Human Fertilisation & Embryology Authority

How research can benefit patients and professionals

Annual conference 2018 workshop

Chair: Bobbie Farsides

15 March 2018

www.hfea.gov.uk

Manchester Academic Health Science Centre

The University of Manchester

NHS

Manchester University NHS Foundation Trust

The current research landscape

St Mary's Hospital, Manchester

Manchester Academic Health Science Centre

MANCHESTER 1824 The University of Manchester

NHS

NHS Manchester University NHS Foundation Trust

Research using donated embryos, eggs and sperm

Research using data held on the HFEA register

Reasons to be Cheerful - about Research!

NHS
Manchester University
NHS Foundation Trust

Patients like to be involved in Research

97% of public want NHS to do research
MORI, 2011

630,000 patients in research studies in 2016 www.nihr.ac.uk

Clinical centres doing research have better results

"Research-active trusts have better patient outcomes, study shows"
NIHR, 2015

Research involvement is a badge of honour

Meets patient expectations

NHS
National Institute for Health Research

IVF Embryo Research

Manchester University
NHS Foundation Trust

But isn't IVF different?

Should we <u>really</u> be asking patients to donate their embryos to research?

Only surplus eggs/embryos are used. Fresh poor quality. Long term frozen.

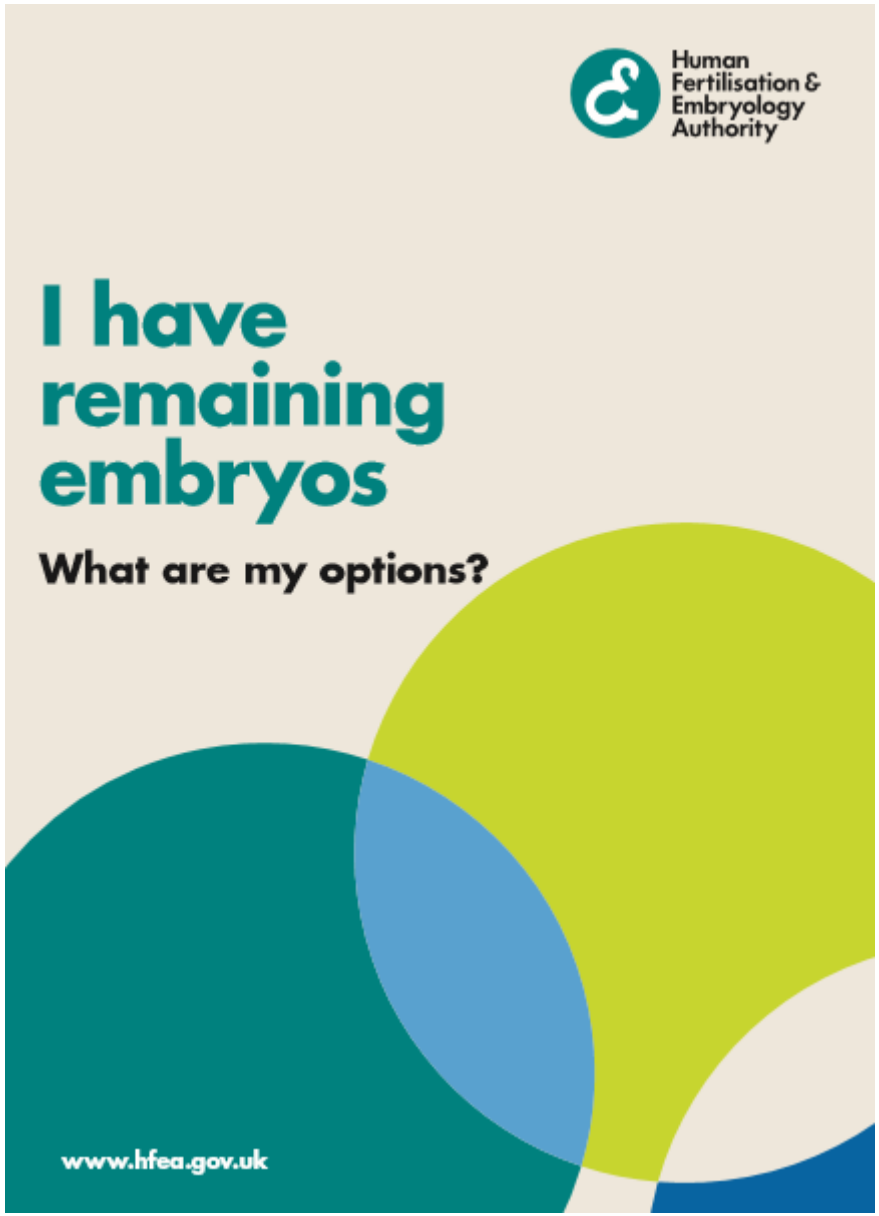
Embryo creation and use 1991 - 2012

- 3.5 million embryos created in the UK (The Telegraph Dec. 2012 FOI Lord Alpine)
- 1.4 million embryos transferred
- 235,480 clinical pregnancies
- <u>1.7 million embryos created , unused & discarded</u>

ART patients and professionals do not like wasting embryos!

Tope Adeniyi

Embryos in storage leaflet



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If you have embryos in storage that you no longer need for your own treatment you may find it difficult to decide what to do next. Whether or not your treatment was successful, letting go of your frozen embryos can be hard to do. This leaflet guides you through the options for your remaining embryos, and where you can find more information and support to help you when making your choice.

Where do I start?

If you decide that you no longer need your embryos for your own treatment, you might be given the option to donate them to research, training or to other patients for their treatment. However, if these choices aren't right for you, you might decide that it's time to allow your embryos to perish. This could be a difficult decision for you to make and you may need to consider all your options very carefully

If you feel you'd like extra support, counselling could help and your clinic may offer this to you. Alternatively, you can organise this yourself. Your GP can give you advice about getting counselling on the NHS or if you'd prefer to go private, the British Infertility Counselling Association (BICA) has a directory of accredited therapists with various options including telephone and Skype counselling. Or, you can contact a patient organisation, such as Fertility Network UK, for support.

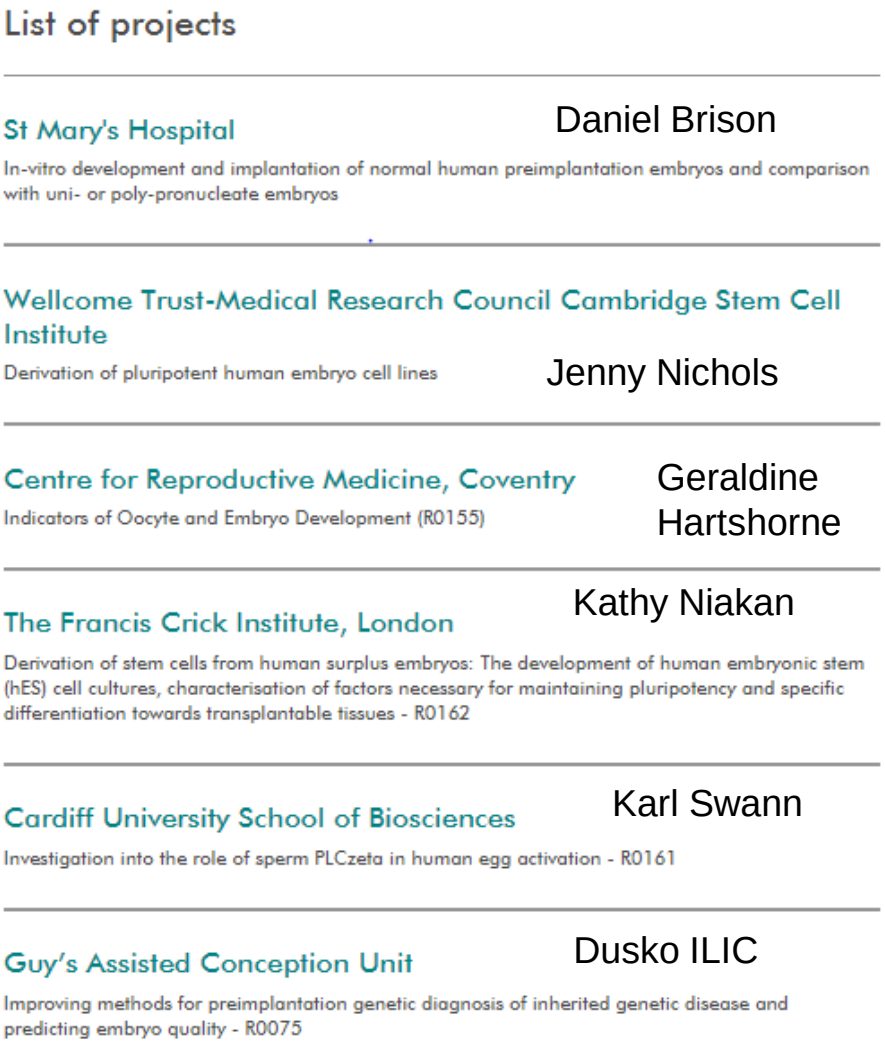
What are my options?

The options for you to consider will depend on what your clinic is able to offer, and could be to:

- donate your embryos to a research project. Embryo research is crucial for developing fertility treatments, and without this IVF would not have been possible. Embryos can only be used for medical research that addresses specific purposes and that we have authorised. This option may only be possible if your clinic has a link with a research project.
- donate your embryos for training purposes. Training is vital for all embryologists to improve or learn new techniques.
- donate your embryos to another person or couple for treatment. This option will help realise others' dreams of becoming parents. If this is something you would like to do your clinic can talk you through the process, including meeting the eligibility criteria for being a donor.
- allow the embryos to perish. If you decide to take this option, the embryologist will complete this process with respect and sensitivity.

www.hfea.gov.uk/donation/donors/donating-to-research

Establishing embryo research partnerships on the Clinic Portal



List of projects

St Mary's Hospital — Daniel Brison

In-vitro development and implantation of normal human preimplantation embryos and comparison with uni- or poly-pronucleate embryos

Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute — Jenny Nichols

Derivation of pluripotent human embryo cell lines

Centre for Reproductive Medicine, Coventry — Geraldine Hartshorne

Indicators of Oocyte and Embryo Development (R0155)

The Francis Crick Institute, London — Kathy Niakan

Derivation of stem cells from human surplus embryos: The development of human embryonic stem (hES) cell cultures, characterisation of factors necessary for maintaining pluripotency and specific differentiation towards transplantable tissues - R0162

Cardiff University School of Biosciences — Karl Swann

Investigation into the role of sperm PLCzeta in human egg activation - R0161

Guy's Assisted Conception Unit — Dusko ILIC

Improving methods for preimplantation genetic diagnosis of inherited genetic disease and predicting embryo quality - R0075

Researchers rely on treatment clinics to help recruit egg, sperm or embryo donors for their projects. This is only possible if researchers and clinics establish partnerships.

