Organ Transplantation in Colombia

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GENERAL AND DEMOGRAPHIC INFORMATION

Colombia is located on the Northern tip of South American. The country is bordering Middle-America, Venezuela, and the Pacific and Atlantic Ocean in the north, Ecuador, Peru and Brazil in the South (Figure 1). Colombia has approximately 50 Mio inhabitants (49293087 as of 2018) living in a 1142000 km^2 surface area that is equivalent to the geographic area of Texas and New Mexico. Regionally, Colombia is divided into 32 states in addition to the Capital District.[1,2] The country has 6 different organ procurement regions. Approximately 95% of the population has health insurance coverage.

HISTORY OF TRANSPLANTATION IN COLOMBIA

Organ transplantation in Colombia started as early as 1965 at the San Juan de Dios Hospital, Bogota with 5 deceased donor kidney transplants under the leadership of the Nephrologist Dr. Enrique Carvajal Arjona, and the Surgeon Dr. Fernando Gomez Rivas. At the time, organs had been procured from donors after cardiac death as the definition of brain death had not been established. The mainstay of immunosuppression had been based on azathioprine and prednisolone. Both transplant pioneers left Colombia in the following years, putting a hiatus on progress.

The first publication on brain death and its legal implications in Colombia appeared in March 1973, in the journal of the Academia de Medicina de Medellín.[3]

By August 1973, a deceased donor kidney transplantation program started at San Vicente de Paul Hospital in Medellin under the leadership of Drs. Jaime Borrero, Jorge Luis Arango, and Alvaro Velasquez. Dr. Velasquez had been trained by Dr. Thomas Starzl at the University of Colorado. The group in Medellin expanded their activities with the implementation of live donor kidney transplants in 1974, deceased donor liver (1979), cardiac (1985), lung (1988) and combined heart and lung transplants in 1989. Cardiothoracic programs had been initiated in cooperation with the hospital Santa Maria in Medellin.

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The first combined kidney/pancreas transplant had been performed at the San Pedro Claver Clinic in Bogota, D.C. (1988); the first trachea transplantation has been done at San Vicente de Paul hospital in 2002.

As of today, the country has 22 kidney transplant programs in 6 cities, 8 liver (in 4 cities), 8 heart (in 4 cities), 4 lung (in 3 cities), 3 pancreas (in 2 cities), and 3 intestinal transplant programs (in 2 cities) (Table 1).

LEGISLATION

- The first law in organ transplant has been issued in February 1979 in Colombia.
- The National Health Institute (*Instituto Nacional de Salud*) is in charge of the organ and tissue transplant network that has been established in 2004. There is a mandatory reporting of every donor (both live and deceased) and every transplant. Although transplant activities are well reported, there is only limited information available on long-term transplant outcomes.

A presumed consent legislation has been introduced in 2016 and is practiced since 2017. Early results show an increase in transplant activity by 24.5% (Table 2).

TRANSPLANT TOURISM

Legislation prohibiting organ transplantation for noncitizens has been introduced in 2004. This law allows deceased donor transplants in foreign patients only if there is not a Colombian citizen waiting for an available organ. Moreover, non-Columbian citizens can only receive living related transplants with permission by the government. In 2016, only 10 foreign patients have been transplanted in Colombia, all having received living donor kidney transplants with the permission by the health authorities of both, their home country and Colombia's National Health Institute. In 2017, only 5 foreign patients (4 livers and 1 kidney) were transplanted, all with living related donors (Figure 2).[4]

Thus, Colombia has spearheaded the international movement combating transplant tourism.

ORGAN DONATION

Colombia's transplant activity is mainly based on deceased donations (Figure 2). Donors per million population (donors/pmp) peaked from 2008 to 2010, however, declined from 2010 to 2014. More recently (2015-2017), rates of deceased donations have recovered slightly (Figure 3). This upward trend is explained, at least in part, by extending the age-limit for donation while more extended criteria donors have been accepted. Deceased donor rates have increased from 7.8 donors pmp to 8.8 donors pmp in 2017.[5]

