What Is Hot and New in Basic and Translational Science in Liver Transplantation in 2019? Report of the Basic and Translational Research Committee of the International Liver Transplantation Society

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Abstract. The International Liver Transplantation Society (ILTS) 2019 Annual Congress was held in Toronto, Canada, in May 2019. Members of the ILTS Basic and Translational Research Committee attended all sessions of the meeting and selected the most promising, innovative, and novel research presented. A total of 900 abstracts were presented at the meeting. The percentage of abstracts presented at the ILTS Congress that contains basic or translational research continues to increase, accounting for 15% of all the abstracts in 2019, up from 10% in 2018. Here, we summarize the "what's hot what's new" in 5 main themes: liver immunobiology and tolerance, ischemia/reperfusion injury and organ preservation, bioengineering and liver regeneration, hepatic primary tumor biology, and pathophysiology of liver failure.

(*Transplantation* 2020;104: 516–521).

INTRODUCTION

The 2019 Annual Congress of the International Liver Transplantation Society (ILTS) was held in Toronto, Canada, in May 2019. It was attended by 1126 delegates from 52 countries. A total of 900 abstracts were presented at the meeting. Keeping up with the trend in the past few years, the percentage of basic research abstracts presented at the ILTS Congress continues to be stable (Table 1). However, the number of abstracts that contains translational research continues to increase, together, accounting for 15% of all the abstracts in 2019, up from 10% in 2018. This increase demonstrates the commitment of the ILTS for advancement of science in liver transplantation. All abstracts and recordings from 2019 ILTS Congress are available to the members of ILTS through its website.[1]

Members of the ILTS Basic and Translational Research Committee attended all sessions of the meeting and selected the most promising, innovative, and novel research presented. Here, we summarize the "what's hot, what's new in 2019" in 5 main themes, covering vast majority of the current research in liver transplantation: (1) liver immunobiology and tolerance; (2) ischemia/reperfusion injury (IRI) and organ preservation; (3) bioengineering and liver regeneration; (4) hepatic primary tumor biology; and (5) pathophysiology of liver damage and failure (Table 2). Overall, genomics, proteomics, and metabolomics approaches combined with new bioinformatics tools are being increasingly integrated into basic and translational research in

Received 28 August 2019. Revision received 12 October 2019.

Accepted 8 November 2019.

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The authors declare no funding or conflicts of interest.

T.T. wrote the first draft. P.N.M. and M.S. helped with writing. B.E. and V.R.M. finalized the draft. All authors contributed in selection of abstracts and papers for the review and all authors contributed in manuscript writing. All authors approved the final version.

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ISSN: 0041-1337/20/1043-516

DOI: 10.1097/TP.0000000000003058

<zdoi;10.1097/TP.0000000000003058>

TABLE 1.

Basic and translational science presentations at the ILTS Congress in 2017–2019

Year/venue	Number of countries represented	Total number abstracts	Number of late-breaking abstracts	Total number of basic and translational research abstracts	Percentage of basic and translational research abstracts
2017/Prague	61	860	65	70	8.1
2018/Lisbon	58	759	112	72	9.5
2019/Toronto	52	900	74	75	8.3%
				138[a]	15.3%[a]

[a]Including 75 abstracts submitted to the ILTS Congress under the Basic Research category and 63 abstracts with significant basic/translational research submitted under other categories.
ILTS, International Liver Transplantation Society.

TABLE 2.

