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Weight Loss Click Bait

Why consumers need to be more aware of the dangers of buying semaglutide (and other medicines) online

Since its FDA approval in 2017, Novo Nordisk's blockbusters Ozempic and Wegovy have a made a habit of hitting news headlines. Both are now experiencing extreme shortages driven by unprecedented demand from consumers who see them as miracle drugs for weight loss. Semaglutide and other GLP-1 drugs are also being investigated as potential treatments for alcohol use disorder and smoking cessation, amongst other things, demonstrating the incredible versatility of this drug class.

Have the developers created a kind of one-shot "wonder drug"? Or did the demand for multifunctional solutions to first world problems originate from the romantic notion of finding happiness in the click of a link?

Either way, the huge demand for semaglutide has led (unsurprisingly) to an explosion in counterfeit products online. National and international health authorities have warned about the increasing prevalence of unlicensed Ozempic. And to demonstrate the point, researchers recently reported how they found more than 1,000 online pharmacies selling Ozempic – many of which were illegal (AR Ashraf et al., JAMA Network Open, 2024, DOI: 10.1001/jamanetworkopen.2024.28280). Test purchases revealed non-delivery scams, extra payment charges, and products containing low-purity semaglutide at levels well above the labeled amount.

What role do you think the pharma industry should be playing to help protect consumers from fakes? Let me know: rob.coker@texerepublishing.com.

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The Choice: To Be Cured or to Have Children?

Fertility support programs for gene therapy Medicare patients are being blocked in the US

Credit: Shutterstock.com

The conditioning required for some cell and gene therapy treatments can lead to fertility issues in both men and women. Vertex's Casgevy, for example, is approved as a potential cure for sickle cell disease and transfusion-dependent beta-thalassemia, but requires patients to receive chemotherapy to prepare for the gene therapy.

Thus there is the dilemma for patients: would you rather be cured or would you rather have biological children? It's also important to note that, although the long-term outcomes of Casgevy are very good, a cure is not guaranteed.

Understanding the dilemma, Vertex has developed a fertility preservation program to help patients that receive its gene therapy. Patients choose their own fertility providers and treatments as part of the program, but receive financial support from Vertex of up to $70,000.

However, it is not allowed to offer the program to patients on federal healthcare programs, such as Medicaid, without violating anti-kickback and beneficiary inducement statute laws. The laws, in theory, prevent pharma companies from offering renumeration or anything of value that may influence patients in government healthcare programs to use a certain drug.

Vertex previously sought an advisory opinion from the HHS Office of Inspector General (OIG) on whether its preservation program would be allowed, but received a negative opinion in January 2024. According to Vertex, OIG stated that the program "poses more than a low risk of fraud and abuse, and does not promote access to gene therapy care."

Vertex is now taking the issue to the courts. "Even though Medicaid and most other insurers already deny Americans with SCD or TDT fertility coverage, the federal government, through OIG's refusal to issue a favorable advisory opinion, has effectively prohibited those patients from receiving free fertility services from others – leaving them with the Hobson's choice between undergoing a potentially curative treatment or becoming biological parents," states the filing.

Vertex wants the court to allow its fertility program to be offered to Medicare patients – without risking enforcement action – and is also demanding the OIG issue a written advisory opinion. The OIG opinion in January 2024 was delivered orally and despite repeated requests Vertex has not received a written opinion – something the company describes as "delaying tactics" in its lawsuit. A written opinion is supposed to be provided within 60 days of receipt of the request.

Vertex is not the only gene therapy company running into issues when it comes to helping patients with their fertility. Bluebird bio offers a handful of gene therapies that also require chemotherapy. It sought advice from OIG on whether its own fertility support program would run afoul of anti-kickback laws. OIG's response was that it could – saying that it did not have the necessary data to determine the risk of fraud and abuse. Essentially, the program could be viewed as remuneration to patients that would encourage them to buy bluebird's therapy.

Vertex argues that its fertility program should not trigger anti-kickback and beneficiary inducement statute laws, claiming that the laws should criminalize "corrupt quid-pro-quo transactions, like a bribe or kickback, in which remuneration is sought or offered to corruptly skew medical decision making."

The lawsuit goes on to emphasize that the laws should not "prohibit assistance like the Fertility Preservation Program because such assistance merely removes a financial or medical barrier to care and thereby allows patients to receive appropriately prescribed medical treatment … the Fertility Preservation Program would not improperly skew medical decision-making or provide an improper inducement to prescribe the Product. Nor would patients choose to undergo treatment with CASGEVY in exchange for the Fertility Preservation Program. Rather, doctors will prescribe CASGEVY, and patients will choose to undergo treatment with CASGEVY, because it offers a potential cure for a debilitating ultimately fatal disease."

Blockbusters

At the BIO 2024 show in San Diego, BrevisRefero's booth caught our attention with this pharma manufacturing facility built of Lego bricks. The Lego facility is based on the CDMO Biodextris.

QUOTE *of the month*

"The EMA's decision will come as a disappointment to many, but there are reasons to remain hopeful. Lecanemab has shown that it is possible to slow down disease progression, and research does work. Now we need to ramp up our efforts to discover new and safer treatments."

Tara Spires-Jones, President of the British Neuroscience Association; Director of the Centre for Brain Science Discovery at the University of Edinburgh; and Group Leader at the UK Dementia Research Institute

EMA: No to Lecanemab

Lecanemab is refused marketing authorization by the European Medicines Agency

Despite being approved in the US, Japan, South Korea, and a handful of other countries, lecanemab (Leqembi) has been refused marketing authorization by the EMA for the treatment of Alzheimer's because the agency does not believe that the benefits of the treatment outweigh the risks.

"EMA's human medicines committee, the CHMP, considered that the observed effect of Leqembi on delaying cognitive decline does not counterbalance the risk of serious adverse events associated with the medicine," said a statement from the agency.

Perhaps the most serious side effect associated with the medicine is the potential for swelling and bleeding in the brain. The CHMP added that the risk of amyloid-related imaging abnormalities seemed higher in people with a certain gene – which also makes them more susceptible to Alzheimer's disease and more likely to be eligible for treatment with lecanemab.

Eisai says it will seek a re-examination of the opinion.

Respecting the Role of the CDMO in the mRNA Era

Few would disagree that mRNA therapeutics are a hot development trend, but with expertise and experience in short supply, who are the unsung heroes?

By Eunseo Lee, Lead specialist in mRNA manufacturing at Samsung Biologics

Not that many years ago, mRNA-based therapeutics were relatively unheard of – with little investment and slow progress in the field. Although innovations in molecular biology and genetic engineering enabled mRNA to be researched as a therapeutic tool, it wasn't until the onset of the COVID-19 pandemic that the mRNA-based medicine field rapidly expanded. As a result, the global mRNA therapeutics market was valued at $33.60 billion in 2021 and is expected to reach $38.15 billion by 2030 (1).

Vaccines that rely on mRNA technologies have the potential to offer inexpensive, rapid, cost-effective, and scalable manufacturing. Indeed, the ability to synthesize mRNA products using relatively simple in vitro transcription (IVT) reactions to provide high yields in a small GMP facility footprint were significant benefits during the global rollout of COVID-19 vaccines.

Post-pandemic, the biopharma industry continues to recognize the therapeutic possibilities of mRNA technologies. Offering ease of editing, the customizable nature of mRNA therapeutics allows for precise targeting of biological pathways. The versatility of this drug modality also presents biopharmaceutical companies with the opportunity to develop tailored medicines for a wide range of therapeutic areas in the form of a "plug-and-play" platform – one that is easily edited with minimal effort. Currently, over 300 mRNA therapies are in development – targeting everything from rare diseases to cancers and metabolic disorders (2).

Evidently, mRNA technologies are paving the way towards a new era of biotherapeutics as a customizable treatment option for a wide variety of indications. However, to realize its potential and ensure efficient delivery on both a large and small scale, mRNA drug developers and manufacturers must overcome numerous hurdles.

"CDMOs had to quickly adapt their facilities, and expand and optimize cold chain capabilities to suit the temperature-sensitive nature of mRNA molecules."

