

What Is Hot and New in Basic and Translational Science in Liver Transplantation in 2020–2021?—Report of the Basic and Translational Research Committee of the International Liver Transplantation Society

Zoltan Czigany, MD, PhD,¹ Isabel M.A. Brüggewirth, MD,² Burcin Ekser, MD, PhD,³ Maen Abdelrahim, MD, PhD, BPharm,⁴ Mamatha Bhat, MD, PhD,⁵ Eliano Bonaccorsi-Riani, MD,⁶ Angela Chen, MD,⁷ Juliet Emamaullee, MD, PhD,^{8,9} Corey Eymard, MD,¹⁰ Cheng-Maw Ho, MD, PhD,¹¹ Valeria R. Mas, PhD,¹⁰ Ali Zarrinpar, MD, PhD,¹² Muhammed Yuksel, PhD,¹³ Paulo N. Martins, MD, PhD,¹⁴ and Markus Selzner, MD⁵

INTRODUCTION

The 2020 Joint Annual Congress of the International Liver Transplantation Society (ILTS), European Liver and Intestine Transplant Association (ELITA), and Liver Intensive Care Group of Europe (LICAGE) was supposed to be held in Istanbul, Turkey, in May 2020. Because of the coronavirus disease 2019 (COVID-19) pandemic, the physical conference was transformed into a virtual congress held between May 5 and 8, 2021. This fully online event was attended by 1098 delegates from 66 countries (Figure 1). A total of 730 abstracts were presented during the meeting. The impact of basic and translational research at the ILTS meetings remains stable over the years with ~8% of the total abstract volume (Table 1).

Members of the ILTS Basic and Translational Research Committee attended all sessions of the meeting to select the most novel, innovative, and promising studies in the field of basic and translational science. Here, we present an overview

of “what is hot and new in 2020–2021” categorized in 6 main themes (Figure 2), including (1) transplant oncology and tumor biology, (2) novel biomarkers, (3) ischemia-reperfusion injury (IRI) and organ preservation, (4) mechanism of disease and injury, (5) liver immunobiology and tolerance, and (6) COVID-19. Most abstracts fell within themes 1–3. In the included abstracts, a variety of state-of-the-art laboratory techniques was used in these studies. In the included abstracts, a variety of state-of-the-art laboratory techniques, such as next-generation molecular assays, multiomics approaches, and bioinformatics, was used.

Transplant Oncology and Tumor Biology

The biology of liver tumors related to liver transplantation (LT) remained to be one of the largest categories among the presented abstracts at the ILTS virtual congress. Understanding the mechanisms of posttransplant tumor recurrence has major clinical significance in the treatment

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¹ Department of Surgery and Transplantation, University Hospital RWTH Aachen, Aachen, Germany.

² Department of Surgery, Section of Hepato-Pancreato-Biliary Surgery and Liver Transplantation University Medical Center Groningen, Groningen, The Netherlands.

³ Division of Transplant Surgery, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.

⁴ Department of Oncology, Houston Methodist Hospital, Houston, TX.

⁵ Multi-Organ Transplant Program, University Health Network, Toronto, ON, Canada.

⁶ Abdominal Transplant Unit, University Hospital Saint-Luc, Laboratory of Experimental Surgery and Transplantation, Université Catholique de Louvain, Brussels, Belgium.

⁷ Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.

⁸ Division of Abdominal Organ Transplantation and Hepatobiliary Surgery, Children's Hospital Los Angeles, Los Angeles, CA.

⁹ Department of Surgery, University of Southern California, Los Angeles, CA.

¹⁰ Department of Surgery, Transplant Research Institute, James D. Eason Transplant Institute, College of Medicine, University of Tennessee Health Science Center, Memphis, TN.

¹¹ Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan.

¹² Division of Transplantation and Hepatobiliary Surgery, Department of Surgery, University of Florida, Gainesville, FL.

¹³ Research Center for Translational Medicine, Koc University Hospital, Istanbul, Turkey.

¹⁴ Transplant Division, Department of Surgery, UMass Memorial Hospital, University of Massachusetts, Worcester, MA.

Z.C. and I.M.A.B. are shared first authors.

P.N.M. and M.S. are shared senior authors.

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Correspondence: Markus Selzner, MD, Multi-Organ Transplant Program, University Health Network, 585 University Ave, 11 PMB 178, Toronto, ON M5G 2N2, Canada. (markus.selzner@uhn.ca).