This section of the Portal contains a list of research projects that are actively looking for clinic partners, to help identify potential donors for their research. It includes details about the projects, the types of research materials needed and any support or resources available to help recruit donors. If you are a treatment centre and are interested in establishing a partnership with one or more of these research groups, please contact the project lead directly.

Human Fertilisation & Embryology Authority

https://portal.hfea.gov.uk/knowledge-base/embryo-research/

St Mary's system

Manchester University
NHS Foundation Trust

Project R0026 'In-vitro development and implantation of normal human preimplantation embryos and comparison with uni- or poly-pronucleate embryos'
University of Manchester and St Mary's Hospital since 1993

Network of Patient Identification Centres (PICs)

NHS National Institute for Health Research

"A PIC is a site where participants are identified and referred to a different centre specifically to take part in a research study. The receiving centre is the research site and is responsible for… taking informed consent to enter the participant into the study."

NHS Health Research Authority

Gives clinics ethical approval status and useful NIHR kitemark?

Lucy Dwyer

NHS National Institute for Health Research | MRC Medical Research Council | COOPERATION

St Mary's system

Manchester University NHS Foundation Trust

Network of Patient Identification Centres (PICs)

NHS National Institute for Health Research

Research Nurse posts
Clinical Embryologist co-ordinator

Funded by NHS National Institute for Health Research
Clinical Research Network/
CRN Portfolio

- ✓ **Obtain PIC approval and handle all research consenting directly with patients**
- ✓ **Arrange transport of embryos by courier to St Mary's**
- ✓ **Close involvement of Embryologists (STP projects, Postgraduate (MSc, PhD) degrees)**
- ✓ **Grant funding - Tope Adeniyi NIHR doctoral (PhD) fellowship**

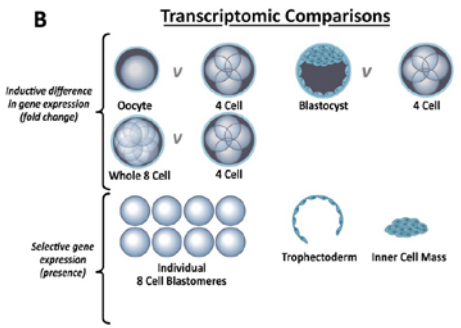
MRC Medical Research Council

Aims of human embryo research?

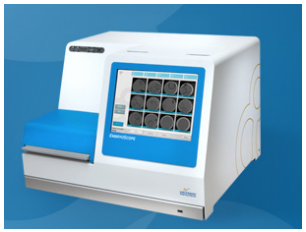
Manchester University
NHS Foundation Trust

Increase basic scientific understanding
Improve the success and safety of ART

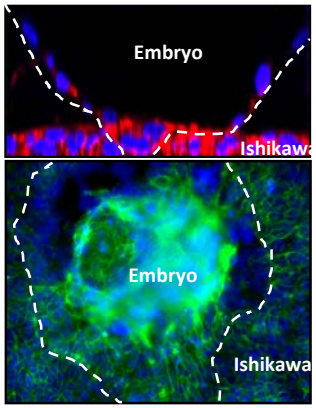
Molecular biology of human embryo development



Impact of ART lab environment on embryo development
e.g. EmbryoScope



Improving ART success rates
e.g. EmbryoGlue and implantation



Validation of technology
e.g. Oocyte vitrification – Tope Adeniyi

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Register Research

- **Background**
- **Update**
- **Future developments**

Caylin Joski-Jethi
Head of Intelligence

www.hfea.gov.uk

Background

- The Register: largest database on fertility treatments in the world
- Until 2009/10: ‘patient identifiers’ could not be disclosed
- Law changed for research in 2009
- Research Regs 2010: provide ethical and legal safeguards for disclosure of register information for research

https://www.hfea.gov.uk/choose-a-clinic/how-we-manage-your-data/

Key facts
Researchers are allowed to request identifying information from us
They can only use information that would identify you with your consent
Research using your data is incredibly valuable to medical science
Only reputable applicants can request data from us

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HFEA Register Research

Manchester University NHS Foundation Trust

Historical problems HFE (1990) Act:

- **Register not originally designed for research**
- **Missing key data fields such as parent and baby unique identifiers e.g. NHS numbers**
- **Specific patient consent for research was not considered**

This changed in the HFE (2010) Act, with changing public attitudes to patient confidentiality and monitoring of safety from medical treatments.

1991-October 2009 – *Presumed Consent* to research for 110,000 children whose health outcomes can be tracked.

October 2009 onwards – Consent to disclosure (CD) required.

HFEA Information for Quality (IfQ) programme - Data quality improved and key fields added such as NHS number

For register research, only CD to non-contact research is required!

NHS National Institute for Health Research

HFEA Register Research

Manchester University
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1991-2009 cohort projects approved by RRP

Cancer (UCL)

EpiHealth: ART child growth and health (Manchester)

Health, hospital admissions (UCL +)

NHS
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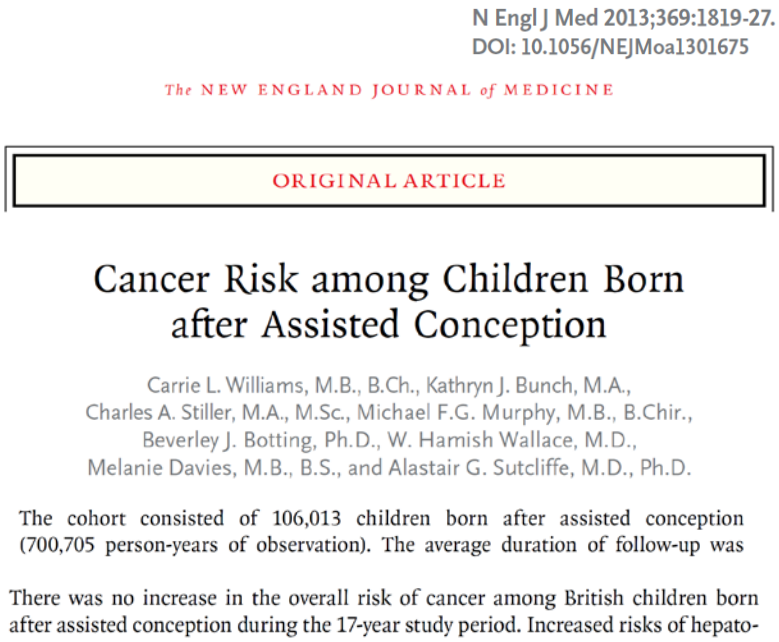


N Engl J Med 2013;369:1819-27.
DOI: 10.1056/NEJMoa1301675

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

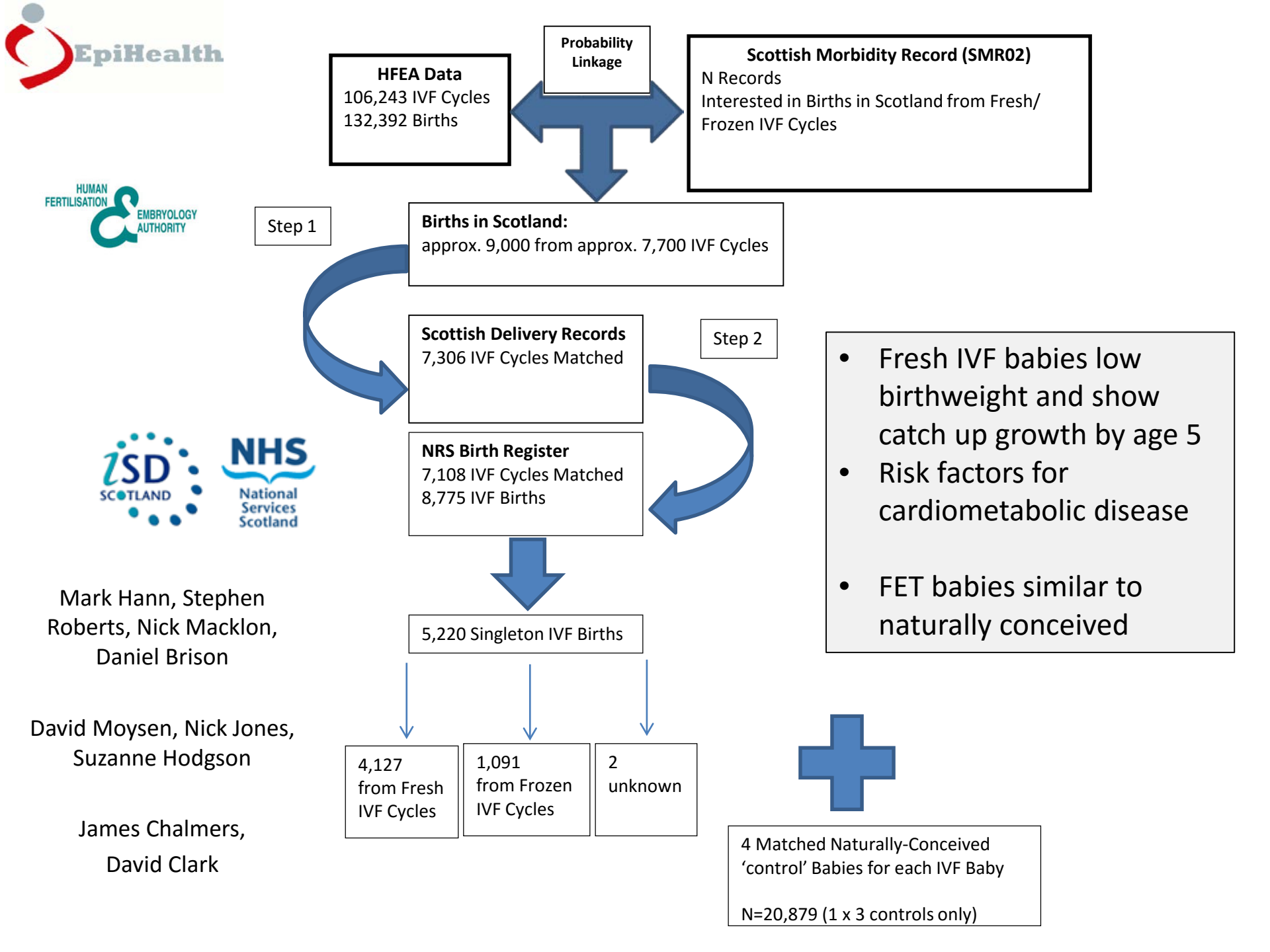
Cancer Risk among Children Born after Assisted Conception

Carrie L. Williams, M.B., B.Ch., Kathryn J. Bunch, M.A., Charles A. Stiller, M.A., M.Sc., Michael F.G. Murphy, M.B., B.Chir., Beverley J. Botting, Ph.D., W. Hamish Wallace, M.D., Melanie Davies, M.B., B.S., and Alastair G. Sutcliffe, M.D., Ph.D.

