt new technologies and excipients to expedite drug development. Conventional approaches like micronization, pH modification, salt and/or complex with cyclodextrin, have limited scope for medium- to high-dose drugs. Therefore, the new molecules belonging to BCS Class IIb (solubility limited) and Class IV require non-conventional approaches like amorphous dispersions or lipid based emulsifying systems (SEDDS/SNEDDS) to achieve higher solubility and bioavailability.

Lipophilic molecules with logP <2-4> are most suited for lipid-based liquid dispersions, while those possessing high melting logP (>4) are ideal candidates for amorphous dispersions, Dr. Ali explains. For example, spray drying (SD) and hot-melt extrusion (HME) are commonly used for preparation of amorphous solid dispersions (ASDs). For NCEs with a high melting point, Ascendia's NanoSol® technology for nano-sized API particle engineering and AustinPX's high shear dispersions (Kinetisol®) have been used to tackle solubility challenges.

"BCS Class II/IV are most challenging molecules and thus require non-conventional approaches to identify the right excipients and formulation technologies," he says. "Ascendia's enabling technologies including AmorSol® for amorphous solid dispersions and EmulSol® for emulsions/nanoemulsions (SEDDS/SNEDDS) can help expedite development and save time and cost. Our approach includes early molecule screening to find maximum solubility and compatibility of APIs in the appropriate excipients (polymers/solubilizers)."

This is achieved by dissolving API and excipients in varied concentration in polar solvents and casting the aliquot on a glass plate for drying in air or heating in oven at low temperature. The resulting film is examined under light microscopy for any immiscibility/crystallinity or homogenous mixing. This procedure allows shorter screen time of a number of molecules for AmorSol. For EmulSol, the APIs are screened against a range of compatible and FDA-approved solvents, co-solvents,

and solubilizers to identify the maximum solubility, which is taken as the benchmark to design the best SEDDS/SNEDDS formulations for an API. "Not one size fits all, so each API is screened individually to identify the appropriate compatible excipients," says Dr. Ali.

BASF: Science-Driven Suite of Apps Result in Actionable Formulation Decisions

BASF approaches solubility and bioavailability enhancement through a platform-based, excipient-driven strategy. Its excipient portfolio is designed to address these challenges from multiple angles, enabling tailored solutions using advanced polymers (i.e., Soluplus®), lipid and surfactant systems, solid dispersion technologies, and BASF's digital formulation platform ZoomLab®.

"BASF's multimodal strategy reflects a broader industry shift: formulators increasingly combine experimental techniques with computational decision support to rapidly identify the most viable bioavailability enhancement pathway," says Gloria Ho, PharmD RPh, Global Technical Marketing Manager, Pharma Solutions, BASF.

For example, a typical oral development challenge involves the formulation of a poorly soluble API. In such cases, traditional solubilizers may be insufficient to achieve clinically relevant exposure. Here, ASDs – produced via HME or spray drying – offer a route to maintain the API in a high energy amorphous state while ensuring improved dissolution, she explains. Before committing to large-scale experimental work, formulation scientists are often now relying on virtual predictive models to assess polymer compatibility, miscibility, and long-term stability.

BASF's open-access virtual formulation assistant, ZoomLab is a science-driven suite of applications based on lab data, machine learning, modeling, and simulation. ZoomLab accelerates formulation evelopment through data-grounded insights, leveraging several AI technologies (excluding GenAI due to current accuracy limitations) by translating the complexity of bioavailability enhancement into a set of mechanistic questions:

- What are the limiting mechanisms?
- What is the most appropriate enabling technology?
- Which excipients are most compatible?
- What polymer classes are most likely to stabilize an amorphous state?
- Would a lipid-based system yield better solubilization?

"Together, these applications form a workflow that converts broad bioavailability challenges into precise, actionable formulation decisions that can also be used to predict performance risk," says Ms. Ho. By enabling data-driven refinement of formulation strategies, ZoomLab serves as a meaningful, complementary decision-support for modern drug product development."

BioDuro: An Optimal Approach Balances Solubilization with Cost and Scalability

Enhancement strategies for improving solubility and bioavailability can be grouped into chemical approaches and physical approaches. Chemical approaches modify the drug molecule to improve solubility and absorption through salt formation, whereby, for ionizable drugs, an appropriate counterion is selected to form salts that can substantially increase dissolution rates; or through the use of prodrugs, used to covalently attach hydrophilic moieties that enhance solubility. The prodrug is enzymatically converted to the active parent drug *in vivo*, preserving pharmacological activity while overcoming delivery barriers.

Physical approaches are used to optimize a formulation without altering its molecular structure, yet directly driving bioavailability gains. Dr. Hong Li, Vice President of Drug Product, BioDuro, says this can be achieved in several ways:

- **Crystal engineering:** tailor polymorphs, cocrystals, or crystal habits or modulate lattice energy to balance solubility and stability and enhance dissolution and absorption.
- **Particle size reduction:** use micronization or nanomilling technology to increase the surface area, thereby accelerating dissolution and improving the rate and extent of absorption.
- **pH modification:** adjust formulation or biological pH and maximize the ionized fraction of ionizable drugs, boosting solubility and membrane permeability.
- **Solubilizers:** surfactants form micelles to encapsulate hydrophobic drugs, increasing apparent solubility and facilitating intestinal absorption.
- **Lipid-based formulations:** lipid matrices (e.g., self-emulsifying drug delivery systems or SEDDS) exploit lipid solubility, bypassing aqueous dissolution limitations and improving oral bioavailability via lymphatic transport.
- **Complexation:** cyclodextrin inclusion can encapsulate drugs within their hydrophobic cavity, increasing apparent solubility.

Spray Dryer

Hot Melt Extruder

State-of-the-art equipment at Jiangsu site, BioDuro.

- **Amorphous solid dispersions (ASDs):** dispersing drugs in polymers as high-energy amorphous forms eliminates crystalline lattice energy, drastically improving dissolution rate and bioavailability.

"There is no one-size-fits-all solution," says Dr. Li. "Success lies in matching the molecule's properties with the most suitable manufacturing approach. If the API is ionizable, salt screening is recommended, as stable, highly soluble salts can offer both cost-effectiveness and scalability. For non-ionizable crystalline APIs, ASD or lipid-based formulations are viable. The selection must also align with the development phase, dose requirements (especially for high-dose candidates), and process simplicity. Ultimately, the optimal approach balances strong solubilization performance with cost control and scalability, ensuring a robust and practical path from IND filing and beyond."

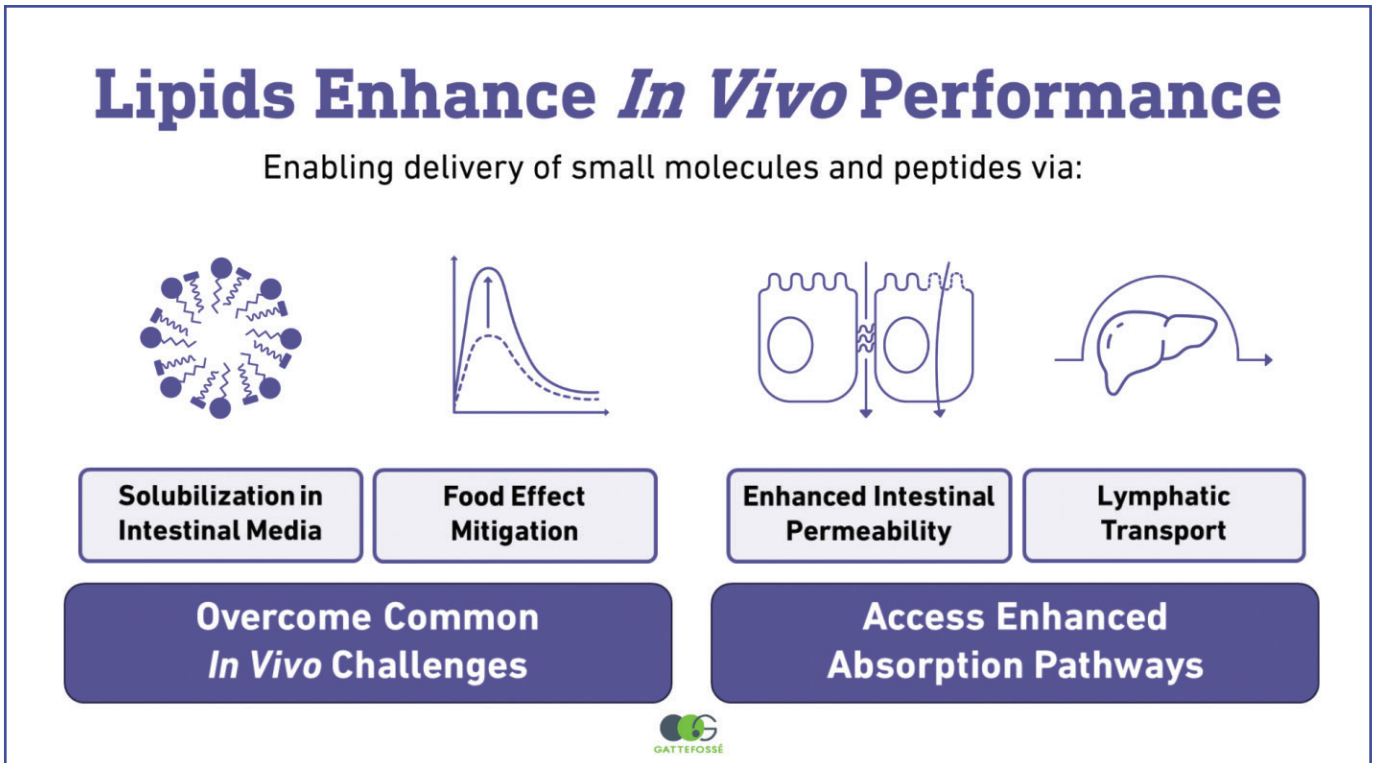
Gattefossé: Lipid Excipients Enable Oral Delivery for New Drug Modalities

For the past several decades, oral drug product development has centered around solubility enhancement, and amorphous solid dispersions (ASDs) based on spray drying or hot-melt extrusion techniques have become a mainstay of oral tablet formulations. While there has been activity around novel polymer development and advanced analytical techniques to better understand the erosion and dissolution behavior of these systems, the products that advance into clinical studies typically utilize the same processing techniques and polymers as their predecessors.

Just as the industry adopted spray drying and hot-melt extrusion to overcome solubility challenges, it must now evolve to master the next frontier: permeability enhancement. "New classes of drugs such as novel targeted protein degraders and macrocyclic peptides cannot be served by traditional solubility enhancement techniques and excipients," says Nick DiFranco, Senior Marketing Manager, Pharmaceuticals, Gattefossé USA. "To be successful, these molecules require new approaches that also address drug permeation and absorption."

The need for permeability enhancement has brought new focus to the established field of lipid-based drug delivery. Lipid-based formulations (LBFs) offer an effective, proven strategy for overcoming *in vivo* barriers and accessing alternative absorption pathways via the oral route, he says. LBFs leverage the body's natural digestive processes to prevent re-precipitation, enable supersaturation, and mitigate food effect. But fresh focus is being brought to their other functionalities – tight-junction opening and lymphatic uptake.

"These unique benefits allow formulators to safely and reversibly enhance both transcellular and paracellular absorption or bypass first-pass metabolism using the lymphatic system," explains Mr. DiFranco. "Such features have been used in commercial products, enabling valuable innovation such as the conversion of



Lipids enhance *in-vivo* performance (Gattefossé USA).

testosterone from an injectable product to a more convenient oral capsule formulation."

Gattefossé leverages its knowledge of lipid chemistry to identify the best excipients for each API. A broad portfolio and formulation experience allows the entire team – from sales to technical service – to recommend excipients that introduce key problem-solving functionalities. Gattefossé's Technical Centers of Excellence offer free-of-charge screening studies to identify the optimal self-emulsifying drug delivery system (SEDDS) formulation for a particular API, factoring in physicochemical properties and *in vivo* functionalities, such as tight junction opening and lymphatic uptake.

"This process accelerates early-stage development and helps to de-risk LBFs," he says. "We also work closely with CDMOs to ensure successful scale-up and commercialization of soft gel and liquid-filled hard capsule formulations."

Recently, Gattefossé's lab in Paramus, NJ, installed a hot-melt extruder and small-scale tableting capability to further explore the use of lipid excipients as surfactants, plasticizers, and absorption enhancers in ternary ASDs. With these new capabilities, Gattefossé hopes to apply the unique functionality of lipid excipients to enhance solubility, permeability, and absorption across a wider range of oral dosage forms.

Hovione: Integrated Offering Combines Advanced Formulation Science With Scalable Manufacturing

In Hovione's view, the most promising technologies are those that address the core challenge of poor solubility, which affects over 70% of new drug candidates. Amorphous Solid Dispersions (ASDs), especially those manufactured by spray drying, have become a leading formulation strategy for overcoming poor solubility, with 48 drug products containing ASDs approved by the FDA between 2012 and 2023, demonstrating their clinical and commercial viability. Spray drying continues to be the preferred manufacturing route for ASDs, owing to its scalability, process control, and suitability for a wide range of organic solvents and polymeric excipients including HPMCAS and Copovidone, says José Luís Santos, PhD, Senior Director, Strategic Business Management – Particle Design, Hovione.

"We are seeing rapid advancement in the platforms used to create these ASDs, supported by better processes and digital solutions," he says. "This includes the use of *in silico* formulation models and integrated intelligent formulation development tools, such as Hovione's ASD-HIPROS. "These technologies enable faster, data-driven process and formulation development with minimal experimental work, rapidly screening for the best combination

of drug loads, excipients, and surfactants using advanced formulation models and high-throughput screening methods."

Furthermore, he adds that the development of better-performing materials is a key trend. This includes novel excipients, such as protein-based carriers like Dispersome®, which are capable of providing further gains in drug bioavailability, especially when used in the formulation of an ASD-based drug product.

Hovione's approach to improving bioavailability and solubility is centered on providing a fully integrated offering that combines expertise in advanced formulation science with robust, scalable manufacturing capabilities. "This means going beyond simply offering capacity to provide proven capability in ASD development and integrated manufacturing, ensuring a seamless technology transfer from spray drying to the final dosage form," says Dr. Santos.