Most significant new findings in basic and translational research from the 2019 ILTS Annual Congress

Liver immunobiology and tolerance	• Immunosuppression was discontinued in 3 of 5 patients with recurrent PSC post-liver transplantation, treated with ablation and autologous hematopoietic stem cell transplantation[2]
	• Reduced lobular antigen-presenting cell: leukocyte pairing and infiltrating macrophages was predictive of operational tolerance[3]
Ischemia/reperfusion injury and organ preservation	• 22 of 31 discarded livers were transplanted after a median preservation time of 18 h on NMP, with 100% 90-d survival but 18% retransplantation rate due to ischemic cholangiopathy[4]
	• Steatotic liver tissue injury markers and lactate were lower in the static cold storage supplemented with the natural oxygen carrier $HEMO_2$Life after 24 h[5]
	• A combination of hepatocyte (lactate and urea) and cholangiocyte (bile/perfusate differential sodium and glucose ratios) functional parameters demonstrated a good correlation with the degree of ischemic injury and post-transplant graft function in real-time assessment of livers on NMP that were later transplanted[6]
Bioengineering and liver regeneration	• Peribiliary glands contain biliary progenitor cells that can restore epithelial integrity in ex vivo human bile ducts[7]
	• Coculturing with hepatic stellate cells improved hepatocyte function in bioprint pig liver constructs[32]
Pathophysiology of liver damage and failure	• Compared with patients with cirrhosis without acute decompensation, those with ACLF had higher levels of proinflammatory cytokines IL-1β, IL-6, TNF-α, MCP-1, and GM-CSF. When macrophages were depleted during NMP of human ACLF livers, the proinflammatory cytokine levels were reduced in the perfusate[9]
Biology of primary liver tumors	• 9-gene serum fingerprint (BAFFTNFSF, IFNα, sIL6Rα, IL12, IL26, osteocalcin, osteopontin, pentraxin, and AFP) was reported to have high predictive power for post-transplant HCC recurrence[10]
	• A model incorporating pretransplant clinicopathologic variables and post-transplant serum markers (inflammatory cytokines and circulating miRNAs) was shown to predict 5-y HCC recurrence risk after liver transplantation with a *c* statistic of 0.9[11]

ACLF, acute-on-chronic liver failure; GM-CSF, granulocyte-macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; ILTS, International Liver Transplantation Society; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NMP, normothermic machine perfusion; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor.

liver transplantation, and account for the main changes in scientific approach in all liver transplant–related research.

LIVER IMMUNOBIOLOGY AND TOLERANCE

Immunobiology and tolerance research remains a major theme across the globe, despite significant changes in areas of research in liver transplantation in the past decade. The most recent studies in these areas reflect the improvements in detection of lymphocyte subsets and their correlation with alloimmune injury in liver allografts. Through a longitudinal investigation of circulating regulatory T cell (Treg) frequency in liver transplant recipients, Han et al[12] found that a lower frequency of Treg on posttransplant day 7 correlated with biopsy-proven rejection in both the discovery and validation cohorts of their transplant center in Korea. The authors also reported that the frequency of Treg was inversely correlated with serum trough tacrolimus levels. In patients with rejection and lower Treg frequency, alloreactive T-cell proliferation was only incompletely blocked by tacrolimus, while rapamycin improved the antiproliferative effect of tacrolimus on alloreactive T cells. In a limited number of liver transplant patients maintained on calcineurin inhibitor–free immunosuppression, Meszaros et al[13] used the predicted indirectly recognizable HLA epitopes score, a novel HLA epitope matching tool, to monitor alloimmunity and predict biopsy-proven rejection.[13] In this pilot analysis, they showed that patients with abnormal liver allograft biopsies had higher predicted indirectly recognizable HLA epitopes scores on average than those with normal biopsies and that a score over 68 was predictive of allograft dysfunction. Because most liver transplant recipients are maintained on calcineurin inhibitor–based immunosuppression, whether these findings could be validated in larger cohorts remains to be seen.

Interim results of the Autologous Hematopoietic Stem Cell Transplantation for Allogeneic Organ Transplant Tolerance (ASCOTT) trial were presented at the ILTS 2019 Congress.[14] This trial, conducted in Canada, aims to test the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) to induce tolerance in liver transplant recipients.[2] All 5 patients who had the HSCT had undergone liver transplantation for primary sclerosing cholangitis and had recurrence of disease at the time of enrollment. Patients had ablative therapy before HSCT.