The cohort consisted of 106,013 children born after assisted conception (700,705 person-years of observation). The average duration of follow-up was

There was no increase in the overall risk of cancer among British children born after assisted conception during the 17-year study period. Increased risks of hepato-

NHS
National Institute for Health Research



- Fresh IVF babies low birthweight and show catch up growth by age 5
- Risk factors for cardiometabolic disease
- FET babies similar to naturally conceived

Mark Hann, Stephen Roberts, Nick Macklon, Daniel Brison

David Moysen, Nick Jones, Suzanne Hodgson

James Chalmers, David Clark

HFEA Register Research

Manchester University NHS Foundation Trust

1991-2009 cohort projects approved by RRP

Cancer (UCL)

EpiHealth: ART child growth and health (Manchester)

Health, hospital admissions (UCL +)

<u>Challenges and hurdles</u> to register research:

Funding. Expertise. Lack of identifying information on the register. Patient awareness,

Rate of patient CD in clinics - now crucial for future funding

NHS National Institute for Health Research

Challenges and hurdles to clinical embryo research

Manchester University NHS Foundation Trust

Funding

Independent patient consenting/research organisation – NIHR CRN

Involving Embryologists in embryo research

Time! Research facilities and training STP programme

Embryo freezing

Frozen/thawed embryos may behave differently to fresh…

Numbers of embryos is critical to designing meaningful studies and obtaining funding

Manchester Academic Health Science Centre

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NHS

NHS Manchester University NHS Foundation Trust

Discussion

What can clinics do to help embryo research?

What can HFEA and researchers do?

What can HFEA do to help with Register Research (data quality, CD forms?)

Manchester University
NHS Foundation Trust

40 years of clinical IVF: *celebrating the birth of Louise Brown in 1978*

Conference to be held in Manchester, July 2018


BRITAIN'S BIGGEST EVENING SALE

Evening News

LONDON: THURSDAY JULY 27 1978 8p

LATE SPECIAL CITY PRICES

Meet Louise, the world's first test-tube arrival

SUPERBABE

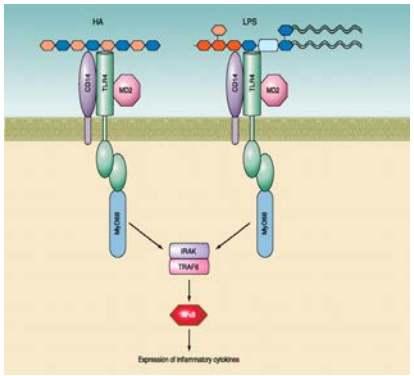
Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she's doing well. See Page Three

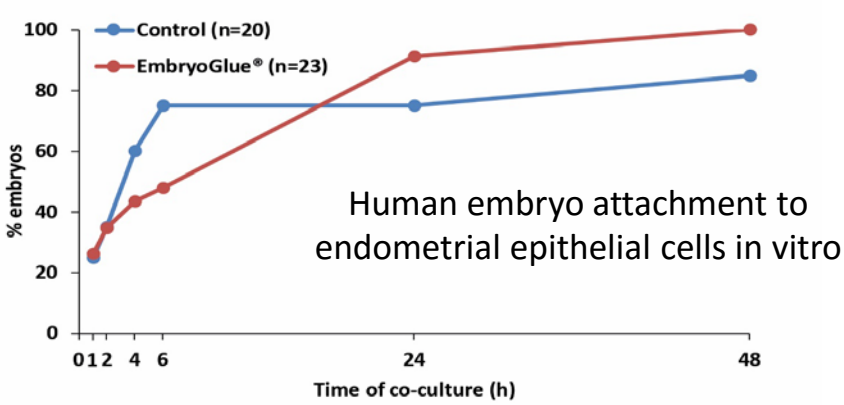
The effect of Hyaluronan on human embryo implantation and gene expression

Manchester University NHS Foundation Trust

Chelsea Buck, Phoebe Babbington, Pete Ruane, Daniel Brison

Does Hyaluronate improve implantation rates by improving embryo development (YES), or acting as an implantation "glue" (NO)?





Human embryo attachment to endometrial epithelial cells in vitro

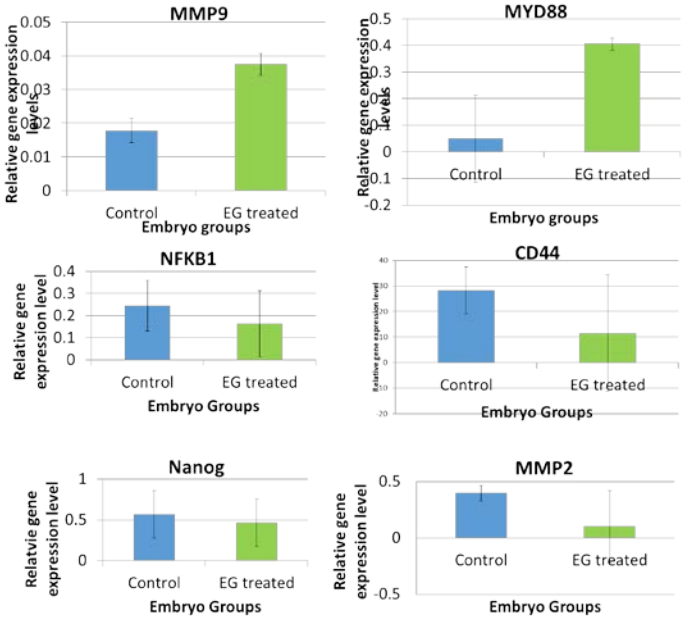


Figure 4- Average gene expression levels across all EmbryoGlue treated embryos vs. controls relative to expression of housekeeping reference gene β-Actin.

Who decides what happens to my embryos?

This depends upon how your embryos were created. If they were created using both your eggs and sperm then it's the decision of you and your partner. However, if your embryos were created using donor sperm or eggs, the consent of those donors would be needed.

How long can I keep my frozen embryos for?

You can keep your embryos frozen for up to 10 years (although if you or your partner have premature infertility, you can store them for longer).

However, your embryos can only be frozen for the length of time you consented to, which could be less than the maximum of 10 years. Once they reach the end of their storage period, they will be allowed to perish. So, if you do decide to donate your embryos, let your clinic know as soon as possible, so there is time to use them.

What happens if I don't make a decision?

If you are unable to reach a decision, or feel you don't wish to donate your embryos, they will be kept for the period agreed with your clinic. After this, your embryos will be allowed to perish.

Can I change my mind?

Yes, you are free to change your decision to donate your embryos at any stage up until they have been used. You can withdraw your consent via your clinic.

For more information about embryo donation options and support, go to

https://www.hfea.gov.uk/donation/donors/donating-your-embryos/

https://www.hfea.gov.uk/donation/donors/donating-to-research/

https://www.hfea.gov.uk/treatments/explore-all-treatments/getting-emotional-support/

Who to contact: **Professor Daniel R Brison**
Clinical Embryologist/IVF Scientific Director
St Mary's Hospital
Email: Daniel.brison@manchester.ac.uk
Telephone: 0161 701 6966

NHS
Manchester University
NHS Foundation Trust

Our team:

Research Nurses: Claudette Wright, Katie Swindells

Clinical Embryologist Research co-ordinator: Kate Goulding/Anna Burdina

Clinical Embryologist researcher: Tope Adeniyi (NIHR PhD fellowship)

PhD students: Maribel Montufar, Liam Hanson

Postdocs: Dr Peter Ruane, Dr Helen Smith, Dr Adam Stevens

Thank You!

MRC Medical Research Council

COOPERATION

Deborah Falconer
Claire Kay

Manchester University NHS Foundation Trust

St. Mary's Hospital
Greg Horne
Cheryl Fitzgerald

Liverpool Women's NHS Foundation Trust

Janet Lee Bijal Patel

midland fertility

Su Barlow
Gill Lockwood

Nuffield Health FOR THE LOVE OF LIFE®

Carolyn Franklin

Lauren Weaver

Jessopfertility Bringing hope to life

Helen Clarke
Rachel Cutting
Mostafa Metwally

LISTER FERTILITY CLINIC
part of HCA Healthcare UK

Safira Bartha

NHS Salisbury Hospital

Bridget Barker

CRGW Centre for Reproduction and Gynaecology Wales

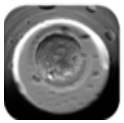
Lyndon Miles

Alison Campbell, Simon Fishel

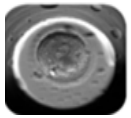
CARE fertility

The Bristol Centre for Reproductive Medicine

Paul Wilson



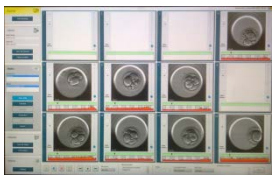
1st day after IVF - tPNf
(n=4 conventional culture)

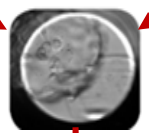


1st day after IVF - tPNf
(n=10 time-lapse culture EMBROSCOPE)

Conventional Screening

Time – lapse parameters monitoring





5-6 days later
Collection of Hatched blastocysts (n=4+10)

