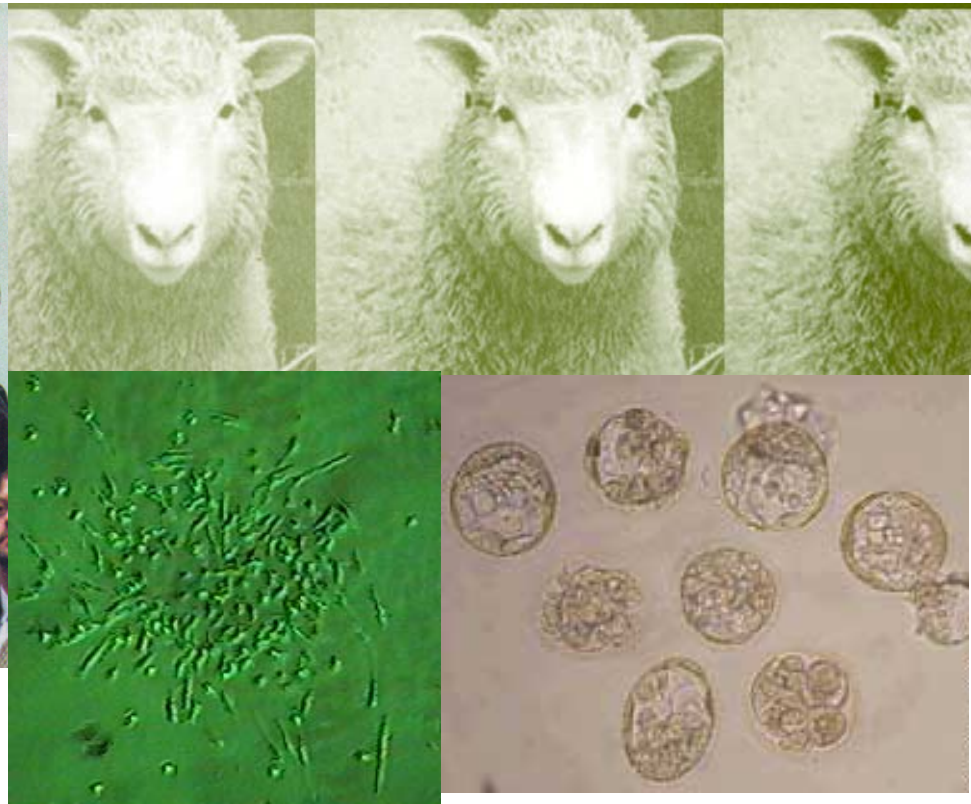


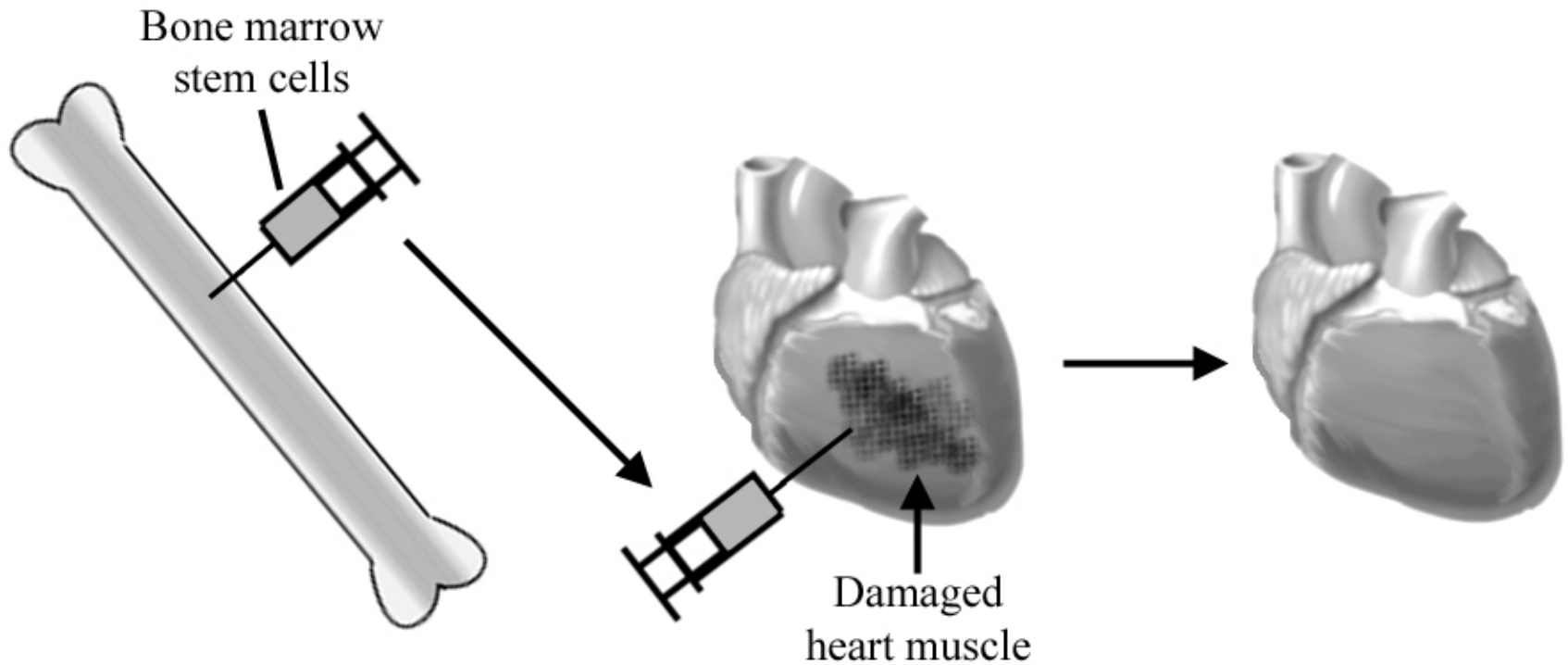
# Stem Cells & Cloning

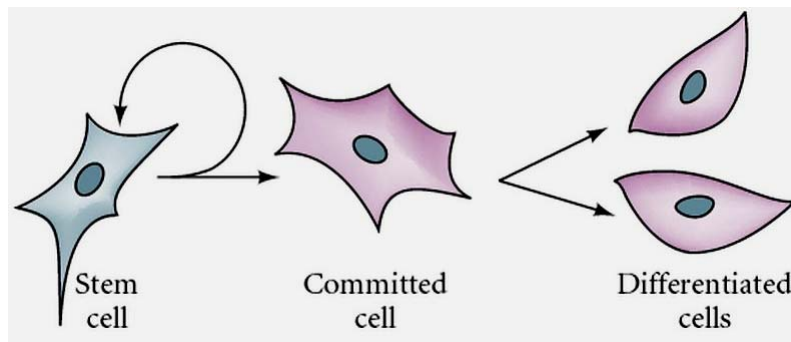


David A. Prentice, Ph.D.

Family Research Council and Georgetown University Medical School  
Washington, D.C., USA

