Recent Developments in the Transmission of Human Life

19-21 January 2023

Berlin, Germany

Welcome to all Participants

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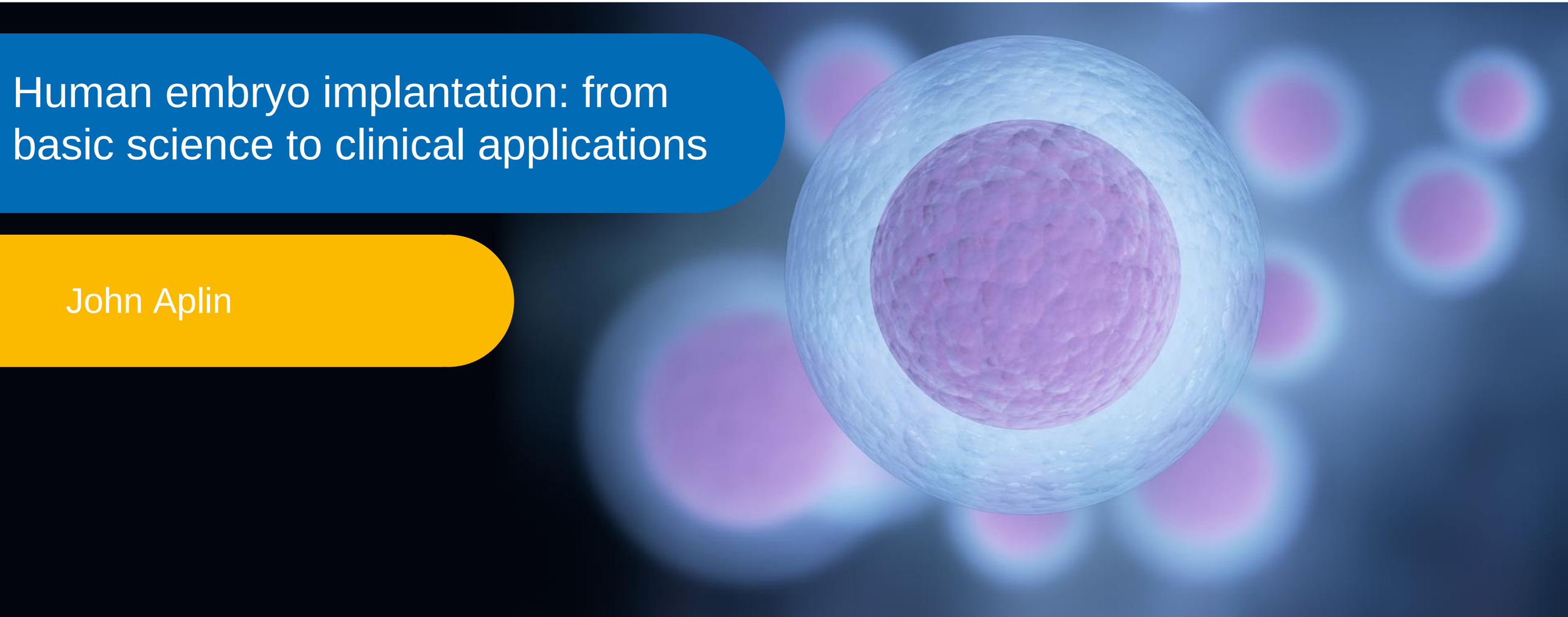
Recent Developments in the Transmission of Human Life

Human embryo implantation: from basic science to clinical applications

John Aplin



Faculty Disclosure

I have no potential conflict of interest to declare

Implantation and beyond, the endometrial perspective

John Aplin, PhD
Professor of Reproductive Biomedicine
University of Manchester
UK

Questions

Is there an embryo-receptive state in endometrium that can be identified and characterised?

Can a transcriptomic test of lysates of mid secretory phase tissue identify an implantation window?

Can single cell transcriptomics lead to advances in endometrial receptivity testing?

Can ex vivo 3D modelling of implantation help in developing a diagnostic for receptivity?

Can improvement in live birthrate be achieved by optimising the condition of the endometrium at embryo transfer?

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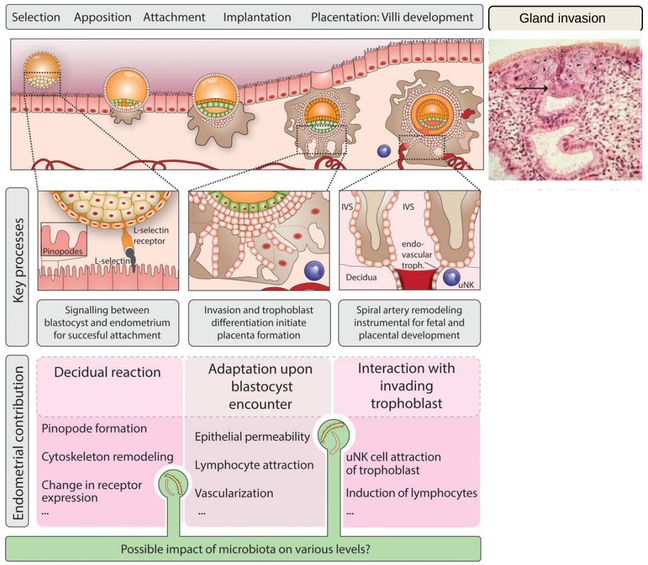
When does implantation fail?



Benner et al, Hum Reprod Update 2018 24:393-415

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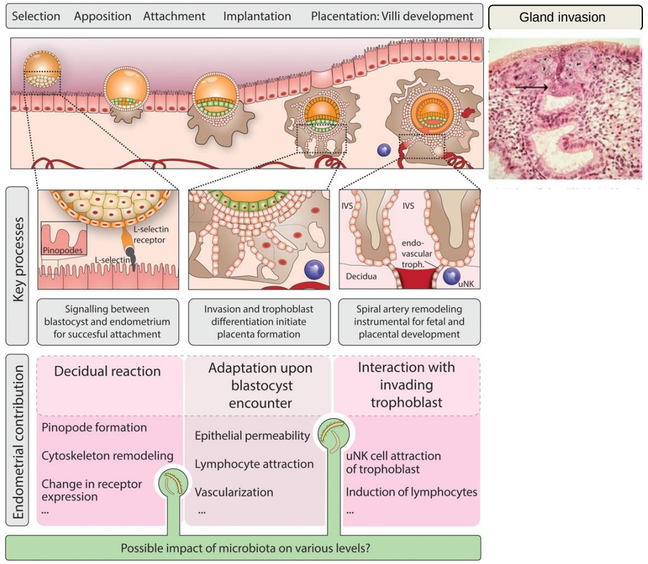
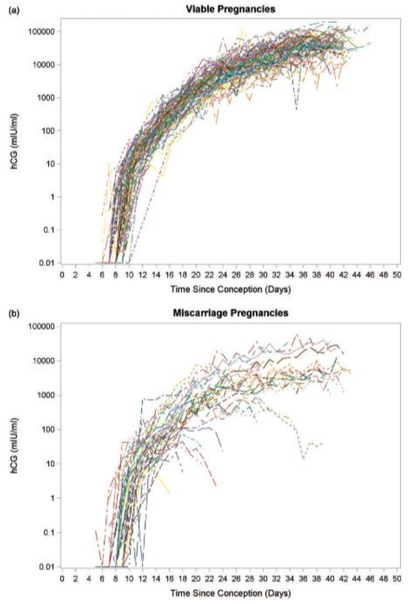


