Balancing Innovation and Research Integrity in Translational Tissue Engineering: A Focus on 3D Printed Scaffolds

Christina Kaliampakou[1], Nefeli Lagopati[2], Costas A. Charitidis[1]

[1] RNanoLab, Research Unit of Advanced, Composite, Nano Materials & Nanotechnology, School of Chemical Engineering, National Technical University of Athens, 9 Heroon, Polytechniou St., Zografos, 15780 Athens, Greece

[2] Laboratory of Biology, Department of Basic Medical Sciences, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece

INTRODUCTION

The Problem: The biomedical **Translational Research is hindered** by the **irreproducibility and inconsistency in published findings**. The "novelty effect", meaning the pursue of innovation, significant or not, emerges as a notable concern, severely impacting scientific practices. Inadequacies in this area are causing increasing concern because of **both their potential impact on human health and the economy** (Fig.1) [1,2].

The Causes: The "novelty effect" is driven by pressing **clinical needs** but also by **societal factors,** like funding**,** generating the development of unreliable solutions [3, 4].

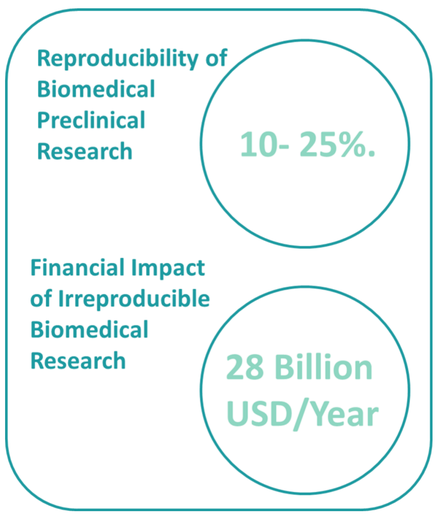

Figure 1. The problem of irreproducibility in Biomedical Preclinical Research [1].

A critical point is the fact that **standardization** needs time. The comparatively slow pace required for standardization of such a complex procedure leads to various technical hurdles. Thus, a **major problem to reproducibility arises**, leading to potential pitfalls in the reliability and consistency of research outcomes (Fig. 2).

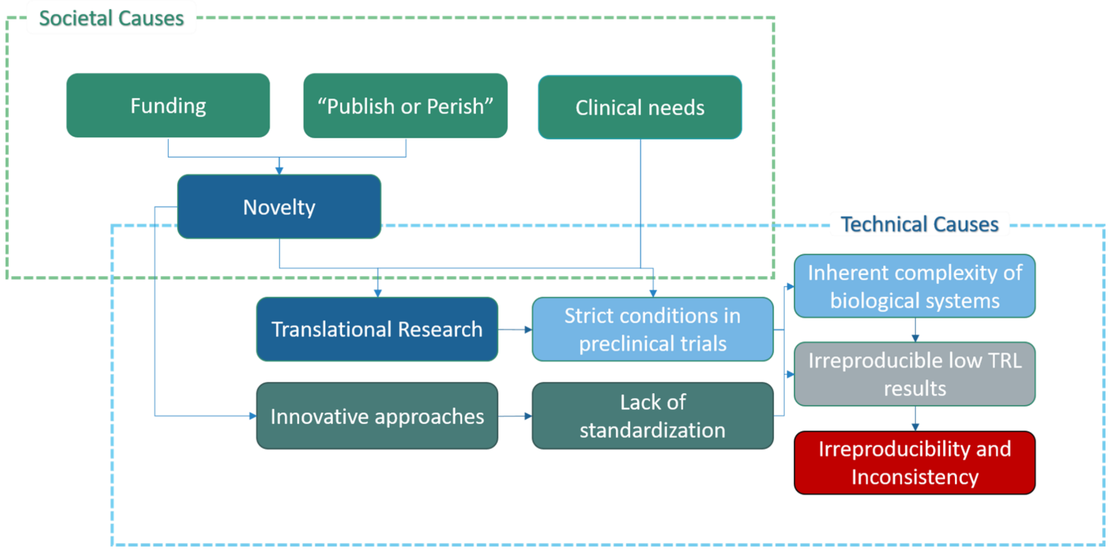

Figure 2. Schematic illustration of societal and technical causes leading to irreproducibility and inconsistency of biomedical research results.

OBJECTIVE

In response to the growing demand for organ transplants worldwide, the field of Tissue Engineering (TE) is witnessing an unmatched need for translational research. The primary objective of this study is to propose approaches aiming **to ensure the reproducibility and integrity of the results presented,** thus strengthening the reliability of research findings.

