

CASE STUDY

From Lead to Pre-Candidate Nomination in 18 Months

A collaboration with STORM Therapeutics,
leveraging Sygnature Discovery's fully
integrated drug discovery services



Why Sygnature?

Expectation and Key Selection Criteria: Commentary from STORM

Selecting the right partner was critical to the success of this program. In a highly competitive therapeutic area with ambitious timelines, STORM required a collaborator with the capabilities, flexibility, and expertise to accelerate progress without compromising scientific rigor. Our decision was guided by several key factors, outlined below

Prior to project initiation, a site visit to Sygnature's Nottingham facility highlighted the impressive capabilities of its high-throughput screening (HTS) infrastructure, particularly the newly established compound management facility. To minimize cycle times and ensure seamless progression through later stages, it was essential to engage a team offering a comprehensive range of integrated functions, including *in vivo* biology and formulation expertise. Additionally, the breadth and diversity of Sygnature's chemical libraries, coupled with strong historical hit rates on comparable targets, represented a critical factor in supporting the success of the program.

At the outset of the collaboration, our expectations were clearly defined to ensure the project could progress at pace. These included the generation of functional protein and the establishment of a robust crystallography pipeline to enable structural insights early in the program. Equally critical was the development and validation of an HTS-suitable assay, capable of reproducing results with tool molecules and improving upon published methodologies to broaden discovery potential. We required a clear and ambitious timeline, underpinned by realistic go/no-go milestones and decision points to maintain momentum. Finally, flexibility was essential - Sygnature needed to remain open to, and even drive, changes in approach as the project evolved, focusing on the most impactful assays to deliver key inflection points.

The ability of Sygnature to deliver a fully integrated drug discovery program was a critical factor in the success of this collaboration. Their strong medicinal and computational chemistry capabilities complemented and augmented our internal expertise, enabling rapid and informed

decision-making. Given our prior experience with low hit rates for this target class, we sought a partner capable of deploying a broad range of hit-finding and hit-expansion strategies. Sygnature's expertise in protein production and crystallography proved invaluable, allowing the project to become structurally enabled at an early stage, which was instrumental in accelerating progress. To further expedite hit expansion, high-throughput chemistry capabilities were essential, and Sygnature delivered on this front. Their innovative use of Direct-to-Biology approaches, including Direct-to-Crystal, had a significant positive impact on the speed and efficiency of hit validation and expansion. Finally, Sygnature's strength in form and formulation became particularly important in the later stages of the program. Overall, we were seeking a true partnership with the flexibility and willingness to accelerate activities where needed and Sygnature consistently met these expectations.

"Sygnature brought real value to the DHX9 programme. Sygnature approached every biological question with curiosity and care. They implemented a flexible multi-tier biological screening cascade that turned complex biology into clear, decision-ready data. The protein sciences, *in vitro* and *in vivo* teams provided valuable insights, responded rapidly to new challenges and adapted constructively when biology didn't behave as expected."

"Sygnature didn't just run studies for us, they thought with us, strengthened our understanding of the target and helped us build a strong biological story along with a confident and efficient best-in-class DHX9i discovery."

