# What Is Hot and New in Basic and Translational Science in Liver Transplantation in 2023? Report of the Basic and Translational Research Committee of the International Liver Transplantation Society

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**Abstract.** The 2023 Joint Annual Congress of the International Liver Transplantation Society, European Liver and Intestine Transplant Association, and Liver Intensive Care Group of Europe were held in Rotterdam, the Netherlands, from May 3 to 6, 2023. This year, all speakers were invited to attend the Congress in person for the first time since the COVID-19 pandemic. The congress was attended by 1159 registered delegates from 54 countries representing 5 continents, with the 10 countries comprising the bulk of the delegates. Of the 647 abstracts initially submitted, 542 were eventually presented at the meeting, coming from 38 countries (mainly North America, Europe, and Asia) and 85% of them (462 abstracts) came from only 10 countries. Fifty-three (9.8%) abstracts, originated from 17 countries, were submitted under the Basic/Translational Scientific Research category, a similar percentage as in 2022. Abstracts presented at the meeting were classified as (1) ischemia and reperfusion injury, (2) machine perfusion, (3) bioengineering and liver regeneration, (4) transplant oncology, (5) novel biomarkers in liver transplantation, (6) liver immunology (rejection and tolerance), and (7) artificial intelligence and machine learning. Finally, we evaluated the number of abstracts commented in the Basic and Translational Research Committee-International Liver Transplantation Society annual reports over the past 5 y that resulted in publications in peer-reviewed journals to measure their scientific impact in the field of liver transplantation.

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## INTRODUCTION

The 2023 Joint Annual Congress of the International Liver Transplantation Society (ILTS), European Liver and Intestine Transplant Association (ELITA), and Liver Intensive Care Group of Europe were held in Rotterdam, the Netherlands, from May 3 to 6, 2023. This year, all speakers were invited to attend the Congress in person for the first time since the COVID-19 pandemic. The congress was attended by 1159 registered delegates from 54 countries representing 5 continents (Figure 1A), with the 10 countries comprising the bulk of the delegates (Figure 1B). Of the 647 abstracts initially submitted, 542 were eventually presented at the meeting, coming from 38 countries (mainly North America, Europe, and ASIA; Figure 2A) and 85% of them (462 abstracts) came from only 10 countries (Figure 2B). Fifty-three (9.8%) abstracts, originated from 17 countries (Figure 2C), were submitted under the Basic/Translational Scientific Research category, a similar percentage as in 2022 (Table 1). Abstracts presented at the meeting were classified as (1) ischemia and reperfusion injury (IRI), (2) machine perfusion (MP), (3) bioengineering and liver regeneration, (4) transplant oncology, (5) novel biomarkers in LT, (6) liver immunology (rejection and tolerance), (7) and AI and ML. Finally, we evaluated the number of abstracts commented in the Basic and Translational Research Committee (BTSRC)-ILTS annual reports over the past 5 y that resulted in publications in peer-reviewed journals to measure their scientific impact in the field of LT.

## ISCHEMIA-REPERFUSION INJURY AND MACHINE PERFUSION

So far, IRI and MP have continued to be high-interest basic/translational science topics. Among the 542 abstracts presented at the meeting, 8 were specifically aimed at investigating or treating IRI, whereas 29 involved the use of normothermic machine perfusion (NMP) and 4 of hypothermic machine perfusion (HMP) (Table 2). MP and IRI are discussed together as MP represents a high potential to counterbalance the harmful effects of IRI on early graft function and post-liver transplantation (LT) complications.[26]

### Ischemia-reperfusion Injury

Key scientific questions aimed to evaluate the relationship between IRI and inflammation and predict IRI's severity. Yang et al[27] studied the correlations among the number of hepatic natural killer (NK) cells (h-NK), liver function, and inflammatory cytokines in IRI. As part of the study, the authors administered anti-NK cell antibodies (anti-ASGM1 or anti-NK1.1) to a mouse model of IRI to investigate the role of TLR4/CXCL10/CXCR3 on the mobilization of h-NK cells. They found that NK cell depletion protected liver function from IRI and that TLR4 or CXCL10 knockout mice attenuated hepatic IRI by decreasing $CXCR3^+$ NK cells. Kim et al[12] hypothesized that the degree of IRI could be predicted before reperfusion by measuring multidrug resistance-associated protein-2 (MRP2), which is immediately internalized upon acute liver injury. They evaluated MRP2 levels in rat livers before procurement and during NMP (performed following 3 h of static cold storage [SCS]). The authors reported a strong correlation between preprocurement MRP2 and postreperfusion ALT levels.

### Hypothermic Machine Perfusion

During the process of liver procurement, preservation, and LT, the graft endures an ischemic phase and additional injury at reperfusion (IRI), predominately led by reactive oxygen species. The benefits of HMP have been previously reported[28,29]; nevertheless, the opportunity to perform liver viability assessment and predict graft outcome during hypothermic oxygenated machine perfusion (HOPE) is still an area of investigation.

