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Mining for osteogenic surface topographies: In silico design to *in vivo* osseo-integration

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ABSTRACT

Stem cells respond to the physicochemical parameters of the substrate on which they grow. Quantitative material activity relationships – the relationships between substrate parameters and the phenotypes they induce – have so far poorly predicted the success of bioactive implant surfaces. In this report, we screened a library of randomly selected designed surface topographies for those inducing osteogenic differentiation of bone marrow-derived mesenchymal stem cells. Cell shape features, surface design parameters, and osteogenic marker expression were strongly correlated *in vitro*. Furthermore, the surfaces with the highest osteogenic potential *in vitro* also demonstrated their osteogenic effect *in vivo*: these indeed strongly enhanced bone bonding in a rabbit femur model. Our work shows that by giving stem cells specific physicochemical parameters through designed surface topographies, differentiation of these cells can be dictated.

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1. Introduction

Medical implants such as stents, hip implants and pacemakers have already made a tremendous impact on the quality of life of millions of patients. Further success can be expected if the response of the host tissue to the implant can be better controlled; often these devices fail to properly embed in the patient's tissue [1,2]. Biomaterial engineering offers a vast design space with properties such as stiffness [3], chemistry [4] and surface topography [5], all of which are known to influence cell behavior and tissue response [6]. A major challenge is to correlate all these material properties to the final tissue response. As a consequence, the current surge of innovations in biomaterial engineering is not yet altering clinical practice.

A parallel to this challenge of correlating design parameters to biological response is found in pharmacology, where quantitative structure activity relationship analysis (QSAR) is used as a strategy to explore chemical design space. The starting point typically is a protein with a validated role in disease pathophysiology; the goal is to alter a (small) molecule's structure to optimize its binding and thus its effects on the protein's activity. The interaction between molecule and protein can be described at the sub-molecular level and thus modeled and optimized. The final, optimized drug can be considered as a molecule-to-molecule therapeutic strategy.

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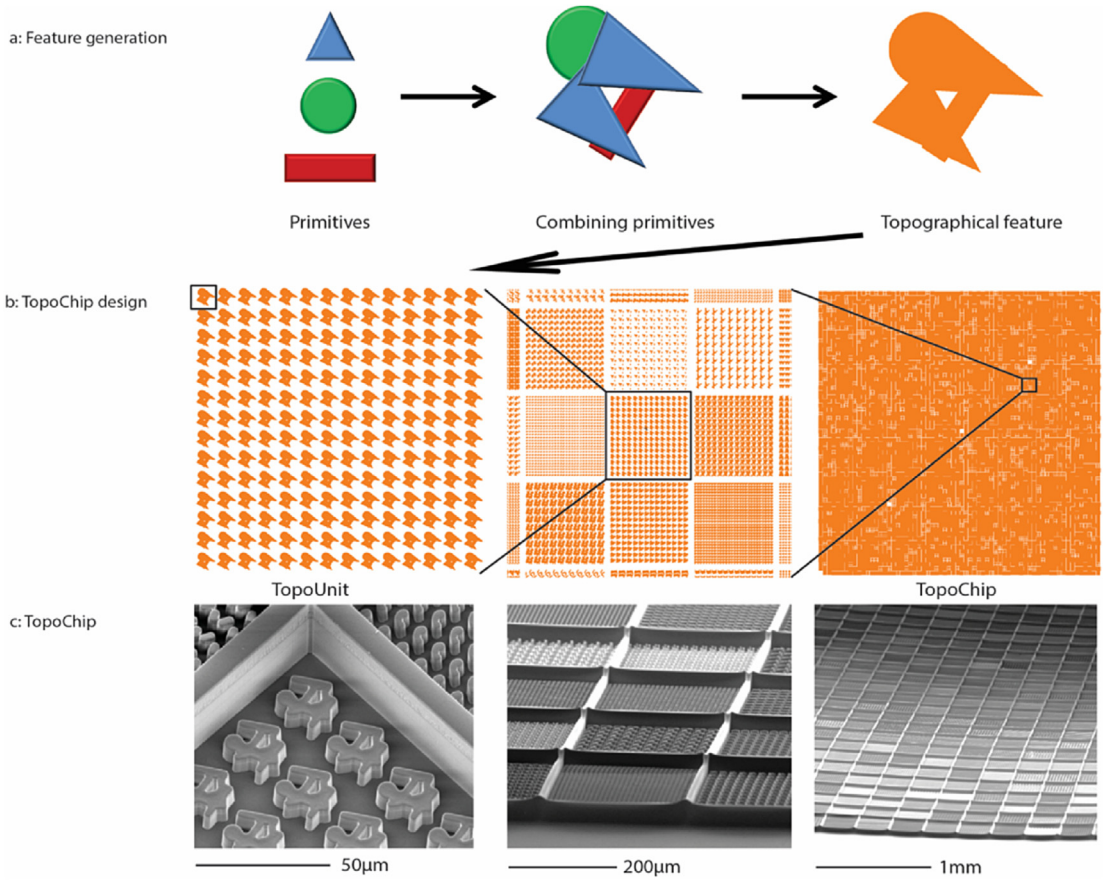

