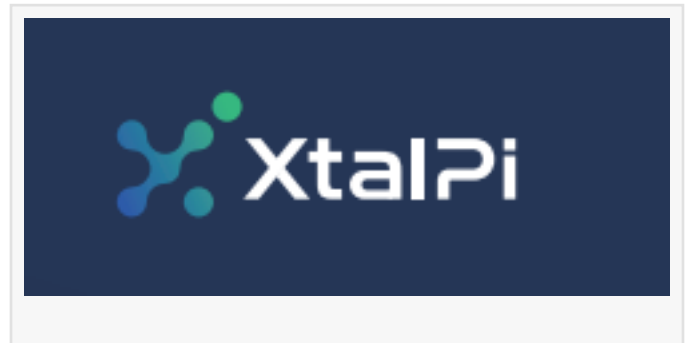


Overcoming the Limitations in siRNA Drug Development: XtalPi's AI-Powered Generative siRNA Therapeutics Design Platform

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/EINPresswire.com/ -- Small interfering RNA (siRNA) therapeutics are RNA-based medicines that silence disease-associated genes by directing the sequence-specific degradation of target mRNA, thereby preventing the production of pathogenic proteins. The landscape of modern medicine is shifting toward precision at the molecular level, yet significant limitations in siRNA drug development continue to hinder the full potential of nucleic acid therapies.



The critical bottlenecks in siRNA therapeutics includes: disconnected sequence design and chemical modification optimization, a crowded intellectual property (IP) landscape, inconsistent translation from in vitro activity to in vivo efficacy, and barriers to effective extrahepatic delivery.

To overcome these challenges, [XtalPi](#) (HKEX:2228) developed Kodexia™, the pioneer platform to apply both generative AI and first-principles approaches to siRNA drug development.

Kodexia™ is an AI-centric platform that embeds artificial intelligence across sequence design, modification recommendation, experimental validation, delivery optimization, and IP-informed design for siRNA therapeutics. By fusing first-principles mechanistic knowledge—such as RNA thermodynamics and structural properties—with AI models, Kodexia™ co-optimizes multiple objectives simultaneously, including in vitro/in vivo silencing efficiency, extended durability, safety, and freedom to operate (FTO), to efficiently identify and prioritize differentiated candidates.

Together, these capabilities form an integrated approach to overcoming key bottlenecks across siRNA therapeutics discovery and development—from molecular design and translational prediction to extrahepatic delivery and next-generation therapeutic innovation.

Kodexia™—An AI-Centric, Integrated Dry-Wet Closed Loop Platform for siRNA Therapeutics Development

Generative AI Models for Sequence and Chemical Modification Design Expands Differentiated Design Space

Kodexia™ has developed generative and discriminative AI models purpose-built for siRNA drug

design. Given a specific target, the platform can generate and prioritize candidate sequences. Compared with conventional approaches that rely heavily on rigid design rules, Kodexia™ explores a broader sequence space and evaluates candidates across predicted silencing activity, stability, and off-target risk.

A key innovation of Kodexia™ is the joint optimization of sequence design and chemical modification within a unified AI framework. Rather than applying a fixed modification template, the platform recommends sequence-dependent modification patterns tailored to each unmodified sequence. Its multi-objective optimization framework is designed to improve gene-silencing performance while balancing off-target risk, durability, and potential IP differentiation. In internal head-to-head studies, Kodexia™-recommended modification patterns achieved stronger silencing activity than the conventional Advanced ESC strategy in more than 70% of tests under low-concentration conditions. Across active pipeline programs, the platform has also supported the early identification of multiple lead molecules with activity comparable to or better than industry positive controls. By exploring sequence space beyond existing patent-protected designs, Kodexia™ may help generate differentiated candidates and support subsequent freedom-to-operate (FTO) assessments for global development.

Predictive Modeling and Closed-Loop Validation Bridge: the In Vitro – In Vivo Gap

A long-standing challenge in siRNA drug development is the disconnection between in vitro activity and in vivo efficacy. Even siRNA candidates with strong cellular activity may underperform in animal studies because their in vivo performance is influenced by multiple factors, including delivery, stability, biodistribution, cellular uptake, endosomal escape, and metabolic clearance.

