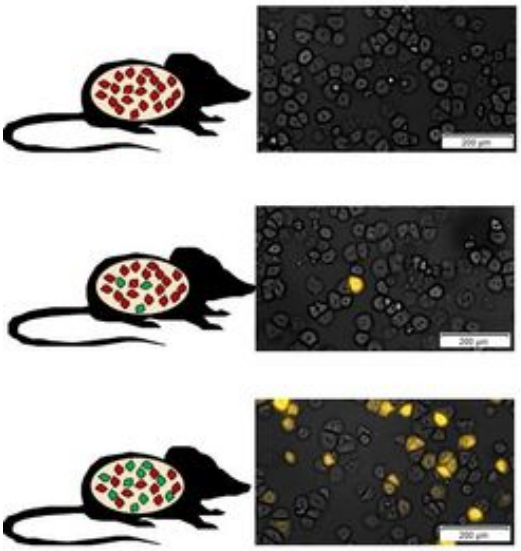
Technology Offer

Mouse models for liver immunity and therapeutic vaccinations

Reference Number 02-00330

Challenge

In hepatotropic viral infections such as HBV and HCV a certain number of hepatocytes present viral antigens while others remain antigen negative resulting in a mosaic antigen expression pattern. Successful immune response can eliminate the antigen expressing, virus infected cells while antigen deficient, non-infected cells can regenerate the liver. Currently, immunotherapies that enhance the antigen clearance efficiency are under development. Thus, there is a strong demand for animal models enabling detailed studies towards the development and evaluation of novel vaccination protocols for immunotherapeutic interventions in patients with a chronically infected liver.



Inducible, liver specific antigen expression mimicking viral antigen expression after infection

Technology

The induced stochastic activation of antigen and consequently its mosaic expression are unique features of this transgenic model. They are based on the particular design of synthetic expression cassettes using the Cre-Lox technology. Ovalbumin was used as model antigen. A fragment of this gene were flanked by inversely oriented LoxP sites and cloned in reverse orientation into the ubiquitously expressed locus ROSA26. The resulting *ROSAOVA* mice were mated to *Alb-Cre-ER^{T2}* mice. *Alb-Cre-ER^{T2}* mice selectively express the recombinase CreER^{T2} in hepatocytes. In the resulting double transgenic mice *ROSAOVA X Alb-Cre-ER^{T2}* tamoxifen induction resulted in reversible recombination events (ON-OFF) and antigen expression in hepatocytes. Clearance of tamoxifen leads to (stochastic) equal fixation of antigen expression in ON or OFF position, thus causing mosaic expression. Importantly, the coexistence of antigen expressing and non-expressing hepatocytes in this model gives the opportunity to monitor changes of antigen level in the liver. The results were confirmed by using HBsAG as antigen.
The model allows defining and adjusting the number of antigen expressing cells in particular tissues depending on specificity of used CreER^{T2} effector mouse strain. Furthermore, it allows quantifying the efficiency of immunotherapeutic interventions by evaluating the antigen clearance efficiency. Taken together, the model provides an *in vivo* tool for the development and evaluation of novel vaccination protocols for immunotherapeutic interventions in chronically infected patients.

Commercial Opportunity

Mouse models are offered for licensing.

Patent Situation

European Patent EP01692936B1 with priority of 2000 was granted to GIE-CERBM. Method for targeted conditional DNA recombination in mice using the cre-ert2 fusion protein.

Further Reading

Ochel et al., Cell Mol Immunol. 2016; 13(6): 805–815.
Cebula et al., PLoS One. 2013; 8(7): e68720.
Cebula et al., Molecular Therapy. 2017; Oct 4;25(10):2289-2298.

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