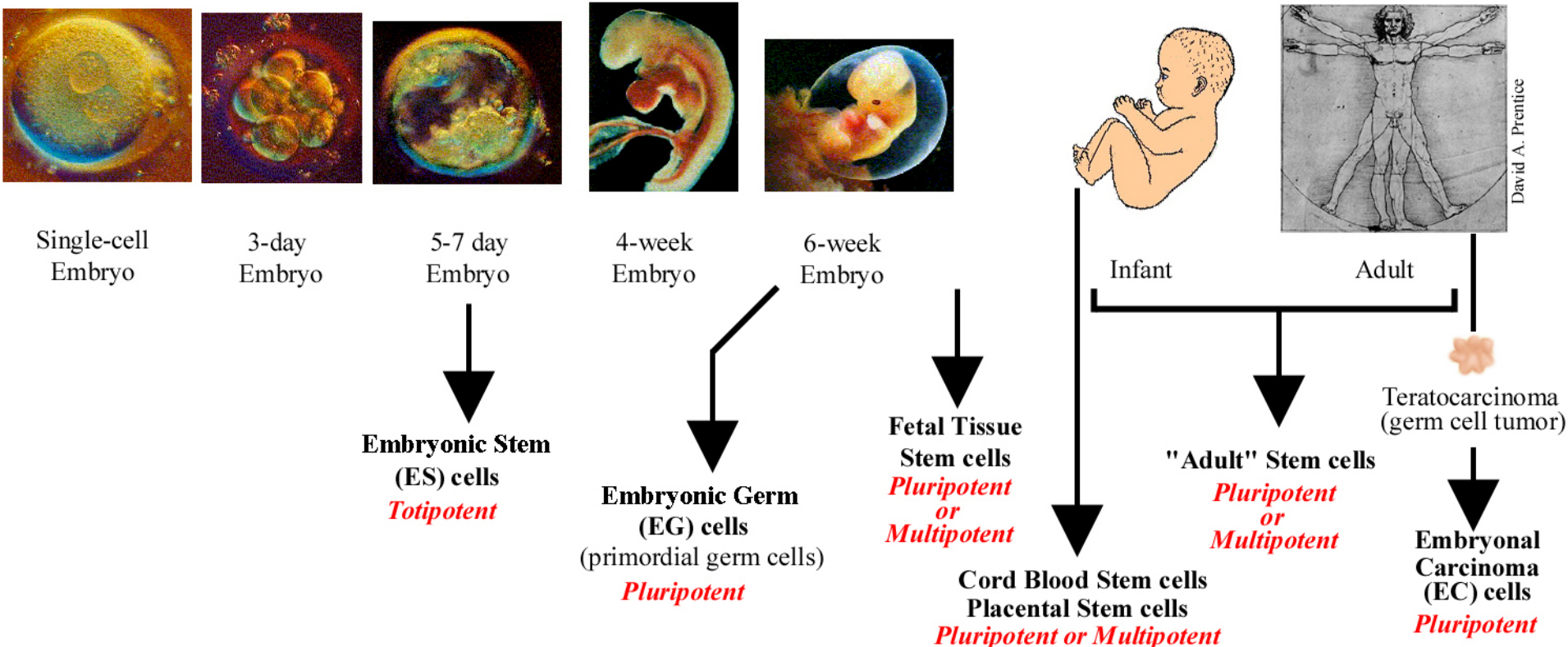
# Regenerative Medicine with Stem Cells





# Stem Cells

Human Developmental Continuum →



# Isolation & Culture of Embryonic Stem Cells

(Human-1998; Mouse-1981)

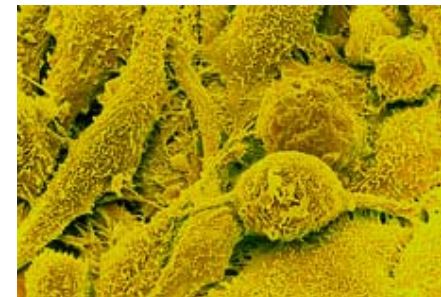
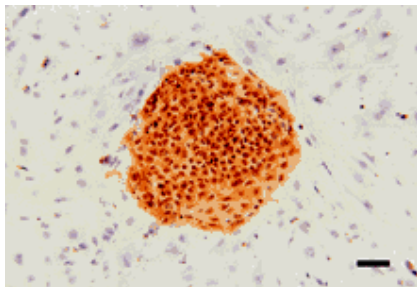
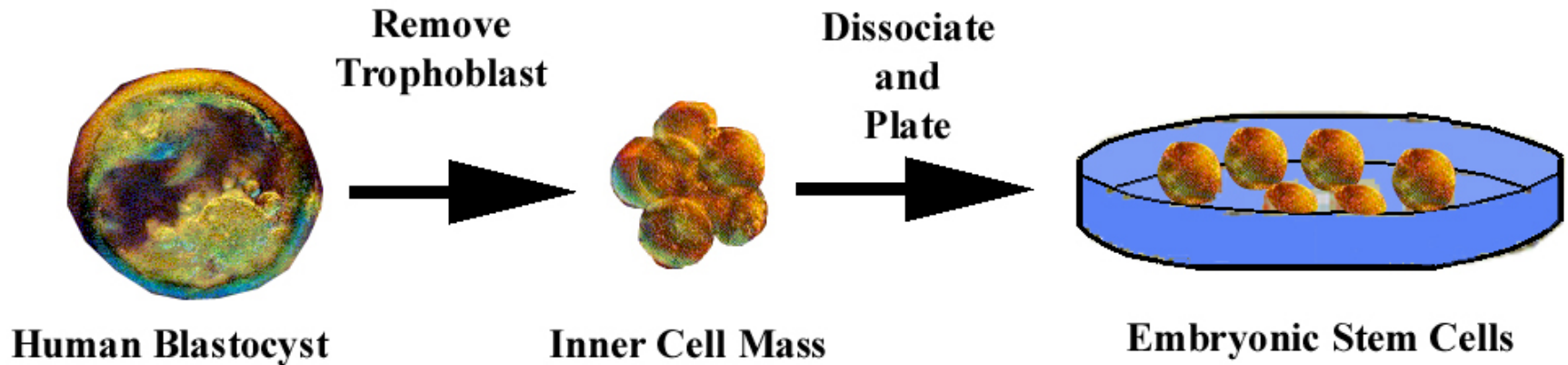
Method patented

U.S. patent held by Univ. Wisconsin

## Purported Advantages:

1) Proliferate indefinitely

2) Form any tissue





## Claims thus far unsubstantiated for embryonic stem cells

### Current or potential embryonic stem cell problems:

- Difficult to establish and maintain
- Difficulty in obtaining pure cultures in the dish
- Potential for tumor formation and tissue destruction
- Questions regarding functional differentiation

\*Hansson M *et al.*, “Artifactual insulin release from differentiated embryonic stem cells”, *Diabetes* 53, 2603-2609, October 2004

\*Sipione S *et al.*, “Insulin expressing cells from differentiated embryonic stem cells are not beta cells”, *Diabetologia* 47, 499-508, 2004 (published online 14 Feb 2004)

\*Rajagopal J *et al.*; “Insulin staining of ES cell progeny from insulin uptake”; *Science* 299, 363; 17 Jan 2003

\*Zhang YM *et al.*; “Stem cell-derived cardiomyocytes demonstrate arrhythmic potential”; *Circulation* 106, 1294-1299; 3 September 2002

- Problem of immune rejection

\*Swijnenburg R-J *et al.*, Embryonic stem cell immunogenicity increases upon differentiation after transplantation into ischemic myocardium, *Circulation* 112, I-166-I-172, 30 August 2005

- Genomic instability

\*Maitra A *et al.*, Genomic alterations in cultured human embryonic stem cells, *Nature Genetics* online 4 Sept 2005

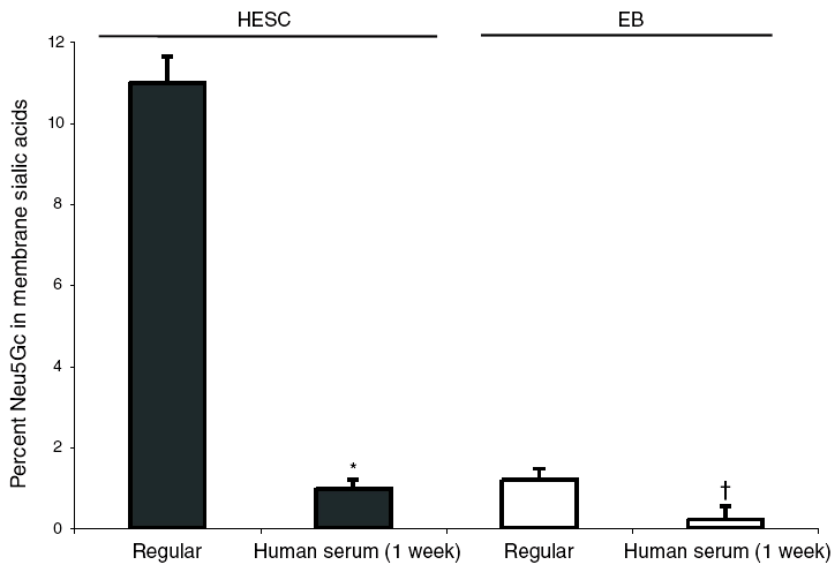
\*Cowan CA *et al.*, “Derivation of embryonic stem-cell lines from human blastocysts”, *New England Journal of Medicine* 350, 1353-1356, 25 March 2004

\*Draper JS *et al.*, “Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells”, *Nature Biotechnology* 22, 53-54; January 2004

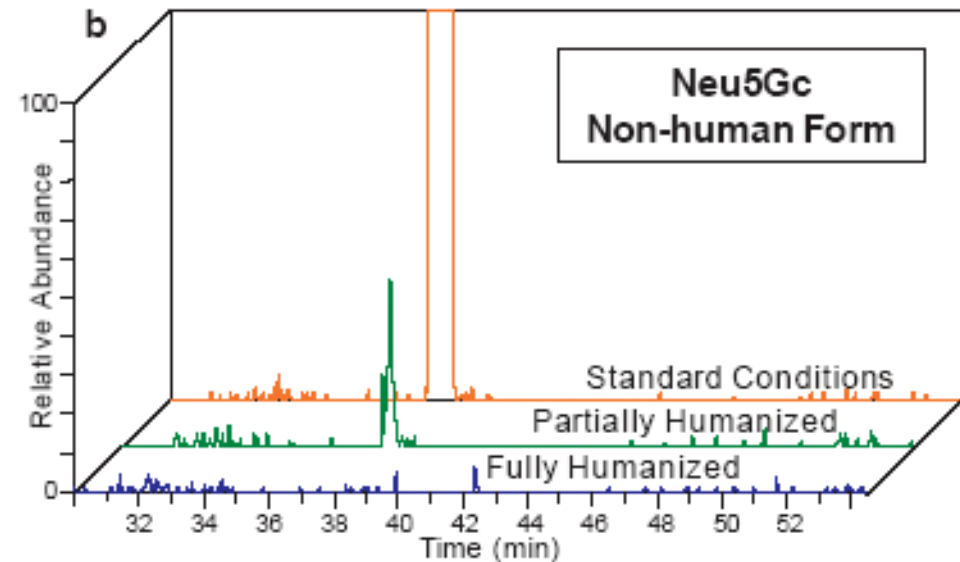
\*Humpherys D *et al.*; “Epigenetic instability in ES cells and cloned mice”; *Science* 293, 95-97; 6 July 2001