At the earliest stages, Hovione deploys *in silico* and data-driven tools, such as ASD-HIPROS, to rapidly characterize the solubility and bioavailability challenge and select the most appropriate enabling strategy. This process begins with expeditious screening for the best combination of drug loads, excipients, and surfactants. The goal is to create a robust, scalable spray drying process from the outset. This scientific foundation is then paired with a focus on scalability and de-risking, applying Quality-by-Design (QbD) principles and standardized tech transfer methodologies that are consistently applied across Hovione's network of regulatory-inspected facilities. "Where ASDs are the selected strategy, we offer integration between spray drying and downstream oral solid dose manufacturing, ensuring that what is developed at lab scale is more likely to translate predictably to clinical and commercial supply," says Dr. Santos.

Artificial Intelligence is accelerating bioavailability enhancement at Hovione through hybrid modeling approaches. "Hybrid mathematical models, combining mechanistic understanding with machine learning methods, are the engines behind these tools, allowing scientists to leverage prior data to predict how a drug and polymer will behave together," explains Dr. Santos. "These models also optimize the formulation composition in a fraction of the time it would take using traditional trial-and-error methods, accelerating the path from a poorly soluble new drug candidate to a robust, bioavailable formulation."

LATITUDE Pharmaceuticals: Identifying Optimal Strategies for Poorly Soluble APIs

LATITUDE Pharmaceuticals improves bioavailability and solubility through a formulation-driven, technology-focused approach tailored for each specific drug candidate. LATITUDE combines detailed preformulation studies – such as pH solubility profiling, solvent screening, and excipient compatibility – to identify optimal strategies for poorly soluble APIs. It then applies its expertise in delivery platforms and formulation technologies, including nanosuspensions (a favorite of LATITUDE's for its simplicity and effectiveness), nanoemulsions (excellent for injectable formulations), amorphous solid dispersions, and its Clearsol™ solubilization system (for both injectable and oral formulations) to enhance dissolution, absorption, and stability. By selecting technologies based on dose, route of administration, and API properties, LATITUDE creates scalable formulations that improve drug exposure, safety, and overall therapeutic performance, says Matthew A. Singer, PhD, Vice President, Business Development, LATITUDE Pharmaceuticals Inc.

LATITUDE Pharmaceuticals developed ClearSol, a proprietary drug-solubilization platform designed to address one of the most common challenges in pharmaceutical development: the poor aqueous solubility of many active pharmaceutical ingredients (APIs). ClearSol is a sterile aqueous vehicle composed of three FDA-approved, generally recognized as safe (GRAS) excipients that enable poorly soluble drugs to form stable, single-phase solutions suitable for administration. The system has demonstrated the ability to solubilize roughly 80% of tested insoluble compounds and often achieves higher drug concentrations than traditional solubilizers such as cyclodextrins or surfactants, while maintaining favorable safety profiles demonstrated in preclinical and Phase 1 clinical stages, explains Dr. Singer.

LATITUDE also uses nanosuspension formulations, which disperse drug particles at nanometer scale in a stabilizing medium. "By dramatically increasing surface area, nanosuspensions enhance dissolution rate and drug absorption, making them especially valuable for lipophilic or poorly soluble compounds," he says. "Together, technologies like ClearSol and nanosuspensions provide innovative approaches to improve drug solubility, bioavailability, and overall therapeutic performance."

Ligand: Combine Mechanistic Clarity, Regulatory Familiarity & Flexibility

Poor aqueous solubility and limited bioavailability continue to be among the most common barriers to successful drug development, particularly as modern dis-

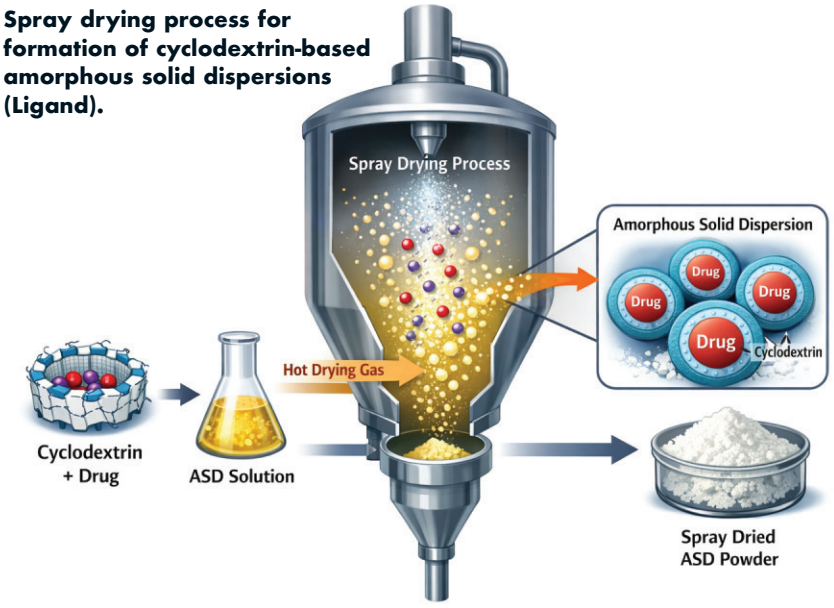
covery efforts yield increasingly lipophilic and structurally complex molecules. In response, recent progress in this area has been characterized less by entirely new concepts and more by the refinement, expansion, and clinical validation of enabling technologies that can be applied predictably across diverse compounds.

Several strategies currently stand out in this area. Amorphous solid dispersions and lipid-based delivery systems remain widely used for oral small molecules, particularly for BCS Class II compounds, due to their ability to enhance dissolution and maintain supersaturation in the gastrointestinal tract. "Research has shown that Captisol® helps spray dried amorphous solid dispersions by improving API solubility in feed solution, stabilizing amorphous drug via molecular complexation, enhancing dissolution and maintaining supersaturation, complementing polymer-based ASD systems, and improving spray drying robustness and particle quality," says Lian Rajewski, PhD, Senior Director Formulation Development, Ligand.

Nanocrystal technologies and particle engineering approaches continue to mature, offering improvements in dissolution rate without altering chemical structure. In parallel, functional excipients – those that actively influence solubility, stability, and exposure rather than serving as inert formulation components – are playing an increasingly important role in formulation design.

Within this category, cyclodextrin-based solubilization strategies, particularly those using chemically modified cyclodextrins, are experiencing renewed attention. While cyclodextrins themselves are not new, advances in their chemical design, safety characterization, and regulatory acceptance have expanded their practical utility.

Spray drying process for formation of cyclodextrin-based amorphous solid dispersions (Ligand).



"Captisol (sulfobutylether β cyclodextrin) is a notable example of this trend," says J.D. Pipkin, PhD, Vice President, New Product Development, Ligand. "Designed to address the limited solubility and safety concerns associated with native β cyclodextrin, Captisol enables reversible inclusion complexation that can substantially improve aqueous solubility and formulation stability without chemically modifying the active pharmaceutical ingredient. What makes Captisol particularly relevant in the current development landscape is its continued appearance in newly approved products and new routes of administration, rather than reliance solely on legacy intravenous formulations."

As of March 2026, eighteen approved products incorporate Captisol, says Vince Antle, PhD, Senior Vice President Tech. Operations & QA, Ligand, reflecting sustained regulatory confidence and ongoing application across therapeutic areas and dosage forms. "Recent approvals demonstrate its role in enabling formulations that were previously difficult to achieve due to solubility or concentration constraints," he says.

One example is Lasix® ONYU, approved by the FDA in October 2025. This product uses Captisol to enable a high concentration subcutaneous formulation of furosemide suitable for at-home administration via a wearable infusor. In this case, the solubility enabling properties of Captisol supported not only drug delivery but also a shift in care setting – from hospital-based intravenous treatment to outpatient self administration – highlighting how formulation technology can influence broader therapeutic strategy, says Dr. Pipkin.

Beyond individual products, Captisol's relevance is linked to its compatibility with contemporary development priorities, including simplified formulations, reduced reliance on organic cosolvents, and adaptability to multiple routes of administration. "Its safety and regulatory history lowers formulation risk, making it attractive for both new chemical entities and lifecycle management efforts," says Dr. Rajewski.

Lubrizol: Novel Excipients Are an Effective Alternative to More Common Ingredients

Poor solubility and bioavailability impede both therapeutic potential and innovation, particularly in oral and injectable dosage forms. Using excipient-based solubilization strategies can enable simplified formulation techniques to streamline manufacture and save time during the development of drug products containing poorly soluble APIs. Yet, many of today's commonly used excipients were developed decades ago and may not be optimal for transforming insoluble APIs into effective therapeutics.

"Novel excipients specifically designed to improve solubility and bioavailability offer an effective alternative," says Dr. Liliana Miinea, Global Technology Manager, Lubrizol.

For example, Lubrizol's novel excipients, Apisolex™ polymer excipient and Apinovex™ polymer excipient, resolve formulation challenges by enhancing the solubility of brick-dust poorly soluble APIs. The polyamino acid-based Apisolex polymer increases the solubility of hydrophobic APIs for parenteral applications by up to 50,000-fold, with high drug loading of up to 40:100 API to solubilizer. Being biologically inert, it has no side effects.

"Based on sarcosine – a non-toxic, non-immunogenic, biocompatible, and biodegradable amino acid – Apisolex polymer excipient offers a high level of safety for parenteral use – unlike PEG-based solubilizers, which may trigger neuropathy, hypersensitivity, and anaphylactic reactions," she says.

For its part, Apinovex polymer excipient is a high molecular weight polyacrylic acid that enables homogenous amorphous dispersion for solid oral dosage forms, with up to 80% drug loading. By comparison, traditional polymer excipients such as hydroxypropyl methylcellulose (HPMC) and povidone typically only support drug loading of up to 40%, she says. Dr. Miinea explains that in case studies with the BCS Class II drug itraconazole and BCS Class IV ritonavir, Apinovex polymer excipient-enabled ASDs with twice the drug loading compared to other commonly used, solubility-enhancing excipients. It also allowed up to tenfold improvements in dissolution for dispersions compared to crystalline APIs, and maintained stable amorphous solid dispersions even after six months under accelerated conditions.

"Compared to excipients with precedence of use, novel excipients can be superior solutions for bioavailability and solubility challenges," says Dr. Miinea. "Yet, the ambiguity surrounding regulatory approval for excipients can lead risk-averse formulators to stick to familiar ingredients."

Lubrizol believes that early collaboration between drug developers and excipient suppliers is the solution to building formulator confidence in novel excipients. Critically, this strategy can enable early identification of the developer's specific unmet needs. Lubrizol actively works with partners to co-develop data and regulatory submissions. Its Drug Master Files (DMFs) in the US, China, and Canada – or data-sharing agreements where DMFs are not used, such as Europe – help streamline the approval process.

"Bridging arguments can also be used to mitigate the regulatory risk of including a novel excipient in a new drug application," she says. "The use of an approved excipient's safety data may support a novel excipient with similar chemistry. For example, Apinovex polymer excipient is chemically similar to our existing, widely used Carbopol® polymers."

Quotient Sciences: Integrated, Data-Driven Approach Accelerates Development

Quotient Sciences' approach to bioavailability and solubility integrates Developability Classification System (DCS) principles with biopharmaceutic experimentation and mechanistic PBPK/PBBM modelling to systematically identify and mitigate solubility and permeability related risks. "Early assessment of intrinsic solubility, pH-dependent solubility, dissolution behavior, permeability, particle size, and solid state properties enables us to determine whether a compound is solubility or permeability limited and select the most appropriate formulation strategy," explains Paloma Benito Gallo, Senior Modelling and Simulations Research Fellow at Quotient Sciences. "Modelling and Simulation (M&S) expertise can be used to review the output and advise on the suitability of M&S to inform for further development and risk assessment."

Jane McGuffog, Director, Modelling and Simulation, Quotient Sciences, goes on to explain that following non-clinical assessment, Quotient Sciences can combine these data with PBPK/PBBM modelling to quantify the impact of particle size, gastric pH, dose, food effect, and transporter interactions on predicted exposure. She says: "This modelling framework guides form/formulation selection, supports dose escalation, and reduces uncertainty when transitioning to FIH studies. Where solubility limits performance, we evaluate enabling technologies such as amorphous solid dispersions, lipid-based formulations, and particle size reduction, using rapid small-scale screening to identify the best performing technology. This integrated, data-driven approach improves bioavailability, accelerates development, and reduces experimental burden."

For Quotient Sciences' client, Boston Pharmaceuticals, a Phase I Translational Pharmaceutics® study was performed, integrating drug product manufacturing and clinical testing to rapidly screen and select an optimal oral formulation of BOS172767, a first–in–class inverse agonist being developed for autoimmune diseases. Previous first–in–human studies using an API blend capsule showed low exposure, high variability, non–linear pharmacokinetics and a pronounced food effect, prompting evaluation of solubility-enhanced formulations, explains Dr. Andrew Lewis, Chief Scientific Officer, Quotient Sciences. Three GMP–manufactured formulations (micronized capsule, lipid capsule, and spray-dried dispersion tablet) were assessed head-to-head in an integrated adaptive clinical study in healthy volunteers. All prototypes improved exposure compared with the IR reference capsule, with the spray-dried dispersion showing the highest Cmax. The micronized capsule was selected as the lead formulation based on comparable AUC and a simpler and cheaper manufacturing process. This formulation demonstrated approximately dose-proportional exposure up to 800mg, a reduced food effect relative to the FIH formulation, and minimal impact of elevated gastric pH when evaluated within volunteers dosed with a proton-pump inhibitor. A Level C IVIVC was established using biorelevant dissolution testing, supporting future formulation development and specification setting.

Quotient Sciences has established a partnership with Intrepid Labs to integrate its proprietary Machine Learning (ML) algorithm Andromeda™ with Quotient Sciences' Translational Pharmaceutics™ platform that integrates drug product manufacturing with clinical testing to rapidly identify formulations that meet the Target Product Profile. "When coupled with automation, many hundreds of prototype lipidic and amorphous dispersion formulations can be screened to fully map the formulation design space," says Dr. Lewis. "Not only does this enable the identification of compositions that achieve the highest solubility and stability, but it reduces API demands and provides improved knowledge of the relationship between composition and performance."

Samsung Biologics: AI Propels Drug Candidates from "Possible" to "Optimally Bioavailable"

AI is turning bioavailability and solubility from experimental bottlenecks into data-driven opportunities early in drug discovery. Jaehoon Jeong, Lead Scientist of AI Technology; Hyunsik Lee, Senior Scientist of Antibody Technology Discovery; and Sangyun Park, Senior Scientist of Antibody Technology Discovery at Samsung Biologics, highlight three key areas where AI is making an impact on solubility and bioavailability.