Fig. 1. TopoChip design. (a) From left to right; the 3 primitive shapes, circle, triangle and rectangle are combined in varying numbers and dimensions, to form a random shape of a topographical feature. Range of parameters within the algorithm allows a theoretical library of topographies with 150 million different possible shapes. (b) For the TopoChip design 2176 topographical features are randomly selected from the theoretical library and arrayed in 290 × 290 μm^2 TopoUnits, as well as TopoUnits without topographical features as flat reference. From left to right the illustrations zoom out from a single TopoUnit to a complete 2 × 2 cm^2 TopoChip. (c) Below the illustrations are SEM images with similar scaling.

In contrast, medical implants act at the tissue level to replace damaged tissues (e.g. artificial heart valves, artificial intra-ocular lenses, or hip implants) or to control malfunctioning tissue (e.g. pacemakers, stents or abdominal wall meshes). As such, medical implant materials can be considered as a material-to-cell therapeutic strategy, in which multiple biomaterial parameters affect various aspects of cell physiology. For instance, surface topography can modulate focal adhesion formation, as well as cytoskeletal and nuclear organization [7].

Computational modeling approaches to describe quantitative material activity relationships have been used in biomaterial engineering [8–11]. For instance, partial least squares analysis of bacterial attachment to a combinatorial polymer library uncovered strong correlation between bacterial attachment and physical parameters [12]. Our prior investigations, using high-throughput screening of topographies, have shown correlations between topographical design parameters and nuclear shape features [13] and colony-forming ability of embryonic stem cells [14]. However, while strong correlations have been found *in vitro*, so far no reports demonstrate translation of these correlations, identified by high-throughput screening, to *in vivo* tissue response.

Here, we aim to demonstrate that proper selection of biomaterial surface topographies based on their parameters plus a robust *in vitro* bioassay can predict *in vivo* tissue response. We designed, produced and screened thousands of randomly selected, designed topographies on a titanium-coated TopoChip for improved osseointegration. The TopoChip platform comprises of an *in silico* designed library of patterns with features in the range of a few to tens of microns that are reproduced into biomaterials of choice using microfabrication technologies. We applied human mesenchymal stem cells (hMSCs) as an *in vitro* cell model to identify osteogenic topographies and further tested candidates *in vivo* using a rabbit model.

This study investigates whether, similar to the pharmaceutical QSAR approach, medical implant design can be approached through computational modeling of material-cell interaction, and can be translated into an improved medical device, validated in a pre-clinical model.

2. Results

2.1. Screening identifies topographies that induce ALP expression of hMSCs

To identify topographies that improve bonding of titanium implants to bone, we produced TopoChips of poly lactic acid (PLA) films coated with a 200 nm layer of titanium (Fig. 1). Fabrication quality and reproducibility was confirmed by scanning electron microscopy (SEM, Fig. 1c).

In a pilot experiment, hMSCs with verified multi-lineage potential (Fig. S1) were seeded, grown on a TopoChip for 5 days and stained for actin and DNA. We observed a wide variety of both nuclear and actin morphologies in response to the micro-topographies (Fig. 2). Within a TopoUnit (indicated by yellow box

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