Taran Khanam

Biology Lead and Principal Scientist
STORM Therapeutics

Sygnature's Approach and Solutions

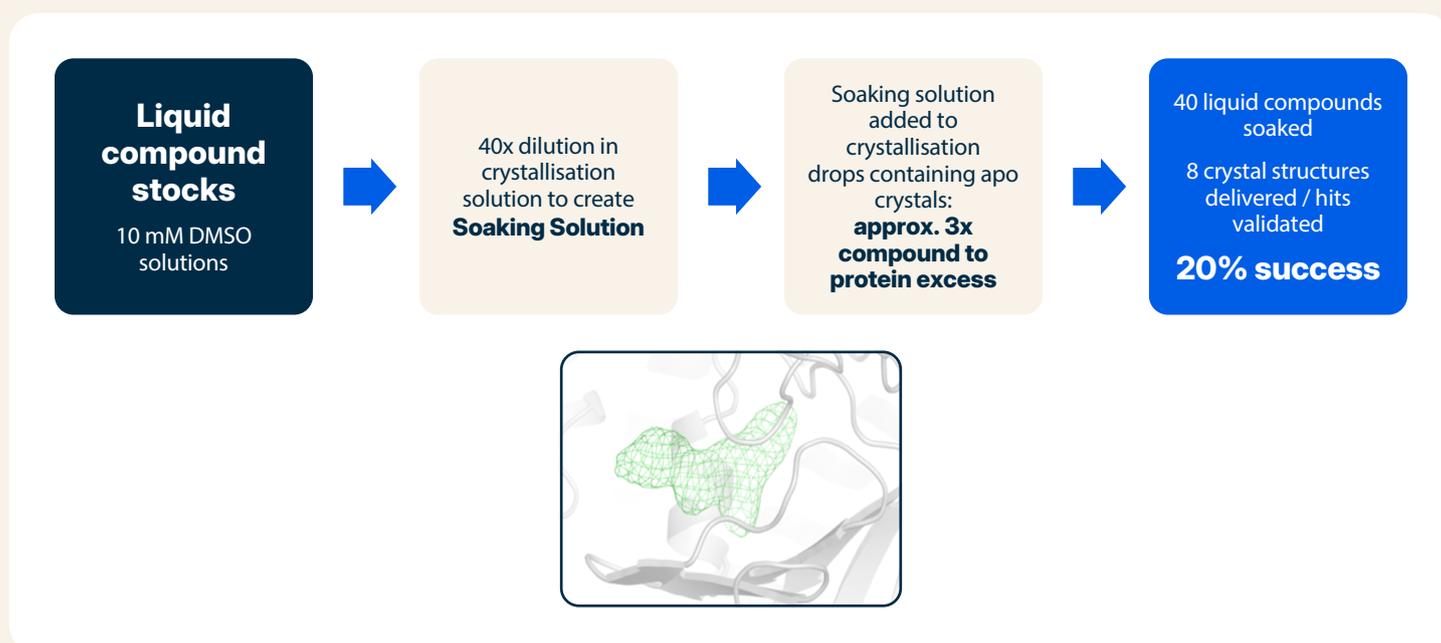
This project drew on Sygnature Discovery's deep knowledge of helicase targets and a wide range of integrated drug discovery capabilities. These included medicinal, computational, synthetic, and high-throughput chemistry; bioscience and biophysics; high throughput screening (HTS); DMPK; translational oncology *in vivo* services; form and formulation; and dedicated project management.

