



Sociological Reflections on Translational Research: Embryonic Stem Cells, Diabetes and Neuroscience

Beyond Pattison: Challenges to Stem Cell Translation & Policy
Wellcome Trust, London, (7-8 May, 2009)

Steven Wainwright

CBAS, School of Social Science & Public Policy

www.kcl.ac.uk/schools/sspp/interdisciplinary/cbas/

Mapping stem cell innovation in action: an ethnography of the bench-bedside interface (2004-2006)

*Clare Williams, Steven Wainwright, Alan Cribb,
Bobbie Farsides, Nigel Heaton & Mike Michael*

Spaces of stem cell science: exploring processes of translational research (2007-2009)

Steven Wainwright & Clare Williams

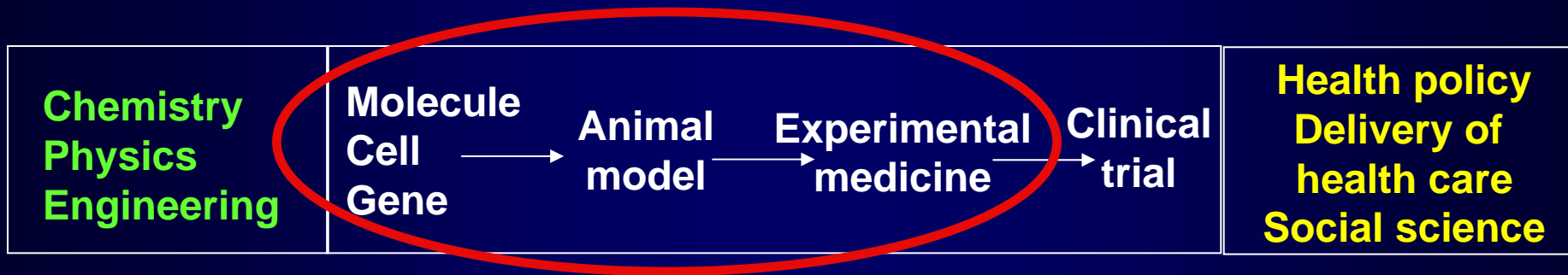


Outline

1. Introduction: sociology and translational research
2. Prospects of hES cells as a cure for diabetes
3. Bourdieu and the fields of science and medicine
4. From cell transplant to disease in a dish?
5. Conclusion: translational research revisited

The Biomedical Translational Research Pathway

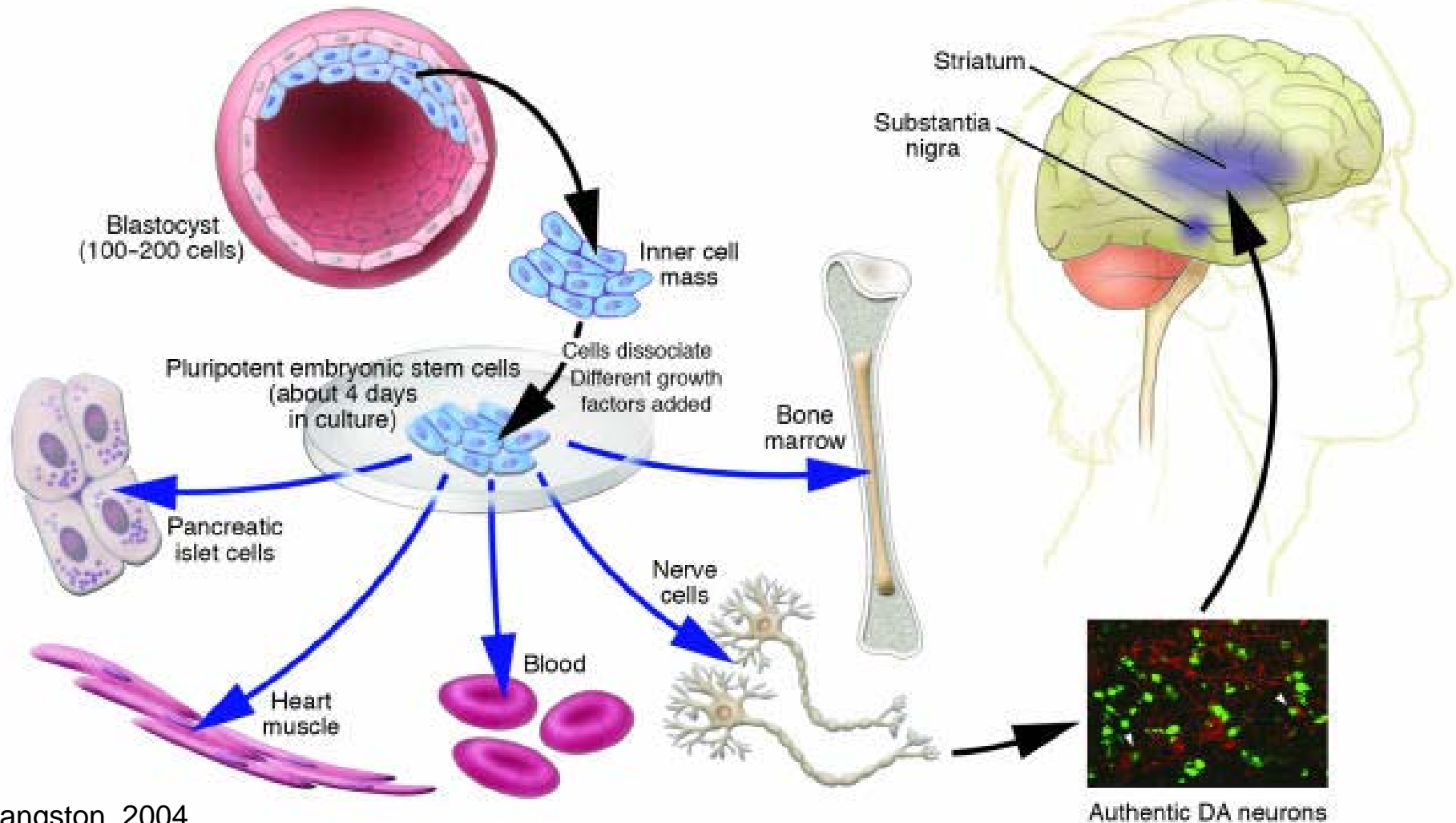
————→ The health-related research pathway —————→



CBAS - ESRC & Wellcome Sociology of New Medical Technologies

Curing Parkinson's? DA Neurons from hES Cells

Wainwright, S.P. (2005) Can stem cells cure Parkinson's disease? Embryonic steps toward a regenerative brain medicine. *British Journal of Neuroscience Nursing* 1 (3): 61-66.



Langston, 2004

4Ms of Translation: Molecules – Mouse – Man – Multicentre Trials

Wainwright et al (2009) *Handbook of Genetics & Society*

Curing Parkinson's: DA Neurons from Foetal Cells

From Experiment to RCT

1. PET: Normal control

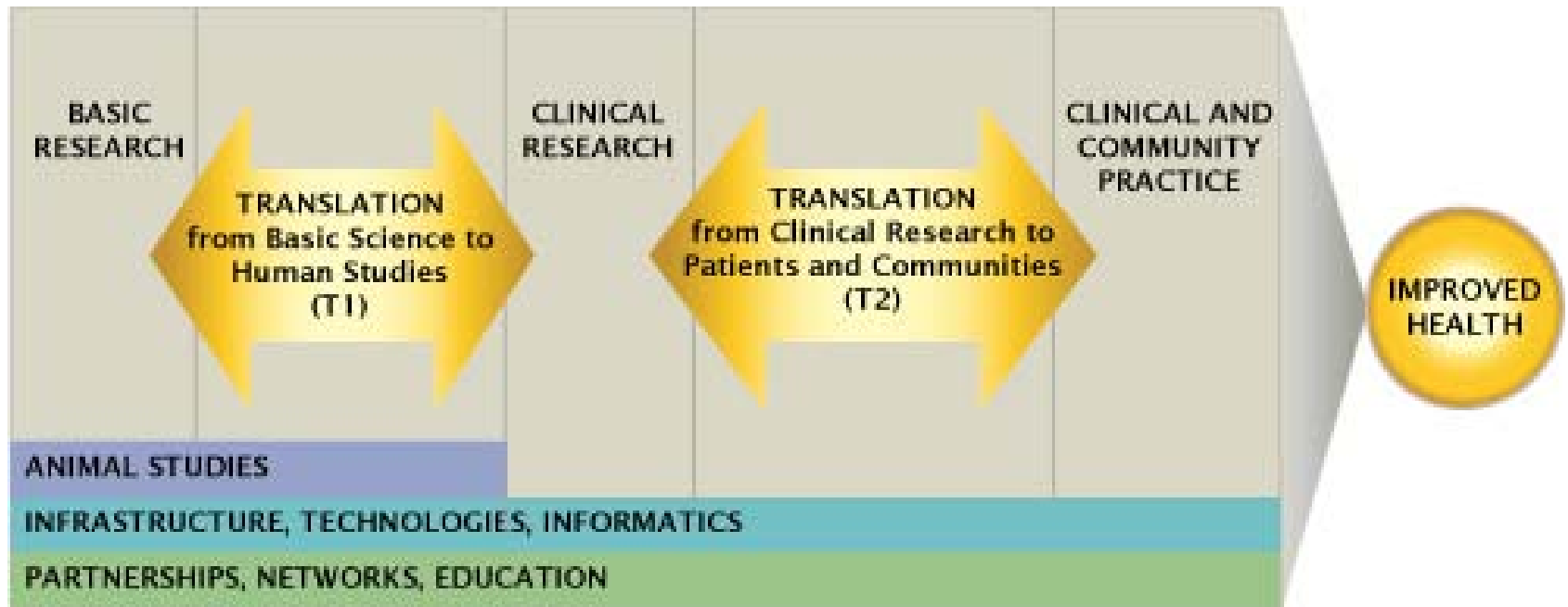
2. PET: PD (L) & PD + FCTx (R) 9/12

3. PET: PD + FCTx 33/12

Proof of Principle vs RCT

Institute of Medicine's Clinical Research Roundtable

Continuum of Biomedical Research: T1 & T2



[NCRR Strategic Plan 2009-2013](#)