The endothelial glycocalyx covers the luminal side of the vascular endothelium, regulates vascular permeability, and modulates the adhesion of leukocytes onto the vascular wall. It is susceptible to reactive oxygen species and degrades during graft preservation and reperfusion. Rauter et al[16] measured glycocalyx degradation via ELISA for its main component, Syndecan-1 (SDC-1), in liver graft effluent after HOPE and SCS. They found that, after 60 min of HOPE, SDC-1 concentration was significantly higher and regenerated faster in those patients developing early allograft dysfunction (EAD). These findings suggested that SDC-1 concentrations during HOPE may predict EAD and that HOPE reduces the duration of glycocalyx shedding. A multicenter study by Panayotova et al[4] compared the proteomic effluent concentration of 41 chemokines/cytokines after HOPE and SCS. They found a significant elevation of 28 analytes of inflammatory and growth factors signaling, leukocytes activation, and inflammatory response amplification after SCS, such as CREB, NFkB, AKT, and STAT3/5, suggesting that HOPE has the potential to mitigate inflammatory activation, decrease leukocyte recruitment, and growth factor signaling.

### Normothermic Machine Perfusion

The characterization of hepatic metabolism and inflammatory cascade during NMP is attracting the efforts of several investigators. Dengu et al[5] compared the quantitative protein expression in liver biopsies obtained at the end of preservation in three different groups: (a) continuous NMP (cNMP, n = 96), (b) NMP after SCS (SCS-NMP, n = 20), and (c) SCS (n = 49). The analysis identified 95 significantly

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*E.B.-R. and D.G. share first coauthorship. P.N.M. and M.B. share last coauthorship.*

*E.B.R. participated in the design of the research, conducted the research, data analysis, wrote the article, critically revised the article, and approved the final article. D.G. participated in the research design, performance of the research, analyses of data, writing the article, critical review of the article, and approval of final article. Z.C. participated in the critical review of the article and approval of final article. D.D. participated in the critical review of the article and approval of final article. J.E. participated on the research design, performance of the research, analyses of data, writing the article, critical review of the article, and approval of final article. M.Y., Y.L.B., D.A.-A., C.-M.H., M.A., L.P., A.B., R.M., S.M., B.A.S., J.P.-G., I.B., A.Z., V.R.M., and M.S. participated in the critical review of the article and approval of final article. P.N.M. participated in the research design, writing the article, critical review of the article, and approval of final article. M.B. participated in the research design, analyses of data, writing the article, critical review of the article, and approval of final article.*

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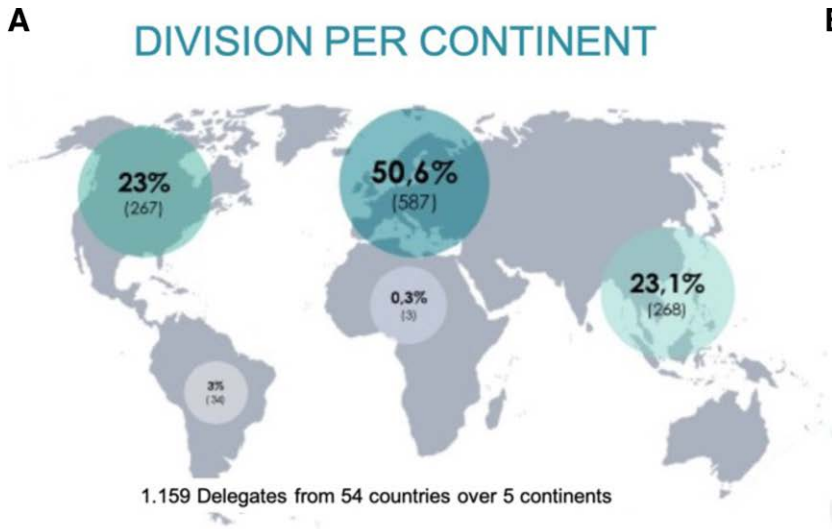
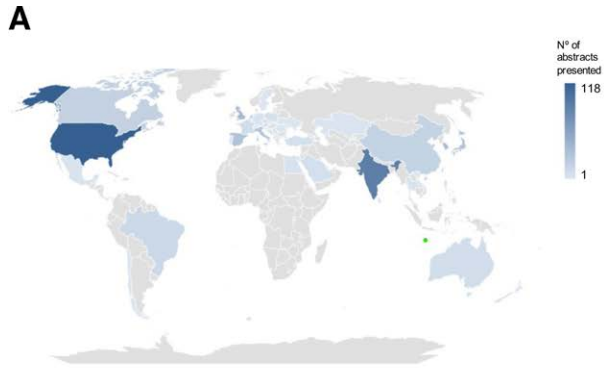



B

| Country | Participants |
|---|---|
| United States | 227 |
| Netherlands | 128 |
| United Kingdom | 107 |
| India | 74 |
| Germany | 60 |
| Korea, Republic of | 49 |
| Spain | 47 |
| Turkey | 43 |
| France | 41 |
| Canada | 40 |
| Others | 343 |
| Total | 1159 |

**FIGURE 1.** Distribution of delegates per continent and per country. A, Map showing the percentage and absolute numbers of delegates attending the meeting per continent. B, Table showing the list of the 10 countries with the most delegates attending the meeting.