METHOD

The study focuses on the transformative technology of **Additive Manufacturing** (AM), which has accelerated the development of biomaterial-based structures with intricate geometries (scaffolds) for guiding 3D cell cultures. It is important to distinguish between **fast production** and **effective production** in the context of innovative approaches like 3D Printing (Fig.3). While these methods enable rapid production of scaffolds, they definitely require more than speed alone, namely functionality similar to the targeted tissue, and reproducibility [5].

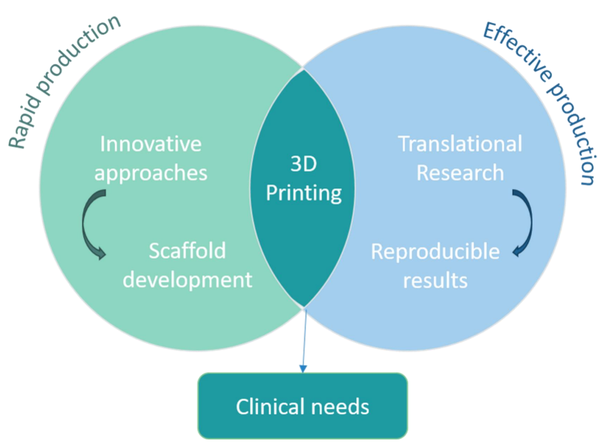

Figure 3. Schematic illustration of requirements for 3D Printing to meet the Clinical Needs.

The study of the printed scaffold in standard cell culture conditions (37 °C, 5% CO_2, 95% humidity, pH=7.4) in terms of degradation and swelling or when it is co-cultured with cells (viability, attachment, proliferation) is a typical case where the above have been examined and confirmed.

RESULTS

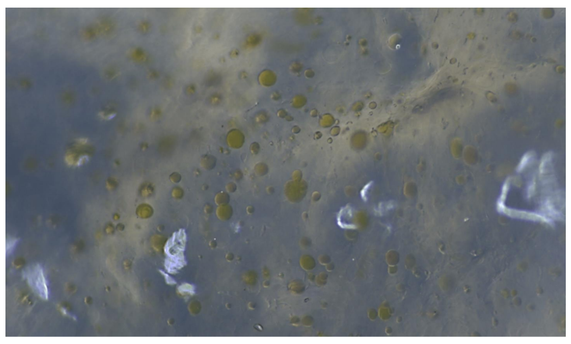

Image 1. Contamination of alginate/gelatin hydrogel scaffold after 7 days of printing.

By examining the relevant research studies all the afore-mentioned problems are well observed and identified, starting from lack of standardization throughout the process, deep variation in terminology, methodology and documentation. I.e. one of the most common problems, the contamination of the scaffold (Image 1,4), has been reported only in very few studies, which definitely compromises the fundamental principles of Research Integrity. Additionally, even the critical pH conditions hardly ever have been monitored.

We also emphasized on studying the results interpretation and presentation that might hinder the fact that the rapid generation of such scaffolds does not automatically guarantee effective scaffold-cell interactions. For example, a test period of 14-days has been proven to be a critical point for cell attachment (Image 2, 3). However, most of the studies limits this period only the very first days of the cell culture, which obviously cannot be taken take as granted for long term assumptions.

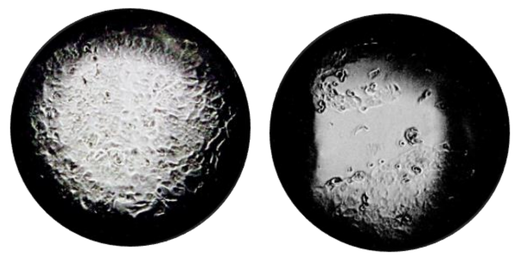

Image 2. (a) Cells inside the scaffold pore, Day 1 after the cell seeding, (b) Cells inside the scaffold pore, Day 3 after the cell seeding. Reduced number of cells observed.

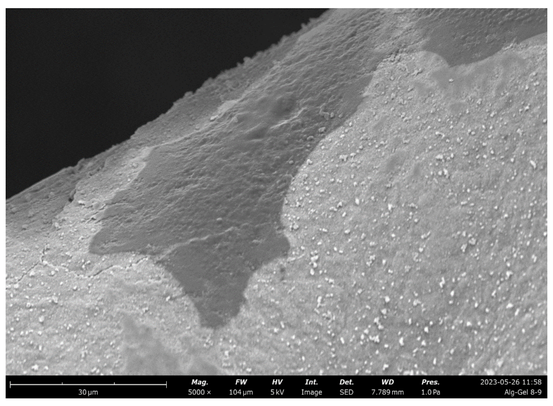

Image 3. No cells identified attached to the scaffold on the 14th Day of cell culture. Just indications of cells.

