What Is Hot and New in Basic and Translational Science in Liver Transplantation in 2022? Report of the Basic and Translational Research Committee of the International Liver Transplantation Society

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INTRODUCTION

The 2022 Joint Annual Congress of the International Liver Transplantation Society (ILTS), European Liver and Intestine Transplant Association, and Liver Intensive Care Group of Europe was held in Istanbul, Turkey, from May 4 to 7, 2022. The meeting was held in a hybrid format with excellent in-person and online engagement. This was the first time in 2 y that the ILTS community was able to meet in-person, enabling rich networking opportunities and extensive discussion. The ILTS Congress was attended by 1123 delegates from 61 countries (648 participants on-site and 475 online; Figure 1).

Out of a total of 465 abstracts, 9.9% fell into the basic/translational science category, representing a 1.7% increase in basic/translational abstracts compared with the previous year (Table 1). This is reflective of the increasing enthusiasm for basic science research to elucidate a mechanistic understanding of transplant processes among the ILTS membership. Beyond the original research presented orally at 2 Basic and Translational Science abstract sessions, the Basic and Translational

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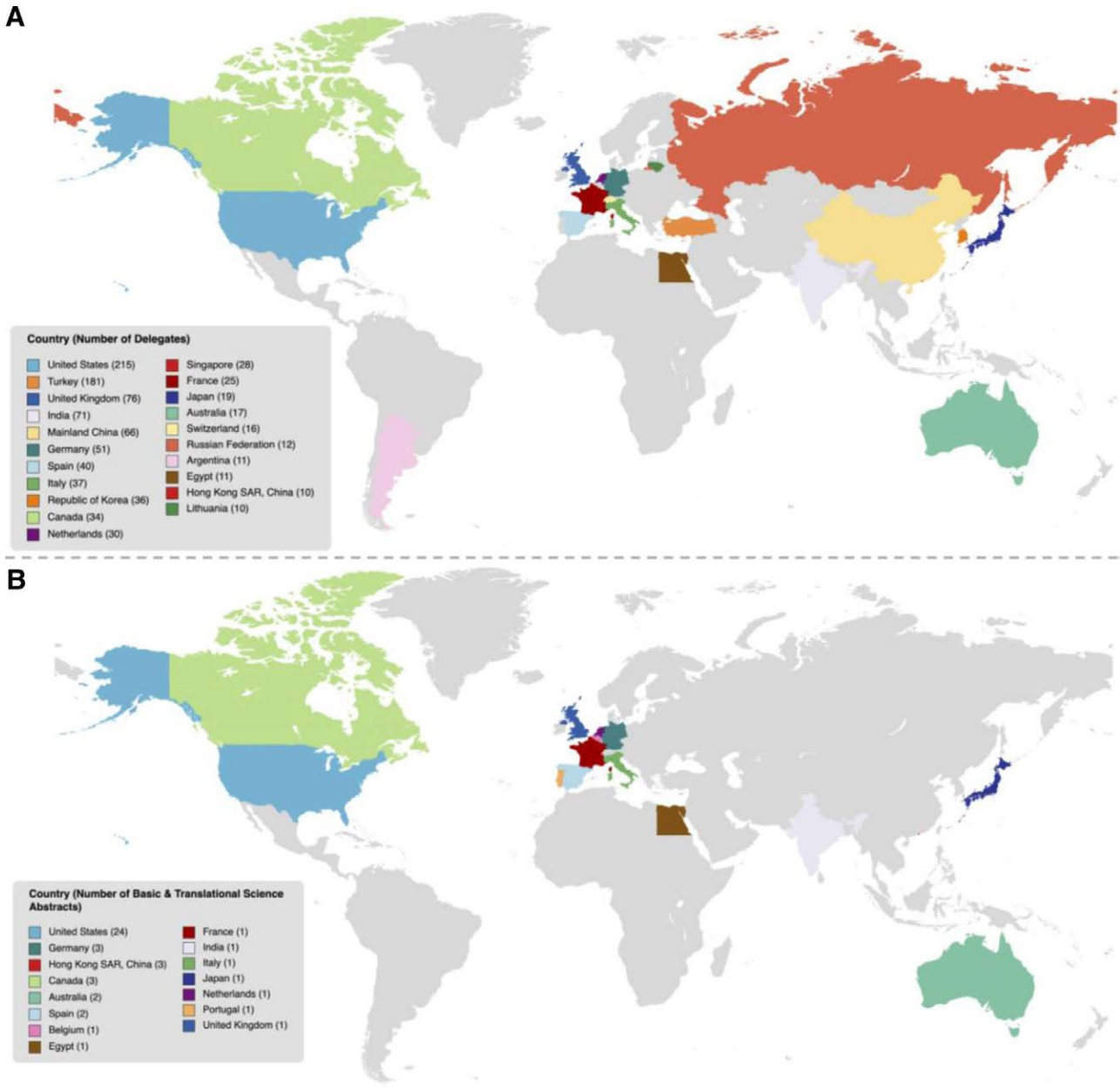