Benner et al, Hum Reprod Update 2018 24:393-415



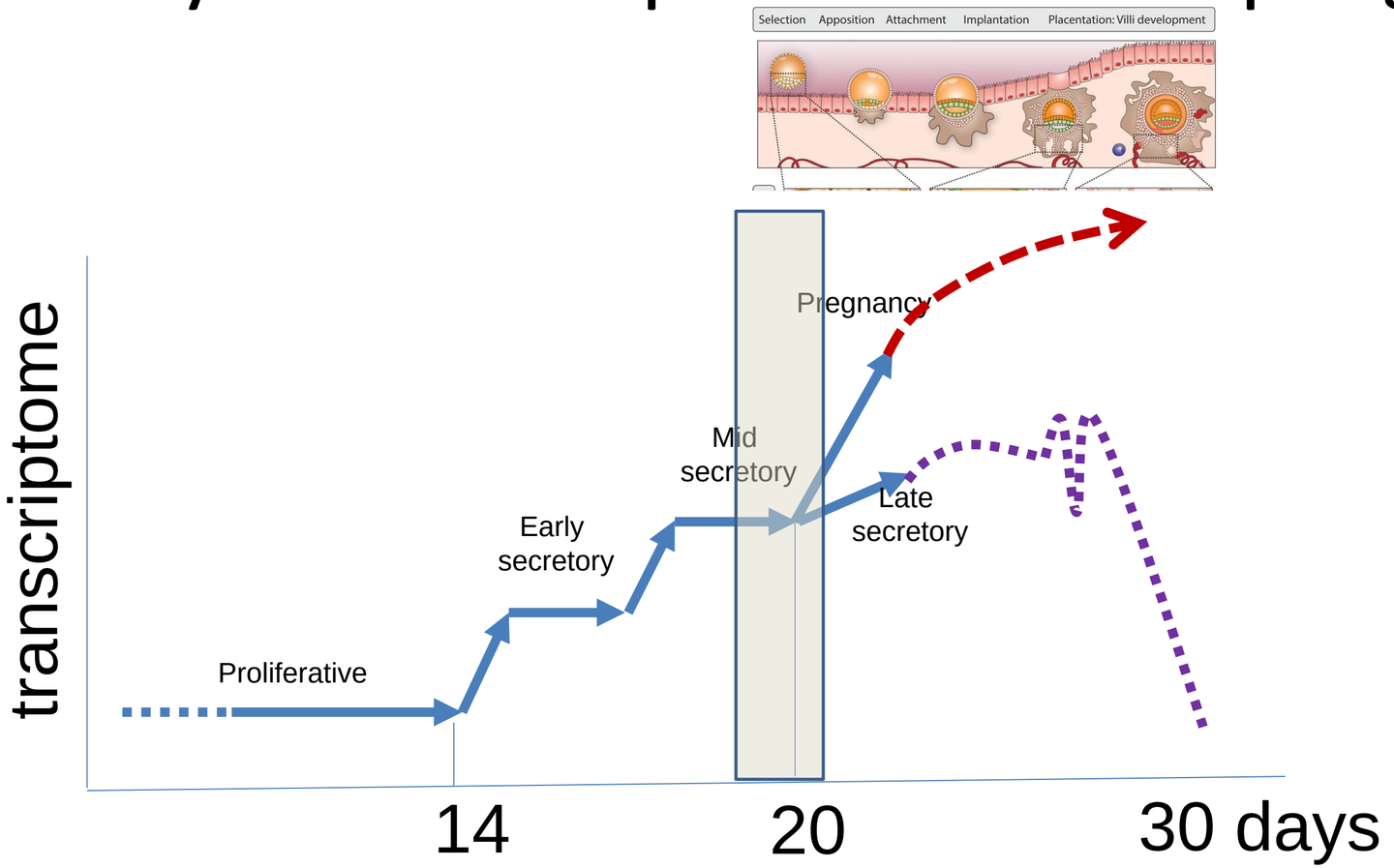
CG profiles

ongoing

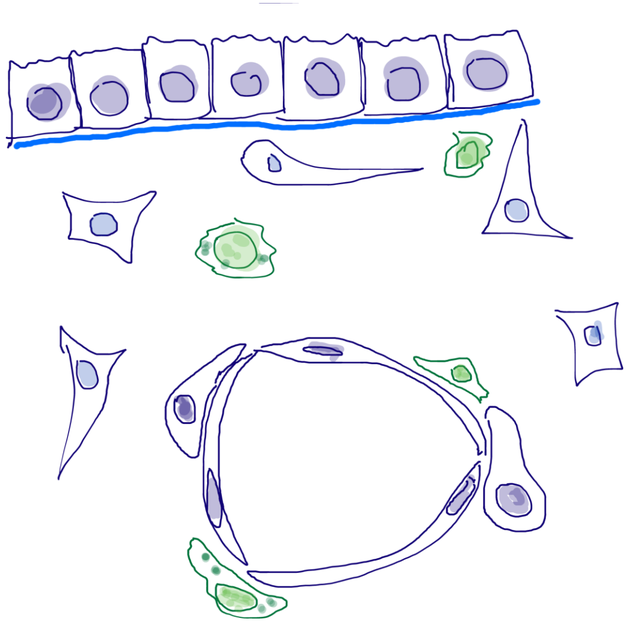
failing

Marriott et al Ann Clin Biochem. 2017 54:548-557.

Cycle transcriptome and sampling



Tissue lysate ‘omics



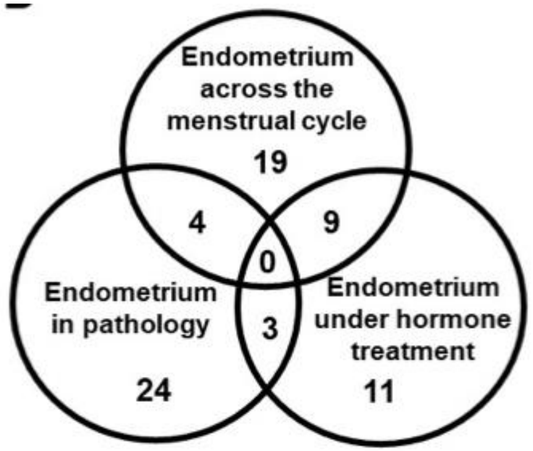
Epithelium

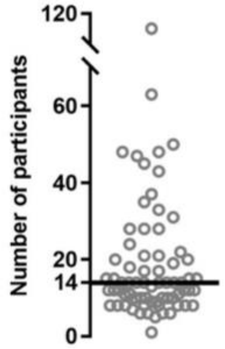
Stroma with inflammatory cells

Vasculature

Differentially expressed genes (DEG) in non-conception cycles

Comparison	Number of Studies	Total Number of Participants	Total Reported DEG	Studies
Secretory vs Proliferative	5	80	3637	Kao et al 2002; Borthwick et al 2003; Talbi et al 2006; Otsuka et al 2007; Sigurgeirsson et al 2017
Mid-secretory vs early secretory	7	112	2795	Carson et al 2002; Riesewijk et al 2003; Mirkin et al 2005; Talbi et al 2006; Haouzi et al 2009; Tseng et al 2010; Hu et al 2014
Mid-secretory endometrium from hormone treated participants vs controls	6	112	1937	Mirkin et al 2004; Horcajadas et al 2005; Horcajadas et al 2008; Liu et al 2008 Macklon et al 2008; Li et al 2020
Mid-secretory endometrium from RIF patients vs controls	7	233	1651	Tapia et al 2008; Koler et al 2009; Ledee et al 2011; Choi et al 2016; Koot et al 2016; Bastu et al 2019; Chen et al 2019
Mid-secretory eutopic endometrium from endometriosis patients vs controls	4	53	1307	Kao et al 2003; Burney et al 2007; Sherwin et al 2008; Cui et al 2018