T1 - transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans

T2 - translation of results from clinical studies into everyday clinical practice

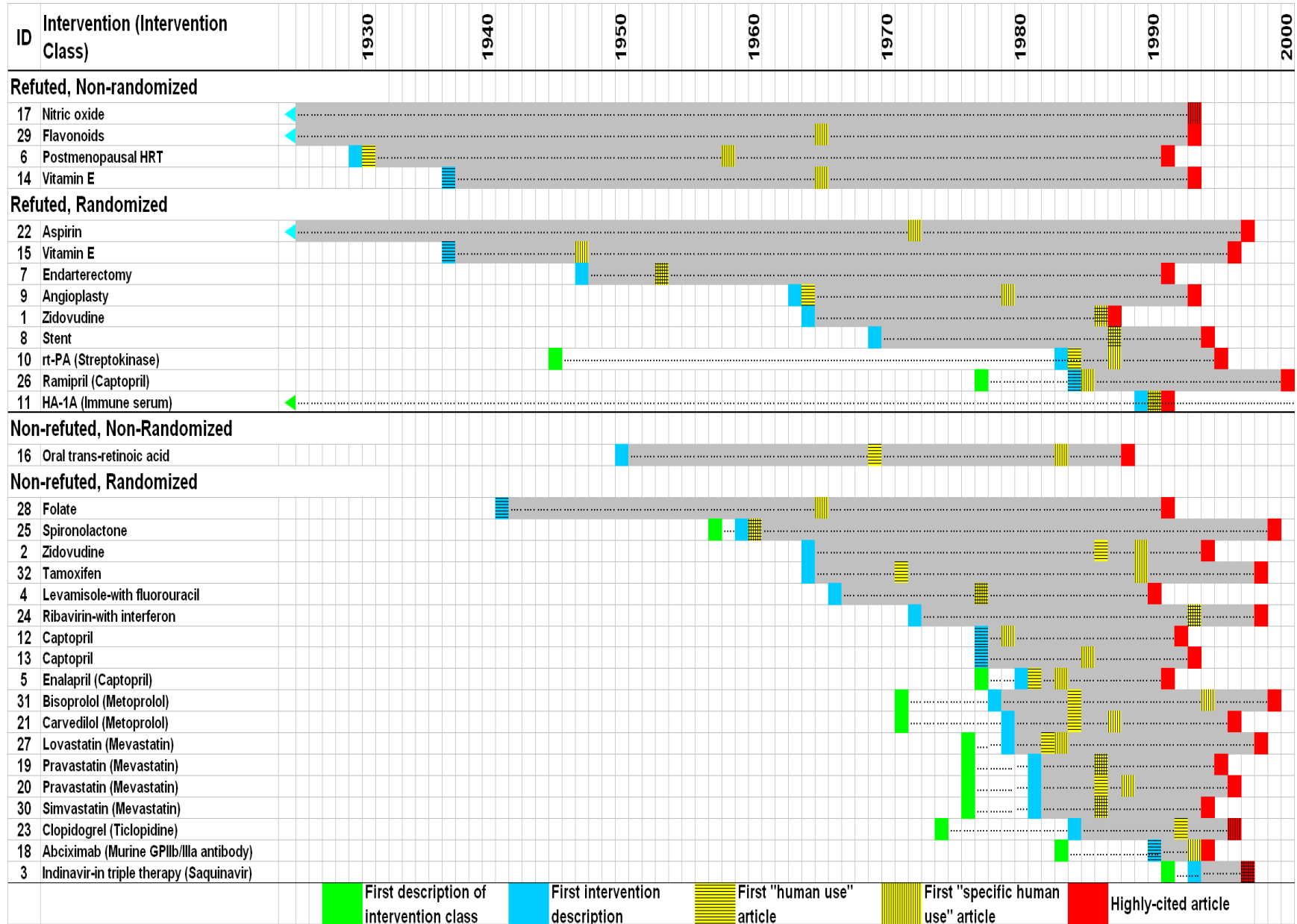
Translation of Major Basic Science Promises

Translation of highly promising basic science research into clinical research occurs sparingly and with considerable time lag

Limited empirical data on:

1. how frequently these promises are materialized
2. reach the stage of clinical application
3. reach the stage of routine clinical use
4. what is the time frame for this translation

The Glacial Pace of Clinical Translation (of Drugs!)



Trial Initiation = Medical Achievement (Geron ESC4SCI)

A trial of one application, not a trial of all ES cells... but

- This... marks the dawn of **a new era in medical therapeutics**. This approach is one that reaches beyond pills and scalpels to achieve a new level of healing

Thomas Okarma, Geron CEO

- Today's news... is **a milestone in the new era of hope**

Amy Comstock Rick, Coalition for the Advancement of Medical Research

- **This is what we've all been waiting for**

Robert Lanza, Advanced Cell Technology

- The announcement **boosted the price of shares** in [Geron]... up 56% from the day before the announcement

Meridith Wadman, Nature, Jan 27, 2009

If embryonic stem cell work is anything like practically every other major medical advancement, be prepared for a very long, tough slog with lots of setbacks (Jon Kimmelman, Blog, 2009)

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Stem Cell Labs Fieldwork in the UK & USA



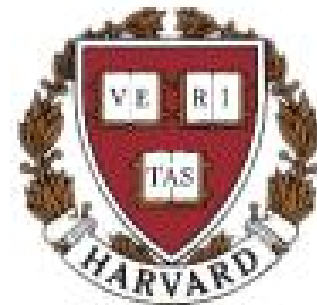
UNIVERSITY OF
CAMBRIDGE



University
of Southampton

KING'S
College
LONDON

University of London



UNIVERSITY OF
BIRMINGHAM

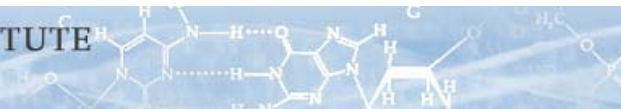


SALK INSTITUTE
FOR BIOLOGICAL STUDIES

Institute of **Psychiatry** at the Maudsley



THE WHITTIER INSTITUTE
FOR DIABETES



Imperial College
London



THE
SCRIPPS
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INSTITUTE®



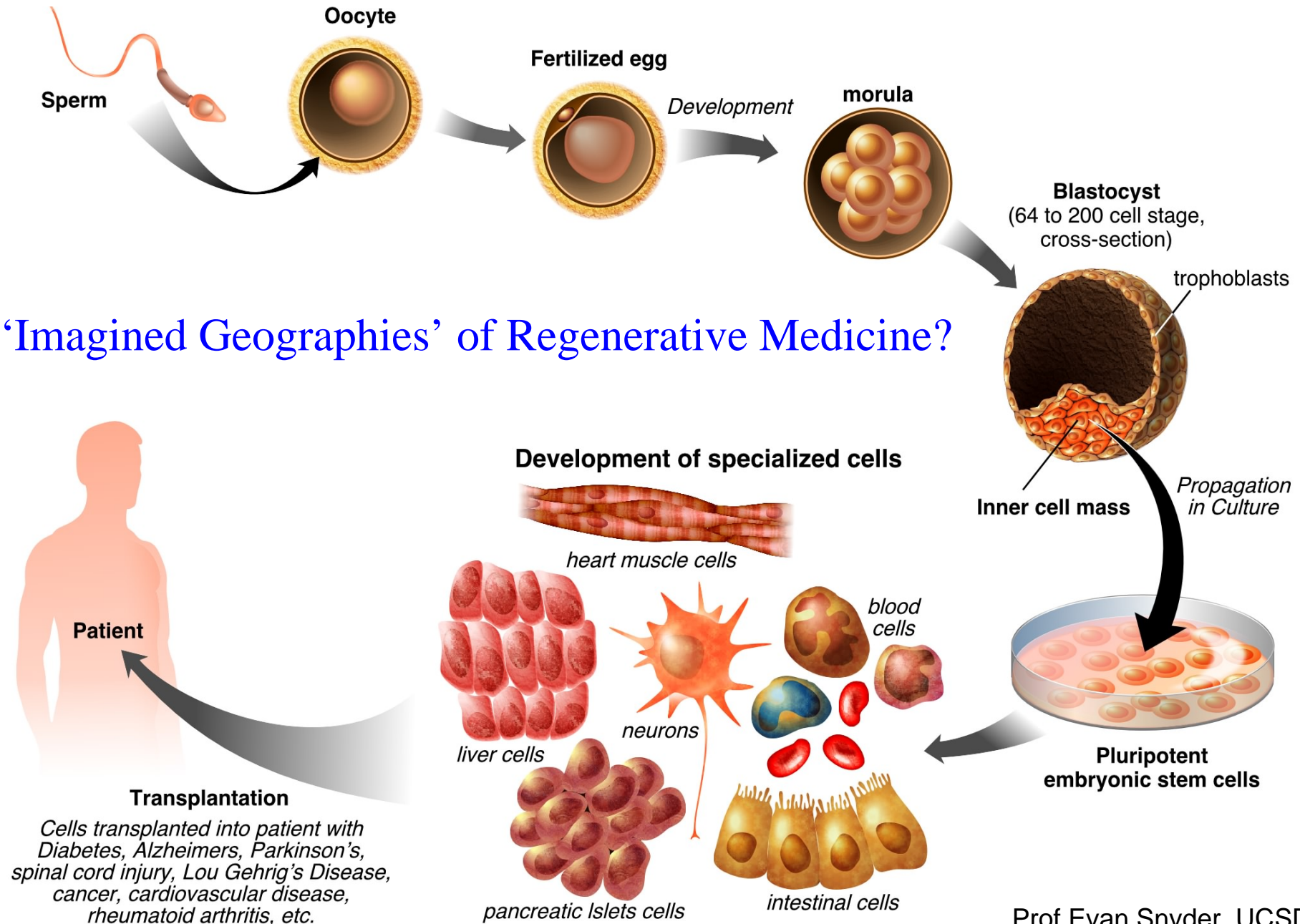
Queen Mary
University of London



Fieldwork: Southern California Stem Cell Consortium / The San Diego Consortium for Regenerative Medicine