Immunosuppression was discontinued in 3 patients post-HSCT, in whom the authors found evidence of alloreactive T-cell clone deletion. The other 2 patients had adverse outcomes (new-onset veno-occlusive disease requiring retransplantation and development of hemophagocytosis leading to death), demonstrating the potential toxicity of HSCT post-liver transplantation. In a different trial (Liver Immune Tolerance Marker Utilization Study [LITMUS]),[15] the same group tested the predictive value of a gene expression panel in both the liver allograft and peripheral blood mononuclear cells on operational tolerance in liver transplant recipients. Of the 9 patients who met the inclusion criteria, 5 were reported to have been off of immunosuppression for >2 years at the time of the ILTS meeting, and the other 4 were continuing immunosuppression withdrawal. Based on these results, the authors argued that the gene panel they have identified could be used to identify patients for prospective immunosuppression withdrawal.

By performing quantitative immunophenotyping of liver biopsies of pediatric liver transplant recipients who were enrolled in the Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients (iWITH) trial with a screening liver biopsy with mild inflammation and/or fibrosis, Bucuvalas et al[3] found that reduced lobular antigen-presenting cell: leukocyte pairing and infiltrating macrophages was predictive of operational tolerance. The above studies represent innovative attempts to predict and induce tolerance in liver transplant recipients.

In summary, cell-based therapeutic approaches targeting alloimmune responses and detailed analyses of liver intragraft immune cells in operationally tolerant patients dominate the current research in liver transplant immunology, reflecting the trend toward individualized immunosuppression after transplantation.

IRI AND ORGAN PRESERVATION

The ILTS Annual Congress remains one of the main platforms for research in liver IRI. Organ preservation through novel techniques of machine perfusion continues to generate significant interest, especially in the Western hemisphere where liver transplantation is still done predominantly through deceased donation and there is an ongoing desire to utilize more liver allografts that are otherwise discarded due to poor quality. Machine perfusion, especially in assessment and optimization of marginal livers, was one of the major research areas represented at the ILTS 2019 Congress. Although there were several abstracts with clinical research in machine perfusion (which will be covered by the ILTS Vanguard Committee), of the 27 abstracts on machine perfusion, 9 had novel basic science data from animal models. The meeting also featured a premeeting machine perfusion workshop, organized and chaired by Dr Markus Selzner.

Several different abstracts collectively summarized the results of the Viability Testing and Transplantation of Marginal Livers trial. This UK-based trial aims to assess the viability and successful transplantation of discarded liver allografts using normothermic machine perfusion (NMP). Of the 31 discarded livers that met the inclusion criteria of clearance of perfusate lactate to ≤2.5 mMol/L, bile production, glucose metabolism, and pH within 4 hours of commencing NMP, 22 were transplanted after a median preservation time of 18 hours. Although the 90-day survival was 100%, the authors reported that at a median follow-up of 197 days, 4 patients (18%) required retransplantation due to ischemic cholangiopathy.[4] By analyzing the proteomics of the perfusate, the authors were able to identify clusters of proteins that were differentially expressed by transplantable versus nontransplantable livers, as well as in those who went on to develop ischemic cholangiopathy,[16] suggesting that this may be used to improve decision-making in using livers on NMP. Similarly, metabolic profiling of the perfusate was able to differentiate the nontransplanted livers from transplanted ones, as the former had higher levels of lipid, phospholipid, and sphingolipid metabolites.[17] Regardless of what method is utilized in the future, the results will need to be validated in a much larger cohort. In hypothermic oxygenated perfusion, investigators from Europe investigated the mitochondrial flavoproteins in the perfusate as a marker of mitochondrial injury, a surrogate of IRI. They reported that the mitochondrial flavoprotein quantity correlated well with the lactate clearance and post-transplant correction of coagulation factors. The authors argued that this provides an accurate and quick way of predicting graft quality and function.[18]

