Developing Cell Therapies to Reduce Liver Inflammation

What is MERLIN?

MERLIN is an EU FP7 Project focused on developing cell-therapies that specifically target the inflammatory components of liver disease. In particular, we have studied mesenchymal stromal cells (MSCs) and their potential therapeutic effects on the liver. As part of the MERLIN project the team has:

- Generated new knowledge about mechanisms of action and bio-distribution of MSCs.
- Developed advanced 3D imaging technologies.
- Devised a novel process for GMP-compliant manufacturing of specially selected MSCs.
- Opened an early phase clinical trial for the treatment of patients with chronic liver diseases PSC (primary sclerosing cholangitis) and AIH (autoimmune hepatitis).

What has MERLIN discovered about MSCs?

Our studies in MERLIN have brought us closer to understanding MSCs and how they work.

We have found evidence that MSCs reduce the hallmarks of liver damage and inflammation in inflammatory liver disease, as well as the number of inflammatory cells present in damaged areas.

We found that MSCs injected under the skin do not migrate to other locations. Even though the MSCs remain at the site of injection, they still reduce inflammation in other areas of the body. This indicates the effects of MSC on inflammation may be due to cytokines released by the cells (soluble mediators). Our results also indicate that the beneficial effects of MSCs are due, at least in part, to the extracellular vesicles (EVs) that MSCs secrete.

MSCs are ultimately phagocytosed (engulfed) by monocytic cells that subsequently migrate to other sites via the bloodstream. These monocytic cells then adopt an immunoregulatory phenotype and induce regulatory T cells. MERLIN imaging studies showed that MSCs delivered by intravenous infusion largely collect in the lungs after administration, with dead MSCs accumulating in the liver after 24 hours.

The immunogenic and immunomodulatory properties of MSCs can be enhanced by optimizing the conditions in which the cells are cultured. This offers the possibility of generating optimised MSCs for therapeutic use. Cell density and proliferation of MSCs also have a major effect on the cells, so cell culture protocols merit careful consideration.

The more we understand about MSCs and how they work, the more effectively we can harness and optimize MSC therapies in the clinic.

What is the MERLIN Clinical Trial?

We have used the results of our work in MERLIN to help design a clinical trial for people with chronic liver disease. The study is focused on people with PSC and AIH, which both involve inflammation of the bile ducts and can result in significant liver damage. Current options for treating PSC and AIH are limited. Many of those affected end up needing a liver transplant.

Participants in the MERLIN trial will receive a single infusion of specially selected MSCs. The study will be carried out in the UK and aims to prove the safety and efficacy of the treatment. Sites in Birmingham, Oxford and Nottingham will be involved.

The trial is being coordinated by the University of Birmingham and is partially funded through the MERLIN Project. The cell product, ORBCEL being administered in the MERLIN trial was discovered by Orbsen Therapeutics and is being manufactured for the trial by the NHSBT.

The MERLIN trial opened in March 2019 and will run until Autumn 2020. Depending on the results achieved a further study with a larger patient cohort may be warranted.

Prof Phil Newsome, University of Birmingham, MERLIN Coordinator.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602363. The material presented and views expressed here are the responsibility of the author(s) only. The EU Commission takes no responsibility for any use made of the information set out.

MERLIN

What are the potential benefits of MERLIN?

We hope that the new knowledge about MSCs generated in MERLIN will inform further research. Advanced imaging tools used in MERLIN can also assist future bio-imaging studies across all disciplines. The cell therapy industry will benefit from the new GMP compliant processes and quality control tests we have established for the manufacture of specially selected MSCs and from the potential unearthed for the optimisation of MSC products.

We hope that participants in the MERLIN clinical trial will benefit from the new cell therapy they receive. Depending on the results achieved a broader clinical trial may be pursued in the future. Ultimately we hope this new cell therapy may be made widely available to those with PSC and AIH. We also hope the treatment can be extended to other inflammatory diseases. The MERLIN clinical trial is the first step along this road.

In the long term, we hope our results may help benefit people with chronic liver disease (and other inflammatory conditions), clinicians and health systems and may deliver wider economic benefits.

Scientific Publications

You can read about our results in more detail in the scientific publications achieved by the project, including:

- *"Epigenetic changes in umbilical cord mesenchymal stromal cells upon stimulation and culture expansion"* Samantha F.H. De Witte et al., Cytotherapy 1 June 2018. DOI: 10.1016/j.jcyt.2018.05.005.
- "Immunomodulation by Therapeutic Mesenchymal Stromal Cells (MSC) Is Triggered Through Phagocytosis of MSC by Monocytic Cells" Samantha F H de Witte et al., Stem Cells 17 January 2018 DOI: 10.1002/stem.2779.
- *"Proteomic analysis of the secretome of human bone marrow-derived mesenchymal stem cells primed by pro-inflammatory cytokines"* Elisa Maffiolia et al., Journal of Proteomics, 21 July 2017 DOI: 10.1016/j.jprot.2017.07.012.
- *"Mouse mesenchymal stem cells inhibit high endothelial cell activation and lymphocyte homing to lymph nodes by releasing TIMP-1"* Zanotti L, Leukemia May 2016:5 30(5):1143-54. DOI: 10.1038/leu.2016.33.
- *"Mesenchymal stem cells: myths and reality"* Sarukhan A et al., Swiss Med Wkly. 2015;145:w14229. 23 Dec 2015. DOI: 10.4414/smw.2015.14229.
- *"Aging of bone marrow and umbilical cord derived mesenchymal stromal cells during expansion"*. Samantha de Witte et al., Cytotherapy 2017 DOI: 10.1016/j.jcyt.2017.03.071.
- *"Cytokine treatment optimises the immunotherapeutic effects of umbilical cord-derived MSC for treatment of inflammatory liver disease"* Samantha F. H. de Witte et al., Stem Cell Research & Therapy 20178:140 DOI: 10.1186/s13287-017-0590-6.

The MERLIN Partners

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NHS Blood & Transplant, United Kingdom

Pintail Ltd, Ireland

Università Degli Studi Di Padova, Italy, Italy

BioInVision, United States

Erasmus Medical Centre, Netherlands

For further information on the project please see the Project website http://fp7merlin.eu/.

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