Arab Journal of Urology (2017) **xxx**, xxx–xxx

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

www.sciencedirect.com

REVIEW

Spermatogonial stem cell transplantation and male infertility: Current status and future directions

Connor M. Forbes [a], **Ryan Flannigan** [b,*], **Peter N. Schlegel** [b]

[a] *Department of Urology, University of British Columbia, Vancouver, British Columbia, Canada*
[b] *Department of Urology, Weill Cornell Medicine, New York, NY, USA*

Received 9 November 2017, Received in revised form 25 November 2017, Accepted 26 November 2017

KEYWORDS

Non-obstructive azoospermia;
Fertility preservation;
Onco-fertility;
Male infertility;
Stem cell therapy;
Allograft

ABBREVIATIONS

ART, assisted reproductive technologies;

Abstract ***Objective:*** To summarise the current state of research into spermatogonial stem cell (SSC) therapies with a focus on future directions, as SSCs show promise as a source for preserving or initiating fertility in otherwise infertile men.

Materials and methods: We performed a search for publications addressing spermatogonial stem cell transplantation in the treatment of male infertility. The search engines PubMed and Google Scholar were used from 1990 to 2017. Search terms were relevant for spermatogonial stem cell therapies. Titles of publications were screened for relevance; abstracts were read, if related and full papers were reviewed for directly pertinent original research.

Results: In all, 58 papers were found to be relevant to this review, and were included in appropriate subheadings. This review discusses the various techniques that SSCs are being investigated to treat forms of male infertility.

* Corresponding author at: Weill Cornell Medicine, Department of Urology, 525 East 68th Street, Starr Pavilion, 9th Floor, Room 900, New York, NY 10065, USA.
E-mail address: ryf9003@med.cornell.edu (R. Flannigan).

Peer review under responsibility of Arab Association of Urology.

Production and hosting by Elsevier

https://doi.org/10.1016/j.aju.2017.11.015

Please cite this article in press as: Forbes CM et al. Spermatogonial stem cell transplantation and male infertility: Current status and future directions, *Arab J Urol* (2017), https://doi.org/10.1016/j.aju.2017.11.015

Bcl6b, B-Cell CLL/Lymphoma 6B;
BMP4, bone morphogenetic protein 4;
CD(24)(34), cluster of differentiation (24)(34);
c-Kit, KIT Proto-oncogene receptor tyrosine kinase;
FGF2, Fibroblast growth factor 2;
FISH, fluorescence *in situ* hybridisation;
GDNF, glial cell line-derived neurotrophic factor;
ICSI, intracytoplasmic sperm injection;
ID4, inhibitor of differentiation 4;
KS, Klinefelter syndrome;
PGC, primordial germ cells;
PLZF, promyelocytic leukaemia zinc finger;
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
RA(R), retinoic acid (receptor);
SSC, spermatogonial stem cell;
SPG, spermatogonia;
Stra8, stimulated by RA 8;
ZBTB, zinc finger and broad complex/Tramtrack/bric-a-brac

Conclusions: Evidence does not yet support clinical application of SSCs in humans. However, significant progress in the *in vitro* and *in vivo* development of SSCs, including differentiation into functional germ cells, gives reason for cautious optimism for future research.

Introduction: the unaddressed need in male infertility

Infertility is defined as an inability to achieve pregnancy despite 12 months of unprotected intercourse at regular intervals [1]. This occurs in ~15% of couples [1]. The prevalence of male factor contribution to infertility is difficult to estimate, probably because of under-reporting. Estimates for male factor-only infertility range from 6.4% to 42.4%, and estimates of male factor contributing to infertility range from 18.8% to 39% [1].

The causes of male infertility include varicoceles, medications, obstruction, and genetic disorders [2]. Treatments currently fall into several categories for the male: relief of obstruction, optimisation of sperm production, and surgical extraction of sperm [3]. Obstruction can be relieved through microsurgical techniques, obviating the need for stem cell therapy. Varicocele repair improves rates of pregnancy with assisted reproductive technologies (ART) for oligospermic and azoospermic men [4]. Although controversial, varicocele repair may even improve semen analysis in selected cases of azoospermic men [5].

For men who are unable to improve their semen analysis adequately for natural conception, ART are available. The most drastic of these is intracytoplasmic sperm injection (ICSI), a micro-manipulation technique

Please cite this article in press as: Forbes CM et al. Spermatogonial stem cell transplantation and male infertility: Current status and future directions, *Arab J Urol* (2017), https://doi.org/10.1016/j.aju.2017.11.015