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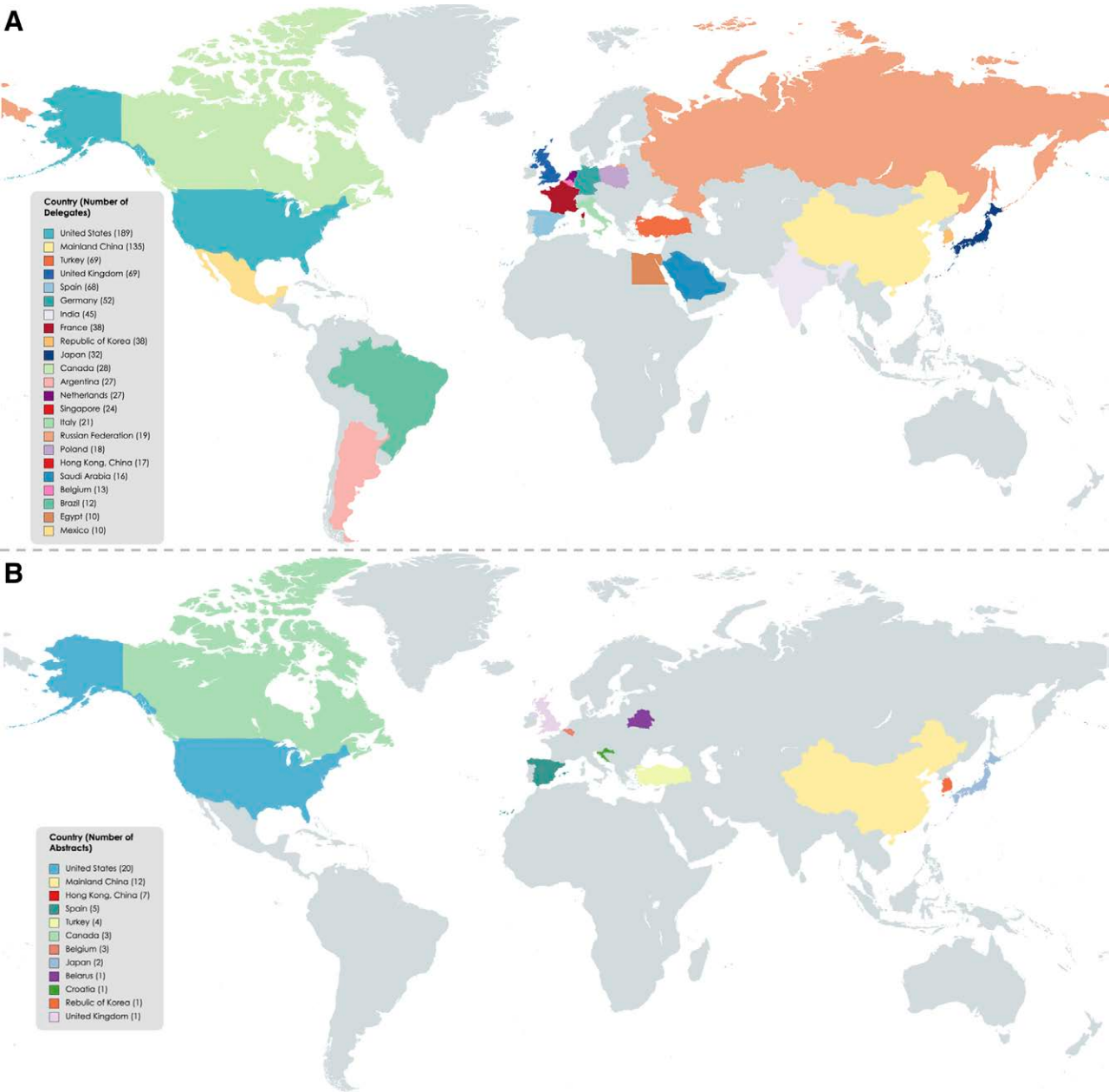


FIGURE 1. Countries with (A) ≥10 delegates and (B) the presenting authors of basic and translational science abstracts at the 2020–2021 Joint ILTS-ELITA-LICAGE Meeting. This figure was regenerated with permission of the ILTS. ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplant Society; LICAGE, Liver Intensive Care Group of Europe.

TABLE 1.

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

Year/venue	Countries represented (no.)	Total abstracts (no.)	Late-breaking abstracts (no.)	Basic and translational research abstracts (no.)	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

^a Due to the COVID-19 pandemic, the 2020 ILTS Congress in Istanbul was postponed and held in a fully virtual setting in 2021. COVID-19, coronavirus disease 2019; ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplantation Society; LICAGE, Liver Intensive Care Group of Europe.

