

The Title of the Project: Effect of immunosuppression agents on human hepatocyte and non-parenchymal liver cells apoptosis

Project acronym: **APOHEPI**

Project Director: **Iacob Maria Speranta, MD, PhD**

Contractor: **Fundeni Clinical Institute**

Project duration: **24 months (2018-2020)**

Summary of the Research Project

The combination of mycophenolate mofetil (MMF) and a calcineurin inhibitor (CNI), or more recently sirolimus, are commonly used for maintenance immunosuppression following liver transplantation (LT). However, there are post-LT complications immunosuppression-related that negatively impact survival and quality of life. In vitro and in vivo studies have demonstrated profibrogenic properties of calcineurin inhibitors with increased hepatic and renal collagen deposition triggered by a high expression of transforming growth factor beta 1 and extracellular matrix genes. Newer studies suggest a role of these agents in promoting and enhancing cell-death in non-liver cell types like pancreatic cells, renal and prostate cells, thereby driving an inflammatory response that promotes fibrosis. Hepatic stellate cells (HSCs) play the critical role in liver fibrosis; reversal of liver fibrosis can be achieved through the apoptosis of activated HSCs. Immunosuppressive agents may also affect the life cycle of HSCs. The co-culture of hepatocytes and HSCs could facilitate the investigation of inter-cellular and molecular mechanisms of the fibrogenic process under the influence of different immunosuppression agents, but in vitro data on human cells is not available. The main objective of the present project is to study the effect of immunosuppressant agents used in clinical practice in LT on apoptosis in human hepatocytes, human HSCs monocultures and co-culture systems, according to CYP3A5 genotypes. Secondary, we aim to propose immunosuppressive regimens that can be safely used on long term without fibrosis development as a translational approach of personalized medicine.

Research activity:

Poster Presentations

Razvan Iacob, Vlad Herlea, Ioan Matei, Raluca Florea, Madalina Ilie, Irit Meivar-Levy, Daniela Lixandru, Simona Dima, Radu Albuлесcu, Ctistiana Tanase, Irinel Popescu and Sarah Ferber. Phenotypic assessment of liver-derived cell cultures during in-vitro cell population

expansion protocol. 6th UpDate on Hepatology Course, „From theory to practice in Liver Disease”, Bucharest 5th-6th April 2019

Speranta Iacob, Razvan Iacob, Cristian Gheorghe, Liana Gheorghe. Shear wave elastography use for screening of clinically significant portal hypertension after HCV cure. Digestive Disease Week, 16-18 May 2019, San Diego, USA

Speranta Iacob, Catalina Stanescu, Razvan Iacob, Roxana Vadan, Cristian Gheorghe, Ioana Lupescu, Liana Gheorghe. Right psoas muscle area: Prognostic factor in patients with cirrhosis Child Pugh class C included on the waiting list for liver transplantation. ILC 2019, 10-14 April 2019, Vienna, Austria

Oral Presentations

Speranta Iacob, Mirela Onica, Corina Pietrareanu, Carmen Ester, Razvan Cerban, Razvan Iacob, Cristian Gheorghe, Irinel Popescu, Liana Gheorghe. Lack of metabolic profile and renal function improvement after HCV eradication - analysis at 24months after interferon-free treatment in It recipients. 19th Congress of the European Society for Organ Transplantation, Copenhagen, Denmark, 15-18 September 2019

Speranta Iacob, Catalina Stanescu, Razvan Iacob, Roxana Vadan, Cristian Gheorghe, Ioana Lupescu, Irinel Popescu, Liana Gheorghe. Right psoas muscle area evaluation in cirrhotics -- predictor of both pre and post-liver transplant death. 19th Congress of the European Society for Organ Transplantation, Copenhagen, Denmark, 15-18 September 2019

Speranta Iacob, Doina Hrehoret, Luminita Stoica, Cristian Apavaloaie, Gabriela Droc, Dana Tomescu, Vladislav Brasoveanu, Laura Vlad, Corina Pietrareanu, Razvan Iacob, Cristian Gheorghe, Liliana Gheorghe, Irinel Popescu. Risk factors for bacterial infections following the first month after liver transplantation and the impact on survival. 19th Congress of the European Society for Organ Transplantation, Copenhagen, Denmark, 15-18 September 2019

Speranta Iacob. Programul de transplant hepatic in timpul si dupa pandemia SARS-CoV-2: o problema rezolvata? Romania 2030 fara Hepatite. Hepatitele virale in timpul si dupa pandemia COVID-19. 28 iulie 2020, Bucharest, Romania

Speranta Iacob. Consequences of antibody mediated rejection in LT recipients. National Congress of the Romtransplant Association – The 11th edition, 23-26 September 2020, Romania, online

Razvan Iacob. Cell therapy in liver diseases. National Congress of the Romtransplant Association – The 11th edition, 23-26 September 2020, Romania, online

Speranta Iacob. Impact of COVID-19 in advanced liver disease: outpatients, inpatients, transplant patients. In Session 3: COVID and the liver: Return to a pre-pandemic state. 7 th UpDate on Hepatology Course Virtual Experience Bucharest 6th-8th November 2020

Razvan Iacob. Precision medicine to guide therapy in hepatocellular carcinoma. In Session 6: Hot topics in 7 th UpDate on Hepatology Course Virtual Experience Bucharest 6th-8th November 2020

Submitted abstracts, accepted for presentation

Speranta Iacob, R Iacob, Ioana Manea, Luminita Stoica, M Manda, Mihaela Uta, A Chiosa, Codruta Popa, C Gheorghe, Simona Dima, I Popescu, Liliana Gheorghe. Impact of tbx21 and cyp3a5 gene polymorphisms on liver graft outcome. Submitted and accepted as oral presentation, Abstract with distinction, top 10% at Digestive Disease Week 2021, USA.

Published papers

Iacob R, Herlea V, Savu L, Florea IR, Ilie VM, Terinte-Balcan G, Gherghiceanu M, Uta M, Popa C, Iacob S, Matei IV, Jordan C, Lixandru D, Dima SO, Meivar-Levy I, Ferber S and Popescu I. Phenotypic assessment of liver-derived cell cultures during in-vitro expansion. *Regenerative Medicine* 2021. Jan;16(1):33-46. doi: 10.2217/rme-2020-0093. Epub 2021 Feb 3

Iacob S, Ghioca M, Csiki IE, Tomescu D, Droc G, Hrehoret D, Brasoveanu V, Pietroreanu C, Iacob R, Gheorghe C, Popescu I, Gheorghe L. Pre and post-liver transplant outcome of cirrhotic patients with acute on chronic liver failure. *Medicine* 2020; 99(44):e22419

Published (or in press) book chapters

Speranta Iacob, Liana Gheorghe. Transplantul hepatic pentru practicianul internist: indicatii, evaluare, management pre- si post-transplant. In *BOLILE HEPATICE IN 2019*. Editura Medichub Media, 2019: 145-148

Iacob S, Gheorghe L. Indications for liver transplantation in adults - selection of patients with end stage liver diseases. Chapter 66 in the *IASGO Textbook of Multi-Disciplinary Management to Hepato-Pancreato-Biliary Diseases*, editata de Drs. Masatoshi Makuuchi, Norihiro Kokudo, Irinel Popescu, Jacques Belghiti, Kyoichi Takaori si Dan G. Duda si publicata de Springer Nature (in press)