Kodexia™ goes beyond predicting in vitro activity by incorporating in vivo efficacy prediction models designed to support translational decision-making. These models assess the in vivo performance of candidate molecules earlier in development, helping prioritize candidates with stronger translational potential and reduce resources spent on low-potential experiments. Built on large volumes of high-quality in vivo siRNA data, Kodexia™ has developed modeling strategies tailored to hydrodynamic injection (HDI) mouse models, adeno-associated virus (AAV)-based mouse models, transgenic mouse models, and non-human primate studies. These models support the prioritization of candidates with the potential to outperform positive controls in initial in vivo screening, helping shorten the path to preclinical candidate (PCC) nomination.

A Multi-Pathway Technology Portfolio Advances Extrahepatic Delivery

Expanding siRNA delivery beyond the liver is key to realizing the full therapeutic potential of RNA interference, as many disease-relevant genes are expressed in tissues not accessible to current liver-targeted systems. Effective tissue-specific and intracellular delivery would enable broader application of siRNA therapeutics across renal, metabolic, neuromuscular, neurological, and ophthalmic diseases.

Although GalNAc conjugation has transformed siRNA delivery to hepatocytes, achieving comparable efficiency and specificity in extrahepatic tissues—including the kidney, adipose tissue, skeletal muscle, central nervous system, and eye—remains a major industry challenge. Each tissue presents distinct biological barriers related to biodistribution, cellular uptake, and

intracellular release, requiring delivery solutions tailored to the target organ and cell type. Drawing on the team's extensive R&D experience in lipid nanoparticles, antibodies, and peptides, Kodexia™ is building a multi-pathway delivery technology portfolio. Current approaches include lipid nanoparticles, small-molecule conjugation, peptide conjugation, and fatty-acid conjugation, with priority programs focused on delivery to the kidney, adipose tissue, and muscle.

Kodexia™ Expands the Possibilities of Next-Generation siRNA Therapeutics

Integrated Dual-Target Design Enables Coordinated Optimization

In complex diseases, silencing a single target does not always produce the desired therapeutic phenotype. Metabolic disorders, complement-mediated diseases, and other conditions driven by multiple biological pathways may require more coordinated intervention. Dual-target siRNA therapeutics offer a potential strategy for simultaneously modulating two disease-relevant targets.

Kodexia™ addresses the long development timelines and optimization complexity associated with dual-target siRNA through an integrated design paradigm. Conventional workflows typically develop two single-target siRNAs separately before combining or chemically linking them. Instead, Kodexia™ treats the dual-target construct as a single chemical entity, jointly optimizing the two antisense-strand sequences, their modification patterns, the spatial topology of the linker, and the overall physicochemical properties from the earliest stage of design.

This integrated approach is designed to achieve a "1+1>2" synergistic effect while increasing development efficiency. By coordinating the optimization of both target arms, Kodexia™'s workflow can deliver at least a two-fold improvement in R&D speed compared with conventional sequential approaches. By reducing redundant optimization, this also lowers R&D costs.

Multi-Omics and AI Support Novel Target and Asset Discovery

Beyond optimizing siRNA molecules against established targets, Kodexia™ integrates human multi-omics datasets with AI prediction models to support large-scale virtual screening for the early identification and prioritization of novel targets. The platform is therefore designed not only to generate molecules faster, but also to enable the discovery of more differentiated next-generation therapeutic assets.

Across dual-target programs, extrahepatic delivery, and novel mechanism discovery, Kodexia™ aims to advance pipelines with first-in-class (FIC) or best-in-class (BIC) potential. By maintaining efficient design and rapid iteration across different target tissues and increasingly complex molecular architectures, the platform seeks to expand the therapeutic possibilities of next-generation siRNA medicines.

By integrating generative AI and first-principles modeling with sequence-dependent chemical modification design, prospective in vivo efficacy prediction, and closed-loop experimental validation, Kodexia™ directly addresses key bottlenecks in siRNA therapeutics development. This AI-powered generative siRNA therapeutics design platform unifies traditionally fragmented stages of discovery into a single, data-driven workflow, enabling systematic exploration of differentiated sequence and chemistry space. As a result, it improves the efficiency and reliability

of candidate optimization, accelerates the identification of extrahepatic and dual-target siRNA molecules, and enhances the probability of clinical translatability.

Kodexia™ is designed to overcome core limitations in siRNA therapeutics development and enable the creation of differentiated, first-in-class or best-in-class candidates, ultimately broadening the therapeutic reach of RNA interference to more diseases and more patients. For more information on the Kodexia™ platform and XtalPi's research capabilities, please visit: <https://en.xtalpi.com/>

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