1. AI-based *in silico* developability assessment: Traditional prescreening of antibody candidates relies on costly wet lab assays. Recent AI models now extend to antibodies, predicting developability risks such as solubility, thermostability, and aggregation. Integrated workflows that enable AI–driven prescreening are being piloted by Big Pharma. "By consolidating multiple predictions into a single pipeline and leveraging internal datasets, these workflows achieve respectable predictive accuracy for expression and stability – attributes that normally require months-long testing," says Dr. Jeong. "This approach delivers substantial time and cost savings and enables more efficient selection of candidates."

2. From accurate structures to physics-based forecasts: AI-driven structure prediction engines such as AlphaFold3, RoseTTAFold, and Boltz-2 provide high resolution antibody structures. When further processed by physics-based simulation platforms, molecular dynamics and free energy calculations can estimate solubility and aggregation propensity, explains Dr. Lee. Metrics such as solvent-exposed patches and conformational flexibility guide rational modifications that improve systemic exposure. "Nevertheless, predicting an antibody's solubility and bioavailability remains challenging," says Dr. Lee. Antibodies are large, flexible proteins that often carry complex glycoforms, can aggregate, and are recycled by the FcRn receptor. "Recent AI advances, especially protein language models and multimodal networks that combine sequence, 3D structure, and glycoform data, are beginning to address these problems," says Dr. Lee. "At the same time, generative AI tools are being used to redesign Fc regions and optimize glycosylation patterns, while microfluidic formulation screens co-optimize excipient blends. Together, these approaches suggest a promising direction, although extensive experimental validation is still required."

3. Lab in the Loop (LITL) – closing the reality gap: Even the best *in silico* model drifts when confronted with zero-shot prediction lacking internal experimental data. The LITL paradigm turns the laboratory into a self-learning engine:

AI proposes candidates, robotic platforms perform expression and assay, and the results retrain the predictors. "This loop compresses the design make test analyze cycle from months to weeks, boosting hit to lead conversion and delivering compounds with experimentally validated bioavailability and solubility," says Dr. Park.

Dr. Jeong summarizes: "AI has evolved from a static predictor to a dynamic partner that continuously integrates structural insight, physicochemical modeling, and empirical feedbac – propelling drug candidates from "possible" to "optimally bioavailable" at unprecedented speed.

Performing in-process sampling inside a lab-scale lyophilizer to monitor freeze-drying conditions (Simtra BioPharma Solutions).

Simtra BioPharma Solutions: Improving Solubility With the End in Mind

In the sterile injectables space, investigating an increase in solubility typically begins with fundamental, direct approaches, such as pH modification, temperature adjustment, or the addition of organic co-solvents. However, Simtra BioPharma Solutions is seeing significant advancements in parenteral products to improve the bioavailability of molecules that are not naturally water-soluble. Among the most promising technologies are liposomes and lipid nanoparticles (LNPs). Both dosage forms allow poorly water-soluble molecules to be placed within a lipid core, which is then dispersed in aqueous media so they can be effectively injected, describes Greg Sacha, PhD, Global Senior Scientist Development and Clinical Services, Simtra BioPharma Solutions.

"Our approach to improving solubility is rooted in a product designed with the end in mind philosophy, which ensures that formulations are robust, scalable, and facilitate high-quality manufacturing," he says. "We have received several requests for developing formulations for molecules that are challenging to dissolve and reconstitute after freeze-drying. Our initial strategies always prioritize simple, proven approaches to maintain efficiency and stability."

This includes:

- Primary adjustments, such as adjusting the pH of the solution, modulating temperature, including an organic co-solvent, or adding a small percentage of surfactant;
- If these do not yield the desired results, cyclodextrins are used to improve solubility;
- The use of polyethylene glycols (PEGs), propylene glycol, and surfactants is explored to improve the reconstitution process after freeze-drying.

Freeze-drying a formulation can be challenging because many highly potent and chemotherapeutic molecules are poorly soluble in water and often require an organic co-solvent to improve solubility. Simtra BioPharma Solutions dissolves the molecule in a customized organic co-solvent solution along with specific excipients. This solution is filled into vials, frozen, and undergoes a specialized freeze-drying process.

"The lyophilization process successfully removes the organic solvent and significantly increases the specific surface area of the molecule," says Dr. Sacha. "This allows the drug to dissolve much more effectively upon reconstitution, ensuring the patient receives the vital injectable product in its intended, most bioavailable form."

In an effort to accelerate the early investigative stages, companies like Simtra BioPharma Solutions are turning to Artificial Intelligence (AI). Dr. Sacha says AI offers scientific teams a rapid method of conducting preliminary research, as it can provide quick answers when posing questions about the behavior of certain excipients or the feasibility of specific formulation strategies. These AI-generated insights are then reviewed by onsite experts to determine the best path forward.

"This synergy between digital intelli-

gence and our deep technical expertise helps save time and money for our customers, ultimately accelerating the delivery of life-changing therapies to patients," says Dr. Sacha. "Our onsite scientific teams support products from initial discovery through to commercial launch, solving the scaling challenges that often accompany complex formulation development."

The Solubility Company: Give Every Promising Asset a Chance to Progress to the Clinic

The available toolset of enhancing and enabling formulation technologies broadly covers the bioavailability and solubility challenges of current chemical space. Poor bioavailability and solubility are now inherent in most development programs and the challenge has moved from a lack of technologies to timely selection of the right technology for a particular asset. "Here, miniaturized technologies, such as The Solubility Company's SPA® platform, work with the material amounts available at the preclinical stage, where decisions lock in development and where actionable insight is most critical and hardest to come by," says Sami Svanbäck, PhD, CEO, The Solubility Company.

The Solubility Company's goal is to give every promising asset a chance to progress to the clinic, says Dr. Svanbäck. "Using as little as 2mg of compound, we screen the entire preclinical formulation space. Having this data on hand early on enables us to support our clients with all *in vivo* PK and toxicology studies before the first scale up of their molecule. The approach is particularly successful for new modalities where the compounds may not behave like traditional small molecules. This paradigm shift ensures that development is never delayed by material scarcity."

One of the company's clients faced a go/no-go decision on a highly lipophilic API with animals booked for toxicology, but no viable vehicle with which to dose. Traditional methods were impossible due to the limited availability of the API. "By applying SPA to map the formulation landscape, we rapidly identified a specific lipid-based surfactant vehicle," he explains. "Using only 1mg for the entire screen, we delivered an α-formulation™ that delivered systemic exposure above 50mg/kg, allowing the program to proceed to toxicology without waiting for a secondary synthesis scale-up synthesis and further delays."

SPA uses standardized, high-precision, automated experimental data to fine-tune Machine Learning models in real time, which Dr. Svanbäck considers to be an active learning loop. "AI is becoming a powerful tool in drug discovery and development, but it is still limited by the lack of high-fidelity training data. Most historical solubility databases are "noisy" due to inconsistent experimental methods and lack of meta-data on experimental conditions. We see AI's greatest value in active learning loops. This hybrid approach, where AI predicts and micro-scale experiments rapidly verify, can significantly cut down on trial-and-error wet-lab experimentation to shorten the path to IND."

Thermo Fisher Scientific: Combining Predictive *In Silico* Workflows with Targeted Experimentation

A shift toward model-informed formulation design is transforming how bioavailability and solubility challenges are addressed. Traditional empirical approaches are increasingly being supplemented by predictive digital tools that integrate Artificial Intelligence (AI), Machine Learning (ML), Quantum Mechanics (QM), Molecular Dynamics (MD), Quantitative Structure–Property Relationship (QSPR), and Quantitative Structure–Activity Relationship (QSAR) models. These approaches enable early prediction of solubility, permeability, and absorption-related risks before extensive laboratory screening, says Sanjay Konagurthu, PhD, Senior Director, Science and Innovation, Thermo Fisher Scientific Pharma Services.

"These tools, or digital platforms like OSDPredict™, identify and prioritize for-

mulation strategies – including technology selection (e.g., amorphous solid dispersions, particle size reduction, lipid systems, fluid-bed processing, complexation etc.), drug-excipient combinations, and drug loading – and inform downstream considerations such as bio-enhancement, manufacturability, and stability," he says.

Key features include:

- AI/ML-powered predictive modeling, such as Thermo Fisher Scientific proprietary AI/ML Quadrant 2® platform, which uses molecular structure and key physicochemical properties to identify probable enabling technologies, guide formulation design for solubility and bioavailability enhancement, and estimate optimal drug loading.

- Predictive stability modeling for determining product shelf life and packaging extrapolated from short-term accelerated data, reducing development time and experimental burden. Both chemical and physical stability aspects are considered for enabling technologies such as amorphous solid dispersions.

- Compaction simulation and process modeling to support scalable and robust oral solid dose manufacturing, scale-up, and technology transfer.

- ADME-PK and PBPK modeling to predict absorption, distribution, metabolism, and excretion, helping align formulation decisions with *in vivo* pharmacokinetic studies and first-in-human (FIH) predictions.

Thermo Fisher Scientific's strategy combines predictive *in silico* workflows with targeted experimentation. Early in development, Quadrant 2® predictive modeling is used to identify suitable formulation technologies, solubility, and bioavailability enhancement strategies, excipients, and optimal drug loading, explains Dr. Konagurthu. This insight guides formulation selection and prioritizes high-value experimental leads, minimizing API usage and avoiding extensive trial-and-error screening – so developers can focus only on what works best.

Once candidate technologies (e.g., ASDs or lipid systems) are identified, accelerated stability models project long-term behavior and inform packaging and storage decisions. Process modeling ensures that formulations are manufacturable and scalable with controlled critical quality attributes. Finally, PBPK/ADME-PK models integrate physicochemical and dissolution data to simulate clinical exposure, supporting dose selection and overall program de-risking.

In a recent engagement involving a poorly water-soluble BCS Class II candidate, predictive modeling was applied at the outset. Quadrant 2 evaluated potential drug–polymer interactions and identified polymer systems with favorable miscibility and potential for supersaturation maintenance. These *in silico* predictions were confirmed experimentally using solvent spike assays and biorelevant dissolution testing, he explains.

Spray-dried dispersion (SDD) formulations were then developed using process simulation to optimize particle characteristics and manufacturability. Accelerated stability modeling provided early insights into the risk of phase separation or crystallization during storage. *In vivo* pharmacokinetic studies demonstrated significant enhancement in oral bioavailability compared with the crystalline form, and PBPK simulations corroborated the observed increases in Cmax and AUC. "This integrated workflow enabled rapid refinement and advancement of an enabling formulation while reducing development risk," says Dr. Konagurthu.

Upperton Pharma Solutions: Screening Platform Evaluates Methods for Improving Solubility/Bioavailability

Upperton believes that creating amorphous solid dispersions (ASDs) by spray drying is the most promising and effective way of improving the bioavailability/solubility characteristics of an API. "Not only does this approach work for a wide range of NCEs, but it offers a fast, scalable formulation approach," explains Dr. Richard Johnson, Chief Scientific Officer & Founder, Upperton Pharma Solutions. "The number and range of polymers that can be considered is increasing, giving us more formulation options and the addition of surfactants to help stabilize the API in solution is an added option."

Dr. Johnson says Upperton will typically screen three enabling technologies; creating ASDs by spray drying, lipid based formulations (semi-solid matrix filled into capsules) and micronisation (to decrease particle size). The pilot formulations are then subjected to a range of tests, including micro dissolution testing, physical testing (thermal properties), and stability. The output of this data is typically a "ranking" order for further testing in a pharmacokinetic (PK) model. This rapid screening approach is called UpperSolv™.

He describes a recent example where Upperton evaluated the use of its UpperSolv screening approach to evaluate different methods for improving the solubility and bioavailability of Oxfendazole, a poorly soluble API with limited bioavailability. "In the study, we evaluated the

Bioavailability enhancement through spray drying at Upperton Pharma Solutions.

three main approaches for enhancing solubility/bioavailability using the UpperSolv approach (ASDs lipidic formulations, and micronization). By far the best enabling technology was spray drying; an ASD was created by spray drying enhanced bioavailability sevenfold compared to the API alone."

Veranova: Improving Dissolution Rates of "Brick Dust" APIs

Key solid form and physicochemical attributes of a molecule, such as crystallinity, pKa/LogP, melting point, and understanding particle characteristics help to identify viable development and formulation routes early in the screening process. The simplest, low cost, and most robust strategies can be prioritized for evaluation first before moving into increasingly complex methods. "As an example, if accessible ionizable centers prevail, tried and tested salt screening and selection is a well understood front line approach for increasing aqueous solubility," explains Craig Grant, Vice President and General Manager, Cambridge, Veranova. "Where salts are not possible, cocrystals, while not as immediately obvious as "simple acid-base" chemistry (sometimes not so simple), are equally valuable for crystal lattice modification that can often result in improving physical properties including solubility. The polymorph landscape of each needs to be understood and control needs to be exerted to link the desired solid form at lab to plant scale to complete the picture."

Moving beyond crystal engineering, particle engineering encompasses a range of techniques that modify an API's particle shape, size, and surface area. These include traditional top-down strategies, such as milling and micronization, often with the goal of reducing particle size to increase aqueous solubility. On the other end of the spectrum, for molecules where traditional methods have been tried and tested, the production of an ASD is a more costly but effective means of improving solubility; provided the appropriate screening strategies have been applied to stabilize the amorphous material, says Mr. Grant.

A typical example of a challenge faced by many of Veranova's clients is how to tackle poor aqueous solubility for a non-ionizable compound, which eliminates salt formation entirely and therefore requires alternative methods of solubility enhancement. Occasionally, this can be tackled with co-solvents or perhaps via cocrystal formation or the formation of complexes, e.g., cyclodextrins. However, he says, it is often the case that molecule properties do not align with these strategies, for example, compounds with a high LogP or the absence of the relevant hydrogen bond motifs and/or suitable molecular shape and size.

"In these cases, one of the approaches Veranova employs is the development of a nanosuspension," says Mr. Grant. "Nanosuspensions vastly improve dissolution rate in "brick dust" APIs by reducing particle size to nanometer (sub-micron) levels and dramatically increasing surface area. As a result, saturation solubility can be increased and dissolution rate is dramatically enhanced, in turn potentially increasing bioavailability." ◆

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POLYMACROCYCLIC PEPTIDES

Engineering Structure for Function in Next Generation Therapeutics

By: Karsten Eastman, PhD, and Vahe Bandarian, PhD

INTRODUCTION

The modern therapeutic toolbox has been dominated by two poles. Small molecules excel at oral dosing, distribution, and manufacturing, and they are superb when a target exposes deep, well defined pockets. Yet their very compactness, typically <600 Daltons, constrains the surface area they can contact, making it difficult to modulate large, relatively flat protein–protein interfaces (PPIs) or to discriminate among closely related binding epitopes.

