

CASE STUDY

Overcoming Complex Cytotoxic Chemistry: Discovery to Clinic in 14 Months

A collaboration with Avacta Therapeutics,
delivering AVA6103 through innovative
FAP-activated drug conjugate discovery.

Brief Summary

Avacta Therapeutics selected Sygnature Discovery to support the development of **FAP-activated peptide-drug conjugates**, with the aim of selectively delivering potent cytotoxic therapies to tumors. Through a highly collaborative and multidisciplinary approach, Sygnature helped overcome complex drug conjugate discovery challenges to successfully deliver AVA6103, progressing the program **from discovery to clinical nomination in just 14 months**.

Customer Background

Avacta Therapeutics is a UK-based, clinical-stage biopharmaceutical company focused on developing precision oncology therapies. Their proprietary pre|CISION® peptide-drug conjugate platform is designed to selectively activate potent cytotoxic drugs within the tumor microenvironment, with the aim of improving efficacy while minimizing systemic toxicity.

Leveraging this platform, Avacta has built a pipeline of novel targeted therapies progressing through to pre-clinical and early clinical studies, with the goal of delivering first-in-class precision oncology treatments to patients.

Sygnature Discovery initially partnered with Avacta to provide form and formulation support for their first candidate, AVA6000. Following the success of this collaboration, the partnership expanded into a fully integrated drug discovery program to design, optimize and progress what would become AVA6103.

The Challenge

Avacta sought to develop fibroblast-activation protein (FAP)-activated prodrugs capable of selectively releasing cytotoxic agents within the tumor microenvironment, maximizing anti-tumor activity while minimizing side effects.

The challenge was finding the right combination of payloads, linkers and activation strategy to achieve effective tumor-selective drug release, while overcoming the limitations of challenging compound classes. Success depended on generating the insights needed to guide rapid decision-making while exploring novel chemical space and establishing a differentiated intellectual property position.

With complex cytotoxic chemistry, bespoke assay development and multiple scientific disciplines involved, bringing together the right expertise and capabilities was critical to advancing the strongest candidate towards development.

Delivering a Clinical Candidate

Scientific Challenges

Selective activation

Tumor specific payload release via FAP activation

Payload & linker design

Optimized selectivity and stability

Cytotoxic chemistry

Overcome challenges associated with highly potent compounds

Novel IP space

Innovative chemistry beyond existing IP

Accelerated candidate nomination

Integrated expertise and rapid weekly screening enabled clinical candidate nomination in just 14 months

Key Outcomes

- >400 compounds screened
- >200 peptide-drug conjugated synthesized
- >40 DMPK studies conducted
- Diverse warhead and linker exploration
- In-house FAP production established
- Novel IP protected