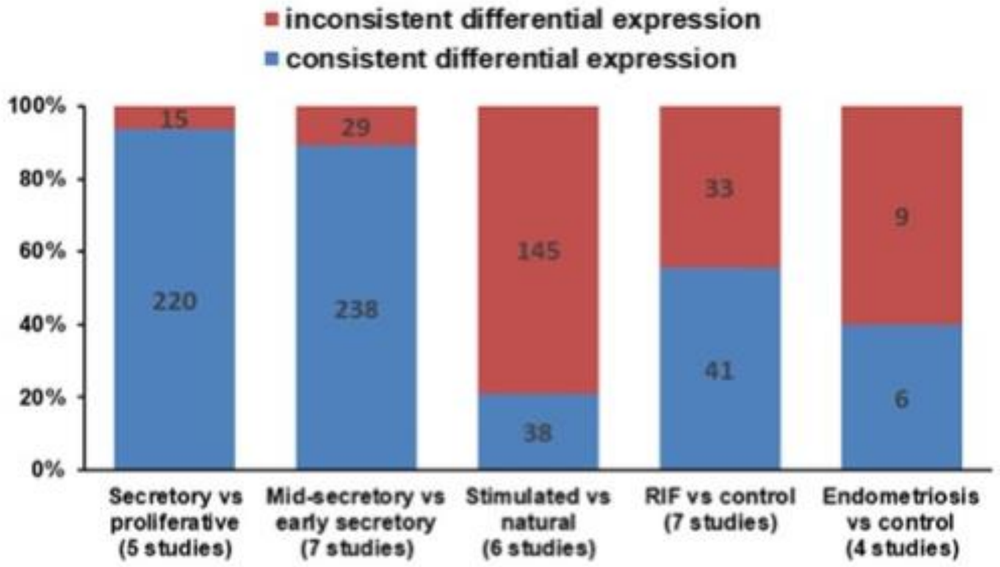




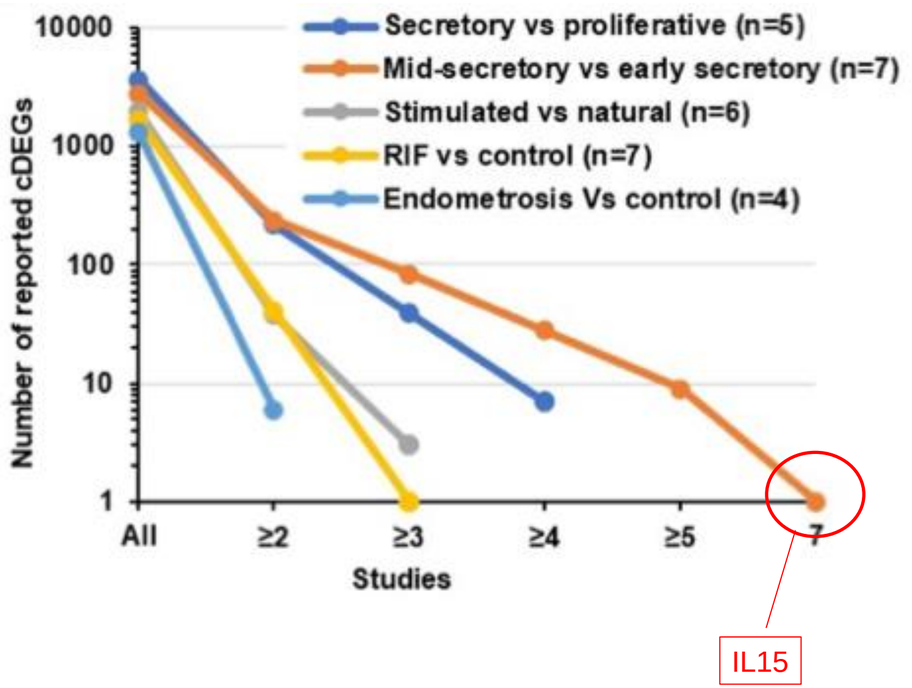
A systematic review of transcriptomic studies of the endometrium reveals variable demographic detail, fertility definitions and hormone treatments, and inconsistently reported differentially expressed genes

E Walker, JD Aplin, DR Brison, PT Ruane, under review

Inconsistent reporting of DEGs in endometrial transcriptomes



Note here that consistent = same *direction* of change



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Progress in interpreting endometrial transcriptomes

Human Reproduction, Vol.37, No.2, pp. 284–296, 2022
Advance Access Publication on December 7, 2021 https://doi.org/10.1093/humrep/deab262

human reproduction **ORIGINAL ARTICLE** ***Reproductive biology***

Identifying and optimizing human endometrial gene expression signatures for endometrial dating

P. Diaz-Gimeno [1,2,*,†], P. Sebastian-Leon[1,†], J.M. Sanchez-Reyes[1,3], K. Spath[4], A. Aleman[1], C. Vidal[1,5], A. Devesa-Peiro [1,3], E. Labarta [1,5], I. Sánchez-Ribas[1,6], M. Ferrando[7], G. Kohls[8], J.A. García-Velasco[8,9], E. Seli[10,11], D. Wells [2,4], and A. Pellicer[1,3,4,12]

[1]Genomic & Systems Reproductive Medicine, IVI Foundation/Instituto de investigación sanitaria La Fe (IIS La Fe), Valencia, Spain [2]Nuffield Department of Women's & Reproductive Health, University of Oxford, Level 3, Women's Centre John Radcliffe Hospital, Oxford, UK [3]Department of Pediatrics, Obstetrics and Gynecology, University of Valencia, Valencia, Spain [4]Research Department, JUNO Genetics, Oxford, UK [5]Reproductive medicine, IVI RMA Valencia, Valencia, Spain [6]Reproductive medicine, IVI RMA Barcelona, Barcelona, Spain [7]Reproductive medicine, IVI RMA Bilbao, Leioa, Bizkaia, Spain [8]Reproductive medicine, IVI RMA Madrid, Madrid, Spain [9]Department of Obstetrics and Gynecology, Universidad Rey Juan Carlos, Madrid, Spain [10]Research Department, IVI RMA New Jersey, Basking Ridge, NJ, USA [11]Department of Obstetrics, Gynecology & Reproductive Science, Yale School of Medicine, New Haven, CT, USA [12]Reproductive medicine, IVI RMA Rome, Roma, Italy

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https://orcid.org/0000-0003-0031-7545

Submitted on July 05, 2021; resubmitted on October 29, 2021; editorial decision on November 08, 2021

Human Reproduction, Vol.37, No.4, pp. 747–761, 2022
Advance Access Publication on January 29, 2022 https://doi.org/10.1093/humrep/deac006

human reproduction **ORIGINAL ARTICLE** ***Reproductive biology***

EndoTime: non-categorical timing estimates for luteal endometrium

Julia Lipecki[1,†], Andrew E. Mitchell [2,†], Joanne Muter[2,3], Emma S. Lucas[2], Komal Makwana[2], Katherine Fishwick[2], Joshua Odendaal[2], Amelia Hawkes[2], Pavle Vrljicak[2], Jan J. Brosens [2,3], and Sascha Ott [2,4,*]

