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Product Discovery & Development

Scaling up in epigenetics

By Mike Ward
Senior Editor

GlaxoSmithKline plc last week confirmed its belief that epigenetics might be a useful tool in the discovery of new anti-inflammatory drugs. Convinced by a growing body of scientific evidence that epigenetic processes such as DNA methylation and histone modifications are critical regulatory events in mammalian gene expression, the pharma has acquired exclusive access to a platform technology developed by **Cellzome Inc.** for the discovery of oral small molecules to treat immuno-inflammatory diseases.

Epigenetics is concerned with heritable changes that do not change the DNA sequence, but instead involve stable modifications of chromatin, DNA or protein conformation. Much of the field's scientific focus has been on histone demethylases, which modify chromatin function and are seen as potential targets for treating immune diseases.

Until recently, commercial interest in epigenetics has been focused on oncology, and only two classes of targets — histone deacetylases and DNA methyltransferases — have yielded approved drugs.

Having worked closely with a number of academic groups, GSK believes the discipline could become a major drug discovery tool. To that end, the pharma has established a discovery performance unit (DPU) within its Immuno-Inflammation Centre of Excellence for Drug Discovery (II-CEDD). The EpiNova PDU will focus its epigenetics ambitions, particularly in inflammation and immunology.

"There is a growing body of scientific evidence which suggests that epigenetics is having a profound impact on immune function," said Kevin Lee, VP and head of EpiNova.

EpiNova has academic collaborations focused on understanding the therapeutic potential of epigenetic pathways in immune diseases. The largest is a public-private partnership involving **The Wellcome Trust** and the **Structural Genomics Consortium** (SGC), a not-for-profit organization. That collaboration aims to develop chemical probes to affect the activity of proteins involved in epigenetic control.

GSK has also established links with laboratories run by key opinion leaders in the field, including Alexander Tarakhovsky, head of the Laboratory of Lymphocyte Signaling at the **Rockefeller University**, and Gioacchino Natoli of the **European Institute of Oncology**.

Tarakhovsky's laboratory is studying cell signaling and epigenetic mechanisms involved in immune cell responses to pathogens. He identified the role of protein lysine methylation in transmitting signals from the T lymphocyte membrane to the nucleus and is now suggesting that protein lysine methylation plays a more general role in the regulation of lymphocyte signaling and function.

His lab also has demonstrated the existence of functional histone-like sequences in non-histone proteins, raising the possibility of a new mechanism for epigenome regulation.

Natoli's laboratory is working on biochemical mechanisms that regulate distinct immune responses, with emphasis on the regulation of inflammation and specifically chromatin-mediated control of inflammatory responses.

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His group is looking to identify mechanisms controlling complex temporal patterns of inflammatory gene expression. Its more recent work has focused on the role of chromatin modifiers, and particularly histone demethylases, in inflammation.

The deal signed last week with Cellzome provides EpiNova with exclusive access to the biotech's Episphere platform in the immuno-inflammation space. The partners hope to identify small molecules against targets associated with four undisclosed epigenetic target classes.

Episphere is a suite of quantitative proteomics technologies involving a bead matrix that captures more than 700 different proteins directly from cells, including epigenetic enzymes in their normal form, typically as large protein complexes.

> ***"Studying epigenetic complexes in the real environment allows us to get greater insights in terms of selectivity that you can't get from recombinant approaches."***
>
> **David Simmons, Cellzome Inc.**

Compounds added to a cell or tissue compete with the Episphere bead matrix to bind with the enzyme targets and their complexes. Using mass spectrometry, Episphere can measure the interaction of drug candidates with epigenetic targets directly in cells and tissues, and it can distinguish between the large complexes in which epigenetic targets operate.

According to CSO David Simmons, a key feature is the ability of the chemical proteomics platform to screen and profile inhibitors of epigenetic targets directly in the lysates of natural cells and tissues.

"Studying epigenetic complexes in the real environment allows us to get greater insights in terms of selectivity that you can't get from recombinant approaches," he said. "This is very important in epigenetics because when working with recombinant cells you sometimes just can't make sense of the data because you don't get the regulator or adaptor proteins — the whole biological context."

The partners expect it will take about a year to identify the most appropriate targets. Over the subsequent 12-36 months, the collaborators will look to optimize lead candidate inhibitors.

"The role of the 150 or so enzymes thought to be involved in the epigenome has yet to be fully understood by either academic or industrial research groups. So it follows that we will be reacting to new publications and insights as they are produced by other people," Cellzome President and CEO Tim Edwards told BioCentury.

Simmons said the partners expect the compounds coming out of the collaboration will be more potent and selective "than the first generation of HDAC and DNA methyltransferase inhibitors. Our platform allows us to optimize the potency and selectivity and can still underpin preclinical developments such as cross-species profiling because we can get the same complexes out of different lysates from different species to support efficacy and tox."

GSK is paying Cellzome €33 million ($45 million) up front, comprising technology access fees and an equity stake. The biotech is eligible for milestones that could exceed €475 million, and tiered royalties for each program.

GSK has exclusive access to the Episphere platform for all immuno-inflammatory diseases until the partners focus on specific research programs or biologic targets. At that point, the broad exclusivity around the platform falls away and will be replaced by exclusivity around therapies associated with a particular target.

This is not the first time GSK and Cellzome have worked together.

In September 2008, Cellzome and GSK entered an alliance to use Cellzome's Kinobeads technology to identify, develop and market therapeutics to treat inflammatory diseases against seven different kinase targets. Under that alliance, Cellzome has operational responsibility for the discovery and early-stage development of the compounds through to clinical proof of concept (POC) in a relevant patient population. To date, GSK has made four milestone payments.

COMPANIES AND INSTITUTIONS MENTIONED

Cellzome Inc., Boston, Mass.
European Institute of Oncology, Milan, Italy
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Rockefeller University, New York, N.Y.
Structural Genomics Consortium (SGC), Oxford, U.K.
The Wellcome Trust, London, U.K.