Developing a Pathway

• Scientific imperative and limits of control

• Demand of unmet clinical need
  – real or imagined

• Poorly understood science and greed of some practitioners
  – money or fame
Replacing the mitochondrial genome to overcome genetic disease & infertility

First baby born using 3-parent technique to treat infertility

Meet the world's first 'three-parent baby': Boy - delivered by US medical team in Mexico - carries a tiny piece of genetic code from a third donor 'parent' to avoid inheriting a disease from his mother

- Three-person baby technique lets parents with genetic mutations edit the mother's egg so they can have a healthy baby
Ooplastic transfer in mature human oocytes

Jacques Cohen\textsuperscript{1,4}, Richard Scott\textsuperscript{1}, Mina Alikani\textsuperscript{1}, Tim Schimmel\textsuperscript{1}, Santiago Munné\textsuperscript{1}, Jacob Levron\textsuperscript{2}, Lizi Wu\textsuperscript{3}, Carol Brenner\textsuperscript{1}, Carol Warner\textsuperscript{3} and Steen Willadsen\textsuperscript{1}

\textsuperscript{1}The Institute for Reproductive Medicine and Science of Saint Barnabas, Livingston New Jersey, USA. \textsuperscript{2}Department of Obstetrics and Gynecology, Tel Hashomer, Tel-Aviv, Israel, and \textsuperscript{3}Department of Biology, Northeastern University, Boston, Massachusetts, USA.
# Outcome of 37 attempts of OI at St Barnabas (1996-2001)

<table>
<thead>
<tr>
<th>Maternal age at cytoplasmic transfer cycle (years)</th>
<th>Number of previous cycles</th>
<th>Number of embryos transferred/fetal heartbeat after cytoplasmic transfer</th>
<th>13 patients pregnant</th>
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</thead>
<tbody>
<tr>
<td>39.5</td>
<td>4</td>
<td>3/1</td>
<td></td>
</tr>
<tr>
<td>38.4</td>
<td>6</td>
<td>6/1</td>
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<tr>
<td>37.6</td>
<td>9</td>
<td>5/1</td>
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<td>30.5</td>
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<td>4/1</td>
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<tr>
<td>37.2</td>
<td>3</td>
<td>2/1</td>
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<td>35.7</td>
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<td>5/2</td>
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<td>31.6</td>
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<tr>
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<td>4</td>
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<tr>
<td>36.3</td>
<td>3</td>
<td>4/2</td>
<td></td>
</tr>
</tbody>
</table>

17 babies born

+ 1 preclinical loss (XO)

(1) XO TOP; (2) XX
(1) OI; (2) OD

Chen et al RBMOnline 33, 737 (2016)
Control of events during early cleavage of the mouse embryo: an analysis of the ‘2-cell block’

By MARTIN J. GODDARD AND HESTER P. M. PRATT

From the Department of Anatomy, University of Cambridge
Cytoplasmic factors influence mitochondrial reorganization and resumption of cleavage during culture of early mouse embryos

A.L.Muggleton-Harris and J.J.G.Brown

MRC Experimental Embryology and Teratology Unit, Medical Research Council Laboratories, Woodmansterne Road, Carshalton, Surrey SM5 4EF, UK

Outcome for
Blocking and
Non-Blocking mouse strains
What factors might be added in OT
Cohen et al. MHR 1988

1. Mitochondria from the donor supplement pool of mitochondria
2. Internal pool of inherited (maternal) mRNAs may be boosted
3. Other organelles (ribosomes, proteins, spindle organizing units)
4. Specific consequences by altering a single mechanism
   e.g. change in the polarization of mitochondria

“*The transfer of small amounts of donor ooplasm (5–15%) probably includes mRNAs, proteins, mitochondria, as well as other factors and organelles*.”
Cytoplasmic Transfer Abroad - Medical Tourism Guide

Details of leading clinics and hospitals performing Cytoplasmic Transfer to foreign patients.

Successful Parents Ukraine
Surrogacy & Egg Donations Agency, Ukraine

An agency that coordinates egg donors, surrogacy and fertility treatments in the Ukraine. Provides European egg donors, Ukraine surrogacy services, PGD, and many other services relevant for couples looking to have a child.

Instituto Bernabeu
Fertility Clinic, Spain

Instituto Bernabeu is staffed by recognised fertility and assisted reproduction specialists. Thousands of patients from over 60 different countries have entrusted Instituto Bernabeu with their dream of becoming parents.

Bahceci IVF Centers, Istanbul, Turkey

Location
Istanbul, Turkey

Successful Parents India
Surrogacy and Egg Donation Centre, India

Successful Parents India is a branch of a European based head office of Successful Parents Agency. The Agency operates in India and accepts clients for fertility treatments in New Delhi: surrogacy, egg donation (Indian and Caucasian egg donors), PGD (not sex selection), as well as many other services.

Cytoplasmic Transfer FOR INFERTILE COUPLES

Published on November 23, 2015

Prashanth Fertility Research Center | Follow
Best IVF treatment in Chennai, Fertility Doctors in Chennai at Pras...
Researchers from the Spanish centre Embryotools—with headquarters in the Barcelona Science Park (Parc Científic de Barcelona, PCB)—are participating in a landmark scientific event in Greece that will shape the future of assisted reproduction. In a pilot clinical trial conducted on women, which is being sponsored by the assisted reproduction centre Institute of Life in Athens, Spanish scientists have achieved the world’s first pregnancy that uses the Maternal Spindle Transfer technique to solve problems of infertility.
MITOCHONDRIAL REPLACEMENT THERAPY GIVES NO BENEFITS TO PATIENTS OF ADVANCED MATERNAL AGE

1. OBJECTIVE:
To determine if mitochondrial replacement therapy (MRT) could increase blastulation rates, euploidy rates and pregnancy rate in infertile patients of advanced maternal age (AMA).