- Few and modest results in animals, no clinical treatments
- Ethically contentious

# “Contamination” removed from current human embryonic stem cell lines



**Figure 3** Effect of growth in NHS on Neu5Gc content of HESC and embryoid bodies. HESC or embryoid bodies were grown in NHS instead of the standard serum replacement. Membrane-bound sialic acids were studied for percentage of Neu5Gc as described in the **Fig. 1b** legend. Data represent the mean of two different experiments (mean  $\pm$  s.d.). \* $P < 0.005$ , † $P < 0.01$ .

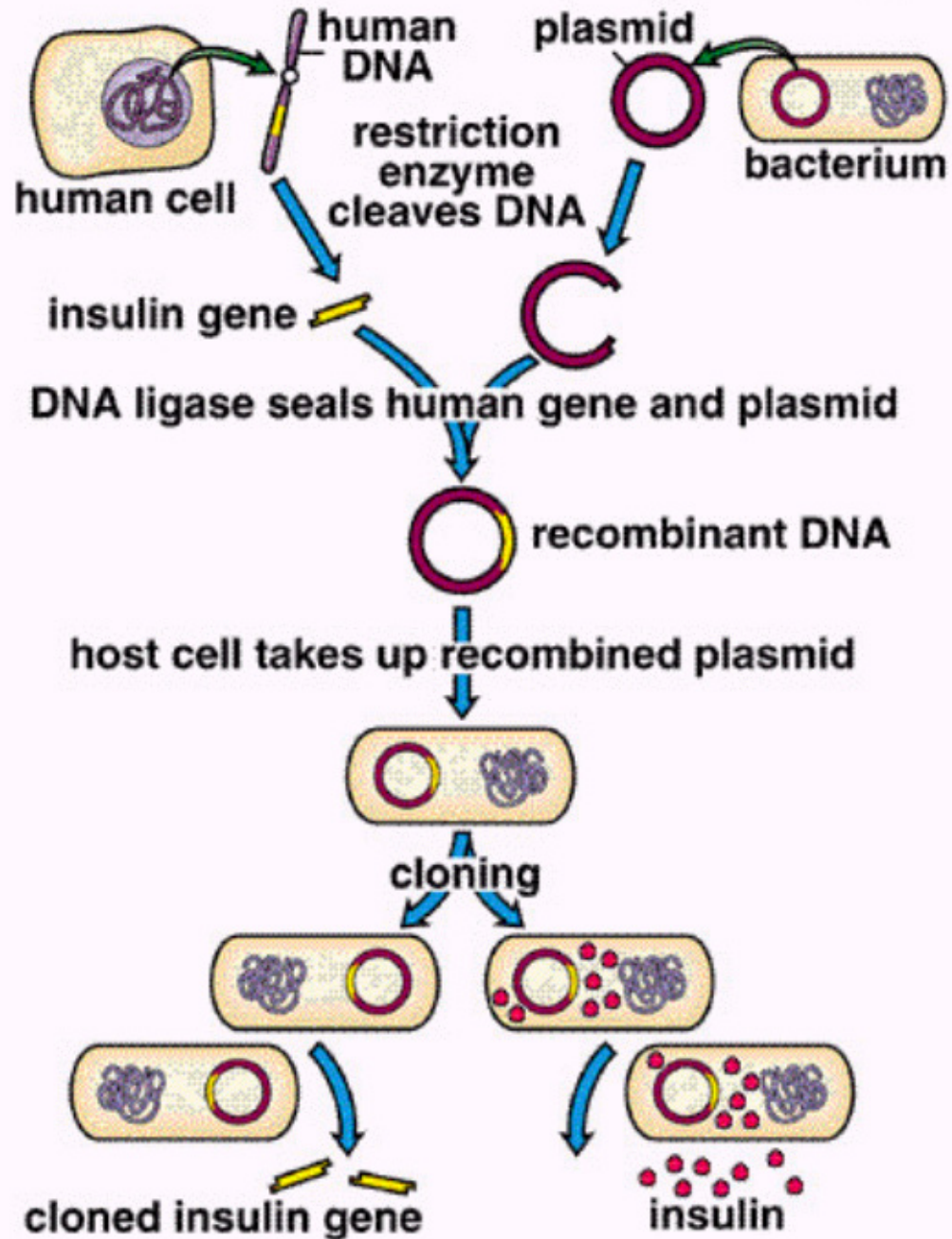


**Supplementary Figure 5.** Absence of sialic acid contamination in human ES cells cultured in defined conditions.

**From: Ludwig, Thomson, et al.,  
Nature Biotechnology 24, 185-187, February 2006**

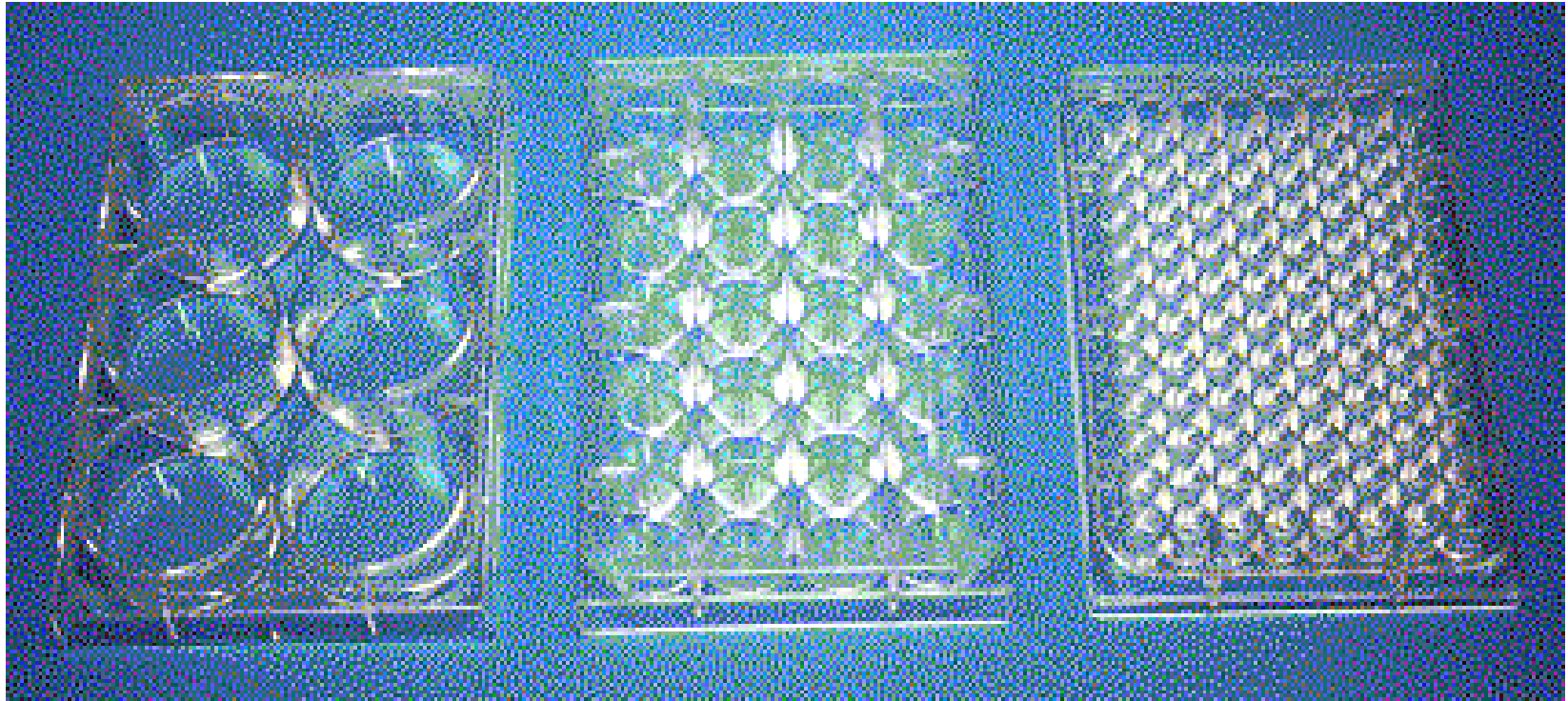
From: Martin MJ et al., Human embryonic stem cells express an immunogenic nonhuman sialic acid, *Nature Medicine* 11, 228-232, February 2005

