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Editorial

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Wound healing and scarring are highly conserved physiological responses to wounding in most tissues in higher organisms, consisting of a sequence of well-characterised stages (coagulation, inflammation, proliferation and remodelling [1-3]), with the aim to repair interrupted tissue structures and to restore tissue function [4]. However, this sequence can come to a halt before completion resulting in undesired outcomes, ranging from the formation of a large local scar to organ-encompassing fibrosis. Whilst the former causes cosmetic annoyance, the latter might lead to grave functional impairment or to chronic non-healing wounds.

Fibrosis is a pathological scarring phenomenon characterised by the formation of wide spread excessive fibrous connective tissue, which alters the microarchitecture of a whole organ, driving it eventually into failure. Fibrosis causes a huge global burden on healthcare, with millions of patients suffering from cosmetic or even functional tissue / organ impairment, which considerably reduces their quality of life [5]. Fibrosis can be fatal: chronic fibro-proliferative diseases have been associated with 45 % of non-accident related casualties in the USA [6]. Besides being the common feature of most chronic inflammatory diseases (e.g. skin, liver and kidney diseases; pulmonary and heart fibrosis), fibrosis is also a major pathological feature of many chronic autoimmune diseases, including scleroderma, rheumatoid arthritis, Crohn's disease and systemic lupus erythematosus [7].

Chronic ulcers (diabetic, vascular, pressure and age-related ulcers) are the product of chronic wounds, which fail to follow and complete the wound healing sequence [1, 3], usually due to a perpetuated inflammatory response, leading to the formation of an ulcer that can last for years [5]. Ulcers are embedded in a surrounding fibrotic wound microenvironment and do not spontaneously close. This is opposed to the acute wound healing process (trauma, burns and surgical wounds), which results in tissue regeneration / repair or circumscribed scar formation [6]. Whilst acute wound care accounts for more than 16 million admitted patients per year [7], it is estimated that chronic wounds cost approximately US\$ 5-10 billion dollars annually in USA alone [6]. The population prevalence of foot and leg diabetic ulcers in the EU is estimated to affect between 1.5-2.0 million of the 491 million inhabitants of the 27 EU countries with an annual estimated cost of €10-12 billion [8].