The role of the CDMO

CDMOs were essential during the COVID-19 pandemic – and will remain important partners for companies looking to develop and manufacture new mRNA vaccines and therapeutics. Until the onset of the pandemic, few manufacturers were able to support mRNA therapeutics, so it fell to CDMOs to take on the challenges of working with this widely unfamiliar technology. CDMOs had to quickly adapt their facilities, and expand and optimize cold chain capabilities to suit the temperature-sensitive nature of mRNA molecules. It was also important to

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determine how lipid nanoparticles (LNPs) used in mRNA encapsulation would behave and how processing conditions would impact drug product characteristics. Determining the behavior of LNPs was particularly challenging because, pre-pandemic, manufacturers predominantly worked with water-like solutions.

Right now, there is little expertise in mRNA manufacturing outside of CDMOs, and services are in high demand because prior experience in mRNA development and manufacturing can help expedite timelines. CDMOs have also been applying learnings gained throughout the pandemic to implement management systems to safeguard and secure supply chains, including securing scarce materials for IVT and LNP production – again, a valuable service.

The voice of experience is also important when it comes to regulatory compliance. As mRNA therapeutics are an emerging technology, regulatory bodies have been under pressure to quickly react to new information, ensuring that guidance reflects the growing understanding in the field. As a result, there is still some discrepancy in regulatory guidance, and critical quality attributes (CQAs) are currently not fully defined. Preventing potential setbacks that could come as a result of these regulatory discrepancies requires manufacturers to have the in-depth expertise needed to suitably define CQAs, as well as robust analytical methods to ensure CQAs are met.

Pushing facilities even further

To effectively provide mRNA therapeutics on both a large and small scale and guide mRNA production through to a commercially viable product, CDMOs will need to evolve further and to ensure their facilities are state of the art.

There are now CDMOs with facilities fully equipped with the necessary capabilities to successfully support mRNA production, from plasmid (pDNA) linearization to IVT, purification and LNP formulation. However, the demand for flexibility in mRNA therapeutic production continues.

"Throughout the pandemic, successfully delivering mRNA vaccines to the global population to limit the impact on patient health relied heavily on the ability of CDMOs to shorten timelines."

In contrast with the global demand for the large-scale manufacturing of COVID-19 vaccines seen in 2020, there is now a growing need for small-batch mRNA therapeutic production. Personalized medicines, targeting chronic diseases and different cancer types, are now a predominant driving force behind the growing mRNA therapeutics market (3). This trend puts CDMOs under pressure to provide GMP manufacturing for clinical and commercial from small to large scale and from IVT pDNA linearization up to the finished product.

There are also challenges stemming from increasing demand for timeline acceleration. Throughout the pandemic, successfully delivering mRNA vaccines to the global population to limit the impact on patient health relied heavily on the ability of CDMOs to shorten timelines. To achieve streamlined timelines, manufacturers had to ensure all aspects of development and manufacturing were highly optimized. The pressure to deliver mRNA therapeutics to key milestones on the journey to market has not wavered since. Patients still need critical therapies delivered as soon as possible to treat diseases and improve their quality of life. Financers also wish to see a rapid return on their investment in the drug product.

With a growing number of mRNA therapeutics in pre-clinical and phase I stages, many biotechs are focused on streamlining timelines to produce material needed for testing and clinical trials to gather data needed to progress to the next key milestones. To meet the need for accelerated development pathways, CDMOs must continue to increase efficiency in existing processes to enable faster delivery while maintaining quality. And that's why you'll see so many CDMOs offering the so-called "one-stop-shop" approach; end-to-end mRNA manufacturing capabilities from process development to fill and finish can help minimize the need for lengthy tech transfer steps, which helps reduce timelines.

Going forward, CDMOs must continue to demonstrate flexibility in response to changes in the market and adapt to enable accelerated timelines. By leveraging their previous experience, expertise, and carefully designed facilities, such organizations will be poised to help meet the ever growing demand for both large- and small-scale production of mRNA-based medicines.

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A Platform for Progress

Miltenyi Biotec on accelerating IND submissions with a platform CMC approach

Exemplary clinical results for patients with severe diseases herald cell and gene therapies as an answer where treatment options have not been available with other treatment modalities. Many more unmet needs remain, but getting new trials off the ground – or even submitting an investigational new drug (IND) application – can be challenging.

Here, Ian Gaudet, Chief Scientific Director for Miltenyi Bioindustry, Miltenyi Biotec's CDMO services, discusses the issues that are slowing drug developers down and explores what approaches can accelerate their mission.

What is the main obstacle in the cell and gene space?

In a word: access. There is still a huge mismatch between the number of patients who need these therapies and the ability to create them in a timely manner. There is clearly work to do to make these therapies easier to manufacture, but we are also seeing many great ideas being proposed by the research community, including new targets, new approaches to CAR T cells, and new constructs. We cannot ignore that the global macroeconomic situation is tough; the funding needed to get innovations into the clinic is extremely hard to come by. Many developers are simply unable to afford the time and costs necessary to generate the data that will allow further investment.

What about in the regulatory landscape?

The last few years have seen a concerted effort by regulatory agencies to generate guidance documents that are specific to cell and gene therapy. In the past, one of the challenges in achieving IND approval was the lack of specific guidance. Everyone had to figure out how to build regulatory submissions based on information crafted for other modalities.

Developers will be able to move more rapidly now that regulators are invested in the space. One recent FDA draft guidance document [*https://bit.ly/4fAAWdR]* explains how platform technologies can be used to accelerate clinical and commercial development for cell and gene therapies. If developers can leverage existing platforms with regulatory precedent, it will reduce the work required to get a phase I trial started.

What exactly does "Platform CMC" mean – and what are the benefits?

One major challenge with getting a new trial started is the IND submission and the data that needs to be included. Platform CMC (chemistry, manufacturing, and controls) essentially minimizes the *de novo* work needed to demonstrate safety, as well as control of the manufacturing process. But it is a new concept for cell and gene therapy. In other modalities, there is greater adoption of the platform CMC approach because there are sufficient existing regulatory submissions that new therapies can leverage or "piggyback" onto from a regulatory perspective.

The cell therapy space has less precedent to leverage such approaches, but we're seeing a shift in that mentality given the number of commercially approved products and technologies. If we can bring all the clinical and commercial success "pieces" together into a bigger picture, it will be easier for customers to leverage what has already been filed. The upside? Much more cost-effective and rapid approval of early phase therapies.

How does Miltenyi Biotec support customers with (platform) CMC?

Most new therapies in development fail. Helping customers get to phase I faster, find a successful asset faster, and fail faster on assets that don't have a commercial future – preferably without having to spend multiple millions of dollars and several years getting that trial started – is key.

At Miltenyi Bioindustry, we are developing end-to-end CMC support – or platform CMC – to help enable a paradigm shift in how cell and gene therapies are brought to the clinic. Developers need to show regulators that their viral vector is manufactured in a safe and consistent manner and demonstrate that the vector can be successfully integrated with the cell source and manufactured into the final product in a controlled manner.

Miltenyi Bioindustry has a number of components that can expedite the journey to an IND-enabling data package. For customers using a Miltenyi Bioindustry lentiviral vector,master file support enables them to use the vectors in a clinical trial with minimal additional development or CMC work required; after all, the FDA has seen our vectors many times! We would also like to expand

upon this approach to include not just the vector, but the cell manufacturing, testing, and release to enable developers to simply point to a master file package and have the FDA (hopefully) accept IND submissions in a much more rapid fashion.

In fact, Miltenyi Bioindustry offers master file support for many manufacturing technologies, as well as our consumables, reagents, and software. Now, our focus is on augmenting master files or generating new master files that include analytical technologies, manufacturing workflows, and facility designs to support significant improvement in the time and effort needed to achieve approval.

Are you essentially talking about a plug and play approach?
Yes and no. The term "plug and play" is often used as a buzzword in the industry and typically refers to technologies that are fit for purpose for manufacturing and characterization; however, the onus is often on the developer to demonstrate that those technologies are, indeed, fit for purpose in their IND application – and that is time consuming. Today, we have a sufficient body of data on how CAR Ts are produced, so there is no good reason why we need to keep doing the same work for every new therapy – particularly when developers are leveraging manufacturing platforms that have regulatory precedent. And that's what Miltenyi Bioindustry offers. In this case, the term "plug and play" is properly fulfilled!