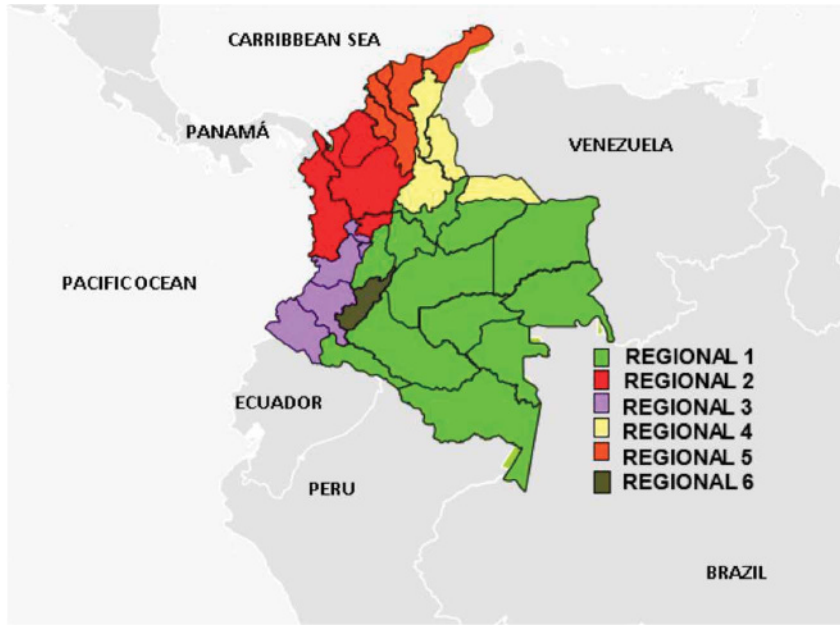

FIGURE 1. Map of Colombia.

ORGAN TRANSPLANTATION

Organ transplantation in Colombia has increased over the last decade and more than 18 000 transplants have been performed since 1966 (76% of those being kidney transplants; Table 3); more than 17% of recipients received liver transplants. It is important to mention that those numbers are based on personal information because there is currently no national registry collecting data on outcomes. In parallel, live donor transplants have increased; by 2016, 16.1% of kidney transplants and 16.3% of liver transplants had been from living donors.[4]

More than 27 000 patients are currently undergoing dialysis in Colombia. Although there is an almost complete health coverage in the country, only 2316 (8.44%) patients are currently waitlisted for renal transplants (Figure 4).[6]

TABLE 1.

Transplant programs per cities and organ

City	Transplantation programs
Bogota	4 Heart, 2 lung, 2 liver, 12 kidney
Medellin	1 Heart, 1 lung, 3 liver, 4 kidney, 2 intestine
Cali	2 Heart, 2 liver, 2 kidney, 1 intestine
Barranquilla	1 Kidney
Bucaramanga	1 Heart, 1 lung, 1 liver, 2 kidney
Neiva	1 Kidney

CHALLENGES AND OPPORTUNITIES MOVING FORWARD

The implementation of a mandatory database for all organ transplants and living donors will be critical in assessing transplant outcomes, allowing center-specific quality assessments and improvements while assuring the safety of live-donor procedures. With only a fraction of dialysis patients listed for renal transplantation, it will be important to assess the candidacy of all patients. Governmental support and a broad assessment of eligibility including political and social obstacles will be relevant in achieving these goals.

Donors after cardiac death (DCD) constitute a significant source of organs in North America and in some European countries. Colombia has of yet not legislated to the procurement of organs from DCD donors.

To identify and optimally manage deceased donors, it will be critical to implement a close communication between emergency medicine, intensive care physicians and procurement coordinators.

TABLE 2.

Organ transplants in Colombia (1966-2017)

Organ	1966-2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Kidney	9164	867	798	767	674	745	845	740	922	15522
Liver	1455	211	185	207	177	211	252	224	258	3180
Heart	591	60	82	99	81	72	65	58	74	1182
Kidney-pancreas	58	12	3	5	3	3	10	5	15	114
Lung	56	6	4	13	8	10	17	16	14	144
Combined	62	8	6	10	14	13	15	13	23	164
Intestine	2	4	2	3	2	5	3	3	0	24
Others	44	1	3	2	2	0	0	0	0	52
Multivisceral	1	2	2	2	0	0	0	0	0	7

