

International Travel Scholar Award 2016
International Liver Transplantation Society

Recipient:

Dagmar Kollmann, MD, PhD
Department of Surgery, Medical University of Vienna, Austria

Project:

Normothermic Ex vivo Liver Perfusion

Receiving Institution:

Toronto General Hospital, Multi Organ Transplant Program, Toronto, Canada

Supervisors:

Nazia Selzner, MD, PhD
Markus Selzner, MD



MaRS Centre, Toronto Medical Discovery Tower

I would like to thank the ILTS committee for awarding me with the ILTS travel scholar award 2016. This award enabled me to study normothermic *ex vivo* liver perfusion (NEVLP) in a pig liver transplantation model at the Toronto General Hospital. I started the research fellowship in July 2016 and I was immediately integrated in the outstanding team led by Dr. Nazia Selzner and Dr. Markus Selzner. During this time I have learned to perform pig liver transplantations independently and to set-up and use the Toronto *ex vivo* liver perfusion protocol. Including me, two surgical fellows worked on different liver transplant projects. In addition we closely cooperated on related models studying normothermic *ex vivo* kidney perfusion. We benefited from the support of our research technician with the logistical challenges of the organization of these complex experiments. We regularly performed two liver transplants and two kidney transplants per week, which made our days busy and led to good progress of our projects. I also got the opportunity to work on clinical projects using a well-maintained database of a high-volume transplant center. Although I have not completed the data analysis, I was able to present preliminary results at national and international conferences.

During the fellowship I became a member of the Canadian Society of Transplantation and had the opportunity to participate at the annual meetings. Furthermore, I participated in the first Organ Donor Surgery Course organized by the Canadian Society of Transplantation.

The Toronto Abdominal Transplant Program is one of the largest programs in North America. With around 200 liver transplants performed per year, including transplantation from NDD, LDLT and DCD donors. The huge expertise enables high-end research in the clinical as well as in the basic science field of liver transplantation. It was a great honour for me to closely work with experts in this field. I am convinced that this fellowship was an important step to advance in my career as an academic surgeon.

With best regards and many thanks for awarding me with the Travel Scholar Award!

Dagmar Kollmann



Figure 1. Perfusion of a porcine liver with the normothermic machine perfusion. Team of the Toronto Organ Preservation Laboratory (<http://www.torontoorganpreservation.com>)
From left to right: Peter Urbanellis, Ivan Linares, Matyas Hamar, Dagmar Kollmann, Markus Selzner, Sujani Ganesh.

Main projects during the research fellowship:

Basic Science Projects:

- **The role of platelets in liver transplantation after normothermic *ex vivo* liver perfusion (NEVLP)**

In this project, I investigated, the impact of NEVLP or static cold storage (SCS) on platelets. The role of platelets in sinusoidal endothelial cell (SEC) injury after ischemia/reperfusion had previously been investigated in SCS but data on NEVLP are lacking. For this purpose, I performed pig liver transplantation (LT) with heart-beating donor (HBD) and donation after circulatory death (DCD) livers (30min warm ischemia) subjected to 8hrs SCS (SCS-group) or NEVLP (NEVLP-group, n=5/group). I obtained liver biopsies 3hrs post-LT and stained them for platelet-specific CD61. Additionally, I determined circulatory TGF- β and Platelet-specific MicroParticles (PMPs). The sinusoidal endothelial cell (SEC)-integrity was determined by CD31-

staining and measurement of Hyaluronic Acid (HA). I measured liver enzymes, platelet-counts and other parameters (Prothrombin Time, INR, Hemoglobin) during a 4-day survival-period.

In summary, our experiments demonstrated that platelet aggregation and SEC injury post-reperfusion was reduced by NEVLP. NEVLP allowed a faster recovery of the platelet count after LT and therefore might protect the liver from platelet-induced SEC injury.

The manuscript for this study is currently in preparation.

- **Evaluation of bile production and bile quality as a prognostic marker during normothermic ex vivo liver perfusion**

In the second project, I worked on the assessment of bile as a prognostic marker during normothermic *ex vivo* liver perfusion. Liver transplantation (LT) with donation after circulatory death (DCD)-grafts is associated with a higher risk to develop ischemic-type biliary strictures. Therefore, I evaluated the bile production and quality during normothermic *ex vivo* liver perfusion (NEVLP) to assess biliary injury.