What are the dangers facing developers who are not moving fast enough?
Companies won't be able to survive financially if they cannot generate enough clinical data to get more funding. Current expectations from the investment community are high, with good clinical data being a prerequisite to receiving the next rounds of funding. If customers are delayed – in getting an IND, for example – they may fall at an unexpectedly early hurdle.

The technical and biological risks have always been present in R&D, but today's focus on speed to clinical data is a real danger for new developers – even with good assets that have clinical promise.

What sets Miltenyi Biotec's solutions apart from its competitors?
Miltenyi Biotec occupies a genuinely unique position. A customer using our manufacturing technologies, our analytical technologies, and our regulatory precedent will benefit from a true platform approach.

Usually, companies will use a collection of different components from different suppliers: vector from supplier A; manufacturing technology from supplier B; bespoke analytics from a collection of other manufacturers, all wrapped up together at a CMO and used to generate a data package. Customers that work with Miltenyi Bioindustry can obtain everything needed to produce a CAR T, including the raw materials, production equipment, knowhow, and regulatory support.

It seems like platform CMC could usher in a new era in advanced therapeutics…
By giving start-ups and academic groups with limited funding an easier path to get therapies into the clinic – I would strongly agree with this statement. A true platform-based CMC approach could be a paradigm shift for early stage developers whose new and exciting therapy may otherwise not see the light of day.

The current economic environment has undoubtedly affected innovation. There is much less funding available, as well as tighter scrutiny on what gets funded. For those developers that want their therapy to show clinical promise, working with Miltenyi Biotec gives them access to a platform CMC approach in a truly "plug and play" fashion. All that is needed is the transgene of interest – and we can take care of the rest.

The best approach to accelerating progress is to remove unnecessary time and hard work from the equation. We can do this by using what we've already invested in for the vector, manufacturing platform, reagents, and manufacturing milieu to allow new developers to do less work, spend less money, and generate IND enabling data packages in less time.

Platform CMC is an enabling technology that Miltenyi Biotec will rely upon to refine guidance, provide expertise, and enable a standard approach to cell and gene therapy development.

Miltenyi Biotec

Cancer Vaccines: *Activate the Immunosoldiers*

What's all this talk of cancer vaccines? We find out how they work – and how mRNA has boosted the field – with the help of five experts: Myriam Mendila, Justin Duckworth, Nicolas Poirier, Paul-Peter Tak, and Jens Bjørheim.

What successes have been seen so far with cancer vaccines?

Jens Bjørheim: The idea behind therapeutic cancer vaccines is that they will be administered post-diagnosis to direct the individual's own immune system to fight cancer. Early on, researchers uncovered the remarkable potential of T cells to recognize and kill cancer cells, and that such T cells could be expanded using different vaccination technologies. Some of these vaccines generated a good immune response towards a tumor, but the clinical benefit for patients was disappointingly modest.

Over the last decade, the development of therapeutic cancer vaccines has seen a new dawn, fuelled by the combination of opportunities that followed the introduction of checkpoint inhibitors (CPIs). Comprehensive research has elucidated the restriction of T cells imposed by the immune checkpoints, representing a likely cause of the earlier failure of cancer vaccines. The CPI combination strategy is therefore likely to boost the T cell responses elicited by vaccination, which may in turn provide greater benefit to patients. Several clinical trials with combination therapies have demonstrated promising clinical efficacy in different cancer indications, and more interesting trials will read out soon.

Myriam Mendila: With peptide-based vaccines, most phase III studies have not shown significant benefit for patients. In the past couple of years, however, we've seen encouraging data emerging for cancer vaccines based on mRNA technology. mRNA-based cancer vaccines have been tested in different clinical settings, and in early or metastatic disease settings in different cancer types, either as monotherapy or combined with PD-1 or PD-L1 antibodies. Data have shown interesting and long-lasting immunological responses in patients with advanced cancers.

More recently, we have seen the first positive data from a randomized phase II trial evaluating an mRNA based cancer vaccine in patients with early-stage melanoma (Moderna's 4157), where the mRNA vaccine in combination with an anti-PD-1 antibody reduced risk of recurrence in patients by more than 40 percent compared with treatment with the anti-PD-1 antibody alone. These early data, though often in small patient groups, raise hopes and expectations that we will be able to crack the challenges of cancer vaccines with mRNA technology in the not-so far future.

Nicolas Poirier: There are now at least three studies in three different indications with three different cancer vaccines that have reported promising results.

We've published positive results with a peptide-based cancer vaccine in monotherapy in a randomized phase III trial in metastatic and advanced lung cancer patients (B Besse et al., Annals of Oncology, 2023). Our data showed that in patients in acquired resistance to anti-PD(L)1, the cancer vaccine in monotherapy significantly improved overall-survival, reduced the risk of death by 41 percent in the first year, displayed three-fold fewer adverse events, and improved patients' quality of life, as compared to chemotherapy. These positive results, for the first time in a randomized trial and in monotherapy, follow the positive phase II study that Moderna reported at the end of 2022 with a personalized cancer vaccine used in combination with anti-PD1 in adjuvant melanoma patients, where they reported a reduction of the risk of tumor recurrence and death by 45 percent. In mid-2023, BioNTech reported promising phase I results with a personalized cancer vaccine used in combination in adjuvant pancreatic cancer patients.

Justin Duckworth: Though there has been extraordinary success seen in the field of prophylactic vaccination, efforts to therapeutically vaccinate a patient when an infection or malignancy are established, often known as "post-exposure" vaccination, have yet to be successful. This was vividly demonstrated in the COVID-19 pandemic, where effective preventive vaccines were not effective in boosting natural immunity if an infection was already present. We must address this weakness by bringing vaccine-induced immunity closer towards the response our natural immune system mounts when it regularly deals with threats.

Cancer vaccines represent perhaps the hardest challenge in the therapeutic vaccine field. Despite decades of effort, Dendreon's Provenge in prostate cancer represents the only example of a therapeutic cancer vaccine that has received US marketing approval. What is striking about Provenge is that it is a hybrid of vaccination and cell therapy, attempting to target the vaccination directly to controlling cells of the immune network (dendritic cells). Whilst traditional vaccination relies on indirect recruitment of the cells governing one's immune system, the concept of "cellular vaccination," in which those cells are more directly engaged, has long intrigued immune therapists. Although successfully approved, Provenge still suffers from serious limitations around efficacy and cost because of how the therapy is manufactured.

The advent of mRNA vaccines has dramatically re-energized the field of anti-microbial and anti-cancer vaccinations. To enhance the potency of this approach, considerable efforts have been made to overcome the challenges of targeting malignant cells, and trials have been performed in combination with checkpoint inhibitors to alleviate the immune suppressive tumor microenvironment.

For those less familiar with this field, how exactly do vaccines prevent and/or treat cancer?

Paul-Peter Tak: Two antiviral preventative vaccines have been shown to decrease the risk of cancer. The first is the human

papillomavirus (HPV) vaccine, which prevents acquisition of the virus that can lead to cancers of the oropharynx, cervix, and anogenital region. The second is the hepatitis B vaccine, which prevents acquisition of hepatitis B, whose infection is associated with development of liver hepatocellular carcinoma. Most cancers, however, are driven by other causes, including genetic predispositions in the host, and/or exposure to carcinogens in the environment. The goal of therapeutic vaccination is to teach the patient's immune system to recognize and eliminate tumor cells. Key challenges, however, are avoidance of clonal escape by tumor cells and the impact of the immunosuppressive tumor microenvironment. Induction of a broad immune response against multiple tumor-associated antigens and injection into the tumor while enhancing local inflammation may help to overcome the issues.

MM: Cancer is driven by alterations in the human genome. These genomic alterations accumulate over time and eventually lead to dysfunction of a cell in a way where a normal cell becomes a cancer cell that begins to replicate in an uncontrolled manner. Cancer cells should be recognized by the immune system as "foreign" in the same way the immune system recognizes pathogens, bacteria, and viruses, but often the immune system tolerates them.

With therapeutic cancer vaccines, the aim is to overcome this immune tolerance. The concept is similar to what we do with infectious disease vaccines. For example, an mRNA cancer vaccine encodes for antigens that are specific to cancer cells in patients. Antigen-presenting immune cells, as well as other cells in the body, are transfected with the mRNA and instructed to present the cancer antigens encoded by the mRNA to other immune cells. With that, the immune cells are activated and taught how to identify cancer cells as malignant and destroy them.