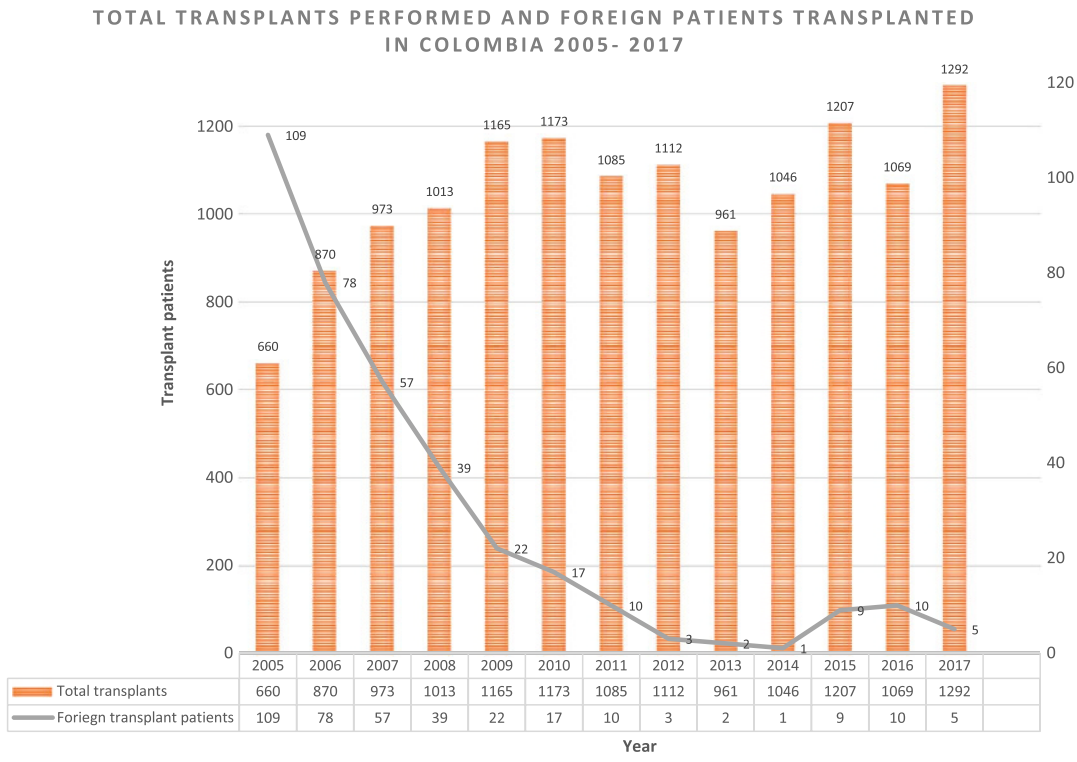

FIGURE 2. Transplants performed in both, Columbian and non-Columbian citizens (2005-2017).

To increase kidney transplantation, Colombia considers compensating donors for lost wages covering healthcare, costs for transportation, and other costs of the donation process.

Implementing paired kidney exchange programs will not only be a way to increase transplant rates but also to improve opportunities for sensitized recipients and those with blood group incompatible donors in a cost-effective way.

To increase liver, cardiac, and lung transplant rates, it will be important to get the attention of internal medicine specialists to achieve a more effective, rapid, and early referral to transplant programs.

For deceased donor liver transplants, it will be relevant to consider organs from older and less than optimal donors while contemplating an increase in the number of live donor liver transplants.