Stem Cell Therapy: Cell Transplants & Regenerative Medicine



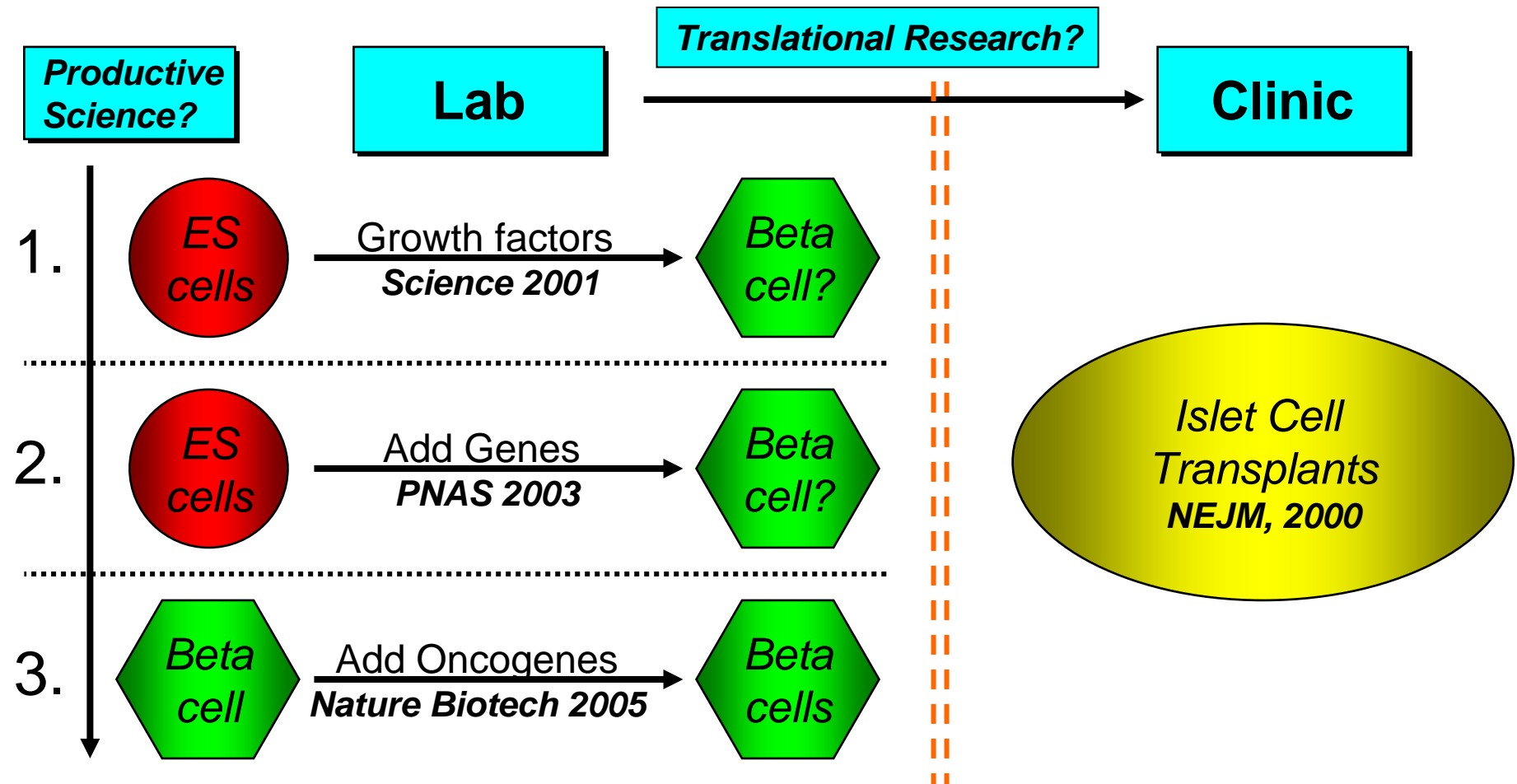
Curing Type-1 Diabetes with 'Stem Cell' Transplants?

Four steps to a holy grail of regenerative medicine?

1. Islet cell transplants *can* cure Type-1 diabetes
2. *Need* new supply of cells (huge shortfall of cadaver cells)
3. ES cells *best* source of unlimited cells
4. Hence, 'ES cell therapy' *will* cure Type-1 diabetes

Bonner-Weir, S. & Weir, G.C. (2005) New sources of pancreatic Beta-cells.
Nature Biotechnology 23: 857 – 886.

Figure 1: Boundary work, boundary crossings and the lab-clinic interface: from stem cells to cell transplants for diabetes?



We argue the perceived success of islet cell transplants helped stimulate scientific demand for 'making beta cells'. In this figure, scientists want to move *horizontally* so as to cross the lab-clinic boundary through translational research. However, this has not yet been possible as with strategies 1 & 2 only approximately 1:1000 cells produce around 0.001% insulin of a primary beta cell. In contrast, with strategy 3, almost all cells produce 40% of the insulin of a primary beta cell. Scientists have, therefore, been 'driven down' the *vertical* axis (from strategy 1 to 3), thereby crossing two clinically and socially contested 'genetic boundaries' (i.e. adding insulin promoter genes, adding oncogenes). These moves maintain expectations of the ability of scientists to make 'functioning beta cells', which can potentially be used in the clinic. Moreover, this series of vertical moves also allows researchers to engage in productive (publishable) science. In brief, the 'pull of the clinic' combines with 'the push of productivity' to lure scientists across 'socially contested boundaries'.

Wainwright et al (2007) *New Genetics & Society*

1. Lumelsky et al: A view from our US Fieldwork - 2005

You look at that [Lumelsky] paper and see that it is fundamentally flawed from the very beginning. How it passed through the review process I have no idea. **When I first read that paper, I thought it was nonsense... There was hardly any insulin message, the PDX1 message, which is critical for pancreas and beta cell formation, went down when she differentiated her cells... People were screaming at one another at one meeting, and Ron McKay was extremely upset. It was amazing. There's some scientific sociology for you!** It's had an enormous impact, a disastrous impact on the field.

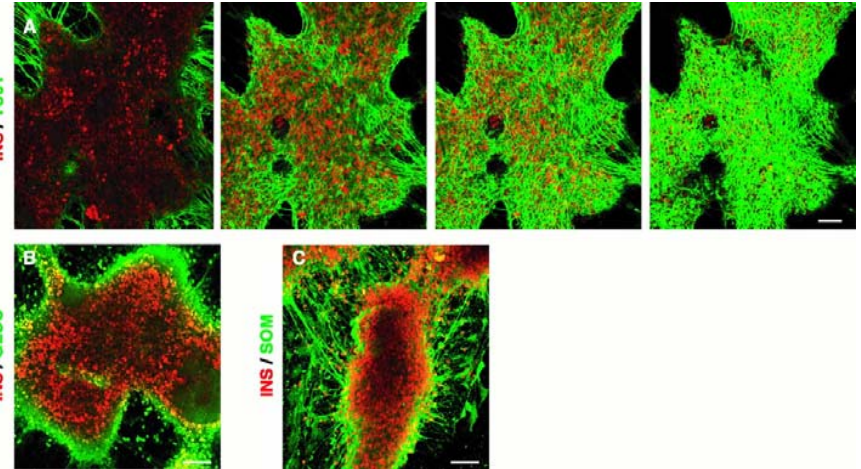
I think it's set the field back for a couple of years. And in this country people were reproducing and extending this result. You still see it today on grants where people reference it. **So I think it was a major fiasco... It was a terrible thing that happened, as they [scientists] dropped everything and tried to repeat and extend their protocol. And the protocol was wrong. So it's a disaster. How many hundreds of scientific man-years and millions of dollars were devoted to that protocol in one way or another? It's just a complete waste. That, for me, is a pretty decent definition of a disaster... Interestingly still not retracted to this day... Lumelski became a tenured track position in NIH based on that paper.** (Scientist 28, USA)

A

Stage 5: (6 days)
Induction of differentiation and morphogenesis of insulin-secreting islet clusters:
withdraw bFGF from N2 medium containing B27 media supplement and nicotinamide.

B

Figure 1 shows RT-PCR analysis of gene expression in Stage 1 and Stage 5 embryos. The figure is organized into a grid with 10 rows of gel images. The columns are labeled 'Stage 1' and '5' under the heading '-RT'. The rows correspond to the following genes: INS1, INS2, GLUT2, GLUC, PDX-1, IAPP, HNF3 β , GATA4, and GAPDH. The PDX-1 row is circled in red. The GAPDH row shows consistent expression across all samples.

