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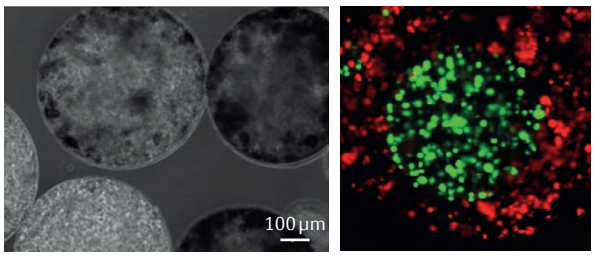
REPRODUCTIVE ENDOCRINOLOGY

Restoring ovarian function

The use of current pharmacological hormone replacement therapy (pHRT) with oestrogen alone or oestrogen and progestogens is controversial as the number of adverse effects (such as breast, endometrial and ovarian cancers) can outweigh the benefits, which include a reduced risk of osteoporotic fractures. Now, Sittadjody and colleagues have developed a cell-based HRT (cHRT) that maintains the beneficial outcomes of HRT, such as increased bone density, under safer conditions than pHRT.

The goal of all clinical HRT is to achieve a steady-state plasma concentration of hormones that is effective for the patient; however, the plasma concentrations of key sex hormones (such as oestradiol and progesterone) in pHRT are different from those associated with functioning ovaries. The disparity between the plasma levels of hormone is due to the lack of integration of the pHRT hormones into the hypothalamic–pituitary–gonadal (HPG) axis, which regulates the circulating levels of different hormones (such as oestradiol and progesterone) in the body.



Left panel: phase-contrast images of the microcapsules. Right panel: 3D-confocal images of bioengineered ovarian construct, granulosa in the inner layer (green-labelled cells) and theca in the outer layer (orange-labelled cells). Permission obtained from Sittadjody, S. *et al. Nat. Commun.* http://dx.doi.org/10.1038/s41467-017-01851-3 (2017), Macmillan Publishers Limited.

In a previous study, the researchers encapsulated theca and granulosa cells isolated from rat ovaries in multilayer alginate microcapsules to resemble natural rat ovarian follicles. The engineered capsules delivered sustained release of key sex hormones, such as oestradiol and progesterone, in *in vitro* cultures. These constructs were not characterised *in vivo*; however, the investigators speculated that the encapsulated ovarian cells would integrate into the HPG axis when used *in vivo*.

In the current proof-of-concept study, Sittadjody and colleagues used the encapsulated ovarian constructs as a cHRT, delivering hormones at a lower dose than pHRT. The isogenic cell-based constructs were implanted into omental pouches created in ovariectomized rats and monitored for 90 days. The 17β-oestradiol and progesterone levels in cHRT-treated animals did not reach the same levels as ovary-intact rats; however, levels of follicle-stimulating hormone and luteinizing hormone, which are both involved in the HPG axis, were suppressed. Rats receiving the cHRT showed increased plasma levels of inhibin, a hormone known to affect the secretion of gonadotropin-releasing hormones from the hypothalamus. Sittadjody and colleagues concluded that the cHRT constructs re-established the HPG axis in the ovariectomized rats. The ovariectomized rats implanted with the cHRT constructs also showed improved bone health, uterine health and body fat composition compared with ovariectomized rats that received placebo.

This cHRT offers a potential alternative to the current pHRT, as it delivers the required sex hormones at a lower dosage.

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ORIGINAL ARTICLE Sittadjody, S. *et al. In vivo* transplantation of 3D encapsulated ovarian constructs in rats corrects abnormalities of ovarian failure. *Nat. Commun.* http://dx.doi.org/10.1038/s41467-017-01851-3 (2017)