Review

CUTTING EDGE

Regenerative medicine, organ bioengineering and transplantation

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Background: **Organ transplantation is predicted to increase as life expectancy and the incidence of chronic diseases rises. Regenerative medicine-inspired technologies challenge the efficacy of the current allograft transplantation model.**

Methods: **A literature review was conducted using the PubMed interface of MEDLINE from the National Library of Medicine. Results were examined for relevance to innovations of organ bioengineering to inform analysis of advances in regenerative medicine affecting organ transplantation. Data reports from the Scientific Registry of Transplant Recipient and Organ Procurement Transplantation Network from 2008 to 2019 of kidney, pancreas, liver, heart, lung and intestine transplants performed, and patients currently on waiting lists for respective organs, were reviewed to demonstrate the shortage and need for transplantable organs.**

Results: **Regenerative medicine technologies aim to repair and regenerate poorly functioning organs. One goal is to achieve an immunosuppression-free state to improve quality of life, reduce complications and toxicities, and eliminate the cost of lifelong antirejection therapy. Innovative strategies include decellularization to fabricate acellular scaffolds that will be used as a template for organ manufacturing, three-dimensional printing and interspecies blastocyst complementation. Induced pluripotent stem cells are an innovation in stem cell technology which mitigate both the ethical concerns associated with embryonic stem cells and the limitation of other progenitor cells, which lack pluripotency. Regenerative medicine technologies hold promise in a wide array of fields and applications, such as promoting regeneration of native cell lines, growth of new tissue or organs, modelling of disease states, and augmenting the viability of existing *ex vivo* transplanted organs.**

Conclusion: **The future of organ bioengineering relies on furthering understanding of organogenesis, *in vivo* regeneration, regenerative immunology and long-term monitoring of implanted bioengineered organs.**

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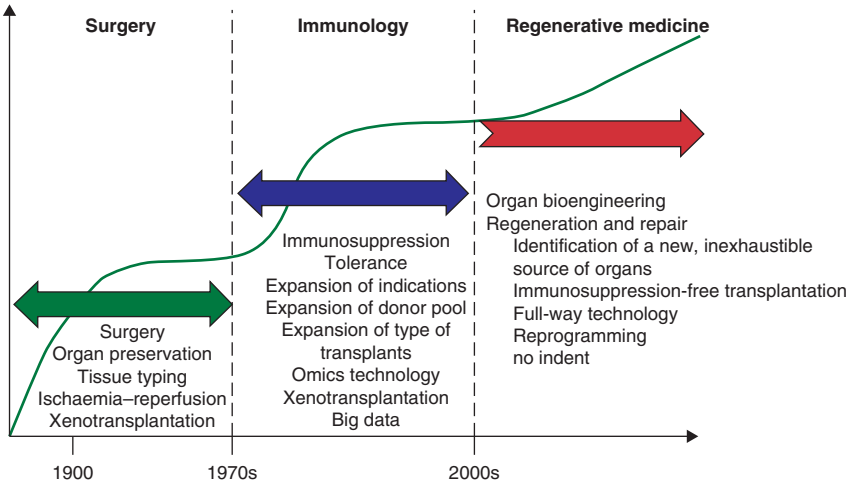
The challenges of organ transplantation have been the overwhelming demand and the ideal of immunosuppression-free strategies[1]. Allocation of donor organs may exhibit racial, sex, age and geographical disparity, and this may worsen as the gap between supply and demand widens[1–5]. Based on the Organ Procurement and Transplant Network database, by the end of 2009, there were 105 567 patients waiting for solid organ transplantation (kidney, pancreas, liver, heart, lung and intestine) and 28 458 transplants performed, whereas by the end of 2019, there were 112 568 patients waiting and 39 718 solid organ transplants performed[6]. Regenerative medicine (RM) is dedicated to replacing and/or repairing tissues and organs for functional restoration, which may represent a solution to these critical challenges.

The history of organ transplantation can be split into three phases, or eras (*Fig. 1*)[7]. The first phase spans from the early days of surgical science (surgery era). Technical feasibility was proven, but outcomes were limited by the lack of effective antirejection therapies until ciclosporin projected the field into the immunology era. On the one hand, immunosuppression allowed transplantation to become the standard of care for many diseases but, on the other, it does so at the cost of side-effects. For

Fig. 1 Phases in the history of organ transplantation



CRISPR, clustered regularly interspaced short palindromic repeats. Reproduced from reference 7 with permission.

this reason, research has focused on strategies to achieve immune tolerance in an immunosuppression-free status (IFS) whereby the recipient accepts an allograft without immunosuppressants. In more recent years, the field has been transitioning into the regenerative era in tandem with other developments, such as big data, exchanged pair donation chains, and transplants across blood groups or among incompatible donors[8–11]. Recent achievements in organ bioengineering and regeneration technologies to manufacture organs from the patient's own cells may offer the genesis of organ-on-demand and IFS.

