Captor Therapeutics
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Uniting the protein degradation generation

Captor Therapeutics is building a singular pipeline of both next-generation bifunctional degraders and molecular glues based on novel E3 ligases, leveraging academic expertise and industry experience in the United States and Europe, while utilizing significant public and private investment.

Things often seem either black or white within the targeted protein degradation (TPD) space. The biology behind degrading therapeutic targets that are difficult or dangerous to inhibit is well established and this leads to developing either naturally derived molecular glues or simple-to-engineer bifunctional degraders. Most research groups focus on one approach or the other, due to the distinct challenges presented by each and the up-front investment in structural biology capabilities. Locking into one path squanders overlapping expertise, limits potential indications, and opens companies to more risk.

To unlock the potential of both types of TPD, scientists from academia and pharma built Captor Therapeutics on a foundation of industry-leading structural biology capabilities, allowing the company to understand the E3 ubiquitin ligases that underpin both approaches in three dimensions. The Swiss–Polish company leveraged significant non-dilutive funding from public efforts meant to boost European drug discovery capacity, primarily from the Polish National Center for Research and Development (NCBR). Through these early investments, Captor built world-class expertise in protein engineering, structural biology methods such as crystallography, and biophysical methodology.

"The strength of our structural biology teams tends to make our peer companies a bit jealous. We're unique in being able to apply such a large in-house capacity in these areas to explore and optimize a wide range of chemistries," said Tom Shepherd, the company's CEO and president. Where most of the industry have programs targeting cereblon, a single E3 ligase that so far has only been demonstrated safe and efficacious in the cancer space, Captor has the tools to explore a much broader range for its TPDs. "These capabilities also helped us create a semi-rational discovery approach for a family of naturally derived molecular glues, pairing computational methods with sophisticated biophysical assays to identify new molecular targets," he added.

Glued together

Having its feet planted in two different worlds simultaneously is fundamental for the balance struck by Captor, which was cofounded in 2017 by industry veteran Sylvain Cottens and academic Michał Walczak. Previously, Cottens had worked on multiple blockbusters while at Novartis. In particular, he utilized his prowess in protein–protein interactions as co-inventor of the oral chemotherapeutic everolimus, now marketed for solid cancers and to prevent organ rejection.

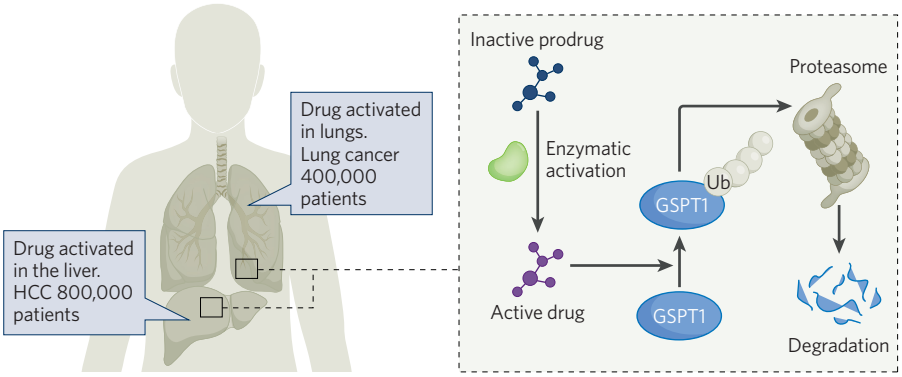

Fig. 1 | How Project CT-01 works. The drug candidate aims to target hepatocellular carcinoma (HCC) and is a molecular glue degrader that, upon oral administration, is first transferred to the liver, its desired site of action. There, it is converted by a specific enzyme into an active form and partially entrapped, reducing its further circulation. The converting enzyme is highly elevated in cirrhotic HCC patients, which make up 80% of all liver cancer patients, as well as in the lungs, making it ideal for localized action. Simultaneously, it mitigates potential side effects resulting from systemic circulation. This feature is unique among known GSPT1 degraders.

Meanwhile, Walczak similarly focused on protein–protein interactions, especially the interactions between E3 ubiquitin ligases and their ligands, during his PhD at ETH Zurich and postdoc experience at the Friedrich Miescher Institute (FMI) in Basel, which is affiliated with Novartis Institutes of Biomedical Research. In time, this overlap drew the two together.