FIGURE 1. Countries with (A) ≥10 delegates and (B) the presenting authors of basic and translational science abstracts at the 2022 Joint ILTS-ELITA-LICAGE Meeting. This figure was regenerated with permission of the ILTS. The authors and the journal remain neutral with regard to jurisdictional claims in published maps and institutional affiliations. ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplant Society; LICAGE, Liver Intensive Care Group of Europe; SAR, Special Administrative Region.

Science Research Committee was also responsible for the organization of a well-received workshop on multiomics and big data in liver transplantation organized by the Basic and Translational Science Research Committee. In addition, a joint workshop was held with the precision medicine and biomarkers special interest groups from ILTS. Our committee also organized an especially well-received and fully booked pre-Congress "hands on" workshop on machine perfusion preservation in conjunction with local transplant leaders in Istanbul and members of the Toronto transplant research team.

Here, we summarize key basic and translational science abstracts categorized into 4 main themes, including (1) ischemia–reperfusion injury (IRI) and machine perfusion, (2) transplant oncology, (3) novel biomarkers, and (4) liver immunobiology (Figure 2). These abstracts used animal models and profiling of patient samples using multiomics approaches and laboratory techniques, including single-cell sequencing and imaging mass cytometry. We will attempt to place these results in the context of the current literature, thereby demonstrating how these studies promise to advance the field.

IRI and Machine Perfusion

IRI is a ubiquitous and unavoidable consequence in all solid organ transplantation with a special impact on liver transplantation (LT). In fact, IRI represents the sum of damages that accumulates at each stage of the

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transplantation process, from the onset of the hypoxia/ischemia phase in the donor (eg, aortic cross-clamp) to reperfusion in the recipient. The degree of IRI directly affects posttransplant organ function and the rate/severity of post-LT complications.[1] Notably, the more extended criteria characteristics the graft has (eg, steatosis, advanced age, ischemia time), the more susceptible it will be to IRI. In this year's ILTS Congress, different studies focused their attention on IRI evaluation and its modulation through both machine perfusion and pharmacological treatments.

Evaluation of IRI

Cell culture, liver resection, in vivo IRI (liver hilum clamping), and transplantation models are all used for the evaluation of the IRI and to provide deeper insight into IRI machinery. An activated inflammatory cascade and a reduced energetic pool secondary to IRI are commonly

TABLE 1.

Absolute and relative frequencies of basic and translational science–related abstracts presented at the Joint ILTS-ELITA-LICAGE Meetings in 2017–2021

Year/venue	Countries represented (n)	Total abstracts (n)	Late-breaking abstracts (n)	Basic and translational research abstracts (n)	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
2020–2021/ virtual[a]	66	730	89	60	8.2
2022/ Istanbul	61	465	76	46	9.9

[a]Because of the coronavirus disease 2019 pandemic, the 2020 ILTS Congress in Istanbul was postponed and held in a fully virtual setting in 2021.
ELITA, European Liver and Intestine Transplant Association; ILTS, International Liver Transplantation Society; LICAGE, Liver Intensive Care Group of Europe.