The long-term management of transplant recipients is focused on reduction in morbidity and mortality and improving quality of life, while balancing side-effects of immunosuppressive drugs with risk of graft failure. Chronic disease management may be termed a halfway technology because the focus is not on cure[12]. Organ transplantation should be considered a halfway technology for two reasons: it does not directly target the underlying disease, and long-term immunosuppression may induce life-changing side-effects. RM may render organ transplantation a full-way technology if medication can be avoided. The feasibility of this approach has been proven with implantation of sections of the urinary tract or upper airways, but it is only a matter of time before complex organs are bioengineered[13–19].

Decellularization is a process in which an acellular extracellular matrix (aECM) scaffold can be obtained by using chemical or physical means to remove cellular components of living tissue[20]. The product of decellularization is a three-dimensional (3D) ultrastructure of ECM that may be used as a natural scaffold for application in tissue engineering and RM[21]. Ideally, the aECM scaffold retains both structural integrity and existing biochemical properties of the native tissue nanostructure. Studies have shown that aECMs exhibit bio-inductive properties comparable to those of native tissue for cellular chemotaxis, including attachment, migration, proliferation and function[22]. These constructs have the advantage of maintaining tissue-specific cell functions and phenotypes to induce host tissue remodelling. Previous studies[23–38] have had success in obtaining aECM scaffolds from virtually all mammalian organs. They preserve the native vasculature for adequate perfusion of constructs able to withstand physiological blood pressures, something that has been a challenge to RM methods relying on progenitor cell embryogenesis[39,40]. Other obstacles include damage to innate ECM during tissue processing or inadequate recellularization of structurally complex organs.

Advantages of 3D printing, as an alternative strategy for organ manufacturing, include automation of construct fabrication, reliable reproducibility, increased resolution and the potential for mass production. Applications of 3D-printed acellular constructs are prolific in orthopaedics and maxillofacial surgery. They are used in preoperative planning, personalized drug delivery, and fabrication of models for use in dentistry, cardiovascular disease, facial plastic and reconstructive surgery, and limb prostheses[19,41–44]. Possibly the most anticipated and exponential applications of 3D printing are those in tissue

engineering, which may collectively be referred to as bioprinting. Biomaterials used for bioprinting constructs compatible with human physiology include both naturally derived polymers (such as alginate, gelatin, collagen, fibrin and hyaluronic acid) and synthetic polymers (for example, polyethylene glycol)[7]. A combination of synthetic and naturally derived polymers produces a functionally superior material that retains both the structural integrity and innate physiological interactions. Current resolution limits of bioprinter technology are 2 μm for acellular constructs, and 50 μm for those that include encapsulated cells[45]. Successful preclinical studies[46–48] have implemented 3D bioprinted cartilage and bone tissues in animal models. It has been difficult to produce vascular, neurological and lymphatic networks in biologically printed constructs, or to maintain viable tissues that exceed 1 cm in thickness[49]. Slow printing speeds and printer resolution restrictions have limited the size of 3D bioprinted constructs so far. It is theorized that current bioprinting techniques lack geometrical complexity owing to insufficient use of multipolymer constructs and multiple cell lines, which consequently extends to inadequate replication of organ vasculature leading to inadequate tissue perfusion.

Use of embryonic stem cells (ESCs) remains one of the earliest forms of RM technologies. ESCs, which are found within the inner cell mass of blastocyst-stage embryos, retain their ability to differentiate into all adult cell types. ESC-based modalities, however, remain limited because of the potential tumorigenic risk, risk of immune rejection, and ethical dilemmas surrounding use of human embryos[7]. Another well described method is the harvesting of mesenchymal stem cells (MSCs) from the patient's bone marrow, periosteum, periodontal ligament or adipose tissue[50]. Initial animal studies[47] suggested that MSC-derived chondrocytes do not retain regeneration abilities and fail to engraft, which limits their practical application in RM therapies. Instead, MSC-based therapies are useful for both direct and indirect stimulation of endogenous repair, relying on paracrine factors to mediate this process[7]. The concept of induced pluripotent stem cells (iPSCs) navigates these challenges by reprogramming somatic stem cells to have the same potential plasticity as ESCs[51].

β-Cell replacement offers a formidable platform for the application of stem cell-based technologies to transplant medicine. A new, potentially inexhaustible source of transplantable insulin-producing cells, β-cells and islets for type 1 diabetes may be available soon[52–54]. Among the RM technologies of interest to transplant medicine, stem cell technology is the one that has the greatest potential for clinical translation (*Table 1*).