Castro-Benitez et al[5] shared their observations on the use of $HEMO_2Life$, a natural oxygen carrier, on IRI of steatotic livers. Through assessment of obese rat liver perfusate, they demonstrated that tissue injury markers and lactate were lower in the static cold storage supplemented with $HEMO_2Life$ after 24 hours. By using a 7-component defatting cocktail in NMP, Raigani et al[19] was able to reduce the percentage of macrosteatosis in obese rat livers from an average of 41.5%–8.5%. This reduction correlated with a reduction in the perfusate lactate content and an increase in bile bicarbonate content. The efficacy of this approach remains to be tested in human livers. Studying 18 discarded steatotic human livers, the Oxford group tested lipid apheresis with or without defatting agents in the NMP.[20] This study tested the total fat content in the livers before and after treatment, in addition to lipid metabolites in the perfusate. A 48-hour perfusion with defatting agents and lipid apheresis resulted in an average of 45% reduction in tissue triglyceride content and a significant decrease in de novo lipogenesis. Again, none of these livers were transplanted, so this will need to be tested in experimental and clinical transplantation.

Linares-Cervantes et al[6] and the University of Toronto group presented their results in real-time assessment of livers on NMP that were later transplanted. A combination of hepatocyte (lactate and urea) and cholangiocyte (bile/perfusate differential sodium and glucose ratios) functional parameters demonstrated a good correlation with the degree of ischemic injury and post-transplant graft function. The same group investigated the utility of indocyanine green fluorescence imaging in determining the severity of ischemic injury in donation after circulatory death (DCD) livers while on NMP and reported that this relatively simple technique helped demonstrate hypoperfused areas on the surface of DCD livers with prolonged warm ischemia times.[21] Investigators from Groningen demonstrated that higher biliary bicarbonate and pH and lower biliary glucose levels during NMP were predictive of lower incidence of bile duct injury.[22]

Following the first report on successful use of selective RNA interference to target genes involved in ischemic

injury during machine perfusion last year, Gillooly et al[23] confirmed delivery of FS—associated surface antigen or CD95 (FAS) and p53 small interfering ribonucleic acid (siRNA) into rat livers by incorporating them into lipid nanoparticles. The result was reduced apoptosis when the siRNA was used in both the hypothermic and NMP. The authors, however, did not investigate the overall impact of reduced apoptosis in grafts in which the predominant injury remains parenchymal necrosis. Similarly, the potential long-term consequences of p53 inhibition on patients with underlying cancer will need to be evaluated in detail. In the next study, by the same group, Bonaccorsi-Riani et al[24] showed that intravenous administration of FAS-siRNA in donors 2 hours before aortic cross-clamping resulted in lower levels of post-transplant transaminases in the recipients in a rat liver transplant model, demonstrating the potential utility of this approach to alleviate IRI.

Among the studies investigating the pathophysiology of IRI was an elegant study from Hong Kong by Zhang et al.[25] They observed that intragraft interleukin (IL)-17A expression was upregulated in livers with IRI and correlated with serum aspartate aminotransferase (AST) levels. In IL-17A knockout mice, there was histological evidence of reduced IRI accompanied by a reduction in graft-infiltrating B1a cells and reduced serum IgM titers. Using a murine liver warm ischemia model, Ni et al[26] reported that resolution of reperfusion injury is dependent on Kupffer cells, as their depletion or inhibition of through TIM-4 blockade delayed the repair of tissue injury, leading to persistent inflammation and fibrosis. Interestingly, blockade of infiltrating macrophages did not result in prolonged ischemic injury, demonstrating the unique role and contribution of Kupffer cells to the pathophysiology of IRI.

By adapting the clinical cytochromal breath test, which tests metabolism of 13C-methacetin to the membrane oxygenator of the NMP device, Schurink et al[27] demonstrate that the maximum liver function capacity test (LiMAx) could be used to assess graft status (transaminases) and function (lactate clearance). This study was limited to only 7 discarded livers, none of which went on to be transplanted. Using high-throughput metabolomics on snap-frozen tissue, Bhat et al[28] found that mitochondrial function and β-oxidation improved in DCD livers on NMP, compared with cold storage. There was also a new approach to test liver graft viability during machine perfusion through flow distribution visualization using thermography.[29]

In summary, recent developments in machine perfusion have allowed researchers to assess and intervene on IRI of liver allografts, promising better evaluation of organs than ever before.

