Current status of cell therapy in autoimmune liver diseases

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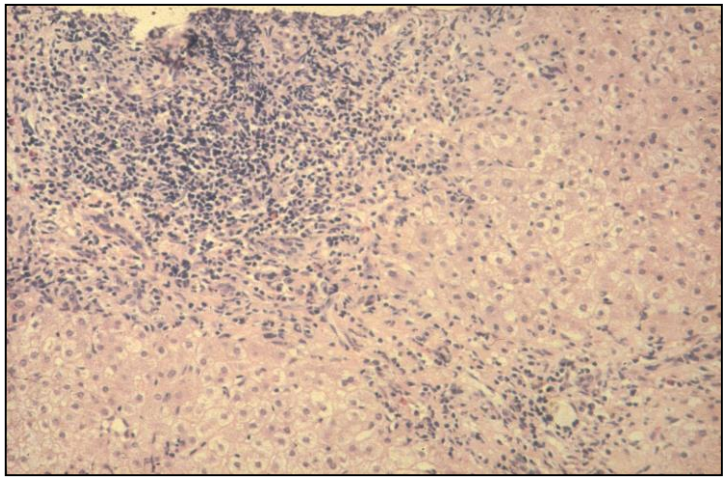
& UHB NHS Foundation Trust

Birmingham Advanced Cellular Therapy

ERN Rare Liver Centre

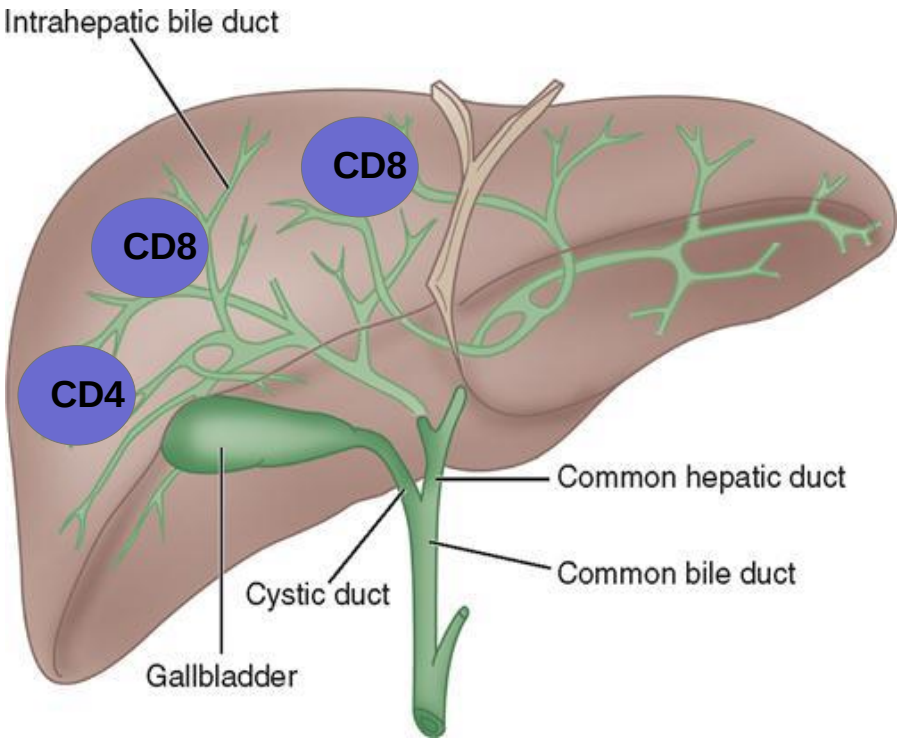
Autoimmune hepatitis is a classical autoimmune disease