JB: As a normal cell develops into cancer cells and eventually tumors, the cancer cells become increasingly different from their healthy counterparts, representing an opportunity for the immune system to detect and kill the cancer cells. The most well-described differences that are potential targets for the immune system are genetic mutations and the presence of proteins that are otherwise repressed. A cancer vaccine can be produced using molecules that mimic these changes observed in the tumor. There are many ways (platforms) that can be used to generate such molecules that the T cells can react to. Common platforms include peptides or DNA and RNA vaccines that encode for sequences of amino acids alike those of the abnormal tumor. Specific T cells then react to these molecules and start to proliferate, searching for cancer cells that have the same mutated or abnormal proteins.

NP: Essentially, cancer vaccines re-educate our immune system by providing the tumor antigens that the immune system should recognize but currently tolerates. Cancer vaccines can hence form new T-cell "troops" that can patrol and detect cancer cells expressing those tumor antigens. After surgery, when cancer vaccines are used as an adjuvant, the trained lymphocytes

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can detect remaining tumor cells and eliminate them to avoid tumor recurrence. In metastatic and advanced cancer patients, T lymphocytes have died or are highly exhausted, in particular after immunotherapy resistance. The cancer vaccine helps form new and fresh immune cells.

JD: Therapeutic vaccination of cancer is one of the most ambitious goals in medicine. It seeks to cure cancer in the same way our natural immunity protects us for much of our lives against nascent malignant cells, by tapping into the extraordinary specificity and firepower of the immune network. Everyone's cancer is unique, making "one-size-fits-all" therapies challenging and crude by design. Cancer vaccines can be either generically targeted or personalized to a specific patient. The former can be expected to be less precise but with economic benefits.

Which cancers can be targeted with vaccines – and why?

NP: Our immune system is capable of eliminating tumor development as soon as it starts. When cancer sets in, it means tumor cells have avoided immune surveillance or hijacked immune regulatory mechanisms. In advanced cancers, some tumors are refractory to immunotherapy, which suggests that attacking the cancer with alternative immune-mediated mechanisms or technology is not the best option. However, most patients treated with immunotherapy will experience resistance after initial benefit. It means these types of tumors are immune-sensitive, but the immune response loses the first battle. If we could train new troops with a vaccine and send fresh immune cells to replace those that are dead or exhausted, then the immune response can once again lead the fight.

JB: In theory, vaccines can target all types of cancers. The fundamental principle is the immune system's capacity to recognize and fight abnormal cellular changes. As long as the immune system can recognize mutated or abnormal proteins, vaccines can potentially be a viable treatment modality for any form of the disease.

MM: I agree; in principle, any type of cancer could be targeted with an mRNA-based cancer vaccine. Genomic alterations causing the cancer lead to the expression of tumor-specific proteins – also called tumor specific antigens – in the cancer cell. The trick is to identify these antigens so they can be encoded on mRNA and used in a vaccine. When the mRNA is translated into the tumor-specific protein it encodes for, it teaches and enables the immune system to differentiate tumor cells from healthy cells, so it can commence a targeted defence.

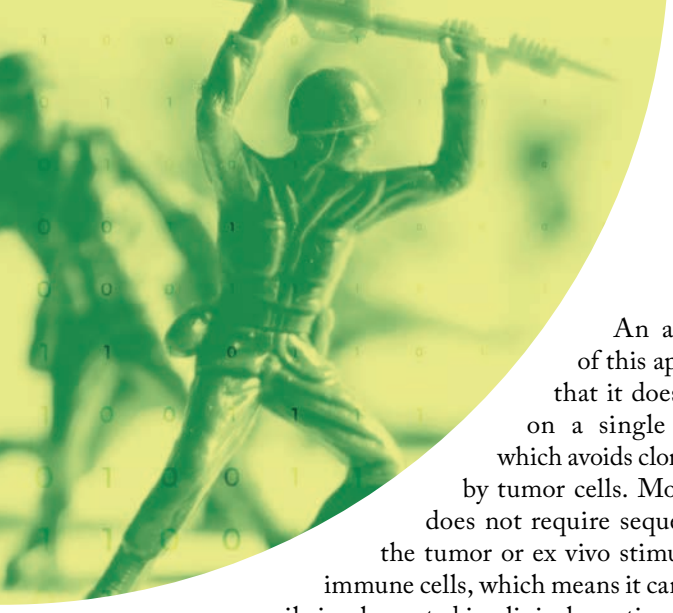
Early data on therapeutic mRNA cancer vaccines have shown that it's mainly the tumors that we qualify as "hot" tumors that respond best. These tumors are called hot tumors because their tissue is infiltrated by immune cells, indicating that the immune system is already active and present – and therefore more ready to respond to further stimulation.

However, we have also seen encouraging data in tumors that you wouldn't necessarily call hot, such as pancreatic cancer. Here, the combination of an mRNA vaccine and PD-1 antibody has shown the potential to turn a cold tumor (little inflammation and presence of immune cells) hot. At present, the most promising approach in clinical trials is the use of mRNA in combination with another immuno therapy (usually a checkpoint inhibitor) in cancers that are sensitive to immunotherapies.

JD: There is much debate over which cancers represent the most promising targets for successful vaccination. Two lenses often used to view a tumor's attractiveness for vaccination are mutational load and the tumor microenvironment. For mutational load, the greater the load, the more likely it is that the immune network can spot abnormalities on the surface of the tumor cell and target it for destruction. In the tumor locality, a loss of systemic and/or local T cell integrity increases the difficulty of creating a successful vaccine. T cell suppression in the tumor microenvironment and lymphoid organs is addressed by checkpoint inhibitors, though imprecisely because they target all T cells, regardless of their specificity, thus resulting in autoimmune side effects.

P-PT: Cancers that express consistent and unique tumor-specific antigens are natural targets for vaccination therapy, but they are not common. Many of the (neo)antigens are specific for the patient's individual tumor, and would require sequencing and analysis of the tumor biopsies prior to treatment. Alternatively, biopsies could be used to support ex vivo expansion of cancer-specific immune cells that, once infused back into the patient, may recognize the tumor. However, these approaches are laborious and costly.

An alternative approach is in situ vaccination, using viral immunotherapy, which, in principle, could work in any solid tumor. Here, an off-the-shelf therapeutic is injected into the tumor, with the aim of inducing tumor cell death, while promoting inflammation in the tumor microenvironment. Together, this creates optimal conditions to induce a broad immune response against the injected tumor and uninjected distant metastases. This can be achieved by viral immunotherapies that cause necrosis and inflammation in the tumor microenvironment, leading to a largely CD8+ T cell-mediated immune response.



An advantage of this approach is that it does not rely on a single antigen, which avoids clonal escape by tumor cells. Moreover, it does not require sequencing of the tumor or ex vivo stimulation of immune cells, which means it can be more easily implemented in clinical practice.

What are the biggest lessons learned to date from current cancer vaccine research?

JB: A pivotal lesson learned is the importance of combining vaccines with checkpoint inhibitors. When tumorigenesis begins, the immune system begins to detect that something is wrong. The cancer cells shield themselves by activating immune checkpoints that protect them from being attacked by the immune system. The checkpoint inhibitors remove these shields, enabling the immune system to eliminate tumors across various cancer types.

However, some patients may lack a sufficient T cell repertoire to combat the tumor. In such cases, therapeutic cancer vaccines can introduce new T cells that are specifically designed to target, recognize, and kill the tumor.

MM: Agreed. We have also learned that vaccines work better in hot (inflamed) tumors. Plus, patients with lower tumor burden or in the earlier stage of disease often derive more benefit from cancer vaccines because their immune system is still functioning well and the tumor volume is smaller.

NP: Treating early is definitely key. Personalized vaccines are very promising for those diagnosed early and when the tumor is not growing too fast. For advanced and metastatic cancers, identifying patients who have benefited from previous immunotherapy treatment is important to select immune-sensitive tumor types that are more likely to benefit from vaccination.