At the other pole, biologics (antibodies, proteins, and related modalities) bring tremendous shape complementarity and affinity to accessible extracellular targets. But macromolecular size, charge, and trafficking obstacles limit efficient penetration into cells, which is why biologics have historically focused on extracellular or lumenal proteins; cytosolic targets remain challenging without specialized delivery tricks.

Small molecules remain the workhorses of medicine, from statins, painkillers, antibiotics, to kinase inhibitors, but they rely on highly complementary pockets and well behaved absorption, distribution, metabolism, and excretion. When the thermodynamic currency of binding is spread over hundreds of square angstroms, as in many PPIs, small molecules often cannot make enough contacts without becoming too bulky or polar to be "drug like". Biologics, by contrast, bring tremendous shape complementarity and affinity to accessible extracellular epitopes, but struggle to reach intracellular targets at pharmacologically useful concentrations.

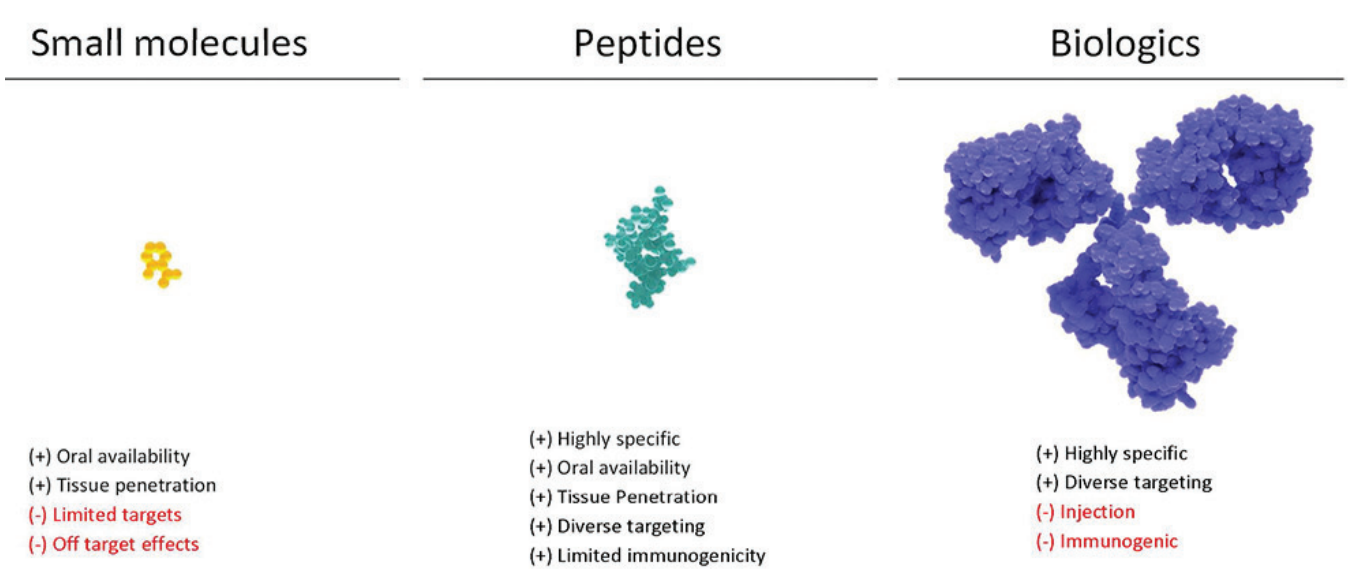
Peptides occupy the space in between. They inherit the sequence programmability of proteins, yet can be engineered to approach the permeability and stability of small molecules. They present more binding surface than small molecules and, unlike large proteins, can sometimes be tuned to cross membranes, occupy shallow clefts, or clamp onto protein surfaces. The key challenge, and opportunity, is to sculpt peptide architecture so that shape and chemistry are presented to the target in the right place, at the right time, and for long enough to matter clinically.

STRUCTURE EQUALS FUNCTION: FROM BIOLOGY 101 TO DRUG DESIGN

One of the first durable lessons in biology is that structure determines function. Proteins fold; the fold creates pockets, surfaces, and defined electrostatics; those features control catalysis and recognition. Drug design is no different: a therapeutic's topology, the way its atoms are organized in space, often dictates its fate. Yet most peptide discovery platforms today search libraries that explore sequence far more than architecture. Many screens limit candidates to a single macrocycle or a narrow set of constrained motifs, which restricts the exploration of shape space.

Consider insulin - the clinically used hormone comprises two chains (A and B) held by disulfide bonds. Efforts to collapse insulin into a single chain receptor agonist underscore how hard it can be to recapitulate a multi segment architecture with fewer connections. The broader point is that architecture is causal and limiting architecture up front can limit what biology you can access. However, there are two root cause problems in peptide therapeutics:

FIGURE 1



Therapeutic modalities at a glance: small molecules, peptides, and biologics; relative size, typical targets, and intracellular access.

Problem 1: Searching Astronomical Sequence Space

High throughput selection technologies have transformed discovery. mRNA display covalently links a nascent peptide to its mRNA via a puromycin "bridge," enabling *in vitro* selections over libraries that can exceed 10^{12} distinct sequences. Phage display genotypically couples peptides to bacteriophage coat proteins (commonly pIII or pVIII, two of the viral "appendages") for iterative biopanning. DNA encoded libraries (DELs) extend the barcode concept to small molecules and peptidomimetic search spaces. Each platform makes it possible to sift through large diversity because the barcode (DNA/RNA) can be amplified from an incredibly small signal.

In each display system, the barcode is the engine: it ties genotype to phenotype and allows exponential amplification of faint signals by PCR or phage replication. That same barcode, however, can perturb physics at the interface. In mRNA display and DELs, long, polyanionic nucleic acids can electrostatically repel negatively charged patches on targets or nonspecifically attract basic surfaces. In phage display, the per virion copy number, orientation, and spatial crowding on the capsid can alter the apparent fitness of certain peptide topologies versus their behavior as free molecules.

Problem 2: Conformational Control (the "Floppiness" Problem)

Linear peptides are intrinsically disordered. Without constraints, they can adopt many conformations, only a small fraction of which align with the bioactive pose, lowering apparent affinity and making them susceptible to proteolysis. Chemistry has long fought back with macrocyclization, historically via disulfide bridges, then with lactams, ring closing metathesis, click reactions, and staples. These strategies often stabilize a single ring. They improve stability and sometimes permeability, but they inherently limit architectural diversity because only a few bond forming reactions are both reliable and library compatible across many sequence contexts.

NATURE'S BLUEPRINT: ENZYMES THAT BUILD RIGID, BIOACTIVE SCAFFOLDS

Nature points to a practical way forward. Ribosomally synthesized and post translationally modified peptides (RiPPs) are encoded as linear precursors and then sculpted by tailoring enzymes into compact, diverse scaffolds with exceptional stability and activity. Among the most celebrated are lantibiotics, such as nisin, which uses multiple thioether (sulfur-to-carbon) bridges to achieve food grade stability and long-term potency. Beyond lanthipeptides, the radical S adenosyl L methionine (rSAM) superfamily forges many unique radical-based transformations in diverse contexts, including generating thioethers in peptide contexts.

Two families of thioether rich RiPPs il-

FIGURE 2

Anaerobic glovebox context for rSAM purification and screening.

lustrate how chemistry grants stability. Lanthipeptides (eg, nisin) are built by first dehydrating serine and threonine residues to dehydroalanine/dehydrobutyrine and then adding generate the thioether through a Michael-addition via a cysteine residue to form lanthionine/methyllanthionine bridges; bonds that resist reduction where disulfides would not. Sactipeptides/ranthipeptides use rSAM enzymes to forge C-S bonds directly to aliphatic carbons, again delivering robust thioether linkages.

A standout example is PapB, an rSAM RiPP maturase that installs thioether cross links between Cys and Asp/Glu residues. In its native substrate PapA, PapB introduces six thioether linkages, and in-vitro studies show striking substrate promiscuity: PapB accepts a range of Cys X_n Asp (or Cys Xn Glu, were Xn is a number of additional amino acids) motifs, can form nested and in line cross links, and tolerates unnatural amino acids at the cross linking positions. These features suggest that enzyme installed linkages could decouple sequence from topology, enabling many ring architectures beyond what chemical methods comfortably deliver.

There is a catch: most rSAM enzymes are oxygen sensitive because their [4Fe 4S] clusters are labile. Practical deployment at discovery scale therefore requires anaerobic handling and careful attention to reducing systems during expression, purification, and catalysis.

WHAT IT TAKES TO EXPLOIT ENZYMATIC MACROCYCLIZATION AT HTS SCALE

To translate these natural capabilities into a discovery engine, three requirements must be met: (1) Enzyme tolerance to library diversity, so that billions of unique sequences with cross link motifs can be processed, (2) Evidence of cyclization in HTS contexts, demonstrating that cross links can be installed on constructs used for phage and mRNA display, and (3) Fast topology confirmation, so that hits can be prioritized by architecture as well as sequence.

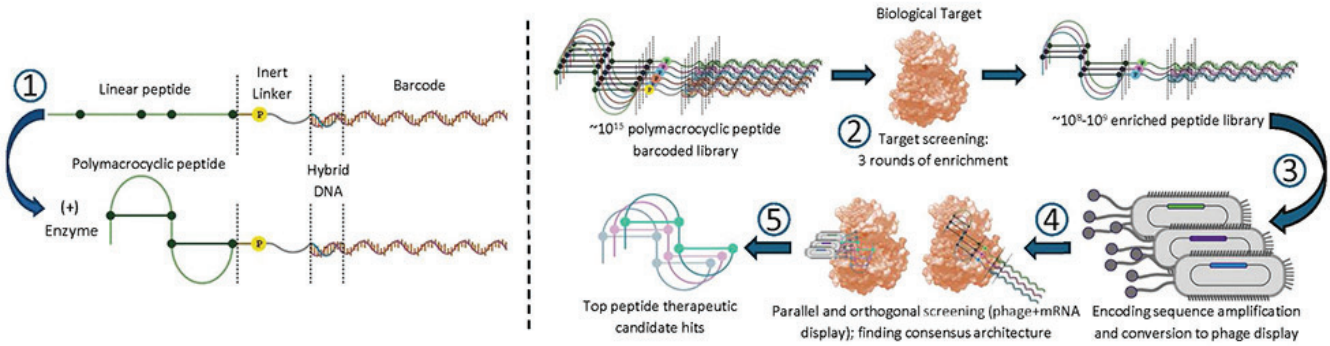
For topology confirmation, mass spectrometry can diagnose the characteristic 2 Da mass loss per thioether, judicious isotopic labeling, and protease mapping can rapidly fingerprint ring count and connectivity. On target functional triage should begin early (eg, receptor activation assays) because architectures that bind but do not signal are often unhelpful for therapeutics. Combining these readouts with next generation sequencing (NGS) enables structure aware enrichment curves in which rises and falls in specific ring patterns are tracked alongside sequence frequency.

SETHERA'S APPROACH: DECOUPLING TOPOLOGY FROM SEQUENCE

Sethera Therapeutics, Inc. is developing an enzymatic platform that decouples topology from sequence, enabling controllable, site specific multi ring formation under biological conditions while preserving chemical handles for downstream conjugation. The working model is straightforward: encode CX_nD/E motifs within diverse peptide backbones, allow PapB like rSAM enzymes to install thioether cross links, and carry out selections on the cyclized, barcoded products.

Early cell free biosynthesis (CFB) experiments and pIII based phage selections already hint at architecture specific enrichment, consistent with the notion that topology, nested versus in line versus triple, can dominate fitness during selection. The platform keeps orthogonal chemical handles available (eg, N termini, C-termini or

FIGURE 3



Workflow schematic: (1) barcoded peptides before/after enzymatic cyclization, (2) selection against a target, (3) porting enriched pools to the orthogonal display, (4) "consensus architecture" calling, and (5) down selection to high confidence hits.

tailored side chains) so that post selection conjugations (fluorophores, affinity tags, payloads) can be attached without disturbing the enzyme set cross links. Together, this enables rapid hit confirmation and assay portability across formats.

To reduce format bias, discovery is run in two orthogonal display contexts on the same targets. mRNA display provides ultra large sequence spaces with a polyanionic barcode (RNA/DNA) that can, in some cases, shift electrostatics near the binding interface. Phage display imposes capsid sterics (eg, pIII spacing, avidity, and orientation) that can mask or exaggerate certain architectures. By selecting an mRNA display and then reformatting enriched pools into phage for orthogonal/parallel screens, Sethera maximizes search breadth while minimizing format artifacts.

Why explicitly combine both HTS systems? Because each has systematic artifacts. In mRNA display, the long nucleic acid barcode can create electrostatic halos that disfavor some topologies or select for peptides that bind in geometries compatible with the tag. In phage, virion proximity effects and copy number can favor architectures that survive secretion and display constraints but are not necessarily optimal in free solution. Convergent enrichment across both formats flags architectures that are more likely to be intrinsically fit, and thus, more likely to survive translation into therapeutic scaffolds.

THE WAY FORWARD: FROM BINDERS TO FUNCTIONAL MODULATORS

Polymacrocyclic peptides are more than "better binders". Multiple rings can pre organize pharmacophores, enforce multivalent effects within a single chain, and bias conformational dynamics in ways that translate into signaling outcomes; for example, agonism versus antagonism at GPCRs or isoform specific engagement of homologous domains. Sethera's development path emphasizes:

Library Design by Topology: construct families that systematically vary ring count, spacing, and order (nested, in line, and triple ring motifs), not just side chain identities.

Orthogonal Discovery: perform parallel mRNA and phage selections on identical targets to identify architectures that reproduce in both contexts.

Rapid Structure Confirmation: use MS/MS fingerprints and enzymatic digestion to verify cross link count and placement early, accelerating hit triage.

Functional Assays, Not Only Binding: prioritize cell based readouts (activation, inhibition, internalization, trafficking) to learn which architectures modulate biology, not merely associate with targets.

Developability Filters: bake in plasma/microsomal stability and permeability screens; leverage the inherent reduction resistance of thioether bonds relative to disulfides, and preserve orthogonal chemical handles to enable payload conjugation or depot strategies.