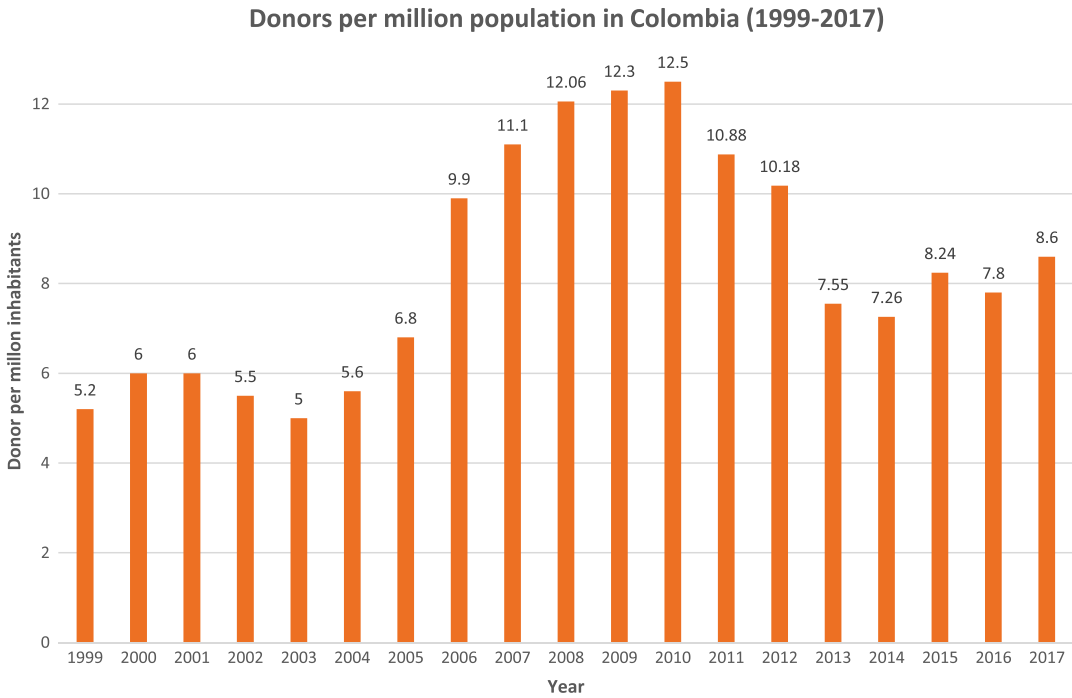

FIGURE 3. Donors per million population in Colombia (1999-2017).

For pancreas and intestinal transplants, a broader education will be necessary to educate patients on the benefits of those procedures.

CONCLUSIONS

Colombia has made great strides in moving organ transplantation forward. Nevertheless, end-stage organ failure rates are on the rise, and it will be important to offer transplantation to any patient eligible.

To increase transplant opportunities, it will be important to identify any potential donor while implementing DCD donor programs and paired kidney exchange registries.

A mandatory registry for any organ donor and transplant will be of critical importance to optimize quality while implementing process improvements.

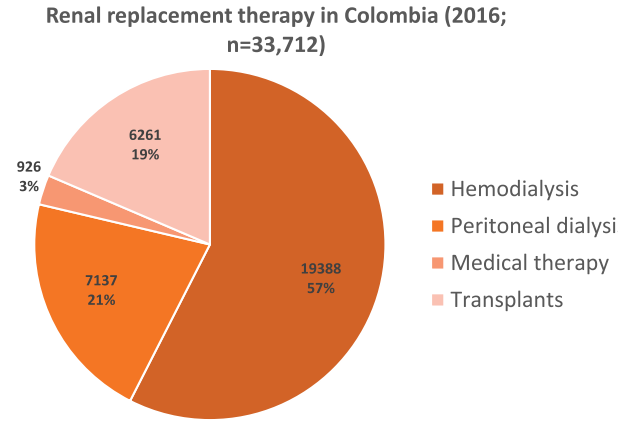

FIGURE 4. Renal replacement therapy in Colombia (as of 2016).[6]

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TABLE 3.

Consequences of implementing presumed consent legislation in Colombia (2016-2017)

Organ	TX 2016 (n)	TX 2017 (n)	% Variation
Kidney	622	788	(↑) 26,68
Liver	187	222	(↑) 18,71
Heart	58	74	(↑) 27,58
Lung	16	15	(↓) 6,25
Total	883	1.099	(↑) 24,46

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Research Highlights

Fadi Issa, PhD[1]

Molecular Pathways Underlying Adaptive Repair of the Injured Kidney: Novel Donation After Cardiac Death and Acute Kidney Injury Platforms

Orlando G, Danger R, Okut H, et al. *Ann Surg.* Published online July 24, 2018. DOI:10.1097/SLA.0000000000002946.

The donor organ shortage remains one of the most pressing issues in transplantation. There is an urgent need to expand the donor pool and explore methods for organ repair or preservation, allowing the use of high risk or "marginal organs." In a proportion of transplanted kidneys, a form of transient acute injury manifests as delayed graft function (DGF) with most allografts undergoing intrinsic adaptive repair and recovery. Thus, there is a unique opportunity to explore the mechanisms that underlie this process aiming to identify targets that may be exploited for therapeutic purposes.