2. MATERIALS AND METHODS:
30 infertile patients (37-47 years old, mean age was 42±2 years) participated in this study. Five types of MRT (germinal vesicle transfer (GVT), Mi spindle transfer (MIST), Mi spindle transfer (MiST), polar body 1 genome transfer (PB1GT) and pronuclear transfer (PNT)) were assisted by H2-E cell fusion kit. Intracytoplasmic sperm injection (ICSI) had been performed for all cases. If possible, reverse reconstitutions were done. Embryos obtained after reconstitution, were cultured until blastocyst stage in time-lapse incubator, were biopsied for array comparative genomic hybridization (aCGH) or next generation sequencing (NGS) analysis and then were vitrified.

3. DESIGN:
The study period was from December 2015 to November 2016. Patients were informed and consent to possible risks and the experimental protocol was approved by ethics committee of local association of reproductive medicine. Inclusion criteria were: (1) no less than two failed previous IVF attempts, (2) low stimulation rates or resumed embryo arrest, (3) low number or absence of expelled embryos, (4) age ≥ 37 years.

4. RESULTS:
After performing various types of MRT (efficiencies of NT types were different), 109 zygotes were obtained, that resulted in 34 blastocysts; 3 of which (one per patient) were euploid. One try of elective single embryo transfer (eSET) of thawed embryo was done for each of three patients. Positive hCG level (>100 mIU/mL) and following heartbeating were confirmed only for one patient (42 y.o., PNT group). The healthy baby boy was born on 15th of March 2018 by Caesarean section. After unsuccessful attempt of MRT, one of 30 patients (41 y.o.) had an euploid embryo from conventional aCGH cycle using donor sperm and the other patient (45 y.o.) became spontaneously pregnant and gave birth to a healthy baby at full term.

Contrary, zygotic cytoplasts of woman of AMA were competent enough to support normal embryo development when carry young karyoplasts: there were 41% blastulation rates and 70% euploidy rates for reversely reconstituted zygotes.

CONCLUSIONS: Although the investigation is limited to obtained zygotes, numbers of euploid embryos and ongoing pregnancies after applying MRT were dramatically low, thereby infertile patients of AMA should be advised not to undergo such procedures in order to increase the number of euploid embryos or pregnancy rates. Sporadic pregnancies could appear after unsuccessful IVP treatment even in infertile patients of AMA. Further investigations of the efficiency of GVT (and sequential nuclear transplantation GVT-MIST) and MIST are needed.
A summary of the outcomes of different embryo transfer methods is shown in the diagram below.

**PNT (Pronuclear Transfer)**
- Total: 22
- Zygotes: 31.2%
- Biopsied blastocysts: 2.7%
- Euploid blastocysts: 2.7%
- Transferred blastocysts: <1%
- Pregnancies/Births: <1%

**MIIST**
- Total: 21
- Zygotes: 66.7%
- Biopsied blastocysts: 5%
- Euploid blastocysts: 4.8%
- Transferred blastocysts: 1%
- Pregnancies/Births: 0%

**PB1GT**
- Total: 6
- Zygotes: 50%
- Biopsied blastocysts: 16.7%
- Euploid blastocysts: 16.7%
- Transferred blastocysts: 16.7%
- Pregnancies/Births: 0%

**MIST**
- Total: 5
- Zygotes: 40%
- Biopsied blastocysts: 20%
- Euploid blastocysts: 20%
- Transferred blastocysts: 20%
- Pregnancies/Births: 40%

**GVT**
- Total: 3
- Zygotes: 100%
- Biopsied blastocysts: 100%
- Euploid blastocysts: 100%
- Transferred blastocysts: 100%
- Pregnancies/Births: 100%

This is limited to obtained zygotes, pregnancies after applying MRT methods of AMA should be advised not to increase the number of euploid embryos or pregnancy rates. Sporadic pregnancies could appear after unsuccessful IVF treatment even in infertile patients of AMA. Further investigations of the efficiency of GVT (and sequential nuclear transplantation: GVT->MIIST) and MIST are needed.
THE LICENSING AND REGULATION OF HUMAN EMBRYO USE IN THE UK

• for therapy (IVF/DI)
• for cryostorage of gametes and embryos
• for research using embryos in vitro up to 14 days

Breach of the Law is a criminal offence

Punishable by 2 years imprisonment a £20,000 fine or both
Self-organization of the *in vitro* attached human embryo

Alessia Deglincerti, Gist F. Croft, Lauren N. Pietila, Magdalena Zernicka-Goetz, Eric D. Siggia & Ali H. Brivanlou

*Nature* **533**, 251–254 (12 May 2016) | Download Citation
Consistency of approach

1. Why do we want/need to do GGE? What is the goal?

2. How does the commission provide advice when there is already so much variation between states/countries about acceptable ART technology – Embryo research MRT?

3. If we are really concerned about GGE, why is ART unregulated in so many countries (e.g. USA) when ART manipulations may cause epigenetic effects transmissible to the next generation?

What is doable now? What is practical? What is honest?