Polymacrocyclic peptides can address intracellular protein-protein interactions long considered "undruggable" to small molecules and too hidden for antibodies; they can be tuned to bias receptor signaling or recruit endogenous machinery (eg,

for targeted degradation or trafficking). Most importantly, they let us search the middle ground by structure, where the best medicines for complex diseases may be hiding.

The field has long known that shape underlies function, but our discovery engines have searched sequences far more than shapes. Enzyme installed polymacrocyclization changes that calculus. By merging RiPP enzymology with genetically barcoded discovery and orthogonal selection formats, we can systematically explore topology as a drug variable. Sethera's platform is designed to do exactly that, turning nature's blueprint into a practical path to specific, stable, and effective peptide therapeutics. ◆

BIOGRAPHIES

Dr. Karsten Eastman is the CEO of Sethera Therapeutics, Inc. He earned his PhD from the University of Utah (under the mentorship of Professor Vahe Bandarian), where they discovered the key processes that enable Sethera Therapeutics' innovative technology. As a co-founder of Sethera, Dr. Eastman is leading the company's efforts to commercialize cutting-edge peptide therapeutics, drawing on their experience in enzyme and peptide research, patent development, and engagement with key business mentors.

Dr. Vahe Bandarian is the CSO and President of Sethera Therapeutics, Inc. He earned his PhD in Biochemistry from the University of Wisconsin-Madison. He is a distinguished faculty member and Associate Dean at the University of Utah, recognized for his exceptional contributions to the field of chemistry. He is a Fellow of the American Chemical Society (ACS), the American Association for the Advancement of Science (AAAS), and the American Society for Biochemistry and Molecular Biology (ASBMB). His groundbreaking research has earned him the prestigious Pfizer Award in Enzyme Chemistry from the ACS and the Distinguished Research Award from the University of Utah.

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TECHNOLOGY TRANSFER

Streamlining Biologics Technology Transfer Through Integrated Operational Models

By: Lalit Saxena

INTRODUCTION

Technology transfer in biologics manufacturing is an inherently complex process that requires the simultaneous control of multiple scientific, technical, and operational variables.1 Biologics are highly sensitive to process conditions, and even minor deviations in mixing geometry, oxygen transfer, or analytical interpretations can alter product quality attributes. When development and manufacturing functions are distributed across sites, communication, decision-making, and troubleshooting can cause delays and increase risk. The transfer of processes, analytical methods, and control strategies from the sending site to the receiving facility, therefore, becomes both a technical exercise and a test of organizational coordination.[1,5] The move toward integrated operational models, in which process development, analytical development, quality control, and supply chain functions are co-located, is reshaping how this coordination is achieved and sustained.[5]

THE ADVANTAGES OF CO-LOCATION

The co-location of process development, analytical laboratories, and production establishes a continuous operational link between research and manufacturing.[4,5] This configuration eliminates sequential dependencies and creates the structural basis for real-time communication. In biologics, where a process can shift with small changes in media composition, filtration pressure, or pH profile, proximity between teams enables immediate investigation. If a manufacturing issue arises, engineers can walk directly to the process development laboratory to reproduce conditions at small scales, analyze deviations, and validate corrective parameters. Analytical scientists, positioned alongside manufacturing and development functions, can conduct same-day assessments of intermediate samples, enabling the early detection of variations. This configuration transforms reactive troubleshooting into a proactive, iterative, and data-supported dialogue occurring in real time.

The acceleration achieved through co-location extends beyond problem-solving. It enables the parallel execution of workstreams that would otherwise be sequential.[1,5] Facility fit assessments, raw material compatibility evaluations, and validation studies, such as resin lifetime or chemical hold time, are executed concurrently with process qualification. Face-to-face coordination allows for the continuous adjustment of project timelines and alignment of resources. The result is a measurable reduction in transfer inefficiencies and a compressed timeline from development to manufacturing.[5] Each incremental efficiency compounds across the overall technology transfer lifecycle, converting what might have been months of delay into a continuous and overlapping operational flow.

INTEGRATED MODEL FOR KNOWLEDGE CONTINUITY

Knowledge continuity represents another critical dimension of this integrated model.[2,5] Biologics manufacturing depends heavily on the accurate transmission of the process context from development to scale-up.[1] Each process parameter carries an im-

Cell line development scientists at Samsung Biologics operating the Beacon equipment.

plicit rationale that informs its acceptable range and interactions with other variables. In distributed systems, this rationale is often diluted through documentation exchanges and secondary interpretation. Co-location preserves continuity by enabling direct knowledge-sharing between development and manufacturing teams.[5] The scientists who define process controls are co-located with those implementing them at scale. Analytical teams contribute to this ecosystem by providing ongoing characterization and verification data, ensuring that process intent remains aligned with analytical observation. The cumulative result is a seamless flow of contextual understanding, which reduces the likelihood of implementation errors that could compromise process reproducibility.[2]

In practice, concurrent execution is most visible in accelerated transfers where development, scale-up, and manufacturing must be aligned within compressed timelines.[1] An illustration of the benefits of this integrated approach was observed during the accelerated transfer of a monoclonal antibody program targeting a viral pathogen. The process originated from a sending site with limited data at the 50-liter scale and required both late-stage process development and commercial manufacturing readiness within a three-month timeframe. The integrated site structure allowed process development and manufacturing science and technology (MSAT) teams to perform scale-up activities while manufacturing preparations proceeded in parallel. Analytical methods were adapted and co-validated in the same period, ensuring that process verification could occur without interruption.[3] The project achieved first GMP batch manufacture at the 15,000-liter scale within the required three months, demonstrating that integrated operations enable both speed and compliance when process development and transfer activities are executed concurrently.[1,5]

CONTINUOUS CLIENT INVOLVEMENT FOR STRATEGIC RISK MANAGEMENT

Technology transfer is not a single event, but a continuous exchange of knowledge and risk ownership between the client and biomanufacturer.[5] The client's role begins before project initiation, during the proposal and feasibility assessment phase, where information from the sending site forms the foundation of the receiving site's gap analysis.[1] Active collaboration ensures that facility fit assessments and process gap evaluations are based on complete technical data. Early client input optimizes equipment compatibility, raw material specifications, and bill of materials alignment. In many cases, facility modifications or capital expenditures must be confirmed based on this shared evaluation. The client remains the ultimate knowledge owner, responsible for providing product-specific context that enables the receiving site to design an ap-

A scientist at Samsung Biologics imaging a cell with Cell Metric.

propriate control strategy.[2] When this collaboration occurs continuously rather than periodically, the transfer benefits from faster decision-making, clearer risk classification, and more predictable execution.

Risk assessments in biologics technology transfer follow a structured, stage-wise progression.[1,5] They begin at the laboratory scale, where pilot experiments evaluate process robustness under controlled variations. Findings from this stage inform the design of engineering and process performance qualification runs at larger scales. The purpose of this iterative evaluation is to identify, quantify, and mitigate risks arising from process changes, equipment differences, or unforeseen interactions between process parameters.[1] High-risk items are typically associated with scale-dependent phenomena, such as mass transfer coefficients, mixing efficiency, gas dispersion within bioreactors, and impurity clearance sensitivity downstream.[2,4] To manage these risks, verification runs are conducted using client processes to confirm performance prior to GMP manufacturing.[1] During these runs, analytical monitoring provides empirical confirmation that mitigation actions are effective.[3] This approach ensures that quality attributes remain consistent and that deviations are addressed before they propagate to commercial production.[1,2]

The use of predictive modeling and digital tools has strengthened the risk management framework.[4] Machine learning models trained on historical process data can simulate scale-up behavior, predict potential deviations, and highlight parameters that contribute most to process variability. These models support decision-making by identifying the optimal set of parameters to monitor during transfer and by reducing the number of engineering runs required to establish process confidence.[1] Combined with small-scale verification and large-scale engineering runs, predictive tools enable a data-driven approach to control strategy development.[2] This evolution toward digital prediction has also introduced strategic foresight into the technology transfer process, allowing organizations to anticipate and mitigate variability before it materializes on the production floor.[4]

ANALYTICAL READINESS THROUGH INTEGRATED PROJECT MANAGEMENT

Analytical technology transfer represents a parallel challenge, as the reproducibility of analytical results across laboratories directly influences batch release.[3] In many cases, analytical readiness lags behind process readiness, creating critical bottlenecks during process qualification.[1] Integrated project management mitigates this risk by treating analytical and process transfers as interdependent activities within a single project

framework.[5] Early in the transfer, project managers from the client and the receiving organization conduct joint risk assessments to identify analytical dependencies, such as differences in equipment configurations, reagent stability, and the sensitivity of the method to operator variations.[3] Once identified, these risks are addressed through concurrent method validation and transfer, known as co-validation.[3] Co-validation allows analytical laboratories at the receiving site to begin implementing the methods while validation is still being finalized at the sending site. This concurrency reduces overall lead times and ensures that analytical verification aligns with process qualification milestones.[1]

Standardized documentation and procedural templates further support analytical alignment.[2,3] Well-defined protocols, agreed upon by all parties in advance, reduce ambiguity and ensure that the transfer data are both traceable and compliant with regulatory requirements.[1] Verification run samples are frequently analyzed before the first GMP batch, providing an additional readiness check that allows laboratories to identify and resolve issues early.[3] The combination of integrated planning, parallel validation, and standardized documentation creates a synchronized analytical environment that progresses at the same pace as process transfer.

PROCESS MONITORING & DIGITAL INTEGRATION

Performance measurement and continuous improvement are central to sustaining efficiency across successive transfers.[1,2] Each department tracks the key indicators relevant to its function, creating a multi-dimensional view of performance. MSAT teams monitor upstream and downstream yield and titer, as well as the comparability of critical quality attributes during verification, engineering, and process performance qualification runs.[1] Quality systems measure deviation frequency, the time to closure for corrective and preventive actions, and right-first-time metrics.[2] Project managers monitor the adherence to client schedules and batch release timelines. These indicators serve as critical measures of operational stability and transfer efficiency.[1] Early in the product lifecycle, attention is primarily focused on achieving comparable product quality and batch success. As the process transitions toward commercial manufacturing, the emphasis shifts to increasing consistency, decreasing deviations, and optimizing batch release intervals.[2] Lessons learned from each campaign are analyzed and incorporated into subsequent transfers, forming a continuous loop of performance enhancement.

Standardization, automation, and data analytics converge to drive progress in technology transfer.[4,5] Standardized process platforms for common modalities reduce variability and provide predictable performance across projects. High-throughput development systems enable rapid small-scale screening and verification, allowing teams to confirm process fit and identify scale-up parameters early in the transfer. Digitalization plays a critical role in linking these elements. Real-time process analytical technology tools, such as multivariate data analysis platforms, digital twins, and simulation systems, enable continuous process monitoring and prediction.[4] Through these tools, engineers can test scenarios virtually, assess process sensitivity, and validate control strategies before implementation. The integration of these technologies into a digital ecosystem creates transparency across all transfer stages, from data capture in development to electronic batch record generation in manufacturing.[1]

Digital data management systems also enhance regulatory compliance and traceability.[1,2] Centralized data-sharing platforms ensure that all process information, from development reports to batch records, is accessible in a controlled and auditable format.[1] This digital continuity not only improves collaboration but also enables faster regulatory documentation by maintaining a consistent and validated data trail.[1] As technology transfer becomes increasingly digital, the distinction diminishes between development and manufacturing knowledge bases, leading to more robust control over process and product quality.[4]

INTEGRATED DATA-CENTRIC OPERATIONS

The evolution of biologics technology transfer reflects a broader shift toward integrated data-centric manufacturing.[1,4] Co-located functions create the operational foundation for real-time collaboration and concurrent execution.[5] Continuous client engagement ensures that risk ownership and decision-making remain aligned throughout the process.[1] Stage-wise risk management, predictive analytics, and standardized analytical transfer collectively ensure reproducibility and speed.[1,2,4] Digitalization and standardization extend these gains by embedding predictability and transparency into every phase of technology transfer.[4] The outcome is a system in which efficiency is

achieved not by reducing oversight but by integrating it into every operational layer.[1] As biologics modalities diversify and process complexity increases, the success of technology transfer will continue to depend on the depth of integration, the strength of digital infrastructure, and the precision of analytical alignment across the value chain.[2,4] ◆

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BIOGRAPHY

Lalit Saxena is a Bioprocess Engineer with more than 21 years of expertise in process development, tech transfer, and GMP manufacturing (clinical/commercial) of biologics drug substance for monoclonal antibodies and complex biologics. He currently serves as Senior Director of MSAT for Technology Transfer to Clinical and Commercial Manufacturing at Samsung Biologics. He leads a team of bioprocess scientists dedicated to advancing DS manufacturing strategies in alignment with evolving biotherapeutic technologies. He is instrumental in accelerating technology transfer, PPQ, and commercialization through the implementation of standardization and process analytical tools, as well as the application of statistical and modeling approaches to drive efficiency and advance innovation in biomanufacturing. He also serves as a board member for the Parenteral Drug Association Biopharmaceutical Advisory board (BioAB) and authors multiple peer-reviewed publications.

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Lonza

Lonza

Lonza: Addressing Solubility Challenges in Early Stages of Drug Development

The pharmaceutical industry's current focus on accelerating all aspects of drug discovery and development has become something of a crusade, with companies rushing to compress the timeline from initial idea to first-in-human safety and efficacy data. As biotech and pharma companies engage in the dash to proof of concept, they are often tripped up by compounds with low solubility and poor bioavailability. The emergence of solubility problems in the early stages of drug development can be especially troubling, creating a domino effect that can delay or possibly derail later stages. Partnering with a CDMO early in the development process can help drug developers avoid many of the pitfalls of low solubility. With their expertise in solubility-enhancing formulation strategies and technologies, CDMOs can ensure that development programs remain on track.

Drug Development & Delivery recently interviewed Adi Kaushal, Director and Technology Head, Bioavailability Enhancement at Lonza, to discuss solubility issues and Lonza's approach to addressing these challenges in the early stages of drug development.

Q: Solubility challenges are a common hurdle in drug development. How can integrating solubility-enhancing strategies earlier in the pipeline help streamline development and improve outcomes?

A: Solubility and bioavailability hurdles are often a challenge in advancing new molecules, as they require enabling technologies even for phase I studies, which makes it critical to choose a development and manufacturing partner as early in the drug development process as possible. Aligning with a single service partner can

reduce the complexities, risks, and costs associated with low-solubility compounds, thereby shortening the timeline to reaching clinical milestones.

Q: How can a CDMO partner help accelerate drug development through solubility enhancement and phase-appropriate processing?