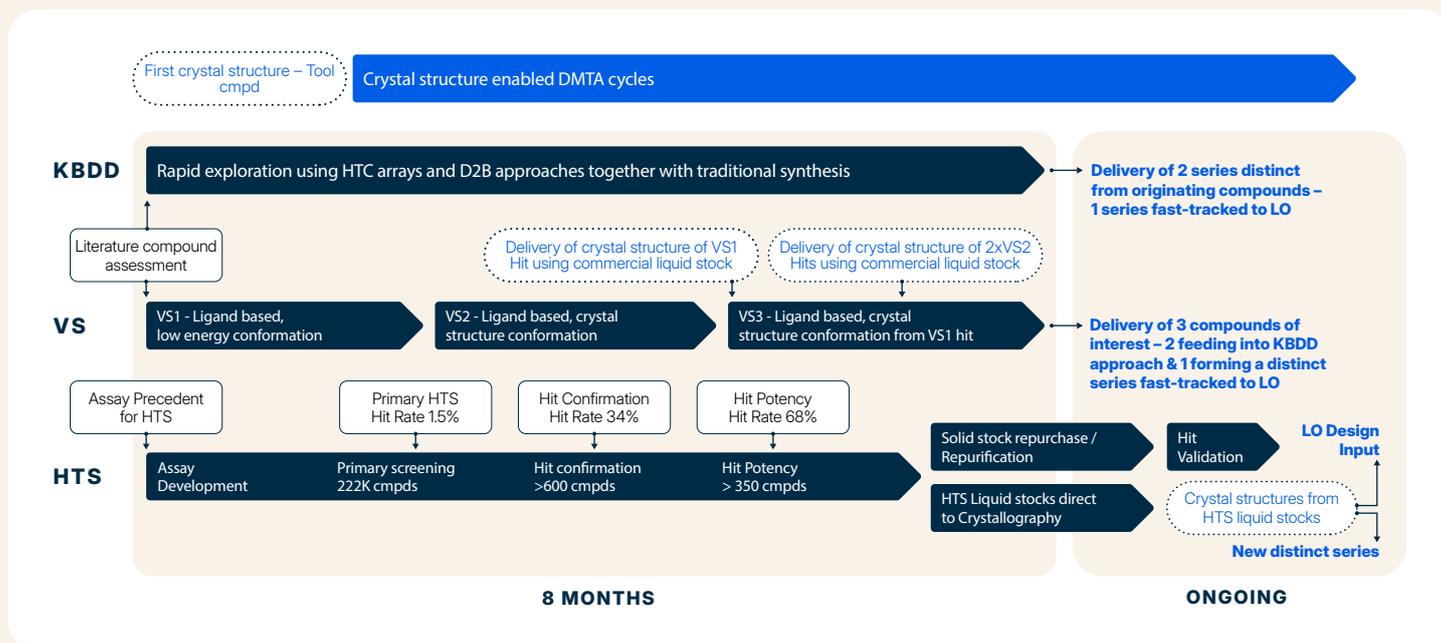
We ran several hit-finding strategies side by side (including high-throughput screening, virtual screening, and knowledge-based design) drawing on our experience with this target to quickly uncover novel hits for the customer. Building on published approaches, Sygnature refined and strengthened the screening and crystallography workflows, ensuring better assay results and more robust data for decision-making. Chemically diverse hits from every approach were rigorously validated with bespoke, orthogonal assays and a Direct-to-Crystal workflow that proved highly successful. To accelerate hit validation and support structure-based design, Sygnature combined the use of liquid compound stocks from HTS with its deep crystallography expertise. This allowed us to quickly resolve structures and understand how ligands interact with the protein, giving the team the insight needed to guide medicinal chemistry with precision and speed. By avoiding delays associated with compound re-synthesis or re-acquisition, this approach ensured faster decision-making and maintained project momentum.

Following hit validation, rapid hit expansion was achieved using high-throughput chemistry (HTC) and Direct-to-Biology approaches, closely integrated with traditional medicinal chemistry design. By harnessing AI-driven design and *in silico* approaches, we generated innovative chemical ideas and strategically selected compounds for synthesis – accelerating progress and improving outcomes.

A key factor in the program's success was Sygnature's ability to draw on expertise from every discipline across the drug discovery spectrum, precisely when needed. With expert insight on hand, the team was able to solve problems quickly, apply solutions efficiently, and keep progress on track.

By leveraging Sygnature's [Hit Synergy platform](#) and fully integrated drug discovery capabilities, STORM was able to accelerate internal efforts and maintain momentum toward their ambitious development goals. Sygnature established the screening cascade and completed Hit identification, including HTS, within 6 months of project initiation. Lead molecules were progressed through lead optimization to pre-candidate nomination within 12 months. Through investigation of these proprietary leads internally, STORM was able to clarify their mechanism of action and identify additional treatment possibilities – validating their importance and expanding the program's scope.

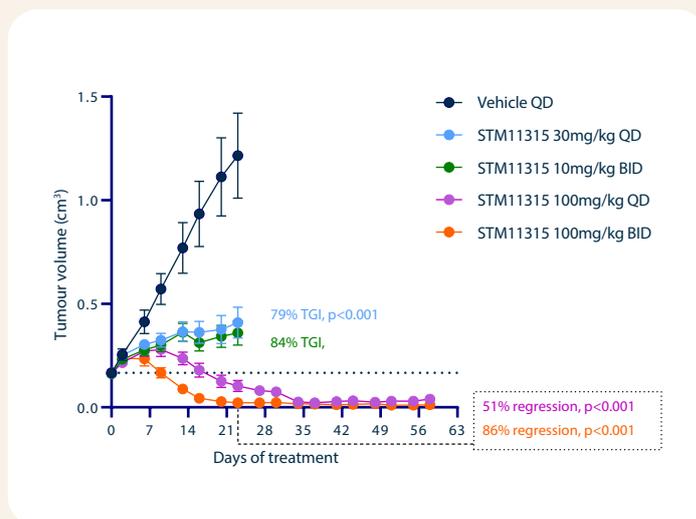




Key Results and Impact

The schematic above shows how multiple hit-finding strategies ran in parallel at Sygnature during the early phase of the project. Each stream worked in sync, enabling cross-disciplinary collaboration that delivered several lead series in novel IP space which were fast-tracked to Lead Optimization.