I performed Pig-LT after 5hrs NEVLP using heart-beating-donor (HBD-group, n=5) and DCD grafts with 30 and 60min warm ischemia (30'DCD-group, 60'DCD-group; n=5 each). I collected bile hourly during perfusion and daily during a 4-day survival-period. Markers of cholangiocyte function (pH, HCO₃⁻, totalCO₂, glucose), injury (AST, GGT, LDH) and cholesterol were assessed in bile. Bile-duct histology was evaluated 3hrs post-reperfusion and on postoperative day (POD)4.

In summary, I found significant differences in bile production and quality during NEVLP of liver grafts with different grades of injury. I determined that bile volume and quality at 2hrs of perfusion could be used as a marker for the severity of bile duct injury.

This manuscript is currently in preparation for submission.

Clinical Projects

- **Living Donor Liver Transplantation Using Grafts with ≥ 2 Bile Ducts – Does it affect patient outcome?**

This was a clinical project in which the impact of multiple bile ducts on outcomes after living donor liver transplantation had been investigated. It had previously been described that the use of live donor (LD) liver grafts with multiple bile ducts (BD) was associated with an increased risk of BD related complications after living donor liver transplantation (LDLT). I evaluated 510 patients receiving a LDLT from 2000-2015 at the Toronto General Hospital. Outcome of patients using grafts with ≥ 2 BD (n=190) were compared to all patients receiving a LD graft with only one BD (n=320).

In summary, I demonstrated that LDLT using selected grafts with 2 BD is safe and does not negatively impact on postoperative biliary complication rates and graft survival.

This manuscript is currently submitted for publication.

- **Acute kidney injury and chronic kidney disease after transplantation of livers from NDD, DCD and live donors**

Recipients of donation after circulatory death (DCD) grafts are reportedly at higher risk of developing post liver transplant (LT) renal dysfunction. I compared the development of acute kidney injury (AKI) and chronic kidney disease (CKD) after LT in recipients of DCD vs. neurological declared death (NDD) or living donor (LD) livers. All adult recipients of single organ NDD, LD and DCD LT from 2012–2016 at Toronto General Hospital were included. AKI was defined as post-transplant increase of serum creatinine (sCr) $>26.5\mu\text{mol/L}$ in $\leq 48\text{hrs}$ or $>50\%$ increase from baseline. CKD was defined as eGFR $\leq 60\text{ml/min}$ for ≥ 3 months. In total, 716 patients (61 DCD, 474 NDD, 181 LD) with similar baseline co-morbidities were included.

Our preliminary results show that recipients of DCD liver grafts have higher rates of post-transplant renal dysfunction compared to NDD or LD, without affecting long-term renal function. However, recipients with perioperative RRT have lower patient survival. Efforts to reduce AKI in the perioperative period may decrease development of CKD and improve patient long-term outcomes.

This manuscript is currently in preparation for submission.



Figure 2. Implantation of a perfused porcine liver into a recipient pig in a fully equipped operating theatre for large animal research.

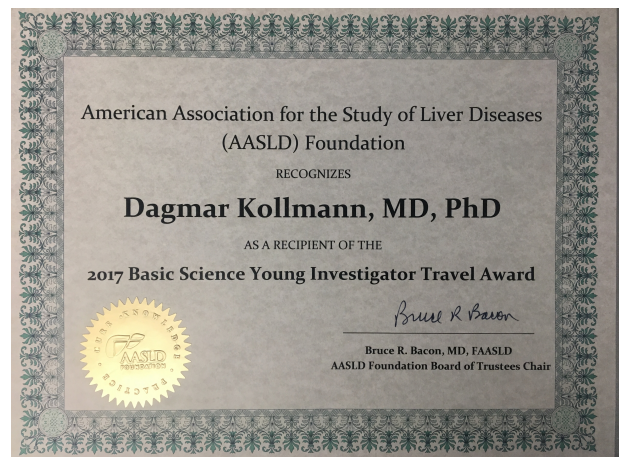


Figure 3. AASLD Basic Science Young Investigator Award for the Abstract: *Normothermic ex vivo liver perfusion prevents platelet sequestration and platelet induced sinusoidal cell injury in the liver after liver transplantation*, presented at the annual AASLD meeting 2017 in Washington DC, USA. Picture with mentor Dr. Nazia Selzner.