P-PT: I'd highlight three important learnings. First, identification of single tumor antigens that are shared between patients and that could be used for an off-the-shelf vaccination strategy have proven difficult across various solid tumors. Second, tumor cells may escape the immune response after vaccination against a single tumor antigen. Third, cancers may elude the immune response by producing factors that exhaust tumor infiltrating lymphocytes or inhibit their migration into the tumor.

JD: The resurgence in interest driven by mRNA vaccines has encountered many of the challenges of previous decades. This is unsurprising – because mRNA technology on its own is not a new angle on trying to overcome the inherent problems of cancer vaccination. In mRNA, considerable research effort has been expended in trying to optimize LNP design to influence the adjuvant effect of the vaccines, as well as mRNA design for potent production of the target antigen.

The area where perhaps most new ground has been broken is in neoepitope discovery. This field aims to customize a cancer vaccine by sampling the individual's tumor and isolating neoepitopes. mRNA vaccines are well placed to capitalize on advances in this field because they can deliver multiple antigen payloads to prime the immune system.

And what are the big challenges moving forward?

MM: A significant challenge is deciding which tumor antigens to target. Some patients have 8,000 tumor-specific antigens; others have just 100 or less. We need to develop smart selection algorithms based on specific criteria, supported by AI, to identify and prioritize the antigens that really matter.

A second challenge is the ability to deliver vaccines quickly. This can go down two routes – the provision of pre-prepared or so-called 'off-the-shelf' cancer vaccines based on tumor antigens known to be shared across different cancer indications or fully personalized vaccines based on a patient's individual tumor genomic profile. The former is faster as relevant antigens can be anticipated while the latter takes longer due to mandatory steps, such as taking a biopsy, sequencing the tumor tissue of a given patient, designing and producing an individualized vaccine, and getting the vaccine to the patient. This can take around 6 weeks to 3 months. We need to find solutions to produce the personalized cancer vaccine in particular in the fastest way as patients with cancer usually can't wait for their treatment.

NP: In addition, identification of the right antigens is not the same at the early versus late stage – because tumors evolve and resistance mechanisms vary. This means we need to diagnose more patients, especially those with solid tumors, at an earlier stage and to prepare 'off-the-shelf' vaccines composed by several shared tumor-associated antigens across tumor development to treat patients quickly and avoid tumor escape from one or two antigen mutations.

JD: Despite considerable effort expended in predicting neoepitopes using AI and machine learning, the current hit rate of predicted neoepitopes remains poor – around 5–10 percent. Significant educated guesses still need to be made because of the sheer number of combinations of MHC class I molecules and nano-peptide extracts of mutated proteins to be sifted through.

Boosting this success will improve the specificity of the vaccine effect and, ultimately, create more potent vaccines. Secondly, despite efforts to indirectly program immunity by skewing the response to become more T cell dominant, it remains more art than science with considerable educated guesswork as to how the downstream complexities of antigen presentation and T cell activation play out.

P-PT: Engineering the right agent to engage the immune system in the right way to yield durable antitumor responses is a challenge. Approaches designed to stimulate the anti-tumoral response ex vivo against multiple antigens are elegant, but implementation is complicated by relatively high costs, extended timelines, and its use is limited to specialized centers. mRNA vaccination is simpler in terms of implementation, but provides different challenges because it typically focuses the immune response against a single antigen.

JB: Though checkpoint inhibitors have demonstrated substantial efficacy, they do not work for all patients. In some indications, such as malignant melanoma and non-small cell lung cancer (NSCLC), a higher proportion of patients respond compared with other indications like mesothelioma and head and neck cancer. Additionally, some cancers, such as prostate and pancreatic cancers, have yet to establish checkpoint inhibitors as standard of care.

Because of the mutual interaction between checkpoint inhibitors on one side and the immune system or vaccines on the other, patients who do not respond to checkpoint inhibitors are likely to see little or no effect from a therapeutic cancer vaccine. To broaden the application of vaccines, we need new checkpoint inhibitors or drugs that make the tumor more accessible for the immune system.

What is the future of cancer vaccines, and how do we separate hype from reality?

MM: Based on data with other immunotherapies in cancer, such as checkpoint inhibitors, we see that targeting the immune system may be the best or even only way to achieve a real cancer cure. It makes sense to combine different immune therapies with cancer vaccines to increase the chance of success in curing cancer and the recent data support the current hype around cancer vaccines. To separate this hype from reality, we need to be very rigorous in the way we conduct clinical trials, how we interpret the data, and how we make decisions based on data.

P-PT: Approaches resulting in vaccination against the patient's tumor represent a new frontier in cancer research. The difference compared with conventional immunotherapies is that a vaccination strategy may help to educate the patient's immune system how to recognize the tumor cells in a specific way, which could lead to durable clinical responses and improved survival with a superior quality of life. We will separate hype from reality by evaluating the benefit/risk of specific new vaccination strategies in patients with cancer.

NP: Large phase III randomized trials in early/adjuvant settings as well as advanced cancer patients are required to confirm the benefit of cancer vaccines for patients in terms of efficacy, better safety, and preserved quality of life compared with chemotherapy. Then, cancer vaccines can become part of the therapeutic arsenal in the quest for a cure for cancer.

JB: I believe that therapeutic cancer vaccines are poised to become an established standard of care in several different tumor types, most likely when combined with checkpoint inhibitors. There is opportunity for several different modalities, such as RND, DNA, and peptide vaccines, as well as strategies ranging from personalized vaccines to more generalized vaccination approaches. Moving forward, the issues of cost and access in terms of affordability and patient accessibility will be increasingly important.

JD: New cancer therapies are mostly incremental to the standard of care and vaccines will find their place, most likely, in patients with minimal signs of being immunocompromised. The apparent safety and cost profile of the most recent mRNA cancer vaccines suggests even modest clinical success will be rapidly adopted. Increasing understanding of tumor biology combined with new technologies will help drive us to an inflection point.

The dramatic success of COVID-19 vaccination has inevitably driven a degree of hype, and mRNA vaccine companies are now revisiting cancer vaccines following their successful incursion into infectious disease. However, to those knowledgeable in the field, there is a strong understanding of the difference between success in a prophylactic setting with a known antigen, versus that in a therapeutic setting with individualized neoantigens. Hype is actually a rare beast in this field as cancer vaccines have endured decades of promise that has underdelivered, resulting in a permanent state of healthy skepticism from the investment community.

Ultimately, the only cure for hype is convincing clinical data, something the field may be moving closer to regularly achieving.

Keeping this short and sweet...