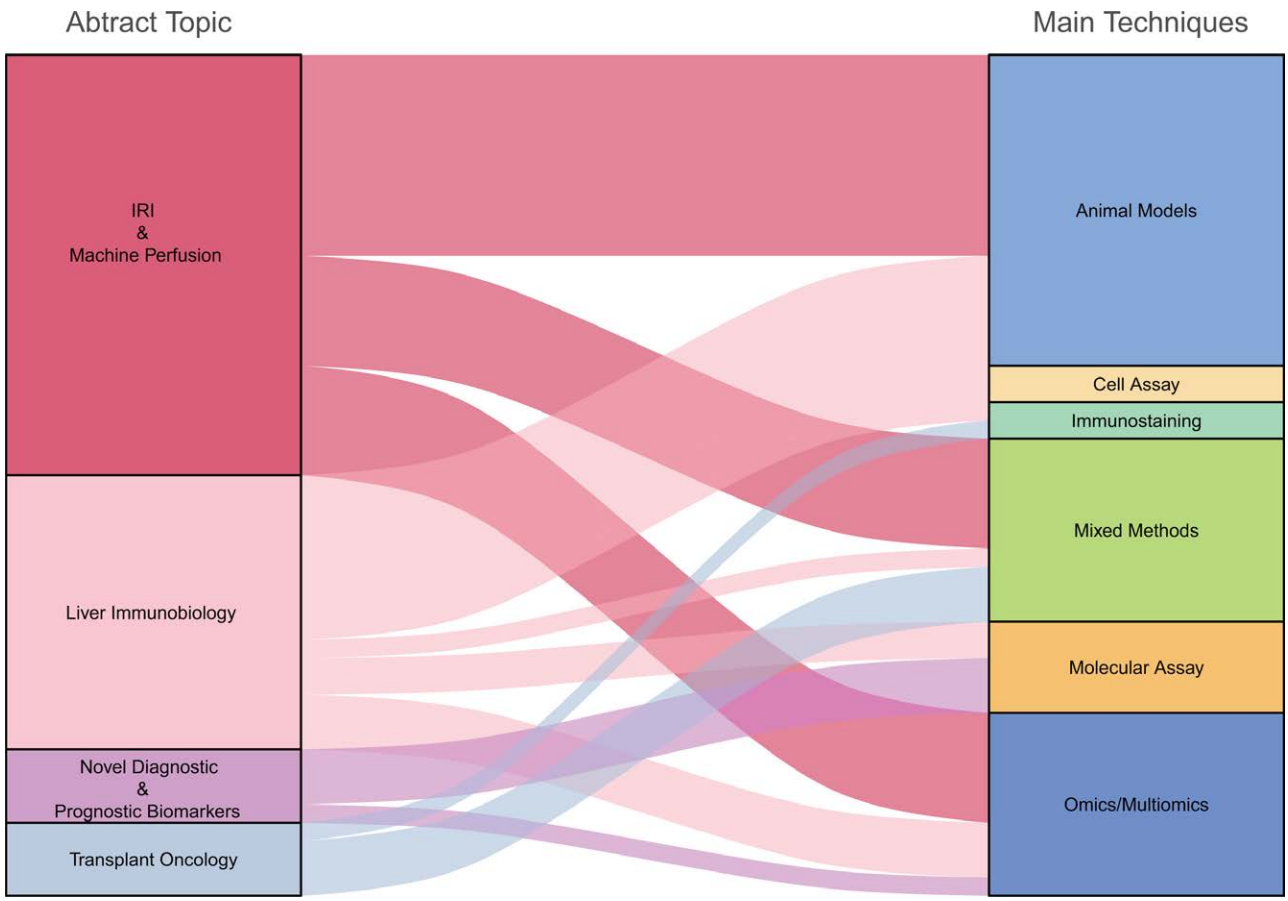


FIGURE 2. Sankey diagram depicting distribution of abstract topics and main techniques used in the 46 basic science studies presented at the 2022 Joint ILTS-ELITA-LICAGE Meeting.* *Each (total N = 46) abstract has been classified into 1 of the 4 topics/themes and based on the main technique and methodical approach used. ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplant Society; IRI, ischemia–reperfusion injury; LICAGE, Liver Intensive Care Group of Europe.