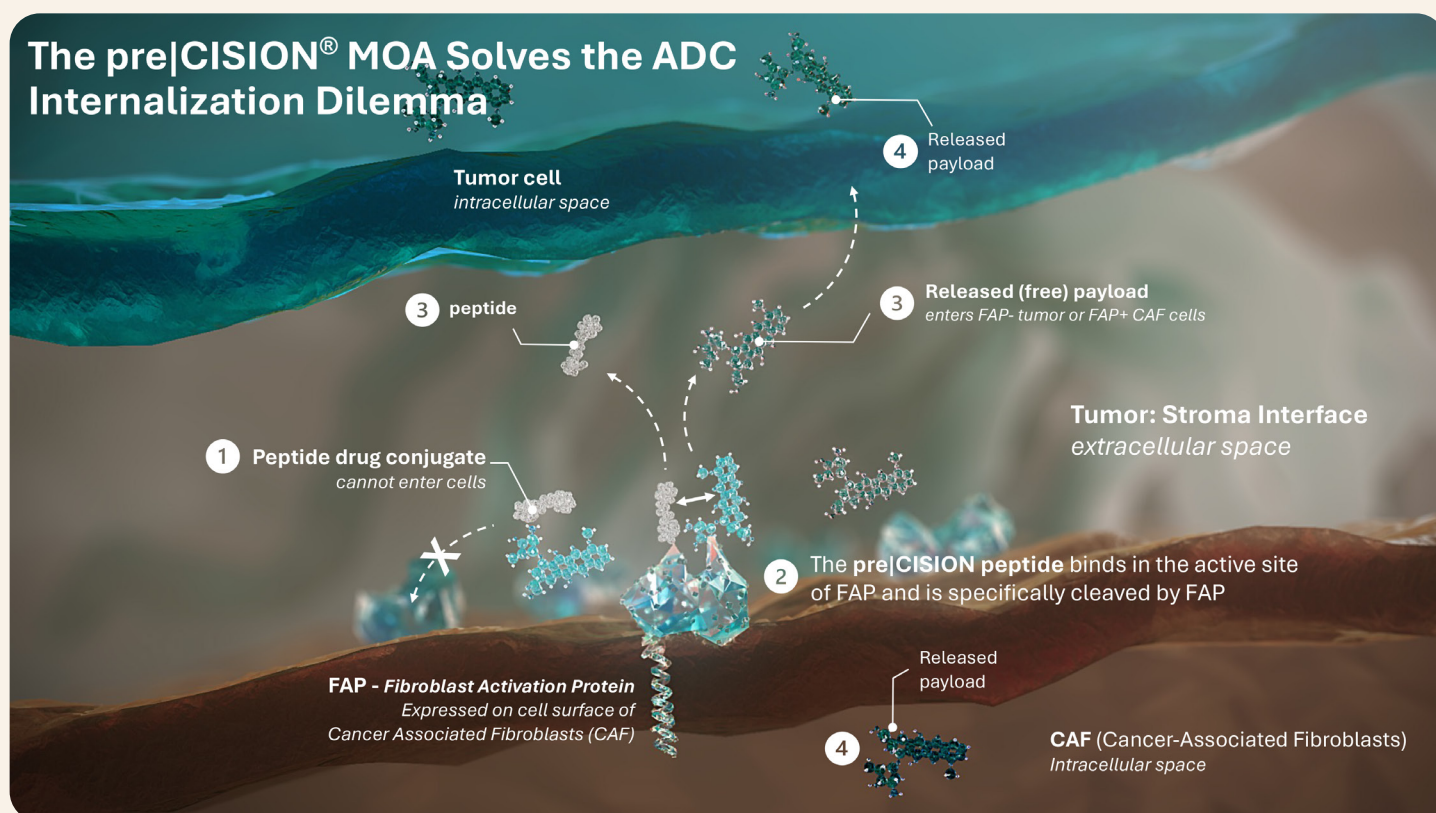
Why Sygnature?

Expectation and Key Selection Criteria: Commentary from Avacta Therapeutics

The AVA6103 collaboration was built on the success of an earlier partnership in which Sygnature Discovery provided form and formulation support for Avacta's first pre|CISION® candidate, AVA6000. Through this work, Sygnature Discovery established a strong track record of scientific expertise, responsiveness, and collaboration, creating a foundation of trust for a broader drug discovery partnership.

Sygnature's experience in integrated drug discovery, medicinal chemistry, biology, DMPK, formulation and project management then made them an ideal partner for collaboration as Avacta looked to develop its pre|CISION® technology further.

The collaboration leveraged the wide experience at Sygnature to develop a deeper understanding of the platform technology, in particular allowing detailed understanding of FAP kinetics to allow the controlled release of payloads.



Sygnature's Approach and Solutions

Over the course of the project, the team designed and synthesized more than 200 peptide-drug conjugates, conducted over 400 cytotoxic and kinetics assays and 40 DMPK studies, generating a diverse and comprehensive dataset to guide optimization, triage and progression of the project.

A key focus of the program was the development of robust analytical and screening methods to support the safe handling of multiple highly potent cytotoxins. Sygnature's expertise in LC-MS-based enzyme kinetics studies, selectivity profiling and specialized analytical methods enabled the rapid generation of accurate datasets needed to establish SAR, guide decision-making and maintain project momentum.