# Human Gene Cloning



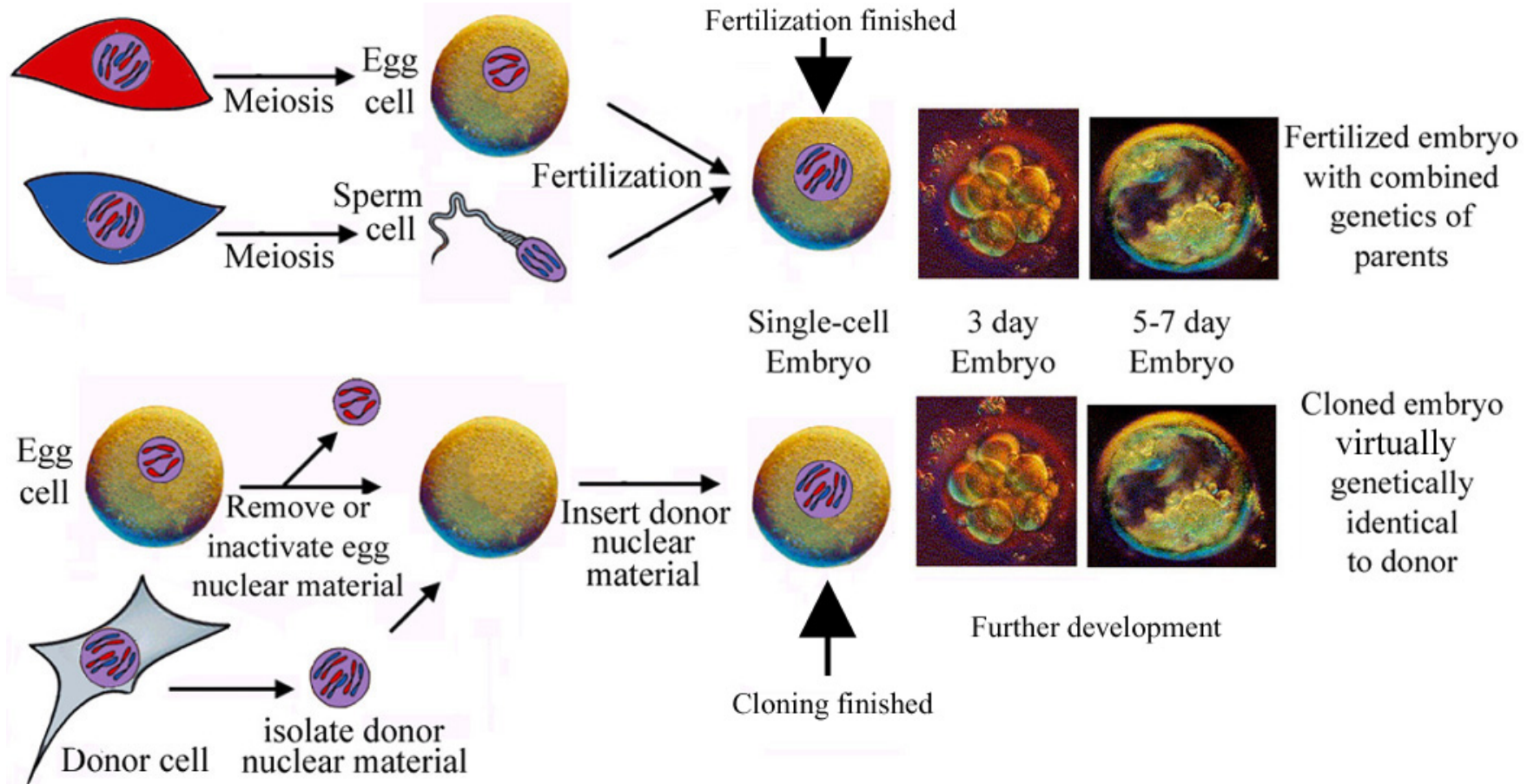
# Cell Cloning

One cell is placed into the dish or well by itself. The cell divides and forms a population of identical cells (cell clones.)