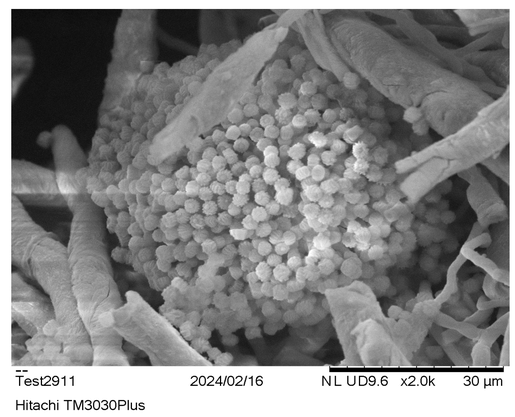

Image 4. Bacteria contamination observed through SEM on the 14th Day of cell culture.

CONCLUSIONS

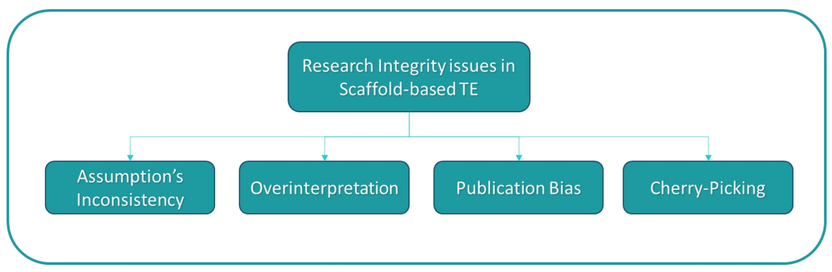

Figure 4. Schematic illustration of Research Integrity pitfalls that can appear in the interpretation of scaffold-based TE results.

First of all, we should admit that several significant issues of Research Integrity are present in the fast growing research of 3D Scaffold-based Tissue Engineering, as indicated in Fig. 4 [1,6] .

In terms of measures to practically address such issues, **our main suggestions** are:

- consistent use of a holistic methodology, covering each phase of scaffold development to ensure Repeatability, Reproducibility and Consistency before every next TRL (Fig.5)
- detailed documentation in every implementation step involved
- FAIR (Findable, Accessible, Interoperable, Reusable) principles in raw data handling

However, at the end of the day it all boils down to **the ethical code of each and every researcher, research group and institute**.

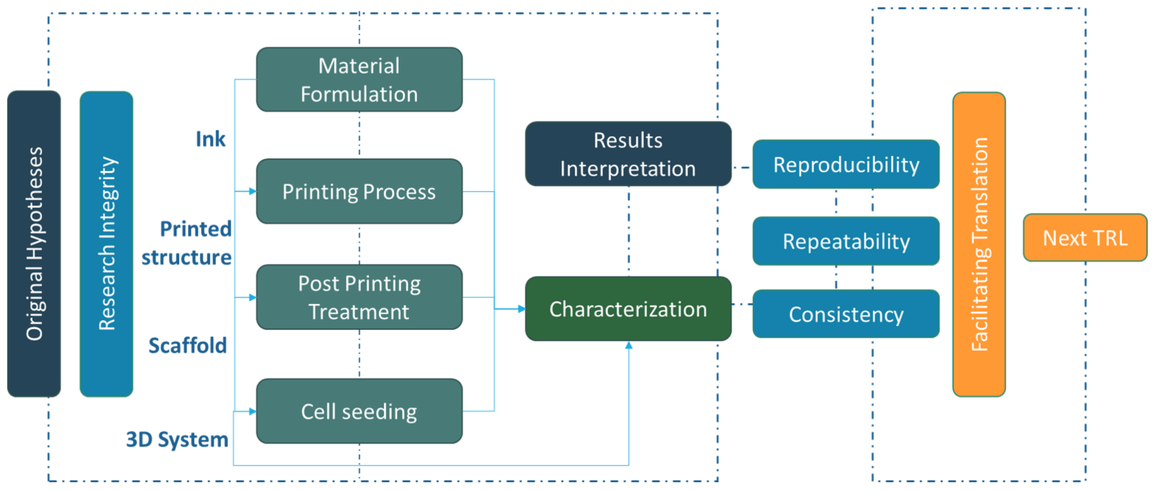

Figure 5. Proposed methodology for addressing both technical and ethical challenges, facilitating the translation of scaffold-based TE.

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