Through iterative rounds of optimization, we were able to develop promising molecules for *in vivo* studies. The molecule used in the efficacy study has been shown to be a cell potent, selective DHX9 inhibitor that induces anti-proliferative effects via increased replication stress, cell cycle arrest and apoptosis. It has an excellent oral drug profile, no safety or CYP DDI liabilities, whilst also demonstrating brain penetration, a differentiating factor to competitor molecules. Our Translational Oncology team, who ran the efficacy study on behalf of STORM, demonstrated that the molecule was well tolerated *in vivo*, achieving complete and durable tumour regression in a CRC CDX model, with no regrowth for five weeks post-treatment. Pharmacodynamic markers confirmed on-mechanism activity.



Within a year, the team successfully advanced from lead optimization to preclinical candidate nomination—underscoring the efficiency and focus of the collaboration.

Working Relationship

One of the key strengths of this program was the close collaboration between the STORM and Sygnature project teams. From the outset, STORM set a clear strategic direction and together, the teams built a highly communicative environment with regular discipline-specific meetings and full team updates.

"It has been a pleasure to work with the Sygnature team on our best-in-class inhibitor project. From project start, the multi-disciplinary team at Sygnature functioned as an extension of our in-house team, providing additional expertise across the drug discovery process; particularly in protein sciences, computational and synthetic chemistry and *in vivo* biology.

They responded fearlessly to our ambitious timelines and collaborated closely to allow us to achieve preclinical candidate compound nomination within a really impressive time-frame. I wouldn't hesitate to work with the Sygnature team again."

Helen Harrison

Director of Discovery Biology
STORM Therapeutics

Sygnature's project management kept everything transparent, with a clear financial and action-based audit trail throughout. Open, honest communication built on trust and respect created a safe space for constructive challenge, enabling both teams to consistently pursue the best ideas and most effective solutions.

Efficient data sharing was critical to success. By streamlining this process at the start of the program, we created a seamless system that supported every assay, captured all data and analyses, and kept the project running smoothly right through to the final stages.

When speaking with STORM, they noted that in addition to demonstrating a high level of technical expertise, Sygnature scientists consistently showed flexibility and openness to scientific dialogue. Areas of disagreement or data-related queries were addressed promptly and professionally, ensuring smooth progress throughout the collaboration. When additional data or studies were required at short notice, Sygnature responded with exceptional speed and efficiency.

A standout example highlighted by STORM, was the urgent need to generate *in vivo* efficacy data on a tool compound within a very tight timeline to meet an internal deadline. Working closely with our *in vivo* scientists, Sygnature devised and executed an aggressive plan that successfully delivered critical data, which has since been presented externally.

Conclusion & Future Outlook

The team's initial goal was to identify lead molecules for hit-to-lead progression within 10 months. Not only was this milestone met, it was exceeded – advancing ahead of schedule into lead optimization.

Sygnature embraced STORM's ambitious timelines to deliver a pre-development candidate within the following 12 months. By the end of the collaboration, we had delivered a molecule with strong selectivity, efficacy, PK/PD, a clean safety profile, high potency, and low predicted human dose.

Next-generation molecules from this series now stand as best-in-class DHX9 inhibitors, ready for preclinical development and reinforcing STORM's leadership in this space.

"Sygnature has a very strong group of scientists who were willing to go above and beyond expectations to help us deliver a very strong development candidate. Their expertise in all aspects of the drug discovery process is among the best I have seen in the industry and I would definitely work with them again."

Peter Astles

Project Lead and Principal Scientist
Chemistry, STORM Therapeutics

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](#)