Histone Deacetylase 9

ICR Licensing Opportunity November 2012

- New class II histone deacetylase identified and isolated (HDAC9)
- Evidence for cancer cell selectivity.
- Catalytic domain identified and cloned.
- Attractive target for development of new anti-cancer therapeutics and diagnostic tests.
- High throughput screening opportunity for new target selective drugs.
- Patent applications filed in EP, US and Japan.
- Reagents and assays available for high throughput screening.

Background

Within the nucleus, DNA is packaged into chromatin in a precise and tightly regulated manner. Structural changes at this level of organisation are known to affect several cellular processes including replication, repair, chromosomal segregation and transcriptional regulation. The major protein components of chromatin are the core histones, around which DNA is tightly coiled to form nucleosomes, which are the basic repeating units of chromatin.

Chromatin structure is influenced strongly by the acetylation status of specific –amino lysine residues of the histone proteins. There is strong evidence that unwinding of nucleosomes due to the acetylation of these histone residues plays a fundamental role in the activation of gene transcription.

The action of two classes of enzymes determine the acetylation state of histones: histone acetyl transferases (HATs) and histone deacetylases (HDACs). To date a family of eight human histone deacetylases have been characterised, which may be broadly divided into two related groups: Class I (HDACs 1,2,3 and 8) and Class II (HDACs 4,5,6 and 7) according to their homology to yeast RPD3 and HDA1 respectively.

ICR scientists have identified and isolated a ninth member of the HDAC family, whose activities may be deregulated in certain cancers. The biological role of HDAC9 is currently being actively investigated.

HDACs and Cancer

Several syndromes associated with increased cancer risk are known also to be associated with HAT mutations or aberrant recruitment of HDACs. Specifically, under normal circumstances HDAC9 appears to be expressed only in a limited range of normal tissues, and at low levels with the exception of brain. However, screening studies reveal high levels of HDAC9 to be expressed in cell lines and samples from patients with certain forms of leukaemia and lymphoma.

HDACs as a Target

Several structurally diverse classes of HDAC inhibitor are now known, and have been shown to cause growth arrest, differentiation, or apoptosis of a range of transformed cells both in culture and in-vivo. A limited number of these compounds have now emerged as clinical leads currently in phase I or phase II trials.

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The catalytic domain sequence of HDAC9 reveals that there is potential for the development of inhibitors specific for this enzyme. Such inhibitors would have considerable potential as therapeutic compounds.

Inventor
Dr Arthur Zelent is the scientist leading this project, and is based at the Chester Beatty Laboratories of ICR, Chelsea, London UK.

Intellectual Property
ICR has filed patents relating to HDAC9 in Europe, US and Japan. These patents cover identification and cloning of this new histone deacetylase, including characterisation of HDAC9 polypeptides with demonstrable deacetylase activity, and the nucleic acid sequences encoding them. The patents claim HDAC9 as a therapeutic target and as a diagnostic marker. In addition the Institute has a considerable body of expertise, model systems and know-how surrounding HDAC9, which will enable screens for HDAC9 inhibitors to be progressed rapidly and accurately.

Commercial Opportunity
The Institute is seeking an industrial partner to collaborate on the next stage of the HDAC9 project, that is a screen for HDAC9 inhibitors. The partner would receive exclusive commercialisation rights.

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The ROYAL MARSDEN NHS Foundation Trust

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