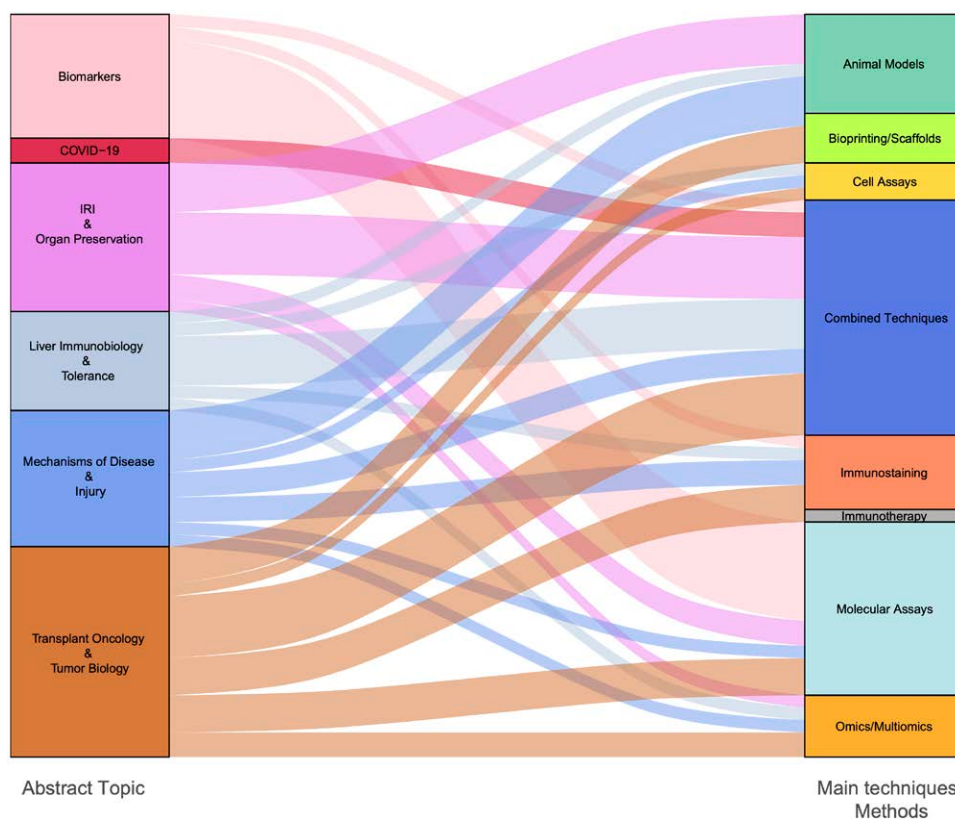


FIGURE 2. Sankey diagram depicting distribution of the topics and main techniques used in the 60 basic science studies presented at the 2020–2021 Joint ILTS-ELITA-LICAGE Meeting. Each (total $n = 60$) abstract has been classified into one of the 6 topics/themes and based on the main technique and methodological approach used. COVID-19, coronavirus disease 2019; ELITA, European Liver and Intestine Transplantation Association; ILTS, International Liver Transplant Society; IRI, ischemia-reperfusion injury; LICAGE, Liver Intensive Care Group of Europe.

of hepatocellular carcinoma (HCC). In a plenary oral presentation, Chakravarthy et al have reported their findings on the clonal evolution of recurrent HCC in the context of the posttransplant immune environment.¹ For this, the authors examined tissue samples from recurrent HCCs in immunocompromised transplant recipients and from immunocompetent patients following partial hepatectomy and compared these with samples from the primary tumor. After performing methylome and whole-exome sequencing, they observed a highly heterogeneous epigenetic evolution in the posttransplant HCC recurrences, where the natural immune reaction was reduced with the use of immunosuppression. Most of the differentially methylated genes in the immunosuppressed versus immunocompetent cohort were involved in the cell cycle. Therefore, they postulated that these novel findings could facilitate the identification of future targets for chemopreventive agents.

Using samples from HCC patients and a murine animal model, Wang et al aimed to explore the role of myeloid-derived suppressor cells (MDSCs) in tumor recurrence. The MDSCs are pathologically activated neutrophils and monocytes with potent immunosuppressive activity that could serve as potential targets in various oncological and autoimmune diseases.² This study suggests that CXCL1/CXCL2 signaling is responsible for MDSCs mobilization, further promoting HCC recurrence.³ Tolerogenic immune cell populations may play a role not only in HCC recurrence but also in response to primary treatment. In a further study, Nunez et al⁴ have performed flow cytometry on

clinical blood samples from HCC patients on the waiting list showing an association between lymphopenia and the parallel increase of MDSCs, regulatory T cells, and failure to respond to transarterial chemoembolization.⁴ In a study from the same group, the otherwise poorly understood role of C3a complement in HCC was explored. First, they showed that increased plasma C3a is strongly associated with the extent of hypoxic/ischemic allograft injury following LT. Second, patients with tumor recurrence and shortened recurrence-free survival expressed higher levels of C3a. This was confirmed in a functional setting showing that HCC cell lines with metastatic potentials also expressed higher C3a receptors and significantly upregulated metastasis-related genes in response to C3a treatment.⁵

Adenosine is a well-known regulator of hypoxia/ischemia related innate and adaptive immunological responses. Pang et al⁶ determined that adenosine and A1-receptor signaling lead to the recruitment of activated plasmacytoid dendritic cells, which subsequently promote posttransplant HCC recurrence via an enhanced differentiation of naive T cells into regulatory T cells in vitro.

Further reports have investigated the immune regulatory background and mechanisms of HCC and cholangiocarcinoma tumor genesis and recurrence using state-of-the-art techniques and in vitro and in vivo models.^{7–11} The use of bioprinting in cancer research holds promise to better mimic the complex microenvironment of hepatobiliary malignancies and has potential to move research from the

traditional planar cell cultures to models that are biologically more relevant.¹² Several talks at the ILTS 2020–2021 meeting focused on the introduction, feasibility, and cost efficiency of 3-dimensional bioprinted models to mimic the microenvironment of HCC, cholangiocarcinoma, and colorectal liver metastases.^{13–15}

In summary, the current research in transplant oncology and tumor biology focuses predominantly on the characterization of the tumor microenvironment and immune responses, especially in post-LT tumor recurrence.

Novel Biomarkers

LT is a complex and major surgical procedure triggering a wide range of physiological responses and subcellular pathways. With the persistent organ shortage, accurate prediction of graft and patient outcomes is of crucial clinical importance to ensure optimal use of allografts.