Interspecies blastocyst complementation (IBC) is another promising application of iPSCs for the generation of autologous tissue. Targeted removal of cells destined for development of a specific organ allows manipulation of a host blastocyst. This permits insertion of donor iPSCs into the host blastocyst to produce an autologous organ in allogeneic and interspecies circumstances[55,56]. It is possible to use a compatible host (such as pig) to create organs for patients that will retain size, function and adequate vascularization comparable to that of host organs. The IBC method holds potential because of its ease of application and increased viability of engineered tissue in host animals, but has yet to produce complex organs[57,58]. Potential problems include zoonoses, host contamination causing organ rejection, and reverse contamination by the donor iPSCs leading to health problems in the animals.

The toxicity of immunosuppressive drugs not only poses a danger to the patient but is also a significant alloantigen-independent factor in chronic allograft nephropathy. As such, 50 per cent of nephropathic kidney transplants are lost within 10 years secondary to chronic allograft nephropathy[59]. The cost and encumbrance of drugs is very difficult for patients[60–62]. A transplanted organ must be from a genetically identical donor or immunological tolerance must be achieved to get IFS. Complete tolerance has been seen in a small proportion of patients weaned off immunosuppressive drugs[54,63,64], such that IFS is not immediate or necessarily durable[18,65,66]. Bioengineered organs hold promise in achieving IFS; however, the immune reaction to these organs remains largely uncharacterized. Regardless of the fabrication method, bioengineered constructs are composed of two structures: the cellular compartment and the ECM. During implantation of acellular allogeneic and xenogeneic scaffolds, the host immunological response results in an acute cellular infiltrate that includes both neutrophilic and giant cell infiltrations[67]. The cellular component of a bioengineered graft may also trigger an acute rejection response because it is well known that both allogeneic pluripotent stem cells and autologous adult cells may still elicit an inflammatory response after manipulation in culture, even when harvested directly from the host. It has also been suggested that the ECM component of scaffolds retains the ability to induce T cell apoptosis and CD4-positive T cell conversion through innate properties of transforming growth factor β[68–70]. The transition of proinflammatory macrophage phenotype M1 to an M2 phenotype occurring 1–2 weeks after implantation may improve remodelling outcomes by using host tissue remodelling and repair mechanisms[7]. Thus, for successful implantation of bioengineered constructs in host organisms, a balance must be achieved