BIOENGINEERING AND LIVER REGENERATION

Driven by the goal of eliminating the need for invasive bile duct biopsies, investigators from the Netherlands explored using bile as a source of cholangiocyte organoids.[30] They demonstrated that bile-derived organoids expressed genetic markers and proteins of cholangiocytes, making this a feasible in vitro model to study biliary disease and potential source for bile duct engineering. The same group reported the first results of the use of a novel human liver hydrogel in liver organoid cultures.[31] This hydrogel was created by decellularizing discarded human livers. The authors demonstrated the human hydrogel improved differentiation of liver organoids toward hepatocytes drastically over the currently used mouse-derived matrigel. By using an innovative ex vivo model utilizing extrahepatic human bile ducts of discarded donor livers, de Jong et al[7] were able to demonstrate that the peribiliary glands contained biliary progenitor cells, which could restore epithelial integrity after restoring oxygenation.

Chen et al[32] shared their initial observations, using hepatic stellate cell and hepatocyte cocultures in the scaffold-free three-dimensional–bioprinted liver model. As they predicted, coculturing with hepatic stellate cells improved hepatocyte function, as measured by albumin secretion and urea clearance. Using the spheres obtained from these cocultures, the authors were able to bioprint pig liver constructs. The same group reported the first three-dimensional scaffold-free printing of an extrahepatic human bile duct model.[8] In this model, the inner layer of the printed tubule was coated with human cholangiocytes and liver endothelial cells, while the outer layer comprised of bile duct fibroblasts and liver endothelial cells. The viability and localization of the cells were confirmed by immunofluorescence. In contrast, Willemse et al[33] used a scaffold obtained from a decellularized human extracellular bile duct to engineer bile ducts. In this model, the luminal side of the bile duct extracellular matrix was recellularized with human bile duct–derived organoids. The authors were able to show polarization of the cholangiocytes after recellularization, resulting in uninterrupted coverage of the luminal surface.

In an effort to produce a model for large-scale expansion of human hepatocytes, Nelson et al[34] used clustered regularly interspaced short palindromic repeats technology to knockout fumarylacetoacetate hydrolase and recombinase activating gene-2 sequentially in pig embryos. The authors had previously reported that fumarylacetoacetate hydrolase–deficient pigs provide a selective advantage for the expansion of human hepatocytes. Ten million human hepatocytes were injected into fetal liver of double knockout pig embryos at day 35 of gestation. After birth, the authors found that the human hepatocytes had engrafted in double knockout piglets, with accompanying human albumin in circulation. Despite these promising results, whether genetically engineered pigs can serve as a source of human hepatocytes for clinical use remains to be seen.

In summary, through improved understanding of the complex cell-to-cell interactions in the liver, novel bioengineering tools are increasingly incorporated into basic and translational research, providing investigators with liver-like organoids in vitro.

PATHOPHYSIOLOGY OF LIVER FAILURE

Zhao et al[9] investigated the role of macrophages in pathophysiology of acute-on-chronic liver failure (ACLF) in patients with chronic HBV. They found that, compared with patients with cirrhosis without acute decompensation, those with ACLF had higher levels of proinflammatory cytokines IL-1β, IL-6, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1 (MCP-1), and granulocyte-macrophage colony-stimulating factor (GM-CSF). They also showed that the liver tissue of patients with ACLF had upregulated pyroptosis-inducing gasdermin D

(GSDMD) in liver-resident macrophages. When these macrophages were depleted during NMP of human ACLF livers, the proinflammatory cytokine levels were reduced in the perfusate. The role of macrophages in acute liver injury was tested in a toxin-induced toxicity model in mice by Zhou et al.[35] In this model, the authors knocked out thecytosine-cytosine-adenosine-adenosine-thymidine-enhancer-binding protein homologous protein in mice, resulting in macrophage M2 polarization, enhanced autophagy, and reduced liver injury.

