

News Release

Cellzome Advances Understanding of Hepatitis C

Heidelberg, Germany, 23rd November 2009 - Cellzome announces that an article* published today in *Virology* has shown that multiple cyclophilins – enzymes that facilitate protein folding – are involved in hepatitis C virus replication. The paper was published by scientists from Cellzome and Novartis Institutes of Biomedical Research (NIBR). In the study, two hepatitis C virus (HCV) drug candidates have been shown to interact with different cyclophilins and thus can attenuate viral replication. Interestingly, the different enzymes are found to participate in different cellular processes, the most prominent one being protein trafficking.

It is the third article within the last six months in which Cellzome's chemical proteomics capabilities were described as being used to unravel the Mode-of-Action of drug candidates and to increase the understanding of fundamental disease biology. In October this year, Cellzome and NIBR scientists co-authored another publication in *Journal of Virology*** , which identified a novel class of therapeutic targets for Hepatitis C, namely the class III PI4 kinases. In both publications the interplay between genomics and chemical proteomics revealed novel insights into HCV biology and opened up new avenues for therapeutic intervention. In September 2009, Cellzome and NIBRI scientists published novel mechanistic insights into the regulation of axin protein homeostasis and presents new avenues for therapeutic intervention in the Wnt cancer pathway.***

Commenting on the publications, David Simmons, CSO of Cellzome, said:

“Hepatitis C affects over a hundred million people around the world and is a major cause of liver cirrhosis and cancer. Current treatments only target about 50% of the HCV genotypes and have severe side effects. The findings reported in these studies will aid the development of new medicines to fight HCV related diseases. We are proud that our chemical proteomics technology can again contribute to the discovery of drug candidates for the treatment of serious diseases .”

* Gaither L.A. et al, “Multiple Cyclophilins Involved in Different Cellular Pathways Mediate HCV Replication”, *Virology*, 2009 Nov 23.[Epub ahead of print]

** Borawski J. et al., “Class III phosphatidylinositol 4-kinase alpha and beta are novel host factor regulators of hepatitis C virus replication”, *Journal of Virology*, 83:10058-74; October 2009

*** Huang S. et al, Tankyrase inhibition stabilizes axin and antagonizes Wnt signaling”, *Nature*, 462, 614-20, October 2009

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For more information, including a copy of the publication, please contact:

Cellzome:

Dr. David Simmons, MBA
Chief Scientific Officer
Tel: +49 (0) 6221-137 57-100
press@cellzome.com

Media contact:

Hogarth Partnership
Sarah MacLeod
Tel: +44 (0) 207 357 9477

Notes to editors

Abstract from *Virology*

Multiple Cyclophilins Involved in Different Cellular Pathways Mediate HCV Replication

Gaither, L.A. et al., *Virology*, 2009 Nov 23. [Epub ahead of print]

Summary

Three cyclophilin binding drugs (DEBIO-025, SCY635 and NIM811) are currently in clinical trials for Hepatitis C therapy. The mechanism of action of these, however, is not completely understood. We describe here our efforts to unravel the role of cyclophilins in HCV replication. We demonstrate that siRNA knock down of cyclophilin A, H, 40 and E decrease viral RNA replication in the Huh-uc/neo-ET subgenomic replicon assay. In a different subgenomic replicon (CloneA) cyclophilin B knock down also affected replication. RNA profiling of cellular pathways affected by the replicon and/or NIM811 also suggest that cyclophilins are instrumental to viral replication. Using chemical proteomics we identified the major cyclophilins and associated proteins that are affected by treatment of replicon containing cell lines with cyclosporin A and NIM811. The identified proteins group into distinct cellular pathways and several were shown to affect viral replication. In addition, siRNA libraries were screened for host proteins essential for the HCV replicon. The identified proteins group into the same pathways observed by the other approaches with protein trafficking as the most significantly regulated and most frequently identified process. Together, these experiments provide strong evidence that multiple cyclophilins are involved in viral replication and indicate that the mechanism of action of NIM811 inhibition of viral replication involves multiple cyclophilins.

About Cellzome Inc.

Cellzome is a privately-owned drug discovery and development company identifying a new generation of kinase-targeted drugs to treat inflammatory diseases. Its pipeline of small-molecule therapeutics is driven by *Kinobeads*[™], a proprietary technology for the screening and profiling of kinase inhibitors in physiologically-relevant cells and tissues. The most advanced program, targeting PI3Ky, is anticipated to enter the clinic in 2010, and several other programs are in early preclinical testing.

Cellzome is expanding its distinctive technology, in a novel form called *Episphere*[™], to the discovery and development of novel drug candidates for epigenetic targets in their protein complexes.

Cellzome has significant collaborations with GSK and Johnson & Johnson. Its holding company is domiciled in the US and it employs about 90 people at its two laboratories in Cambridge, UK and Heidelberg, Germany.