Verseon Corporation
www.verseon.com

Broadening the drug discovery pipeline

Verseon's unique computational platform is driving the identification and optimization of novel drug candidates for a broad range of indications.

Patients and doctors alike hope for 'magic bullets'—exquisitely precise drugs that treat disease effectively while leaving normal physiology intact. Advances in structural biology and computer modeling suggested to some that virtual drug discovery would soon bring the industry closer to this goal, yet the promise of computational drug discovery has remained largely unfulfilled. Verseon, after a decade of R&D, has created a proprietary, computation-based drug discovery platform that can be used to drive the identification and optimization of novel drug candidates for a broad range of indications. The results obtained so far serve as proof of concept that the company's computational platform yields unique molecules unlikely to be found by conventional methods.

Despite a recent uptick in US Food and Drug Administration approvals driven by fast-tracking of compounds designated as 'breakthrough' therapies, the overarching trend in the biopharmaceutical sector is a decline in return on investment. Novel protein targets and structural data are widely available, but, despite the widespread use of high-throughput screening (HTS) of millions of compounds, the process of discovering new active chemical entities remains a bottleneck. Computational methods and modeling seem to offer clear advantages over HTS: no up-front compound synthesis is needed, and a much wider range of chemotypes can be explored. But past computational methods, based largely on empirical models, have proven inadequate for accurate modeling of protein–ligand interactions in water, and to date virtual drug discovery has yielded few drugs.

The Verseon computational discovery platform, comprising a Molecule Creation Engine (MCE) and a Molecule Modeling Engine (MME) (**Fig. 1**), relies on first principles of chemistry and physics, rather than training on 'big data'. The platform achieves more accurate results than competing methods by going beyond classical physics to approximate quantum interactions, while avoiding the excessive computation that would be required for a full quantum simulation. According to David Kita, Verseon's cofounder and vice president of research, "We do on the order of trillions of calculations per small molecule against the target protein, but [success] is all about doing the *right* trillions of calculations."

The company's MCE engineers novel molecules by exploring a chemical 'space' that theoretically spans as many as 10^{40} compounds. Kita compared this increase in the coverage of chemical 'space' relative to that of existing screening collections to "searching in an ocean rather than a tide pool." The MCE also filters for drug likeness (e.g., modifications of Lipinski's rule of five, identification of potential toxic or reactive motifs, etc.). Although drug likeness is commonly assessed in computational chemistry, Verseon's MCE is the first to also directly incorporate synthesis reaction rules into its compound-construction algorithms to ensure that the compounds generated virtually can be readily synthesized for testing.

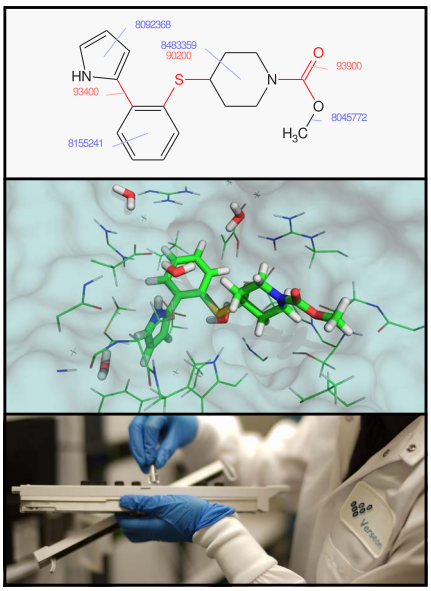

Figure 1: Verseon's discovery platform at a glance. The molecule creation engine (MCE) generates novel and drug-like compounds with predetermined synthesis routes. The molecule modeling engine (MME) accurately predicts binding affinity to the proteins of interest. Compounds that show promise are synthesized and tested in the company's fully equipped laboratories.

The MME relies on proprietary algorithms to model protein and small-molecule interactions in all their complexity. These physics-based algorithms accurately represent, for example, polarization and solvation, discrete ordered waters, hydrogen bonding, and entropic effects to estimate the binding affinity of various 'docking' configurations for a small molecule and the target protein. Compared to approaches that rely on empirical models, Verseon's approach offers greater precision over a wider range of molecular interactions and protein–small molecule systems.

Using its proprietary platform, Verseon has identified diverse chemotypes with potent activity against a number of target proteins. Having multiple chemical series per program reduces risk, allowing multiple 'shots on goal' and improving the overall probability of success in reaching the clinic. According to Verseon, this potential to "broaden the drug discovery pipeline" could be transformative for the industry. Verseon has built in-house biology, medicinal chemistry, and pharmacology capabilities with the intention of moving its programs into the clinic independently while retaining the option to partner some programs as the portfolio matures.

Verseon has drug programs in three areas: anticoagulation, diabetic macular edema (DME), and angiogenesis inhibitors for solid-tumor cancers. The anticoagulation project is the most advanced, with multiple new chemotypes demonstrating preclinical *in vivo* efficacy. Although new oral anticoagulants have permeated the market, major bleeding events remain a risk with these medications. In preclinical testing, Verseon's candidate compounds show a lower risk of bleeding than current therapies. Across a variety of preclinical studies, the Verseon candidates demonstrated efficacy comparable to that of approved drugs, including arteriovenous shunt and venous stasis models in rats. Verseon's lead candidates have a novel mode of action: they bind reversibly and covalently to thrombin, with one portion of the molecule conferring selectivity and the other delivering potency by covalently binding to block the enzyme's active site.

In its other programs, Verseon has also identified novel and promising compounds. In DME, the program goal is to develop a topical therapy to replace current injectable drugs. The Verseon compounds inhibit plasma kallikrein, a clinically relevant target associated with inflammation and retinal vascular permeability. In its angiogenesis-inhibitor program, Verseon has identified non-kinase inhibitors that effectively block angiogenesis in cell-based functional studies but show little cytotoxicity or disruption of existing blood vessels. Verseon is working aggressively to move all three projects forward, and it is also initiating new projects, with the ultimate goal of bringing new drugs to market and making a difference in people's lives.

contact
David Williams, Director R&D
Verseon Corporation
Fremont, California, USA
Phone: +1-510-225-9000
Email: info@verseon.com