B

| Country | N° of abstracts presented (all categories) |
|---|---|
| United States | 118 |
| India | 91 |
| United Kingdom | 39 |
| Republic of Korea | 38 |
| Spain | 31 |
| Italy | 30 |
| Netherlands | 21 |
| China | 17 |
| Singapore | 17 |
| Brazil | 12 |
| Subtotal | 462 |
| Others | 80 |
| Total | 542 |

C

| Country | N° of Basic and Translational abstracts presented |
|---|---|
| United States | 18 |
| Canada | 8 |
| Korea, Republic of | 4 |
| United Kingdom | 4 |
| Australia | 3 |
| China and Hong Kong | 2 |
| India | 2 |
| Italy | 2 |
| Netherlands | 2 |
| Spain | 2 |
| Turkey | 2 |
| Austria | 1 |
| Brazil | 1 |
| Kazakhstan | 1 |
| Portugal | 1 |
| Saudi Arabia | 1 |
| Total | 53 |

**FIGURE 2.** Distribution of abstracts (all categories and Basic and Translational Scientific Research category) presented at the meeting per country. A, Map the countries who presented at least 1 abstract at the meeting. B, Table showing the list of the 10 countries with the most abstracts presented the meeting. C, Table showing the list of the 17 countries and the number of their Basic and Translational Scientific Research abstract presented the meeting.

**TABLE 1.**

**Absolute and relative frequencies of basic and translational science–related abstracts presented at the Joint ILTS-ELITA-LICAGE meetings in 2017–2023**

| 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 | 66 | 730 | 89 | 60 | 8.2 |
| 2022—Istanbul | 61 | 465 | 76 | 46 | 9.9 |
| 2023—Rotterdam | 41 | 542 | 83 | 53 | 9.8 |

ELITA, European Liver and Intestine Transplant Association; ILTS, International Liver Transplantation Society; LICAGE, Liver Intensive Care Group of Europe.

differentially expressed proteins. cNMP and SCS-NMP showed similar profiles in the upregulation of protein translation and hemoglobin-based oxygen transport, downregulation of fatty acid degradation, and biosynthesis of fatty acids but also 8 major differences in the expression of proteins reflecting mitochondrial activity at the mitochondrial complex-1 and the electron transport chain. Bodewes et al[13] evaluated the production of hemostatic proteins (factor II, VII, X, fibrinogen, antithrombin, tissue-plasminogen activator, von Willebrand factor and proteins induced by

**TABLE 2.**

**Summary of the main findings on machine perfusion explored in the 2023 combined international congress of ILTS, ELITA, and LICAGE**

| Author | Type of MP | Model | Aim | Findings |
|---|---|---|---|---|
| Firl[1] | NMP | IGA pig | Perfuse IGA pig livers with human whole blood | LT-NMP of IGA pig livers with human blood is feasible |
| Ly[2] | NMP | Rat | LT-NMP using customized MP | LT-NMP of rat livers up to 7 d |
| Dengu[3] | NMP | Human | Characterize perfusate immuno-molecular profile | Cytokines, cells (T, NK), nucleosomes and neutrophils extracellular traps characterization in the perfusate |
| Panayotova[4] | HMP | | Proteomic assessment of liver injury in preservation effluent post-HMP compared with SCS | HMP mitigates inflammatory activation, decreases leukocyte recruitment and diminishes growth factor signaling |
| Dengu[5] | NMP | Human | Characterize perfusate molecular profile in continuous (cNMP) vs end-ischemic NMP (SCS-NMP) | Molecular levels in c- vs SCS-NMP are very similar, with few differences related to mitochondrial activity |
| Lonati[6] | NMP | Rat | Explore the potential of MSCs-bioreactor-based NMP | Integration of MSCs-bioreactor allows the liver to maintain its mitochondrial function, sustain cell viability, reduce inflammation, and trigger the healing process |
| Dengu[7] | NMP | Pig | Evaluate the impact of circulating nucleosome removal during NMP | Removal of circulating nucleosomes improves graft function and mitigates IRI |
| Filz von Reiterdank[8] | NMP | Rat | Evaluation of genetic transduction during NMP using lentiviral vectors | Feasibility of in vitro genetic engineering biosensors using lentiviral particles |
| Huang[9] | NMP | Human | Define metabolic changes during Long-NMP | Grafts show lipid accumulation, accelerated aerobic glycolysis, buildup of toxic TCA metabolites and FFA |
| Al-Adra[10] | NMP | Rat | Investigate the effects of NMP on TRM | NMP downregulates multiple inflammatory gene pathways on TRM |
| Abbas[11] | NMP | Human | Evaluate hypoxia-inducible factor (HIF) with an established NMP-defatting protocol | HIF accelerates defatting |
| Kim[12] | NMP | Human | Evaluate the extent of IRI during NMP by measuring MRP2 | A strong association between pre-LongT MRP2 function and the severity of IRI |
| Ly[2] | NMP | Rat | Develop a system for LongT-NMP | LongT-NMP is feasible |
| Bodewes[13] | NMP | Human | Measure the concentration and functionality of hemostatic proteins | Livers produce functional hemostatic proteins during NMP |
| Torri[14] | NMP | Human | Evaluate cytokines perfusate concentrations | Cytokine concentrations differ based on the donor type (type 2 or 3 DCD and DBD). Higher IL-10 is associated with AKI |
| Ali[15] | NMP | Human | Quantify FMN and NADH during NMP and correlate to outcomes | Mitochondrial injury and function predict post-LT outcomes |
| Rauter[16] | HMP | Human | Measure glycocalyx degradation to evaluate the potential for viability assessment | SDC-1 could serve as a potential viability assessment marker |
| Clarke[17] | NMP | Human | Evaluate LiMAx measurements during LongT-NMP | Measure qualitative hepatocyte function during LongT-NMP is feasible |
| Lascaris[18] | NMP | Human | Investigate the utility of dialysis in LongT-NMP | Dialysis maintains a physiologic perfusate for up to 7 days |
| Clarke[19] | NMP | Human | Evaluate a LongT-NMP protocol | Human livers can be successfully preserved beyond 5 days |
| Clarke[20] | NMP | Human | Evaluate N-acetylcysteine to meliorate methemoglobin accumulation during LongT-NMP | N-acetylcysteine administration during LongT-NMP meliorates methemoglobin accumulation |
| Huang[9] | NMP | Human | Investigate the utility of dialysis integrated into a commercial NMP device for LongT-NMP | Dialysis is an essential component for LongT-NMP and can be easily integrated into commercial NMP devices |
| Babekuhl[21] | NMP | Human, rat | Evaluate an add-on automated blood gas system during NMP | The system was able to maintain physiologic pH and oxygen during NMP |
| Stevens[22] | NMP | Human, pig | Evaluate the effect of taurocholate infusion during NMP | Taurocholate infusion resulted in a decreased expression of bile acid-related genes, increased gene expression of cholesterol metabolism-related genes and reduced expression in bile acid-dependent uptake |
| Rivas[23] | HMP | Human | Evaluation of the use of an ECMO device as an HMP measuring FMN and thermographic assessment | A customized HOPE-ECMO device can be used for ex-situ perfusion. FMN perfusate concentration has a good correlation with clinical outcomes |
| Obara[24] | SNMP | Pig | Evaluate a flow dynamic index to assess liver function | Flow dynamic index can evaluate preserved liver function during SNMP |
| Yoshimoto[25] | HMP | Pig | Evaluation of a new environmental pressure-controlled perfusion system in DCD grafts | The environmental pressure-controlled perfusion system improves the dynamics of the DCD liver grafts |