A: A CDMO partner helps accelerate drug development by tackling a critical challenge: poor compound solubility. Many promising drug candidates are poorly soluble, which hinders their absorption and effectiveness in the body. A specialized CDMO can employ a variety of advanced techniques to enhance the solubility and bioavailability of the active pharmaceutical ingredient (API). This expertise ensures the development of an effective and stable formulation early on, preventing costly delays and reformulation efforts later in the clinical pipeline.

Furthermore, a CDMO's ability to implement phase-appropriate processing streamlines the entire development timeline. This involves tailoring the manufacturing process to the specific needs of each clinical phase. For early-stage trials, they focus on rapid, flexible, and scalable processes to produce small batches for "first-in-human" studies. As the drug progresses to larger, late-stage trials, the CDMO scales up manufacturing and optimizes the process for efficiency and reproducibility, preparing for commercial production. This strategic, phased approach avoids overinvesting in complex manufacturing too early, while ensuring a smooth, seamless transition from clinical development to commercialization.

Q: What are some of the latest innovations aimed at overcoming solubility and bioavailability challenges?

A: One effective formulation strategy involves the use of amorphous solid dispersions (ASDs). These formulations work by increasing drug solubility, thereby facilitating dissolution in gastrointestinal (GI) fluids and optimizing the quantity of drug that enters the bloodstream. This boost in oral bioavailability holds the potential to improve patient outcomes by reducing variations in plasma exposure, lowering required dosages, and mitigating potential drug interactions with other medications or food.

ASDs can be produced through several platform technologies and manufacturing techniques. One of the leading approaches is hot-melt extrusion (HME), which offers the advantages of mature process understanding, a small process footprint, continuous operation, and ready scalability. These attributes can enhance the flexibility of the unit operation, resulting in relatively lower manufacturing costs and a more appealing commercial process train. HME is also a solvent-free unit operation that can eliminate concerns about solvent impurities while enabling sustainability.

Q: As more complex molecules enter the pipeline, what trends are you seeing in customer demand or formulation needs when it comes to enhancing solubility?

A: We continue to see an increase in demand from biotech and pharma companies for highly complex solubility enhancement solutions due to the rising number of poorly soluble new chemical entities entering clinical pipelines. This growing demand is shifting formulation needs toward advanced technologies and strategies that can mitigate risks early in development, such as quality and reproducibility challenges.

One approach is establishing bioavailability techniques like spray-drying or HME as a core component in early-phase development. Deciding between these two depends on which technique is more suitable for the molecule, provides optimal solubility and physical and chemical stability. This decision also can be challenging when a company's needs change as a drug moves through the pipeline. For example, early in development, companies are focused on performance and rapidly getting their drugs into the clinic rather than cost. However, as the drug progresses through clinical trials towards commercialization, cost, throughput and sustainability become increasingly important.

Both spray-drying and HME have their own unique advantages. As we continue to see molecules become increasingly more challenging, CDMOs like Lonza must continue to have more tools to advance them in the clinical pipeline. Through new and more versatile applications we can solve these early phase challenges in a more sustainable way.◆

THERAPEUTIC FOCUS

Advancing Adjunctive Therapies for Depression & OCD Using Translational Pharmaceutics®

By: Jacob Jacobsen, PhD, Bret Berner, PhD, and Dr. Vanessa Zann - VP, Scientific Consulting, Translational Pharmaceutics & Clinical Pharmacology

ABSTRACT

Depression affects an estimated 5% of adults globally, and in the US, depression diagnoses have risen 33% since 2013; twelve-month depression prevalence is 10.7%; and healthcare spending by a patient suffering from depression is twice that of the average patient.[1] Unfortunately, less than one-third of patients respond adequately to first-line serotonin reuptake inhibitor antidepressants (eg, Prozac®) therapy.[2] Current next-line options are limited by modest efficacy and safety concerns.[3] For patients who do not respond adequately to first-line antidepressants, new next-line options are urgently needed.

Quotient Sciences (Nottingham) partnered with Evecxia Therapeutics to support the development of EVX-101, an investigational adjunctive drug for depression and obsessive-compulsive disorder (OCD) responding inadequately to first-line antidepressants. EVX-101 is a first-in-class drug acting via Serotonin Synthesis Amplification. Using Quotient Sciences' Translational Pharmaceutics® platform, the team developed and manufactured the drug product and conducted an adaptive clinical study to optimize performance against the target product profile.

A gastro-retentive (GR), bilayer modified-release (MR) EVX-101 tablet formulation combining 5-hydroxytryptophan (5-HTP) — the natural immediate serotonin precursor — with low-dose carbidopa (enhances 5-HTP's bioavailability) was developed and manufactured for clinical testing. This formulation approach effectively addressed the inherent challenges of 5-HTP's short half-life, narrow absorption window, and low bioavailability.

The two-part clinical study involved a sipping protocol to confirm the GR strategy and to define the carbidopa dose range (Part 1) and a formulation optimization study using a 2-dimensional design space to vary the release rate of the two drugs and the GR retention time (Part 2). The formulations were radiolabeled with not more than 1 MBq 111indium allowing gamma scintigraphy to be used to assess *in vivo* formulation performance. The optimized formulation was then progressed to a Phase 1 program, which included single ascending dose (SAD) and multiple dose titration (MAD) study in healthy volunteers treated with escitalopram.[4]

The program achieved significant time savings compared to conventional formulation optimization strategies with two Phase 1 trials completed in a timely manner. The following reviews the Phase 1 study design and clinical outcomes, leveraging data presented at the 2023 AAPS Annual Meeting.[5,6]

INTRODUCTION

Inadequate response to antidepressant treatment is a significant issue for many patients with depression.[2,3] Enhancing brain extracellular serotonin (5-HT) levels beyond those produced by serotonin reuptake inhibitors may treat depression more effectively.[7] Adjunctive treatment with 5-hydroxytryptophan (5-HTP), the natural precursor to 5-HT, can amplify brain serotonin.[8] However, 5-HTP absorption is restricted to the upper intestine, bioavailability is low, and 5-HTP has a short half-life ($t_{1/2}$), making 5-HTP a poor drug.

To overcome these pharmacokinetic (PK) limitations, a gastro-retentive (GR) modified release (MR) formulation was required to maximize the absorption window for sustained delivery expo-

sure. Carbidopa inhibits amino acid decarboxylase, the enzyme that converts 5-HTP to 5-HT in the intestine, resulting in decreased first-pass metabolism and increased 5-HTP bioavailability. The effective dose of carbidopa was unknown. The goals of each part of the study were as follows:

- **Part 1:** administering 5-HTP as a sipping protocol to simulate GR formulation input and to demonstrate proof of concept (PoC) for the GR formulation. Additionally, the flexibility to adjust carbidopa dose to define the dose range for the GR formulation was considered.

- **Part 2:** developing and optimizing EVX-101 as a novel GR MR 5-HTP/carbidopa bilayer tablet formulation and conducting PK and safety assessments. The target product profile (TPP) was to achieve a twice a day (BiD) dosing regimen with a steady state C_{avg} (ssC_{avg}) of >100 ng/mL.

Quotient Sciences' Translational Pharmaceutics platform was used to conduct the study, integrating drug product formulation development and GMP manufacturing with clinical dosing activities.

METHODS

The conventional paradigm for the development of GR dosage form is to screen a range of prototypes in preclinical species, usually dogs, and use this data to select two or three fixed compositions to manufacture and subsequently dose in a human PK study. The inherent risk of this model is the acknowledged lack of predictability of animal bioavailability to that which might be expected in humans. For GR products, this is particularly true given the significant physiological and anatomical differences between species.

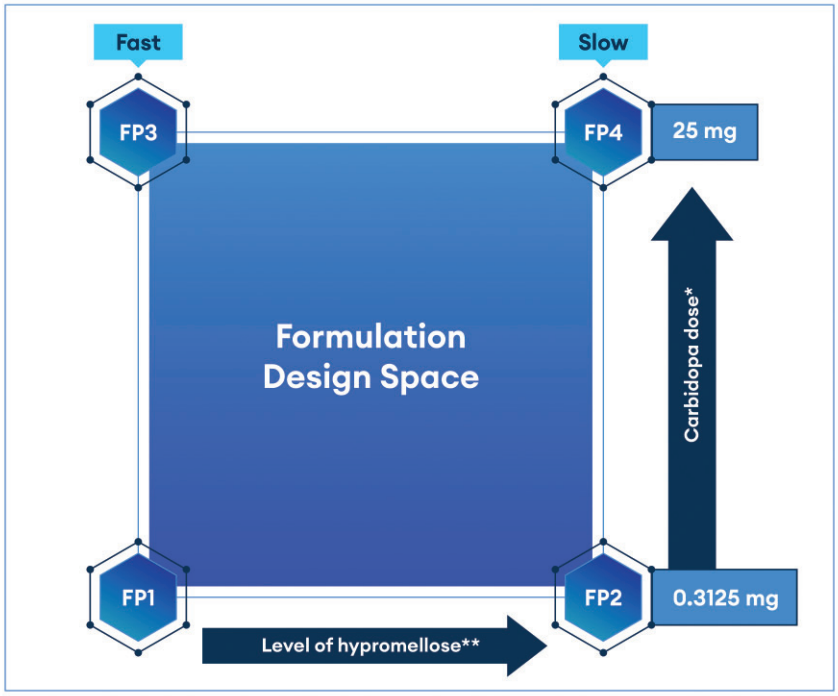
When Translational Pharmaceutics is applied in drug product optimization, multiple formulation technologies or prototypes can be assessed during a clinical study. Formulations are then optimized based on clinical data, addressing the issue of poor preclinical predictability. Small batches are manufactured immediately prior to dosing, saving time in formulation scale up and stability data generation. Interim data reviews after each dosing period assess safety, tolerability and PK to determine the next technology or prototype to be manufactured and evaluated, typically on a 2-3 week cycle time.[9]

In Part 1, 12 healthy subjects were dosed in a 5 period sequential study, with each subject receiving a fixed dose (250 mg) of 5-HTP as an immediate release (IR) bolus dose, a sipping regimen (divided into 10 aliquots administered over a 9-hour period) and 5-HTP with three different dose levels (0.625 mg, 2.5 mg, and 10 mg) of carbidopa as sipping regimens. Both drug products were administered as solution formulations.

In Part 2, a new cohort of 16 healthy subjects received five sequential dosing periods. Quotient Sciences developed a bilayer GR/MR tablet containing a fixed 5-HTP dose (250 mg) and a two-dimensional design space (Figure 1) to enable variations in carbidopa dose (0.3125 mg - 25 mg) and the level of hypromellose (K4M, 7%-18%) and K100M (0%-25%) to control release rate of 5-HTP and carbidopa (target 80% release 8.5 to 12 hours. The formulations were radiolabeled with 111indium, allowing gamma scintigraphy to be used to assess in vivo performance based on gastric emptying (GE) time,

FIGURE 1

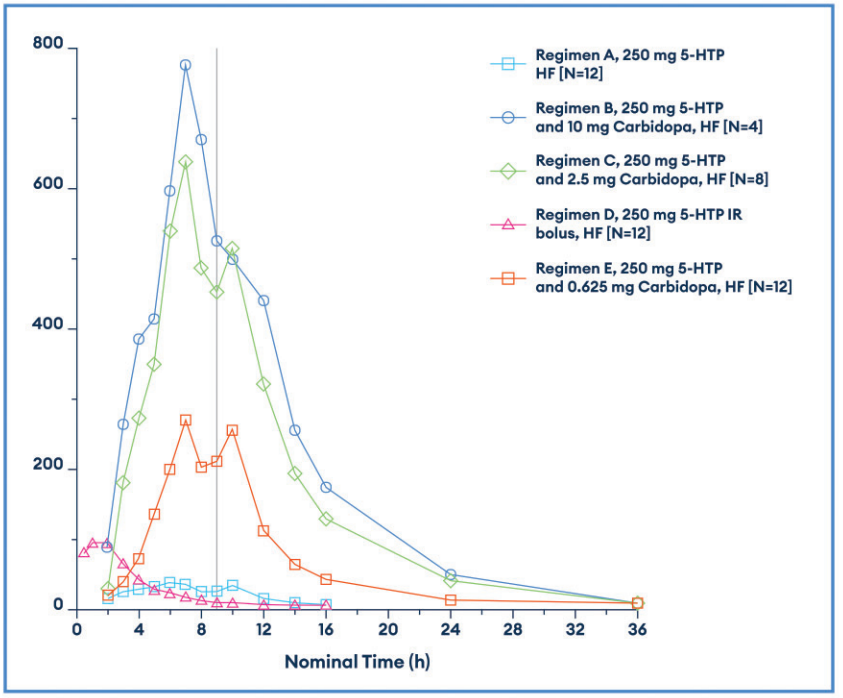
Figure 1: 2-D design space for the MR layer



*5-HTP dose fixed at 250 mg for all prototype formulations
**The hypromellose level and type determines the release rate of the 5-HTP

FIGURE 2

Figure 2: Mean plasma concentration-time profiles for 5-HTP when administered as a sipping protocol and IR bolus



Initial sipping protocol dose and IR bolus dose administered at 0 hours, final sipping protocol dose administered at 9 hours, HF = high fat

gastrointestinal (GI) transit parameters, and initial and complete tablet disintegration (ITD and CTD). The carbidopa dose-response relationship to 5-HTP exposure was also assessed. In periods 1-4 subjects received GR prototype formulations in the fed state following a high fat/high calorie breakfast, with period 5 dosed in the fed state following a moderate fat/moderate calorie breakfast.

For both study parts, interim decisions occurred between dosing periods, whereby PK, safety, and scintigraphy data (Part 2 only) were reviewed to assess formulation performance and decide what formulation prototype to dose in the subsequent period.

RESULTS

When 5-HTP was delivered as a sipping protocol in Part 1, it gave the expected profile with a delayed Tmax of 6.5 hours compared to the bolus IR dose Tmax of 1 hour and also reduced exposure. Carbidopa had the anticipated effect on 5-HTP exposure (Figure 2) increasing exposure and t½, with a 2.5 mg dose resulting in a 16-fold increase in 5-HTP exposure. 10 mg carbidopa resulted in additional increases in 5-HTP exposure; however, there was a limited data set for the 5-HTP 250 mg and carbidopa 10 mg regimen due to subjects withdrawing due to adverse events (AEs), and hence the data should be viewed with caution. Carbidopa plasma levels were only above the LLOQ (1 ng/mL) for the 10 mg carbidopa dose. Note, all the 5-HTP and carbidopa sipping regimens dosed, achieved or exceeded the steady state target plasma concentrations for 5-HTP. However, when switching to a GR formulation, the 5-HTP exposure is predicted to be lower than when compared with the sipping regimen data, and hence a wider dose range for carbidopa was anticipated to be required.