T cell mediated destruction of hepatocytes



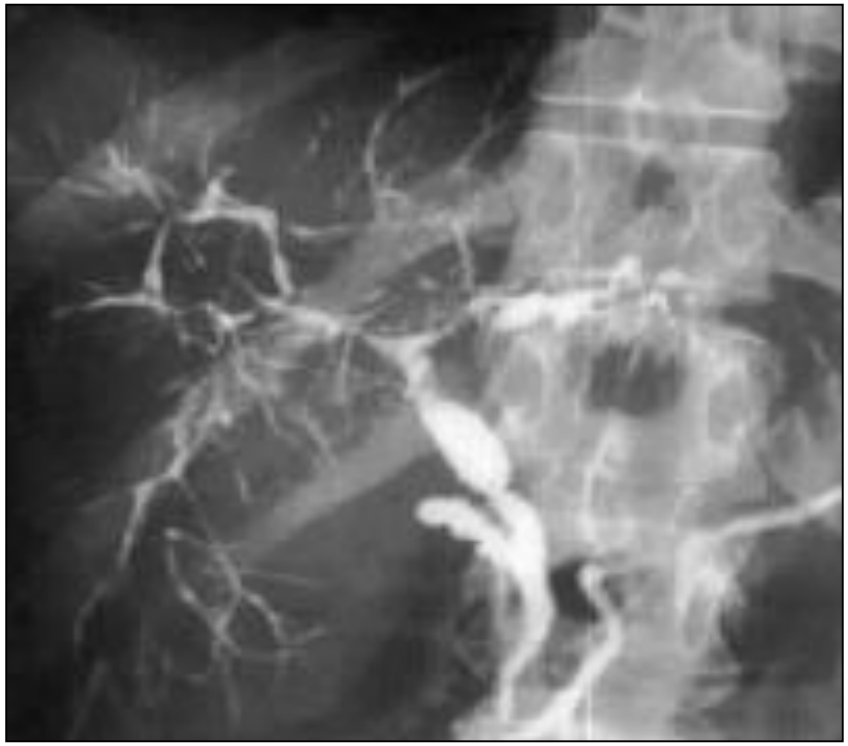
Primary biliary cholangitis

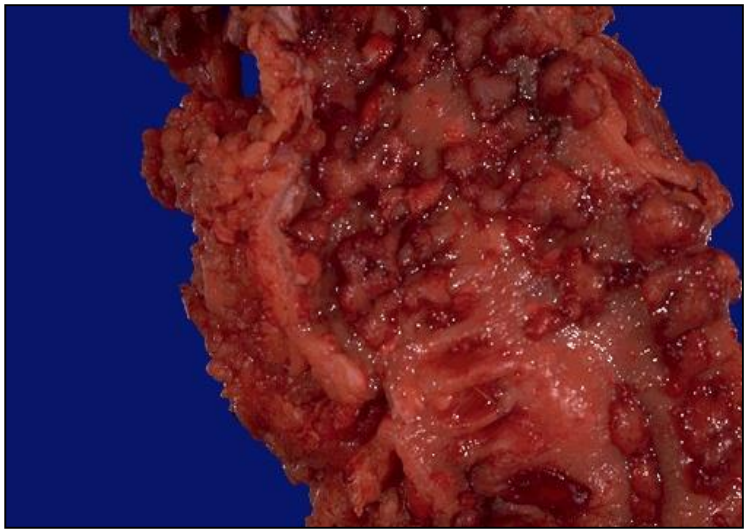
T cell mediated destruction of bile ducts