AKI, acute kidney injury; cNMP, continuous NMP; ELITA, European Liver and Intestine Transplant Association; FFA, free fatty acids; IGA, intentionally genome altered; ILTS, European Liver and Intestine Transplant Association; IRI, ischemia-reperfusion injury; LICAGE, European Liver and Intestine Transplant Association; LongT-NMP, long-term normothermic machine perfusion; MRP2, multidrug resistance-associated protein-2; MSCs, mesenchymal stem cells; OW, oxygenated washout; SCS-NMP, end-ischemic NMP; SDC-1, syndecan-1; TCA, tricyclic-acid cycle; TRM, tissue resident memory T cells.

vitamin K absence) during NMP. They found that all livers produced hemostatic functional proteins, and their production did not correlate with hepatocellular function or previously established viability criteria, such as lactate clearance, perfusate pH, and bile production. However, such production of functional hemostatic proteins suggests that adequate anticoagulation of the perfusion fluid is required to avoid the generation of (micro)thrombi that could damage the graft. Torri et al[14] evaluated perfusate concentrations of pro- and anti-inflammatory cytokines (IL-6, IL-10, and TNF-a) during NMP, describing their kinetics according to the donor type (controlled-DCD [donation after circulatory death], uncontrolled-DCD and DBD [donation after brain stem death]). They reported a correlation between IL-10 levels and the incidence of post-LT acute kidney injury. Ali et al[30] reported a correlation between higher effluent mitochondrial flavin-mononucleotide (FMN) and nicotinamide dinucleotide (NADH) concentrations during human grafts NMP and the development of post-LT EAD, postulating that FMN and NADH could serve as a potential biomarker of graft quality during both NMP and SCS.

Obara et al[24] evaluated whether using a fluid dynamic index based on pressure, and flow rate can predict liver graft function before transplantation. For this purpose, they preserved porcine livers in subnormothermic machine perfusion (SNMP) conditions and evaluated their function in a NMP model. The index showed a positive correlation (r = 0.8) with lactate clearance during reperfusion in NMP, concluding that the fluid dynamic index has the potential to predict liver function.

### Novel Approach and Organ Therapeutics During MP

The development of technologies capable of providing long-term normothermic perfusion (LongT-NMP) is gaining relevance, since LongT-NMP is fundamental for administration of pharmacological or cytoprotective agents, while evaluating the graft viability.[31] Several groups presented their customized MP device model. Ly et al[2] developed a model for small animals (rats), allowing proper liver preservation for up to 5 d. The system was composed of an organ reservoir, a heat exchanger, a hollow fiber oxygenator, a peristaltic pump and a dialysis filter, and hormonal and nutritional support were continuously infused. Lascaris et al,[18] Clarke et al,[19] and Huang et al[9] demonstrated the fundamental role of a dialysis system associated with NMP in maintaining a physiological perfusate, avoiding electrolytes disturbances, and ultimately keeping livers alive for several days.

Huang et al[32] evaluated the metabolic profile of human livers during LongT-NMP using a customized MP. They found a significant reduction in free carnitine and accumulation of triglyceride and phosphatidylcholine, and a correlation between graft dysfunction and elevated levels of lipotoxic free fatty acids, ceramides and injurious tricyclic-acid-cycle (TCA) intermediate as succinate. These findings suggested that liver grafts show metabolic adaptation during LongT-NMP with lipid accumulation and accelerated aerobic glycolysis. In contrast, the accumulation of toxic TCA metabolites and free fatty acids is related to ongoing mitochondrial injury during graft dysfunction.

