

## Press Release

### Landmark Study Demonstrates that ‘Complexes Matter’ in How Epigenetic Inhibitors Interact with Their Drug Targets

#### Cellzome Scientists Publish First Chemoproteomic Characterization of HDAC Inhibitors in *Nature Biotechnology*

**Heidelberg, Germany and Cambridge, UK 24<sup>th</sup> January 2011** – Results of the first ever chemoproteomic study of inhibition of HDAC (Histone Deacetylase) complexes published today in *Nature Biotechnology* (Bantscheff *et al.* Advanced online Publication, DOI: 10.1038/nbt.1759) opens up the potential for a new way of studying potency and selectivity for inhibitors of epigenetic drug targets, such as HDACs. In the study, scientists from Cellzome have demonstrated for the first time that complexes really matter to how small molecule inhibitors ‘see’ their target.

Epigenetic targets, those are targets that modify either DNA or its histone packaging to switch genes on or off, are of increasing interest in drug discovery. HDACs are emerging as an important class of epigenetic targets but existing drugs, and many in development, are non-selective with potential safety issues. The paper published today, entitled '*Chemoproteomic profiling of HDAC inhibitors reveals targeting of multiple HDAC complexes with compound class-dependent selectivity*' describes a detailed analysis of 16 HDAC inhibitors and reports distinct patterns of selectivity not only within the HDAC family, but also between the different complexes within which these enzymes operate. This is the first study that measures the binding of small molecules to native large protein complexes: results show that distinct complexes, all of which contain HDAC1/HDAC2 as the catalytic core, exhibit differential inhibition across a set of inhibitors.

Commenting on the results, Gerard Drewes PhD, senior author of the publication said: “The scientific and drug discovery community may need to revise their concept of a ‘drug target’ to include consideration not just of the target protein but also of the protein’s associated complex, as we continue to learn more about the subtle interactions between drugs and proteins in their natural environments rather than as purified enzymes”.

This chemoproteomic study uses Cellzome’s unique *Episphere*<sup>™</sup> platform, to identify compounds which target not only the correct enzyme, but the correct complex.

Based on these new data, the Cellzome team was able to define a novel HDAC complex formed during mitosis termed MiDAC, that may be of relevance in oncology.

Tim Edwards, CEO of Cellzome added: “This publication demonstrates how important it is to measure the action of drugs in the physiological context in which the targets operate. We look forward to extending our studies and in exploring collaborations with others, both in the HDAC space and in other epigenetic areas of interest outside of inflammation such as oncology and neurology where we have considerable expertise”.

Cellzome signed an agreement with GSK in February 2010 to apply its *Episphere*<sup>™</sup> platform to deliver candidate drugs for immuno-inflammatory diseases against certain epigenetic targets of four different target classes.

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**About Cellzome**

Cellzome is a world leader in chemoproteomics, transforming the sciences of epigenetics and signal transduction into novel drug candidates in inflammatory diseases and oncology. The Company maintains the highest levels of scientific expertise and has active collaborations with the foremost academic laboratories around the world. Cellzome's technologies work with native proteins in a physiological setting to discover small molecule drugs targeting protein complexes that underlie diseases. The Company has a track record in delivering significant collaborations with top pharmaceutical companies including GlaxoSmithKline, Johnson & Johnson and Novartis. Cellzome is a privately-held, international, company located in Heidelberg, Germany and Cambridge, UK employing about 100 people. For more information please visit: [www.cellzome.com](http://www.cellzome.com)

**About *Episphere*<sup>™</sup> and epigenetics**

*Episphere*<sup>™</sup> is a chemoproteomics technology for the discovery of novel drugs directed against targets involved in epigenetic regulation. The technology allows the screening and profiling of inhibitors of epigenetic targets in their native environment, directly in the lysate of cells and tissues, and can also differentiate between the complexes within which these targets operate.

The term epigenetics refers to heritable changes in gene expression and phenotype caused by mechanisms other than changes in DNA sequence. One major mechanism is the specific enzymatic modification of histone tails, which affects the packaging of DNA into chromatin and through that controls the transcription of specific genes. Enzymes, such as histone deacetylases (HDACs) or methyltransferases (HMTs) can change the modification of the histone tails and therefore change the 'histone code'. Dysregulation of these modifications is thought to play a central role in cancer and in chronic degenerative diseases like neurological and autoimmune disease. The enzymes which carry out these histone modifications are part of large multifunctional protein complexes, which represent attractive novel targets for drug discovery.