[1]School of Life Sciences, University of Warwick, Coventry, UK [2]Warwick Medical School, University of Warwick, Coventry, UK [3]Tommy's National Centre for Miscarriage Research, University Hospitals Coventry and Warwickshire National Health Service Trust, Coventry, UK [4]Bioinformatics RTP, Research Technology Platforms, University of Warwick, Coventry, UK

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Submitted on July 31, 2021; resubmitted on December 09, 2021; editorial decision on January 06, 2022

Human Reproduction, Vol.37, No.4, pp. 644–650, 2022
Advance Access Publication on February 11, 2022 https://doi.org/10.1093/humrep/deac022

human reproduction **OPINION**

Use of 'omics for endometrial timing: the cycle moves on

John D. Aplin * and Adam Stevens

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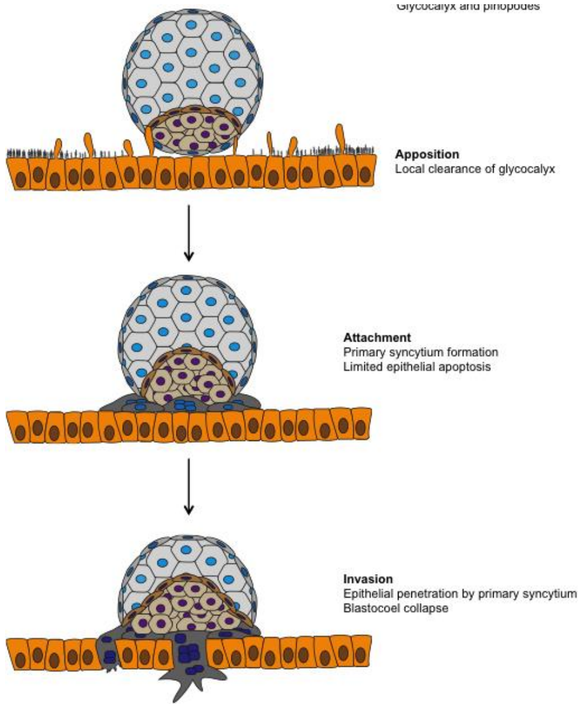
Submitted on November 24, 2021; resubmitted on January 5, 2022; editorial decision on January 21, 2022

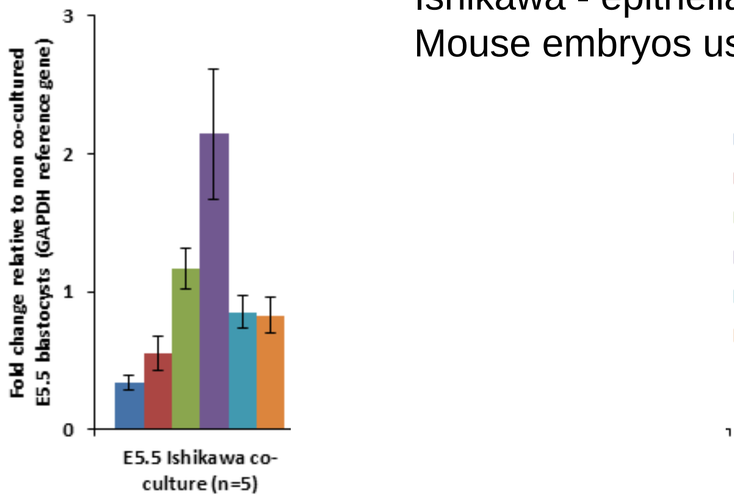
The only aspect of receptivity that is *directly* assessed in mid secretory phase is epithelial

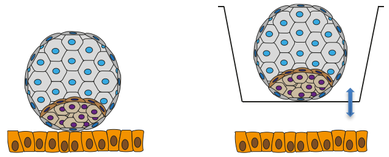


Receptivity requires participation in a dialogue, and is not a state of the endometrium that can be measured in isolation

Hand1 (invasive trophoblast transcription factor) is upregulated by direct embryo-epithelial intercellular contact

Ishikawa - epithelial cell monolayer
Mouse embryos used for proof of principle

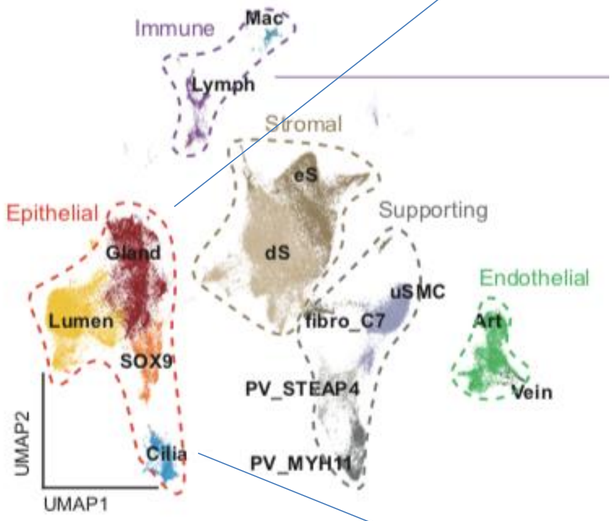


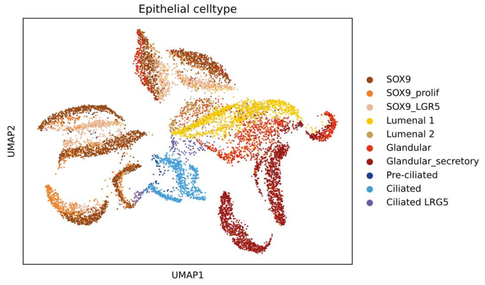


Apposition to endometrial epithelial cells activates mouse blastocysts for implantation. Ruane PT, Berneau SC, Koeck R, Watts J, Kimber SJ, Brison DR, Westwood M, ***Aplin*** *JD. Mol Hum Reprod. 2017 23:617-627*.

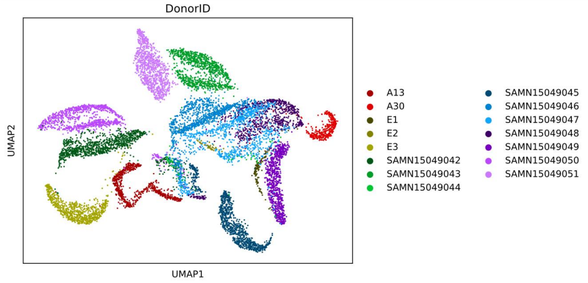
Single cell RNAseq

Epithelium

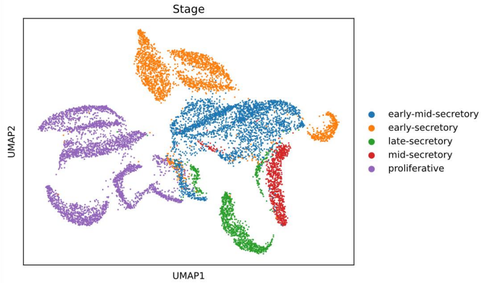




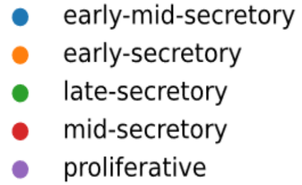
Using Garcia-Alonso cell type classification