Several therapeutic interventions have been proposed to improve organ quality during NMP. Clarke et al[20] aimed to alleviate methemoglobin accumulation during LongT-NMP by administering the antioxidant compound N-acetylcysteine (NAC) to discarded human livers. In fact, the accumulation of methemoglobin results from the oxidation of iron within hemoglobin ($Fe^{2+}$ to $Fe^{3+}$), thereby reducing its oxygen-biding capacity. Continuous administration of NAC during LongT-NMP significantly reduced methemoglobin accumulation. In addition, Abbas et al[11] explored whether modulation of hypoxia-inducible factor (HIF) using deferoxamine (DFO) (a potent activator of HIF-1 and HIF-2) together with a defatting protocol was able to decrease steatosis during LongT-NMP. Although HIF-1 has been associated with a hepatoprotective effect by improving hepatic fat metabolism, HIF-2 promotes intrahepatic lipid metabolism. By adding a selective HIF-2 dimerization inhibitor (PT2385) plus DFO to the defatting protocol, they demonstrated in a preliminary study that the DFO/PT238-treated group experienced a 76% decrease in steatosis after 24 h of NMP. Firl et al[1] perfused intentionally genome altered mini-pigs with frameshift insertion/deletions at 3 xenoantigen-producing glycosyl-transferase, porcine endogenous retrovirus loci and insertion of synthetic polycistrons conferring human transgene expression with whole human blood. Liver grafts were then successfully perfused for 48 or 72 h with human blood, providing an interesting new platform for studying xenotransplantation.

## BIOENGINEERING AND LIVER REGENERATION

An interesting study was presented by Lonati et al[6] showing an advanced perfusion system for rat liver NMP equipped with a bioreactor seeded with human adipose tissue-derived mesenchymal stem cells (MSC). They collected perfusate samples of rat liver perfused for 4 h on an NMP circuit with and without an MSC-bioreactor, showing that perfusate collected during bioreactor-based NMP developed a liver-tailored, MSC-derived secretome profile. Moreover, compared with NMP alone, they produced more bile and released fewer damage biomarkers and more acute phase proteins. MSC bioreactors supported mitochondrial function with higher ATP production, reduced succinate accumulation, lower release of proinflammatory mediators, and induction of factors involved in resolution and regeneration.

Currently, no in vitro models are available to study the effects of organ preservation strategies, ischemia time and reperfusion injury on the integrity of the biliary epithelium. Although the 3-dimensionally cultured intrahepatic cholangiocyte organoids (ICO) allow for the expansion of cholangiocytes, the organoid lumen, representing the luminal side of a bile duct, can only be accessed by disrupting the 3-dimensional organoid structure.[33] Willemse et al[34] established a bile-duct-on-chip platform using ICO and an accessible lumen to study the biliary epithelium in vitro. The authors prepared a 4-channel bile-duct-on-chip using polydimethylsiloxane filled with type-1 collagen and a viscous finger patterning to create a 300-mc lumen inside the hydrogel. ICO were initiated from human donor liver biopsies and added to the channels. Within 21 d, the ICO cells self-organized into a columnar monolayer, expressed cholangiocytes markers (cytokeratin-7 and -19 [CK7, CK19]), the cells were polarized similar to the biliary epithelium, and the cell layer formed an impermeable barrier against 70 kDa FITC-Dextran.

Stimulating liver regeneration and the capacity for repair could minimize the incidence of post-LT complications.[26] Biliary regeneration during LongT-NMP was assessed by Ly et al[35] in 10 discarded human grafts by the evaluation of multiple bile-duct biopsies for injury, proliferation of peribiliary glands (PBG) using immunohistochemistry (CK19, Ki67, and Sox9) and the biliary concentration of TNF-a, IL-6, and VEGF. After a median perfusion time of 7.5 d, 7 livers showed biliary regeneration with a median reepithelialization of 46% by day 6, whereas PBG proliferation was only 11%. Interestingly, there was an association between bile concentrations of IL-6 and VEGF and biliary viability criteria but not with biliary regeneration, suggesting their potential use as markers of early regeneration.

Nguyen-Lefebvre et al[36] studied differential gene expression profiles in (1) during liver grafts undergoing regeneration early postliving donor liver transplantation and in (2) liver graft fibrosis in patients with recurrent NASH. In the first study, they compared regenerating livers within 3 mo postliving donor liver transplantation, showing that the expression of YAP1, TEAD1, and YAP1 downstream target genes along the Hippo signaling pathway was specially upregulated in regenerating grafts (living) than in controls (deceased). This suggests that the Hippo signaling pathway plays an important role in human liver regeneration, which confirms what has been seen in mice studies. Separately, the same group compared single nucleus profiling in LT biopsies of recipients showing graft fibrosis equal to or greater than stage 2 due to recurrent NASH and compared with recipients with no fibrosis. Fifteen distinct clusters contributing to 2 homogeneous populations (normal and fibrotic) were identified. ADAM-10 (a disintegrin and metalloprotein domain-containing protein 10) and IGF2R (insulin-like growth factor 2 receptor) were highly expressed in graft fibrosis biopsy.[37] Further validation studies in a larger cohort are ongoing and could point to targets for prevention of fibrosis.