"When I retired from Novartis, Michał approached me with the idea for the company," said Cottens, who is Captor's SVP Chemistry. "The idea of inducing targeted protein degradation with a small molecule was fascinating, and the quality of the science was equally impressive. So we started planning the company, in his kitchen."

The pair developed a nontraditional entrepreneurial plan that would forgo in-licensing foundational intellectual property or chasing venture capital investors. Instead, Captor obtained grant contracts worth about PLN 175 million ($41.7 million) in non-dilutive funding from NCBR alongside additional funds from some local private investors to build its discovery platform. The company recruited Shepherd, whose leadership experience in both the United States (US) and Europe included moving multiple products into clinical trials over several decades, ahead of a 2021 initial public offering, where Captor raised about PLN 150 million ($38 million) as it listed on the Warsaw Stock Exchange.

Captor is now well positioned to go global through its two-pronged approach to TPD discovery and development, advancing both a molecular glue and a bifunctional degrader toward the clinic. Its most advanced molecular glues are built upon understandings gleaned from the first family of approved therapies in the class. "The idea of directing ubiquitin-mediated protein degradation for therapeutic purposes is only a few decades old," said Walczak, who is Captor's CSO. "And in fact, it was even more recently when the industry realized that protein degradation was the mechanism behind approved cancer drugs like thalidomide, though they have been studied for 70 years. These turned out to be molecular glues that can degrade as many as three distinct cancer targets."

Captor's lead asset, CT-01, is a proprietary molecular glue in this mold. It targets three proteins for degradation and epitomizes the company's rational approach to discovery (Fig. 1). One of its targets is the transcription factor GSPT1, which is essential for normal cell function but promotes tumor growth if it becomes dysregulated—and can be degraded to induce apoptosis.

Due to its chemistry, CT-01 functions as a prodrug that is specifically activated in situ by an enzyme found only in specific organs after oral administration, with potential for targeting lung cancer and certain gastrointestinal tumors.

The molecular glue degrades two other targets, SALL4 and NEK7, helping optimize the therapeutic window for its first target indication of hepatocellular carcinoma. "SALL4 is a transcription factor that is overexpressed in liver cancer at levels that correlate with poor prognosis," said Shepherd.

"Meanwhile, NEK7 promotes inflammation via IL-1β, a cytokine procarcinogen linked to multiple solid tumors." Captor has CT-01 in investigational new drug (IND)-enabling studies.

Outside the field of cancer research, NEK7 is a well known inflammation target, linked to inappropriate activation of the NLRP3 inflammasome in multiple inflammatory, autoimmune, and neuroinflammatory disorders. But inhibitors of this pathway have been shown to increase susceptibility to dangerous infections—something that targeted degradation may avoid. That's the rationale behind Captor's second molecular glue program, CT-02, highly selective NEK7 degraders with promising preclinical data showing they can cross the blood–brain barrier and, potentially, improve upon the limitations of NLRP3 inhibitors.

Making de-grade

Captor decided early to also develop next-generation bifunctional degraders, which are engineered by linking moieties that bind an E3 ligase to ones for therapeutic targets (Fig. 2). But the founders rejected oversimplified efforts to rapidly design molecules. "People thought it would be like building with Lego—you start with a basic chemistry toolset, figure out the ligands for your therapeutic target and your E3 ligase, and stitch them together with a linker," Walczak said. "This mechanistic concept is really appealing, but drug discovery has never been so straightforward. We showed that if you understand how proteins are positioned in three-dimensional space, you can design bifunctional degraders better and without having to produce and evaluate hundreds of thousands of compounds. With our strong internal capabilities in this area, our platform accelerates discovery and allows for designing best-in-class compounds," he added.

The structural biology-based approach has been advantageous for challenging targets. Captor's second-most advanced pipeline program, CT-03, is a bifunctional degrader that targets the so-called "undruggable" MCL-1 protein. MCL-1 is one of the most amplified genes in cancer and critical for chemoresistance in tumors, but decades of research have yet to produce inhibitors that demonstrate clinical efficacy. This is in part due to physical challenges in targeting the protein, but also because strategies to block MCL-1 have led to protein overaccumulation, which could result in a potential adverse event risk and complicate the dosing regimen.