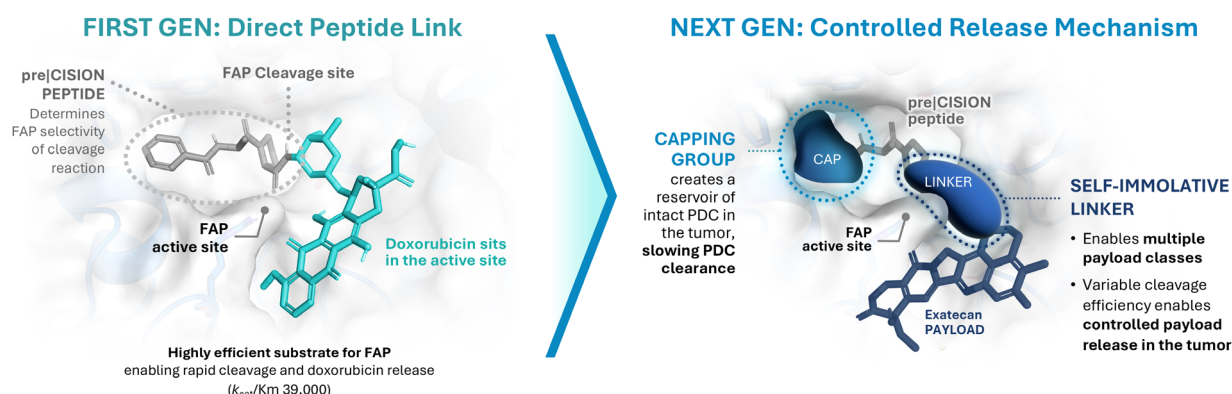
Computational chemistry played an important role throughout, supporting compound design and optimization as well as Avacta's scientific and commercial activities. Modeling studies were used to rationalize and illustrate the selectivity provided by the pre|CISION® precision technology, exploring the binding mode of the key dipeptide within both the FAP and PREP catalytic binding sites.

Using a combination of conformational sampling, template docking guided by 3D Atomic Property Fields, quantum mechanical calculations and molecular dynamics simulations, candidate peptide-drug conjugates were evaluated. These studies helped prioritize promising compound designs and identify opportunities to optimize capping groups and linkers whilst contributing to design discussions.

Sygnature Discovery also leveraged its in-house protein production capabilities to generate FAP. This provided a consistent supply of high-quality enzyme, reducing dependence on commercial suppliers while lowering costs and accelerating assay development across both the AVA6103 program and other pre|CISION® platform projects.

The team further streamlined program execution through coordinated management of solubilizations, storage and distribution across Sygnature Discovery, Avacta and external collaborators. As the project progressed, responsibility transitioned to Sygnature Discovery's dedicated compound management group, ensuring centralized inventory control, efficient logistics and rapid compound deployment to maintain project momentum.

The pre|CISION® Controlled Release Mechanism Opens the Pipeline to a Large Number of Small Molecules



CONTROLLED RELEASE ENABLES

Greater PK control • Controlled release in the tumor • Expanded pipeline potential

Avacta
THERAPEUTICS

k_{cat}/K_m : defined as the catalytic efficiency of an enzyme. A high k_{cat}/K_m means the enzyme converts substrate to product more efficiently under low-substrate conditions

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Key Results and Impact

Key outcomes

- Clinical candidate nomination achieved within 14 months, leading to IND acceptance and FDA study approval
- >200 peptide-drug conjugates synthesized to support SAR exploration and optimization
- >400 compounds screened across cellular efficacy and enzyme kinetics, through rapid weekly testing cycles
- >40 DMPK studies completed to support compound progression and candidate selection
- Broad exploration of diverse cytotoxic warheads, linkers and capping groups to create a pre|CISION® toolbox
- >40 warhead strategies evaluated, including dual-warhead approaches
- Bespoke proof-of-concept, triage and selectivity assays developed to accelerate decision-making
- In-house FAP production established, improving assay consistency while reducing cost and supplier dependency
- Patent filed, including three Sygnature Discovery inventors, reflecting the collaborative innovation generated during the program

The collaboration between Avacta and Sygnature Discovery successfully delivered AVA6103, a FAP-activated peptide-drug conjugate selected for advancement towards Phase I trials in Q1 2026. Building on the project success of AVA6000, the program progressed from concept to clinical candidate nomination in just 14 months, highlighting the effectiveness of the close partnership between the two organizations.