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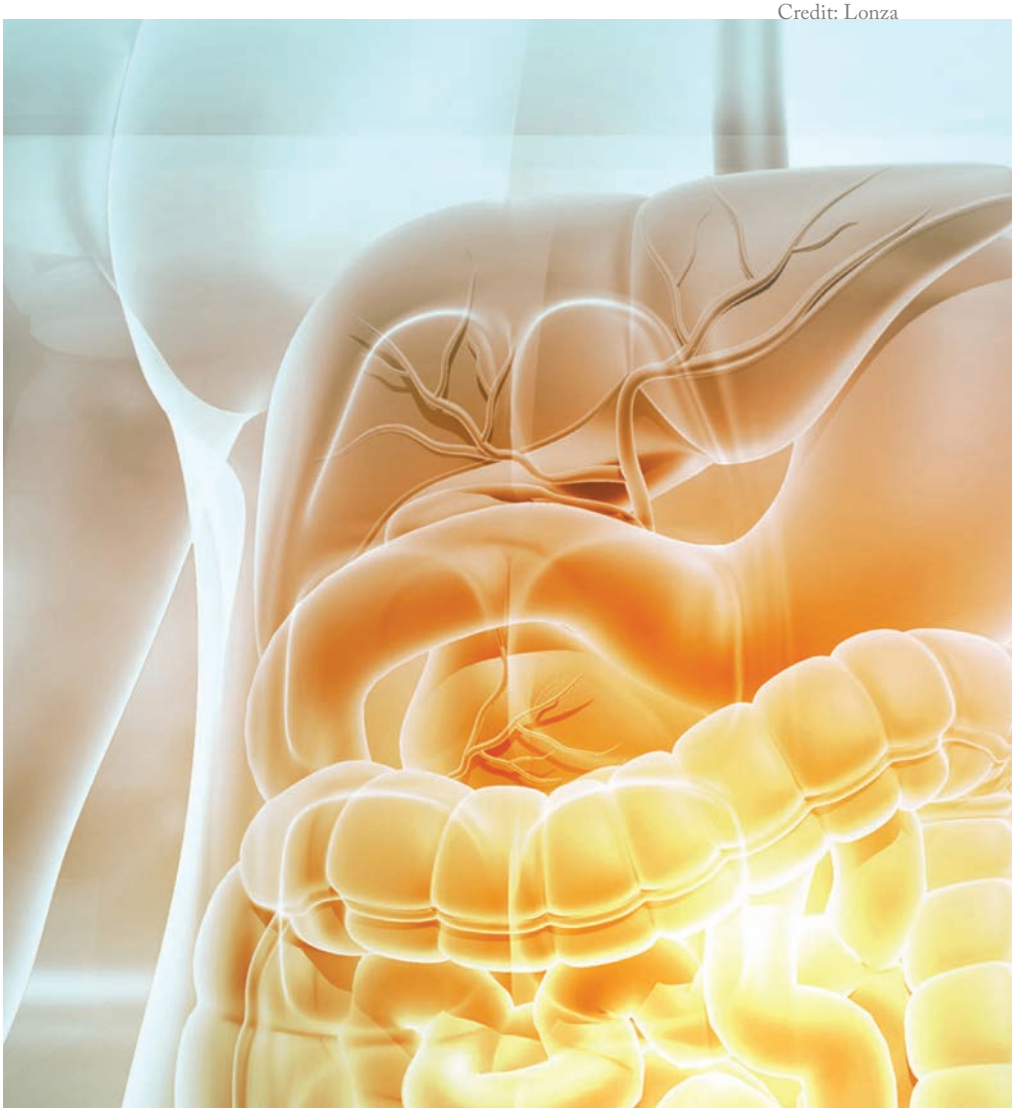


NEXTGEN

Go for the Gut: A Dose of Enteric Innovation

The team of dreamers and achievers behind the 2023 Innovation Awards winner, Lonza's Enprotect Capsule, discuss their technology

When the call for nominations for the 2023 Innovation Awards went out, we cannot say we expected something as seemingly ordinary as a capsule to be named the grand winner. Innovation, however, can be present in all things – given the right amount of time, hard work and partnerships. And if we are neglecting to innovate in the everyday, then we are failing altogether.

In a hotly contested list of entrants that included AI accelerators, nanoparticle analysis, cell therapy robots, and microfluidic chips, Lonza's Capsugel Enprotect capsule emerged as the winner. The capsule – as the name suggests – provides enteric drug delivery. It is a bi-layer capsule that consists of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMC-AS) polymers.

Lonza's chemical engineers and material scientists found a way to enhance the performance of a seemingly ordinary drug delivery product whilst simultaneously saving time, effort, and costs for pharmaceutical manufacturers; improving efficacy and easing the treatment burden for patients; and keeping in mind the company's sustainability targets. It is all too easy to hold an everyday capsule between one's fingers without considering the R&D efforts that got it there. Here, we speak with the team of dreamers and achievers behind the Enprotect Capsule to get the story behind its development.

What challenges do drug developers face when it comes to enteric delivery?

Jannin: Enteric targets delivery into the small intestine, which means the payload API must be protected from the acid and enzymes of the stomach. Developing an enteric formulation is a delicate process that can be time-consuming and expensive. And most of the time, the manufacturing process involves steps that are detrimental to certain APIs – particularly monoclonal antibodies, peptides, nucleic acids, and other fragile drug modalities, making the oral delivery an unviable delivery form.

We wanted to develop a solution that could make enteric formulation an option for these drug modalities. The result is the Enprotect capsule. It is a bi-layer capsule that is ready to use; you just need to fill the API or formulation into the capsule and close it. No post-filling treatment is required, and the bi-layer technology ensures the API is released in the small intestine.

We hope we have prepared the ground for many more new developments in enteric drug delivery. These capsules can

be used for many classes of APIs that could not traditionally be delivered orally.

How did you overcome the challenges of enteric delivery?

Palangetic: Looking into how oral enteric delivery is achieved today, coating capsules after filling them becomes the lead, if not the only, technology available to reach the goal. It is a lengthy, laborsome process that can also have a negative impact on the APIs. The key question for us was, how can we make a capsule that would be truly enteric but that would at the same time keep all the simplicity and advantages of using a capsule for oral dosages? This led to the concept of an enteric pre-coated or a bi-layer capsule and the great question of how to make it. As a technical person, you imagine a few different technologies that could be used; the advantages and disadvantages of those; the materials selection challenges and whether they will generate the right capsule quality or the right enteric performance. And while a lot of these can be relatively easily explored at the lab level, it was definitely a challenge to achieve this on an industrial scale.

We selected HPMC as the basis or the inner layer of the capsules, which has the right properties for forming a hard capsule. The outer layer uses HPMC acetate succinate (HPMC-AS), which ensures the capsule opens in the small intestine rather than the stomach. Both polymers are established cellulose derivatives well-known in solid dosage formulations. The materials offer good compatibility and long-term stability, which is important for both the capsule and the API within it.

"We overcame key challenges in the drying process by combining our knowledge of polymers and years of experience in standard capsules."

When it came to manufacturing, we stuck with what we know best – the standard process for manufacturing capsules – the dip molding process. Thanks to our technology R&D group, we were able to modify machines to allow the creation of the right process window for both layers and ensure that we could perform a subsequent dipping to create the two layers.

We overcame key challenges in the drying process by combining our knowledge of polymers and years of experience in standard capsules. Extensive in vitro testing by our research group and by our customers gave us good insights to move forward. Then, we conducted in vivo tests that showed the capsule's content delivery to the intestine. The list is long, but with every challenge we faced, we learned to improve and innovate further.

We also did all of this while maintaining the standard size of the capsules, which means that customers can use them with any filling machine without a need to upgrade or purchase new instruments. Because they are filled directly into the capsule with no additional processing to follow, there is no stress on the APIs.

Jannin: HPMC can dissolve in any part of the gut, stomach, or intestine. We selected this material to give the capsule its shape, and it allows us to produce it on a large scale. Our customers are happy with the compatibility with the classic fill materials, which we checked with a range of solid fill excipients. The trick for enteric delivery is to then have an outer layer composed of an enteric polymer.

The final Enprotect capsule contains an enteric polymer that is unable to dissolve in acid up to pH 6.0. It protects the payload from releasing in the stomach but will readily dissolve in the intestine when reaching pH 6.2. There is no additional excipient or plasticizer that can negatively affect the properties of the capsule. The capsule is ready to use with no need to seal, band, or coat them after filling.

What makes Enprotect capsule a deserved Innovation Awards winner?

Seufert: Innovation depends on inclusive and empowering teamwork. Enprotect capsule was a cross-functional effort between different R&D teams, operations, engineering and other functional experts at Lonza. In only 18 months, the team brought this innovation to life, from conceptualization to the first capsules in our hands, all under the constraints of the COVID-19 pandemic. From our perspective, the dual layer capsule technology enables us to reimagine capsule properties and functionalities for the future.

Palangetic: This project shows our dedication as an organization to offering formulators new solutions. Enprotect capsule was our baby, and it takes a village to raise a baby. All the stakeholders came through to make sure it was delivered in the fastest possible way. I truly believe that our team has moved a mountain and created solid ground for new developments. It is a new technology, using old knowledge – and it will certainly be a catalyst for future innovation in solid dosage form delivery.

MEET THE EXPERTS

Christian Seufert is the President of the Capsules and Health Ingredients Division at Lonza.

Ljiljana Palangetic is a chemical engineer/material scientist who heads Lonza's Hard Capsules research and development team.

Vincent Jannin is the Director of R&D, heading a research group focusing on capsule applications.

One could already imagine the Enprotect capsule playing a role in helping drug manufacturers with sustainability – replacing the traditional process of filling capsules and then coating them could be a game changer for some products. Furthermore, this capsule could be an enabling tool for the conversion of certain vaccines into oral dosages, which would not just improve patient comfort but eventually even allow better access to vaccines where the cold supply chain is a great challenge. It has been shown that enteric capsules are well suited to replace the traditional method of fecal microbiota transplant (FMT) and greatly improve patient's experience. And we believe that these examples are just scratching the surface.