By individual donor

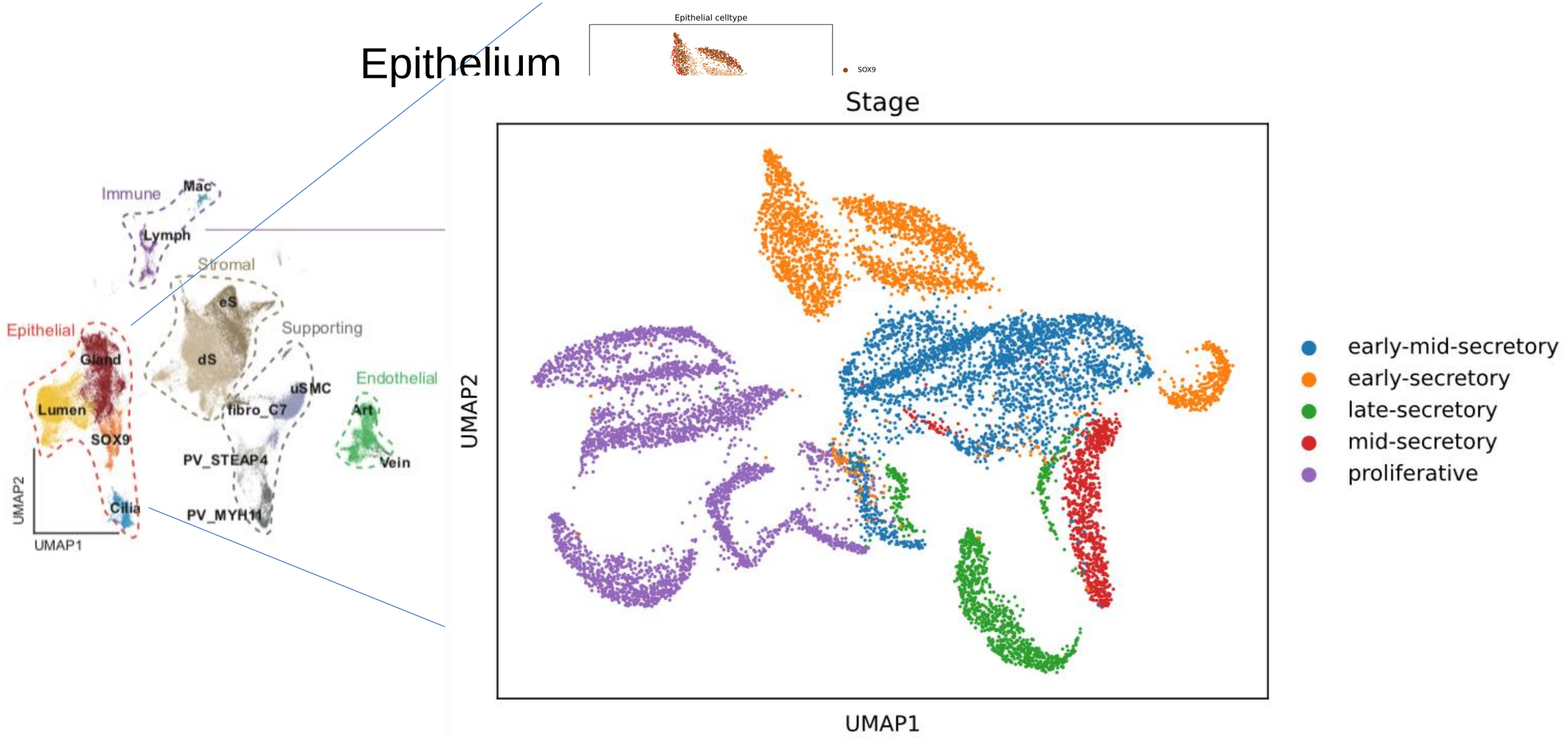


By cycle phase



Mapping the temporal and spatial dynamics of the human endometrium in vivo and in vitro
Garcia-Alonso et al Nat Genet. 2021;53(12):1698-1711
Stevens, Khashkhusha, Ruane, Garner, Aplin, in submission

Single cell RNAseq



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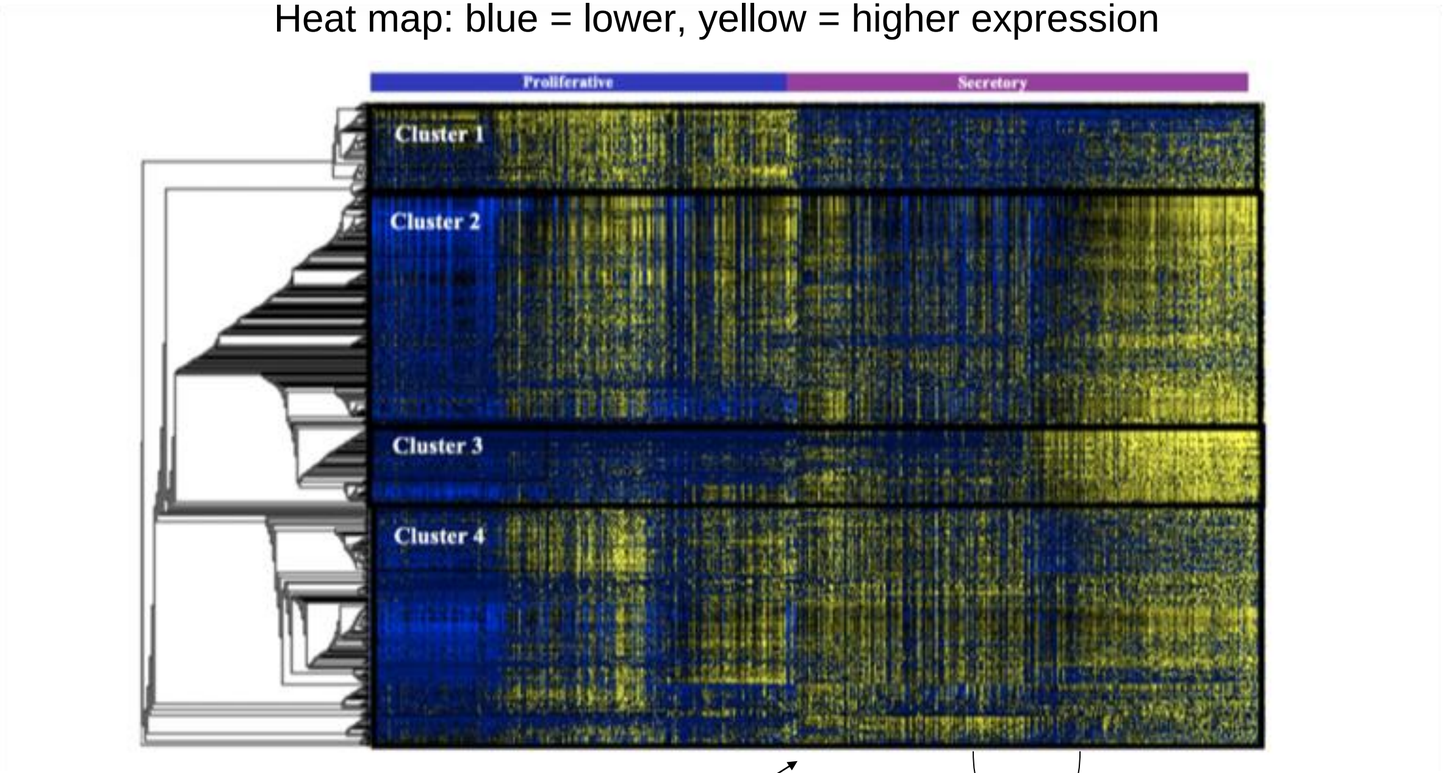
LE-TE (human day 6/7) interactome ➞ top 500 LE genes