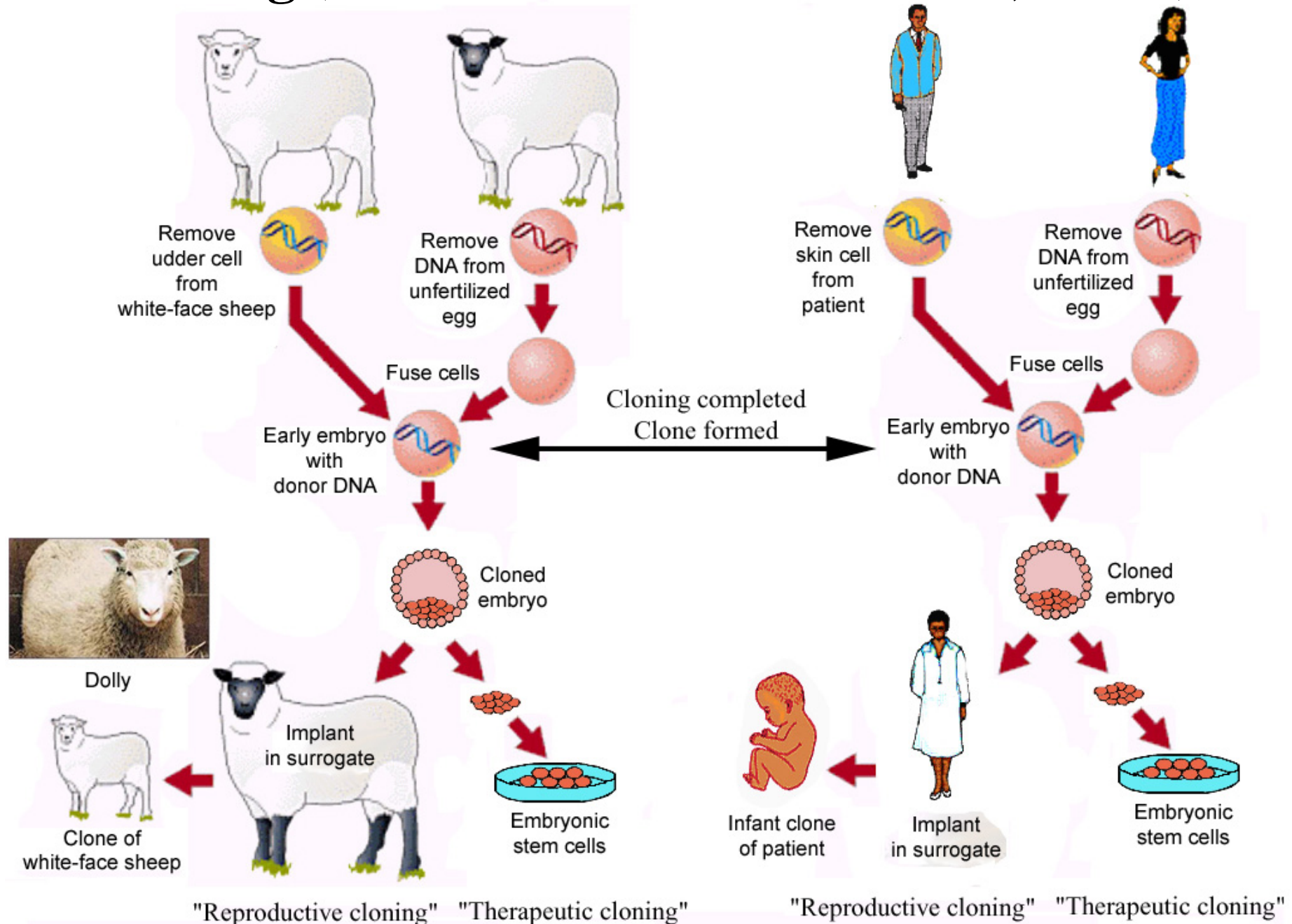


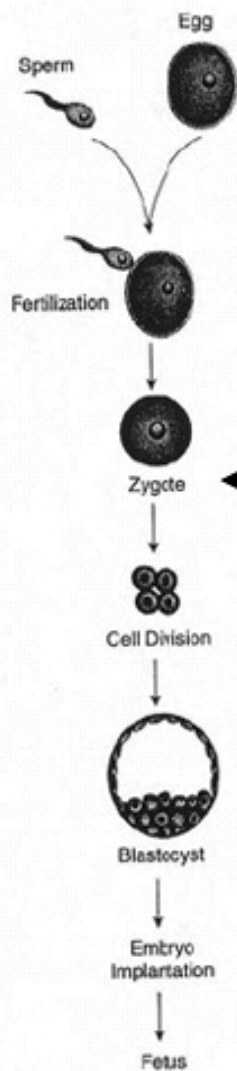


# Fertilization vs. Cloning (somatic cell nuclear transfer, SCNT)

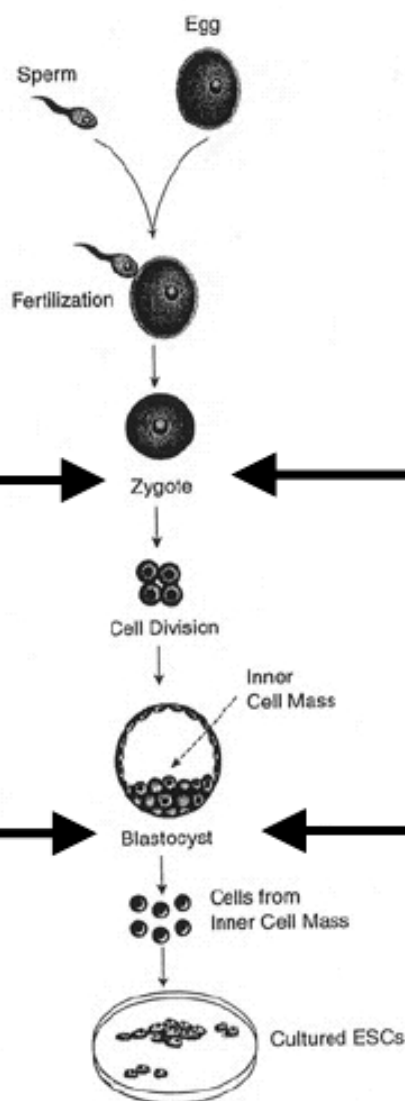


# Cloning (Somatic Cell Nuclear Transfer, SCNT)

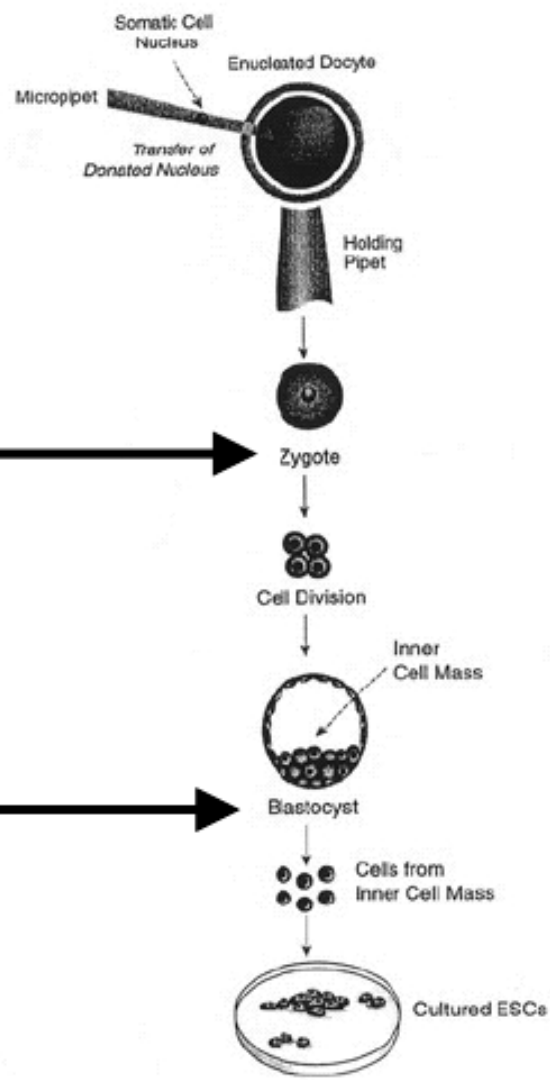




**Figure 1 Stages of Development of the Human Embryo**



**Figure 2 Isolation and Culture of Human ESCs from Blastocysts**



**Figure 4 Somatic Cell Nuclear Transfer (SCNT).**

[From: Stem Cells and the Future of Regenerative Medicine, Report of the National Academy of Sciences and the Institute of Medicine, National Academy Press, Washington, DC, Sept. 2001; Pg. 10, 11, 26]

## **Cloning (SCNT) produces a human embryo**

“The Commission began its discussions fully recognizing that any effort in humans to transfer a somatic cell nucleus into an enucleated egg involves the creation of an embryo, with the apparent potential to be implanted in utero and developed to term.”

*Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission* (Rockville, MD: June 1997), p. 3

“The first product of SCNT is, on good biological grounds, quite properly regarded as the equivalent of a zygote, and its subsequent stages as embryonic stages in development.”

*Human Cloning and Human Dignity: An Ethical Inquiry, Report of the President's Council on Bioethics, July 2002; p.50*

# **Cloning (SCNT) produces a human embryo**

“The method used to initiate the reproductive cloning procedure is called either nuclear transplantation or somatic cell nuclear transfer.”

*Scientific and Medical Aspects of Human Reproductive Cloning*, Report of the National Academy of Sciences and the Institute of Medicine, National Academy Press, Washington, DC, Jan 2002

“anything that you construct at this point in time that has the properties of those structures to me is an embryo, and we should not be changing vocabulary at this point in time. It doesn’t change some of the ethical issues involved.”

Dr. John Gearhart, Johns Hopkins University, 25 April 2002; before the U.S. President’s Council on Bioethics.

“Moreover, because therapeutic cloning requires the creation and disaggregation ex utero of blastocyst stage embryos, this technique raises complex ethical questions.”

“CRNT [Therapeutic cloning] requires the deliberate creation and disaggregation of a human embryo.”

**Robert P. Lanza, Arthur L. Caplan, Lee M. Silver, Jose B. Cibelli, Michael D. West, Ronald M. Green;** "The ethical validity of using nuclear transfer in human transplantation"; *The Journal of the American Medical Association* 284, 3175-3179; Dec 27, 2000.



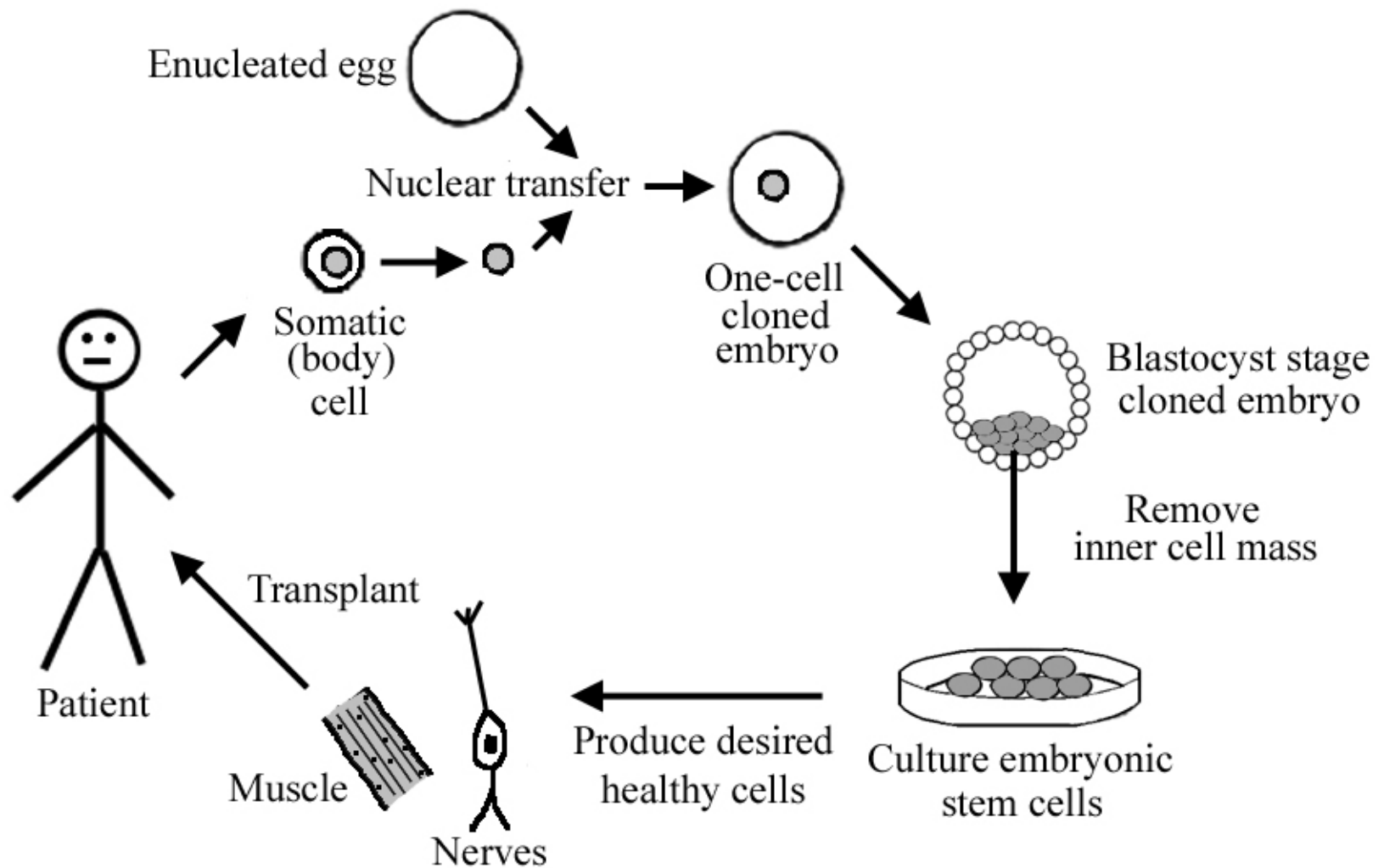
## **Cloning (SCNT) produces a human embryo**

**Q:** The people who use nuclear transfer generally say that the technique is optimized for producing the stem cells rather than making babies. They would not want to equate this with the process that produces embryos that were fit for implantation, and they'd argue that they're using the reproductive process differently ...