Table 1 State-of-the-art regenerative medicine technologies

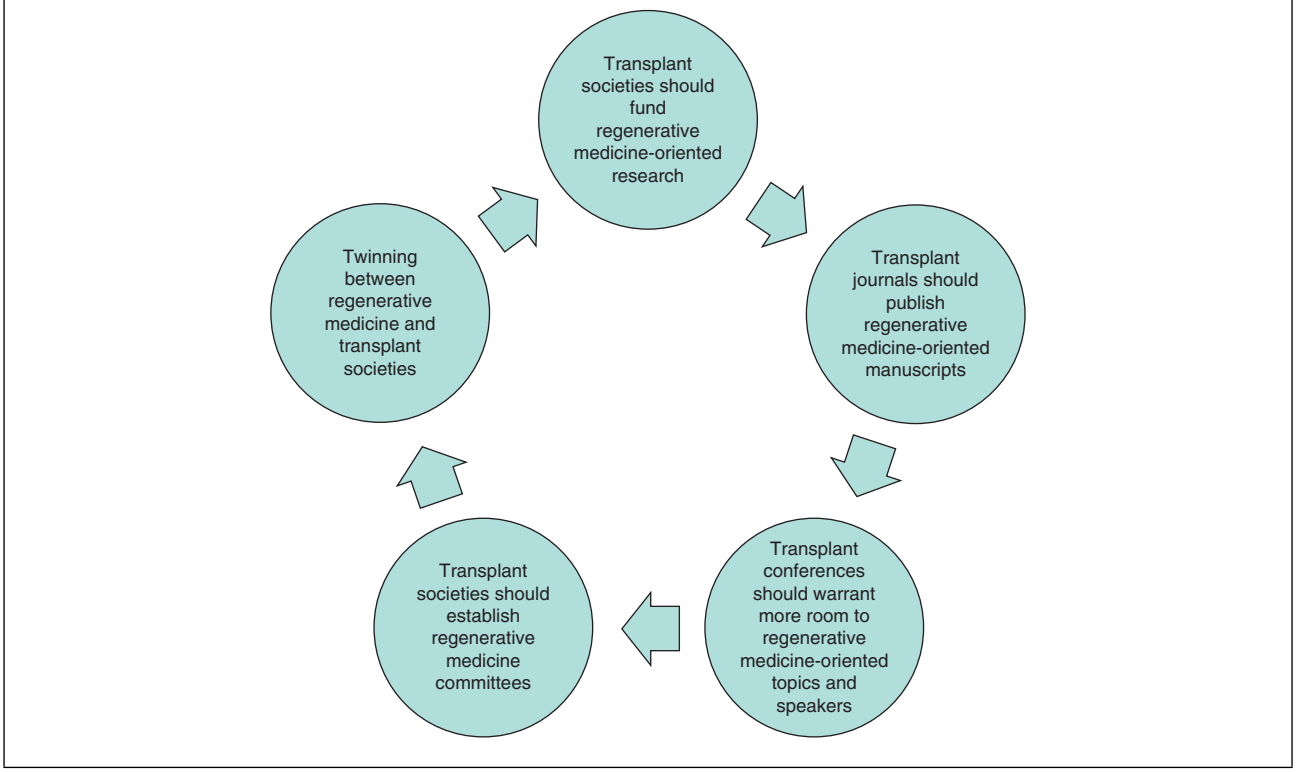
	State of the art	Perspective and hurdles to overcome	Potential for translation within the next decade
Decellularization	Virtually all organs from all clinically relevant mammalian species including humans can be decellularized to obtain acellular ECM scaffolds Acellular ECM scaffolds preserve most, yet not all, molecular and physical characteristics of the innate ECM, as the decellularization process damages the ECM to an extent that depends on the method and organ Partial regeneration of endothelial and parenchymal compartments has been reported, yet results are inconsistent and difficult to reproduce The maturation phase reported in the literature for different organs was always far inferior to the time needed *in utero* to develop the organs in question Implantation *in vivo* of a viable and functioning bioengineered organ has never been reported	In-depth understanding of mechanisms underlying organ development, regeneration and homeostasis In-depth understanding of the mechanisms of ECM scaffold–cell interactions Cell selection for recellularization Harmonious harnessing of lymphatic, nervous and vascular components Improving the design of *ad hoc* bioreactors to support maturation Strategies to achieve adequate recellularization	Low, not in the foreseeable future for solid organs like kidneys, hearts, etc.
3D printing	Successful isolation and expansion of many functional and supportive cell types Replication of mechanical and biophysical properties of simple tissues at the macro level Bioprinting of cells with natural and synthetic biomaterials with high resolution Implantation and *in vivo* maturation of small avascular tissues	Production of an adequate number of regeneration-competent cells that do not elicit an immune response following transplantation ECM-based materials that provide much stronger mechanical strength while maintaining cell-supportive environment Improvements in speed, resolution, material flexibility and scalability of bioprinters Bioprinting of multiscale vascular networks within instructive bioink that promotes angiogenic sprouting and neovascularization	Low, likely not in the foreseeable future
Stem cells	Generation of various types of complex organoids *in vitro* (e.g. renal, liver, heart, pancreas) from different strains of human progenitors including iPSCs Generation of human pancreatic tissue *in vivo* following transplantation of multipotent progenitor-derived organoids in mice Multipotent progenitors can be generated from individual patients, circumventing the need for immunosuppressants after transplantation	Organoids derived from multipotent progenitors typically resemble fetal tissues/organs and are unlikely to mature into functioning adult organs Organoids derived from multipotent progenitors that are generated *in vitro* do not have the blood vessels, lymphatics and neuronal innervation required to function *in vivo*	High, likely within the next decade
IBC	Development of functional rat pancreas following IBC of *Pdx1*−/− mouse blastocysts Generation of a biallelic knockout in pigs using nuclease-based genome editing shows it could be possible to generate pig embryos for IBC that lack specific organs Development of mouse–human and pig–human chimeric embryos using 'primed' human iPSCs	Low yield and efficiency: chimerism is extremely low (< 1%) To improve the efficiency of generating human–pig chimeric embryos, greater understanding is needed of how the status of human iPSCs (whether they are naive, primed or intermediate) affects their ability to integrate into postimplantation pig embryos The contribution of human iPSCs to developing pig embryos is limited and it has not yet been possible to generate human organs using IBC Even if the above challenges were addressed, a further problem is that human organs developed using IBC would have pig blood vessels, lymphatics and neuronal innervation, which would lead to immune rejection	Low, likely not in the foreseeable future

Table 1 Continued

	State of the art	Perspective and hurdles to overcome	Potential for translation within the next decade
RM for ischaemia–reperfusion	Multiple candidate cell populations showing efficacy beyond previous small molecule alternatives Emerging evidence of favourable biodistribution avoiding off-site effects Natural organ architecture available in transplant context Complementary benefits with normothermic *ex vivo* perfusion	Obtaining adequate numbers of point-of-care-derived autologous cells Obtaining adequate numbers of efficacious, non-immunogenic GLP-manufactured allogeneic cells Reassurance regarding potential vascular/microvascular complications	High, likely within the next decade

ECM, extracellular matrix; 3D, three-dimensional; iPSC, induced pluripotent stem cell; IBC, interspecies blastocyst complementation; RM, regenerative medicine; GLP, good laboratory practice.