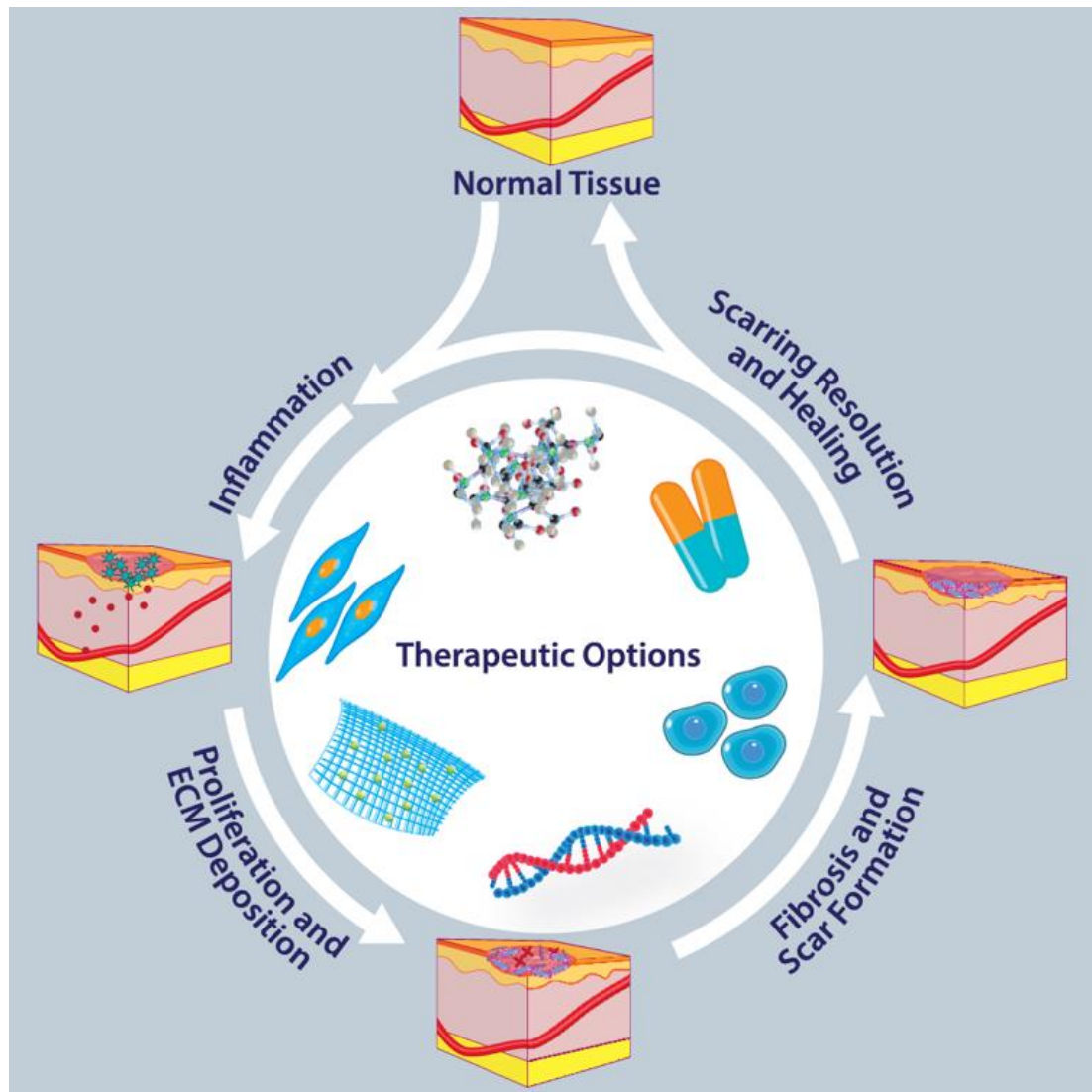
Despite their enormous impact on human health, there are currently no approved treatments that effectively treat and cure fibrosis or chronic wounds. Current limitations in developing therapies for normal and pathological tissue repair are partially due to the broad range of imbalanced and interconnected signalling pathways underlying such pathologies and the inherent difficulty in pinpointing exactly the affected pathways in each case [9]. This further hinders the development of new therapies, as it is difficult to determine which specific drugs to use and the most appropriate vehicles of delivery. Another reason might be that single agent therapies, such as growth factors, due to their rapid degradation at the wound site, or due to the redundancy and plasticity of the wound healing mechanisms involved, have failed so far to make a significant impact in controlling these pathologies [10]. In a similar manner, administration of corticosteroids, which has been used as the method of choice for treating scarring diseases by decreasing exacerbated inflammation and matrix deposition, has also been associated with considerable side-effects (e.g. osteoporosis, glaucoma, atrophy and pain at the injection site) [15].

It is evidenced that there is an urgent need for the development of systems capable of delivering multiple bioactive agents in a controlled manner, using a synergistic approach for yielding an improved therapeutic potential [11]. Achieving closure of chronic wounds has also remained a challenge. Split-thickness autografts, despite being considered the gold standard in wound healing due to their capability to accelerate wound healing and prevent immune-rejection, have several disadvantages, such as donor site morbidity and pain [12]. Recent tissue engineering approaches in wound healing and fibrosis treatment have tried to circumvent these limitations by using autologous cultured grafts, stem cells, wound dressings from natural and synthetic materials, negative pressure therapy systems, gene / drug / growth factor / small molecule / cell delivery systems alone or in combination with an appropriate carrier (**Figure 1**).

This special issue provides insights into some of the molecular mechanisms inherent to wound healing and fibrosis [13-16] and highlighting the use of cell- and tissue- models for basic research and drug discovery [17, 18]. The use of several approaches for treating or preventing such pathologies is also

discussed, including bioactive [19-21], electroactive [22] and stimuli-responsive [23] biomaterial-based approaches; gene, drug, proteoglycan and growth factor based approaches [24-34]; cellular and cellular-derived based therapies [35-37]; and matrix modulation strategies [38]. Considering the significant strides made in understanding the molecular mechanisms operating in normal and pathological wound healing and the promising therapeutic approaches described herein, it is expected that in the near future, some of these technologies will satisfy clinical needs and enter commercialisation.

Figure 1: Physiological and pathological wound healing sequences share three common phases after wounding: inflammation, proliferation and remodelling phase. When failing to complete the wound healing sequence, a pathological outcome (fibrosis or chronic wound) can occur. Different therapeutic approaches that can be pursued in each phase (e.g. drugs, genes, proteins, growth factors, small molecules and cells alone or in combination with an appropriate carrier) are at the forefront of scientific research, technological innovation and clinical translation.



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