**A:** “See, you’re trying to define it away, and it doesn’t work. If you create an embryo by nuclear transfer, and you give it to somebody who didn’t know where it came from, there would be no test you could do on that embryo to say where it came from. It is what it is. It’s true that they have a much lower probability of giving rise to a child. ... But by any reasonable definition, at least at some frequency, you’re creating an embryo. If you try to define it away, you’re being disingenuous.”

**Stem-cell pioneer does a reality check. James Thomson reflects on science and morality**  
By Alan Boyle Science editor MSNBC 4:13 p.m. ET June 22, 2005

# Theoretical Concept of “Therapeutic Cloning”



# Therapeutic Cloning is a Failure

- **Transplanted cells from cloned mouse embryo rejected**

\*WM Rideout *et al.*, “Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy,” *Cell* 109, 17-27; 5 April 2002 (published online 8 March 2002)

“Our results raise the provocative possibility that even genetically matched cells derived by therapeutic cloning may still face barriers to effective transplantation for some disorders.”

- \*RYL. Tsai, R Kittappa, and RDG McKay; “Plasticity, niches, and the use of stem cells”;

*Developmental Cell* 2, 707-712; June 2002

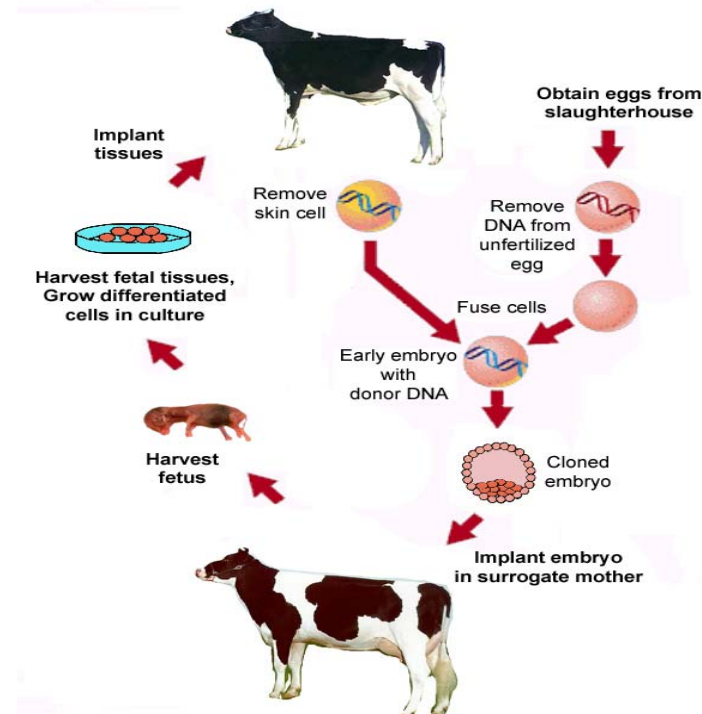
“Jaenisch addressed the possibility that ES clones derived by nuclear transfer technique could be used to correct genetic defects... However, the donor cells, although derived from the animals with the same genetic background, are rejected by the hosts.”

- **Clones may need to be gestated to “harvest” already-differentiated tissues**

\*R Lanza *et al.*; “Generation of histocompatible tissue using nuclear transplantation,” *Nature Biotechnology* 20, 689-696; July 2002

\*R Lanza *et al.*, “Regeneration of the infarcted heart with stem cells derived by nuclear transplantation,” *Circulation Research* 94, 820-827, April 2004

\*R Lanza *et al.*, “Long-term bovine hematopoietic engraftment with clone-derived stem cells”, *Cloning and Stem Cells* 7, 95-106, July 2005



# **Transplant rejection still likely using cells from cloned embryos**

- **“Robert Lanza**, chief scientist at Advanced Cell Technology in Worcester, Mass., an ardent advocate for both embryonic stem cell studies and therapeutic cloning, agreed that in the course of the political debate, the need for cloning to overcome immune system rejection has been overstated. ‘It’s not all or nothing. You can move ahead.’”

San Francisco Chronicle, Monday, March 18, 2002 Page E – 1

- “There is no question in my mind that the possibility exists that if you are doing an egg donor, and nuclear transfer into an egg, that there possibly exists that that cell -- that the embryonic stem cells derived from that could be rejected. Absolutely.”

**Dr. John Gearhart**, Johns Hopkins, 25 April 2002 meeting of the President’s Council on Bioethics

- “I should say that when you put the nucleus in from a somatic cell, the mitochondria still come from the host.” He concluded, “And in mouse studies it is clear that those genetic differences can lead to a mild but certainly effective transplant rejection and so immunosuppression, mild though it is, will be required for that.”

**Dr. Irving Weissman**, Stanford, 13 February 2002 meeting of the President’s Council on Bioethics

# “Therapeutic cloning”—unlikely chance of clinical success

- “[T]he poor availability of human oocytes, the low efficiency of the nuclear transfer procedure, and the long population-doubling time of human ES cells make it difficult to envision this [therapeutic cloning] becoming a routine clinical procedure...”  
Odorico JS, Kaufman DS, **Thomson JA**, “Multilineage differentiation from human embryonic stem cell lines,” *Stem Cells* 19, 193-204; 2001
- “However, it is unlikely that large numbers of mature human oocytes would be available for the production of ES cells, particularly if hundreds are required to produce each ES line. The technical capability for nuclear transfer would also need to be widely available and this is unlikely. In addition, epigenetic remnants of the somatic cell used as the nuclear donor can cause major functional problems in development, which must remain a concern for ES cells derived by nuclear transfer. ...it would appear unlikely that these strategies will be used extensively for producing ES cells compatible for transplantation.”  
**Alan O.Trounson**, “The derivation and potential use of human embryonic stem cells”, *Reproduction, Fertility, and Development* 13, 523-532; 2001
- **Thomas Okarma**, CEO, Geron Corporation says: “The odds favoring success are vanishingly small, and the costs are daunting.” “It would take thousands of [human] eggs on an assembly line to produce a custom therapy for a single person. The process is a nonstarter, commercially.”  
Denise Gellene, “Clone Profit? Unlikely”, Los Angeles Times, 10 May 2002



## **Development of “therapeutic” cloning techniques can lead to “reproductive” cloning:**

“It is true that the techniques developed in CRNT [cell replacement through nuclear transfer, a.k.a. therapeutic cloning] research can prepare the way scientifically and technically for efforts at reproductive cloning.”

**Robert P. Lanza, Arthur L. Caplan, Lee M. Silver, Jose B. Cibelli, Michael D. West, Ronald M. Green;** “The ethical validity of using nuclear transfer in human transplantation”; *The Journal of the American Medical Association* 284, 3175-3179; 27 Dec 27 2000

“If undertaken, the development of SCNT for such therapeutic purposes, in which embryos are not transferred for pregnancy, is likely to produce knowledge that could be used to achieve reproductive SCNT.”

**American Society for Reproductive Medicine Ethics Committee;** “Human somatic cell nuclear transfer (cloning)”; *Fertility and Sterility* 74, 873-876; November 2000

## “Cloning Unnecessary and Obsolete”

--leading embryonic stem cell expert

- **Alan Trounson**, Australian embryonic stem cell expert and a leader in the field worldwide, says that stem cell research has advanced so rapidly in the past few months that therapeutic cloning is now unnecessary. “My view is there are at least three or four other alternatives that are more attractive already,” he said. Trounson abandoned his call for therapeutic cloning, saying scientific breakthroughs mean there is now no need for the controversial technique. Professor Trounson said therapeutic cloning faced logistical problems, and that other techniques were showing great promise and offered better options. “I can't see why, then, you would argue for therapeutic cloning in the long term because it is so difficult to get eggs and you've got this issue of (destroying) embryos as well.”  
“Stem-cell cloning not needed, says scientist”, The Age (Melbourne), pg. 2, July 29, 2002;  
“Stem-cell research outpaces cloning”, The Australian, pg. 3, July 29, 2002;  
“Therapeutic cloning no longer necessary: expert”, AAP Newsfeed, July 29, 2002

# “Therapeutic” cloning places women at risk

Because both cloning and embryonic stem cell production are extremely inefficient, a tremendous number of eggs will be required.