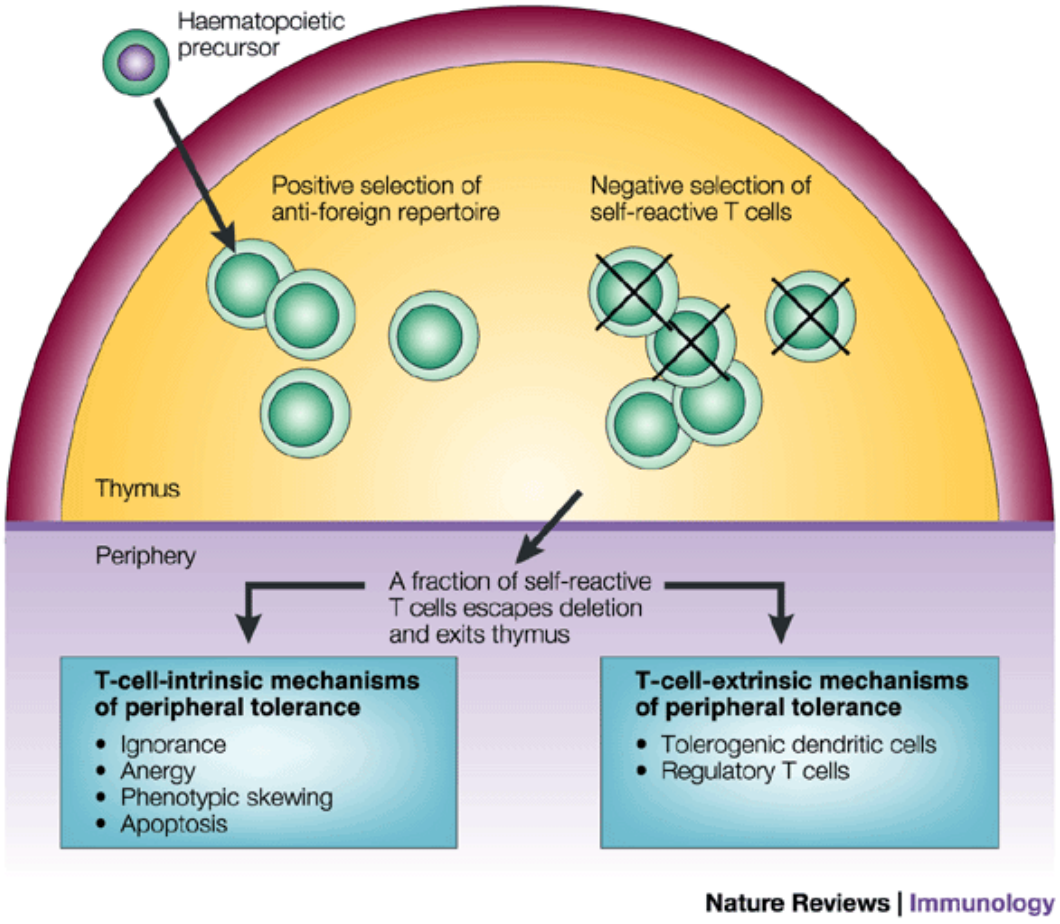
PSC

T cell mediated destruction of bile ducts and gut





Central and peripheral tolerance



Lucy Walker; Nature

Cell therapy safe to use in liver patients, clinical trial suggests

Posted on: 9th October 2019

Liver disease patients could one day benefit from a new cell therapy that has just completed its first clinical trial.

Researchers who tested the potential treatment in patients with liver cirrhosis – where long term damage produces scarring – found the therapy had no significant adverse effects.

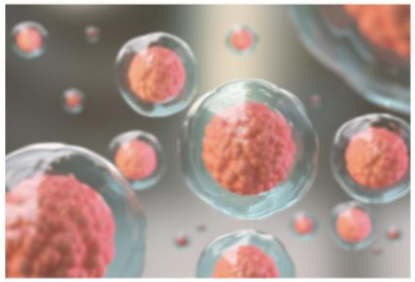
Now the team, based at the University of Edinburgh's MRC Centre for Regenerative Medicine, is to gauge the effectiveness of the treatment – which is based on white blood cells called macrophages, that are key to normal liver repair.

The next stage of the trial will measure whether the therapy helps the liver to reduce scarring and stimulate regeneration. The results should be known within the next two years.

Pamela Healy, CEO of the British Liver Trust, said: "Across the UK we are facing a liver disease epidemic. The number of people affected has been rising at an alarming rate and liver disease is now the biggest killer of 35 to 49-year olds.

"Chronic liver disease occurs when the liver is damage irreparably and becomes scarred (cirrhosis). At this stage, there are very few treatments available. This new innovative approach is an exciting development and could in the future reduce the need for transplantation. More research is needed and the next stage of this work will be to really test the potential benefit for patients."

At present the only successful treatment for end-stage liver cirrhosis is an organ



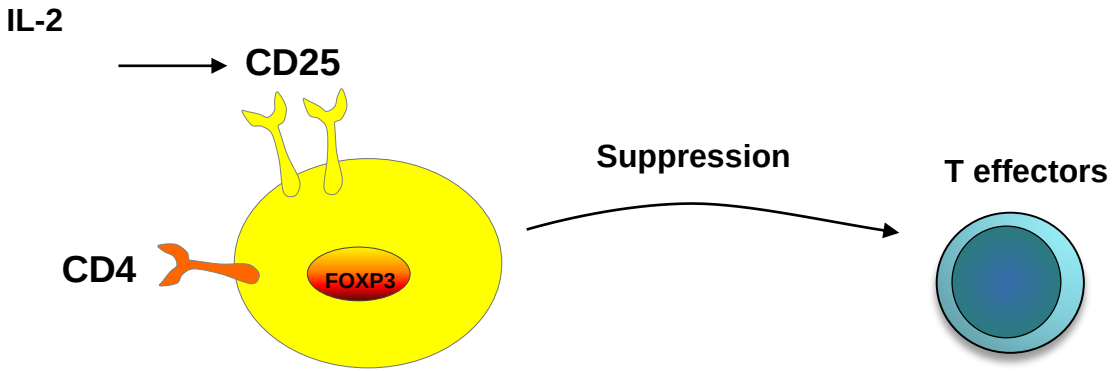
RECENT POSTS

- Fresh support for Scotland's liver services is allowing all voices to shape vital research
- New research reveals late detection of liver disease crisis with more than a third dying within a year of