Martin et al[38] developed a 3D biocompatible scaffold made by gelatin and hyaluronic acid impregnated with antioxidant molecules (N-acetyl-cysteine and N-acetyl proline), which supported the proliferation of infrapatellar fat pad-derived stem cells and transdifferentiated into hepatocytes, demonstrating its potential as a model for liver tissue engineering.

## TRANSPLANT ONCOLOGY

Hepatocarcinoma (HCC) is still one of the leading indications of LT. There is a relevant interest of translational research in identifying features related to tumor recurrence to be used as potential therapeutic targets.[39] Previous literature suggests that circular RNA (circRNA) plays a pivotal role in metastatic HCC. However, the underlying molecular mechanisms are not fully understood.[40] Hu et al[41] screened 10 pairs of HCC with and without microvascular invasion using qRT-PCR and in situ hybridization assays to measure the expression level of circRNA. At the same time, migration and invasion ability was confirmed by transwell assay, patient-derived tumor xenografts (PDX), and organoids (PDO). The main findings from this elegant study showed that circRNA was associated with a poorer prognosis and that silencing circRNA inhibited the invasion and migration of HCC in vitro. In previous studies, Pang et al[42] have found that HCC relapse after LT was correlated with the activation of plasmacytoid dendritic cells; however, the underlying pathway was not well understood. Now, they focused on the role of inflammation triggered by IRI and plasmacytoid dendritic cells (pDCs) activation by analyzing the dynamics of pDCs and plasma IFN-a in 153 specimens of LT recipients with HCC and in mouse hepatic IRI models. Clinically, HCC recipients with higher IFN-a showed shorter disease-free survival, whereas the neutralization of IFN-a significantly suppressed tumor growth in C57bl/6 mice. Differential gene expression analysis demonstrated that IFN-a synergistically promoted IDO1 gene expression in macrophage upon inflammatory stimuli (eg, LPS and TNF-a), that HDAC2 (Histone deacetylase 2) was downregulated in IFN-a treated macrophages. At the same time, interferon regulatory factor 1 gene (IRF1) knockdown rescued HDAC2 expression in macrophages upon IFN-a stimulation. They concluded that IFN-a-producing pDC promoted macrophage IDO1 via the IRF1/HDAC2 axis, thus driving HCC recurrence after LT, and suggested that targeting the pDC-IFN-a-IDO1 axis could prevent post-LT recurrence.[43]

Zhan et al[44] investigated the crosstalk between histone deacetylase 9 (HDAC9) and the macrophages that enables immune evasion of histone deacetylated in intrahepatic cholangiocarcinoma (iCCA). They analyzed the expression of HDAC9 in iCCA tissues and adjacent tissue (ANT) and the effects of HDAC9 knockout in an orthotopic xenograft iCCA mouse model. Moreover, an HDAC9 inhibitor (TMP195) was used to investigate the therapeutic potential in a mouse model. The authors reported higher HDAC9 expression levels in iCCA tissue and an association with longer disease-free and overall survival. The loss or inhibition of HDAC9 facilitated the proliferation and invasion in vitro and increased M2 (tolerogenic) phenotype macrophages in vivo. The contribution of the macrophage subpopulation (MS) in iCCA and ANT was further studied by Badshah et al[45] using single-cell RNA seq. The authors identified 3 distinct MS: 2 MS in ANT expressed tolerogenic (M2-ANT) and inflammatory (M1-ANT) phenotypes, whereas MS-iCCA presented only 1 distinct population with tolerogenic and inflammatory gene markers. Interestingly, MS-iCCA showed upregulation of apolipoprotein E (APOE) and apolipoprotein C1 (APOC1), which are well-known contributors to tumor progression and could represent a potential therapeutic target.

## IMMUNOSUPPRESSION, REJECTION, AND TOLERANCE AFTER LIVER TRANSPLANTATION

Liver transplant recipients should receive immunosuppression (IS) treatment to prevent immunologic damage to the allograft, with calcineurin inhibitors, primarily tacrolimus, being the main drugs in current IS regimens. However, the efficacy of IS can be influenced by inter- and intrapatient variability, resulting in unnecessary and harmful over-IS or inefficient under-IS.[46] Bruner et al[47] conducted a study using an AI approach (phenotypic personalized medicine) to address the tailoring IS question. Their algorithm recommended a decrease of IS for stable patients and a modulation of IS for patients at risk of rejection and infection. Furthermore, Abecassis et al[48] proposed

a protocol that combines gene expression profiles (immune quiescence/activation) with donor-derived cell-free DNA (dd-cfDNA graft injury) to define liver recipients immune phenotype. They analyzed 210 samples divided in training set and test set and compared with the patients biochemical and histological immunologic phenotype. By doing so, they were able to define 3 precise phenotypes: rejection, acute dysfunction but without rejection, and normal graft evolution. Based on this, the authors suggest that their protocol could eventually be used to adapt IS after LT.