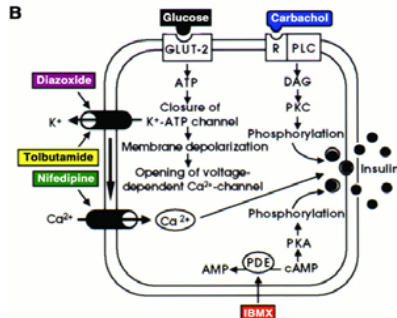
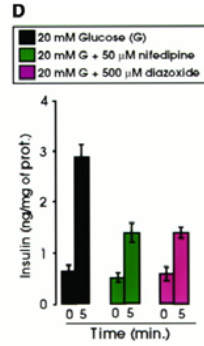
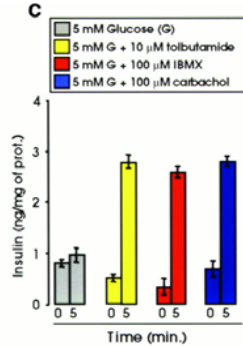
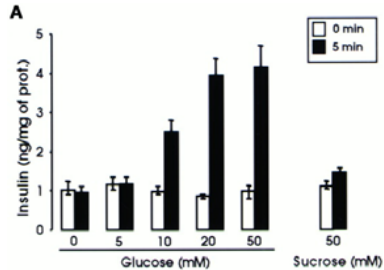


BREVIA

Jayaraj Rajagopal, William J. Anderson, Shoen Kume,
Olga I. Martinez, Douglas A. Melton*

When medium is supplemented with FITC-conjugated albumin, a distinct cell population con-

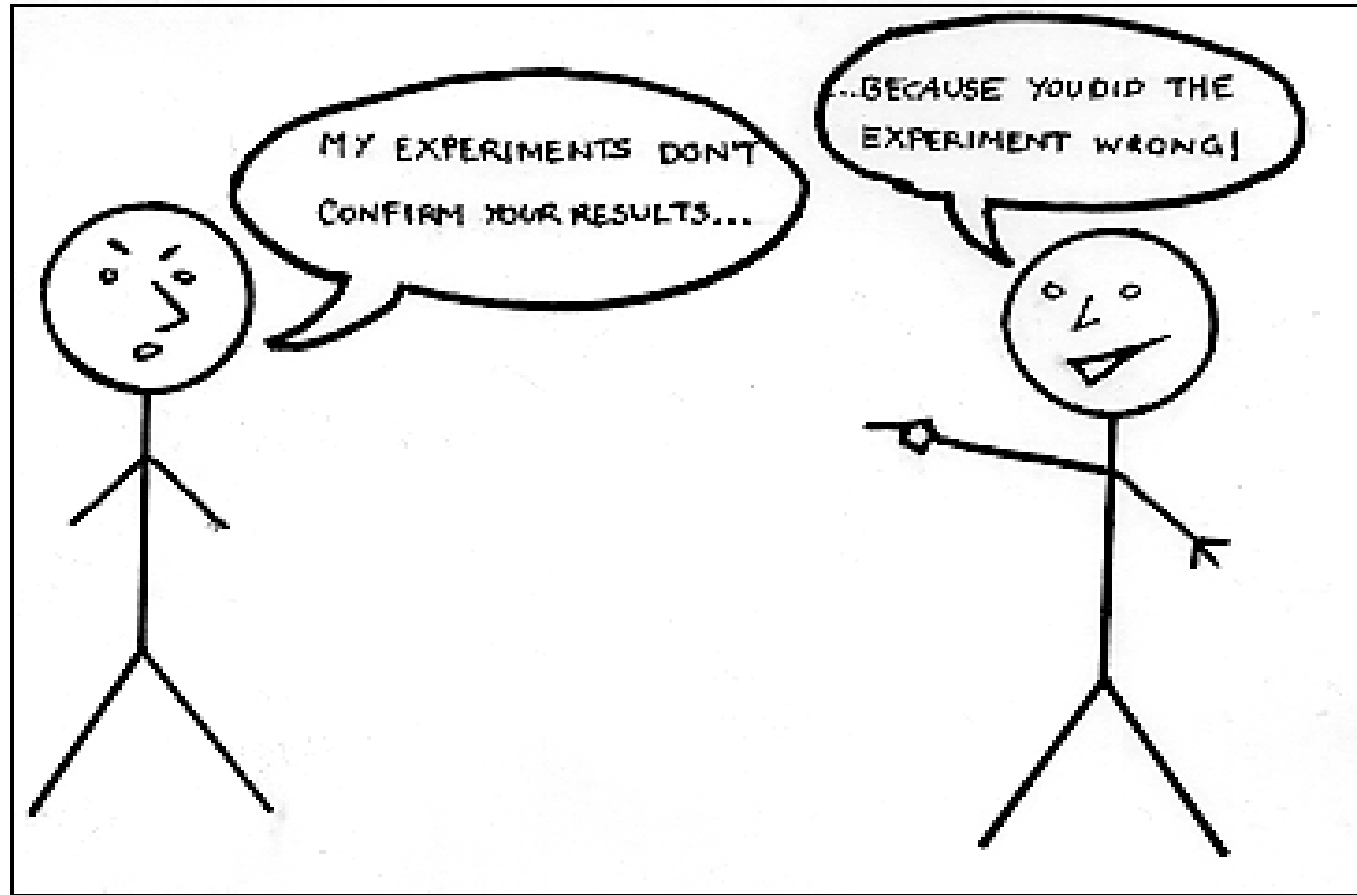
JANUARY 2003



When medium is supplemented with FITC-conjugated albumin, a distinct cell population con-

*To whom correspondence should be addressed. E-mail: daniel@mcch.harvard.edu (D.A.M.)

Core Set: Contested Science in Action



A lot of people have used the '**shake and bake**' approach. They're now learning how to do the **molecular approach**. (Scientist 25, USA)

Sociology of Expectations & Translational Research

(Williams et al, 2003, *SHI*; Kitzinger et al, 2005, *SSM*)

Over the coming years *we intend to accelerate the rate at which MRC research is translated* into new methods of diagnosis and treatment – a process that can take anything from a few years to decades... *to bring our knowledge and discoveries into the healthcare system and so to patients.*

(Colin Blakemore, MRC, 2004: 1)

Problems: Wainwright et al (2006) *Social Science & Medicine*

- Can hES cells be turned into functioning cells?
- Different cultures of medicine and science

Clinical use of ‘cardiac stem cells’

‘Third rate scientists misled by bad data’ (Scientist 27, USA)

From Bench to Bedside? The Two Cultures Revisited

Science versus Medicine

Bench scientists tend not to talk to, or respect, true clinical scientists and vice versa, and there are very few people that cross over truly between the two... If you talk to most basic scientists they will say that clinical research is very 'Mickey Mouse' and if you talk to most clinical scientists I guess they will say that most basic science is a waste of time and money. Scientist 3

Problems with animal studies

I think there are two very clear groups of researchers, those who have done a lot of animal work, who very rarely do anything in humans, and then there are a group who say, 'working on mice is a waste of time!' Quite often what you find is that there isn't so much crossover. Scientist 5

Promoting interaction between 'the two cultures'

So there is a little bit of them providing us with tissue plus us experimenting with them and feeding them back information. Scientist 4

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Bourdieu: Key Concepts

(Habitus + Capital) + Field = Practice (Bourdieu, 1984: 101)

Field: a structured system of social positions of power

Habitus: ‘a feel for the game’; ‘When habitus encounters a social world of which it is the product, it is like a “fish in water”’ (B&W, 1992: 127)

Illusio: ‘is the game worth the candle’

Forms of Capital:

<i>Physical Capital</i>	the body
<i>Emotional Capital</i>	emotions
<i>Economic Capital</i>	money etc
<i>Symbolic Capital</i>	prestige; recognition of economic / cultural capital
<i>Social Capital</i>	relations with ‘significant others’
<i>Cultural Capital</i>	legitimate knowledge

Scientific Capital? Economic, Symbolic, Social & Cultural Capitals
+ **Ethical Capital** + **Expectational Capital?**

Bourdieu - King's Health Schools Review 2005-2006



There is an enormous amount to celebrate in this Review of 2005-6. I can honestly say that I have never lived through such a period of accelerated progress. The most recent success resulted from the Department of Health's competition for Biomedical Research Centres as part of the 'Best Research for Best Health' initiative.

A total of five comprehensive Centres were awarded to partnerships between NHS Trusts and their academic partners within the UK. The Guy's and St Thomas' NHS Foundation Trust was one of the winners in this competition based on the strength of translational research that has grown up within the Health Schools of King's. Indeed, ours was the only Centre to be funded in full. In addition, the South London and Maudsley NHS Foundation Trust with the

types of Centre. This is a telling endorsement of the position that we have achieved in UK Biomedicine and reflects progress in numerous domains. First, we have enjoyed unparalleled success in the recruitment of Professorial level clinical and non-clinical scientists of international repute across a broad range of disciplines. Thus far we have made sixteen new Chair appointments, with a further eight in train. Second, we have taken steps to improve the infrastructure

Success breeds success

We have secured a fifth MRC Centre, in translational research in the field of Psychogeriatrics, and maintain our position as the UK university with the largest number of such Centres. King's is now fourth in the UK for MRC income, and enjoys a strategic partnership with the MRC. We were also successful in the recent competition for Wellcome Trust, Wellcome, and Department of Health funding for Clinical Research Facilities: a sum of £9.5 million has been made available to establish a facility on the King's Denmark Hill Campus. The major focus of this facility will be on novel interventions in mental health, but it will also incorporate several applications of cell therapy. In addition, Tate & Lyle have invested £4.5 million in a Centre for Nutrition and Health based at the Waterloo and St Thomas' Campuses and the Guy's and St Thomas' Charity have provided close to £3 million to fund an experimental facility on the Guy's Campus.

Several major collaborative grants have also been won, including a capacity building grant of £3 million in integrative physiology from a consortium of funders led by the BBSRC, and an ESRC Centre for Evidence Based Policy and Practice directed from the Florence Nightingale School of Nursing & Midwifery.

A fifth and final area of progress has been in the continuing development of close working partnerships with our major NHS partners, at Guy's and St Thomas', King's College Hospital and South London and The Maudsley Trusts, all of which now have Foundation Trust status. These partnerships are essential if we are to realise our ambition to provide complete research pathways from basic discovery to first in man studies, clinical trials and health services research.

All the successes outlined above have established a strong platform on which to build during the next few years. Now that we have a platform, the challenge that confronts us is that of delivering high quality research across the whole span of Biomedicine. In this

Biomedical Research centres. The ambition is to create new linkages between the major academic institutions, their NHS partners, and industry to foster high quality research innovation and, ultimately, patient benefit.