For example, to treat only the 17 million Diabetes patients in the U.S.:

Will require at least 1.7 billion human eggs

(Optimistically 100 human eggs/patient, estimated cost US\$100,000-200,000)

Mombaerts P, “Therapeutic cloning in the mouse”, *Proceedings of the National Academy of Sciences USA* 100, 11924-11925; 30 Sept 2003; Prentice DA, Stem Cells and Cloning, 1st edition, San Francisco: Pearson Education/Benjamin-Cummings, July 2002

--Collecting 10 eggs/donor:

Will require at least 170 million women - childbearing age donors

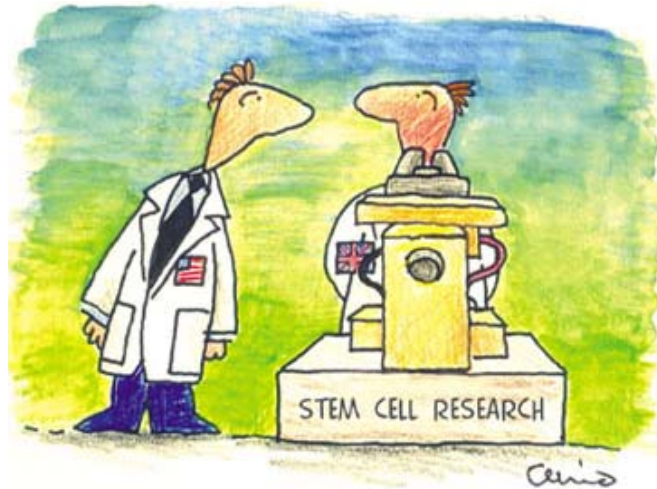
**Health risks**—High-dose hormone therapy and surgery to obtain eggs risks the donor’s health and future reproductive success

**Commercial exploitation**—of women globally

**SOUTH KOREAN HUMAN CLONING FRAUD**

**Cloned human embryos?-- no cells, faked data,  
egg payments, coercion of women students**

## GLOBAL VIEW



- **All uses of human SCNT cloning banned:**  
**France (7 yrs jail), Canada (5 yrs jail), Australia (10 yrs jail), Germany (5 yrs jail), Norway, Switzerland, et al.**
- **United Nations, 8 March 2005—**  
**Declaration to prohibit all forms of human cloning**  
**(b) Member States are called upon to prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life**



## U.S. FEDERAL LEGISLATION

- **HHS Appropriations language (since 1996)**

SEC. 510.

(a) None of the funds made available in this Act may be used for (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).

(b) For purposes of this section, the term “human embryo or embryos” includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.



# Adult stem cell capabilities

“There is no evidence of an adult stem cell that is pluripotent. It has not been demonstrated that one adult stem cell can be directed to develop into any cell type of the body. That is, *no adult stem cell has been shown to be capable of developing into cells from all three embryonic germ layers.*”

*Stem Cells: Scientific Progress and Future Research Directions*, National Institutes of Health, June 2001; Pg. ES-6 (*emphasis added*)

“Thus, at this stage, any therapies based on the use of human ES cells are still hypothetical and highly experimental.”

“Whether embryonic stem cells will provide advantages over stem cells derived from cord blood or adult bone marrow hematopoietic stem cells remains to be determined.”

*Stem Cells: Scientific Progress and Future Research Directions*, National Institutes of Health, June 2001; Pg. 17, 63

“Some adult stem cells appear to have the capability to differentiate into tissues other than the ones from which they originated; this is referred to as plasticity. Reports of human or mouse adult stem cells that demonstrate plasticity and the cells they differentiate or specialize into include: 1) *blood and bone marrow (unpurified hematopoietic) stem cells differentiate into the 3 major types of brain cells (neurons, oligodendrocytes, and astrocytes) [ectoderm], skeletal muscle cells, cardiac muscle cells [mesoderm], and liver cells [endoderm]*; 2) bone marrow (stromal) cells differentiate into cardiac muscle cells, skeletal muscle cells, fat, bone, and cartilage; and 3) brain stem cells differentiate into blood cells and skeletal muscle cells.”

*Ibid*, Pg. ES-7      [*emphasis added*]

# Adult Stem Cells

## Bone Marrow



Marrow  
Bone  
Cartilage  
Tendon  
Muscle  
Fat  
Liver  
Brain/Nerve  
Blood cells  
Heart  
*All Tissues*

## Stem Cells from Fat



Bone  
Cartilage  
Muscle  
Nerves

## Peripheral Blood



Bone Marrow  
Blood cells  
Nerves

## Hair Follicle



Skin Brain  
Smooth Muscle Fat

## Gastrointestinal



Esophagus Small Intestine  
Stomach Large Intestine/Colon

## Placenta



Bone Nerve  
Cartilage Muscle Tendon  
Bone Marrow Blood vessel

## Skeletal Muscle



Skeletal muscle  
Smooth muscle  
Bone  
Cartilage  
Fat  
Heart

## Brain



Brain  
Nerves  
Blood cells  
Muscle  
*All Tissues*

## Cornea

## Retina

## Pancreas

## Liver

## Heart

## Lung

## Spermatogonia

## Amniotic Fluid

## Umbilical Cord Matrix

## CORD BLOOD



*Various Tissues*

# **Evidence that Some Adult Stem Cells show Pluripotent Capacity**

## **Testicular Stem Cells express Oct-4, Nanog, and can form derivatives of all 3 primary germ layers**

Guan K *et al.*, Pluripotency of spermatogonial stem cells from adult mouse testis, *Nature* 440, 1199-1203, 27 April 2006

## **Umbilical Cord Blood Stem Cells express Oct-4, Sox-2, repair neurological damage**

Xiao J *et al.*, Transplantation of a novel cell line population of umbilical cord blood stem cells ameliorates neurological deficits associated with ischemic brain injury, *Stem Cells and Development* 14, 722-733, December 2005

## **Umbilical Cord Blood Stem Cells with embryonic-like stem cell properties**

McGuckin CP *et al.*, Production of stem cells with embryonic characteristics from human umbilical cord blood, *Cell Proliferation* 38, 245-255, August 2005

## **Placental Amniotic Stem Cells express Oct-4, nanog; potentially form any tissue, no tumors**

Miki T *et al.*, Stem cell characteristics of amniotic epithelial cells, *Stem Cells* published online 4 Aug 2005; doi:10.1634/stemcells.004-0357

## **Nasal Stem Cells form multiple tissues, patient-specific stem cell lines**

Murrell W *et al.*, "Multipotent stem cells from adult olfactory mucosa, *Developmental Dynamics* 233, 496-515, June 2005

## **Common Pluripotent Adult Stem Cell isolated from multiple mouse tissues**

Case J *et al.*, Clonal multilineage differentiation of murine common pluripotent stem cells isolated from skeletal muscle and adipose stromal cells, *Annals NY Acad Sci* 1044, 183-200, June 2005

## **Bone Marrow Stem Cells can form all 3 germ layers, and regenerate damaged heart**

Yoon Y-s *et al.*, "Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction", *Journal of Clinical Investigation* 115, 326-338, February 2005

## **Human Cord Blood stem cells show pluripotent potential and extensive proliferation**

Kögler G *et al.*, "A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential", *J. Experimental Medicine* 200, 123-135, 19 July 2004

## **Human Bone Marrow Adult Stem Cells with pluripotent potential, Oct-4 expression**

D'Ippolito G *et al.*, "Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential", *J. Cell Science* 117, 2971-2981, 15 June 2004

## **Peripheral blood stem cells can form cells from all 3 germ layers**

Zhao Y *et al.*; "A human peripheral blood monocyte-derived subset acts as pluripotent stem cells"; *Proceedings of the National Academy of Sciences USA* 100, 2426-2431; 4 March 2003

## **Adult stem cells from bone marrow can form all body tissues**

Jiang Y *et al.*; "Pluripotency of mesenchymal stem cells derived from adult marrow"; *Nature* 418, 41-49; 4 July 2002

## **A single adult mouse bone marrow stem cell can form multiple functional tissues**

Krause DS *et al.*; "Multi-Organ, Multi-Lineage Engraftment by a Single Bone Marrow-Derived Stem Cell"; *Cell* 105, 369-377; 4 May 2001

## **Adult stem cells effective in tissue repair**

**Stroke—Adult stem cells from brain, bone marrow, and umbilical cord blood provide therapeutic benefit after stroke. First clinical trials under way.**