RNA

polyA PCR

cDNA

hybridization

Affymetrix® Gene Profiling Array cGMP U133 P2

4

gene expression analysis

10

time lapse parameters analysis;
quality control

Good embryo viability

Poor embryo viability

Hui Xiao
Helen Smith

tPNf - the time of the pronucleous fading, known also as syngamy

Human Fertilisation & Embryology Authority

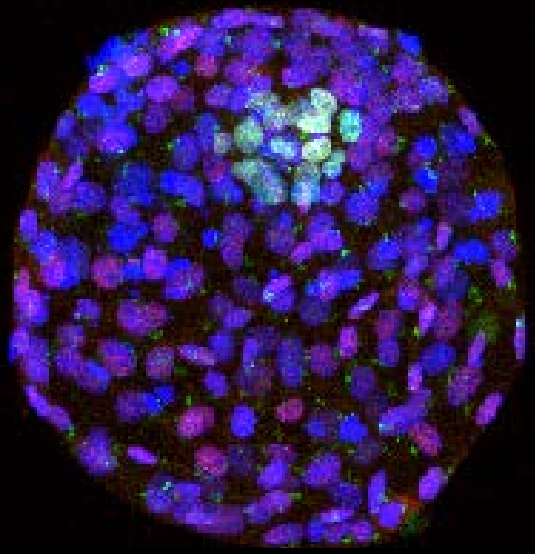
The importance of research

Professor Daniel Brison

15 March 2018

www.hfea.gov.uk

Wellcome Trust - Medical Research Council
Cambridge Stem Cell Institute

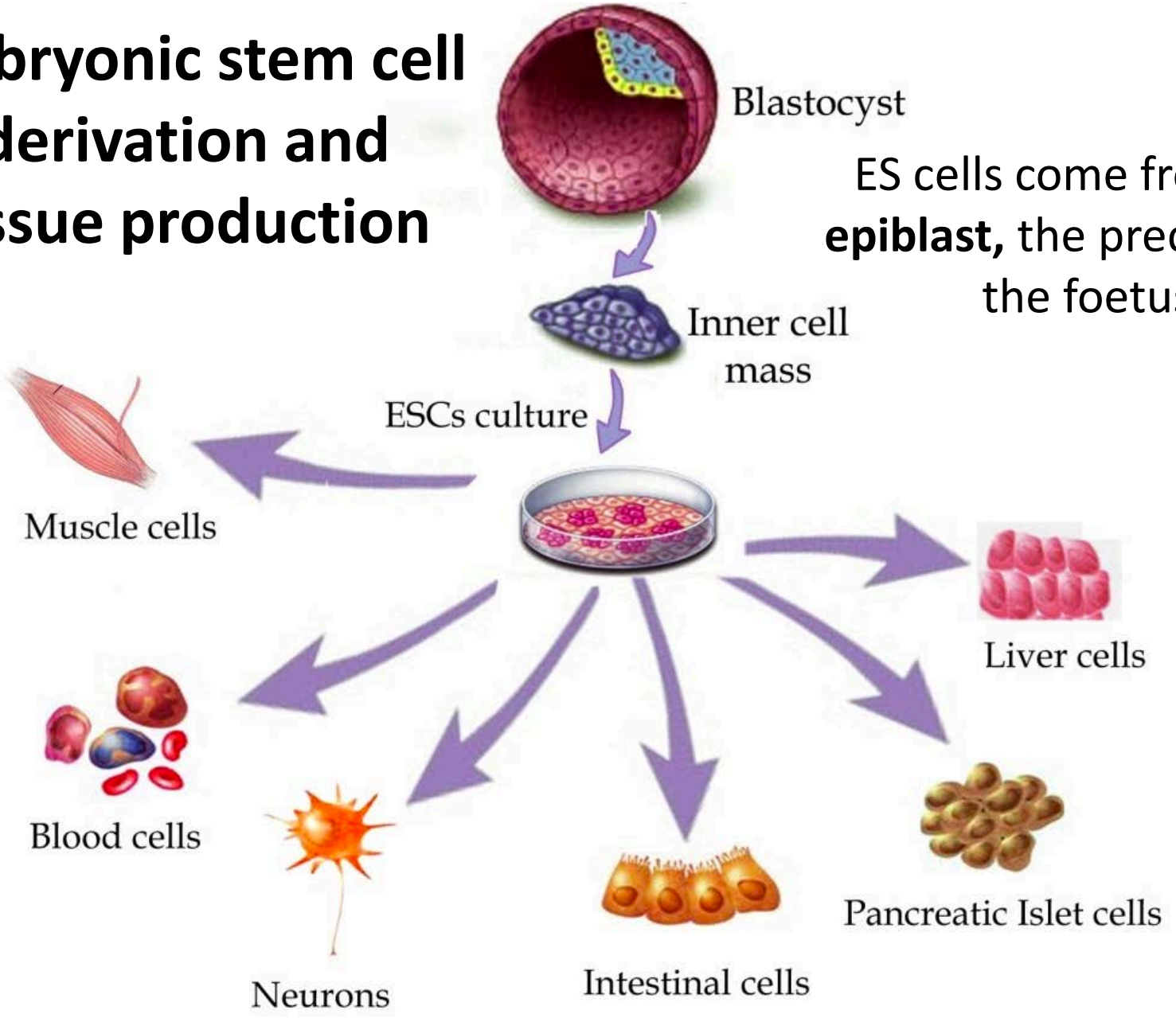


Deriving clonal pluripotent stem cell lines and understanding mechanisms of early development

Austin Smith and Jennifer Nichols

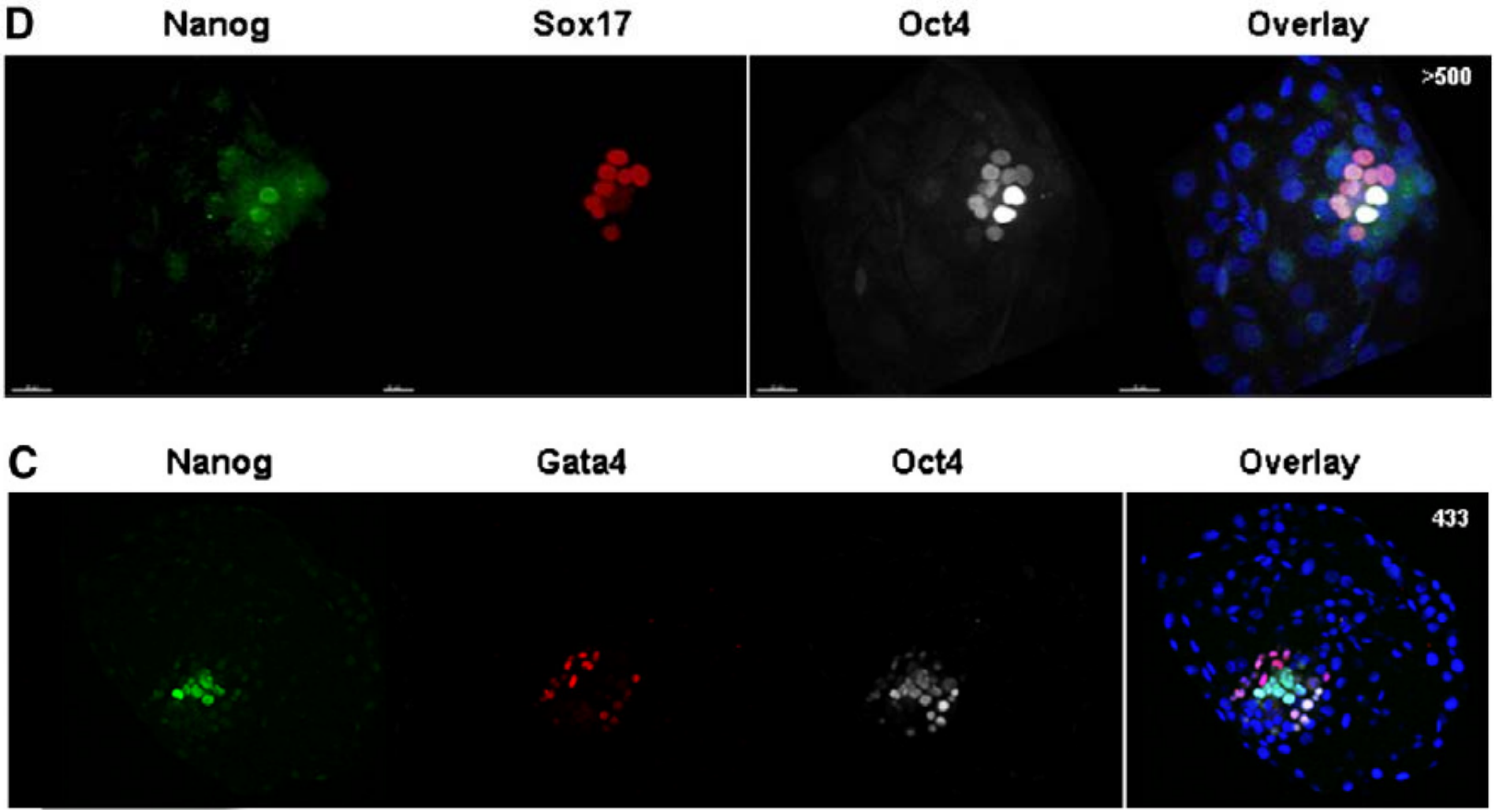
wellcome trust
MRC Medical Research Council
UNIVERSITY OF CAMBRIDGE

