

Episphere™ Technology

What is Episphere™?

Episphere™ is a suite of quantitative proteomics technologies for the discovery of drug candidates for epigenetic targets. Episphere™ can:

- Measure the interaction of drugs with epigenetic targets directly in cells and tissues
- Distinguish between complexes - the 'cellular machines' - which epigenetic targets operate in
- Monitor the effects of a drug on the 'epigenetic signature' in cells and tissues

With Episphere™, epigenetic targets can be screened in their native environment as part of their protein complexes without the need for recombinant protein or any other artificial labelling.

What are the advantages over other techniques?

There are three major advantages:

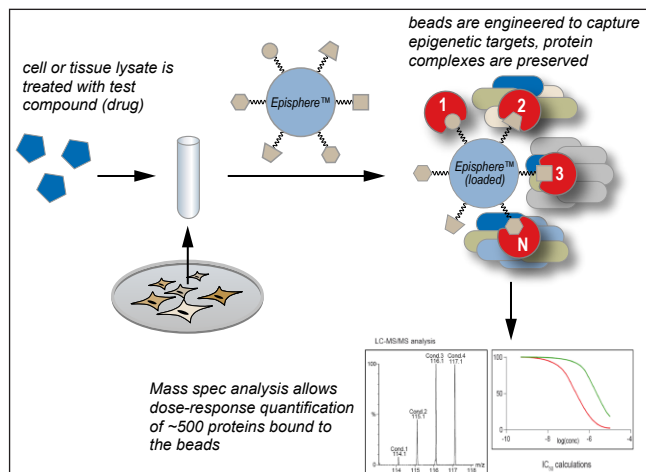
- With Episphere™ technology native proteins are used, exactly as they are found in the cell in their natural environment, instead of recombinant (artificially produced) enzymes. This is particularly important for epigenetic enzymes, since inhibition data of compounds generated with artificial assay systems seem to be often unreliable.
- Epigenetic enzymes operate in large protein assemblies (protein complexes), which regulate the activity of the enzyme and target it to its site of action. These protein complexes represent the true target of any drug and are used in Cellzome's Episphere™ screening and profiling assays.
- Assessing the selectivity of inhibitors across the epigenetic target classes is a key factor in understanding its mechanism of action and potential side effects.

Why target epigenetic enzymes?

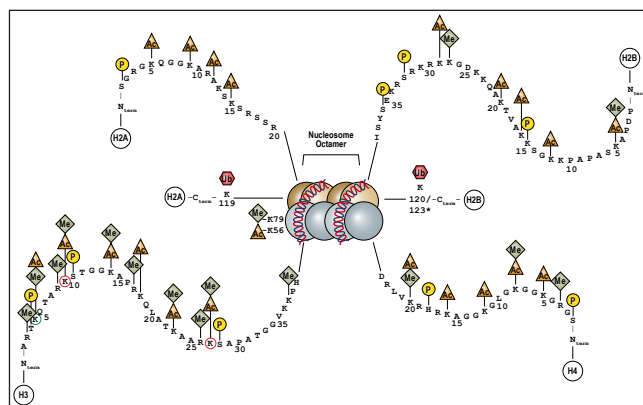
Epigenetic enzymes regulate histones (the DNA 'packaging') or DNA by chemical modifications like methylation or acetylation. Such modifications determine whether genes are switched on or off in a highly specific manner. Dysregulation of these processes plays a central role in a number of diseases, ranging from cancer to chronic degenerative diseases, like auto-immune and neurological disorders.

Epigenetics and drug discovery

The first, nonselective HDAC inhibitor, Zolinza™ (Vorinostat) was approved in 2006 for cancer, and demonstrated that interfering with epigenetic enzyme function has great medical utility. However, the role of many of the more than 150 epigenetic enzymes encoded in the human genome is still poorly



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Genome dynamics under epigenetics control: The histone code. Histone tail modification (acetylation, methylation, phosphorylation) and nucleosome positioning controls gene transcription and cell fate.

understood. This provides a wealth of new opportunities for novel therapeutic approaches, provided selective inhibitors can be found and their mechanism of action can be well characterized. Episphere™ is the ideal technology to achieve this.

How does Episphere™ work?

• Capturing a sub-proteome of drug targets

The Episphere™ bead matrix captures more than 700 different proteins, including many epigenetic enzymes, in their native form directly from cells – typically as large protein complexes in which the actual drug target is decorated with several regulatory and targeting subunits.

• Measuring the effect of compounds

A compound or drug added to a cell or tissue (either in vitro or in vivo) will compete with the Episphere™ bead matrix for binding of the enzyme targets and their complexes. This competition is quantified with mass spectrometry and a full target profile is determined from a single tissue sample.

Episphere™ - powering drug discovery in epigenetics

Episphere™ drives Cellzome's drug discovery projects in epigenetics from hit seeking through lead optimization and profiling in human tissues:

• Screening and Lead Optimization

We screen compound libraries of about 50,000 compounds against targets, which are otherwise difficult to screen. The targets are assayed in their natural environment, in the correct activation state and with the correct protein partners.

• Selectivity profiling driving Lead Optimization

One of the big hurdles in epigenetic drug discovery is poor understanding of how inhibitors act, whether they are selective for one or more epigenetic protein complexes and what the total effect of the inhibitor on the histone code is. With Episphere™, we can address these questions to provide more effective and better characterised inhibitors.



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