The data from INTERLIVER study demonstrated the role of microarray-based gene expression analysis in advanced molecular diagnostics in LT, introducing the concept of a “molecular microscope diagnostic system.” The INTERLIVER study is a large-scale prospective observational multicenter study aiming to improve the traditional semiquantitative histological evaluation and investigate the relationship of molecular phenotypes in LT biopsies in context of the histological phenotypes and the clinical features and outcomes (NCT03193151). Madill-Thomsen et al¹⁶ presented the INTERLIVER data on molecular injury phenotypes in human LT describing novel molecular characteristics for steatohepatitis and fibrosis/cirrhosis. In another talk based on the same study, the authors demonstrated an association of molecular microscope diagnostic system phenotypes with histological rejection in a large cohort of 235 liver biopsies.¹⁷ These findings suggest that unsupervised and semiautomatic molecular phenotyping and machine learning may play an important role in the near future by improving accuracy and precision of molecular diagnostics in the clinical setting.

Besides the above-described multicenter study, further innovative reports focused on prognostic tissue biomarkers. Posttransplant allograft fibrosis/cirrhosis is a relatively uncommon but serious long-term complication often leading to graft loss and re-LT. Although most cases can be attributed to recurrent disease, such as hepatitis C and autoimmune liver diseases, little is known about the underlying mechanisms and risk factors of allograft fibrosis without evidence of recurrent liver disease.¹⁸ Wang et al analyzed a set of 23 single-nucleotide polymorphisms, which were associated with liver fibrosis using 232 liver allograft samples. They were able to identify 4 donor single-nucleotide polymorphisms (rs430397, rs1695, rs12304647, and rs1800630) associated with graft fibrosis, suggesting that the inclusion of donor gene polymorphisms in prognostic models may serve as a potential clinical instrument for the prediction of post-LT allograft fibrosis. These findings are in line with previous reports on the key contribution of genetic susceptibility to clinical outcomes in chronic liver disease and LT.^{19,20}

In contrast to most tissue-based biomarkers, circulatory markers may serve as simple, less-invasive, and real-time screening tools. Exosomes are small endosomal-derived microvesicles, receiving an increased scientific interest over the past decades.²¹ Because of their regulated formation and

cell-targeting specificity, they could serve not only as non-invasive diagnostic biomarkers but also as potential therapeutic nanocarriers.^{22,23} Qiu et al analyzed the association of exosomal micro ribonucleic acids (microRNAs) with viral hepatitis B virus (HBV) reactivation after LT. In a pilot cohort of patients with and without HBV reactivation, they identified exosomal microRNA-766 as a promising prognostic biomarker and a potential functional target for the treatment of HBV reactivation.^{23,24}

Further exploring the role of novel, innovative circulatory biomarkers, Izzy et al determined that symmetric dimethylarginine, as a marker of endothelial injury, may predict future renal failure in LT recipients.²⁵ Glycomic signatures, a comprehensive analysis of glycans in a specific biological setting, is an emerging tool in the identification of prognostic biomarkers. A prospective study from Belgium analyzed the serum glycomic signatures of 117 LT patients. In this cohort, graft loss at 3 mo was associated with increased undergalactosylation (a marker of inflammation) and an increased presence of fucosylated and triantennary glycans, which are both signs of liver regeneration. The multivariable logistic regression analysis showed a strongly significant association of graft loss and altered glycomics signature. Such markers may assist in the difficult clinical decision making with respect to early re-LT.²⁶

Achievement of operational tolerance and long-term stability without immunosuppression would be ideal in solid organ transplantation to avoid the consequences of sustained exposure to immunosuppression. Circulating small RNAs were among the main targets of biomarker research for many years. Kusu et al reported a decrease of transfer RNA fragments in tolerant patients (17 tolerant out of 55 pediatric LT patient samples), whereas the proportion of YRNA fragments was increased. Distribution of small RNA species in healthy subjects was similar to that observed in the tolerant group. Based on these findings, lower levels of transfer RNA fragments and higher levels of YRNA fragments may result in lower levels of immune activity in tolerant patients.²⁷

Recent improvements in biomarker discovery, molecular diagnostics, multiomics, extracellular vesicle research, and liquid biopsy approaches hold promise for an improved depiction of complex biological responses. Current research in the field of biomarkers in LT is focusing on various molecular or genetic tissue signatures and circulatory markers to better characterize and predict clinical outcomes post-LT.

IRI and Organ Preservation

Warm and cold ex situ machine perfusion and ischemia-free LT continue to be a strong focus of preservation injury research.²⁸ In a study with discarded human livers, it was shown that fibrinogen levels increased during normothermic machine perfusion, which was associated with higher rouleaux formation of erythrocytes more vascular plugging, and consequently, increased vascular resistance.²⁹ In an attempt to improve the preservation solution used for hypothermic machine perfusion, the effect of different oncotic agents was investigated in rodent models. Beneficial effects for solutions containing polyethylene glycol 35 as an oncotic agent (eg, Institute George Lopez) compared with solutions containing hydroxyethyl starch

(eg, University of Wisconsin) were observed with better mitochondrial protection,³⁰ reduced oxidative stress, and less inflammatory response.³¹

A novel technique to improve mitochondrial function was investigated by Bajwa et al.³² The authors intravenously administered mitochondria isolated from healthy mouse livers to living mice 1 d before LT. Hepatocellular uptake of mitochondria was demonstrated and it was associated with higher adenosine triphosphate levels, higher oxygen consumption, improved histology, and higher levels of energy metabolism-enhancing genes (Pgc1a and Ppar).