Embryonic stem cell derivation and tissue production

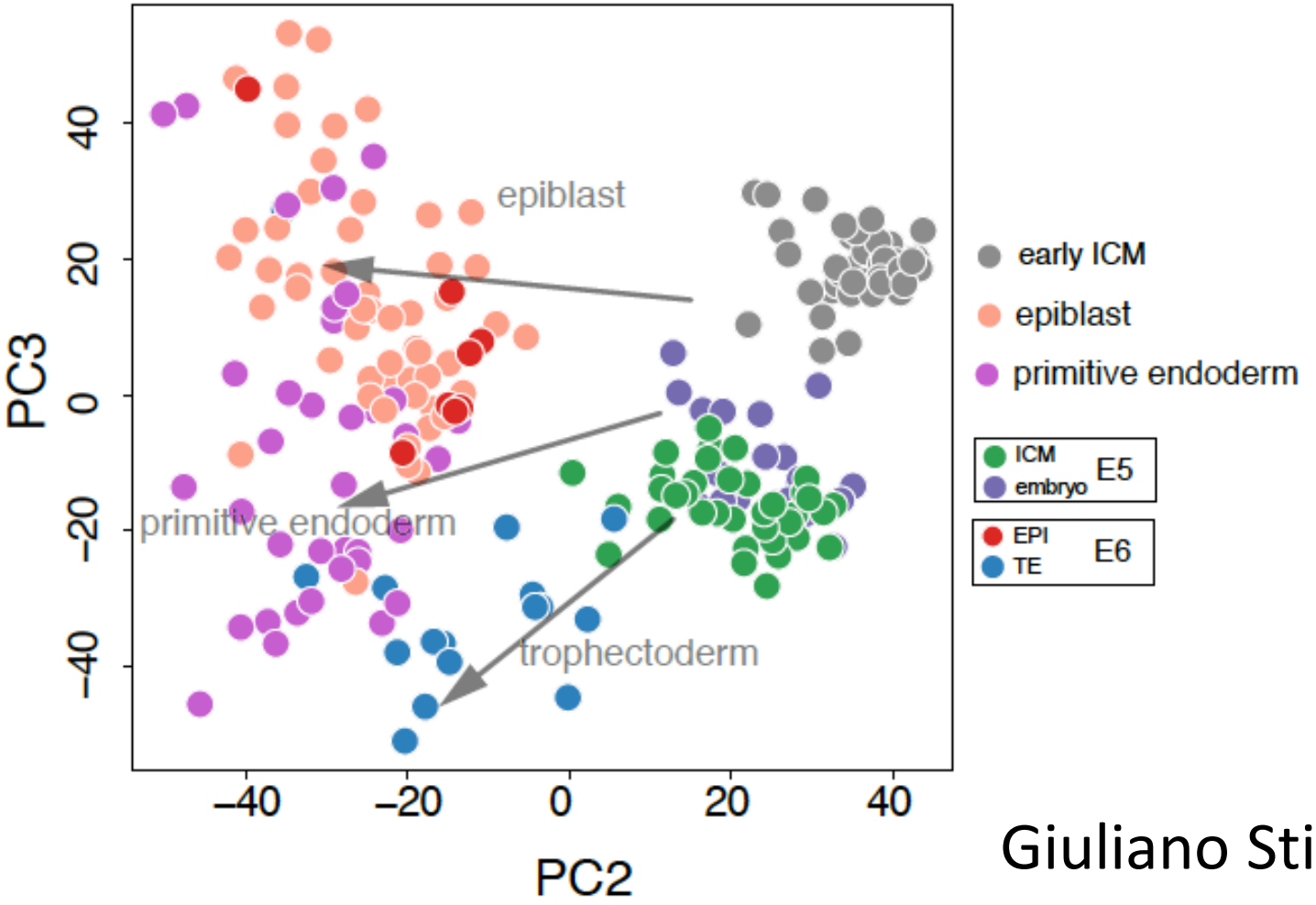


ES cells come from the **epiblast,** the precursor of the foetus

D6 and D7 embryos show segregation of ICM into epiblast (Nanog+) and primitive endoderm (Gata4+)



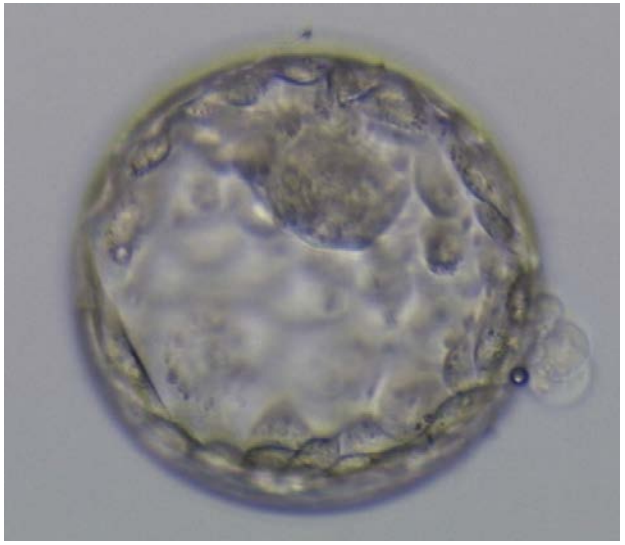
Single cell transcriptional profiling of human embryos