Beyond the nomination of AVA6103, the project generated valuable scientific insights that strengthened Avacta's pre|CISION® platform and expanded the available design space for future drug conjugates. This collaboration demonstrated how combining Avacta's platform expertise with Sygnature's discovery capabilities could rapidly solve complex scientific challenges and translate innovative concepts into clinical development candidates.

2022

Program Launch

- Pilot purification studies for three compounds
- Formulation support and biophysical studies
- Integrated project officially launched
- Multidisciplinary team established across Chemistry, Bioscience, DMPK, Project Management, Separation Sciences, Formulation and Protein Science

2023

Early evaluation and insights

- FAP enablement of multiple warheads achieved
- Cytotoxicity and kinetics assays established to allow detailed profiling of FAP-mediated warhead release
- Screening cascade determined; plasma stability concerns optimized

2024

Platform evolution and second-generation development

- Initial exploration of camptothecins started
- Exatecan methods optimized; first FAP-enabled Exatecan compound (27 February)
- Cytotoxicity screening scaled up; FAP kinetics and payload release studies expanded

2025

Candidate optimization and IND submission

- Lead molecule selected for multi-dose studies; AVA6103 selection planned
- Scale up, purification and new warhead strategies explored
- AVA6103 patent filed
- IND submission for AVA6103 confirmed December 2025

Working Relationship

One of the key strengths of this program was the close integration between Avacta, Sygnature Discovery and external collaborators. Working as a single extended team, the partnership combined scientific expertise, operational flexibility and open communication to maintain momentum throughout the discovery campaign.

Transparent decision-making and rapid data sharing enabled the team to respond quickly to evolving priorities, address challenges as they arose, and identify new opportunities. This collaborative approach supported efficient progression of compounds, accelerated decision making, and ensured project objectives remained aligned.



Avacta AVA6103 Program Team

From left to right: Rachel Helmsley, Francis Wilson (Avacta – CSO), Stuart Paine, Florian Dato, Sophie Oakley, Tom Clough (Avacta – Senior Medicinal Chemist), Elizabeth Rosethorne, Catriona Scott, Shouming Wang, Phil Addis, Michelle Ward, Hanae Benelkebir, Girinath G Pillai

Missing from picture: Chris Blunt, David Jones, Allan Jordan, Alexa Kennedy, Katrina Lee, Folake Orafidiya, David Pearson, Curtis Rink, Rupert Satchell, Falguni Vyas, Kerry Waters, Ellen Watts

Conclusion & Future Outlook

The collaboration between Avacta and Sygnature Discovery successfully progressed from early discovery activities to the nomination of AVA6103, a clinical candidate now progressing into Phase I clinical evaluation. The first patient was dosed in the FOCUS-01 study in March 2026, marking a significant milestone for both the program and the broader development of the pre|CISION® platform. Through a combination of innovative science, multidisciplinary expertise and close collaboration, the teams overcame significant technical challenges to develop a differentiated FAP-activated peptide-drug conjugate with the potential to improve the delivery of potent cancer therapies.

Beyond AVA6103, the program expanded the scientific understanding of Avacta's pre|CISION® platform and demonstrated its potential to be applied across a broader range of drug conjugate therapies. Through its multidisciplinary discovery expertise, Sygnature helped build the knowledge base supporting future development opportunities, while generating valuable intellectual property and strengthening the platform's attractiveness for further collaborations and investment within Avacta's IP space.

Every discovery program is different, and working openly together always leads to better decisions. Our co-located, multidisciplinary teams collaborate in real time, helping ideas move quickly from data to action. We stay flexible, practical, and focused on what your program needs next.

Visit our website to explore how we can support your next steps.

Discover more