How could this innovation affect new drug development for patients?

Jannin: We collaborated with academic partners to develop an in vitro test that mimics the cystic fibrosis condition in the stomach and small intestine to ascertain that the capsule can withstand this condition and release the payload exactly where it should be. We also designed two in vivo studies in human volunteers – in fasted and fed conditions – and in both cases, the capsule was able to tolerate the stomach conditions, even the higher pH and shear of the fed stomach. In fact, it remained intact even after more than four hours in the stomach. These studies demonstrate the robustness of the capsule in very harsh conditions. Our academic partners said they had never seen this with enteric delivery before!

This solution is also good for many new drug modalities, such as proteins, enzymes, LBPs, and drugs that are not acid-sensitive but need to be delivered specifically in the small intestine.

We are also collaborating with hospitals on FMT. We have shown that the capsule is compatible with FMT and able to deliver the payload while reducing the number of capsules a patient must take. We also think it could be a transformative treatment for patients with Crohn's disease by enabling the development of targeted-release Enprotect capsules that can deliver RNA-loaded nanoparticles.

"I hope that capsules will be given more consideration within new drug development projects because of the benefits in functionality, customization possibilities, patient preferences, and so on."

What interest have you seen from the pharma industry so far?

Seufert: Formulators have responded very positively to the launch of Enprotect capsules, and, as a result, many new projects have already been initiated with our customers. We have seen a wide range of applications, from small molecules and proteins to medical devices. We are always looking ahead at further improvements and new applications, and as a first next step, we are planning to provide formulators with more color and capsule size options.

How vital is innovation in solid dosage? And what would you like to see in the pipeline in the future?

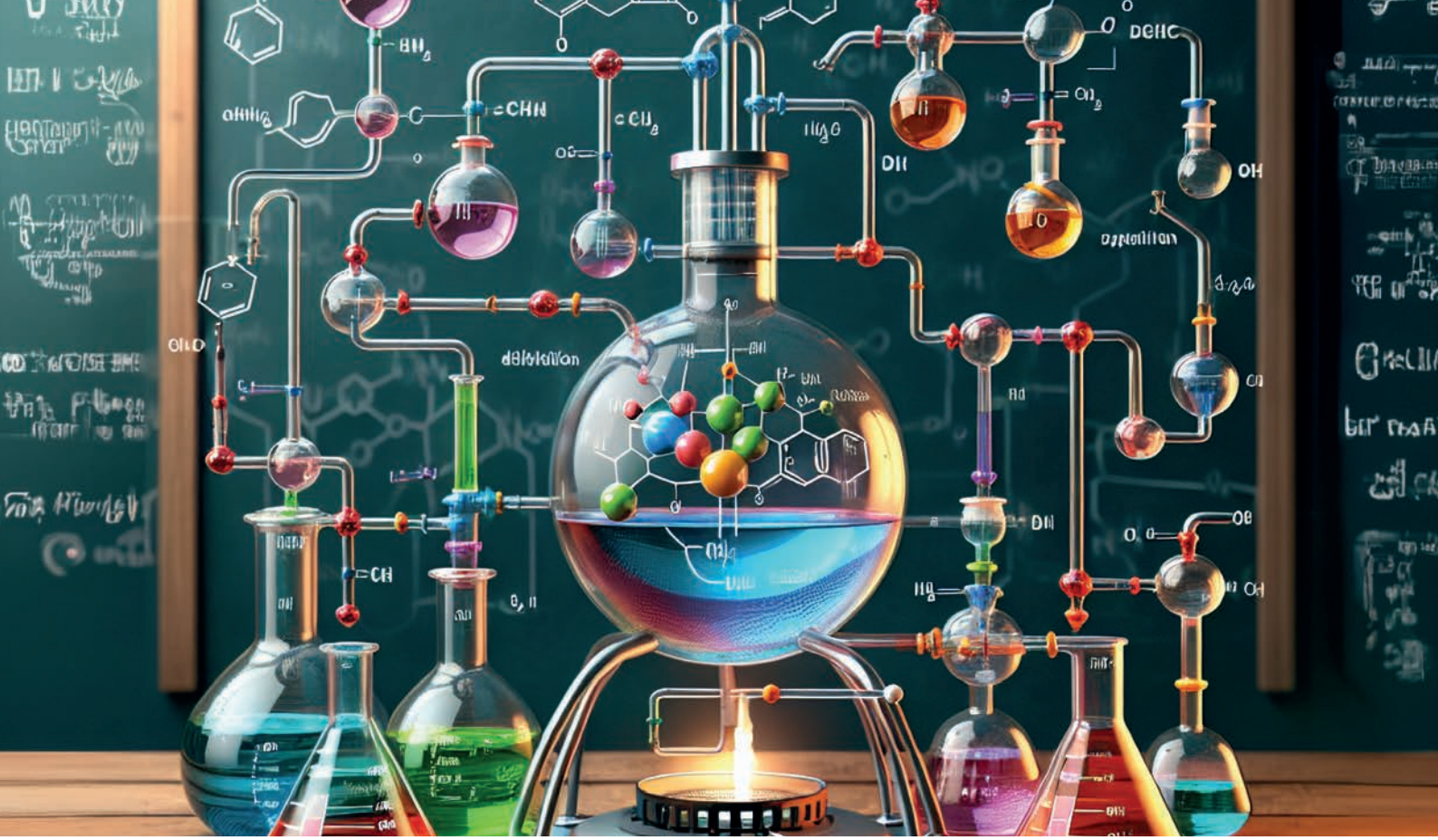
Seufert: I would like to see the industry pushing the limits of oral solid dose delivery. Innovative capsule technology could play a big role in the delivery of oral and inhalable biologics. It is not only about formulating such products for oral delivery but how we can provide access to cost effective solutions in a more sustainable way. This is something that will require a lot of work and much more innovation. But if you ask me to dream a little, that is what I would aim for.

Palangetic: I am convinced that the capsule's potential in solid dosage forms has been unjustly underestimated for a very long time.

A capsule was originally an excipient/container intended to mask/cover badly-tasting contents, but it has evolved, and it has so much more to offer. The Enprotect capsule is a good example; pushing the boundaries with delivering products to the intestine and opening the possibility to deliver actives that previously could not be envisioned in oral dosage forms. I hope that capsules will be given more consideration within new drug development projects because of the benefits in functionality, customization possibilities, patient preferences, and so on. We are keen on exploring new innovation paths and are ready to partner with customers so we can generate new ideas to help patients.

Jannin: For me, the dream for the next couple of years would be to have another capsule that targets a specific segment in the intestine. We are working with GeneGut to help Crohn's disease patients. These patients have a very poor quality of life, and the standard treatment has many side effects. A drug with a local effect could change lives – and so a capsule that can deliver APIs deeper into the intestine is next on the wish list. I hope to have the opportunity to work with many customers on adaptations involving Enprotect capsules. Whether it is earlier, later, quicker, or slower release, there is a clear need in the market for oral biologics, and the potential for further innovation is certainly there.

Nominations are currently being accepted for The Medicine Maker 2024 Innovation Awards. The deadline for submission is October 15 2024. Find out more at: https://themedicinemaker.com/awards/the-innovation-awards



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BEST PRACTICE

Predictive AI in Drug Discovery: Five Steps to Success

The use of AI in small molecules drug discovery is driving the sector forwards in big ways – but there are big challenges too. Here are five steps to success.

By Mirit Eldor, Managing Director, Life Sciences Solutions, Elsevier

The preclinical phase of drug discovery is the most time intensive stage of the R&D lifecycle – taking up to six years and accounting for more than 40 percent of total drug development costs. To reduce the billions spent on preclinical drug development, faster, more efficient R&D workflows must be a priority across the industry. So it's no surprise that pharmaceutical and biotechnology companies are looking to use machine learning (ML) to revolutionize R&D and AI to generate and validate small molecule drug discovery pipelines.