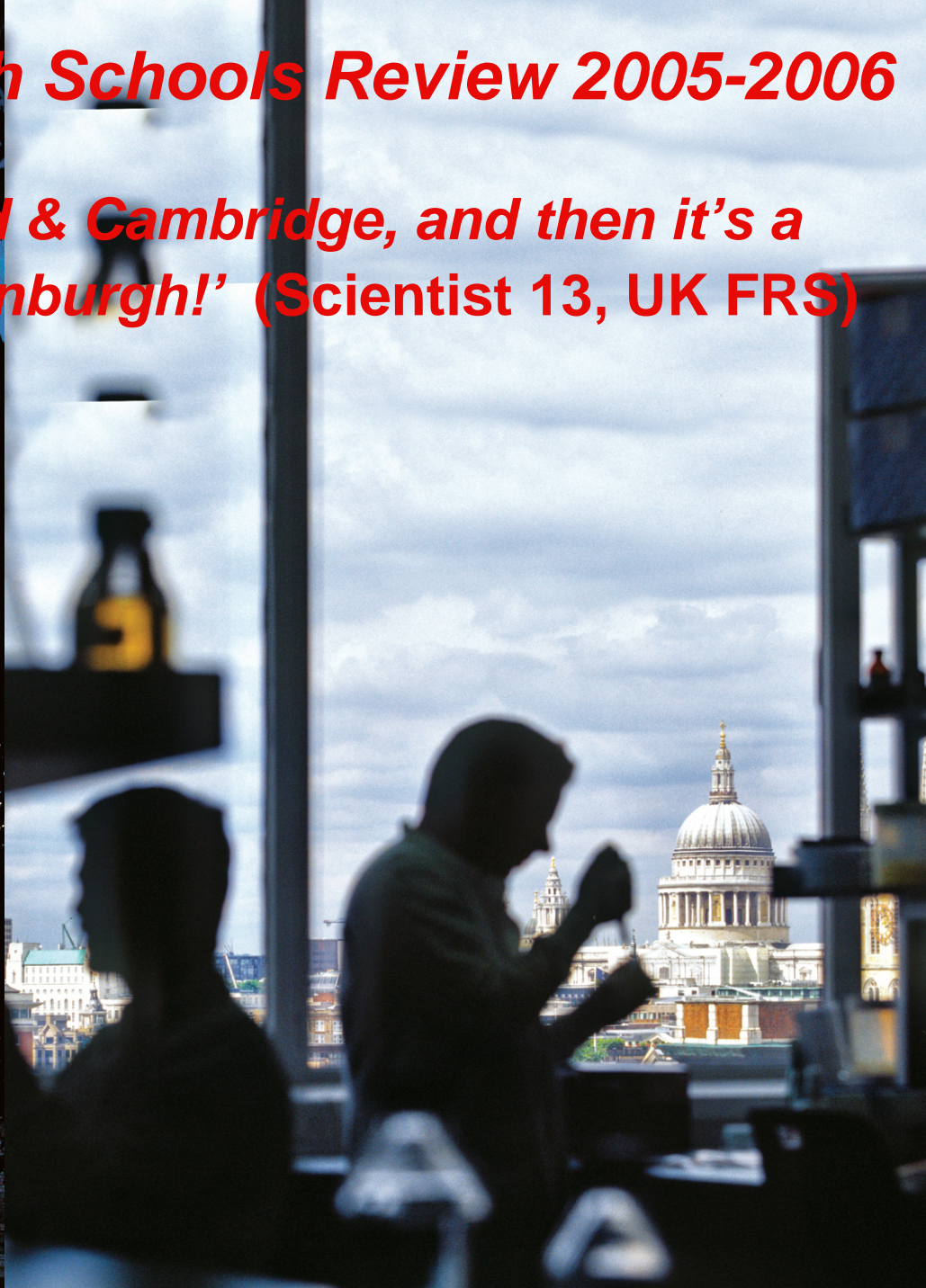
Another key aspect of our mission is to teach and to train and there have been many successes here too. Recruitment to undergraduate clinical and basic science courses remains very strong. King's continues to be the most popular choice for undergraduate medicine and dentistry in the UK, as judged by the number of applications. King's widening participation Extended Medical Degree Programme – which will see its first graduates in 2007 – and fast-track graduate entry programmes in medicine continue to thrive. King's also offers a unique range of health-related professional degrees in dentistry, nursing, dietetics, physiotherapy and pharmacy, each of which is linked to strong discipline-based research programmes. In keeping with the rise in our research standing, it is important that we are a breeding ground for leading biomedical researchers of the future. We are in the process of establishing a clearly set out postgraduate training pathway for medical graduates aspiring to become division scientists, starting with the Academic Foundation Programme, through academic clinical fellowships, PhD programmes and on to Lecturer posts. For basic scientists, we have been steadily increasing the numbers of PhD studentships, now under the King's Graduate School umbrella.

There is much yet to be achieved. However, the last two years have witnessed a rate of progress that it has been a privilege to be associated with. Long may it continue!

**Scientific capital / economic capital / symbolic capital are interrelated -
HEFC funding, Research Council Grants, RAE scores, league tables etc**

Bourdieu - King's Health Schools Review 2005-2006

'There's London, Oxford & Cambridge, and then it's a desert until you reach Edinburgh!' (Scientist 13, UK FRS)



The Field of Diabetes - 'A world without insulin' (JDRF)

Backing Scientific Winners & Making Beta Cells?

Time & Place
Expectations,
Science & Society

Strategy 1 - 2001

Strategy 2 - 2003

Strategy 3 - 2005

Feel for the game?
Is the game worth it?



β Cell Stakes

Name: _____

(Circle only one number)

RUNNERS



1. Isolated Islets from Cadaver Pancreas



2. Stem Cells Embryonic



3. Stem Cells Pancreatic Duct



4. Stem Cells Blood



5. Stem Cells Liver



6. Stem Cells Intestine



7. Cultured Foetal/Neonatal Pancreas



8. Nuclear Transfer Techniques



9. Cultured Tumour Cell Lines



10. Encapsulated Cells



11. Xenograft Cells



12. Direct Gene Therapy
e.g. Single Chain Insulin Analogue



13. Engineered Intestinal K Cells



14. Dark Horse **IPS cells**

The fields of ES cells and diabetes revisited: are cell transplants the answer for Type-1 Diabetes?

- (i) Islet transplants: '*unlimited* stem cells' needed?
- (ii) Immunology: *any* cells needed for Type-1?
- (iii) Diabetes industry: innovative insulin pump therapies?
- (iv) hESC research: 'disease in a dish'?

Do islet transplants only function short-term?

Diabetes UK: Should focus be on Type-2 Diabetes?

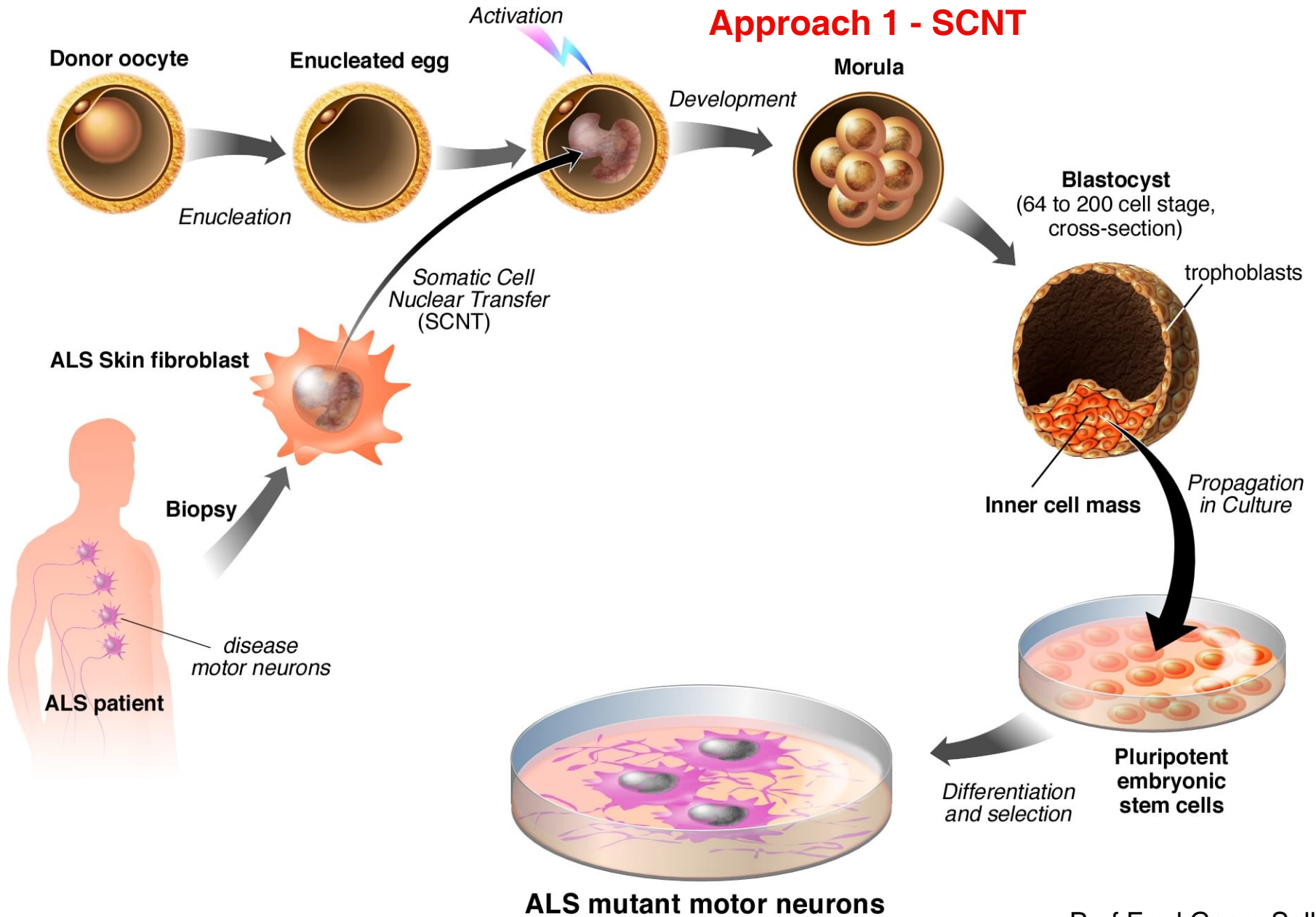
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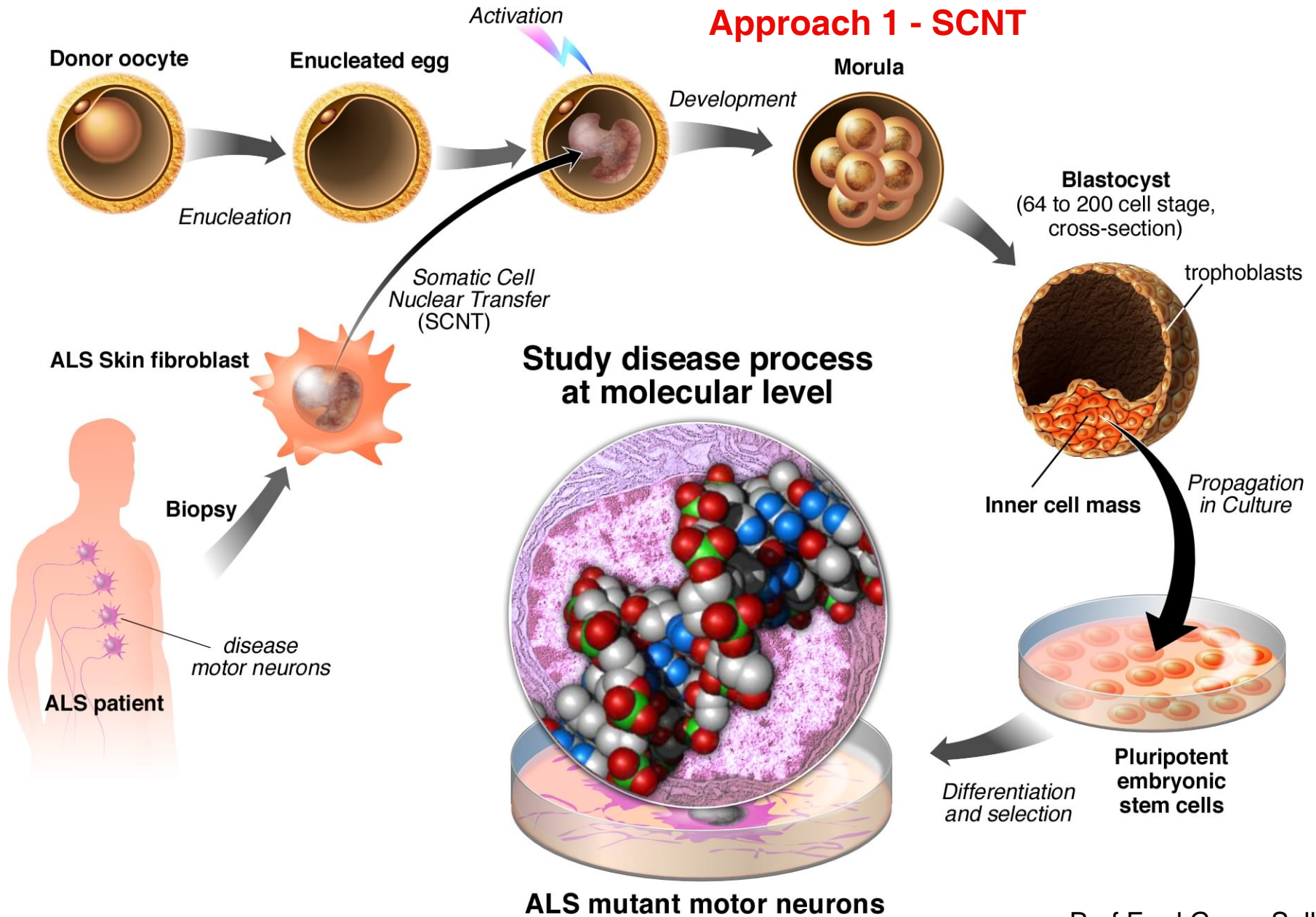
hESC Research: From Tx to 'Disease in a Dish'?

