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Technologies in kidney development or replacement

Extracellular matrix scaffolds as a platform for kidney regeneration

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ABSTRACT

Chronic and end stage renal disease (ESRD) have reached pandemic levels and pose a substantial public health burden. Unfortunately, available therapies lack efficacy in preventing progression to its end stage phase. Regenerative medicine promises to restore function of diseased organs among which the kidney, through two possible approaches: firstly, the maximization of the innate ability of tissues to repair or regenerate following injury; secondly, the *ex vivo* bio-fabrication of the organ in question. When regenerative medicine is applied to the setting of chronic or ESRD, it is intuitive that endeavors to improve renal repair, promote nephrogenesis in damaged kidneys, or the *de novo* engineering of transplantable kidneys, could have a major impact on the current management of this pandemic. Among the different regenerative medicine technologies currently under development, cell-on-scaffold seeding technology (CSST) – involving cells seeded throughout supporting scaffold structures made from biomaterials – is the most favorable candidate in the context of realistic clinical application. In this review, we outline and describe current investigations taking place in the field of CSST as it pertains to the restoration of kidney function.

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1. Introduction

As of March 6th, 2016, 121,576 patients are registered on the organ transplant waiting list in the US (https://optn.transplant.hrsa.gov/, accessed on April the 15th 2016). This number increases by 5% every year, with one more patient being added to the list every ten minutes. In 2015, 30,973 transplants were performed and they were made possible by the generous consent granted from families of 15,064 donors. On average, 21 people die every day, while waiting for a transplant. Moreover, because transplantation can often be the solution to many of the diseases associated with aging, the hidden demand is estimated to be far beyond current levels. It therefore becomes evident that the lack of donor organs is considered a major health crisis that dramatically impacts the finances of any given country, if we consider that the market for organ failure treatments is estimated at about $80 billion per year. Importantly, this critical situation has been a major driving force behind the rise of regenerative medicine (RM) in the past decades. This term refers to a field within the health sciences that aims at repairing, regenerating or replacing functionally impaired human cells, tissues, or organs to ultimately restore or establish normal function (Katari et al., 2015). Regeneration of physiological systems and structures (*e.g.* organs) can occur *in vivo* or *ex vivo*. This process may require cells, natural or artificial scaffolding materials, growth factors and/or gene editing. Indeed, sometimes a combination of these elements is required (Orlando et al., 2011). Given the immense potential that RM has shown to meet the most urgent needs of organ transplantation, RM is becoming a field of major interest and research investment for the transplant community (Orlando et al., 2013a, 2013b; Orlando and Walker, 2014; Rogers et al., 2016), as well as for related specialties of health sciences like nephrology (Morales et al., 2014).

Chronic and end stage renal disease (ESRD) have reached pandemic levels and pose a substantial public health burden (Liyanage et al., 2015). Unfortunately, etiology and pathophysiology are unclear and treatment is often inadequate. Ideally, patients with chronic kidney disease should receive treatment strategies aimed at counteracting disease causes and mechanisms and

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enhancing intrinsic processes of repair and regeneration. For patients with ESRD, the best treatment option is kidney transplantation, which nevertheless, is dramatically limited by an inadequate supply of transplantable grafts and by the heavy toxicity related to lifelong immunosuppression.

Tissue engineering is a subfield of RM that aims at restoring function of diseased organs mainly through two possible approaches: firstly, the maximization of the innate ability of tissues to repair or regenerate following injury; secondly, the *ex vivo* biofabrication of a diseased organ. When tissue engineering is applied to the setting of chronic or ESRD, it is intuitive that endeavors to improve renal repair, promote nephrogenesis in damaged kidneys, or fabricate transplantable kidneys, could have a major impact on the management of this pandemic.

2. Tissue engineering approaches to kidney repair, regeneration and replacement

The technologies that are currently being developed in order to meet the ultimate objectives of kidney tissue engineering – namely, repair, regeneration and replacement of terminally diseased kidneys with new functioning ones – may be scholastically subtyped in five categories: cell-on-scaffold seeding technology (Salvatori et al., 2014), developmental biology, stem cell, 3D printing and kidney-on-a-chip technology (Table 1).

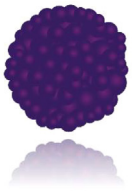
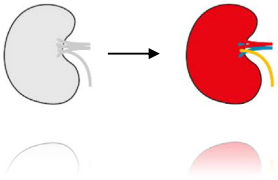
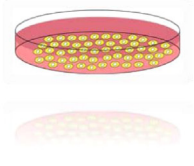
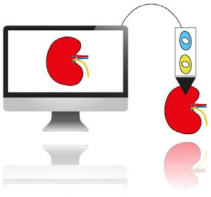
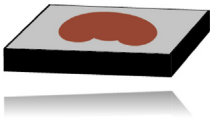
2.1. Cell on scaffold seeding technology (CSST)

This technology is centered upon the idea to regenerate the cellular compartment of a given tissue or organ, via the seeding of cells on- or into supporting scaffolding material. The rationale for this lies on the evidence that ECM's molecular, physical and architectural characteristics are critical for the differentiation, proliferation, welfare, and migration of cells within any given tissue. In other words, cells do well only when they reside in their natural niche represented by the innate ECM that Mother Nature has engineered for them.

Scaffolds may be either synthetic or natural. Natural scaffolds are obtained from animal (including human) organs through a process called decellularization, whereby the cellular compartment of the organ in question is destroyed and cell remnants are cleared from the remaining extracellular matrix (ECM) scaffold. The rationale for using natural scaffolds lies on the evidence that

Table 1
The table summarized the state of the art of the five RM technologies as they are being applied to kidney disease.

Regenerative Medicine Solution for Kidney Bioengineering

Renal Organoids	Re-Cellularised Scaffold	Stem Cell Technology	3D Printing	Kidney On-A-Chip
				
Key Strengths: - Self-Organising - Easy to Generate **Key Weaknesses:** - Unlikely to provide sufficient filtration - Difficult to connect to host's excretory system **Potential for translation in next 10 years**: -Moderate	**Key Strengths:** - Native ECM induces RPC differentiation - Microarchitecture conserved - Easy connection to host excretory system **Key Weaknesses:** - Difficult to achieve complete Re-Cellularisation **Potential for translation in next 10 years**: -High	**Key Strengths:** - Autologus SCs can be cultured if Cell Therapy is needed - SCs can be cultured to understand their growth, development and differentiation - Useful for Drug Screening **Key Weaknesses:** - Ethical limitation - Difficult to achieve consistent results in terms of regeneration and repair **Potential for translation in next 10 years**: -Low	**Key Strengths:** - ECM and Cells printed together (solves problem of re-cellularisation) - Consistent Reproducibility **Key Weaknesses:** - Printed ECM unlikely to induce differentiation of RPCs - Not yet technically feasible **Potential for translation in next 10 years**: -Moderate	**Key Strengths:** - Native ECM induces RPC differentiation - Easy to replicate - Drug screening **Key Weaknesses:** - Not feasible for connection to host excretory system - Microarchitecture not conserved - Sufficient Oxygenation may be difficult and may not consistent throughout the chip **Potential for translation in next 10 years**: -Moderate

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