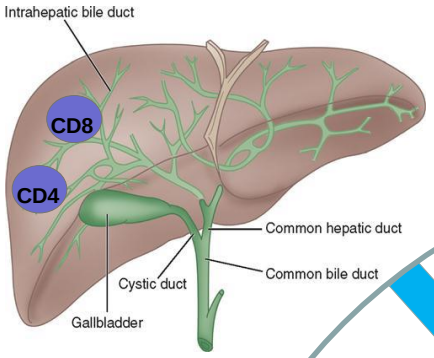
What is regulatory T cells (Treg)

Subset of CD4 T cells which express CD25, Interleukin 2 receptor

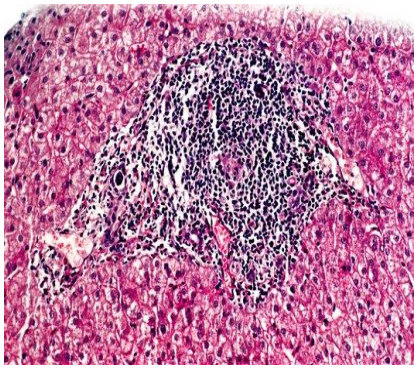
Treg control tissue damaging effector T cells thereby prevent autoimmune diseases



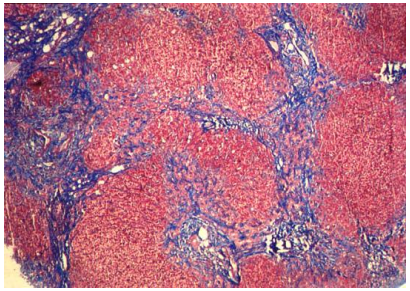
Change immune balance to dominant regulatory arm with Treg to stop autoimmune hepatitis/cholangitis

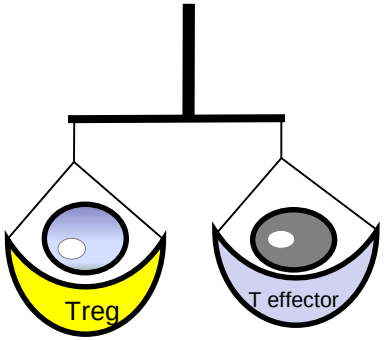


Oo et al,
Journal of Hepatology,
2014



Fibrosis- cirrhosis





AUtologous Treg infUsion in autoiMmuNe liver disease patients (AUTUMN)

Research type

Research Study

Full title

Autologous T-regulatory cell tracking after infusion in autoimmune liver disease patients