Overall, patients who receive a kidney from a living donor (LD) display a reduced propensity to DGF in comparison to those receiving a kidney after cardiac death (DCD) or a kidney that underwent acute kidney injury (AKI) either before or during procurement. There is currently a wealth of techniques available to analyze molecular pathways in transplantation, providing exceptionally detailed datasets for exploratory research.[1] Here, Orlando and coinvestigators examined the peripheral blood of patients in the first 30 days after kidney transplantation to detect molecular changes that may be associated with transient kidney injury.[2] Peripheral blood RNA from 15 patients was analyzed by microarray pretransplantation and at 11 further time points posttransplantation. Among these 15 patients, 2 experienced DGF.

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There were no episodes of acute rejection. In the longitudinal analysis, several gene transcripts were found to be differentially expressed between patients receiving LD grafts versus those receiving DCD or AKI grafts. Examining each group separately (LD, DCD, or AKI) revealed specific patterns. Differences between groups were always greatest in the first few days after transplantation, returning to baseline over time. This return to baseline was more rapid in the LD than the DCD/AKI group. Additionally, several genes that may be related to repair and regeneration were differentially expressed between these 2 groups. While the data require further extensive interrogation to identify pathways that are nonredundant and targetable, the technique used and the large data set generated are of enormous value to the community. The ability to use peripheral blood rather than kidney biopsies to examine broad transcriptomic changes posttransplantation is an advantage.

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Pancreatic Islets Communicate With Lymphoid Tissues via Exocytosis of Insulin Peptides

Wan X, Zinselmeyer BH, Zakharov PN, et al. *Nature*. 2018;560:107-111.

Autoimmunity requires adaptive immune responses that recognize specific autoantigens by T cells. However, it is neither clear why tolerance to these antigen breaks nor why specific autoantigens are 'triggering' immune responses. In type 1 diabetes (T1D), the loss of pancreatic β cells is due to a destructive immune response against islet cell autoantigens mediated by both T cells and autoantibodies.[1] A genetic risk therefore exists for certain HLA alleles encoding molecules that present islet autoantigens. Before clinical disease onset, autoantibodies can be detected in high-risk individuals heralding islet damage and indicating autoantigen recognition, a process that is distinct from injury. However, it is not clear why autoimmune responses directed against pancreatic islets are so frequent, and how T cells gain access to specific autoantigens. Wan and coinvestigators[2] dissected some of those mechanisms in nonobese (NOD) mice. In NOD mice, there is a spontaneous presentation of insulin that sets in motion the development of pathology. A 12-20 segment of the insulin β-chain is recognized by autoreactive T cells, with this epitope generated from insulin peptides directly presented by antigen-presenting cells (APCs). Different segments are not recognized by these T cells, even if there is only a single residue shift. Here, the authors show that the 12-20 segment is transmitted via secreted exosomes and then presented by APCs to autoreactive $CD4^+$ T cells. Notably, this process is not operative through the standard APC processing machinery. This bypassing "normal" processing pathways means that the epitope is not selected during lymphocyte development in the thymus, leading to the survival of autoreactive $CD4^+$ T cells that recognize the 12 to 20 insulin β-chain segment. These catabolized insulin peptide fragments are also released in humans.

This landmark study highlights a previously undiscovered mechanism for autoimmune T-cell activation and provides important insight into the pathways underlying the development of T1D. The development of immune modulatory therapies that target T1D may benefit from taking those findings into consideration.

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GameChanger

Disrupting the Field of Organ Preservation: Normothermic Preservation in Liver Transplantation

Cristiano Quintini, MD[1] and Qiang Liu, MD[1]

Liver transplantation represents an effective treatment for patients with end-stage liver disease. However, patient access to this lifesaving procedure continues to be limited by the lack of organs resulting into high mortality rates while awaiting transplantation.[1] Attempts to expand the donor pool during the last decade using marginal organs and partial grafts have reached a plateau. At the same time, organ discard rates (organs procured but never transplanted) continue to remain mainly related to the poor quality of donor organs.[1] In 2014, more than 25% of all livers procured in the United States were discarded after procurement owing to concerns of primary graft nonfunction.[1] Clearly, many of those organs represent missed opportunities as (i) most of these livers were working perfectly well in the donor before procurement, and (ii) the decision to discard these organs was most likely based on the surgeon's "gut feeling," as objective and scientific criteria to accept (or discard) a liver are largely lacking.