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identified as key events that lead to lower results after LT using steatotic grafts. McDaniels et al (J. McDaniels, MDD, unpublished data) investigated the particular susceptibility of steatotic liver grafts to IRI. They used single-cell transcriptomic analyses on steatotic and normal human hepatocytes and were able to confirm a decrease in coagulation factors, increase in proinflammatory profiles, and activation of peroxidation during IRI in fatty liver hepatocytes, confirming in vivo experimental data. In addition, single-cell transcriptomic analysis was able to identify pathways that may represent targets for IRI therapeutic intervention and factors that could reduce regenerative capacity post-IRI.[2] Bardhi et al[3] explored the role of micro-RNAs (miRNAs) in the regulation of donor organ damage on human liver biopsies. They further emphasized the upregulation and downregulation of these miRNAs and found specific miRNAs that could serve as potential therapeutic targets,[3] a promising approach to reduce early graft dysfunction.[4]

Normothermic Machine Perfusion

Machine perfusion preservation represents one of the most promising and translational technology in the field of IRI prevention and treatment from a clinical and research perspective. Although hypothermic oxygenated machine perfusion (HOPE) achieved significant results in the clinical setting, normothermic machine perfusion (NMP) reserves the opportunity to maintain liver graft physiology and assess liver homeostatic functions.[5] At this year's Congress, a higher number of abstracts were focused on the application of NMP technology (Table 2). Several groups explored the possibility of NMP to prolong ex situ preservation. Building on these results, Lau et al used a modified commercial NMP system (with dialysis filter) to surgically split human livers without interrupting perfusion and preserve them for several days. As a result, the grafts were able to meet the viability criteria for as long as 13 d.[6] The same group showed that, after 72 h NMP, biliary reepithelialization could occur, and biliary viability criteria could be met even by grafts that did not meet them at the beginning of NMP.[7] As long as NMP can be prolonged, more opportunities for ex situ organ treatment could be achieved. Despite these promising prospects, a more thorough evaluation of the mechanisms of NMP is needed to better understand these findings and fully exploit the potential for NMP preservation, treatment, and reconditioning. In a metabolomics study of an NMP rat model, Lonati et al[8] demonstrated that even in the presence of physiological oxygen supply, numerous changes in energy, glucose, mitochondrial and lipid metabolism, and redox occur during NMP. These findings are consistent with previous observations on the regulation of metabolic pathways in early allograft dysfunction (EAD) and phospholipid turnover.[9] In an effort to provide a more physiological environment during ex situ perfusion, Wu et al used normothermic venoarteriovenous cross-circulation between a discarded human donor liver and an immunosuppressed, complement-deprived pig to maintain normothermic perfusion. They successfully preserved biliary integrity and gross architecture for 24 h, but clinical application is still far off.[10]

Although prolongation of ex situ perfusion was one of the most attractive perspectives that emerged from the Congress, a deeper understanding of the exact biological mechanisms elicited during machine perfusion is essential to further progress. To achieve this goal, optimization and standardization of ex situ protocols (preclinical setting) together with more homogeneous graft quality (clinical setting) are key steps. In addition, taking advantage of the methodology of IRI and regeneration studies, the integration of results obtained by different models and advanced laboratory technologies is of paramount importance to achieving this aim.

Other Dynamic Machine Perfusion Techniques

Normothermic regional perfusion, an in situ perfusion approach, is widely adopted (in combination or not with other end-ischemic machine perfusion modalities) to improve donation after circulatory death outcomes. Panconesi et al directly compared normothermic regional

TABLE 2.

