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Special Issue Devoted to a New Field of Regenerative Medicine: Reproductive Tissue Engineering

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In recent decades, epidemiological studies have shown a steady increase in the incidence of disorders in both female and male reproductive system disorders, which can lead to sexual dysfunction, subfertility or infertility, and a drop in global conception rates.[4,7,15] Equally important is the psychosocial impact of such disorders have on patients, potentially influencing their sense of self and social competence, and negatively affecting self-esteem, sexuality and relationships with others.[3]

Although most conditions can be treated with hormone therapy, medication or surgery, such options may have adverse effects, constitute only palliative therapy, or fail to provide optimal results. Consequently, an increasing number of research teams have adopted revolutionary strategies from the field of tissue engineering and regenerative medicine, developing novel alternatives to restore sexual function and preserve fertility in both female and male patients. Despite being relatively new, this emerging trend has advanced rapidly, already gaining recognition as a new branch of tissue engineering and regenerative medicine that we can call "reproductive tissue engineering" (REPROTEN). REPROTEN can be defined as an interdisciplinary field that applies tissue engineering strategies to restore fertility and/or improve the quality of life of patients affected by reproductive dysfunction through creation, replacement or regeneration of cells, tissues or organs of the reproductive system.

The goal of this seminal issue is to promote this new scientific discipline by compiling all relevant papers, divided into reviews and original research articles, demonstrating the swift progress of REPROTEN. The special issue begins with a review of different biomaterials used for regeneration of female and male reproductive tissues,[16] followed by Morohaku *et al's.*[13] review of various approaches adopted to culture germ cells, as well as their method to obtain oocytes from primordial germ cells. Thanks to growing interest in stem cell differentiation into female and male gametes to restore fertility, we have also included a review exploring the ethical concerns of this approach.[19]

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The largest area of interest to emerge in the field of REPROTEN has been fertility restoration in female patients, as indicated by the numerous papers on the subject in this special issue, mainly focusing on ovarian tissue engineering. Studies by our group[2,20] and Motamed *et al.*[14] have demonstrated that different scaffolds, using materials like fibrin, alginate and amniotic membranes, can be successfully applied to grow isolated preantral follicles. He[9] and David *et al.*[5] developed exciting new strategies to encapsulate isolated follicles or fragments of ovarian tissue for further *in vitro* culture or transplantation to restore fertility or endocrine function. Another way of maintaining normal levels of circulating estrogen is through hormone replacement therapy. Prakapenka *et al.*[17] reviewed the delivery of this hormone using poly (lactic-co-glycolic acid) micro- and nanocarriers, pointing out the advantages of this approach compared to current methods of administration.

Reviwes by Campo *et al.*[1] and Hellström *et al.*[11] on uterine tissue engineering provide a broad overview of advances made in repairing fragments of this organ until a whole artificial uterus can be created through utilization of natural matrices, such as a decellularized uterus and stem cells. A bioengineered uterus would overcome current limitations of whole organ allotransplantation, like required immunosuppression for recipients and risky surgery for donors. Two subsequent reviews discuss 3D culture systems used to mimic the oviduct and myometrium,[6,10] which play an essential role in the initial and final stages of

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pregnancy. In their original research article, Gnecco *et al.*[8] demonstrated successful application of a dual-chamber microfluidic device with a resin-based porous membrane to *in vitro*-coculture human endometrial stromal and endothelial cells, looking to evaluate the interactive role of these cells.

Further contributions to this issue concern male REPROTEN. Vermeulen *et al.*[21] discuss different approaches using tissue engineering techniques to improve spermatogonial survival in immature testicular tissue after transplantation. Two original research papers demonstrate the impact of knock-out serum replacement and melatonin on *in vitro* maturation of male germ cells, and urethra reconstruction using decellularized human urethras.[12,18]

Finally, we included an original research paper describing a system using human embryonic-derived stem cells in 3D collagen-embedded silk scaffolds as a model to study in utero obesogen exposure.[22]

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