Fig. 2 Strategies to bring the two fields of regenerative and transplant medicine together



between subduing an immune response to the introduction of a foreign body while retaining an immunological response to augment host regenerative processes.

Ante litteram, transplant medicine has applied RM concepts since the dawn of the modern era. All attempts to minimize organ damage – from procurement, storage/transportation to implantation – are strategies to enhance tissue repair and function. *Ex vivo* lung perfusion allowed a quadrupling of transplantable lungs by encouraging 'marginal' organs to achieve better functional reserve in a modern world. In order for the organ to be repaired, numerous therapies are being investigated, among which are the *in situ* delivery of interleukin (IL) 10 or the infusion of MSCs[71]. RM therapies may augment existing organ transplantation by reducing need for donor tissue and increasing the viability of tissue *ex vivo*. Selected RM technologies are currently in phase I and Ib clinical trial studies, including the first RM therapeutic drug (MSI-1436) for myocardial tissue repair[72]. A preclinical large animal study[73] has investigated the use of *in situ*

delivery of IL-10 to repair injured donor lungs *ex vivo* for transplantation, and combat ischaemia–reperfusion injury.

RM may be the new frontier for transplant medicine[74]. Transplant conferences are now incorporating sessions on RM and tissue engineering (*Fig. 2*). Transplant societies are funding tissue engineering-driven research and launching RM committees. The Cell Transplant Society, a sister society to The Transplant Society, was founded in 1992 and has been quite active ever since. As RM progressed, the name of the society was recently changed to its current Cell Transplant and Regenerative Medicine Society[75]. The American Society of Transplantation established the Transplant Regenerative Medicine Community of Practice[76] at the World Transplant Conference held in San Francisco in 2014, and the European Society for Organ Transplantation inaugurated the European Cell Therapy and Organ Regeneration Section[77] in 2019, at its biannual congress held in Copenhagen, Denmark.

Disclosure

The authors declare no conflict of interest.

References

1 Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S *et al.* OPTN/SRTR 2017 annual data report: kidney. *Am J Transplant* 2019; **19**: 19–123.

2 Perico N, Remuzzi G. Chronic kidney disease: a research and public health priority. *Nephrol Dial Transplant* 2012; **27**: iii19–iii26.

3 McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD incidence and prevalence in the United States through 2030. *J Am Soc Nephrol* 2019; **30**: 127–135.

4 Wedd J, Basu M, Curtis LM, Smith K, Lo DJ, Serper M *et al.* Racial, ethnic, and socioeconomic disparities in web-based patient portal usage among kidney and liver transplant recipients: cross-sectional study. *J Med Internet Res* 2019; **21**: e11864.

5 OPTN/SRTR 2018 annual data report. Introduction. *Am J Transplant* 2020; **20**: 11–19.

6 Organ Procurement and Transplantation Network. https://optn.transplant.hrsa.gov/ [accessed 9 April 2020].

7 Orlando G, Murphy SV, Bussolati B, Clancy M, Cravedi P, Migliaccio G *et al.* Rethinking regenerative medicine from a transplant perspective (and vice versa). *Transplantation* 2019; **103**: 237–249.

8 Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L *et al.* Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med* 2016; **374**: 333–343.

9 Massie AB, Kucirka LM, Kuricka LM, Segev DL. Big data in organ transplantation: registries and administrative claims. *Am J Transplant* 2014; **14**: 1723–1730.

10 Bozek DN, Dunn TB, Kuhr CS, Marsh CL, Rogers J, Rees SE *et al.* Complete chain of the first global kidney exchange transplant and 3-yr follow-up. *Eur Urol Focus* 2018; **4**: 190–197.

11 Orandi BJ, Luo X, Massie AB, Garonzik-Wang JM, Lonze BE, Ahmed R *et al.* Survival benefit with kidney transplants from HLA-incompatible live donors. *N Engl J Med* 2016; **374**: 940–950.

12 Asch DA, Volpp KG. Reimagining halfway technologies with behavioral science. *Ann Intern Med* 2017; **167**: 505–506.

13 Orlando G, Bendala JD, Shupe T, Bergman C, Bitar KN, Booth C *et al.* Cell and organ bioengineering technology as applied to gastrointestinal diseases. *Gut* 2013; **62**: 774–786.