IRAS ID

177127

Contact name

Ye Htun Oo

Contact email

y.h.oo@bham.ac.uk

Duration of Study in the UK

1 years, 3 months, 31 days

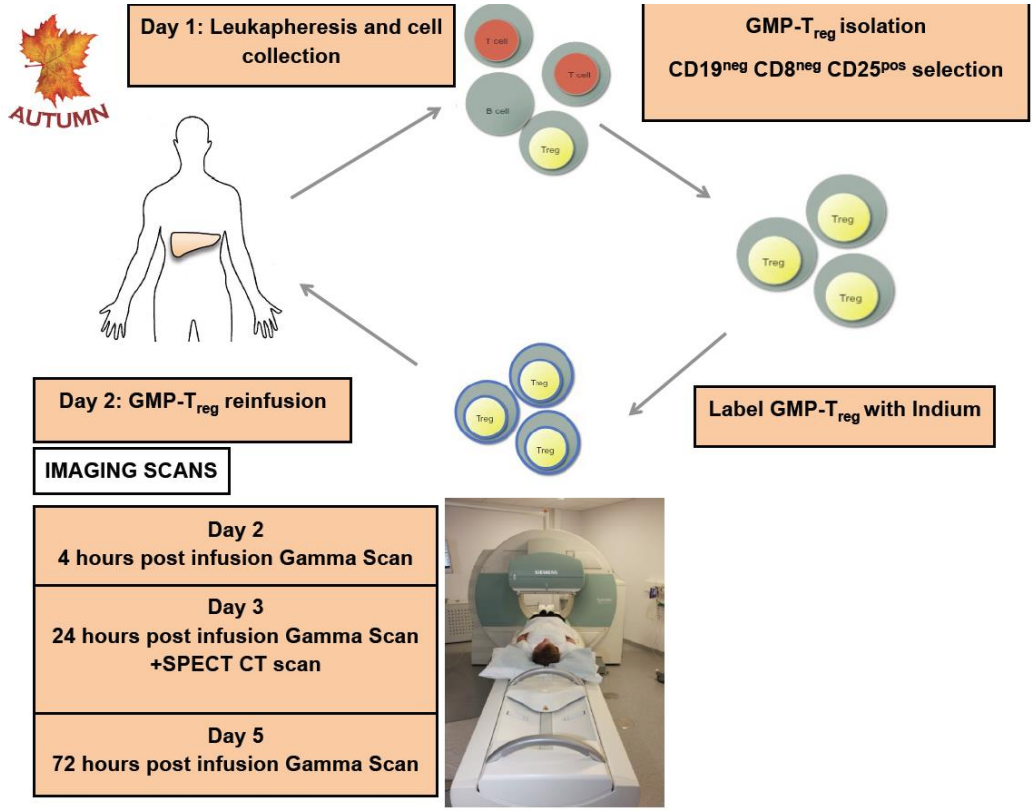
AUTUMN Trial

AUtologous **T**-regulatory cell tracking after infU**s**ion in autoi**M**mu**N**e liver disease patients