Repressor-activator protein (Rap-1) is a telomere-binding protein, part of a complex group of proteins that protect telomeres in a wide variety of organisms.[36] Rap-1 knockout mice develop early obesity and hepatic steatosis. In a high-fat diet mouse nonalcoholic steatohepatitis (NASH) model, Li et al[37] found that the Rap-1 is markedly reduced in the liver tissue. In Rap-1 knockout mice, the authors found severe steatohepatitis, marked by elevated AST and alanine aminotransferase. They also demonstrated increased expression of proinflammatory cytokines TNF-α, IL-1β, CXCL10, and MCP-1, highlighting the role of Rap-1 in the inflammatory process that underlies the pathophysiology of NASH. In an attempt to target this inflammation, Perroud et al[38] administered encapsulated human adipose- or bone-marrow–derived mesenchymal stem cells into mice with NASH.[38] They found that mice treated with mesenchymal stem cells had significantly less weight gain, plasma insulin levels and reduced genetic markers of inflammation in the liver. In summary, new research findings presented at the ILTS 2019 confirm the role of inflammation in the progression of liver damage and failure in both viral and steatosis-associated liver diseases.

BIOLOGY OF PRIMARY LIVER TUMORS

The researchers from eastern Asia continue to dominate basic research on primary liver tumor biology, due primarily to the high incidence of these tumors in the Eastern hemisphere. Yang et al[10] investigated the correlation of pretransplant plasma inflammatory profiling and post-transplant tumor recurrence in patients with hepatocellular carcinoma (HCC).[10] After starting with 38 inflammatory-related markers, they were able to narrow down to a 9-gene serum fingerprint (BAFFTNFSF, IFNα, sIL6Rα, IL12, IL26, osteocalcin, osteopontin, pentraxin, and AFP), which had very a very high predictive power for post-transplant HCC recurrence. Using a more comprehensive model incorporating pretransplant clinicopathologic variables and post-transplant serum markers (inflammatory cytokines and circulating miRNAs) through the restricted Botzman Machine network, Ng et al[11] were able to predict 5-year HCC recurrence risk after liver transplantation with a *c* statistic of 0.9. These promising results will need to be validated in larger cohorts and in other parts of the world.

In patients undergoing resection for HCC, Pang et al[39] found that plasmacytoid dendritic cell (pDC) infiltration in tumors, known for their immunosuppressive properties, was correlated with worse disease-free survival. They also demonstrated that the pDC recruitment into transplanted livers was more common in recipients of small-for-size grafts, suggesting that early graft injury may promote HCC recurrence through recruitment of pDC. The same group investigated the role of T-cell functional exhaustion in HCC.[40] They were able to show that intragraft expression of Δ42PD1, an isoform of PD1, is upregulated after liver transplantation in patients with tumor recurrence. Δ42PD1+ T cells isolated from HCC patients demonstrated functional exhaustion in vitro, with lower proliferative capacity and diminished interferon-ɤ production. Furthermore, the authors were able to suppress tumor growth in the humanized-mice HCC model through blockade of Δ42PD1.

In summary, the current research in primary liver tumor biology focuses on markers predictive of post-transplant tumor recurrence and characterization of the antitumor immune responses.

CONCLUSIONS

Representation of basic and translational research continues to increase in the ILTS Annual Congress. Sessions dedicated to such research themes were among the best-attended ones of the congress, reflecting the ongoing transformation and maturation of the field of liver transplantation, as well as the commitment of the ILTS to the advancement of science in liver transplantation.

ACKNOWLEDGMENTS

Members of the ILTS Basic and Translational Research Committee thank all members of the ILTS Vanguard Committee for their professionalism and help to select necessary work from the 2019 ILTS Meeting.

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