Summary of the main findings on machine perfusion explored in the 2022 ILTS Congress

Author	Model	Preservation modality	Aim	Key findings
Lau et al[6]	Human-discarded liver	NMP	Prolong perfusion	After ex situ liver split, liver graft viability criteria were maintained up to 13 d
Lau et al[6]	Human-discarded liver	NMP	Bile duct evaluation	After 72 h, bile reepithelialization was observed
Lonati et al	Rat	NMP	Metabolic profiling during NMP	Compared with normal liver metabolism, changes in energy, glucose, mitochondrial and lipid metabolism, and redox occurred during NMP
Wu et al[10]	Human/pig	Cross-circulation	Prolong perfusion	Using pig to isolated liver cross-circulation, successful preservation of human liver biliary tree, and gross architecture was observed after 24 h
Panconesi et al	DCD rat	NRP/HOPE	Mitochondrial preservation	HOPE showed lower mitochondrial damage and higher survival compared with NRP
Muller et al[11]	DCD pig	SCS/HOPE	Development preservation solution	Polyethylene glycol and glutathione-enriched solutions could be used for both static and dynamic hypothermic perfusion
Gomez Bardallo et al[12]	Obese rat	SCS	Development preservation solution	Polyethylene glycol and glutathione-enriched solutions reduced peroxidation and mitochondrial damage in fatty liver

DCD, donation after circulatory death; HOPE, hypothermic oxygenated machine perfusion; ILTS, International Liver Transplantation Society; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; SCS, static cold storage.

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perfusion and dual HOPE in a donation after circulatory death setting. In a rat model, the authors found lower mitochondrial damage and inflammation in the dual HOPE group as well as higher survival. The implementation of static cold storage and machine perfusion preservation solutions is needed to improve these results further. In a rat and pig model, adding polyethylene glycol and glutathione to the standard solutions during cold preservation (both static and dynamic) allows for better preservation of both lean and steatotic grafts.[11,12]

Alternative Approaches to Ischemia–reperfusion Modulation

Besides machine perfusion, several strategies are being investigated to prevent and mitigate IRI in the LT setting. Concomitantly, multiomics approaches have been applied to elucidate the effect of different compounds on IRI.[3] As a result, the search for new therapeutic approaches to mitigate IRI led to a deeper understanding of its mechanisms. Liu et al used a small-molecule macrophage migration inhibitory factor inhibitor in a rat LT model to protect liver donation after circulatory death grafts from IRI damage. Through the administration of this compound, they were able to downregulate IRI in the early reperfusion phase, thus contributing to supporting the role of migration inhibitory factor as a proinflammatory mediator in liver reperfusion.[2,13] Duarte et al further investigated the role of inflammatory modulation. They used a mouse IRI model (partial hilum clamping) to evaluate the role of tryptophan immunometabolism as a possible anti-inflammatory/immunosuppressive target. By administering PEGylate-indoleamine 2,3-dioxygenase 1, they showed protection against IRI by reprogramming tryptophan immunometabolism.[14] Ferroptosis was shown to be a further promising target for IRI modulation by Rokop et al.[15] Indeed, in a mouse model of in situ IRI, ferroptosis was upregulated in the fatty liver group together with lipid peroxidation. Mitochondrial damage is closely related to ferroptosis, inflammation, and lipid peroxidation, whereas the degree of mitochondrial damage was related to liver survival after reperfusion in grafts subjected to machine perfusion.[16] Histone deacetylase inhibition was shown by Samuvel et al[17] as a protective treatment against IRI and mitochondrial damage. Histone deacetylase acts at an epigenetic level by regulating antioxidant and iNOS expression as well as suppressing NFk-B activation.[18]

Novel Diagnostic and Prognostic Biomarkers in LT

With the complexity of LT mobilizing multiple physiological and cellular processes, there remains a sustained focus on ensuring optimal graft usage. This combined with the organ shortage fortifies the need for the inquiry into biomarkers (Table 3) that can predict and elucidate ideal graft-related outcomes.