More recently, gene silencing through either RNA interference or clustered regularly interspaced short palindromic repeats-associated protein 9 technology has gained interest in the field of organ transplantation.^{33,34} Small interfering RNA delivered during hypothermic machine perfusion of rat livers effectively inhibited gene expression of apoptosis-associated gene fetal alcohol syndrome in rat livers with decreased apoptosis, inflammation, and IRI.³³ Identification of novel gene targets inducing liver IRI could be performed with clustered regularly interspaced short palindromic repeats-based library screening³⁴ or by using single-cell RNA sequencing.³⁵ Wang et al³⁵ collected tissue of donor livers at different time points during preservation and then performed single-cell sequencing. This way, they were able to describe the atlas of intrahepatic cells during LT and their expression profiles after IRI, which may help to identify novel therapeutic targets in the future. One of the main observations was the upregulation of the plasminogen activator urokinase receptor gene after reperfusion (plasminogen activator urokinase receptor) that was mainly concentrated in vascular cell adhesion molecule-1^{low} endothelial cells and tumor necrosis factor⁺ macrophages, indicating that it may play an important role in recruiting monocytes and promoting leukocyte-endothelial cell interaction.³⁶

Immune cells, including neutrophils and natural killer (NK) cells, are known as main amplifier of hepatic IRI.³⁷⁻³⁹ Cheng et al³⁸ quantified gene expression profiles of novel infiltrated immature neutrophils (cluster of differentiation [CD]66b⁺, CD10⁻) in 31 human liver allograft biopsies taken 2 h after portal vein reperfusion. Quantitative PCR and flow cytometry data showed that CD10⁻ was downregulated after reperfusion, and CD10⁻ levels were reversely correlated with postoperative liver enzymes and total bilirubin. Neutrophil marker CD66b⁺ and HLA-DR mRNA levels were elevated after reperfusion and correlated with each other. This study indicates a novel immunostimulatory role of immature neutrophils in promoting posttransplant graft injury, which could be a target for future therapies. Yang et al³⁹ retrospectively assessed 110 patients on dynamic change of peripheral immune cells before and 2–4 d after LT. Peripheral immune cell profiling revealed a depletion of NK cells after LT, which was more prominent in patients with early allograft dysfunction compared with those with immediate graft function. These results were substantiated in a mouse model showing recruitment of NK cells to the liver after reperfusion. Specific depletion of NK cells through anti-Asialo GM1 antibody attenuated IRI, which could also represent a novel therapeutic strategy.

In summary, recent developments in IRI and organ preservation research resulted in further refinement of machine perfusion techniques and both identified and exploited novel therapeutic targets in the complex pathophysiology of IRI.

Mechanisms of Disease and Injury

Researchers from the United States aimed to further elucidate the pathophysiology of alcoholic liver disease. Using a murine model, it was demonstrated that hepatic mitochondrial depolarization and subsequent type 2 mitophagy after ethanol are driven by acetyl aldehyde formation.⁴⁰ Two studies by Ozdemir et al^{41,42} investigated hypercholesterolemia-induced liver injury. In one study, 70 biopsies of LT recipients were analyzed and they found that high serum cholesterol levels were associated with apoptosis and activation of hepatic stellate cells, inducing inflammation, fibrosis, and oxidative stress, leading to progression of allograft injury.⁴¹ In another study by the same group, they showed that hepatocyte growth factor (HGF) is critical for organ protection and liver regeneration in LT patients with hypercholesterolemia via its angiogenic and antiapoptotic effects.⁴² A further report from the Ankara group found an important role for HGF in hepatocyte proliferation (Ki-67) after transplantation of partial liver grafts from living donors.⁴³ For this study, posttransplant biopsies of 62 patients were scored for inflammation and fibrosis and analyzed for the development of liver failure 18 mo after the initial biopsy. Higher expression of HGF on immunohistochemistry was associated with increased angiogenesis (studied with CD31) and hepatocyte proliferation (studied with Ki-67). The development of liver failure decreased with increasing expression of HGF. In this light, HGF-based drugs could be further explored to suppress allograft failure because of incomplete liver regeneration, such as in small-for-size living donor liver allografts. Liu et al⁴⁴ found that increased signaling of the glycoprotein amphiregulin after partial mice LT promotes mitochondrial biogenesis and regeneration. After implantation, amphiregulin expression increased markedly in split liver grafts but not in full-size grafts. Suppressed amphiregulin signaling and subsequent inhibition of mitochondrial biogenesis may partly be responsible for poor outcomes of small-for-size grafts.

On another note, microbiota in bile may be involved in the pathogenesis of biliary complications. Bile of patients with biliary complications after LT was found to be enriched with *Proteobacteria* and *Staphylococcus*.⁴⁵

In summary, results from studies animal models as well as immunohistochemistry analysis of human biopsies add to our understanding of the mechanisms of alcoholic liver disease, hypercholesterolemia-induced liver injury, and liver regeneration.

Liver Immunobiology and Tolerance

Rejection remains an important cause of graft loss after LT and several research groups investigated mechanisms of liver tolerance.⁴⁶⁻⁵⁰ Emamaullee et al⁴⁷ developed a liver-specific imaging mass cytometry panel and an informatics-based analysis pipeline to quantify which lymphocytes are involved in chronic rejection. Using this technique, few CD3⁺ and CD8⁺ effector T cells were identified in biopsies of livers undergoing re-LT because of chronic rejection,

but more CD68⁺ macrophages. Additionally, heterogeneous lymphocyte subsets were present in livers with chronic rejection compared with controls. This technique may provide quantitative information regarding lymphocyte subsets to better understand graft rejection and search for novel therapeutic targets.