The work from Nasralla and colleagues[2] recently published in "Nature" is a clear "game changer" in addressing those key issues. In one of the most elegant and calculated evolutions from bench-to-bed-side research, the University of

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Oxford group designed a randomized, controlled study to test the potential of normothermic machine preservation (NMP). This technology is based on the rationale that the deleterious effects of cold injury and ischemia sustained by the graft during static cold storage (SCS) can be ameliorated by perfusing organs at physiologic temperatures with a preservation solution able to deliver oxygen, nutrients, and, potentially, medications. Extensive preclinical work[3-5] has demonstrated that NMP is superior to SCS in preserving and potentially resuscitating severely injured grafts. Most importantly, research shows[6,7] that this preservation modality holds the potential to assess organ quality guiding clinicians during the difficult decision of organ acceptance.

Over a period of almost 2 years, 334 livers offered for transplantation to 8 European Centers were randomized to either conventional SCS preservation or NMP.[2] Sixty-four livers were subsequently excluded from the study (with organs from donation after cardiac deaths [DCDs] donors not progressing to circulatory arrest during the allotted time interval, recipient consent not obtained or donors not eligible to the study protocol). In the SCS arm, organs were stored and transplanted according to standard practice. Livers in the NMP arm were connected to the NMP machine (OrganOx Metra; OrganOx Limited, Oxford, England, UK) after retrieval and perfused through the hepatic artery and portal vein with a blood-based oxygenated perfusion solution until surgery.[2]

The primary endpoint of the study was the difference in peak serum aspartate transaminase (AST) during the first week after transplant.[2] Median peak AST in the NMP group was reduced by 49.4% when compared with the SCS group (488.1 vs 964.9; interquartile range, 408.9-582.8 vs 794.5-1172.0 IU/L) despite NMP livers having had longer functional warm ischemia times (DCDs), longer overall preservation times, and fewer organ discards. The greatest benefit in reduction in AST levels was observed in the DCD group (73.3% reduction compared with 40.2% of donation after brain death [DBD] livers. Notably, the primary outcome data for NMP DCD livers were superior to those of both DCD and DBD livers preserved under SCS conditions.[2]

In addition, the authors collected a number of very relevant secondary outcomes.[2] Early allograft dysfunction, defined as any one of the following clinical indicators: bilirubin >170 μmol/L on day 7 after transplant; international normalized ratio (INR) > 1.6 by day 7, and peak-AST > 2000 IU/L. The odds of NMP livers developing early allograft dysfunction were 74% lower compared with the SCS arm (10.1% versus 29.9%). Although the trial has not been designed to demonstrate that NMP can prolong preservation time, median total preservation time was longer for NMP compared with SCS livers (11:54 hrs vs. 7:45 hrs; $P < 0.001$).[2] This difference was likely based on an increasing operator confidence during the trial. Post reperfusion syndrome[8] was more likely to occur in SCS livers (33.0% vs 12.4% in NMP grafts). The rate of anastomotic (NMP 8.6%; SCS 10.8%) and nonanastomotic (NMP 43.2%; SCS 45.9%) biliary strictures was comparable in both arms, with 1 patient in each group developing severe ischemic cholangiopathy. There were no differences in the length of time recovering in the ICU or of the overall hospital length of stay. One-year patient and graft survival were comparable between arms (patient survival: NMP 94.9% vs 95.8% in SCS; graft survival: NMP 95% vs 96% in SCS).

In one of the most elegant and calculated evolutions from bench-to-bed-side research, the University of Oxford group designed a randomized, controlled study to test the potential of normothermic machine preservation.

