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Press release

Targeting a host receptor instead of the virus: a new experimental approach against hepatitis C virus.

An international collaboration led by Professor Thomas Baumert (Inserm/University of Strasbourg Joint Research Unit 1110, "Institute for Viral and Liver Disease") has shown that a monoclonal antibody directed specifically against claudin-1, a liver protein essential for infection by the hepatitis C virus (HCV), enables the prevention and treatment of chronic infection by this virus in an animal model. It turns out that this antibody, which was known to inhibit HCV entry and thereby prevent the initiation of infection, can also eliminate infected cells. This discovery, published in a letter in the *Nature Biotechnology* issue of 23 March 2015, opens the way to developing an approach to hepatitis C that is not only preventive, but therapeutic as well.

Infection with hepatitis C virus (HCV) leads to cirrhosis of the liver and liver cancer, the second leading cause of cancer death in the world. These complications are major indications for liver transplantation, but HCV reinfection of the transplant is a challenge. To date there is no vaccine, and the new treatments developed recently can be accessed by only a minority of patients worldwide because of their high cost. The development of new preventive and therapeutic strategies therefore continues.

The team directed by Prof. Thomas Baumert (Inserm/University of Strasbourg Joint Research Unit 1110, "Institute for Viral and Liver Disease"), in collaboration with international teams, decided to target a liver protein essential for viral infection instead of targeting the virus. They chose claudin-1, a molecule that is important in the initial steps of HCV infection, and involved in cell-cell contacts.

Using mouse models with humanised liver, the researchers show that a monoclonal antibody directed against claudin-1 can prevent HCV infection by blocking the entry of the virus into liver cells. Surprisingly, the researchers also observed that this antibody enables the treatment of chronic HCV infection by inhibiting the activation of intracellular signalling pathways needed by the virus for survival. As a result, the infected cells disappear and are gradually replaced by uninfected cells.

The advantage of this strategy is that it does not need to be combined with an antiviral agent. Moreover, by using different viral strains, the researchers show that it is difficult for the virus to escape from this antibody and develop resistance.

"Claudin-1" is a protein that is usually localised in the tight junctions that are the points of contact between adjacent cells. It is interesting to note that tight junction proteins constitute receptors for other pathogens, such as dengue virus and *Shigella* species. This innovative approach, employing injection of a monoclonal antibody directed against a protein on the host cell, makes it possible to

foresee the development of a vaccine strategy and new therapeutic approaches against HCV, and also against other pathogens that use similar infection mechanisms.

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Source

Clearance of persistent hepatitis C virus infection in humanized mice using a claudin-1-targeting monoclonal antibody

Laurent Mailly[1, 2], Fei Xiao[1, 2, *], Joachim Lupberger[1, 2, *], Garrick K. Wilson[3], Philippe Aubert[4, 5, 6], François H. T. Duong[7], Diego Calabrese[7], Céline Leboeuf[1, 2], Isabel Fofana[1, 2], Christine Thumann[1, 2], Simonetta Bandiera[1, 2], Marc Lütgehetmann[8], Tassilo Volz[8], Christopher Davis[3], Helen J. Harris[3], Christopher J. Mee[3], Erika Girardi[2, 9], Béatrice Chane-Woon-Ming[2, 9], Maria Ericsson[10], Nicola Fletcher[3], Ralf Bartenschlager[11, 12], Patrick Pessaux[1, 2, 13], Koen Vercauteren[14], Philip Meuleman[14], Pascal Villa[2, 15], Lars Kaderali[16], Sébastien Pfeffer[2, 9], Markus H. Heim[7], Michel Neunlist[4, 5, 6], Mirjam B. Zeisel[1, 2], Maura Dandri[8], Jane A. McKeating[3], Eric Robinet[1, 2, §] and Thomas F. Baumert[1, 2, 13, §]

[1]Institut National de la Santé et de la Recherche Médicale, U1110, Institut de Recherche sur les Maladies Virales et Hépatiques, Strasbourg, France; [2]Université de Strasbourg, Strasbourg, France; [3]Hepatitis C Research Group, Institute for Biomedical Research, University of Birmingham, Birmingham, United Kingdom; [4]Institut National de la Santé et de la Recherche Médicale, U913, Nantes, France; [5]Université de Nantes, Nantes, France; [6]Institut des Maladies de l'Appareil Digestif, CHU Nantes, Hôpital Hôtel-Dieu, Nantes, France; [7]Department of Biomedicine, Hepatology Laboratory, University of Basel, Basel, Switzerland; [8]I. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [9]Architecture et Réactivité de l'ARN, Institut de Biologie Moléculaire et Cellulaire du CNRS – UPR 9002, Strasbourg, France; [10]Electron Microscopy Facility, Harvard Medical School, Boston, USA; [11]Department of Infectious Diseases, Molecular Virology, Heidelberg University, Heidelberg, Germany; [12]German Centre for Infection Research, Heidelberg University, Heidelberg, Germany; [13]Pôle Hépato-Digestif, Institut Hospitalo-Universitaire, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [14]Center for Vaccinology, Ghent University, Ghent, Belgium; [15]Plateforme de Chimie Biologique Intégrative de Strasbourg, UMS 3286 CNRS-UdS & FMTS, Illkirch, France; [16]Institute for Medical Informatics and Biometry, Medical Faculty, Technische Universität Dresden, Dresden, Germany.
**These authors contributed equally to the work.*
§These authors contributed equally to the work.
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Contacts

Prof. Thomas Baumert
Inserm Joint Research Unit 1110, "Institute for Viral and Liver Disease"
Tel.: +33 (0)3 68 85 37 03
Mobile: +33 (0)6 11 58 23 87
Thomas.Baumert@unistra.fr

ANRS

Noella Lefebvre
Tel.: +33 (0)1 53 94 60 21
Noella.lefebvre@anrs.fr

Inserm

Juliette Hardy
Tel.: +33 (0)1 44 23 60 98
presse@inserm.fr

University of Strasbourg

Anne-Isabelle Bischoff
Tel.:+33 (0) 3 68 85 16 27
Mobile: +33 (0)6 47 58 72 05
anne-isabelle.bischoff@unistra.fr