Manuscripts originating from the Fellowship in Toronto:

Normothermic ex vivo liver perfusion prior to liver transplantation prevents platelet sequestration and platelet induced sinusoidal cell injury in the liver when compared to static cold storage

Dagmar Kollmann, Ivan Linares, Sujani Ganesh, Roizar Rosales, Nicolas Tessandier, Eric Boilard, Matyas Hamar, Peter Urbanellis, Aryn Wiebe, Yip Paul, Oyedele Adeyi, Markus Selzner, Nazia Selzner

Manuscript in preparation

Evaluation of bile production and bile quality as a prognostic marker during normothermic ex vivo liver perfusion

Dagmar Kollmann, Ivan Linares, Sujani Ganesh, Roizar Rosales, Matyas Hamar, Peter Urbanellis, Aryn Wiebe, Yip Paul, Oyedele Adeyi, Markus Selzner, Nazia Selzner

Manuscript in preparation

Transplantation of DCD livers leads to a higher rate of post-transplant acute kidney injury, but not chronic kidney disease when compared to NDD or LDLT

Dagmar Kollmann, Shuet Fong Neong, Bettina Hansen, Roizar Rosales, Gonzalo Sapisochin, Mamatha Bhat, Mark S. Cattral, Paul D. Greig, Les Lilly, Ian D. McGilvray, Anand Ghanekar, David R. Grant, Markus Selzner, Florence S. H. Wong, Nazia Selzner

Manuscript in preparation

Impact of Human Albumin/Dextran vs Gelatin as Perfusate During Normothermic Ex Vivo liver Perfusion on Pig Liver Transplant Outcomes in a DCD model

Ivan Linares, Dagmar Kollmann, Juan Echeverri, Moritz Kathz, Matyas Hamar, Peter Urbanellis, Roizar Rosales, Claudia Bruguera, Sujani Ganesh, Oyedele Adeyi, Paul Yip, Markus Selzner, Nazia Selzner

Manuscript in review

Expanding the Donor Pool: Donation after Circulatory Death and Living Liver Donation does not Compromise the Results of Liver Transplantation

Dagmar Kollmann*, Gonzalo Sapisochin*, Nicolas Goldaracena, Bettina Hansen, Nazia Selzner, Mamatha Bhat, Stuart McCluskey, Mark S. Cattral, Paul D. Greig, Les Lilly, Ian D. McGilvray, Anand Ghanekar, David R. Grant, Markus Selzner

Manuscript in review

Live Donor Liver Transplantation Using selected Grafts with Two Bile Ducts compared to One Bile Duct Does not Impact on Patient Outcome

Dagmar Kollmann, Nicolas Goldaracena, Gonzalo Sapisochin, Ivan Linares, Nazia Selzner, Mamatha Bhat, Mark S. Cattral, Paul D. Greig, Les Lilly, Ian D. McGilvray, Anand Ghanekar, David R. Grant, Markus Selzner

Manuscript in review

Normothermic Ex Vivo Kidney Perfusion Reduces Warm Ischemic Injury of Porcine Kidney Grafts Retrieved After Circulatory Death (DCD)

Matyas Hamar, Peter Urbanellis, Moritz Kathz, Dagmar Kollmann, Ivan Linares, Sujani Ganesh, Aryn Wiebe, Danny Cen, Paul Yip, Rohan John, Anna Konvalinka, Istvan Mucsi, Anand Ghanekar, Darius Bagli, David Grant, Lisa Robinson, Markus Selzner

Manuscript accepted for publication in the Journal Transplantation

Comparison of BQ123, Epoprostenol, and Verapamil as Vasodilators During Normothermic Ex Vivo Liver Machine Perfusion.

Juan Echeverri, Nicolas Goldaracena, Moritz J. Kathz, Ivan Linares, Roizar Rosales, Dagmar Kollmann, Matyas Hamar, Peter Urbanellis, Sujani Ganesh, Oyedele Adeyi, Mahmood Tazari, Markus Selzner, Nazia Selzner

Transplantation. 2017 Nov 20. doi: 10.1097/TP.0000000000002021. [Epub ahead of print]

Recent advances in the field of warm ex-vivo liver perfusion.