Korotkov et al⁴⁸ treated 10 patients with portal venous infusion of mesenchymal stem cells (MSCs) during allograft reperfusion as an induction immunosuppression. Two patients developed mild acute cellular rejection and there were no adverse events of MSC therapy. All patients were switched to 3-component immunosuppression with tacrolimus, mycophenolate mofetil, and steroids. Considering patients are still on triple therapy, no conclusion can yet be drawn from additional MSC therapy. A prospective controlled trial is needed to confirm superiority of this approach compared with standard immunosuppressive regimens. Pierre et al⁴⁹ investigated the association between tolerance and the plasma microbiome of 55 patients after LT. Patients with operational tolerance (no immunosuppression) displayed the highest levels of alpha diversity compared with patients on maintenance immunosuppression (tacrolimus) and weaning immunosuppression (monitored tacrolimus withdrawal). *Candida albicans*, *Flavobacterium*, and *Phialophora* were scarce in patients with operational tolerance, but there was greater abundance of *Cystofilobasidium*, *Helicogloea*, and *Sebacina*. The same group evaluated stool samples of 21 patients with recurrent nonalcoholic fatty liver disease and found significant loss of *Akkermansia* and *Firmicutes* and increased *Fusobacterium* and *Bacteroidetes*.⁵⁰

Novel immunological approaches seek to overcome common problems in LT, such as cytomegalovirus (CMV) after LT. Researchers from Spain showed that quantification of CMV-specific polyfunctional T-cell responses with intracellular cytokine staining could be a specific marker to identify patients who achieve spontaneous CMV control.⁵¹

To conclude, novel diagnostic and quantitative measures for graft tolerance are investigated to ultimately find targets for therapeutic therapies.

Coronavirus Disease 2019

Two studies on COVID-19 and its impact on LT outcomes were presented. In a multicenter study from Spain, the persistence of antinucleocapsid immunoglobulin G antibodies in 71 LT recipients 6 mo after COVID-19 resolution was evaluated. Recipients of LT exhibited a lower incidence of antinucleocapsid immunoglobulin G antibodies compared with immunocompetent controls (62 versus 62).⁵² Lovatt et al⁵³ report successful re-LT in 3 patients previously infected with COVID-19. Despite being clinically immunosuppressed, all patients demonstrated competent CD4⁺ T-cell responses against COVID-19 after infection and after the first vaccine.

DISCUSSION

High quality of basic and translational research was presented at the 2020–2021 joint ILTS-ELITA-LICAGE meeting, despite the multiple clinical, technical, and potentially life-threatening challenges, which have arisen from the global COVID-19 pandemic. The future of LT research was presented within 6 thematic areas during the

conference. With advanced laboratory techniques, a better understanding of liver tumor biology is being revealed, which provides potential targets for novel therapies. As transplant oncology continues to evolve as a promising clinical field in LT and cancer management, more landmark studies are expected and will be encouraged in future ILTS meetings. Developments in biomarker discovery have identified numerous novel targets and prognostic tools to predict outcome after LT, which may aid in clinical decision making and better donor–recipient matching. Ongoing scientific efforts are aimed at optimizing organ preservation, mainly by the introduction of various ex vivo machine perfusion technologies. Graft modification via application of allograft therapies during machine perfusion before transplantation is likely to emerge as a major rehabilitative and assessment intervention in the coming years. In addition, methods to induce tolerance and reduce rejection after transplantation show promise in experimental models and may be translated to clinical application as research advances. In summary, the virtual platform of the 2020–2021 joint ILTS-ELITA-LICAGE congress provided an interactive environment for researchers to share their experiences and studies. Future hybrid events, face-to-face and virtual, will be essential for greater dissemination of research advances in the field of LT.