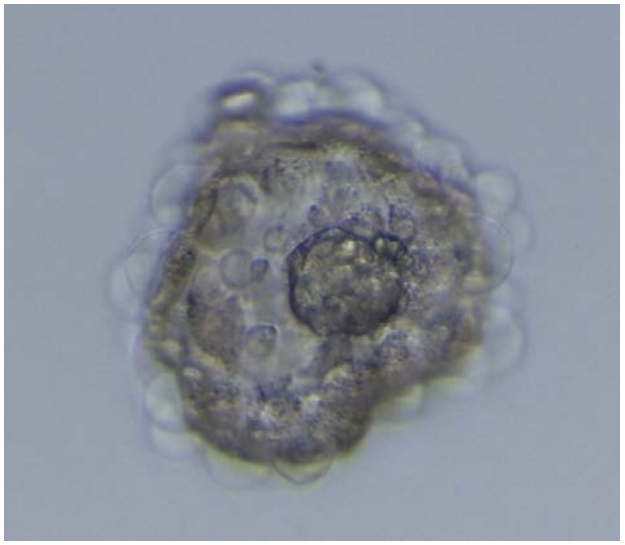


Giuliano Stirparo

Isolation of inner cell mass cells

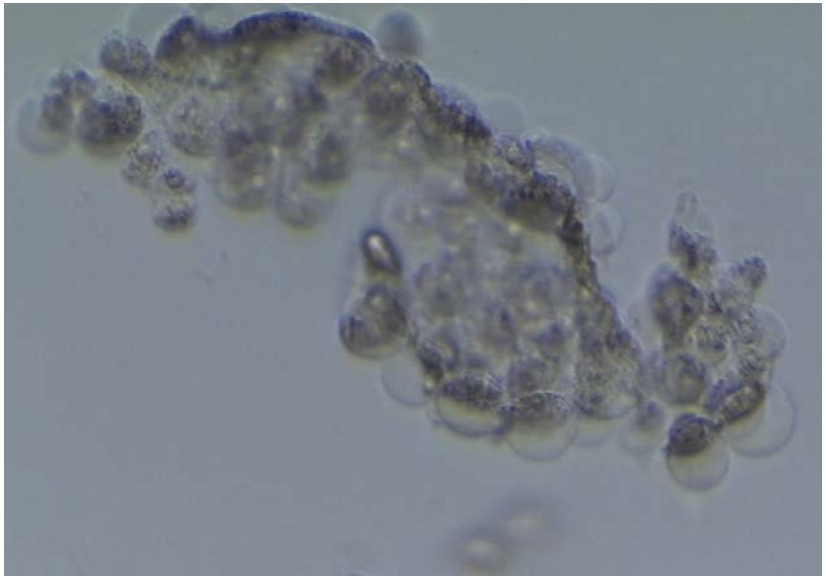
Blastocyst d6

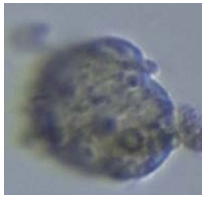


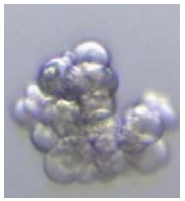


Trophoblast lysis

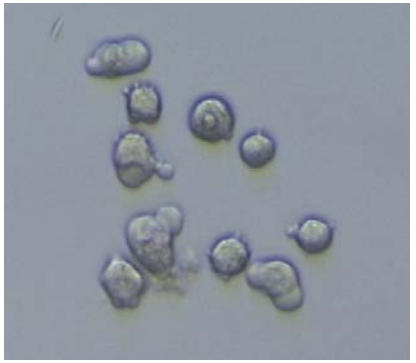
Discarded trophoblast







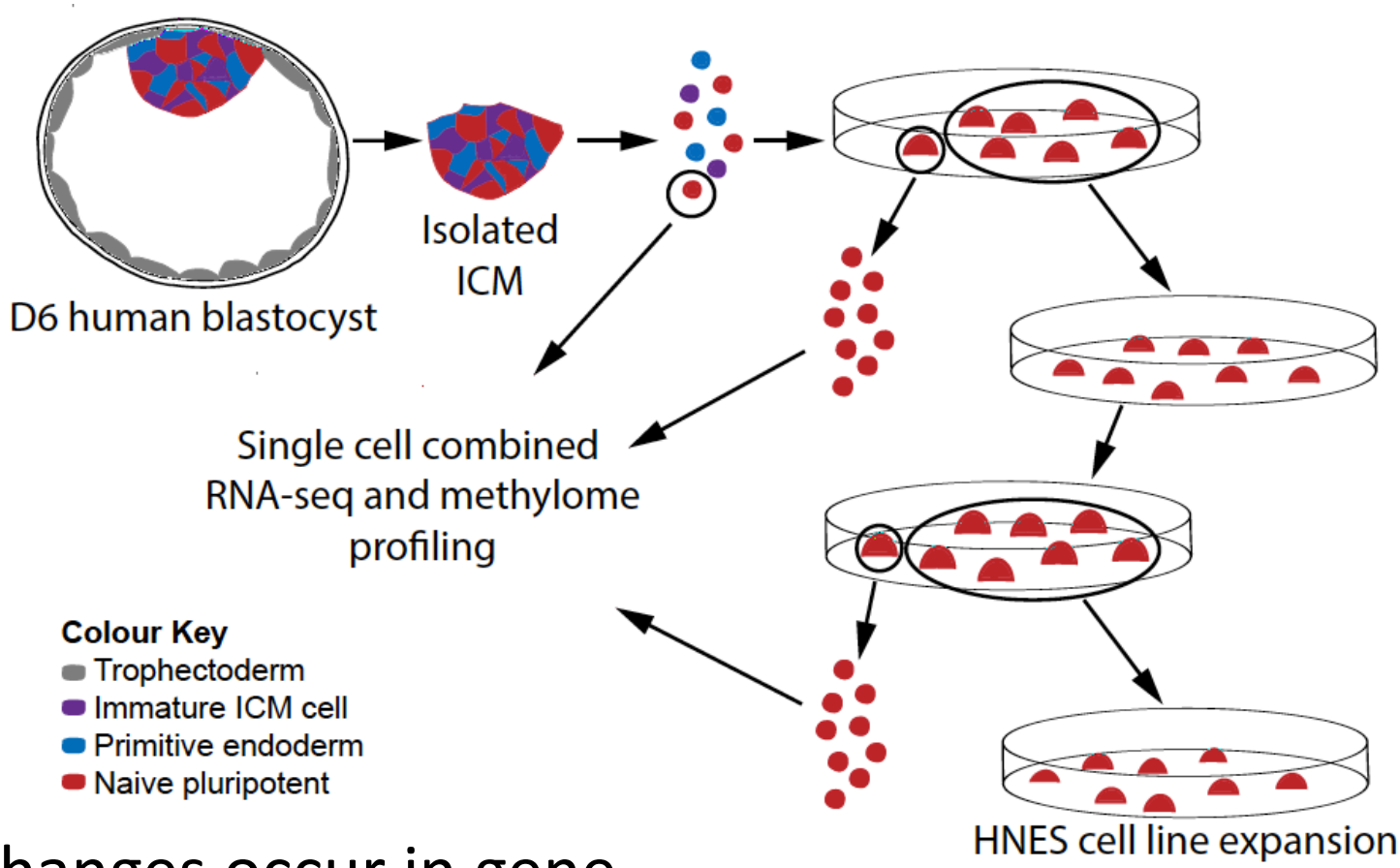
Isolated inner cell mass



Single cells ready for plating

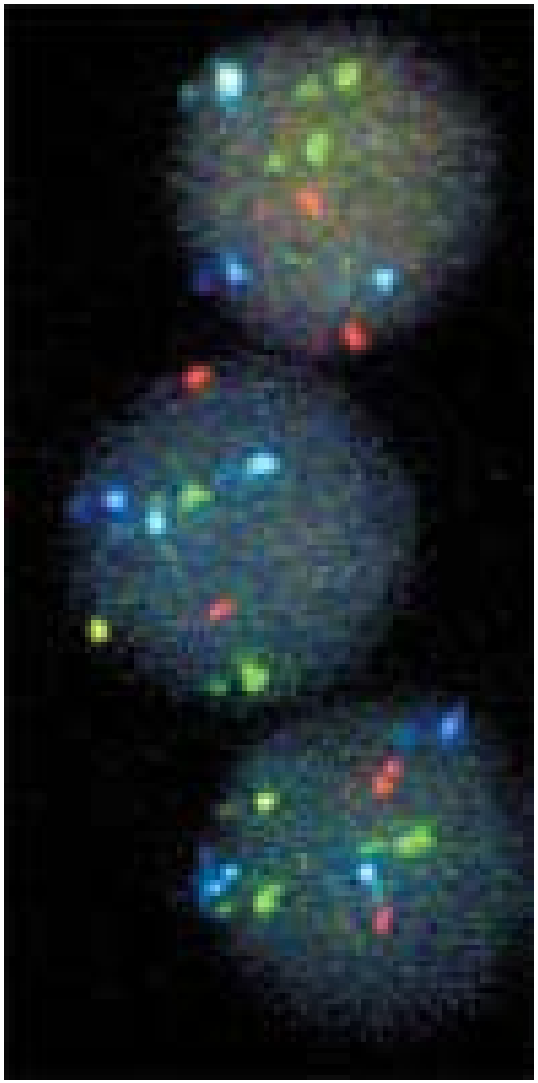
Guo et al., 2016

Single cell profiling to determine the changes occurring during ES cell derivation



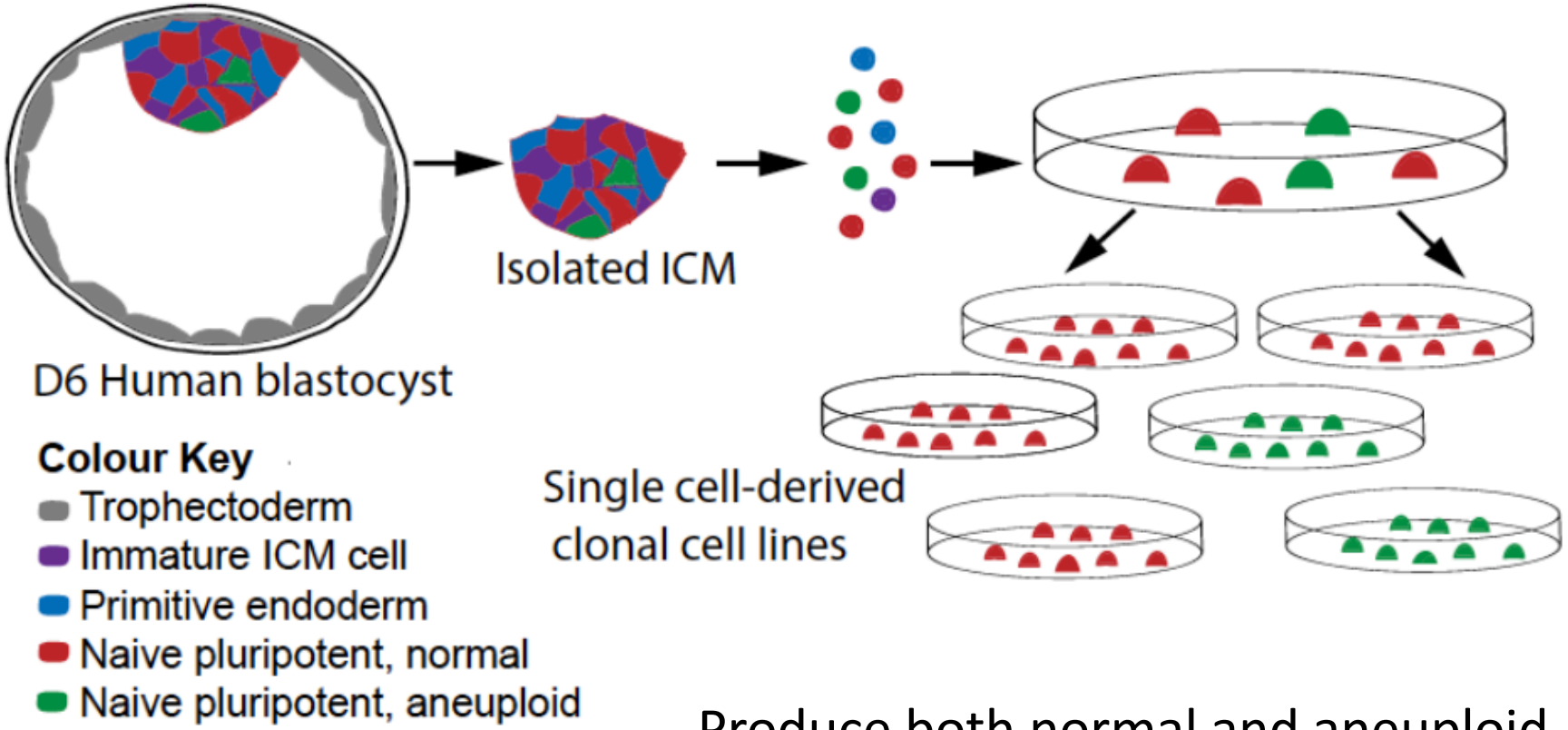
What changes occur in gene expression and its control?

Derivation of clonal ES cell lines



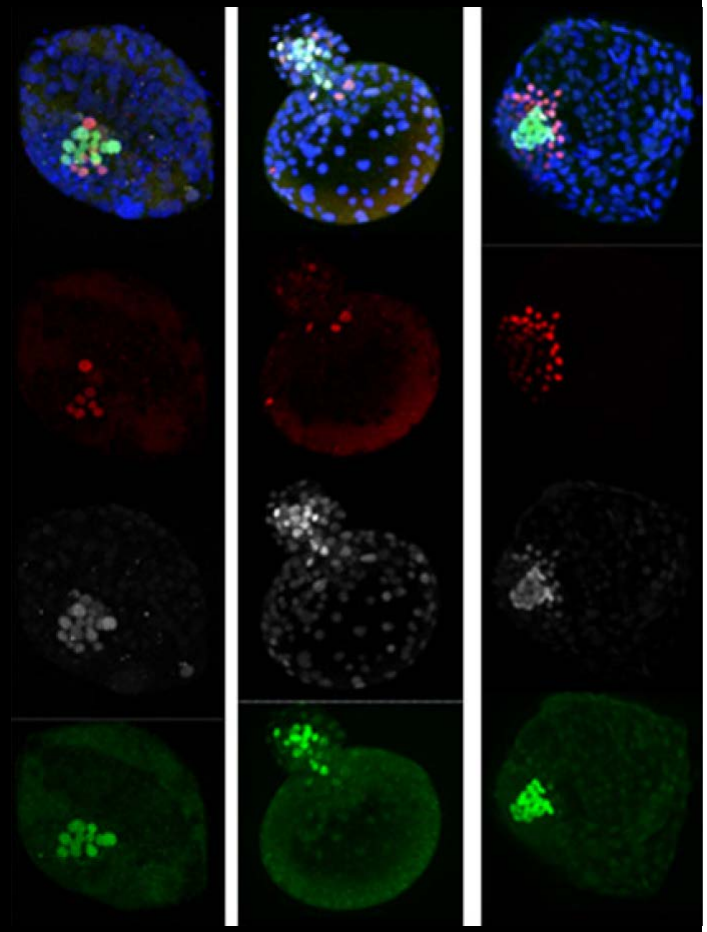
- Many (~60%?) of human embryos tested are a mixture of normal and aneuploid cells
- The most common aneuploidy is trisomy 21 or 22 (Downs Syndrome)
- Having lines of both normal and abnormal karyotype from the same embryo would provide a valuable tool to study the effects of a particular defect on differentiation
- Tissues derived from these lines could be used for drug testing

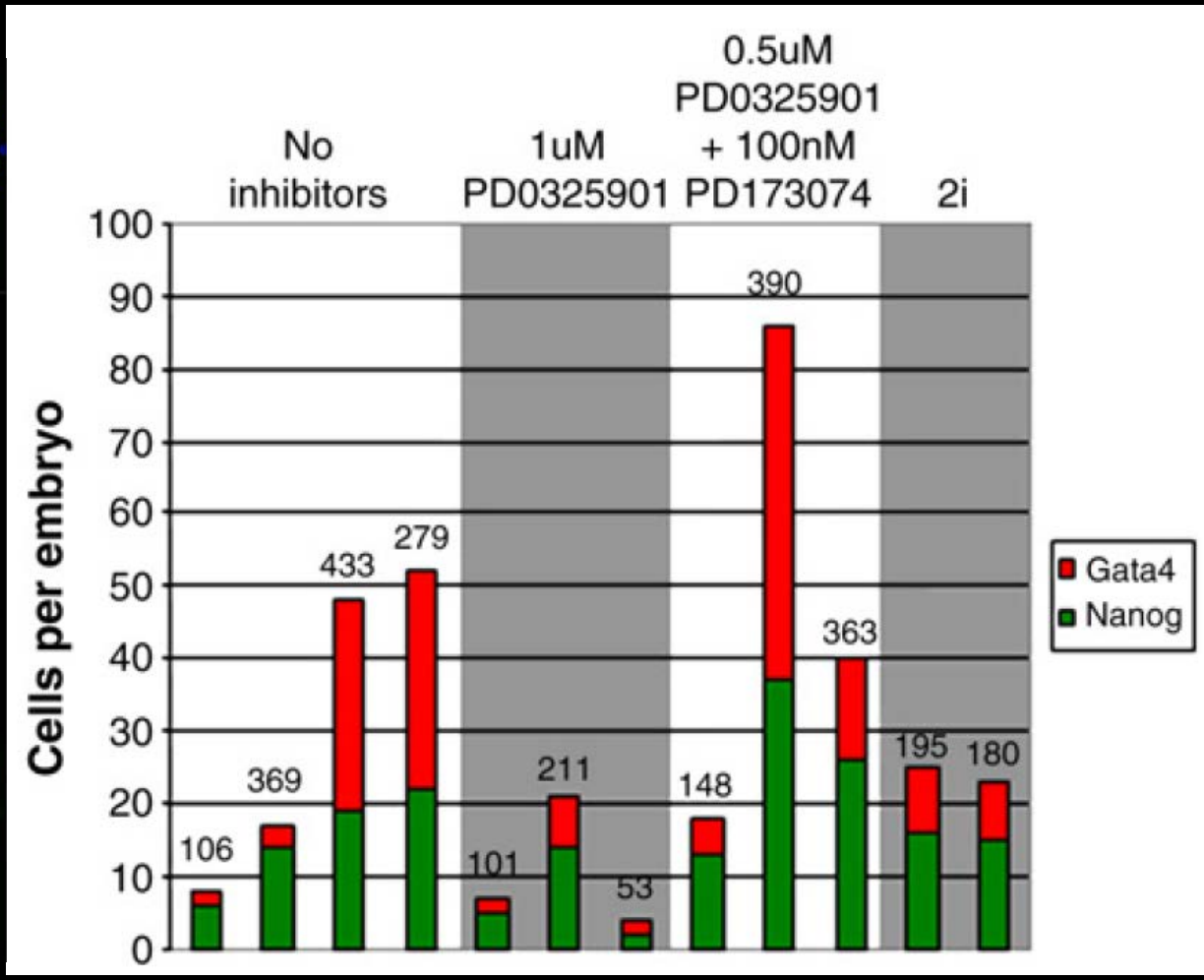
Deriving clonal ES cell lines from human embryos