Protocol Version 2.0 30-Jul-2015

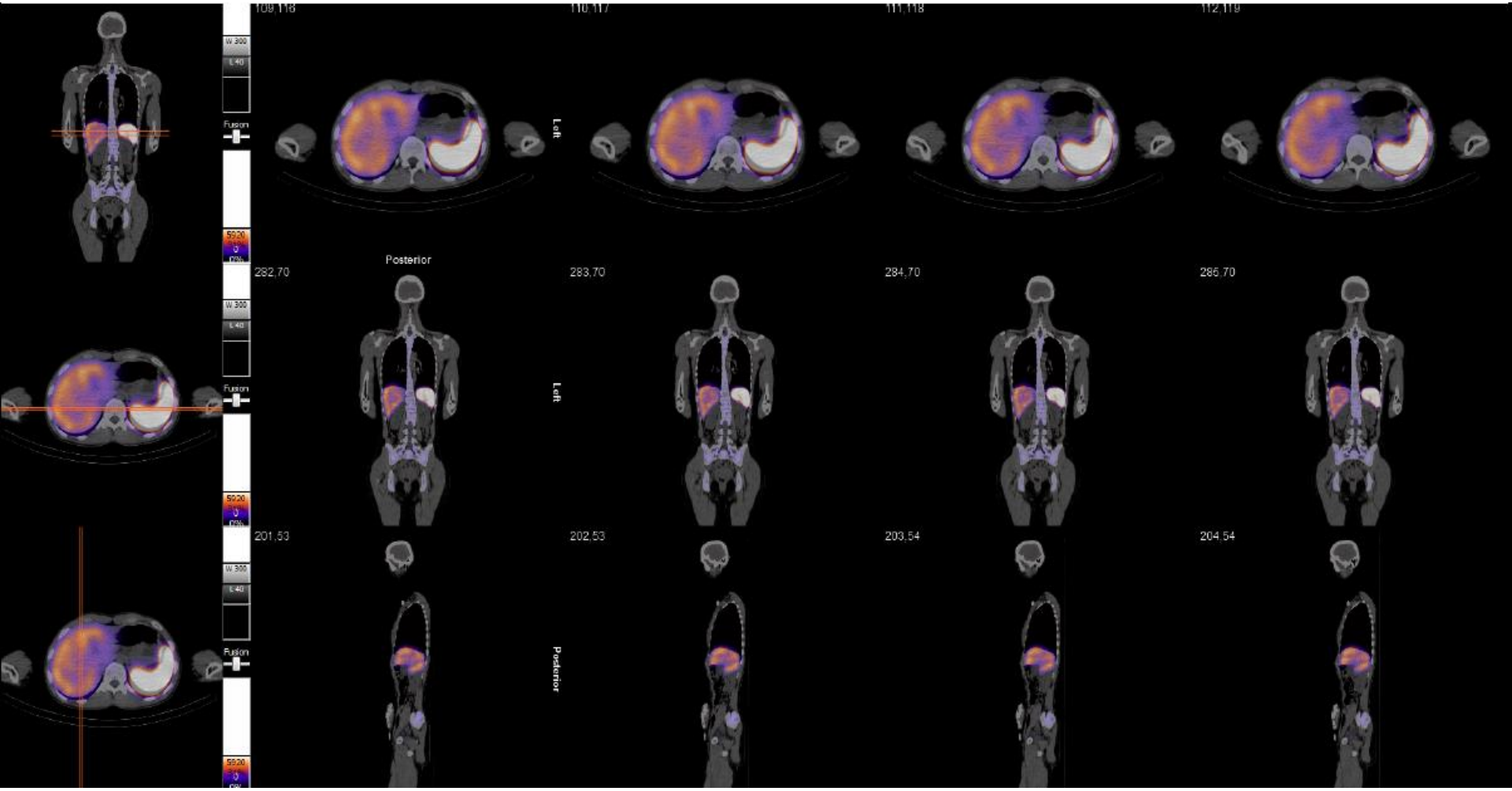
Sponsor Number: RG_15-121

CAS number: HE9002



Oo et al, jHep Reports

Infused GMP Treg home to autoimmune liver (SPEC-CT)



Oo et al, jHep Reports

Challenges and opportunities in achieving effective regulatory T cell therapy in autoimmune liver disease

N. Richardson[1,2] · G. E. Wootton[1,2] · A. G. Bozward[1,2] · Y. H. Oo[1,2,3,4]

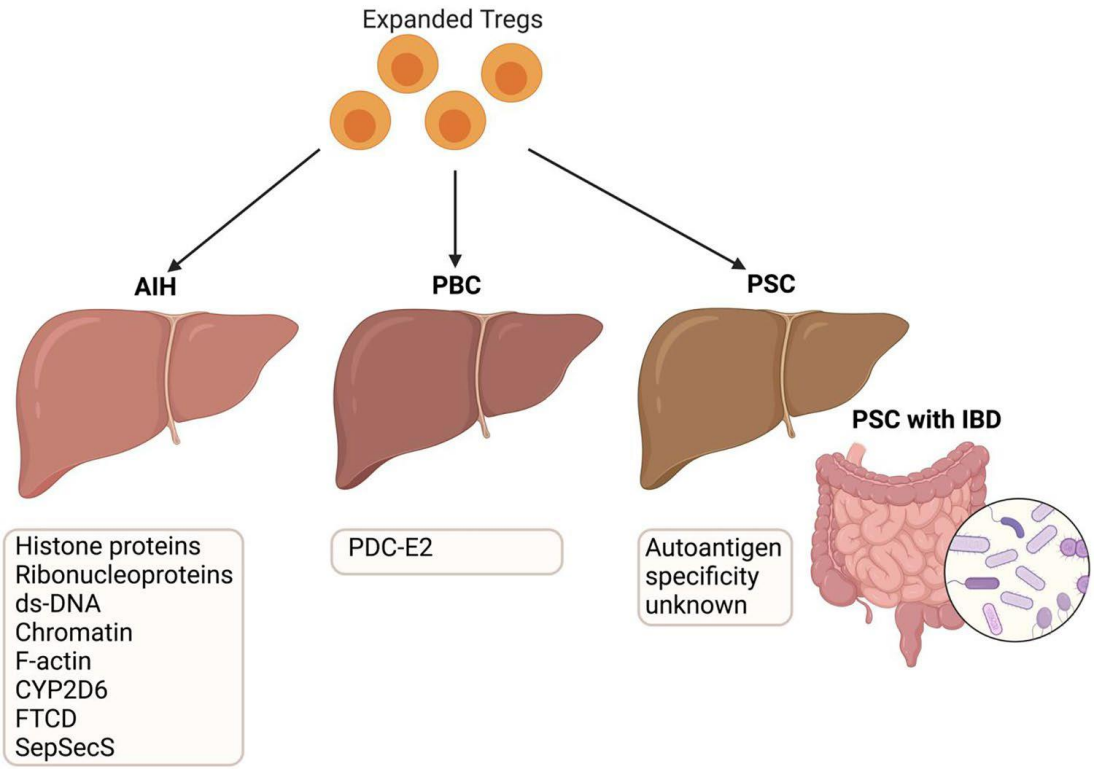
Received: 17 January 2020 / Accepted: 15 April 2020