Dagmar Kollmann, Markus Selzner

Curr Opin Organ Transplant. 2017 Dec;22(6):555-562.

Bridging to liver transplantation in HCC patients.

Dagmar Kollmann, Nazia Selzner, Markus Selzner

Langenbecks Arch Surg. 2017 Jul 28. doi: 10.1007/s00423-017-1609-2. [Epub ahead of print]
Review

Abstracts accepted at national and international conferences originating during the Fellowship in Toronto:

Platelet Aggregation Contributing to Reperfusion Injury can be prevented by Normothermic ex vivo Liver Perfusion prior to Liver Transplantation

D. Kollmann, I Linares, S. Ganesh, R. Rosales, M. Hamar, P. Urbanellis, C. Bruguera, A. Wiebe, P. Yip, M. Selzner, N. Selzner, O. Adeyi

EASL 2018, Paris, France (accepted for oral presentation)

Platelet Aggregation Contributing to Reperfusion Injury Is Histologically Detectable and Prevented by Normothermic ex vivo Liver Perfusion

D. Kollmann, I Linares, S. Ganesh, R. Rosales, M. Hamar, P. Urbanellis, C. Bruguera, A. Wiebe, P. Yip, M. Selzner, N. Selzner, O. Adeyi

USCAP 2018, Vancouver, Canada (accepted for poster presentation)

Normothermic ex vivo liver perfusion prevents platelet sequestration and platelet induced sinusoidal cell injury in the liver after liver transplantation

D. Kollmann, I Linares, S. Ganesh, R. Rosales, M. Hamar, P. Urbanellis, C. Bruguera, A. Wiebe, P. Yip, O. Adeyi, M. Selzner, N. Selzner

AASLD 2017, Washington DC, USA (oral presentation), *Young Investigator Basic Science Award*

Using Grafts with 2 or more than 2 Bile Ducts for Living Donor Liver Transplantation – Does it affect Patient Outcome?

D. Kollmann, N. Goldaracena, G. Sapisochin, N. Selzner, M. S. Cattral, P. D. Greig, L. Lilly, I.D. McGilvray, A. Ghanekar, D. R. Grant, M. Selzner

AASLD 2017, Washington DC, USA (poster presentation)

Normothermic ex vivo liver perfusion prevents platelet sequestration and platelet induced sinusoidal cell injury in the liver after liver transplantation

D. Kollmann, I Linares, S. Ganesh, R. Rosales, M. Hamar, P. Urbanellis, C. Bruguera, A. Wiebe, P. Yip, O. Adeyi, M. Selzner, N. Selzner

CST 2017, Halifax, Canada (oral presentation)

The usage of live donor grafts with multiple bile ducts does not negatively impact patient outcome in LDLT

D. Kollmann, N. Goldaracena, G. Sapisochin, N. Selzner, M. S. Cattral, P. D. Greig, L. Lilly, I.D. McGilvray, A. Ghanekar, D. R. Grant, M. Selzner

ESOT 2017, Barcelona, Spain (oral presentation)

Living Donor Liver Transplantation Using Grafts with ≥ 2 Bile Ducts – Does it affect patient outcome?

D. Kollmann, N. Goldaracena, G. Sapisochin, N. Selzner, M. S. Cattral, P. D. Greig, L. Lilly, I.D. McGilvray, A. Ghanekar, D. R. Grant, M. Selzner
Sheila-Sherlock Meeting 2017, Toronto, Canada (oral presentation), *Award for best Oral Presentation*

Impact on Patient Outcome after Live Donor Liver Transplantation Using Grafts with ≥ 2 Bile Ducts

D. Kollmann, N. Goldaracena, G. Sapisochin, I. Linares, N. Selzner, M. S. Cattral, P. D. Greig, L. Lilly, I.D. McGilvray, A. Ghanekar, D. R. Grant, M. Selzner
ILTS 2017, Prague, Czeck republic (poster presentation)

Live Donor Liver Transplantation Using Grafts with more than Two Bile Ducts – Does it affect patient outcome?

D. Kollmann, N. Goldaracena, G. Sapisochin, N. Selzner, M. S. Cattral, P. D. Greig, L. Lilly, I.D. McGilvray, A. Ghanekar, D. R. Grant, M. Selzner
ATC 2017, Chicago, US (oral presentation)