Stem cells have been, over the last two or three years, sold to the public as a potential therapeutic applications for transplantation, almost explicitly, and it is the simplest way to think about it... When are we first going to see the real cure, when are the benefits going to be in the clinic? Is it going to be diabetes, is it going to Parkinson's Disease? And I think some opportunists have jumped into this field, done some rat studies with human ES cells and some changes occurred. I think that people were shaken and some scientists started backing off and saying it's all hype. There are no real cures in this domain... For the last year or so I've been talking about how you can study 'diseases in a dish' through cell culture. This is a revolution in human biology. This is a paradigm shift... This is going to happen. It's too clear. It's too right. (Scientist 29, USA)

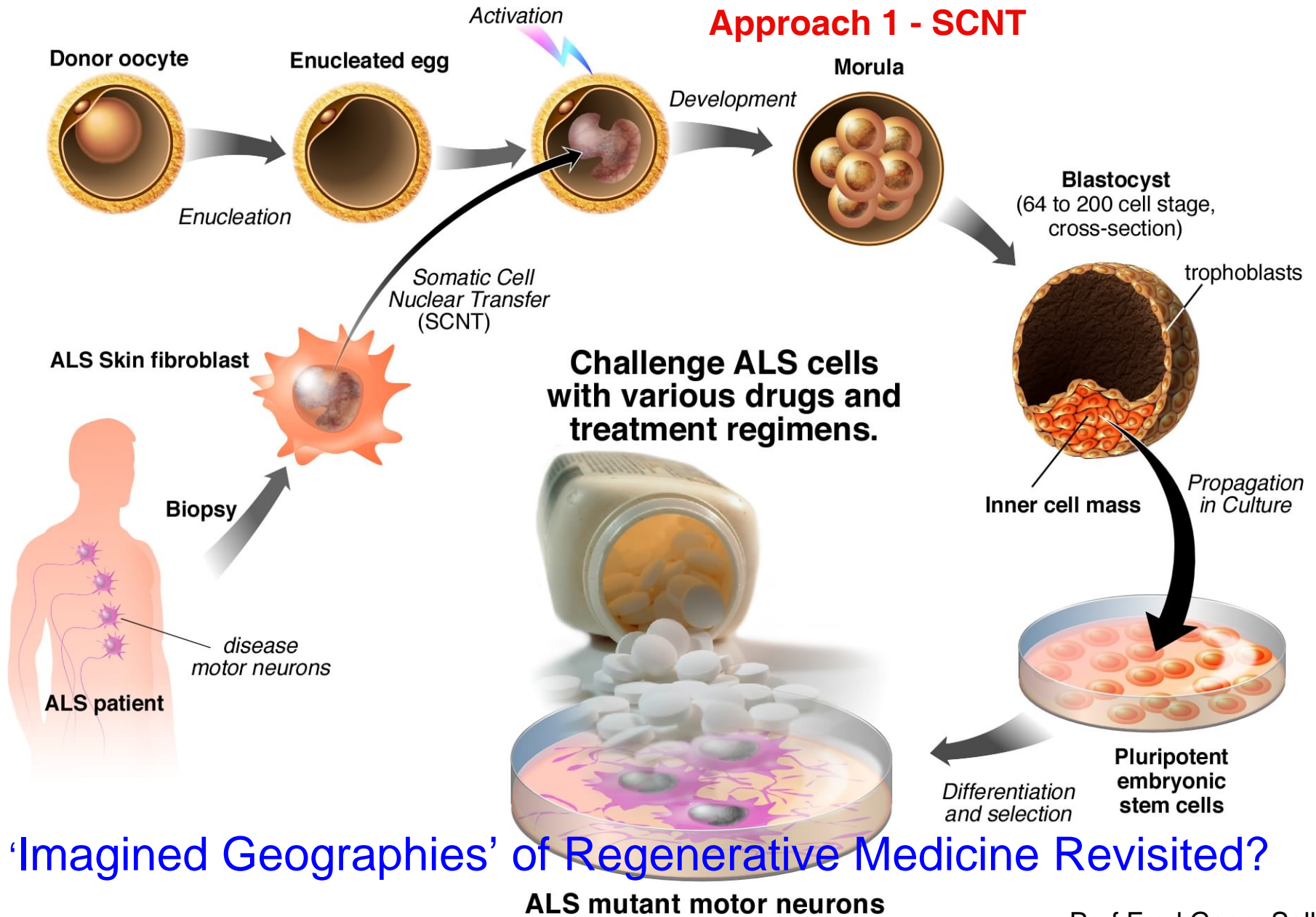
hES Cell Therapy: Cellular & Molecular Mechanisms of Disease