REFERENCES

1. Chakravarthy A, Pasini E, Gore G, et al. Clonal evolution of recurrent hepatocellular carcinoma posttransplant and dependence on the immune environment. *Transplantation*. 2021;105(suppl 8):67–68.
2. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol*. 2021;21:485–498.
3. Wang Y, Liu H, Yang X, et al. Myeloid-derived suppressor cells mobilization through CXCL1–CXCR2 signaling facilitates tumor recurrence after liver transplantation. *Transplantation*. 2021;105(suppl 8):67–68.
4. Nunez K, Sandow T, Hilbino M, et al. Pre-treatment lymphocyte status in HCC patients associates with DEB-TACE response and correlates with liver synthetic dysfunction and increased regulatory immune cells. *Transplantation*. 2021;105(suppl 8):39.
5. Yeung WHO, Liu H, Ng TPK, et al. Complement components C3a promoted tumor recurrence after liver transplantation. *Transplantation*. 2021;105(suppl 8):43–44.
6. Pang L, Ng KTP, Liu H, et al. Alternatively-activated plasmacytoid dendritic cells promote posttransplant hepatocellular carcinoma recurrence via adenosine A1 receptor. *Transplantation*. 2021;105(suppl 8):18.
7. Lin Z, Lu D, Zheng S, et al. Multiomics profiling reveals the crosstalk between sarcopenia and hepatocellular carcinoma in liver transplantation. *Transplantation*. 2021;105(suppl 8):132–133.
8. Zhu J, Pang L, Yeung OWH, et al. CX3CL1/CX3CR1-dependent regulatory macrophage infiltration promotes tumor recurrence after liver transplantation for intrahepatic cholangiocarcinoma. *Transplantation*. 2021;105(suppl 8):127–128.
9. Nakagawa C, Nagaraj M, Uthay Kumar DB, et al. Hepatitis B immunoglobulin reduced cell proliferation, viability and stem-like characteristics of hepatocellular carcinoma cells in vitro and offers tumor control in vivo. *Transplantation*. 2021;105(suppl 8):167.
10. Tan MY, Rovgaliyev B, Oh SC, et al. Sirolimus attenuates calcineurin inhibitor induced epithelial-mesenchymal transition in hepatocellular carcinoma cell line. *Transplantation*. 2021;105(suppl 8):83.
11. Cheng YHF, Yeung WHO, Pang L, et al. Role of novel immunosuppressive CD10⁺ antigen-presenting neutrophils in promoting HCC tumorigenesis. *Transplantation*. 2021;105(suppl 8):31.
12. Datta P, Dey M, Ataie Z, et al. 3D bioprinting for reconstituting the cancer microenvironment. *NPJ Precis Oncol*. 2020;4:18.
13. Chen AM, ZW, Smith LJ, et al. Hepatocellular carcinoma 3D bioprinted model with 7 days of sorafenib perfusion: modeling the cancer microenvironment's chemotherapy response. *Transplantation*. 2021;105(suppl 8):14–15.