Produce both normal and aneuploid ES cell lines from the same individual

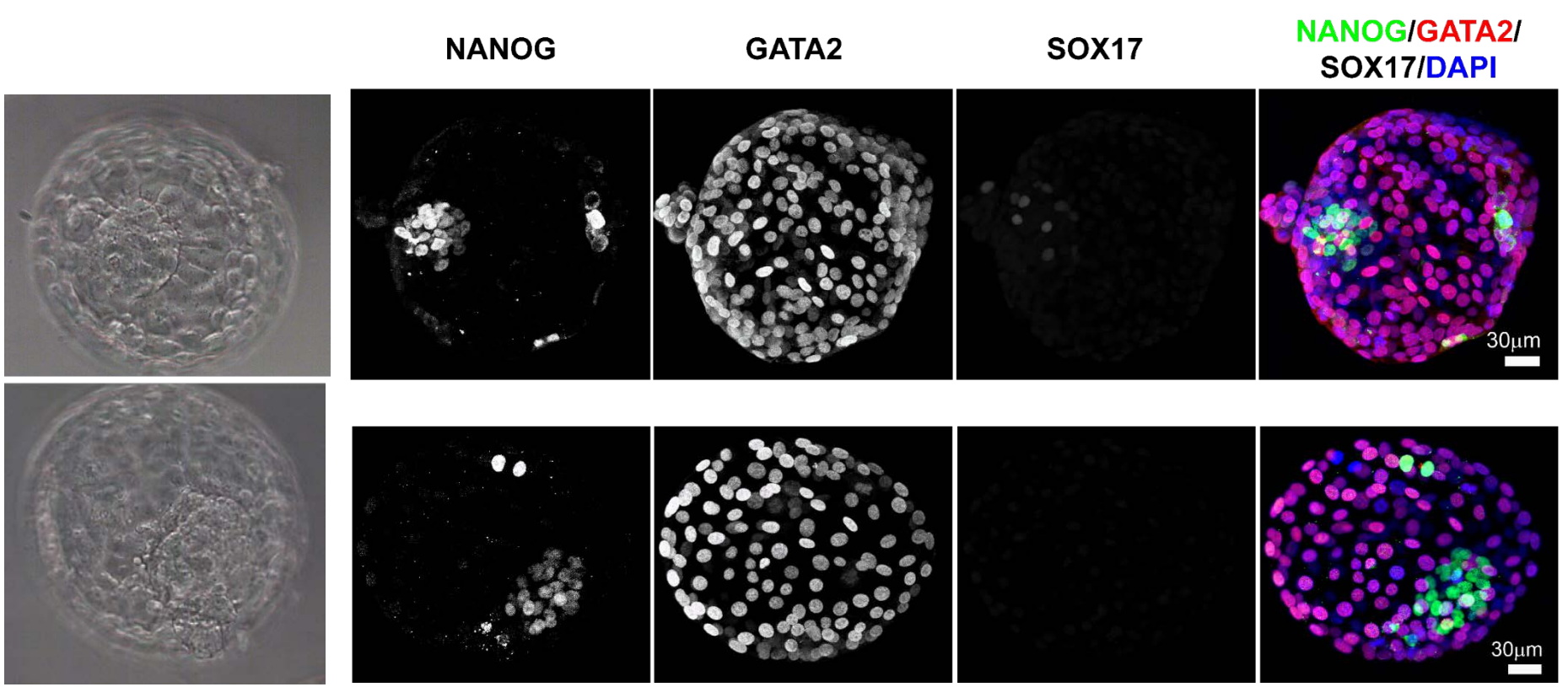
PrE formation in human embryos cannot be blocked by inhibiting FGF signalling





Roode et al., Dev. Biol. 2012

Human embryos cultured from morula stage in inhibitors of FGF and Wnt signalling



Progress and future plans

- Further improve culture regime to generate stable ES cells
- Track the transcriptional and epigenetic properties during ES cell derivation
- Derive clonal lines from the same embryo, some of which may have medically relevant aneuploidies
- Devise improved protocol for transfer to other clinics using epiblast expansion

Acknowledgements

Patients and staff at Bourn Hall,
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Charlotte Hall

MRC Medical Research Council

BBSRC bioscience for the future

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2018

Research collaborations at Sussex Downs Fertility Centre

Dr Charlotte Hall

Sussex Downs Fertility Centre, BMI Esperance Hospital, Eastbourne

BMI The Esperance Hospital

Serious about health.
Passionate about care.

Sussex Downs Fertility Centre

- Small IVF centre on South Coast
- Approx 300 Fresh IVF/ICSI cycles (NHS & Private)
- 120-140 Frozen cycles
- Clinical team - 2 consultants, 4 embryologists (2 full, 2 part-time), 4 nurses (part-time)

Development of Research Links at SDFC

2004

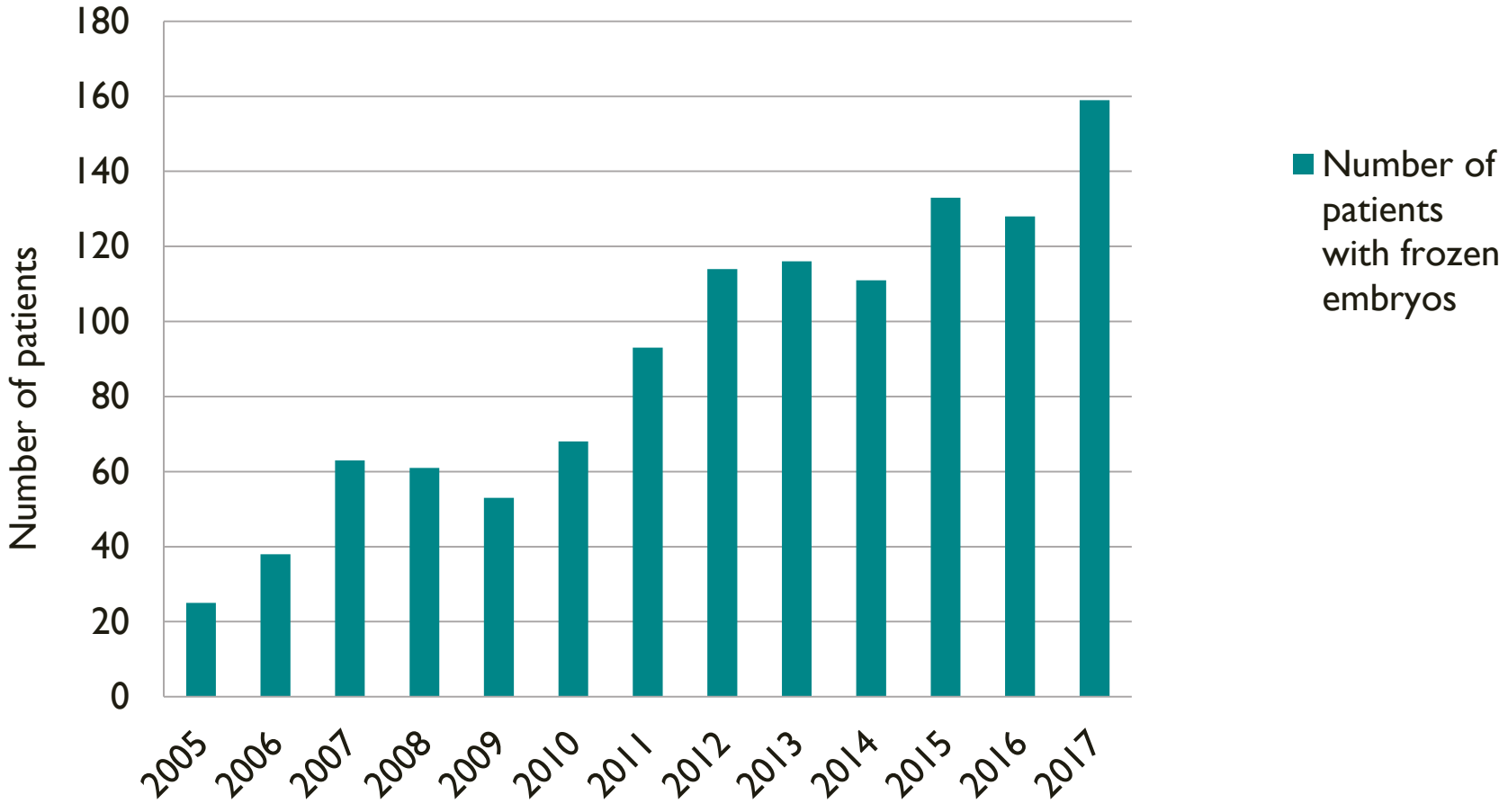
- Only option to couples was to discard or donate to another couple
- Very few couples feel they are unable to donate to another couple (particularly around this time when donor anonymity was removed - 2005)
- Couples don't like the idea of embryos going to waste
- Embryologists don't like throwing good embryos away.