hES Cell Therapy: Cellular & Molecular Mechanisms of Disease



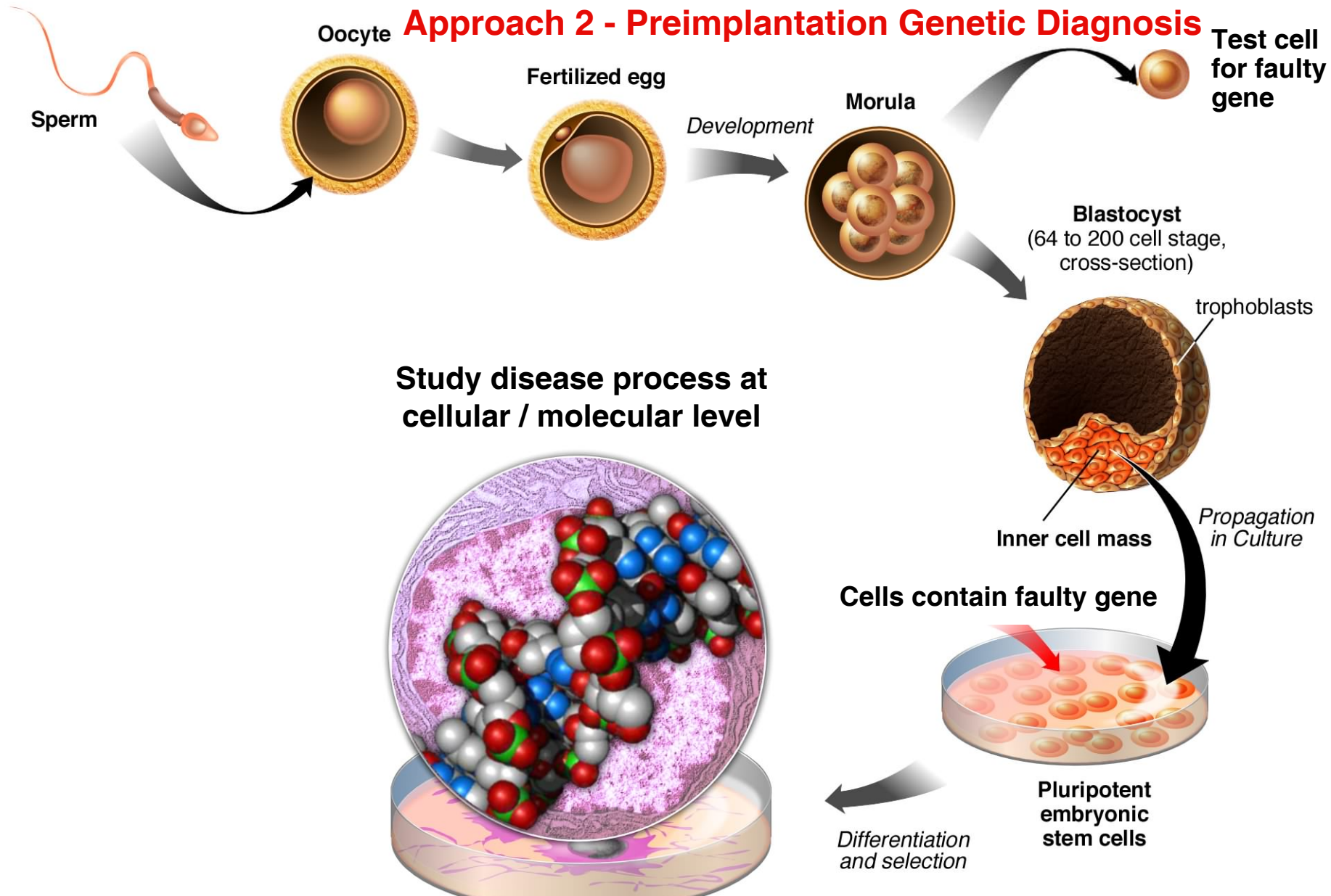
hES Cell Therapy: Cellular & Molecular Mechanisms of Disease



‘Imagined Geographies’ of Regenerative Medicine Revisited?

Human ES Cells: Studying the Cellular and Molecular Mechanisms of Disease

Approach 2 - Preimplantation Genetic Diagnosis

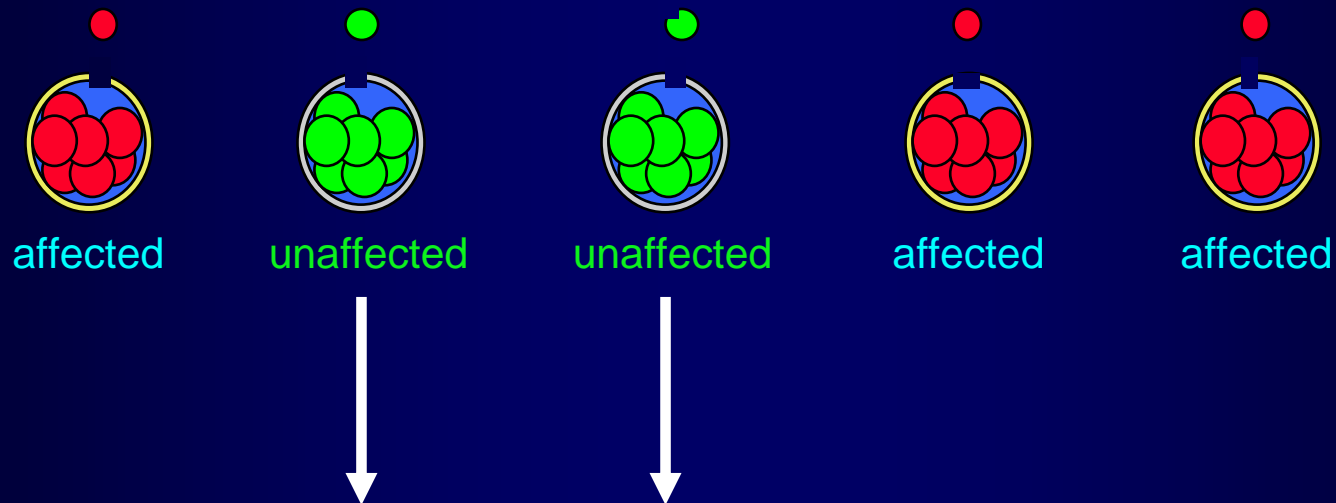


Modified from original
courtesy of Dr Fred Gage

hES Cells with genetic mutation

J. SIMON 24

Pre-implantation Genetic Diagnosis (PGD): Making Healthy Babies?

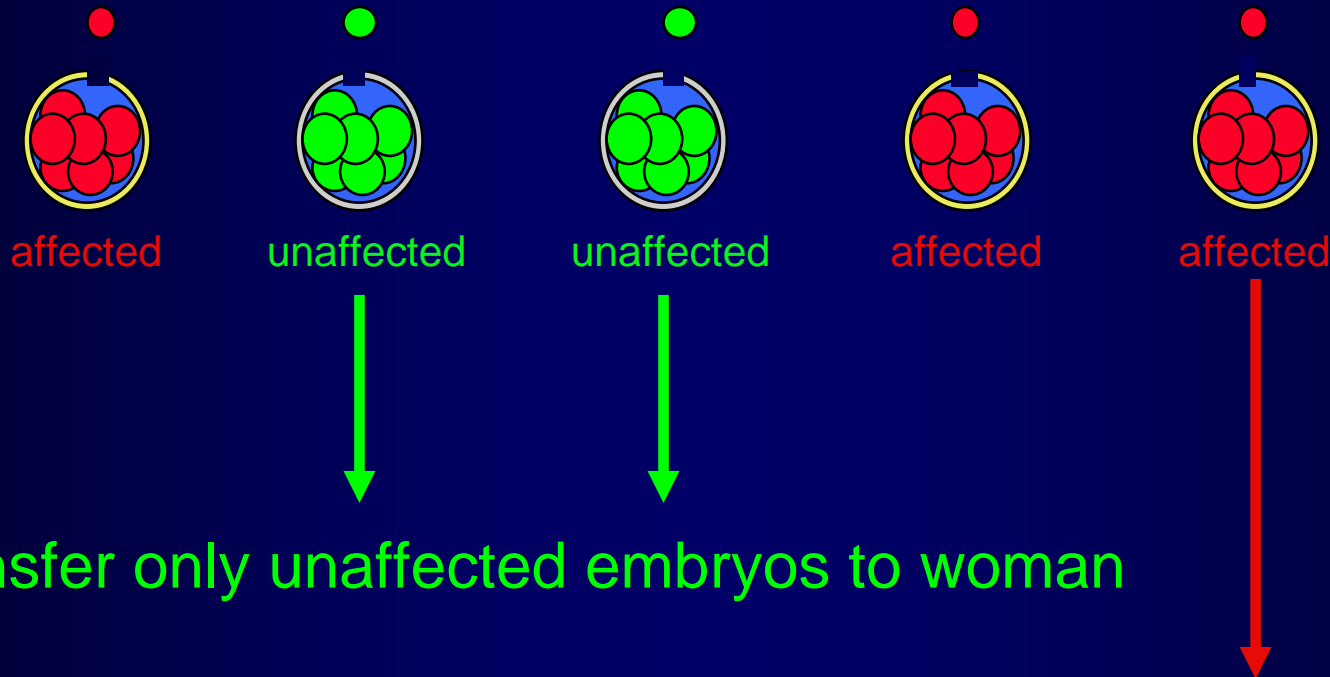


Transfer only unaffected embryos to woman

Pre-implantation Genetic Diagnosis (PGD): Making Healthy Babies & Creating 'Disease in a Dish'?

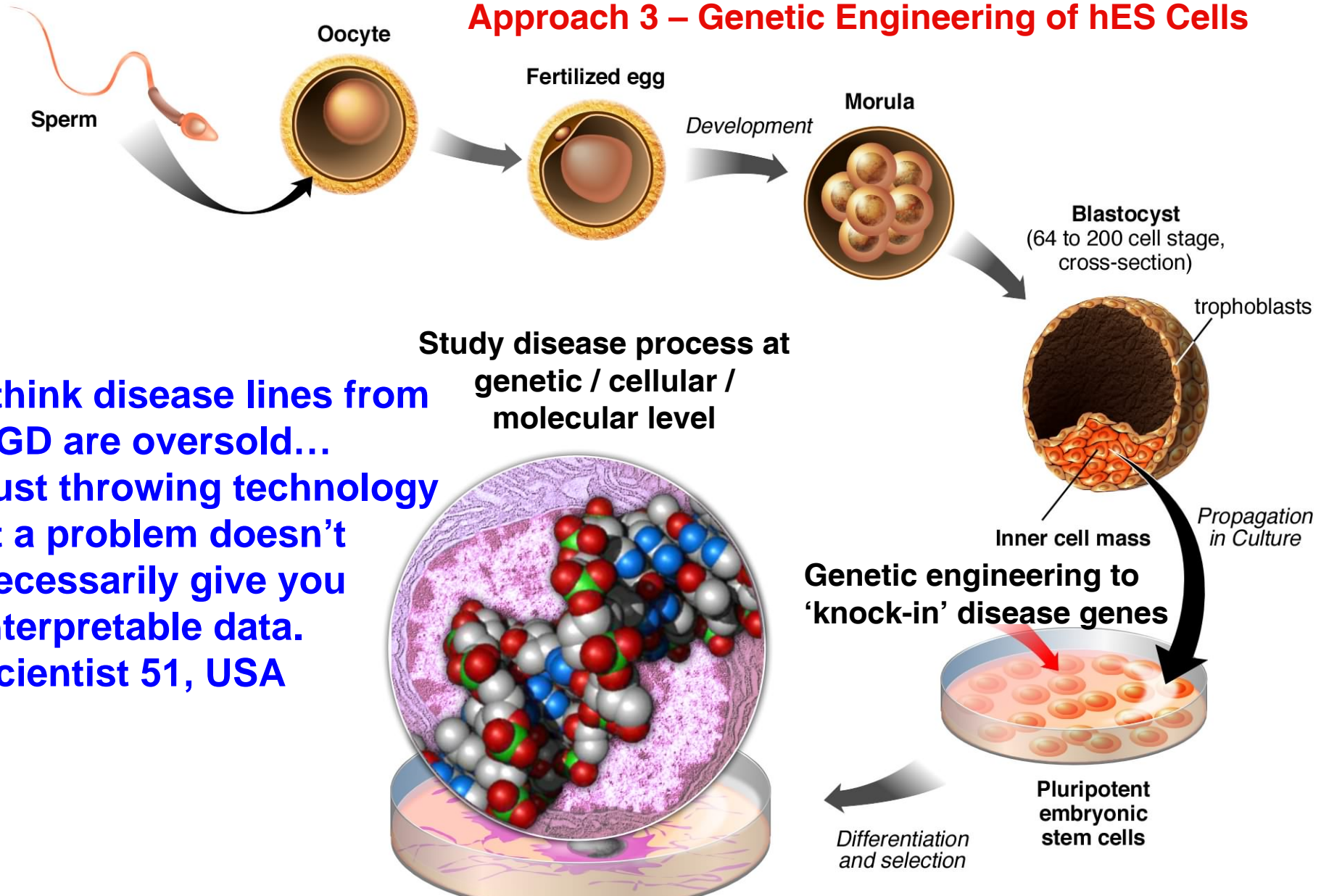
PGD lines could be very important... stem cells for therapy... This is a potential source to study genetic conditions. You could actually look through the very early stages where the genes switch on. What actually happens? Can you change it? Could it be a pharmaceutical target?