14. Chen AM, Zhang W, Isidan A, et al. 3D bioprinted intrahepatic cholangiocarcinoma model and 7-day perfusion with gemcitabine and cisplatin: modeling the tumor microenvironment and response to chemotherapy. *Transplantation*. 2021;105(suppl 8):78.
15. Chen AM, Zhang W, Smith LJ, et al. 3D model for colorectal liver metastases microenvironment. *Transplantation*. 2021;105(suppl 8):77.
16. Madill-Thomsen K, Abouljoud M, Bhatti C, et al. Molecular injury phenotypes in human liver transplant biopsies: the INTERLIVER Study. *Transplantation*. 2021;105(suppl 8):81–82.
17. Madill-Thomsen KS, Abouljoud M, Bhatti C, et al. The molecular diagnosis of rejection in liver transplant biopsies: first results of the INTERLIVER study. *Transplantation*. 2021;105(suppl 8):17–18.
18. Seyam M, Neuberger JM, Gunson BK, et al. Cirrhosis after orthotopic liver transplantation in the absence of primary disease recurrence. *Liver Transpl*. 2007;13:966–974.
19. Karlsen TH, Lammert F, Thompson RJ. Genetics of liver disease: from pathophysiology to clinical practice. *J Hepatol*. 2015;62:S6–S14.
20. Miller H, Czigany Z, Lurje I, et al. Impact of angiogenesis- and hypoxia-associated polymorphisms on tumor recurrence in patients with hepatocellular carcinoma undergoing surgical resection. *Cancers (Basel)*. 2020;12:3826.
21. Carlson K, Kink J, Hematti P, et al. Extracellular vesicles as a novel therapeutic option in liver transplantation. *Liver Transpl*. 2020;26:1522–1531.
22. Zhang Y, Liu Y, Liu H, et al. Exosomes: biogenesis, biologic function and clinical potential. *Cell Biosci*. 2019;9:19.
23. Aksoy F, Dundar HZ, Ak Aksoy S, et al. Liver-derived exosomes in liquid biopsies: advantage before liver transplantation—a pilot study. *Transplantation*. 2021;105(suppl 8):80. [Abstract P-033].
24. Qiu W, Lam YF, Zhu J, et al. Identification of novel exosomal miRNAs associated with HBV reactivation after liver transplantation. *Transplantation*. 2021;105(suppl 8):20.
25. Izzy M, Angirekula M, Bentall A, et al. Utility of symmetric dimethylarginine in predicting future renal failure in liver transplant recipients. *Transplantation*. 2021;105(suppl 8):51.
26. Verhelst X, Geerts A, Colman R, et al. Serum glycomics 7 days after liver transplantation relate to graft loss 3 months after liver transplantation independently of early allograft dysfunction. *Transplantation*. 2021;105(suppl 8):83.
27. Kuscü C, Wolen A, Bajwa A, et al. Tolerant liver transplant patients have higher level of Y RNA fragments in the circulation. *Transplantation*. 2021;105(suppl 8):29.
28. Guo Z, Zhang Z, Gao N, et al. Metabolism reprogramming during conventional versus ischemia-free liver transplantation. *Transplantation*. 2021;105(suppl 8):44–45.
29. Harris M, Raigani S, Claire A, et al. Rouleaux formation in human livers during normothermic machine perfusion increases vascular resistance and impedes viability. *Transplantation*. 2021;105(suppl 8):75–76.
30. Panisello Rosello A, Castro Benitez C, Rosello-Catafau J, Adam R. IGL2 as a new perfusate for liver graft HOPE preservation. *Transplantation*. 2021;105(suppl 8):74.
31. Gomez Bardallo R, Silva Teixeira R, Panisello Rosello A, et al. Oxidative stress and inflammasome response in fatty liver graft preservation. *Transplantation*. 2021;105(suppl 8):74.
32. Bajwa A, Rousselle T, Patterson EC, et al. Intravenous administration of mitochondria minimizes liver ischemia reperfusion injury in lean and diet induced obese mice. *Transplantation*. 2021;105(suppl 8):16.
33. Bonaccorsi-Riani E, Gillooly A, Isari S, et al. Inhibition of the FAS pathway of apoptosis with RNA interference during liver machine perfusion preservation reduces ischemia reperfusion injury after liver transplantation. *Transplantation*. 2021;105(suppl 8):162–163.
34. Kuscü C, Wolen A, Kuscü C, et al. Identification of novel gene targets inducing resistance in liver ischemia reperfusion injury by CRISPR screening. *Transplantation*. 2021;105(suppl 8):79.
35. Wang L, He S, Xu J, et al. Single-cell RNA sequencing reveals gene expression profiling of ischemia reperfusion injury. *Transplantation*. 2021;105(suppl 8):65–66.
36. Huang S, Ju W, Zhu Z, et al. Comprehensive and combined omics analysis reveals factors of ischemia-reperfusion injury in liver transplantation. *Epigenomics*. 2019;11:527–542.
37. Lu L, Zhou H, Ni M, et al. Innate immune regulations and liver ischemia-reperfusion injury. *Transplantation*. 2016;100:2601–2610.
38. Cheng YHF, Yeung WHO, Pang L, Man K, Lo CM. Hepatic IR injury induced de-differentiation of neutrophils which exacerbated graft inflammation. *Transplantation*. 2021;105(suppl 8):17.
39. Yang X, Lu D, Pan L, et al. Dynamic immune cell profiling reveals NK cell shift as dominant process in early allograft dysfunction after liver transplantation. *Transplantation*. 2021;105(suppl 8):149.
40. Zhong Z, Li L, Krishnasamy Y, et al. Acetaldehyde drives mitochondrial depolarization-induced type-2 mitophagy after acute ethanol treatment in mice. *Transplantation*. 2021;105(suppl 8):84.
41. Ozdemir BH, Ozgun G, Ayvazoglu Soy EH, et al. Increased level of serum cholesterol and apoptosis together induces the development of liver fibrosis and early allograft loss. *Transplantation*. 2021;105(suppl 8):74–75.
42. Ozdemir BH, Ozgun G, Yucel Polat A, et al. Hepatocyte growth factor (HGF) prevents the apoptotic and antiangiogenic effect of hypercholesterolemia on hepatocytes in liver allografts. *Transplantation*. 2021;105(suppl 8):138.
43. Ozdemir BH, Ozgun G, Yucel Polat A, Haberal M. Multifactorial effect of hepatocyte growth factor (HGF) on the microscopic regeneration of liver allograft in recipients who underwent transplantation from living donors. *Transplantation*. 2021;105(suppl 8):32.
44. Liu Q, Rehman H, Krishnasamy Y, Lemasters J, et al. Role of amphiregulin signaling in mitochondrial biogenesis after partial liver transplantation. *Transplantation*. 2021;105(suppl 8):7.
45. Liu Y. Bile microbiota: a new insight into liver transplant recipients with biliary complications. *Transplantation*. 2021;105(suppl 8):93–94.
46. Yigitbilek F, Park W, Abrol N, et al. Unique genomic & proteomic profile of liver mesenchymal stromal cells is associated with their superior immunomodulatory properties. *Transplantation*. 2021;105(suppl 8):80–81.
47. Emamaullee J, Man C, Hoefflich J, et al. Multiplexed imaging mass cytometry analysis reveals a new role for CD68+ macrophages in chronic liver transplantation rejection. *Transplantation*. 2021;105(suppl 8):15–16.
48. Korotkov S, Primakova E, Petrovskaya E, et al. The results of pilot study of the mesenchymal stem cells local therapy efficiency for induction of immunosuppression in the early postoperative period after liver transplantation. *Transplantation*. 2021;105(suppl 8):166–167.
49. Pierre JF, Kuscü C, Bajwa A, et al. Plasma microbiome profiles of liver transplant patients with operational tolerance. *Transplantation*. 2021;105(suppl 8):5.
50. Pierre JF, Satapaty S, Banerjee P, et al. Characterization of gut microbiome in liver transplant recipients with non alcoholic steatohepatitis. *Transplantation*. 2021;105(suppl 8):53–54.
51. Carvalho-Gomes Â, Cubells A, Pallarés C, et al. Cytomegalovirus specific polyfunctional T-cells control CMV reactivation after liver transplantation. *Transplantation*. 2021;105(suppl 8):76–77.
52. Caballero Marcos A, Salcedo M, Alonso Fernández R, et al. Changes in humoral immune response after SARS-CoV-2 infection in liver transplant recipients compared to immunocompetent patients. *Transplantation*. 2021;105(suppl 8):155–156.
53. Lovatt J, Lam S, Carter C, et al. T cell response in immunosuppressed redo-liver transplant recipients after COVID-19 infection and after first dose of vaccine against SARS-CoV-2. *Transplantation*. 2021;105(suppl 8):156.