Galectin-3 (Gal3) exerts various biological functions, including regulation of inflammation, angiogenesis, collagen synthesis, and cell death.[21] Yoeli et al determined Gal3 to be predictive of EAD. Using citrated plasma from LT recipients 1 d after LT, they measured Gal3 in relation to outcomes surrounding EAD, intensive care unit length of stay, and posttransplant dialysis, finding a correlation between Gal3 and more prolonged intensive care unit stay. When combined with alcohol-related cirrhosis and being a non-Hispanic White, Gal3 was found to be highly predictive of EAD.[22] The same group found Gal3 to be predictive of 30-d rejection post-LT. In this study, they found a significant association between transplant Gal3 and 30-d acute cellular rejection.[23] Gal3 shows promise in being a predictive biomarker for outcomes posttransplant outcomes.

Exploring the pathways leading to disease as well as treatment continues to be of great interest in transplant research this year. Various researchers explored paradigms of liver disease from those involving liver scarring to biliary complications.

Despite recent advances in antiviral therapy, progressive liver fibrosis is a ubiquitous issue after transplantation for patients with recurrent hepatitis C.[24] Fibrotic livers are unable to effectively regenerate. Nguyen-Lefebvre et al found that the regenerating fibrotic liver used different pathways different from those in normal regeneration, with regenerating fibrotic livers exhibiting reduced fibrosis when compared with control fibrotic livers. These data suggest that through the regenerative process, fibrotic liver tissue can eventually be replaced

TABLE 3.

Physiological targets and discriminative abilities of novel biomarkers explored in the 2022 ILTS Congress

Biomarker	Physiological target	Main findings	Key takeaway
Galectin-3	β-galactoside–binding lectin implicated in inflammation, immune regulation, and liver fibrosis[19]	Predictive of early acute rejection and early allograft dysfunction in those with extended ICU stay and those undergoing dialysis	Multivariable model of galectin-3 can be used to assess risk of acute rejection and allograft dysfunction
Glycan composed of trianten-nary and fucosylated glycans and decreased amount of undergalactodylated glycans	Liver sinusoid of malignant tissue[20]	Discriminative pretransplant parameter of hepatocellular carcinoma recurrence	Glycomics-based serum panel can improve allocation strategies for transplant candidates with HCC
cfMeDIP-seq	Methylation pattern on circulating DNA	Noninvasive biomarker of TCMR and recurrent NASH	Distinctive methylation patterns on regulatory genes can identify NASH posttransplant in a specific noninvasive way

HCC, hepatocellular carcinoma; ICU, intensive care unit; ILTS, International Liver Transplantation Society; NASH, nonalcoholic steatohepatitis; TCMR, T cell–mediated rejection.

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by healthy liver tissue.[4,25] This cutting-edge research suggests a new avenue of research that can limit the progression of graft fibrosis.

Transplant Oncology

Transplant oncology is a key topic of research within the LT landscape, given that 35% to 40% of LT recipients worldwide currently undergo transplants for hepatocellular carcinoma (HCC). Abstracts in this category were mainly in the clinical category, but there were a few basic and translational abstracts also in transplant oncology. Understanding the biological mechanisms underlying response to bridging therapy or recurrence posttransplant is critical to optimizing posttransplant outcomes.

HCC recurrence remains a notable issue within the LT paradigm. Vergeist et al assessed the serum protein *N*-glycan in patients with HCC recurrence compared with those without. Through this analysis, they developed a composite serum biomarker based on the increased presence of triantennary and fucosylated glycans and the decreased presence of undergalactosylated glycans in patients with HCC recurrence. This panel has the potential to advise allocation in transplant candidates with HCC.[26]

Ding et al explored fatty acid desaturase 1 (FADS1) and polyunsaturated fatty acids and their role in HCC suppression. Within mouse models, they found that in liver-specific FADS1 knockout mice, there was delayed tumor formation as well as a noted decrease in tumor mass alongside upregulation of $CD8^+$ T cells.[27] Given that a fatty liver-related oncogene drives FADS1, this work highlights the role of polyunsaturated fatty acids in posttransplant HCC recurrence.