PGD Clinician/Scientist 16



Human ES Cells: Studying the Cellular and Molecular Mechanisms of Disease

Approach 3 – Genetic Engineering of hES Cells



I think disease lines from
PGD are oversold...
Just throwing technology
at a problem doesn't
necessarily give you
interpretable data.
Scientist 51, USA

Modified from original
courtesy of Dr Fred Gage

J. SIMON 24

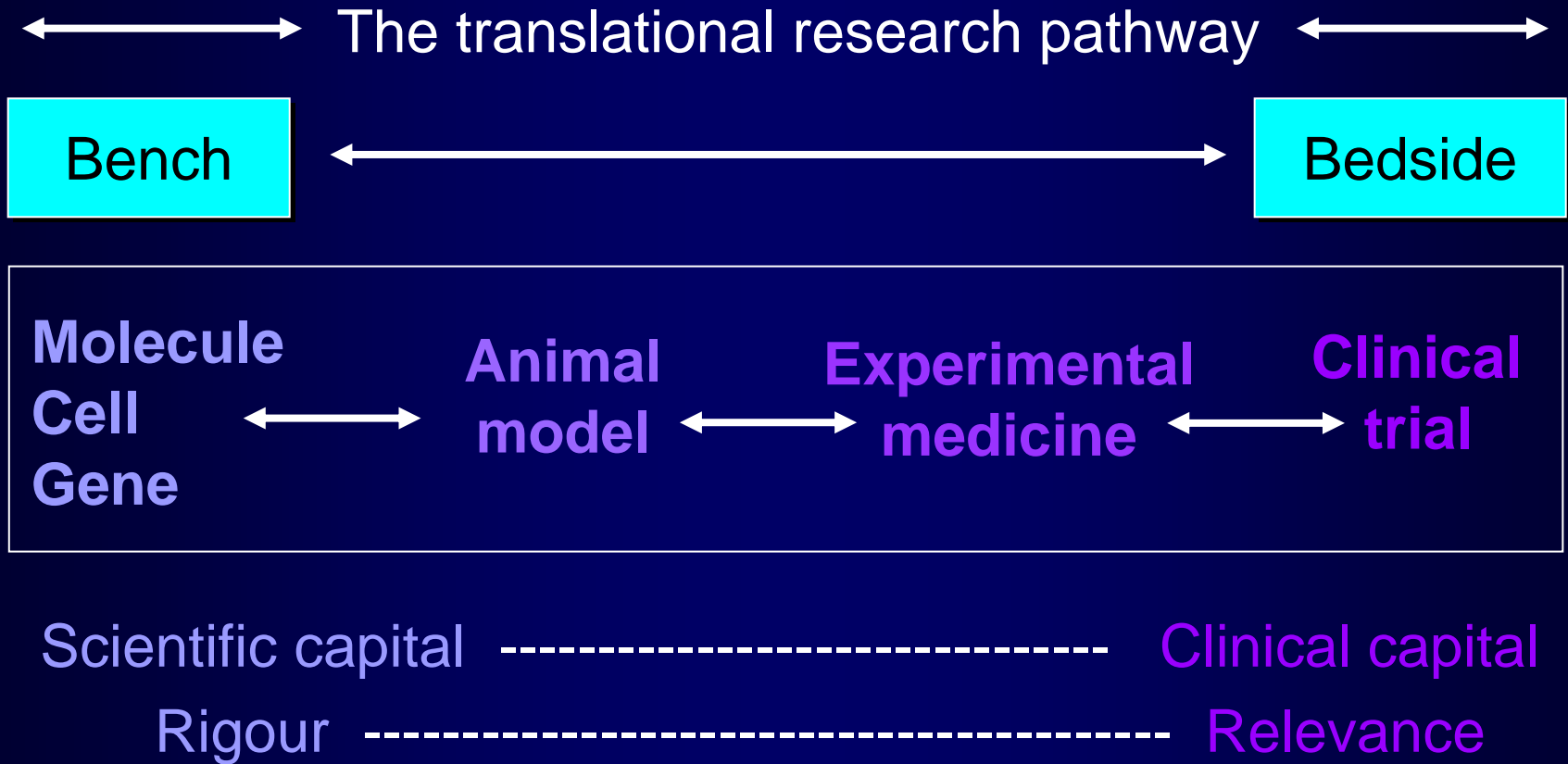
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Sociology of 'ES Stem Cell Translational Research'

1. Media & Ethics	<i>Sociology of Health & Illness</i>
2. Media & Expectations	<i>Social Science & Medicine</i>
3. Core Set	<i>Science Studies</i>
4. Epistemic Things	<i>Configurations</i>
5. Scientific Realism	<i>Social Theory & Health</i>
6. Translational Bioethics	<i>Medicine, Healthcare & Philosophy</i>
7. Cell Tx for PD ('PUS')	<i>British Journal of Neuroscience Nursing</i>
8. Ethical Boundary-Work	<i>Sociology of Health & Illness</i>
9. Boundary Objects	<i>New Genetics & Society</i>
10. Expectations	<i>Social Science & Medicine</i>
11. Boundary-Work	<i>New Genetics & Society</i>
12. Geography of Science	<i>New Genetics & Society</i>
13. Expectational Capital	<i>Sociology of Health & Illness</i>
14. STS & Bourdieu	<i>Handbook of Genetics & Society (Book)</i>
15. Sociology & Ethics	<i>Bioethics & Stem Cells (Book)</i>

From Bench to Bedside? The struggle for Power in the Fields of Science & Medicine



If I'm not prepared to do something, someone else will do it. There's someone right behind me, who's going to clamber over my back, prepared to do that. **There is great pressure on individuals and institutions to 'push ahead'.**
Surgeon 32.

LABTEC - London & Brighton Translational Ethics Centre (2009-2014)

The ethics of translational research: from 'unnatural entities' to experimental treatments

Prof Williams (King's, Sociology, CBAS)

Prof Braude (King's, Medicine)

Prof Cribb (King's, Ethics, SSPP)

Prof Farsides (Brighton & Sussex, Ethics)

Prof Michael (Goldsmiths, Sociology)

Dr Minger (King's, Stem Cell Science)

Prof Salter (King's, Politics, CBAS)

Prof Scott (King's, Ethics & Law, Law)

Prof Seale (QMUL, Sociology)

Prof Shaw (King's, Neuroscience, IOP)

Prof Wainwright (King's, Sociology, CBAS)

- Significant contribution to empirical /normative ethics
- Esteemed interdisciplinary research programme
- Develop research capacity and expertise
- Build local, national, and international collaborations
- Engage with policy makers, users and publics
- Contribute to public debates and the policy process

Ethics of translational research

Interface between research ethics / experimental treatment ethics

Two major themes

- Human animal hybrids (admixed embryos) and IPS cells
- Experimental neuroscience (PD & MND)

Four perspectives

- Scientists', clinicians' views
- Stakeholders' views (law, policy, regulation)
- Patients' perceptions
- Media reporting

Summary: Challenges for Stem Cell Translation

- What counts as translation?
- Basic versus applied science?
- What sort of stem cells?
- Is IPS a problematic panacea?
- Cell therapy and/or pharmacological tool?
- What timescale?
- Will competing approaches / technologies win out?
- What role should social science play?

Questioning Translation: The Politics of the Future

- Biotechnology and genomics marked by constant (re)creation of 'regimes of hope'
- Role of social scientists and bioethicists in the co-production of biofutures? e.g. ESRC SCI projects
- What principles and values should be adopted? Danger of 'going native'?
- Should social scientists be involved in creating alternative discourses eg about resource allocation, production of health, health inequalities [what counts as translation] etc?

What Counts as 'Translational Research'?

1. Better Science --> 2. Improved Health

What is a drug?

A substance injected into a rat that produces a paper!

What is translational research?

A phrase used in a proposal that produces a grant!

Is biomedical science the best way to improve health?

1. The challenge from social science...
2. The challenge from geoscience...

What is Translational Research? The Future as the Key to the Present **OR** the Past as the Key to the Future

The Spirit Level

Why
More Equal
Societies
Almost
Always Do
Better

Richard
Wilkinson
and Kate
Pickett



Reconstructing Quaternary Environments



2nd Edition

PEARSON
Prentice
Hall

J J Lowe and
M J C Walker

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