Abstract

Autoimmune liver diseases (AILD) include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). These immune-mediated liver diseases involve a break down in peripheral self-tolerance with largely unknown aetiology. Regulatory T cells (Treg) are crucial in maintaining immunological tolerance. Hence, Treg immunotherapy is an attractive therapeutic option in AILD. Currently, AILD do not have a curative treatment option and patients take life-long immunosuppression or bile acids to control hepatic or biliary inflammation. Clinical investigations using good manufacturing practice (GMP) Treg in autoimmune liver disease have thus far demonstrated that Treg therapy is safe and that Treg migrate to inflamed liver tissue. For Treg immunotherapy to achieve efficacy in AILD, Treg must be retained within the liver and maintain their suppressive phenotype to dampen ongoing immune responses to hepatocytes and biliary epithelium. Therefore, therapeutic Treg subsets should be selected for tissue residency markers and maximal functionality. Optimisation of dosing regime and understanding longevity of Treg in vivo are critical to successful Treg therapy. It is also essential to consider combination therapy options to complement infused Treg, for instance low-dose interleukin-2 (IL-2) to support pre-existing and infused Treg survival and suppressive function. Understanding the hepatic microenvironment in both early- and late-stage AILD presents significant opportunity to better tailor Treg therapy in different patient groups. Modification of a hostile microenvironment to a more favourable one either prior to or during Treg therapy could enhance the efficacy and longevity of infused GMP-Treg. Applying recent technology to discovery of autoantigen responses in AILD, T cell receptor (TCR) sequencing and use of chimeric antigen receptor (CAR) technology represents the next frontier for disease-specific CAR-Treg therapies. Consideration of all these aspects in future trials and discovery research would position GMP Treg immunotherapy as a viable personalised-medicine treatment option for effective control of autoimmune liver diseases.

Keywords Regulatory T cell · Autoimmune liver · Cell therapy · Liver microenvironment

Treg therapy



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CAT Treg therapy

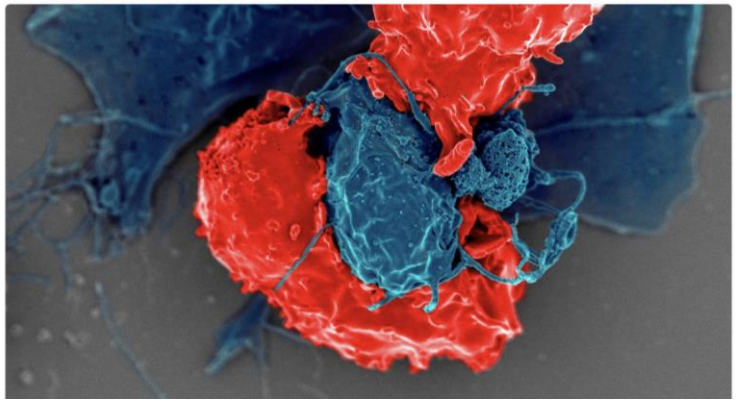
State of Play

‘Treg’ cell therapy: bringing CAR-T to autoimmune disease

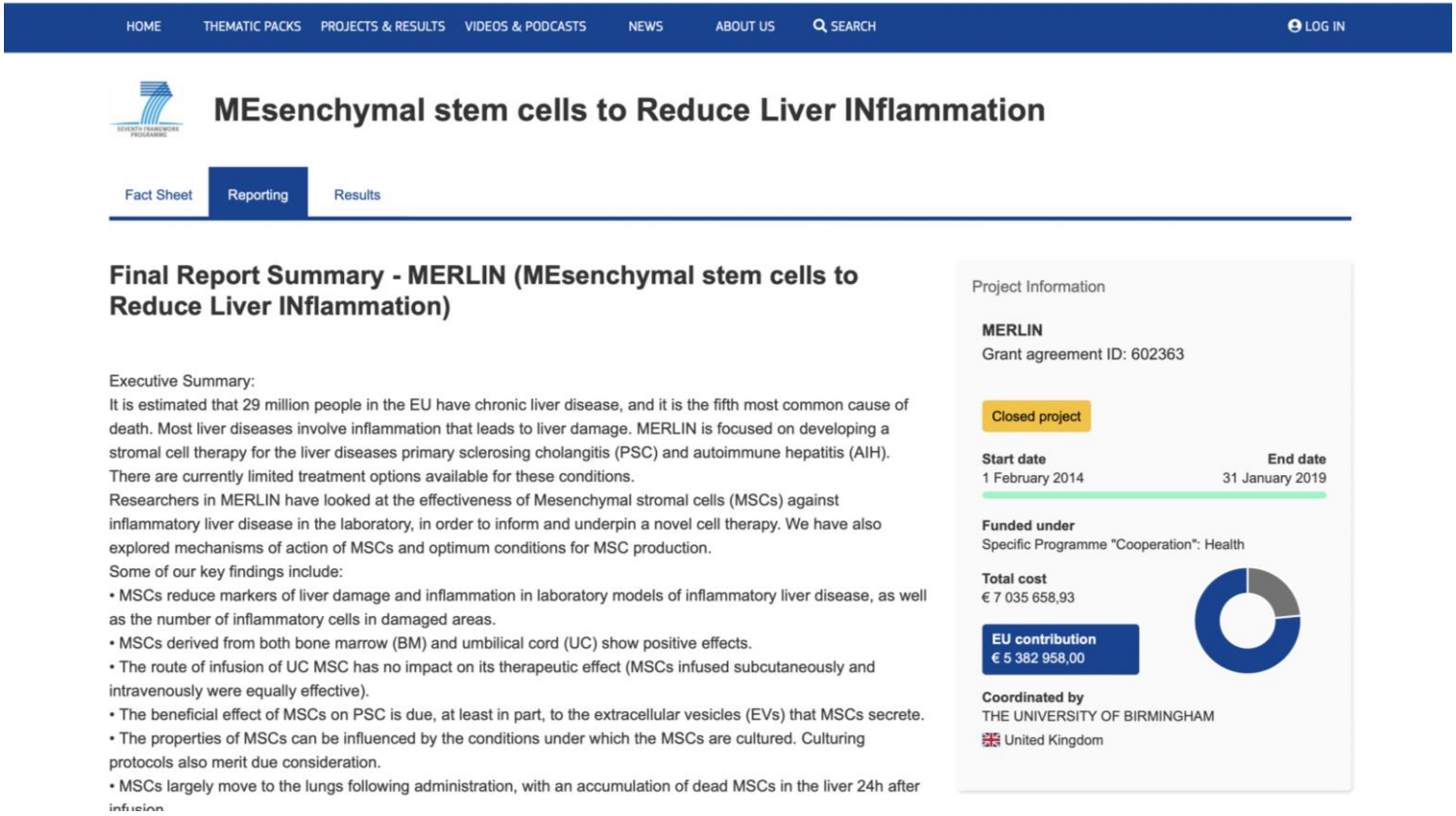
Several richly funded startups have emerged with plans to broaden the use of cell-based medicines beyond cancer.