Zhe et al explored how HCC cells may protect themselves from the immune system. They examined the role of ferritin heavy chain 1 (FTH1) in tumor-derived exosomes as a protective mechanism against $CD8^+$ T cell–associated ferroptosis, in a series of elegant in vitro and in vivo experiments. Uptake of FTH1 by tumor-derived exosomes led to impaired cytotoxic $CD8^+$ T-cell function. This was reversible with a ferroptosis inhibitor. Additionally, they discovered that FTH1 expression was upregulated in HCC tissues and negatively correlated with clinicopathological scores and overall survival.[28]

Liver Immunobiology

With the evolution of diagnostic and laboratory technologies, the comprehension of the biological and immunological functions of the liver can be improved. In this setting, liver regeneration represents unique crosstalk between biological and immunological mechanisms that could take place within a human being. Indeed, to overcome a liver injury, several adaptive mechanisms are elicited at local and systemic levels. The net balance between cell death, repair, and regeneration plays a key role in organ fate. Therefore, the understanding of these events could help to not only improve the knowledge of liver immunobiology but also improve the comprehension of clinical issues, such as IRI and rejection. Abu Rmilah et al,[29] building from research by Wuestefeld et al[30] that found MKK4 silencing increased the regenerative capacity of hepatocytes in mouse models, explored a novel proregenerative drug in a model of liver failure after resection. This randomized controlled preclinical study was conducted on pigs and found that the MKK4 inhibitor was able to increase the regeneration index compared with the placebo. These data have the potential to pave the way for larger clinical studies within the landscape of postresection liver failure.

Alpha-1 antitrypsin (AAT) is considered a molecule with potential antiapoptotic and proregenerative effects after reoxygenation. For these reasons, Nguyen-Lefebvre et al explored AAT as a potential therapeutic agent to increase cell engraftment in the livers after 70% hepatectomy and concomitant hepatocyte transplantation. They found that AAT and hepatocyte coadministration resulted in improved cell engraftment. Shi et al[31] further pushed this concept by exploring AAT as a new potential agent to protect against ischemic cholangiopathy. Indeed, post-LT biliary complications remain the Achilles' heel of LT and ischemic cholangiopathy is a significant threat to the quality of life posttransplant.[32] In their study, the authors used human cholangiocyte organoids exposed to hypoxia and reoxygenation to assess apoptosis and cell proliferation. They determined AAT to be an effective inhibitor of hypoxia and apoptosis triggered by reoxygenation, as well as a stimulator of cholangiocyte proliferation. Interestingly, AAT was previously reported to be a common albeit underdiagnosed cause of liver disease in LT patients. This study offers another piece to the puzzle underlying genetic causes of liver disease and potential therapeutic options.[33]

FUTURE PERSPECTIVES

In conclusion, the quality and quantity of basic and translational research representation have continued to grow at the ILTS meeting. The uptake of such research that offers mechanistic insights into transplantation is critical to improving patient outcomes. Organ demand continues to exceed supply, which is when advances in organ perfusion and living donor LT are essential to expanding the donor pool. As nonalcoholic steatohepatitis and HCC continue to grow as indications for LT, new considerations emerge. Therefore, the science must evolve along with these changes in patient profiles over time. We foresee growth in biomarker research in these areas with evolving omics technologies. Newer techniques, including single-cell sequencing and organ perfusion models to improve organ function, will drive this innovation. Xenotransplantation represents an interesting opportunity to meet organ demand, and we anticipate that this research will have a growing presence at future ILTS conferences. The Basic and Translational Research Committee fully committed itself to fostering and promoting the dissemination of basic and translational research in LT during the annual congress of the International Society of Liver Transplantation, not only with the organization of sessions and scientific presentations but also through publications of what has been presented in Congress as this current summary. In addition, the Committee is dedicated to the development of new projects, stimulating interaction between researchers throughout the year through webinars and seminars.

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