Viability assessment during preservation was a major focus of this trial. Because of the low graft failure rate, no marker (either alone or as a composite measure) was identified as an absolute predictor of viability. Interestingly, 18 successfully transplanted livers produced little to no bile during perfusion. One liver presented with a highly increased lactate (>4 for the duration of NMP) and low pH; this graft went on to develop primary nonfunction. Baseline enzyme levels in the perfusate (soon after connecting the organ to the device) predicted the enzyme release in the posttransplant phase. However, the most striking secondary outcomes of all was the difference in organ discard rates with 24.1% for the SCS group compared to 11.7% for the NMP group ($P = 0.008$) resulting in 20% (!) more transplants performed in the NMP arm (121 vs. 101).[2]

If confirmed by future studies, this study would represent a monumental milestone in our field. In addition to the benefits of NMP on organ quality less obvious aspects may have contributed to the success. Research in the field of decision-making behavior[9] shows that decisions made under stressful conditions, such as the one encountered during acceptance of a marginal organ, have a tendency to be less rational. Moreover, decisions made under time pressure have a tendency to prefer lower risk choices while spending more time debating the negative consequences. As a result, risk-adverse people tend to make more conservative choices and risk takers tend to make riskier decisions, with neither approach representing an ideal scenario. Providing the accepting surgeon more time and data on organ quality (though the design of the study did not allow the surgeon to discard an organ based on viability assessment), NMP may have also improved the decision making process. After all, improving pH, lactate levels, and bile productions represent very powerful indicators of organ quality reassuring transplant caregivers.

In conclusion, this well-designed and conducted randomized, controlled study represents a major achievement in the field of liver transplantation. Normothermic machine preservation appears to be a powerful preservation technology and a promising organ assessment platform that has the potential to increase organ utilization dramatically. Future studies will need to confirm these findings, expand them to other organs, refine perfusion protocols, and test the potential of NMP in reconditioning severely injured grafts.

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People inTransplantation

Herman Waldmann, FRS, FRCP, FMEDSci: Emeritus Professor of Pathology, Sir William Dunn School of Pathology, University of Oxford, United Kingdom

You grew up in North-East London and joined the Department of Pathology at the University in Cambridge in 1973. What motivated you to enter a career in Pathology?

My father was a General Practitioner—the "plan" was that I would take over his practice when I qualified in medicine. However, my father's "iatrogenic" death in hospital changed my plans and I reevaluated my career, and what Clinical Medicine was able to offer at the time. I had always felt (from my Cambridge undergraduate training) that Immunology contributed a lot in understanding the pathogenesis of diseases and in providing the basis for new treatments. Thus, I "interrupted" my medical career (after qualifying) to undertake an Immunology PhD in the department of Pathology, Cambridge, UK

You were a visiting scientist with the Nobel Laureate Cesar Milstein at the Laboratory of Molecular Biology in 1978. How formative was this time been for your future career?

I gained much from seeing how Caesar approached science. Moreover, the hybridoma technology described by Cesar opened up huge opportunities to probe the immune system with precise antibody reagents, and to target disease-related molecules in therapy. Being there at the beginning was a fantastic opportunity and privilege.

You have achieved the dream of many clinicians/scientists in bringing a therapeutic from bench-to-bedside. Can you share a few critical steps in developing Campath-1?

Hard to speak of "dreams"—certainly offering treatments for unmet medical needs fulfilled one of my hopes when I entered research. Perhaps more surprising to me was the additional fulfillment to unravel mechanisms in immunity and immunological tolerance—all rendered possible through monoclonal antibody reagents. Throughout my career I found research a humbling process, and could only evaluate my performance on the basis of what we might uncover next, rather than what we might have already discovered.

You mentioned critical steps:

- *I had hypothesized on how the immune system made decisions, whether to attack and destroy, or become tolerant. Monoclonal antibodies provided tools to test these hypotheses with the view to providing short-term therapeutic interventions in immunological diseases to gain long-term benefit.*
- *We generated antibodies to both, mouse and human lymphoid cells, so that we could always run basic and clinical studies in parallel.*
- *I was able to attract a fantastic team of enthusiastic young scientists who bought into this ambitious project.*
- *Early on we focused on finding antibodies with appropriate effector functions, and "operational" rather than "precise" specificities. CAMPATH-1 emerged as one of the few antibodies that could utilize the human complement system to kill lymphocytes while sparing stem cells.*