About the lifelong consequences of IS, Zubair et al[49] used RT-qPCR to analyze urine samples from patients under tacrolimus based immunosuppressant regimen and proposed a 7-gene signature by analyzing urine samples (7 genes) that was able to distinguish patients with nephrotoxicity related to calcineurin inhibitors with an ROC curve of 0.85. Wang et al[50] presented an interesting study using a combination of in vitro and airway organoid models to test the effect of different immunosuppressants on the replication of varying coronavirus variants. They showed that while mycophenolic acid inhibited viral replication in a dose-dependent manner, dexamethasone modestly promoted coronavirus replication. This study highlighted the multifaceted effects of immunosuppressants on coronavirus replication and infection. Nieuwenhuis et al[51] analyzed the impact of donor-recipient non-HLA genetic mismatch on the risk of post-LT rejection. They demonstrated that a higher non-HLA mismatch score was associated with a higher incidence of rejection within 1 y after LT, suggesting that screening for patients with high-risk immune burden may help personalize immunosuppressive regimens and prevent early graft rejection.

Interactions among immune cell subpopulations during a rejection episode were characterized by Rocque et al[52] who analyzed liver allograft biopsies using imaging mass cytometry with a 22-antibody panel from 38 patients with acute T cell–mediated rejection, 14 with chronic rejection, and 26 with no-rejection. They found a higher proportion of immune cells in the rejected patient samples, with an expansion of $CD4^+FoxP3^+$ Treg and proliferating $CD4^+$ T cells. Furthermore, a higher ratio of $PD1^+CD8^+$ T cells versus cytotoxic T cells and a greater proportion of $PD1^+CD8^+$ T cells were observed during rejection, with more proliferating M1 and M2 macrophages. Interestingly, there was geographic avoidance between macrophages and the entire $CD8^+$ T-cell subpopulation during the rejection episode. Together, these findings pointed to the potential for therapies that promote the expansion and interaction of macrophages and $PD1^+$ regulatory T cells for post-LT rejection. Hong et al[53] explored the potential of using MD-3, an anti-human intercellular adhesion molecule-1 (ICAM-1) monoclonal antibody, to replace calcineurin inhibitors as IS maintenance therapy. Using a challenging experimental rhesus macaque LT model, they showed long-term survival (>500 d) under MD-3 monotherapy, whereas the conventional IS-treated group presented with acute or chronic rejection leading to graft failure for up to 66 d after LT. These results enlightened the potential for MD-3 to replace calcineurin inhibitors as maintenance IS and thus avoid the clinical consequences of lifelong calcineurin inhibitor treatment. Further studies using large sample sizes are needed to validate these findings.

## NOVEL DIAGNOSTIC AND PROGNOSTIC MARKERS IN LT

Several studies proposed new the implementation of new devices or new methods to predict organ quality or tumor (HCC and iCCA) behavior. To evaluate organ quality, Sorbini et al[54] measured donor-derived cell-free DNA (dd-cfDNA) in liquid biopsies on postoperative days 0 to 7, 28, 90, and 180 by Droplet digital PCR. They found that dd-cfDNA reflected the severity of IRI (as per hepatocytolysis values), suggesting that it is a promising, reliable marker of graft injury after LT. Finally, Connor et al[55] performed targeted next-generation sequencing of 324 genes in paraffin-embedded iCCA samples from 27 LT patients and reported 21 mutations in 27 tumors. The most frequently altered genes included TP53, BRAF, IDH1, KRAS, and CDKN2A. Five pathways were altered: RAS-RAF, TP53, epigenetic, SWI-SNF, and RB, but while neither KRAS nor BRAF were alone prognostic, RAS-RAF was predictive of iCCA prognosis. They found specific clusters associated with exclusive subtypes and concluded that molecular profiling may aid personalized care and give relevant information on biology and prognosis.

## ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Artificial intelligence (AI) has been transforming daily life recently, especially with generative AI tools such as chat generative pretrained transformer (ChatGPT). AI has entered healthcare in recent years, particularly with FDA-approved imaging applications in radiology and pathology. As a subset of AI, machine learning (ML) tools enable the integration of large amounts of data, deciphering complex patterns, and interrelationships for personalized predictions in real-time in fields including LT.[56]

Oh et al[57] examined the potential for a convolutional neural network model (DeepLabV3+) to identify the anatomic region of the bile duct and the transection site in a retrospective study analyzing 30 videos of pure laparoscopic donor hepatectomy. They used the 5-fold cross validation method using 24 videos as training set and the next 6 videos as validation set. The dice similarity coefficient (DSC) metrically evaluated the performance of their AI model. DSC reflects the intersection between the ground truth (the actual biliary anatomy) and the bile-duct region predicted by the AI, and ranges from zero (low precision) to 1 (high precision). In the end, their AI model predicts the bile-duct region with a DSC of 0.66 and correctly identifies the transection site region, which suggests that AI may be used to optimize minimally invasive living donor liver procedures contributing to minimize postoperative donor complications and provide high-quality grafts. Abbas et al[58] examined the ability of the ImageDx AI tool to identify significant steatosis on H&E slides accurately. A surgeon's macroscopic assessment had poor concordance with the AI tool assessment. This speaks to the potential for such a rapid assessment tool to avoid unnecessary organ discards or harvests.