The data from Part 1 allowed the dose range for carbidopa to be set at 0.3125 mg to 25 mg for the GR prototype formulation to be dosed in Part 2 of the study. The PK profile achieved by dosing the sipping protocol with 5-HTP and carbidopa confirmed PoC for a GR formulation.

During the GR bilayer formulation development, it was observed that the order of the two layers being compressed can also affect MR layer's surface area and the drug release rate. Hence, it is a critical factor to achieve the desired release rate. When the bilayer tablets were pressed in the order of GR-to-MR, the drug release rate was faster and more sensitive to the polymers used in the MR layer. The bulk density of the GR layer was less dense compared to the MR layer. Therefore, the decision to compress the MR layer first was deemed suitable to improve the manufacturability of the formulation. This finding is useful for development of bilayer MR tablet to achieve the required drug release profiles and is also critical for downstream scale up process development as the sequence of compression will impact on the release profile.

In Part 2, a new cohort of 16 healthy subjects each received GR prototype 1 (0.625 mg carbidopa and 250 mg 5-HTP, target release rate 80 % at 8.5 hours) in the fed state in period 1. GR prototype 1 produced a similar 5-HTP exposure to the 250 mg 5-HTP IR bolus dose in Part 1 of the study, suggesting a higher dose of carbidopa is required to achieve the target 5-HTP exposure. Imaging of the radiolabeled formulation within the gastrointestinal tract showed that GR formulation had a mean gastric emptying time of 5.863 hours, initial tablet disintegration

FIGURE 3

Figure 3: Representative Scintigraphic images showing GE

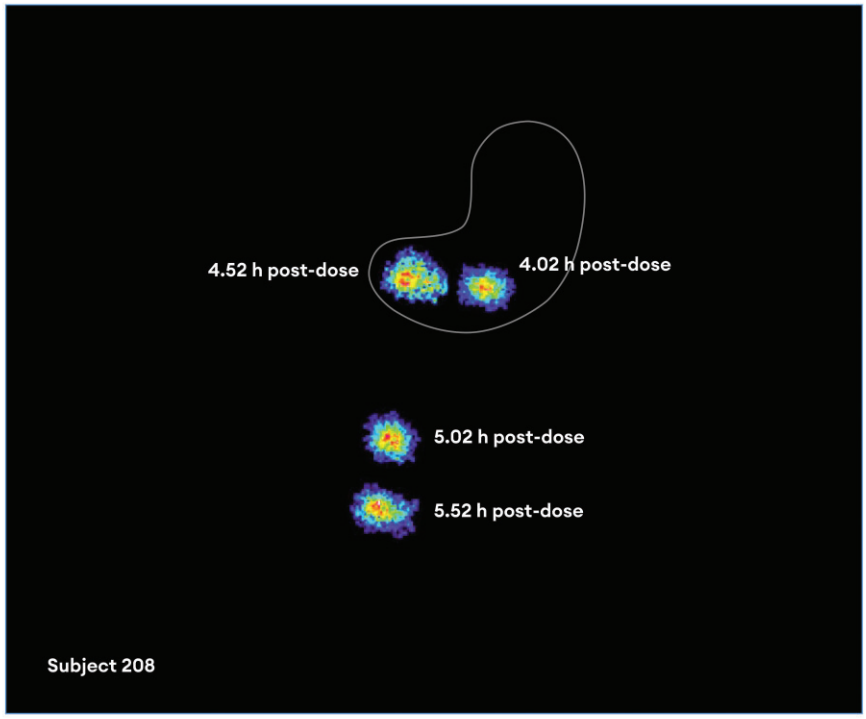
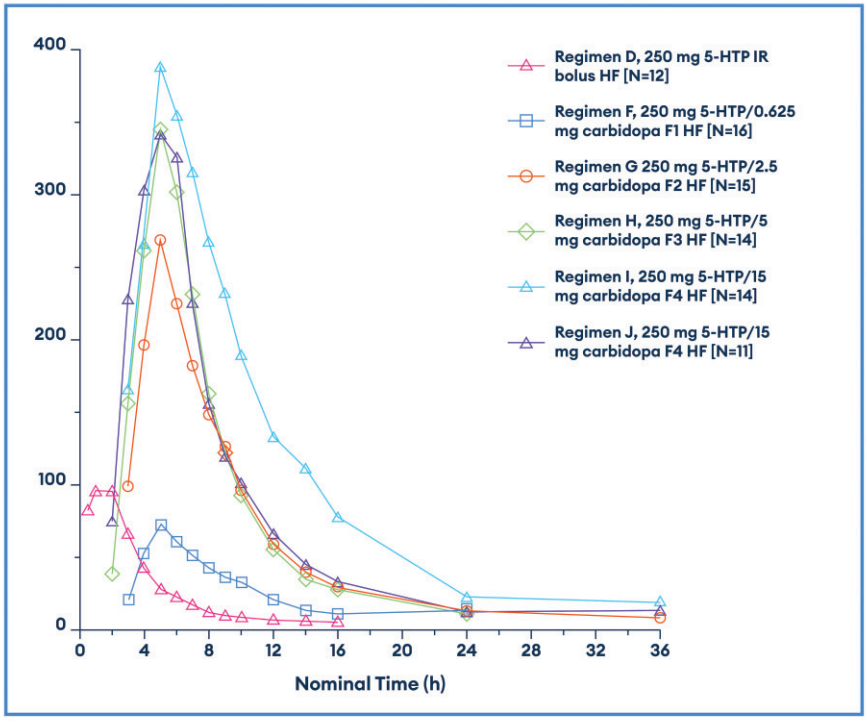


FIGURE 4

Figure 4: Mean plasma concentration-time profiles for 5-HTP when dosed with various EVX-101 GR prototype formulations



HF = high fat, MF = moderate fat

of 0.691 hours, and complete tablet disintegration at 18.501 hours. The *in vivo* imaging showed that adequate gastric retention was achieved from the GR formulation with the target 80 % release at 8.5 hours (Figure 3). Therefore, the release rate properties for 5-HTP (target 80 % release at 8,5 hours) were fixed for future GR prototypes and exposure modified by changing the carbidopa dose level. GR prototypes with 2.5 mg, 5 mg, and 15 mg carbidopa were also dosed to explore the effect of increasing dose levels on 5-HTP exposure (Figure 4). Exposure with all these dose levels increased 5-HTP exposure, and it was predicted (using modelling data) that these prototypes would meet or exceed the target ssCavg on multiple dosing. Carbidopa plasma levels were only above the LLOQ (1 ng/mL) for the 15 mg carbidopa dose. The GR properties (GE time) for all 4 GR prototype formulations dosed were consistent as assessed by scintigraphic imaging, and when a prototype was dosed with a moderate fat meal, gastric emptying time was reduced compared to when dosed with a high fat meal, as expected with the reduced calorie and fat content, however the gastric emptying properties were still acceptable for a BiD GR formulation dosing regimen.

SUMMARY

Translational Pharmaceutics allowed emerging clinical data to be used within a clinical study to validate PoC for a GR formulation, refine the carbidopa dose range, confirm MR release rate and GR properties, and identify an EVX-101 GR

tablet formulation to achieve the target profile of BiD dosing and ssC_{avg} >100 ng/mL. The optimized EVX-101 GR tablet formulation was safe and tolerated within the target ssC_{avg} range, and was recently used to successfully complete a single and multiple ascending dose study.[4] ◆

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BIOGRAPHIES

Dr. Jacob Jacobsen serves as CEO of Evecxia Therapeutics, a company he co-founded and spun out of at Duke University in 2019. Evecxia is dedicated to realizing the therapeutic potential of Serotonin Synthesis Amplification, a novel pharmacology for the treatment of psychiatric disorders. Prior to joining Evecxia, he was a scientist at Duke University and Duke-National University Singapore, where he was the driver of a cross-disciplinary team executing seminal research on Serotonin Synthesis Amplification. He also executed several basic and applied neuroscience projects that resulted in multiple first and co-author publications in journals of repute. Prior to Duke, he spent 8 years in pharma-biotech in Copenhagen, Denmark, ie, NeuroSearch and Lundbeck, where he executed drug discovery and target validation projects in preclinical models. He is well-published, including in the highest-ranking journals in the field of Psychiatry, and is an inventor on all Evecxia issued and pending patents. He earned his PhD in Neuropharmacology and MS in human biology from the University of Copenhagen.

Dr. Bret Berner has 47 years of industrial experience in drug delivery. After earning his PhD in Neurosciences/Physical Chemistry at UCLA, he joined Procter & Gamble Co. studying surfactants, diffusion, and skin permeation. He was Director, Basic Pharmaceutics Research at Ciba-Geigy, followed by Vice President, Development, at Cygnus Therapeutics, and then Chief Scientific Officer at Depomed. For over 15 years, he has been a pharmaceutical consultant in drug delivery, formulation, and pharmacokinetics. He holds over 70 US patents, authored more than 80 publications, and edited 3 books on drug delivery.

Dr. Vanessa Zann has over twenty-five years industry experience providing expert biopharmaceutic support to drug discovery, early drug development and clinical program design. Vanessa holds a PhD in Pharmaceutical Science from Aston University, and completed postdoctoral research in buccal transport, before joining AstraZeneca as a permeability expert in the Pharmaceutical Development department, leading the global Caco-2 facility and selection of new chemical entities with appropriate biopharmaceutical properties. Since joining Quotient Sciences in 2012, Vanessa has provided study design and scientific leadership to over 100 clinical pharmacology and drug product optimization studies across a wide range of applications including first-in-human, drug-drug interaction and development and optimization of solubility enhanced and modified release formulations. She led the implementation of modelling and simulation services and application of *in-vitro* characterization strategies to Quotients development programs.

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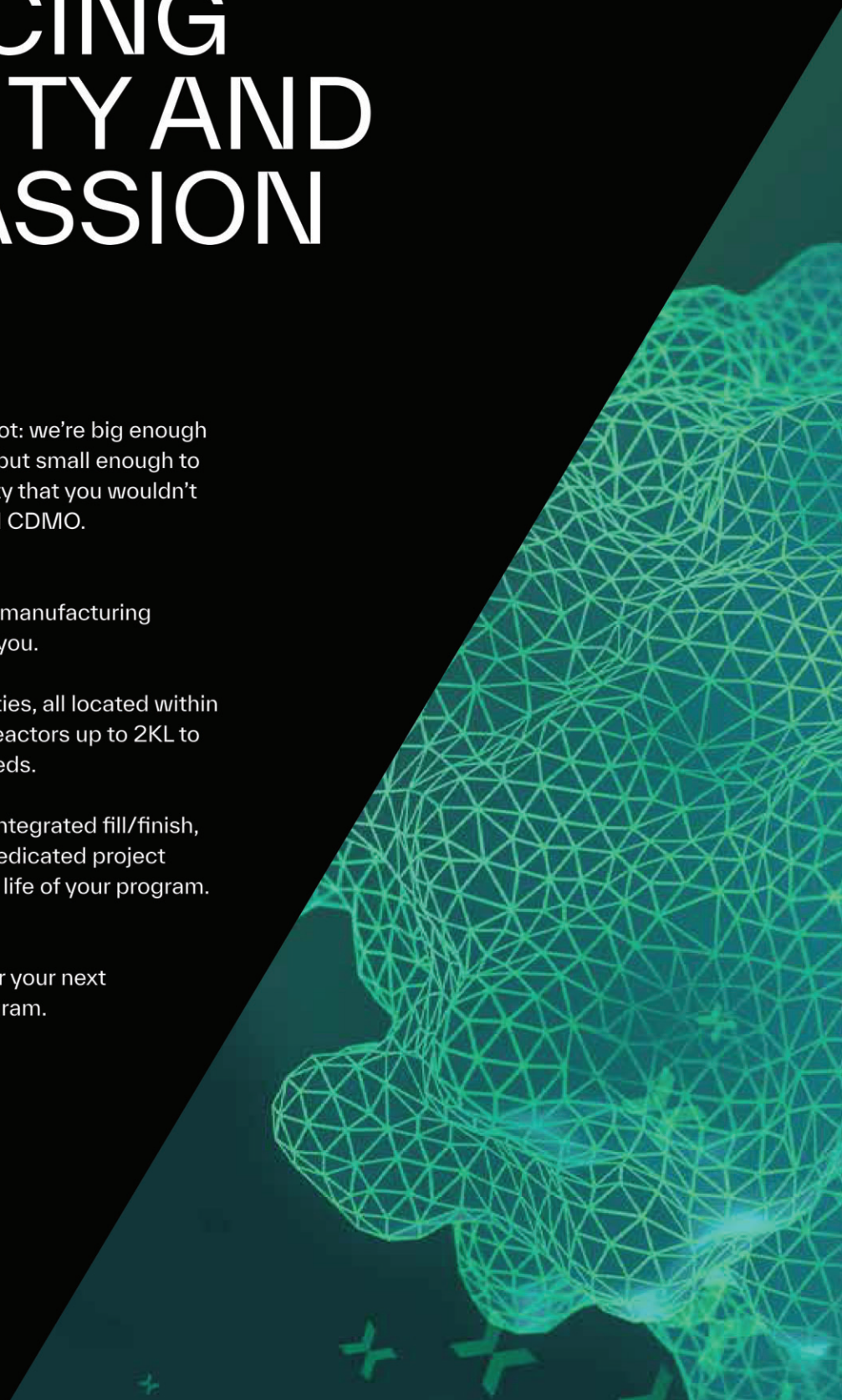


RADIOLIGAND THERAPIES

Affibody Molecules: A Versatile Approach to Radiopharma

By: Fredrik Frejd

INTRODUCTION

Radiopharmaceuticals are therapeutic compounds that contain a radioactive isotope used for the diagnosis, imaging, or treatment of diseases. The role of radiotherapy in precision oncology is already well established in tumor types, such as prostate cancer and neuroendocrine tumors. There are now emerging studies on the application of radiopharma in other cancer types, including metastatic breast cancer.

Following initial attempts to address radiopharma using full-size monoclonal antibodies (mAbs), recent advances in the radiopharma field have predominantly focused on peptides. These significantly smaller molecules can penetrate deep into solid tumors and allow more efficient internalization into cells. They also offer lower immunogenicity, easier chemical modification, speedier diagnostics, and changed non-target toxicity.