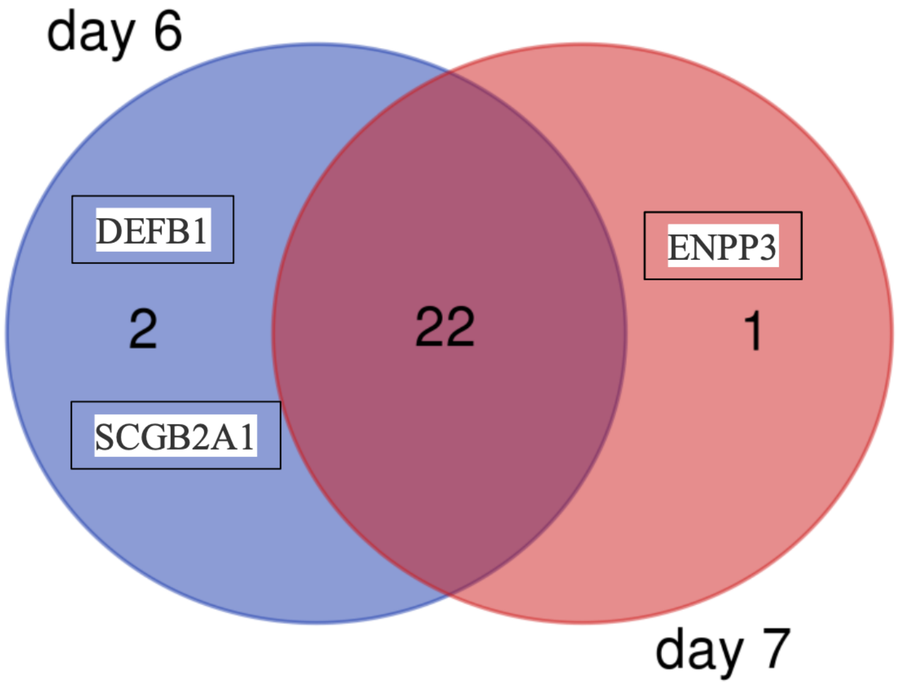
Expressed in pseudotime (X axis)

Heat map: blue = lower, yellow = higher expression



TE data: Petropoulos et al 2016 Cell 167(1):285

LE (non-ciliated) cluster genes interacting with TE surface components



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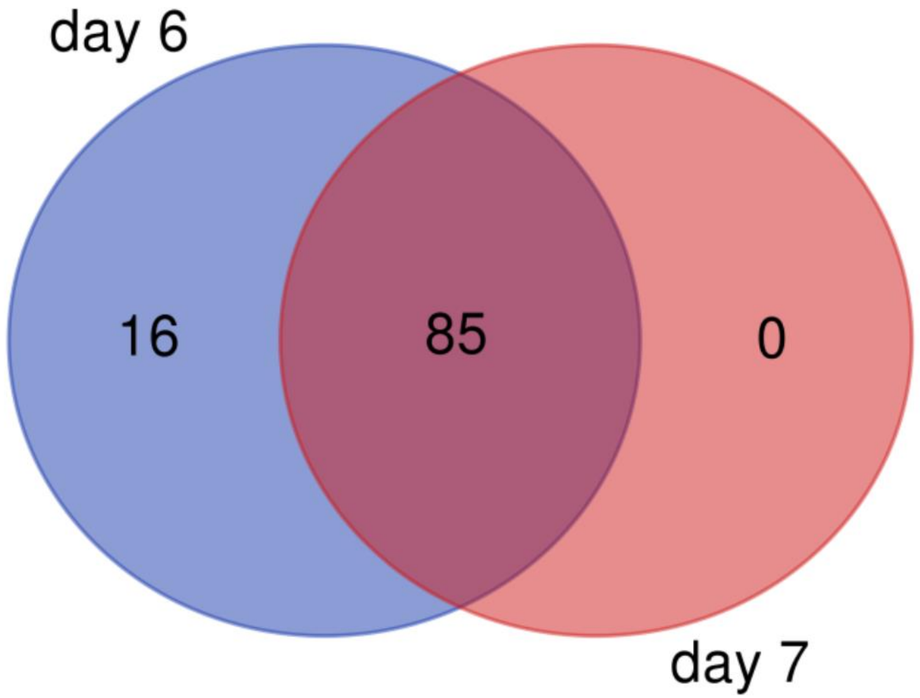


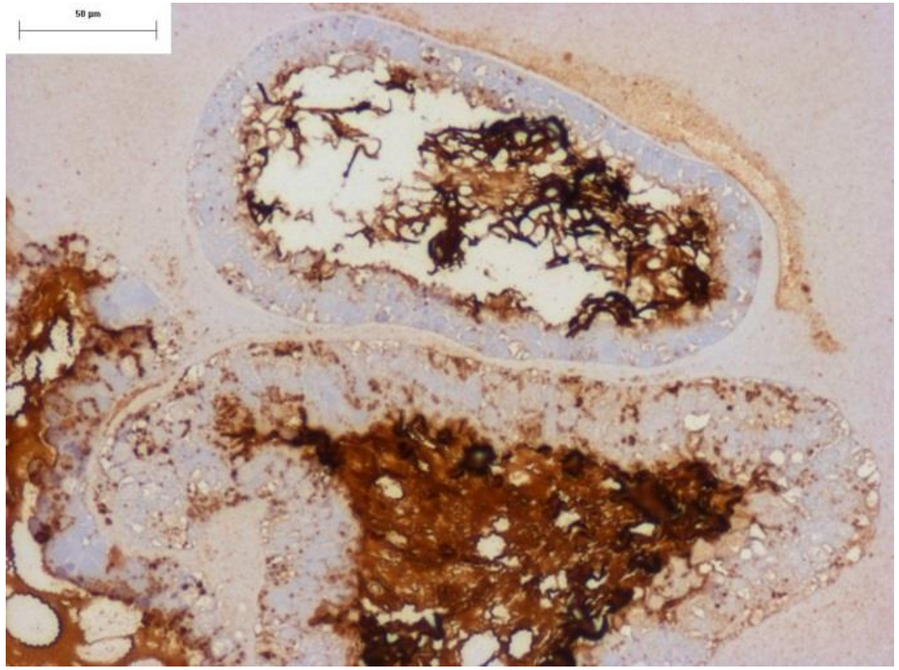
Ciliated cells as well as non-ciliated cells are predicted to interact with the blastocyst at implantation

Functional testing: in vitro studies

Can 3D models of endometrium assist in defining the receptive state?