Published Aug. 16, 2022

Ben Fidler
Senior Editor



MSC therapy - (enhance Treg suppressive function)



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MEsenchymal stem cells to Reduce Liver INflammation

Fact Sheet | Reporting | Results

Final Report Summary - MERLIN (MEsenchymal stem cells to Reduce Liver INflammation)

Executive Summary:
It is estimated that 29 million people in the EU have chronic liver disease, and it is the fifth most common cause of death. Most liver diseases involve inflammation that leads to liver damage. MERLIN is focused on developing a stromal cell therapy for the liver diseases primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). There are currently limited treatment options available for these conditions.
Researchers in MERLIN have looked at the effectiveness of Mesenchymal stromal cells (MSCs) against inflammatory liver disease in the laboratory, in order to inform and underpin a novel cell therapy. We have also explored mechanisms of action of MSCs and optimum conditions for MSC production.
Some of our key findings include:
• MSCs reduce markers of liver damage and inflammation in laboratory models of inflammatory liver disease, as well as the number of inflammatory cells in damaged areas.
• MSCs derived from both bone marrow (BM) and umbilical cord (UC) show positive effects.
• The route of infusion of UC MSC has no impact on its therapeutic effect (MSCs infused subcutaneously and intravenously were equally effective).
• The beneficial effect of MSCs on PSC is due, at least in part, to the extracellular vesicles (EVs) that MSCs secrete.
• The properties of MSCs can be influenced by the conditions under which the MSCs are cultured. Culturing protocols also merit due consideration.
• MSCs largely move to the lungs following administration, with an accumulation of dead MSCs in the liver 24h after infusion

Project Information

MERLIN
Grant agreement ID: 602363

Closed project

Start date 1 February 2014
End date 31 January 2019

Funded under
Specific Programme "Cooperation": Health

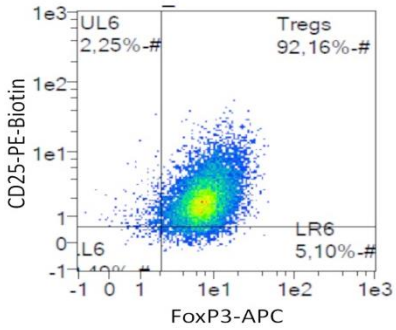
Total cost
€ 7 035 658,93

EU contribution
€ 5 382 958,00

Coordinated by
THE UNIVERSITY OF BIRMINGHAM
United Kingdom

GMP Treg production as new therapy in AILD

Advanced Therapy Treatment Centre



Cancer Research UK Clinical Trials Unit @CRCTU

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