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- *In the early period, there was some pessimism about whether antibodies would be useful drugs, as they were produced in rodents, and would be rejected by humans. All that changed in the late 1980s when, in collaboration with Greg Winter, we were able to convert the rat form of CAMPATH-1 into a humanized form. This was the first humanized antibody to be injected into patients, and we believe, was a catalyst for the antibody revolution which followed.*
- *We created our own GMP manufacturing facility which allowed us to perform clinical studies based on our best academic information, rather than commercial and institutional considerations that drive the pharmaceutical industry.*
- *We were able to identify many gifted medical collaborators who were able to undertake clinical studies that guided further basic science as well as future clinical application.*
- *All this can be summarized by saying that I do not think CAMPATH-1 could have emerged through the conventional drug discovery route in Pharma, nor through professional opinion-leaders who advise them.*

What would you consider the ideal transplant population benefiting from the treatment with Campath-1?

My experience tells me that it is too early to answer that question, as the outcome depends on how it is used. In general terms I could, at least, say "to encourage drug minimization".

While being a very effective lymphocyte depleting agent, homeostatic proliferation subsequent to Campath-1 treatment requires the 'right' drug combination to reboot the immune system in an optimal way. Can you speculate on an optimal immunosuppressive maintenance therapy applied with Campath-1?

*We are working hard on that ourselves in what we call **P**hysician **A**ided **R**econstitution of the **I**mmune **S**ystem (PARIS). Thus far, we know that some degree of favorable reconstitution can be achieved in rodent models; however, this needs to be a treatment that is as simple as possible based on licensed drugs with known safety profiles. Perhaps a more promising avenue is to ensure that the lymphocyte depletion is "staggered' during the induction phase so as to be less prone to a chaotic rebound. In regard to an optimal maintenance treatment, all I can say at this stage is that we need a regimen that gives an advantage to the reconstitution of cells with strong regulatory properties over conventional immune cells.*

The commercialization of Campath-1 had been an exciting 'adventure' by itself. What have been critical steps?

This has indeed been a special and very educational experience. Some key experiences included:

- *Dealing with unfounded perceptions of opinion leaders, and heads of Pharma with evangelical opinions of what is needed.*
- *Persuading Pharma that profits can be made from short-term therapy rather than prolonged immunosuppression.*
- *Trying to maintain contact with the pharmaceutical companies to be able to express opinions and advise. CAMPATH-1H has been through numerous biotech/pharmaceutical company owners, only one of which (early on) encouraged good 2-way communications. For example, our laboratory demonstrated early on that Lemtrada could be given subcutaneously with less immediate side effects, and much more convenience to the patient. Unfortunately this patient-friendly approach has not been taken up.*

Understanding how Tregs Cells contribute to health disease has been another research interest. How can we best use the knowledge on Tregs Cells to induce tolerance?

To early again, I think, for me to give a wise comment—but my intuition is that we need to understand the privileged microenvironments that Treg cells can establish in tissues, and investigate ways to encourage these. Perhaps we can learn a lot from studying subsets of tumors that resist immune attack.

Looking back to a most productive career in immunological research what do you consider the most relevant 'soft skills' for a successful career in transplantation research?

Indeed a good repertoire of soft skills is critical. Just to name a few:

- *Choose the right partner in your domestic life*
- *Do not let the b…s… grind you down*
- *Run a good team and keep your colleagues fulfilled in their career/life aspirations*
- *Do not believe everything you read, but believe in scientific rigor.*
- *Keep hoping that grant-awarding bodies and journals create a milieu where scientists can adequately pursue and convey their work, without being at the mercy of a few oligarch-transients.*

How do you enjoy spending time away from work? What is intellectually inspiring outside of the laboratory?

Not an easy question—and things change as I get older…a few key observations:

- *As perhaps predicted—spending time with my family and admiring the way they forge their own lives keeps me intellectually stimulated; I hope that our society will find routes to support that ultimate satisfaction in as many as possible.*
- *Listening and playing music by Chopin and Liszt (although nonimmunological neurological issues are a current challenge!)*
- *Reading different views on historical events-which constantly teach me that one should always leave an element of doubt in one's mind on any matter.*
- *Finally—a great enthusiast for DIY around the house (**Do not I**nvolve **Y**ourself)!*