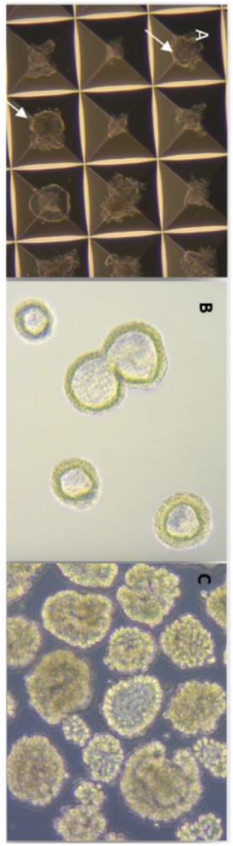
We can make hormone-responsive gland organoids, but their apical epithelial surface is inward-facing

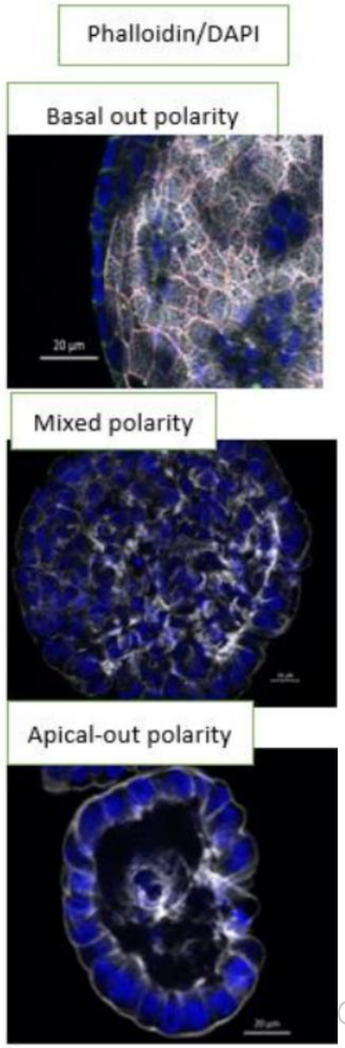
Image: organoids after P treatment, with brown staining of secretory glycoprotein



Turco MY et al Nature Cell Biol 2017 doi: 10.1038/ncb3516.
Long-term, hormone-responsive organoid cultures of human endometrium in a chemically defined medium

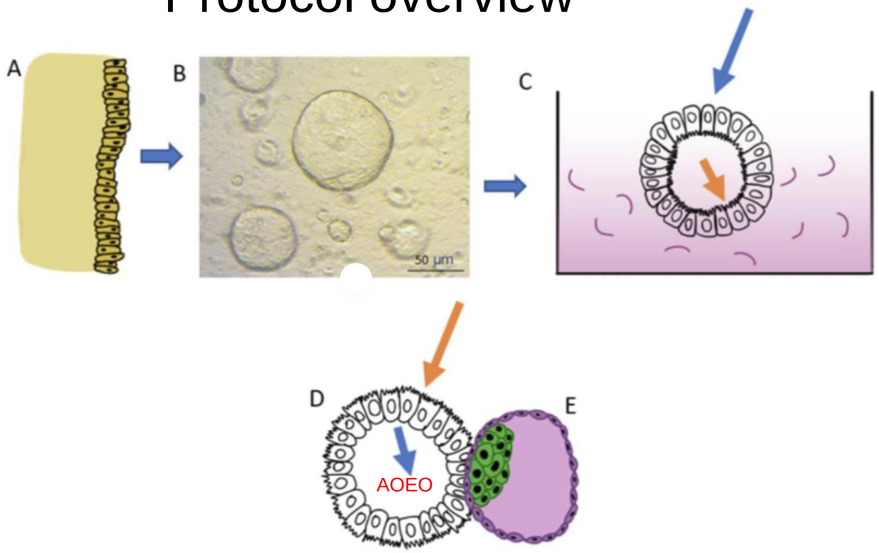
Endometrial epithelial organoids can be polarity-reversed so the apical surface faces outwards (AOEO)



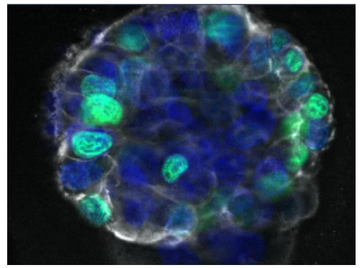


Assay of attachment: trophoblast (TSC) spheroid to endometrial organoid (AOEO)

Protocol overview



Human trophoblast spheroid



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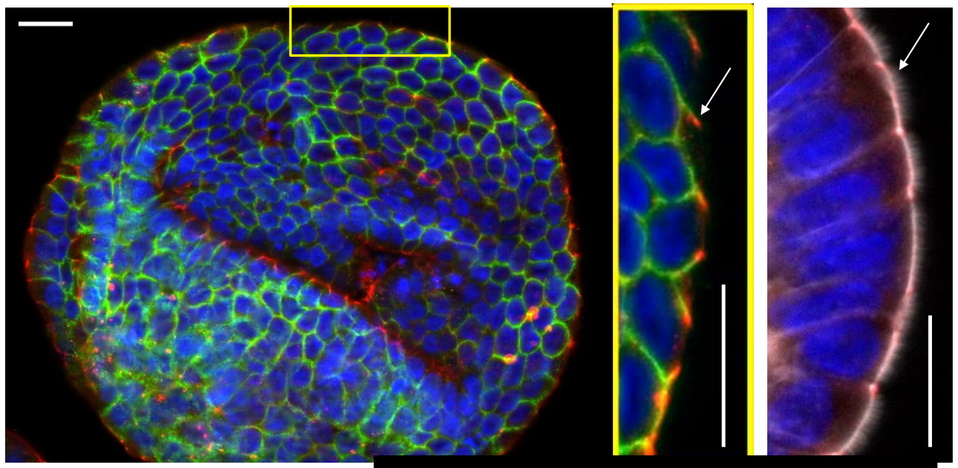
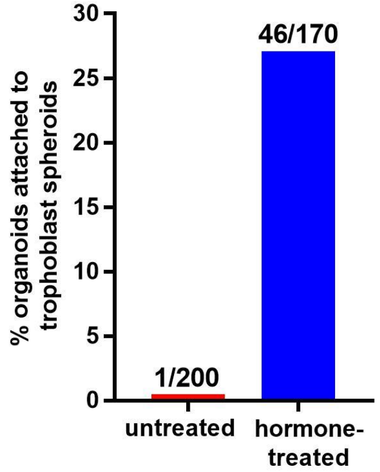
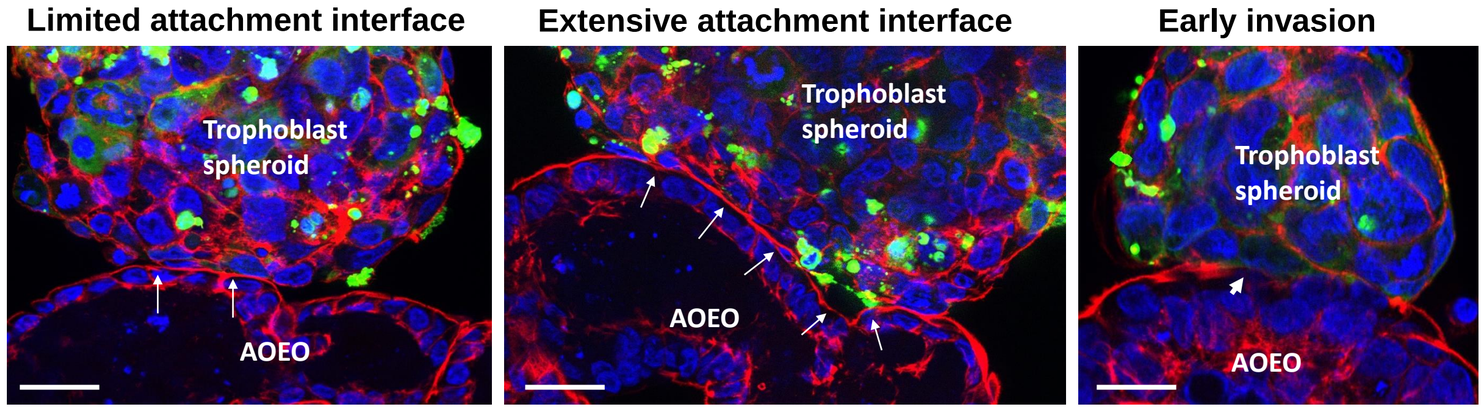


P stimulation renders AOEOs receptive to attachment





Implications

Develop tests that identify non-receptive cycles so that viable embryos are not replaced with no chance of success

Develop approaches to improve the quality of the endometrium starting at post-menstruation, keeping in mind cell dynamics, cell trafficking, and current advances in stem cell biology

Integrate with ex vivo 3D implantation modelling

Shift the focus away from minor adjustments to the timing of embryo replacement

Take-home messages

Is there an embryo-receptive state in endometrium that can be identified and characterised?