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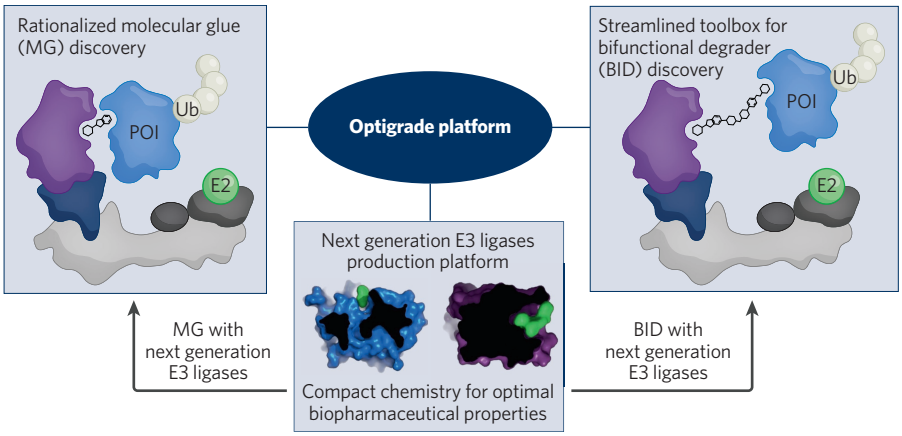

Fig. 2 | Captor's technology platform, Optigrade. The Optigrade platform focuses on three main pillars: molecular glues (MG), bifunctional degraders (BID), and ligands for novel E3 ligases (LiLi). MG discovery has been semi-rationalized with computational methods, state-of-the-art biophysical tools, and in-house structural biology. Our chemical biology toolbox allows for fast progression of BID design and optimization, exploiting proprietary chemistry with superior properties. The third component of the Optigrade platform, LiLi, is a product of internal and industry-leading capabilities in the production of E3 ubiquitin ligases. It enables the translation of knowledge from MG and BID discovery to new E3s that feature biological profiles suitable for the disease of interest.

By degrading MCL-1 instead, CT-03 induces programmed cell death without potentially dangerous protein accumulation. The compound has already demonstrated in vivo efficacy in mouse models of leukemia, as well as in solid tumors including lung and breast cancers.

Like first-wave bifunctional degraders that are beginning to demonstrate clinical promise, CT-03 binds cereblon, the E3 ligase targeted by thalidomide-based molecular glues. This approach remains highly valuable for cancer indications, but like thalidomide, it could limit their safety profile outside of cancer in chronic indications.

"Thankfully, there are more than 600 other human E3 ubiquitin ligases, and we've built one of the largest libraries of E3 proteins and ligands in the world," said Cottens. "The space is comparable in size to the kinase field, which has resulted in dozens of approved therapies over the past two decades. That means if one can access it—as we can—the potential for TPDs is even greater, given their added ability to hit challenging targets like transcription factors."

To do so, Captor leans on the expertise of its industry-leading protein engineering and biophysics group, including more than 30 people dedicated to understanding how drug candidates interact at the atomic level with ubiquitin ligase targets. "This is how we design first-in-class degraders, because we can highly differentiate our molecules on so many levels," said Walczak.

Bound for a bright future

Captor is on track to launch its first of several phase 1 trials this year, 2023, starting with CT-01. "Thanks to our strong in vitro and in vivo data, we're looking forward to both an initial monotherapy trial in the fourth quarter, and a combination clinical trial shortly thereafter," said Shepherd. The company also has CT-03 in IND-enabling studies and expects to begin first-in-human testing in 2024, both as a monotherapy and then in combination trials.

Given the platform's broad applicability, that's just the beginning. The company is continuing to bolster its TPD pipeline, starting with in vivo proof-of-concept testing to demonstrate the potential of its CT-02 molecular glues and CT-05 bifunctional degraders for autoimmune diseases, and more. As small molecules, CT-02 in particular will be evaluated for their potential to cross the blood–brain barrier, with promise for treating neuroinflammatory diseases.

Captor is exploring a range of potential partnerships as it lines up its next funding round to support clinical trials. "We've had great feedback from investors who are knowledgeable about TPD," said Shepherd. "They talk highly about our approach, the way our team has leveraged non-dilutive funding and our European valuation to build an impressively capital- and cost-effective research and development machine, with the experience to pivot to the US capital market."

Ultimately, science is what defines Captor. "What drew our team together is what continues to generate the most interest in the company: the ability to use advanced structural biology and biophysics expertise to capitalize on the untapped potential of the space," said Cottens. "Based on the progress we've already made, it's clear we're ready to grow and execute on our vision."

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