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UROLOGICAL ONCOLOGY

Is a functional urinary bladder attainable through current regenerative medicine strategies?

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The concise yet poignant review article by Adamowicz et al. [1] appearing in this issue of the "Central European Journal of Urology" delves into two critical aspects of urinary bladder tissue engineering. The use of appropriate scaffolding material as an architectural foundation for bladder regeneration combined with multipotent stem/progenitor cell populations is paramount to a physiologically functional bladder. The article presents a critical review of the current state of bladder regeneration and its applicability to a variety of bladder based states including bladder cancer.

The use of autologous intestinal segments as a strategy to augment poorly functioning bladders has been a surgical main stay for several decades utilized by the clinical urologist. Although this strategy does provide a stop–gap measure for those in need to increase physiological output of a potentially failing bladder, a myriad of short– and long–term complications still plague this method with the potential of providing a fatal outcome [1, 2, 3]. Tissue engineering strategies that have evolved over the last several decades for bladder regeneration have been monumental to the field undergoing multiple iterations from different researchers [4, 5]. Although many attempts have been made to create a physiologically functional bladder or replacement bladder tissue, the reality of this endeavor is still waiting in the wings. Recent clinical trial data in the United States suggests that current strategies need to be re–evaluated and honed in order to obtain optimal results [6]. As tissue engineering encompasses multiple scientific disciplines including aspects of engineering, cell biology, and medicine, the products derived from these groups must act in concert. This would lead to the creation of the optimal graft for patients in need of bladder tissue replacement. Two critical areas, in this regard, are scaffold design and the cells to be utilized in the graft. Researchers have demonstrated the use of a variety of scaffolding material including biologic based materials such as small intestinal submucosa (SIS) and bladder acellular matrix (BAM) as well as synthetic materials including poly glycolic acid (PGA) and its derivatives and the elastomer family of poly (diol citrates) (POC). Problems that have been encountered with biological materials include graft contraction issues once placed in vivo as well as material reproducibility as batch to batch variation of these materials poses a problem in the regenerating milieu. The synthetic materials that have been produced to date vary quite broadly in their chemical composition and their mechanical characteristics. The task of the chemical engineer entrusted to create a suitable scaffold should be to create a material that can not only mimic the mechanical properties of the bladder including elasticity and biaxial stretch ability but also produce a material that is biologically compatible and biodegradable. Lastly, the material should also provide a water–impermeable barrier during early phases of graft growth with the ability to allow for the simultaneous transposition of small molecules needed for induction of tissue growth and development. To date, the only published clinical trial data to use a very rigid, synthetic scaffold (PGA) demonstrated just marginal results although the study itself was highly novel in approach. Future endeavors towards scaffold design should focus upon "smart" elastomers such as POC that can truly mimic the mechanical parameters and aid in the early stages of regeneration as mechanical stimulation have been shown to be crucial in these early stages [7].

The cellular make up of the potential grafts must be considered carefully as certain biological parameters must be met in order to achieve

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maximum utility from the graft. Cells should be autologous in nature as to avoid any undue immunological responses from the recipient host or potentially from the graft itself. The cells should not be compromised in any way (i.e., pathologic in nature or obtained from sources that may be suspect such as bladder smooth muscle cell and urothelial cells taken from a patient diagnosed with bladder cancer) and should be able to recapitulate the native bladder environment. This would include the bladder smooth muscle that encompasses the bladder, the urothelial lining of the bladder lumen, new blood vessels to nourish developing tissue, and peripheral nerve regeneration to allow for proper bladder contraction/expansion cycles of the bladder. The ideal situation would be to utilize a single non–pathogenic cell source potentially derived from induced pluripotent stem cells (iPS cells) or embryonic stem cell (ES cells). The power that these cells harness has yet to be refined as these two biological endeavors are still in their respective scientific infancies. In the meantime, other studies have clearly demonstrated that specific populations of adult stem cells derived from the bone marrow are more than capable of regenerating bladder tissue in a small animal model [7]. In this scenario, there are no ethical concerns about the derivation of the cells as well as anxieties with regard to bio– compatibility and the preponderance of disease in the cells. This is viable alternative to past studies with obvious clinical translation.

Future strategies for bladder regeneration must first clearly address and critically dissect the issues that have been encountered in recent trials in order to advance the field forward. Care must be taken to focus upon the materials (scaffold and cells alike) in order to achieve ideal results. These goals can be accomplished by the increased interplay between the basic and clinical sciences.

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