14 Orlando G, Wood KJ, De Coppi P, Baptista PM, Binder KW, Bitar KN *et al.* Regenerative medicine as applied to general surgery. *Ann Surg* 2012; **255**: 867–880.

15 Orlando G, Baptista P, Birchall M, De Coppi P, Farney A, Guimaraes-Souza NK *et al.* Regenerative medicine as applied to solid organ transplantation: current status and future challenges. *Transpl Int* 2011; **24**: 223–232.

16 Orlando G, Wood KJ, Stratta RJ, Yoo JJ, Atala A, Soker S. Regenerative medicine and organ transplantation: past, present, and future. *Transplantation* 2011; **91**: 1310–1317.

17 Orlando G. Transplantation as a subfield of regenerative medicine. Interview by Lauren Constable. *Expert Rev Clin Immunol* 2011; **7**: 137–141.

18 Orlando G, Wood KJ, Soker S, Stratta RJ. How regenerative medicine may contribute to the achievement of an immunosuppression-free state. *Transplantation* 2011; **92**: e36–e38.

19 Hsieh T-Y, Dedhia R, Cervenka B, Tollefson TT. 3D printing: current use in facial plastic and reconstructive surgery. *Curr Opin Otolaryngol Head Neck Surg* 2017; **25**: 291–299.

20 Gupta SK, Mishra NC, Dhasmana A. Decellularization methods for scaffold fabrication. *Methods Mol Biol* 2018; **1577**: 1–10.

21 Edgar L, McNamara K, Wong T, Tamburrini R, Katari R, Orlando G. Heterogeneity of scaffold biomaterials in tissue engineering. *Materials (Basel)* 2016; **9**: 332.

22 Saldin LT, Cramer MC, Velankar SS, White LJ, Badylak SF. Extracellular matrix hydrogels from decellularized tissues: structure and function. *Acta Biomater* 2017; **49**: 1–15.

23 Law JX, Liau LL, Aminuddin BS, Ruszymah BHI. Tissue-engineered trachea: a review. *Int J Pediatr Otorhinolaryngol* 2016; **91**: 55–63.

24 Song JS, Takimoto K, Jeon M, Vadakekalam J, Ruparel NB, Diogenes A. Decellularized human dental pulp as a scaffold for regenerative endodontics. *J Dent Res* 2017; **96**: 640–646.

25 Wang S, Wang Y, Song L, Chen J, Ma Y, Chen Y *et al.* Decellularized tendon as a prospective scaffold for tendon repair. *Mater Sci Eng C Mater Biol Appl* 2017; **77**: 1290–1301.

26 Chani B, Puri V, Sobti RC, Jha V, Puri S. Decellularized scaffold of cryopreserved rat kidney retains its recellularization potential. *PLoS One* 2017; **12**: e0173040.

