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Convergence of regenerative medicine and synthetic biology to develop standardized and validated models of human diseases with clinical relevance

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In order to progress beyond currently available medical devices and implants, the concept of tissue engineering has moved into the centre of biomedical research worldwide. The aim of this approach is not to replace damaged tissue with an implant or device but rather to prompt the patient's own tissue to enact a regenerative response by using a tissue-engineered construct to assemble new functional and healthy tissue. More recently, it has been suggested that the combination of Synthetic Biology and translational tissue-engineering techniques could enhance the field of personalized medicine, not only from a regenerative medicine perspective, but also to provide frontier technologies for building and transforming the research landscape in the field of *in vitro* and *in vivo* disease models.

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Introduction

Personalized or individualized medicine has evolved as a paradigm that aims to transform translational research into a patient-specific concept, which incorporates tailored diagnostic measures, disease prevention and customized targeted therapies [1]. In recent times, personalized medicine has received unprecedented attention from both clinicians and scientists [2] and its fundamental philosophies and values have found their way into the wider biomedicine field. This field, however, is still relatively new as modern medical research becomes focused on identifying and delivering targeted therapies to the patients most likely to respond. Tissue Engineering and Regenerative Medicine (TE&RM) is a growing field, emerging from the end of the 20th and now into the 21st century, which aims to augment the intrinsic processes of the body involved in repair and/or regeneration of injured or dysfunctional tissues, or even entire organs [3•,4–6]. Tissue engineers have also recently sought the translation of TE&RM strategies in other biomedical research areas to develop customized diagnostic and therapeutic strategies for patients suffering from cancer or other diseases [7••,8]. Synthetic Biology is placed in the context of the industrial translational process of bioengineering and a critical aspect of the field is the standardization of experimental protocols and platform technology development. This concise review presents the rationale and a broad overview of the significant potential of tissue engineering strategies for the development of personalized, clinically relevant *in vitro* and *in vivo* models.

It is evident from the most recent literature that successful translational of discovery research relies on having appropriate model systems — both *in vitro* and *in vivo* — to recapitulate and study diseases in order to develop novel diagnostic tools and/or therapeutic strategies. However, recent data also clearly demonstrates that current conventional models are not able to sufficiently recapitulate human disease and the value and relevance of current models is increasingly evaluated in this context. This is particularly apparent in drug development and testing, where it has been shown that more than 80% of drugs that enter clinical studies are ineffective despite previous

successful preclinical testing [9]. For the other 20% it has been estimated that it takes more than 10 years and on average $1 billion USD to get their regulatory approval [10]. Given the time and expense required to develop a novel drug and bring it to the market, the present process is ineffective.

Over the last decade there has been remarkable progress within the fields of TE&RM and Synthetic Biology which now makes patient-specific *in vitro* or *in vivo* models a distinct possibility, something that was only recently thought all but impossible [11]. The conceptualization of Synthetic Biology arose in the late 1990s, inspired by proposals from tissue regeneration, bio-sensing, and mathematical programming. One of the primary goals of Synthetic Biology is to create or add functionality to biological systems by constructing new parts, or modifying existing biological systems under the umbrella of standardization of experimental protocols [12]. This field has undergone considerable growth, and it can now be argued that, in the 21st century, the definition of Synthetic Biology has grown to be synonymous with Biological Engineering and Biotechnology [13].

From a translational medicine point of view, new disease models are developed to enhance the efficacy of existing platforms and accelerate the translation of novel therapeutic options from bench to bedside [14]. The basic principle behind these models is to use the patient's own cells, culturing them with other cells and factors derived from their natural microenvironment in order to engineer a three-dimensional (3D) system that replicates a certain stage of the disease. These modular and scalable platforms can incorporate diseased cells or cancer cells to test their responsiveness toward new drug candidates and eventually develop more personalized treatment strategies for patients [15].

Importantly, this approach can also be extended to *in vivo* applications with the advantage of being able to mimic multi-cellular interactions and dynamic processes involved in disease development [16]. A relatively new but very promising approach is to generate humanized mice by integrating TE&RM and Synthetic Biology concepts into their design and developmental process. With these mice, it is not only possible to study diseased human cells *in vivo*, but also to investigate their behaviour within humanized organ systems, ultimately producing data that more accurately predicts the results in human medicine [17–19].

Conceptualization of disease models

The design and process of building a clinically relevant model platform is challenging and involves multiple critical steps that are necessary to experimentally replicate a disease and/or stages of a disease. A model does not have to be an exact replica of an entire disease pattern — and will most likely never be — yet it does have to be able to mimic the essential key components to study the biological and clinical question being asked. Since the biological reality of a disease is always complex, in our view, it necessitates the development of modular technology platforms, rather than analysis of isolated steps, in order to answer clinically relevant questions. However, the establishment of customized and personalized disease models is not always straightforward and so far these platforms cannot be seen as the 'Rosetta Stone' of translational research.

Understanding and identifying the key features of a disease is a *conditio sine qua non* and the following important questions have to be answered before the modelling process can be started [20]. What are the organs, tissues, key cell populations, molecular pathways and factors involved in the disease development? How are the cells arranged within their native 3D microenvironment? How do they interact with each other? What are the structural and biophysical characteristics of the microenvironment? Does it harbour homogenous, heterogeneous or hierarchical structures? What is the composition and distribution of extracellular components, such as collagen fibres, proteoglycans, polysaccharides, and so forth? Importantly, the development of patient-specific models requires an additional question: what are the key characteristics of the disease in the particular patient of interest [20]?

In vitro disease models

Many *in vitro* models allow systematic, repetitive, in-depth and quantitative studies of specific physiological and patho-physiological processes to identify critical cellular and molecular contributors to the disease [21]. Modern 21st century three-dimensional (3D) culture models have been shown to mimic the *in vivo* situation more realistically than traditional two-dimensional (2D) monolayer cultures [22,23••,24,25]. Using TE strategies it is now possible to recapitulate complex multicellular structures, cell-to-cell contacts, tissue interfaces, physicochemical properties and blood flow of tissues [26••,27]. Advances in biomaterials science, stem cells, tissue engineering, biotechnology and translational medicine are paving the way to more physiological *in vitro* models that have the potential to not only uncover key biological processes involved in organ physiology and metabolism but also to identify determining factors involved in disease development [28,29]. In the literature, two different methods are used to resemble human tissue *in vitro*, the bottom-up and the top-down approach [30]. In the top-down technology, the cells are cultured on a scaffold; they produce extracellular matrix proteins eventually resembling the desired tissue architecture. At the moment, this technology is at a crossroads because it is challenging to engineer large tissue volumes. This is mainly due to the fact that the engineered tissues have to be properly

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