However, with these advances have come challenges, such as difficulty generating potent binders to a broader range of targets and the rapid excretion rate that requires very high amounts of radioactivity to be used since most of it misses the tumor and is excreted directly via the kidney. Affibody molecules (first described in 1997) are versatile molecules significantly smaller than MAbs that offer increased stability compared to peptides. They are also highly customizable, allowing increased specificity in a range of applications.

Swedish biotech Affibody AB is a pioneer in the field with decades of innovation in Affibody molecule discovery and engineering. It is developing next- generation Radioligand Therapies (RLTs) designed to deliver highly selective tumor targeting across a wide range of cancers and is advancing a novel pipeline focused on oncology indications with high unmet medical need.

Affibody's lead RLT candidate, ABY-271, is currently being evaluated in a first-in-human clinical study in HER2 positive metastatic breast cancer. This targets a novel epitope (a specific small region on an antigen) compared to concurrent therapies. Additional key areas of interest for Affibody's RLT pipeline are advanced gastroesophageal adenocarcinoma (GEAC), non-small cell lung cancer, triple negative breast cancer, and pancreatic ductal adenocarcinoma.

THE DEVELOPMENT OF RADIOPHARMA & THERANOSTICS

Theranostics combines therapy and diagnostics, typically combining targeted radioactive agents that first locate cancers with imaging and then delivering treatment directly to the site. It has been described as a "smart missile" that finds specific cells with a diagnostic tracer, then uses a therapeutic isotope to destroy them.

Throughout the past few years, the use of radiotherapy and theranostics in precision oncology has received significant renewed interest. Modern radiotherapy has changed from a "one-size-fits-all" treatment, into highly personalized therapy targeting specific biological mechanisms, pathways, or molecules. It can also integrate advanced imaging, AI, and systemic therapies. This allows radiation to be delivered with extreme accuracy, reducing damage to healthy tissue while increasing the effective dose to the tumor.

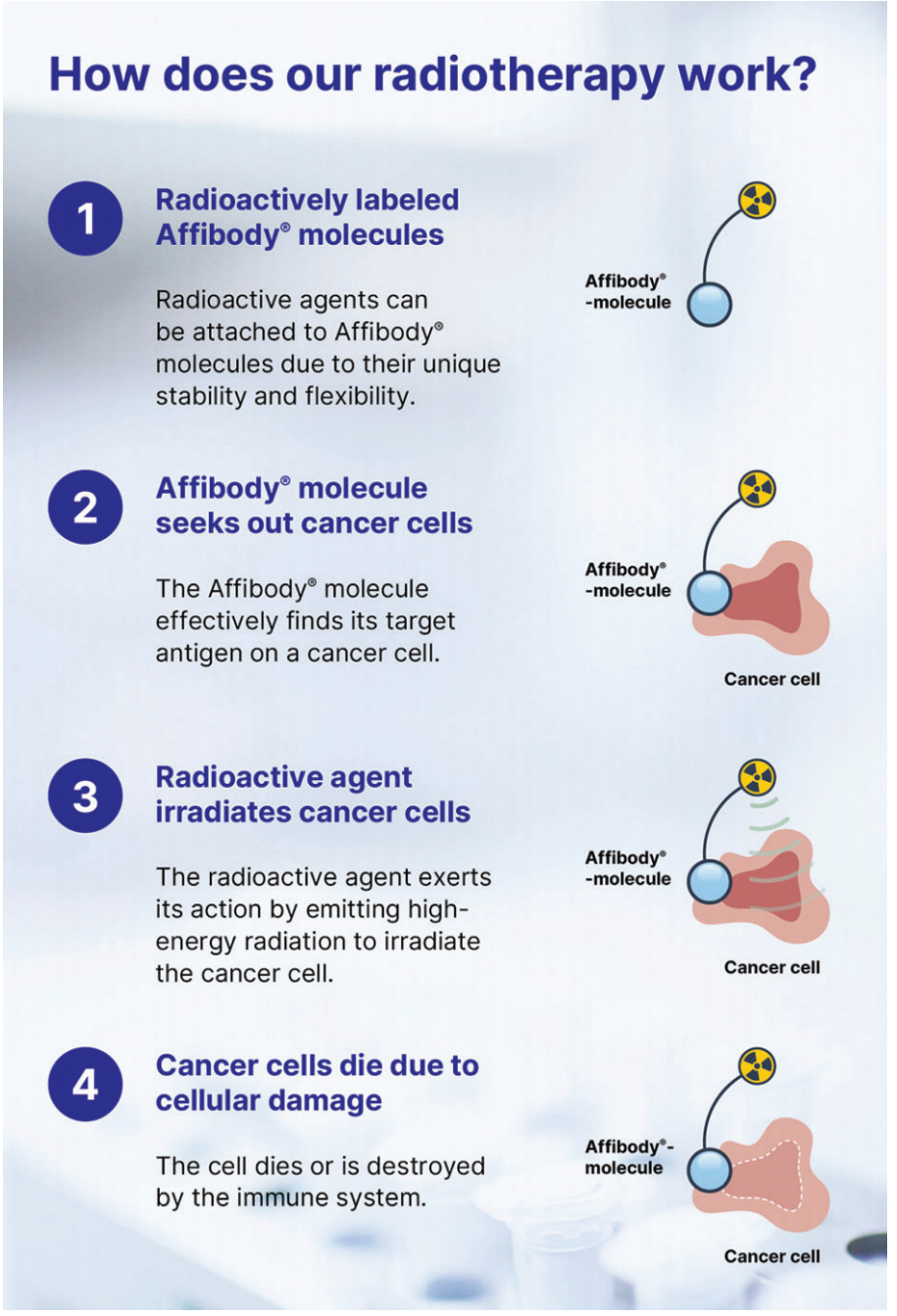
THE USE OF RLTS FOR THE TREATMENT OF METASTATIC BREAST CANCER

Breast cancers are responsible for the deaths of over 40,000 women each year, and this figure has not changed significantly in 20 years. HER2 is a growth receptor involved in many breast cancers. There is an obvious need for continued exploration to discover effective treatments, highlighting a clear pathway for the application of other tumor therapies.

Radioligand therapy (RLT) is a targeted, systemic cancer treatment combining a radioisotope with a molecule (ligand) that binds to specific cancer cells to destroy them with radiation from within. It is regularly used in conjunction with radioligand imaging to form a theranostic approach – where metastatic cancers can be developed and treated with the same targeting molecule, often with PET or SPECT scanners.

While some radioligand therapies have already received regulatory approval for the treatment of neuroendocrine and prostatic tumors, none have yet been approved for HER2 cancers. Here, other compounds, such as antibody drug conjugates (ADCs), are currently used; for example, Kadcyla (trastuzumab emtasine) and Enhertu (trastuzumab deruxtecan) with dozens more in development.[1]

The RLTs available for use in other tumors have shown blockbuster successes, emphasizing the opportunity for development across the board. These include Novartis' peptide bound Lutathera (lutetium Lu 177 dotatate) and Pluvicto (lutetium Lu 177 vipivotide tetraxetan), which are expected to have achieved a growth rate of over 10 times by 2031 to more than $6 billion. This is driven by strong clinical evidence, as Lutathera has demonstrated a reduced risk of disease progression or death in 72% in certain patients as a first line therapy.[2]



THE DISCOVERY OF AFFIBODY MOLECULES

Affibody molecules were first described in 1997 in Nature Biotechnology as small (6.5 kilodaltons) robust three-helical protein scaffolds. By substituting different amino acids on two of the three helixes, researchers at Sweden's KTH Royal Institute of Technology created a large library consisting of more than 10 billion Affibody® molecules, all with unique binding sites, from which binders to given targets are selected. Using Affibody's patented platform technology, the molecules can be engineered for specific properties, such as resilience, or for specific uses, including conjugation to toxic mole-

cules and fusion to protein modules.

These molecules immediately made themselves known as incredibly robust, lending their use to all areas of biotech; for instance, in a hot start PCR kit, where they can withstand multiple heat cycles.[3] Compared to antibodies, they are also more practical and less costly to produce as there is no need for antigen immunization and lengthy mammalian cell line engineering and production.[4]

The proprietary Affibody platform has now been clinically validated with more than 1,300 subjects and has demonstrated safety and efficacy for more than 3 years of continuous dosing.

ADVANTAGES OF AFFIBODY MOLECULES OVER ANTIBODIES & PEPTIDES

Affibody molecules are known as a class of antibody mimetics – sitting between antibodies and peptides, Affibody molecules are engineered to co-opt the advantages of both. Having a structured target binding surface area at the same size as a typical antibody, the ability for very high affinity and selectivity binding is much greater than that of most peptides that have a more limited target space. The small size of Affibody molecules (1/20th that of antibodies) allows similar tissue penetration to peptides and enables rapid clearance through the bloodstream, which minimizes non-target organ uptake and rapidly produce high tumor to non-target tissue contrast, which is a major limitation of antibodies. Increased speed due to the small size allows faster imaging; following administration, images can be obtained in mere hours as opposed to days, quickly identifying patients who are likely to respond to treatment.

The structure of Affibody molecules allows for significant modification, and Affibody has created a library of tens of billions of molecules with unique binding sites enabling a broad target space. The flexibility they have created means alterations can be made for specific applications and radioisotopes. The molecules are also more predictable than peptides with behaviors remaining consistent between different molecules allowing for systematic optimization. Rather than trying to make an existing structure work, Affibody can create their own molecule specifically.

The leading Affibody radioligand has been engineered to target a different epitope compared to traditional HER2 treatments. This enables a multimodal approach that can detect and treat patients with low target-expression in collaboration with diagnostic companion tools, or those that have become resistant to more conventional therapies and makes it possible for combination with approved HER2 products.

COMPANY MANUFACTURE & FACILITIES

Affibody has more than 2 decades of experience in the sector. There have been more than 1,000 publications of which more than 400 have been specific to radiopharmaceuticals.

Affibody's pipeline also includes immunology partnership programs in addition to its RLT work. Its leading drug candidate in this field is izokibep, which is currently in Phase 3. With wide applications for indications, such as psoriatic arthritis and hidradenitis suppurativa, izokibep addresses autoimmune diseases driven by the protein IL-17 and is best-in-class with superior selectivity and blocking affinity 10 to 100 times stronger than current leading equivalents.

Affibody has a wealth of expertise, with more than 60 full-time employees forming a team of multidisciplinary experts to create a strong driving force. It also has a long-standing collaboration with Uppsala University, which provides unique access to world-class RLT laboratories, animal facilities, and radiochemistry expertise.

CURRENT DIRECTION

Taking an active approach to challenges of regulatory duality as both radioactive substances and drugs, Affibody has been in discussion with regulators across Europe and the US and engaged in extensive pre-clinical work.

Other traditionally significant practical hurdles, such as manufacturing and transport, are diminished by the stability of their molecules, and existing networks are being utilized to create efficient pathways. The reversible albumin binding has multiple uses and is well validated in other areas within the field; using an endogenous protein carrier, which is widely distributed within the body allows an extended half-life and greater tumor exposure, while promoting reduced renal clearance, an approach comparatively underutilized within radiopharmaceuticals.

Potential risks to human health have been major factors in the commercial poor-performance of early RLTs.[5] Concerns over radiation-induced myelodysplasia (MDS) and acute myeloid leukemia (AML) have been cited, despite these not being found to be significantly different to

standard chemotherapeutic agents at the time. The recent successes of peptide bound RLTs exemplify the appreciation of alternatives that can offer improved tissue distribution and therefore reduced cumulative doses of radiation.

Despite early concerns over radiation, there are unique benefits that cannot be ignored. As treatment progresses, its potential to destroy tumor sites remains strong and resistance against treatment is unlikely to develop due to direct DNA damage. This coupled with the unique epitope paves the way for an independent position within the clinical pathway without displacing concomitant treatments.

SIGNIFICANT CLINICAL EVIDENCE

These critical advantages are not just in the scientific model, but have also been demonstrated in preclinical trials, with biodistribution studies using mice bearing HER2-expressing SKOV-3 xenografts.

Affibody's leading asset, ABY-271, showed accumulation in tumors exceeding that in all other organs and with balanced clearance to provide an increased safety profile. Histopathological evaluation cemented this supporting progression to first-in-human trials.

Therapeutic effects were likewise promising. Median survival was extended compared to both controls or trastuzumab (a standard HER2-targeted therapy) with just a single dose of 21 MBq ABY-271, and combination with trastuzumab increased the rate of complete tumor remissions even further.

Furthermore, preclinical results allow us to predict that doses received at the tumor sites being both within the approved therapeutic range and clinically meaningful is achievable based off human dosimetry estimates and comparable to existing products.

In October 2025, Affibody announced it had dosed the first human patient in the first part of their open-label, two-part randomized Phase 1 clinical study with ABY-271 in HER2-positive metastatic breast cancer. In December 2025, promising initial results from the first cohort of patients was announced, demonstrating tumor targeting and a favorable safety profile with low uptake in kidneys and other critical organs.

KEY DEVELOPMENTS & A FUTURISTIC OUTLOOK

With successes in its early Phase 1 trial, Affibody decided in December 2025 to advance the Phase 1 clinical study to its second part, in which higher radioactivity levels will be evaluated. Advances and testing will allow the identification of ideal configurations and further safety evaluation to inform dose selections for future trials.

Developments, such as these aren't only relevant in the world of HER2 cancers or breast cancers but demonstrate and strengthen the promise of the Affibody molecule as a powerful technology for developing next-generation targeted radiotherapeutics.

The relative successes of recent RLTs compared to historical radioantibodies highlight the increased understanding and uptake of these therapies across the medical fields. As antibody therapies continue to excel in medical trials and prove their use, the sector is growing to support their development.

With its place within the treatment pathway where HER2-positive metastatic breast cancers may have become resistant to or are responding to other treatment options, ABY-271 is an encouraging avenue and may change outcomes significantly, offering new hope to patients. ◆

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BIOGRAPHY

Fredrik Frejd is Chief Scientific Officer at Affibody. He has more than 20 years of experience in biomedical research with expertise in tumor biology, biotechnological phage display, and therapeutic protein technique with antibody fragments, as well as artificial scaffold proteins. He is an adjunct Professor at the Department of Cancer Precision Medicine at Uppsala University. He is a Board Director of Mergus development AB, Akiram Therapeutics AB, Immuneed AB, and Deputy Board Director of Amylonix AB. He is also a member of Technische Universität Dresden Center for Molecular Bioengineering's scientific council.

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