Zhao et al[59] determined using a random survival forest ML approach that primary sclerosing cholangitis specific parameters, such as recurrent cholangitis and concomitant inflammatory bowel disease, were critical to optimize waitlist prioritization of this currently disadvantaged

population. The absence of such specific factors resulted in a c-index of 0.749. In contrast, the addition of such elements significantly improved the prediction of waitlist mortality or dropout of primary sclerosing cholangitis patients with a c-index of 0.94. Bangerth et al[60] used 2 ML techniques, bootstrapping for feature selection and LASSO regression, to build a new predictive model of clinical outcomes for pediatric acute liver failure using common admission laboratory values at the Children's Hospital Los Angeles (CHLA). The CHLA Acute Liver Failure (CHALF) Score was externally validated using NIH data and can predict survival with native liver versus liver transplant with high accuracy (C-statistic 0.83).

Overall, these studies show the significant promise for AI tools to personalize care in LT and require prospective validation to enable clinical deployment.

## RETROSPECTIVE ANALYSES OF PREVIOUSLY CITED ABSTRACTS IN THE PREVIOUS CONGRESS REPORTS

We reviewed all abstracts mentioned in earlier reports to verify whether the basic and translational studies mentioned in the previous ITLS-BTSRC conference reports resulted in complete original manuscripts in a scientific journal. We checked using the PUBMED platform whether they were published (before or after the respective ILTS Annual Congress). The PUBMED research was conducted by searching for the name of the first or last author of the abstract, the topic, and the methodology, which included the number of animals or patients and the respective experimental analyses. In total, 136 abstracts were cited in 4 reports covering 5 y, with an average of 27 abstracts per year. As of August 2023, 67 studies have been published as full original manuscripts, representing 49.3% of all abstracts cited in the ILTS-BTSRC annual reports. Furthermore, the median of the impact factors of the journals was 5.4. Taken together, these findings could reflect the high level of studies presented at the ILTS conferences (Table 3). It is worth noting that these numbers are likely to increase over time, as most abstracts are eventually published up to 2 or 3 y after their presentation at the ILTS meetings and up to now, there are only 6 abstracts presented at the 2022 ILTS congress already published as full original article. Regardless, this exercise points to the high level of studies presented at the ILTS Annual Meeting and reinforces the role of the society as an important platform to share and discuss the basic and translational scientific activity in the field of LT.

## CONCLUSIONS

At the first fully in-person meeting after the COVID-19 pandemic, the 2023 ILTS-ELITA-LICAGE joint meeting fulfilled its primary goal of connecting the global liver transplant community. We attended vibrant sessions where high-quality scientific studies were presented, followed by interesting debates and exchange of experiences.

Although the number of abstracts related to basic and translational science remained constant compared with previous years (~10%), many abstracts classified in other categories used basic or translational tools in their methodology. Considering this, the ILTS-BTSR-Committee aimed to select the most expressive abstracts in the 7 aforementioned areas of interest from the studies presented and discussed throughout the 60 scientific sessions held during the congress. Promising advances in the understanding of IRI, liver MP, liver regeneration, organoids, transplant oncology, liver allograft immunology, and AI were reported here. We believe that MP technology has certainly improved organ preservation protocols—the challenge now is to use this technology as a platform to reliably assess organ viability and improve quality and function of organs by delivering treatments such as defatting cocktails, cellular, and genetic treatments, such as siRNA and/or CRISPR gene editing during infusion sessions.[61–65] Similarly, an improved understanding of the mechanisms and pathways associated with liver fibrosis and regeneration is critical to the development of innovative therapies to block the progression of fibrosis and stimulate regeneration. Organoid development can be used not only to answer these questions but also to understand the mechanisms involved in the development of biliary lesions, liver tumors, and recurrence of immune associated liver diseases after transplantation, among others. The discovery and clinical validation of biomarkers is required in Transplant Oncology to predict tumor progression and/or recurrence posttransplant for optimal outcomes. We believe that progress in clinical biomarkers to predict tolerance after transplantation will guide safe immunosuppression withdrawal clinical trials in future. There is significant work in clinical protocols to induce tolerance in the first years after LT, and the use of chimeric antigen receptor T-cell therapy is promising. And last but not least, we will expect to see increasing use of AI and ML in the field of LT, from the development of more precise indication algorithms and to graft/recipient matching protocols, to optimization of immunosuppression protocols, among many other possibilities.[56] In conclusion, talking in account the high quality of abstracts presented

**TABLE 3.**

**Number of abstracts cited in each ILTS—Basic and Translational Scientific Research Committee annual congress report and the number of abstracts ultimately published as full original manuscripts**

| Year | Total number of cited abstracts | Number of abstracts published as full original manuscripts | Percentage of abstracts finally published | Journals impact factors median (range) |
|---|---|---|---|---|
| 2018 | 32 | 15 | 46.9% | 4.1 (1.8–14.7) |
| 2019 | 38 | 27 | 71.0% | 6.0 (1.7–24.5) |
| 2020–2021 | 47 | 19 | 40.4% | 6.2 (0.9–13.3) |
| 2022 | 19 | 6 | 31.6% | 6.2 (0.6–13.5) |
| Total/average per year[a] | 136/27 | 67/13.4 | 49.3%/9.9% | 5.4 (0.6–24.5) |

[a]Although only 4 reports have been published, the report of 2020–2021 was considered as 2 y, then the calculation was made for 5 y.
ILTS, European Liver and Intestine Transplant Association.

in basic and translational topics, and also in the other areas of interest in LT, the ILTS-ELITA-LICAGE 2023 annual meeting cemented its role as a fundamental platform for the discussion and exchange of the most recent scientific progress in the liver transplant field.

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