Yes

Can ‘omics tests based on lysates of mid secretory phase tissue identify an implantation window?

Not at present

Can single cell transcriptomics lead to advances in endometrial receptivity testing?

Probably

Can ex vivo 3D modelling of implantation help?

Yes

Can improvement in live birthrate be achieved by optimising the condition of the endometrium at embryo transfer?

Yes

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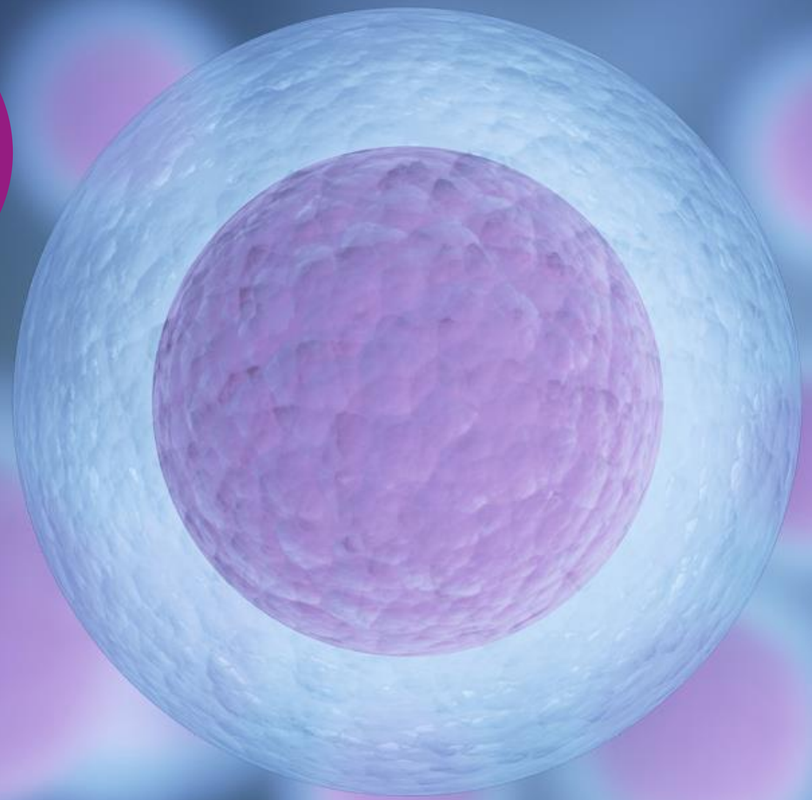
Recent Developments in the Transmission of Human Life

Human embryo implantation: from basic science to clinical applications

John Aplin

Peter Ruane
Adam Stevens
Evie Walker
Taqua Ramzi
Fehmida Qur
Daman Adlam
Terry Garner
Rebecca Koeck
Daniel Brison
Megan Sharps
Melissa Westwood



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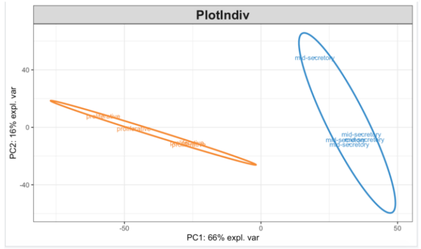
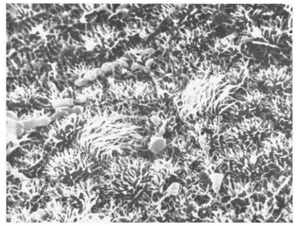
Computational biology workflow

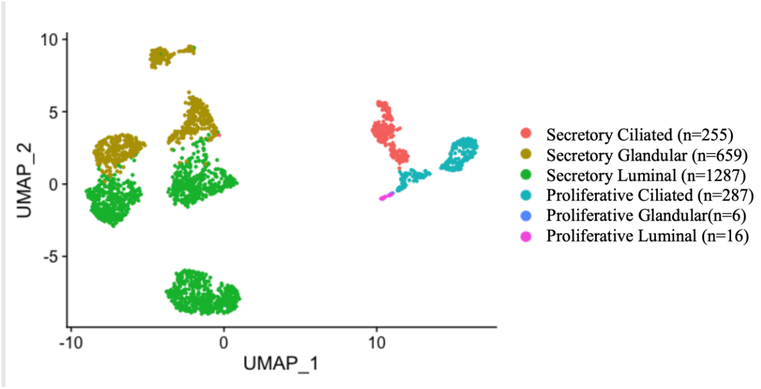
Epithelial cell transcriptomes



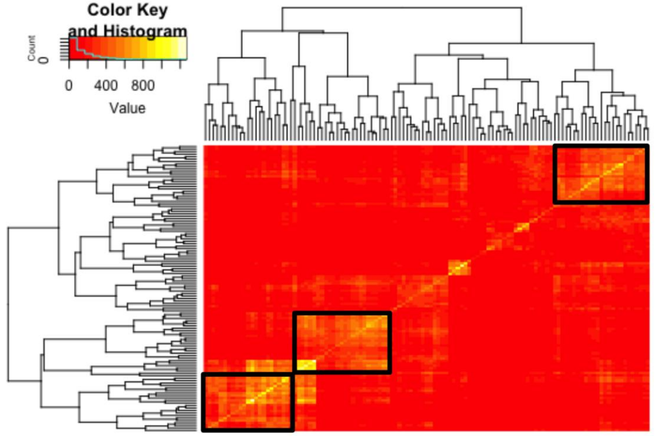
Proliferative, mid secretory phase



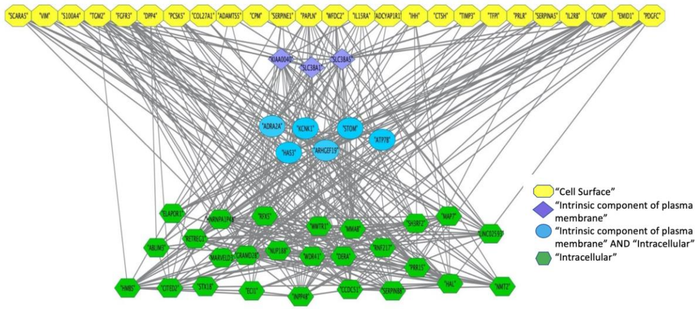
Ciliated, non-ciliated



Hypernetwork analysis: correlation of gene expression changes



Cell surface networks



Integration with blastocyst TE(d6, d7) surface transcriptome

Interactome: possible ligand-receptor relationships at implantation