Research Collaborations at SDFC

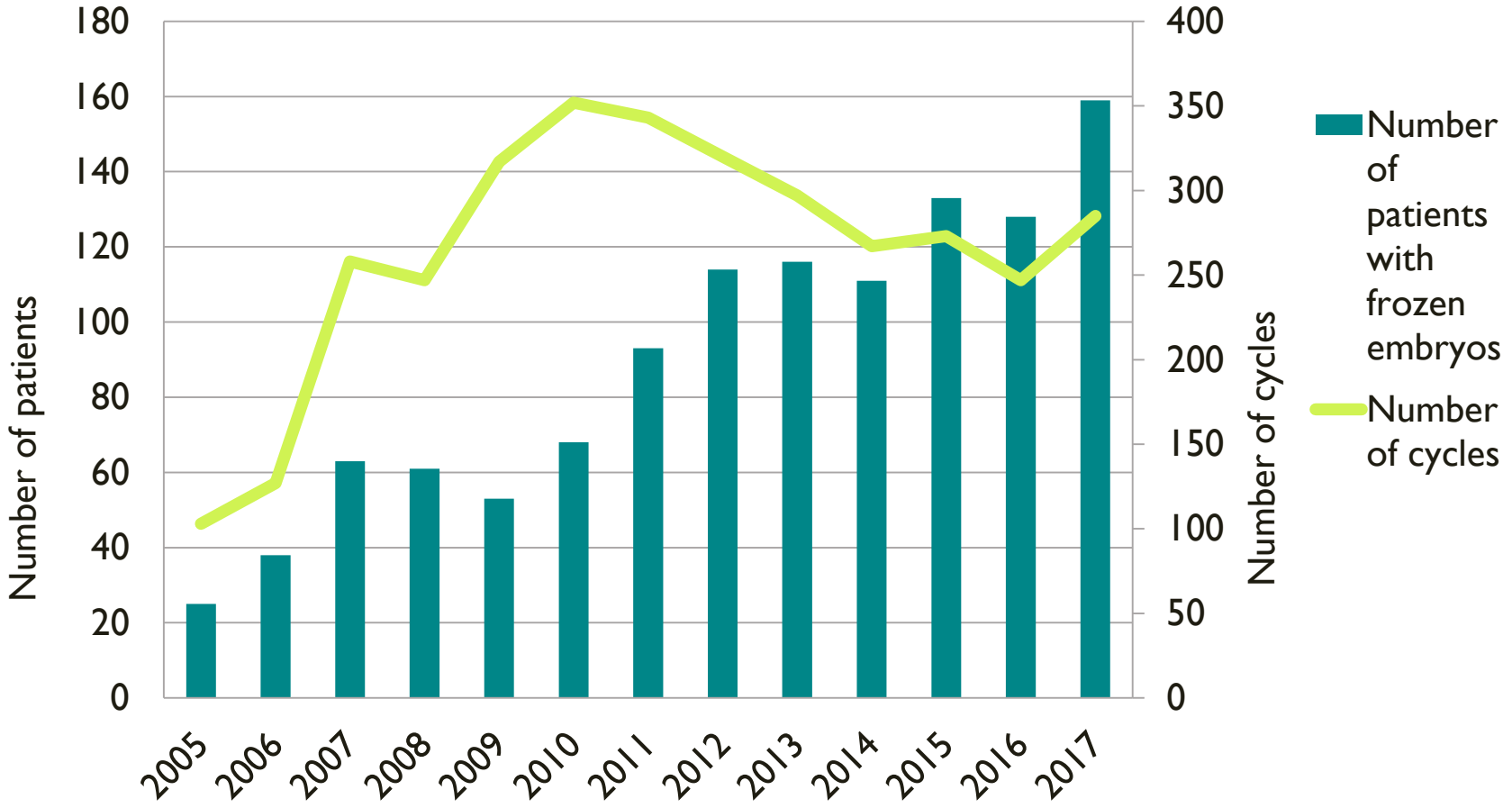
2006

- Started a collaboration with Guy's and St. Thomas', London
- Allowing patients with existing frozen embryos to opt to send embryos for research
- Patients were sent paperwork detailing choice of projects to be involved with (fertility-based or stem-cell research)
- Provided access to research nurse
- HFEA consent forms updated to indicate use in research
- Advised can withdraw at any time up until point of donation
- Collected by research nurse (10-12 sets accumulated)

Embryo Freezing at SDFC



Embryo Freezing at SDFC



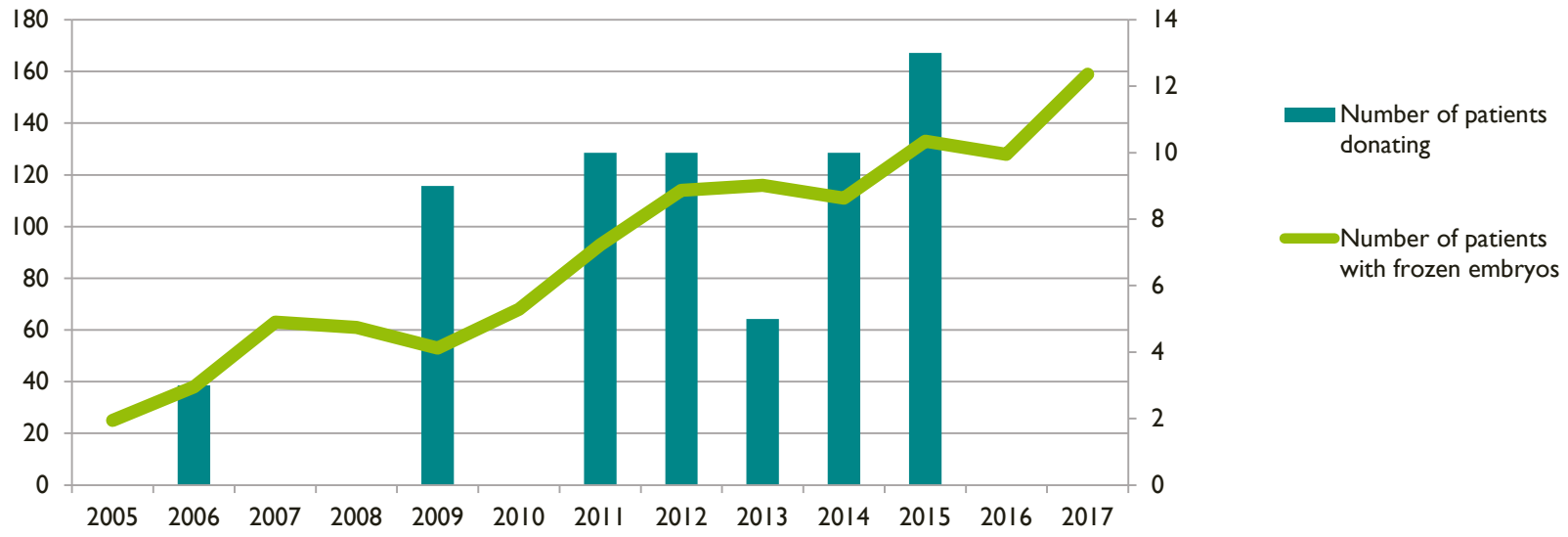
Changes in Embryo Freezing Practices

Availability for freezing based on change in policies/practices

- 2006 – 2008 mostly day 2/3 embryos – needed at 3 embryos to freeze (slow)
- 2009 – routinely freezing as blastocyst - min 2 to freeze (slow)
- 2010 - freezing single blastocysts = more patients freezing (slow)
- 2011 – started vitrification – frozen multiple times/later in the day
- 2014 – only blastocysts frozen (even for freeze all)
- 2015 – started using single step culture medium – more on time blastocysts available

SDFC Embryos donated to Research

- Between 2006 -2015 - 60 patients donated 248 embryos



- 2015 – Project Funding ceased
- 2016 – Attempted new collaboration
- 2017 – HFEA Workshop "Establishing Embryo Research partnerships"

HFEA Workshop – Establishing Research Partnerships

Oocyte Kinetochore to explore female ageing
Requirement: GV and MI oocytes frozen after egg collection

Embryo Metabolism Project to identify viable embryos
Requirement: Spent medium or embryos

Which Project?

Gene Inactivation in Embryos
Requirement: Frozen embryos (Pronculeate stage)

Creation of stable cell lines from Embryonic stem cells
Requirement: Frozen embryos

SDFC- Cambridge Stem Cell Institute

- Discussed requirements for the project
- Suitable for both parties
- Involvement mirrored our existing process
  - Cambridge supply paperwork for us to give to patients
  - Collect embryos when a group are ready
  - Ensure collection of the embryos personally

Where are we now?

- Submitted an acknowledgement to be a participating centre to HFEA
- Agreed to:

  - Displaying the cover page of our research licence in the clinic;
  - consenting the couples
  - providing the consented embryos to CSCI at agreed time points in advance of their expiry date
  - maintaining the original consent forms securely and confidentially

- Update our patient letters/paperwork to show we can now donate to research
- Provide interested patients with information leaflets (CSCI/HFEA)
- Already have embryos waiting
- Looking forward to being involved and eventually hearing how the research progresses

ACKNOWLEDGEMENTS

- HFEA
- Jenny Nichols & Austin Smith CSCI
- SDFC Team





BMI Healthcare

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Passionate about care.

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Supporting patients to take part in research

Laura Riley
Head of regulatory policy
15 March 2018

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Our strategy 2017-2020

Improving the quality of patient care and treatment relies on encouraging more research.

We are supporting:

- clinics to be more proactively research-focused, and to report research consent more accurately,
- patients to understand why research is needed and what research they could take part in,
- easier patient donation of embryos for research, and access to those donated embryos by more research centres.

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Research consent: barriers to participation?

HFEA data shows:

- Significant variation in HFEA consent rates between licensed centres to any research participation.
- Significant variation in consent rates between licensed centres, to ‘contact’ research model, vs. ‘non-contact’ model.
- Informed patient choice is key: ‘non-contact’ consent doesn’t support recontact with research invitations by clinics or HFEA, nor some research using patient data.

Consent for embryo donation

- is only permitted to be given to specific research projects (not to embryo research biobanking)

Others?

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Next steps: 2018-19

Supporting world class research at licensed centres, by:

2018: continue to

- improve patient information about embryo donation for research,
- streamline HFEA research applications process,
- support clinic-research project collaborations.

2019: new Embryo research landscape review, evaluating potential impact of this work on research participation

- numbers of embryos donated
- numbers of clinic-research project collaborations.

Dependent on these outcomes, we will consider also reviewing the patient research consent process

Thanks and over to you

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Questions and discussion

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