Beactica's drug discovery platform delivers promise for brain tumour therapy

Beactica's CEO, Dr Per Källblad, explains how the company's specialist small molecule drug discovery platform is developing a novel therapy for glioblastoma

Glioblastoma is a particularly malicious type of fast-growing brain cancer that occurs spontaneously and progresses aggressively, with patients rarely surviving longer than one year after diagnosis. The disease is characterised by the involvement of a broad variety of genetic and epigenetic mechanisms.[1] There is currently no cure and the treatment – which is based on surgery, chemotherapy, radiation therapy and orphan drugs – may, at best, slow down the progress and reduce symptoms. As the tumour grows and migrates into the surrounding brain tissue, complete removal becomes very challenging and there remains an unmet need for new glioblastoma therapies.

Fragment-based drug discovery

Finding such therapies can be a long, complex and risky business. Drug discovery and development is the process of bringing a novel compound to market as a pharmaceutical drug. The journey from being a molecule in a compound library to becoming a candidate drug requires a great deal of profiling in order to define the molecule's potency as well as possible side effects. As a part of the process, fragment-based drug discovery is an established method to find chemical compounds that, after enrichment, are more likely to be therapeutically useful. It uses screening to select small chemical fragments that can be further optimised in order to generate a potent lead.

For a drug to work, it must first bind to its target protein. During the 1980s the method of surface plasmon resonance (SPR)-based biosensors was initiated, introducing a binding assay without radio or fluorescent labelling. This label-free, optically based method allows the study of real-time interaction between target proteins and analytes to show a complete picture of the binding events that take place in affinity-based assays. Molecules that are structurally similar can have similar binding affinities but different interaction kinetics and, therefore, exhibit a different therapeutic effect.

Over the years, the throughput capacity of SPR-based sensors has improved considerably from the early, manually performed low-throughput assays. By being able to determine not only affinity, but also kinetics, directly in complex samples, the information about the compound and thus also the range of applications is extended. SPR-based biosensors therefore allow researchers to investigate molecular interactions under near physiological conditions.[2]

The Beactica SPR biosensor platform

Beactica AB is a specialist drug discovery company, utilising proprietary methodologies to

evaluate the interactions of molecules in order to generate novel and mechanistically defined therapeutics. Beactica was founded in 2006, based on SPR biosensor research carried out at Uppsala University in Sweden. The company has since then applied its drug discovery platform to efficiently deliver solutions for challenging projects, both within Beactica's pipeline as well as to some of the world's largest pharmaceutical companies. Beactica is now prioritising its world-leading platform to build a pipeline of small molecule therapeutics to address unmet medical needs.

The small molecule drug discovery platform upon which Beactica has built its success is based on state-of-the-art SPR biosensor technology, augmented by the in-house development of proprietary methodology, approaches, algorithms and experimental designs at Beactica. The platform generates unique insights into how small molecules interact with a target protein of potential therapeutic importance. This allows the scientists to both identify and optimise novel selective lead compounds with a high development potential as well as a reduced risk of failure, in both early and late stages of the drug discovery process. The approach works also when protein crystallisation is not feasible, meaning that a wider range of protein targets can be addressed than would be possible using structure-based approaches.

Novel cancer therapeutics

Following a collaboration with researchers at Uppsala University, who provided a unique capability to study glioma-initiating cancer stem cells,[3,4] Beactica embarked on developing a new type of glioblastoma therapy. The company's drug discovery platform is being used to build a pipeline of novel compounds, with the most advanced programme currently focusing on modulators of LSD1. This target protein is known to be relevant for the treatment of several common cancers, and enzymes that control epigenetic alterations of gene expression are of significant interest as targets for cancer therapy.

LSD1, which was discovered in 2004, is a histone demethylase involved in epigenetic modifications by regulating a broad spectrum of biological processes essential for normal development and tissue-specific patterns of gene expression. LSD1 can affect gene transcription through dual functions; both as an epigenetic eraser removing histone methyl marks, and as a scaffolding protein in suppressor and promoter complexes. The enzyme is required for normal differentiation and stem cell maintenance but is found to be overexpressed in several types of cancer[5] and just recently, researchers presented a strong connection between LSD1 and immuno-oncology.[6]

These findings make LSD1 highly interesting from a novel cancer therapy point of view. The first-generation LSD inhibitors that were developed displayed many off-target, fairly toxic effects but currently, more specific LSD1 catalytic inhibitors are undergoing clinical testing.[7]

Beactica's novel and potent allosteric LSD1 modulators have a mechanism of action that is fundamentally different from their catalytic counterparts. LSD1 is here impacted without inhibiting its enzymatic activity, thus giving unique biological efficacy and the potential to provide an improved therapeutic response. Non-toxic doses have resulted in significant reductions of the LSD1 protein in cancer cells, indicating potential for a broad oncology scope. The compounds show full *in vitro* efficacy in more than 40 diverse cancer cell lines and exhibit a unique sensitivity profile that is distinctly different from over 300 tested diverse reference compounds.

The progress made in the LSD1 programme has led to international recognition from official sources and Beactica has been awarded two grants during the last year. These grants have provided the company with SEK 2.5 million (~€240,000) to develop the LSD1 modulators as therapeutics against glioblastoma. The first grant was awarded in November 2017 by VINNOVA, the Swedish Governmental Agency for Innovation Systems. The second grant was awarded in March 2018 by the European innovation fund Horizon2020.

Against the significant need for improved therapies for glioblastoma, Beactica's LSD1 programme is accelerating rapidly as the compounds have shown very promising results in pre-clinical studies so far. In August, Beactica commenced the first *in vivo* proof-of-concept study for its LSD1 modulators. Discussions with several leading pharmaceutical companies indicate that a positive result from such a study would open up for partnership negotiations.

Elevating the technology to the next level

Diverse components that can interact successfully with a particular binding site can be efficiently identified through screening of well-designed fragment libraries with only a few thousand members. Moreover, fragment-based methods tend to generate more efficient starting points for lead generation than traditional high-throughput screening methods. This is important, since retrospective analyses have shown that ligand efficiency tends to decrease during lead generation and optimisation of compound series. The weak interactions between fragments and proteins demand sensitive detection systems. High sensitivity, combined with low protein consumption and flexible experimental design, therefore make SPR biosensor-based interaction analysis ideal for fragment-based drug discovery.

The Beactica fragment library is designed for diversity and extensively validated for SPR biosensor-based drug discovery on a wide range of challenging target proteins. The specificity, binding site location and thermodynamic profile of hits can be included as criteria, thus increasing the quality of hits in the screening.

Beactica's proprietary software provides a decision tool for the evaluation of SPR biosensor-based dose-response data of the prospective lead. The software is designed to distinguish non-specific signals from real binding events and is also suited for understanding and exploiting data from targets lacking positive controls. The software enables quantification of the degree of specificity of the dose-response signals, accomplished through unique algorithms.

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