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Review article

# Diversification and enrichment of clinical biomaterials inspired by Darwinian evolution

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ABSTRACT

Regenerative medicine and biomaterials design are driven by biomimicry. There is the essential requirement to emulate human cell, tissue, organ and physiological complexity to ensure long-lasting clinical success. Biomimicry projects for biomaterials innovation can be re-invigorated with evolutionary insights and perspectives, since Darwinian evolution is the original dynamic process for biological organisation and complexity. Many existing human inspired regenerative biomaterials (*defined as a nature generated, nature derived and nature mimicking structure, produced within a biological system, which can deputise for, or replace human tissues for which it closely matches*) are without important elements of biological complexity such as, hierarchy and autonomous actions. It is possible to engineer these essential elements into clinical biomaterials via bioinspired implementation of concepts, processes and mechanisms played out during Darwinian evolution; mechanisms such as, directed, computational, accelerated evolutions and artificial selection contrived in the laboratory. These dynamos for innovation can be used during biomaterials fabrication, but also to choose optimal designs in the regeneration process. Further evolutionary information can help at the design stage; gleaned from the historical evolution of material adaptations compared across phylogenies to changes in their environment and habitats. Taken together, harnessing evolutionary mechanisms and evolutionary pathways, leading to ideal adaptations, will eventually provide a new class of Darwinian and evolutionary biomaterials. This will provide bioengineers with a more diversified and more efficient innovation tool for biomaterial design, synthesis and function than currently achieved with synthetic materials chemistry programmes and rational based materials design approach, which require reasoned logic. It will also inject further creativity, diversity and richness into the biomedical technologies that we make. All of which are based on biological principles. Such evolution-inspired biomaterials have the potential to generate innovative solutions, which match with existing bioengineering problems, in vital areas of clinical materials translation that include tissue engineering, gene delivery, drug delivery, immunity modulation, and scar-less wound healing.

**Statement of Significance**

Evolution by natural selection is a powerful generator of innovations in molecular, materials and structures. Man has influenced evolution for thousands of years, to create new breeds of farm animals and crop plants, but now molecular and materials can be molded in the same way. Biological molecules and simple structures can be evolved, literally in the laboratory. Furthermore, they are re-designed via lessons learnt from evolutionary history. Through a 3-step process to (1) create variants in material building blocks, (2) screen the variants with beneficial traits/properties and (3) select and support their self-assembly into usable materials, improvements in design and performance can emerge. By introducing biological molecules and small organisms into this process, it is possible to make increasingly diversified, sophisticated and clinically relevant materials for multiple roles in biomedicine.



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**Contents**



## 1. Darwinian evolution as a driver for biomaterials design & diversification

Darwinian evolution by natural selection has been the main force of creativity in biology [1]. It has generated integrated complexity of the highest high order and function. It is a process that has been copied and simulated in biotechnology mainly to redesign biological molecules for new purposes and more efficient roles. However, it has been difficult to capture, direct and control. Organic evolution is messy, opportunistic and contingent on what has occurred and developed before. Current developments highlight the increasing promise of experimental evolution to produce new biological products. Populations of small organisms have been cultivated, artificially mutated and selected within imposed environments to evolve new traits. Experimental evolution has been a tool to study evolutionary changes. In the science of biomaterials the explicit use of evolutionary processes and mechanisms to fabricate new natural biomaterials or biomaterials with living and adaptive qualities. The biomaterials we are discussing are those that can be evolvable. This is a substrate made within biological systems that can be processed and manipulated by a living cell, virus or small organism.

Current biomaterials lack essential adaptation behaviour. Also current biomaterials need improvements to adapt and function in the laboratory, in the clinical environment, at implantation and in the wound environment. These are all prior to integration with natural healthy tissue they are typically designed to match. We review approaches and technical strategies to implement Darwinian evolution, in real time during biomaterials design, synthesis and fabrication. The literature in this regard is patchy. The purpose of this review is to consolidate the disparate areas of evolution related inputs to biomaterial development. We describe the potential of using Darwinian mechanisms in biomaterials development. In one of few examples, directed evolution has been used to diversify and preferentially select optimal functioning collagen mimicking materials derived from self-templating (the presence and activity of the first building blocks drive and build together the remaining building blocks entering the assembly) assemblages of virus capsids [2,3]. The harnessing of bacteriophage capsules (with wide range of shape and architecture), as a versatile and tunable material building block, for production of multiscale biomimetic collagen architectures ideal for cell and tissue engineering [4]. It is a way of diversification and making new unnatural biomaterials. In this review we cover and incorporate all other areas where Darwinian knowledge can be applied to the development of biomaterials. This includes, learning from the patterns of evolution during history, learning about the mechanisms and how they can be translated into the laboratory and learning how small organisms can be evolved and programmed to manufacture biomaterial building blocks. The learning is broad and encompasses evolutionary trends across history, comparative/convergent evolution analyses of biomaterials over time, harnessing synthetic biology, directed evolution artificial selection and the technologies to make evolution controlled, such as, microfluidics. It will include practical lessons on techniques to establish the controlled evolution habitats to enable our biomaterial assembly with evolution inputs. There exist protocols and techniques for carrying out experimental evolution [5].

The goal is to improve existing biomaterials in a number of useful ways. To help make synthesising biomaterials from small molecules more efficient in the laboratory-tailored to specific functions, tailor these biomaterial building blocks (e.g. so that they self-organise in specified ways), and to help in the design of new biomaterials with additional functions for the laboratory and the clinic. Darwinian evolution has produced countless bounty of materials design and innovation. This is possible with small organisms single cell (*E. coli*, bacteriophages and other viruses) or (lower invertebrates e.g. sponges), open to genetic manipulation and reprogramming, with rapid generation times and high tolerance to environmental stress. Such organisms are able to generate technologically viable yields of biomaterial substrates.

These are the creations we are inspired to mimic and reproduce in nature's image. In contrast the nuts and bolts of evolutionary mechanics is the tool for composing biomimetic inventions. This review will illustrate these two different elements, the products of evolution and the mechanisms used to make them. It is aimed at promoting the use of mechanisms for bioinspiration and biomimicry projects.

The evolutionary based approaches to developing the new wave of dynamic, biologically enriched biomaterials will be exemplified by 4 strategies: (1) evolutionary screening of peptides from bacteriophage libraries that select biomaterial components with best functions, (2) repeat selection of bacteriophage or bacterial materials (viral nanoparticles, viral coat proteins and bacterial coat proteins) for designated properties conditioned and guided by living cells, (3) comparative and retrospective analysis of evolutionary biomaterial trends and innovations, (4) directed evolution of building block molecules for biomaterials.

### *1.1. The role of biomaterials in regenerative medicine*

Use of biomaterials as space-filling frameworks and templates is one of three major pillars, alongside living cells (adult stem cells) and biochemical (growth factors), supporting laboratory-grounded tissue self-assembly, self-organisation, developmental morphogenesis and regeneration strategies for tissues and organs [6–8].