\*Shyu W-C *et al.*, “Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells”, *Circulation* 110, 1847-1854, 2004

\*Willing AE *et al.*, “Mobilized peripheral blood stem cells administered intravenously produce functional recovery in stroke”, *Cell Transplantation* 12, 449-454; 2003

\*Arvidsson A *et al.*; “Neuronal replacement from endogenous precursors in the adult brain after stroke”; *Nature Medicine* 8, 963-970; Sept 2002

\*Riess P *et al.*; “Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury”; *Neurosurgery* 51, 1043-1052; Oct 2002

\*Li Y *et al.*; “Human marrow stromal cell therapy for stroke in rat”; *Neurology* 59, 514-523; August 2002

\*Chen J *et al.*; “Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats”; *Stroke* 32, 2682-2688; November 2001

# **Adult stem cells effective in tissue repair**

## **Spinal Cord Injury—Adult stem cells capable of re-growth and reconnection in spinal cord. Clinical trials started in Portugal, South Korea and Australia.**

\*Zhang X *et al.*, Role of transcription factors in motoneuron differentiation of adult human olfactory neuroepithelial-derived progenitors, *Stem Cells* 24, 434-442, March 2006

\*\*Kang K-S *et al.*, A 37-year-old spinal cord-injured female patient, transplanted of multipotent stem cells from human UC blood, with improved sensory perception and mobility, both functionally and morphologically: a case study, *Cytotherapy* 7, 368-373, September 2005

\*Sigurjonsson OE *et al.*, Adult human hematopoietic stem cells produce neurons efficiently in the regenerating chicken embryo spinal cord, *PNAS* 102, 5227-5232, 5 April 2005

\*Lu J *et al.*, Olfactory ensheathing cells promote locomotor recovery after delayed transplantation into transected spinal cord, *Brain* 125, 14-21, 2002

\*Ohta M *et al.*, Bone marrow stromal cells infused into the cerebrospinal fluid promote functional recovery of the injured rat spinal cord with reduced cavity formation, *Experimental Neurology* 187, 266-278, 2004

\*Hofstetter CP *et al.*, "Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery", *Proc Natl Acad Sci USA* 99, 2199-2204; Feb 19, 2002

\*M. Sasaki *et al.*, "Transplantation of an acutely isolated bone marrow fraction repairs demyelinated adult rat spinal cord axons," *Glia* 35, 26-34; July 2001

\*A. Ramon-Cueto *et al.*, "Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia," *Neuron* 25, 425-435; Feb 2000.

\*M.S. Ramer *et al.*; "Functional regeneration of sensory axons into the adult spinal cord," *Nature* 403, 312-316; Jan 20, 2000.

\*Barnett *et al.*; "Identification of a human olfactory ensheathing cell that can effect transplant-mediated remyelination of demyelinated CNS axons," *Brain* 123, 1581-1588, Aug 2000

\*A. Ramon-Cueto *et al.*, "Long-distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glial transplants," *J Neurosci* 18, 3803-3815; May 15, 1998



## Adult stem cells effective in tissue repair

**Diabetes—Pancreatic, liver, intestinal, spleen or bone marrow cells can form insulin-secreting islets. FDA approval of clinical trial, Denise Faustman, Harvard.**

\*Hao E *et al.*, Beta-cell differentiation from nonendocrine epithelial cells of the adult human pancreas, *Nature Medicine* 12, 310-316, March 2006

\*Ta M *et al.*, The defined combination of growth factors controls generation of long-term replicating islet progenitor-like cells from cultures of adult mouse pancreas, *Stem Cells* doi:10.1634/stemcells.2005-0367, published online March 23, 2006

\*Timper K *et al.*, Human adipose tissue-derived mesenchymal stem cells differentiate into insulin, somatostatin, and glucagon expressing cells, *Biochem Biophys Res Comm* 341, 1135-1140, 24 March 2006

\*Yoshida S *et al.*, Human cord blood-derived cells generate insulin-producing cells *in vivo*, *Stem Cells* 23, 1409-1416, October 2005

\*Sapir *et al.*, Cell-replacement therapy for diabetes: generating functional insulin-producing tissue from adult human liver cells, *Proceedings of the National Academy of Sciences USA* 102, 7964-7969, 17 May 2005

\*Seaberg BM *et al.*, “Clonal identification of multipotent precursors from adult mouse pancreas that generate neural and pancreatic lineages”, *Nature Biotechnology* 22, 1115-1124, Sept 2004

\*Oh S-H *et al.*, “Adult bone marrow-derived cells transdifferentiating into insulin-producing cells for the treatment of type I diabetes,” *Laboratory Investigation* 84, 607-617, 1 May 2004

\***Kodama S *et al.***, “Islet regeneration during the reversal of autoimmune diabetes in NOD mice”, *Science* 302, 1223-1227; 14 Nov **2003**

\*Hess D *et al.*, “Bone marrow-derived stem cells initiate pancreatic regeneration”, *Nature Biotechnology* 21, 763-770; July 2003

\*Ianus A *et al.*; *In vivo* derivation of glucose competent pancreatic endocrine cells from bone marrow without evidence of cell fusion; *Journal of Clinical Investigation* 111, 843-850; March 2003

\***S. Ryu *et al.***; “Reversal of established autoimmune diabetes by restoration of endogenous  $\beta$  cell function,” *J. Clin. Invest.* 108, 63-72; July **2001**

# Adult stem cells effective in tissue repair

## Heart Damage—Bone marrow, muscle, and heart stem cells repair heart.

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## **Heart Repair—Bone marrow, muscle, and heart stem cells repair heart.**

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# **Adult stem cells effective in tissue repair**

**Parkinson's Disease—Neural stem cells can form all neuronal types, migrate throughout brain to repair damage, and prevent loss of neurons associated with Parkinson's disease.**

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**Using the patient's own adult neural stem cells, a group at Los Angeles Cedars-Sinai Medical Center report a reversal of symptoms in the first Parkinson's patient treated.**

Lévesque M and Neuman T, “Autologous transplantation of adult human neural stem cells and differentiated dopaminergic neurons for Parkinson disease: 1-year postoperative clinical and functional metabolic result”, American Association of Neurological Surgeons annual meeting, Abstract #702; 8 April 2002

**Injecting growth signals into the brain stimulates the patients' own adult neural stem cells, provided a 61% improvement.**

\*Gill SS *et al.*; “Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease”; *Nature Medicine* 9, 589-595; May 2003 (published online 31 March 2003)

# Current Clinical Trials of Adult Stem Cells

- **Cancers**—Lymphomas, multiple myeloma, leukemias, breast cancer, neuroblastoma, renal cell carcinoma, ovarian cancer
- **Autoimmune diseases**—multiple sclerosis, systemic lupus, rheumatoid arthritis, scleroderma, scleromyxedema, Crohn's disease
- **Anemias** (incl. sickle cell anemia)
- **Immunodeficiencies**—including human gene therapy
- **Bone/cartilage deformities**—children with osteogenesis imperfecta
- **Corneal scarring**—generation of new corneas to restore sight
- **Stroke**—neural cell implants in clinical trials
- **Repairing cardiac tissue after heart attack**—bone marrow or muscle stem cells from patient
- **Parkinson's**—retinal stem cells, patient's own neural stem cells, injected growth factors
- **Growth of new blood vessels**—*e.g.*, preventing gangrene
- **Gastrointestinal epithelia**—regenerate damaged ulcerous tissue
- **Skin**—grafts grown from hair follicle stem cells, after plucking a few hairs from patient
- **Wound healing**—bone marrow stem cells stimulated skin healing
- **Spinal cord injury**—clinical trials currently in Portugal, Italy, S. Korea
- **Liver failure**—clinical trials in U.K.

# Diseases Treated in Human Patients

STEM CELL RESEARCH TREATMENTS

EMBRYONIC

0

ADULT

65

# **Regeneration Mechanism?**

(evidence for all of these)

Dedifferentiation-Redifferentiation

Cell fusion with already-differentiated cell

Transdifferentiation

Stimulate Differentiation of Tissue Cells

“[Robert] Lanza noted ‘there is ample scientific evidence that adult stem cells can be used to repair damaged heart or brain tissue... if it works, it works, regardless of the mechanism,’ he said.”

Steve Mitchell, UPI; 12 October 2003



# Adult Stem Cells



**Most promising source for treatments**

**Able to generate virtually all adult tissues**

**Can multiply almost indefinitely, providing numbers sufficient for clinical treatments**

**Proven success in laboratory culture**

**Proven success in animal models of disease**

**Proven success in current clinical treatments**

**Ability to “home in” on damage**

**Avoid problems with tumor formation**

**Avoid problems with transplant rejection**

**Avoid ethical quandary**

[www.stemcellresearch.org](http://www.stemcellresearch.org)