27 Gupta SK, Kumar R, Mishra NC. Influence of quercetin and nanohydroxyapatite modifications of decellularized goat-lung scaffold for bone regeneration. *Mater Sci Eng C Mater Biol Appl* 2017; **71**: 919–928.
28 Chen G, Lv Y. Decellularized bone matrix scaffold for bone regeneration. *Methods Mol Biol* 2018; **1577**: 239–254.
29 Faust A, Kandakatla A, van der Merwe Y, Ren T, Huleihel L, Hussey G *et al.* Urinary bladder extracellular matrix hydrogels and matrix-bound vesicles differentially regulate central nervous system neuron viability and axon growth and branching. *J Biomater Appl* 2017; **31**: 1277–1295.
30 Mellott AJ, Shinogle HE, Nelson-Brantley JG, Detamore MS, Staecker H. Exploiting decellularized cochleae as scaffolds for inner ear tissue engineering. *Stem Cell Res Ther* 2017; **8**: 41.
31 Seo Y, Jung Y, Kim SH. Decellularized heart ECM hydrogel using supercritical carbon dioxide for improved angiogenesis. *Acta Biomater* 2018; **67**: 270–281.
32 VeDepo MC, Detamore MS, Hopkins RA, Converse GL. Recellularization of decellularized heart valves: progress toward the tissue-engineered heart valve. *J Tissue Eng* 2017; **8**: 2041731417726327.
33 Gu Y, Wang F, Wang R, Li J, Wang C, Li L *et al.* Preparation and evaluation of decellularized porcine carotid arteries cross-linked by genipin: the preliminary results. *Cell Tissue Bank* 2018; **19**: 311–321.
34 Crapo PM, Gilbert TW, Badylak SF. An overview of tissue and whole organ decellularization processes. *Biomaterials* 2011; **32**: 3233–3243.
35 Shan Z, Lin X, Wang S, Zhang X, Pang Y, Li S *et al.* An injectable nucleus pulposus cell-modified decellularized scaffold: biocompatible material for prevention of disc degeneration. *Oncotarget* 2017; **8**: 40 276–40 288.
36 Duisit J, Maistriaux L, Taddeo A, Orlando G, Joris V, Coche E *et al.* Bioengineering a human face graft: the matrix of identity. *Ann Surg* 2017; **266**: 754–764.
37 Mirmalek-Sani SH, Orlando G, McQuilling JP, Pareta R, Mack DL, Salvatori M *et al.* Porcine pancreas extracellular matrix as a platform for endocrine pancreas bioengineering. *Biomaterials* 2013; **34**: 5488–5495.
38 Duisit J, Amiel H, Wüthrich T, Taddeo A, Dedriche A, Destoop V *et al.* Perfusion-decellularization of human ear grafts enables ECM-based scaffolds for auricular vascularized composite tissue engineering. *Acta Biomater* 2018; **73**: 339–354.
39 Song JJ, Ott HC. Organ engineering based on decellularized matrix scaffolds. *Trends Mol Med* 2011; **17**: 424–432.
40 Kim JJ, Hou L, Huang NF. Vascularization of three-dimensional engineered tissues for regenerative medicine applications. *Acta Biomater* 2016; **41**: 17–26.
41 Witowski JS, Coles-Black J, Zuzak TZ, Pędziwiatr M, Chuen J, Major P *et al.* 3D printing in liver surgery: a systematic review. *Telemed J E Health* 2017; **23**: 943–947.
42 Giannopoulos AA, Mitsouras D, Yoo SJ, Liu PP, Chatzizisis YS, Rybicki FJ. Applications of 3D printing in cardiovascular diseases. *Nat Rev Cardiol* 2016; **13**: 701–718.
43 Liaw CY, Guvendiren M. Current and emerging applications of 3D printing in medicine. *Biofabrication* 2017; **9**: 024102.
44 Ten Kate J, Smit G, Breedveld P. 3D-printed upper limb prostheses: a review. *Disabil Rehabil Assist Technol* 2017; **12**: 300–314.
45 Kang HW, Lee SJ, Ko IK, Kengla C, Yoo JJ, Atala A. A 3D bioprinting system to produce human-scale tissue constructs with structural integrity. *Nat Biotechnol* 2016; **34**: 312–319.
46 Cui X, Breitenkamp K, Finn MG, Lotz M, D'Lima DD. Direct human cartilage repair using three-dimensional bioprinting technology. *Tissue Eng Part A* 2012; **18**: 1304–1312.
47 Markstedt K, Mantas A, Tournier I, Martínez Ávila H, Hägg D, Gatenholm P. 3D bioprinting human chondrocytes with nanocellulose–alginate bioink for cartilage tissue engineering applications. *Biomacromolecules* 2015; **16**: 1489–1496.
48 Kundu J, Shim JH, Jang J, Kim SW, Cho DW. An additive manufacturing-based PCL–alginate–chondrocyte bioprinted scaffold for cartilage tissue engineering. *J Tissue Eng Regen Med* 2015; **9**: 1286–1297.
49 Murphy SV, Atala A. 3D bioprinting of tissues and organs. *Nat Biotechnol* 2014; **32**: 773–785.
50 Gamie Z, MacFarlane RJ, Tomkinson A, Moniakis A, Tran GT, Gamie Y *et al.* Skeletal tissue engineering using mesenchymal or embryonic stem cells: clinical and experimental data. *Expert Opin Biol Ther* 2014; **14**: 1611–1639.
51 Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. *Nature* 2007; **448**: 313.
52 Kelly OG, Chan MY, Martinson LA, Kadoya K, Ostertag TM, Ross KG *et al.* Cell-surface markers for the isolation of pancreatic cell types derived from human embryonic stem cells. *Nat Biotechnol* 2011; **29**: 750–756.
53 Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S *et al.* Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*. *Nat Biotechnol* 2008; **26**: 443–452.
54 Veres A, Faust AL, Bushnell HL, Engquist EN, Kenty JH, Harb G *et al.* Charting cellular identity during human *in vitro* β-cell differentiation. *Nature* 2019; **569**: 368–373.
55 Matsunari H, Nagashima H, Watanabe M, Umeyama K, Nakano K, Nagaya M *et al.* Blastocyst complementation generates exogenic pancreas *in vivo* in apancreatic cloned pigs. *Proc Natl Acad Sci USA* 2013; **110**: 4557–4562.
56 Chang AN, Liang Z, Dai HQ, Chapdelaine-Williams AM, Andrews N, Bronson RT *et al.* Neural blastocyst complementation enables mouse forebrain organogenesis. *Nature* 2018; **563**: 126–130.
57 Yamaguchi T, Sato H, Kato-Itoh M, Goto T, Hara H, Sanbo M *et al.* Interspecies organogenesis generates autologous functional islets. *Nature* 2017; **542**: 191–196.