Research organizations that successfully deploy AI are already gaining a competitive edge. There is emerging evidence that these organizations get through preclinical stages quicker and cheaper than the traditional approach, with savings of around 30 percent of time and cost. The approach is already gaining traction; one study by the Boston Consulting Group found that biotech companies that have adopted an AI-first approach, "…have more than 150 small molecule drugs in discovery and more than 15 already in clinical trials."

Predictive AI is one AI approach that many pharmaceutical and biotech companies are exploring today. Here are five steps that research leaders should follow to realize success.

1. Identify the right use cases

Before investing in predictive AI, research leaders must define the problems, or use cases, that they want to tackle. Typically, the best applications for predictive AI are discrete tasks and processes where measurable, tangible gains can be achieved. In early drug discovery, examples of predictive AI use cases include predicting the 3D structure of a protein, relationships between molecules based on their chemical structure, and drug-target interactions.

In small molecule discovery, predictive retrosynthesis combines high-quality reaction data with AI to find structural or chemical patterns that correlate with specific compound properties and accelerate synthesis planning of novel molecular entities. Routes can be generated for novel compounds in minutes rather than weeks.

2. Source accurate and high-quality data

The nuance of research questions demands a level of precision that requires high-quality, verified training data. Without high-quality data, researchers will lack confidence in predictive AI outcomes. For predictive models to work, researchers will want to include data from multiple sources in addition to their internal data. This will typically include data from scientific literature, plus other databases containing patent data, regulatory data, clinical trials data, safety data, and patient records. For example, a predictive AI chemistry model requires a breadth of chemistry inputs that includes not only proprietary data and data on failed reactions, but also published literature. A predictive model that is fine tuned using incomplete data will produce inferior results whose shortcomings may not be immediately identified, leading to expensive incorrect decisions.

"AI will be a game-changer for every industry."

3. Prepare and structure the data

Once data is acquired it must be structured to power predictive AI successfully. Much of the data R&D organizations source are not AI-ready; datasets are siloed and stored in myriad formats with insufficient metadata, making it difficult to retrieve and use in predictive AI models. Standardizing and structuring datasets via the application of ontologies is a critical step.

Ontologies are human-generated, machine-readable descriptions of categories. They standardize data against an agreed vocabulary, providing a shared language across an organization. Vocabularies can include terms specific to an organization – such as product names – alongside industry recognized concepts and terms. Ontologies define semantic relationships to other classes and capture synonyms, which is essential where there are multiple ways to describe the same entity in scientific literature and

other datasets. For example, the gene *PSEN1* can also be referred to as *PSNL1* or *Presenilin-1*.

4. Semantic enrichment

To extract insights, datasets must be enriched and annotated. Semantic enrichment is a key step that unlocks the full potential of data in structured and unstructured, public and proprietary, datasets. It transforms text into clean, contextualized data, free from ambiguities and synonyms, through annotation, tagging and adding metadata. It works by employing text analytics to extract key words, concepts, and terms for predictive models, and harmonizes synonymous terms for better accuracy.

Data harmonization is especially important when using databases from multiple sources as technical terms or abbreviations are often used. For example, sophisticated semantic enrichment software can identify and extract relevant terms or patterns in text and harmonize synonyms, such as "heart attack" and "myocardial infarction," so they are identified as the same entity by a predictive model.

5. Domain specificity

Structuring data for predictive AI through ontologies and applying semantic enrichment methods is highly specialized work that requires expert understanding of the domain under investigation. General purpose AI models developed by technology companies have utility in broad areas such as marketing and operations, but scientific research represents a set of niche challenges that necessitates domain expertise.

Few biopharma companies today will have the right mix of skills needed for tasks such as creating ontologies in-house. Best positioned to solve this challenge are data scientists who can couple technology skills with scientific domain expertise. Such data scientists can bring an understanding of the context of questions asked in relation to the data available. They can further ensure ontologies and vocabularies are built so that predictive AI models return relevant results, and no essential data is missed.

The world is in agreement: AI will be a game-changer for every industry. For those working in preclinical drug discovery, the opportunity is huge – but so is the challenge. To accelerate drug discovery to meet the medical needs of patients around the world, pharma and biotech organizations need to bring together data, technology, and expertise. When these elements converge, AI can serve as a valuable support tool for researchers to usher in a new era of drug discovery.

"At the end of the day, all of this is about patients and ensuring they have the best medicines."

Think Smaller

Sitting Down With… Edward Hæggström, CEO of Nanoform

Did you always want to be a scientist?
No! I was a sea scout and I wanted to be a fighter pilot. In school, I was interested in everything and I took all of the advanced classes I could. At university, I started out as a math major, and then progressed to theoretical physics, applied physics, and electronics. I chose my mentoring professor because he competed in offshore sailing, which I liked. He also had an innovative streak to his science that inspired me.

How did you become interested in drug formulation?
My PhD was in applied physics, with a focus on food processing. I then did my MBA in innovation management, before moving abroad to the US. I worked at Harvard Medical School and I was a visiting assistant professor in applied physics at Stanford. When I returned to Finland to the University of Helsinki, I was introduced to Jouko Yliruusi, who was a professor in pharmaceutical technology. He asked if I was interested in working on solutions for poor solubility in pharma.

Stanford had really opened my eyes to academic entrepreneurship. It had a solid commercialization office and it taught me to think about academic breakthroughs as something that could be commercialized. When I returned to Finland, I geared my lab in that direction. Meanwhile, Harvard taught me to work on big problems – and poorly soluble drugs are definitely a big problem in drug development.

So, I said yes to Yliruusi. We combined our expertise in physics and pharmaceutical technology to develop a novel particle engineering technology, which led to the founding of Nanoform.

What is the technology behind Nanoform?
The technology was inspired by the advanced classes I received in nonlinear thermodynamics. Thermodynamics is usually about linear relationships between pressure, temperature, and density, but when you delve further you learn that you can cheat physics if you use short timescales for processes. This phenomenon has always intrigued me. We used thermodynamics to create nanoparticles using a bottom up approach – because my gut feeling was that it would be better to use a precipitation-like process rather than a grinding process to create nanoparticles.

The technology is called Controlled Expansion of Supercritical Solutions, and is designed to create nanoformulations that offer several benefits, including higher drug loading, improved bioavailability, and better release profiles. Essentially, we use a non-equilibrium thermodynamic process to recrystallize an API in a controlled manner through supercritical carbon dioxide.

Given all the advances made by the industry, why is formulation still so difficult?
The art of cooking is hard, which is why there are so many famous chefs! Pharmaceutical formulation is also hard. Formulated forms, especially at the nanoscale, have very large surface energy gradients and many different physical faces. Even with computation, massive-scale systems are hard to master and understand. We've actually been experimenting with AI at Nanoform to control and improve nanoformation, but it's still not an easy task.

When you are working on a new technology, it has to make a difference in the marketplace and in the patient community – otherwise it's just a gimmick.

How has the company changed since its beginnings?
It has changed through different iterations. For me, the transition from a university lab operation into a startup was definitely a large step from a mental perspective. And now we have become a fully fledged GMP company – which is now listed. We did all of this in four years.

I'm proud of what we have accomplished. At the end of the day, all of this is about patients and ensuring they have the best medicines. We have made a significant contribution to a blockbuster drug (Erleada; apalutamide), and shown we can use our technology to take a product formulated with an amorphous solid dispersion approach and turn it into a superior product.

We've worked with a hydrogel product, which has received FDA fast track designation and is now entering the clinic, and we're now working on a nanotechnology-enhanced formulation of enzalutamide. This project is exciting because it's a big blockbuster product. The current version of this medicine requires cancer patients to take many large pills, but our nanoformulation could reduce that burden to a single tablet. Right now, we're in the process of partnering on the molecule so that it can reach patients in different global markets.

You also work at the University of Helsinki…
That's right – I teach classes in ultrasonics and electronics, and I guide students on the topic of academic entrepreneurship. The University of Helsinki is one of the top science universities in Europe. My classes are either senior master or junior PhD classes. Working with the students keeps me intellectually honest, because I have to earn their scientific trust every time I enter the class. I think that keeps my brain sharp; other people do crosswords, I do this!

What traits should a good scientist have?
Intellectual curiosity, discipline, and fearlessness. But, most importantly, you need to be persistent. You cannot be wasting time on TikTok!

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Small Molecules | **Biologics** | **Cell & Gene Therapies**

Cyclosporine