58 Wu J, Greely HT, Jaenisch R, Nakauchi H, Rossant J, Belmonte JCI. Stem cells and interspecies chimaeras. *Nature* 2016; **540**: 51–59.

59 Coulson MT, Jablonski P, Howden BO, Thomson NM, Stein AN. Beyond operational tolerance: effect of ischemic injury on development of chronic damage in renal grafts. *Transplantation* 2005; **80**: 353–361.

60 Karam VH, Gasquet I, Delvart V, Hiesse C, Dorent R, Danet C *et al.* Quality of life in adult survivors beyond 10 years after liver, kidney, and heart transplantation. *Transplantation* 2003; **76**: 1699–1704.

61 Karam V, Sebagh M, Rifai K, Yilmaz F, Bhangui P, Danet C *et al.* Quality of life 10 years after liver transplantation: the impact of graft histology. *World J Transplant* 2016; **6**: 703–711.

62 Galbraith CA, Hathaway D. Long-term effects of transplantation on quality of life. *Transplantation* 2004; **77**: S84–S87.

63 Orlando G. Finding the right time for weaning off immunosuppression in solid organ transplant recipients. *Expert Rev Clin Immunol* 2010; **6**: 879–892.

64 Orlando G, Hematti P, Stratta RJ, Burke GW III, Di Cocco P, Pisani F *et al.* Clinical operational tolerance after renal transplantation: current status and future challenges. *Ann Surg* 2010; **252**: 915–928.

65 Orlando G, Soker S, Wood K. Operational tolerance after liver transplantation. *J Hepatol* 2009; **50**: 1247–1257.

66 Tisone G, Orlando G, Angelico M. Operational tolerance in clinical liver transplantation: emerging developments. *Transpl Immunol* 2007; **17**: 108–113.

67 Wilshaw SP, Kearney J, Fisher J, Ingham E. Biocompatibility and potential of acellular human amniotic membrane to support the attachment and proliferation of allogeneic cells. *Tissue Eng Part A* 2008; **14**: 463–472.

68 Cravedi P, Farouk S, Angeletti A, Edgar L, Tamburrini R, Duisit J *et al.* Regenerative immunology: the immunological reaction to biomaterials. *Transpl Int* 2017; **30**: 1199–1208.

69 Scheiner ZS, Talib S, Feigal EG. The potential for immunogenicity of autologous induced pluripotent stem cell-derived therapies. *J Biol Chem* 2014; **289**: 4571–4577.

70 Zakrzewski JL, van den Brink MRM, Hubbell JA. Overcoming immunological barriers in regenerative medicine. *Nat Biotechnol* 2014; **32**: 786–794.

71 Brasile L, Henry N, Orlando G, Stubenitsky B. Potentiating renal regeneration using mesenchymal stem cells. *Transplantation* 2019; **103**: 307–313.

72 Smith AM, Maguire-Nguyen KK, Rando TA, Zasloff MA, Strange KB, Yin VP. The protein tyrosine phosphatase 1B inhibitor MSI-1436 stimulates regeneration of heart and multiple other tissues. *NPJ Regenerat Med* 2017; **2**: 4.

73 Cypel M, Liu M, Rubacha M, Yeung JC, Hirayama S, Anraku M *et al.* Functional repair of human donor lungs by IL-10 gene therapy. *Sci Transl Med* 2009; **1**: 4ra9.

74 Orlando G, Soker S, Stratta RJ. Organ bioengineering and regeneration as the new Holy Grail for organ transplantation. *Ann Surg* 2013; **258**: 221–232.

75 Cell Transplant and Regenerative Medicine Society; Fisher RA. *President's Message*. https://www.tts.org/ctrms-about/ctrms-presidents-message [accessed 5 March 2020].

76 American Society of Transplantation. *Transplant Regenerative Medicine Community of Practice (TRM COP)*. https://www.myast.org/communities-practice/transplant-regenerative-medicine-community-practice-trm-cop [accessed 5 March 2020].

77 European Society for Organ Transplantation/European Cell Therapy and Organ Regeneration Section. https://www.esot.org/ECTORS/home [accessed 5 March 2020].

European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM
ETHICON

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM
Medtronic
Further,Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM
INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM
BD

15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM
Takeda

17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration **www.colorectalsurgery.eu**