Nobel Prize 2012 for stem cell research- what the obstetricians/ gynecologists shoul know

universitätbonn

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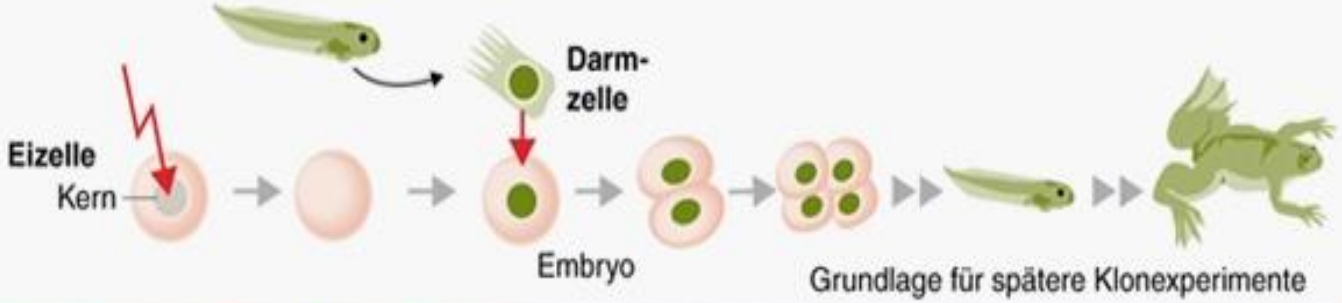
Rückprogrammierung erwachsener Körperzellen

Die Nobelpreisträger für Medizin 2012 erhalten die Auszeichnung für ihre Experimente zur Rückprogrammierung erwachsener Körperzellen in den embryonalen Zustand. Sie trugen damit maßgeblich zum Verständnis von Zellentwicklung und Krankheiten bei.

1962: Grundlagenforschung

John B. Gurdon beweist, dass sich die Spezialisierung von Zellen wieder umkehren lässt.

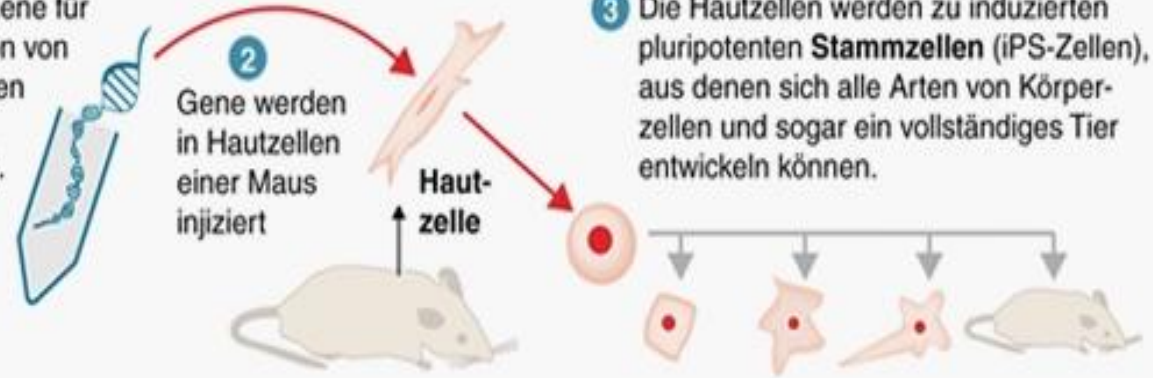
1. Zellkern einer Frosch-Eizelle wird durch den Kern einer Kaulquappen-Darmzelle ersetzt.
2. Aus der so veränderten Eizelle entwickelt sich eine normale Kaulquappe.



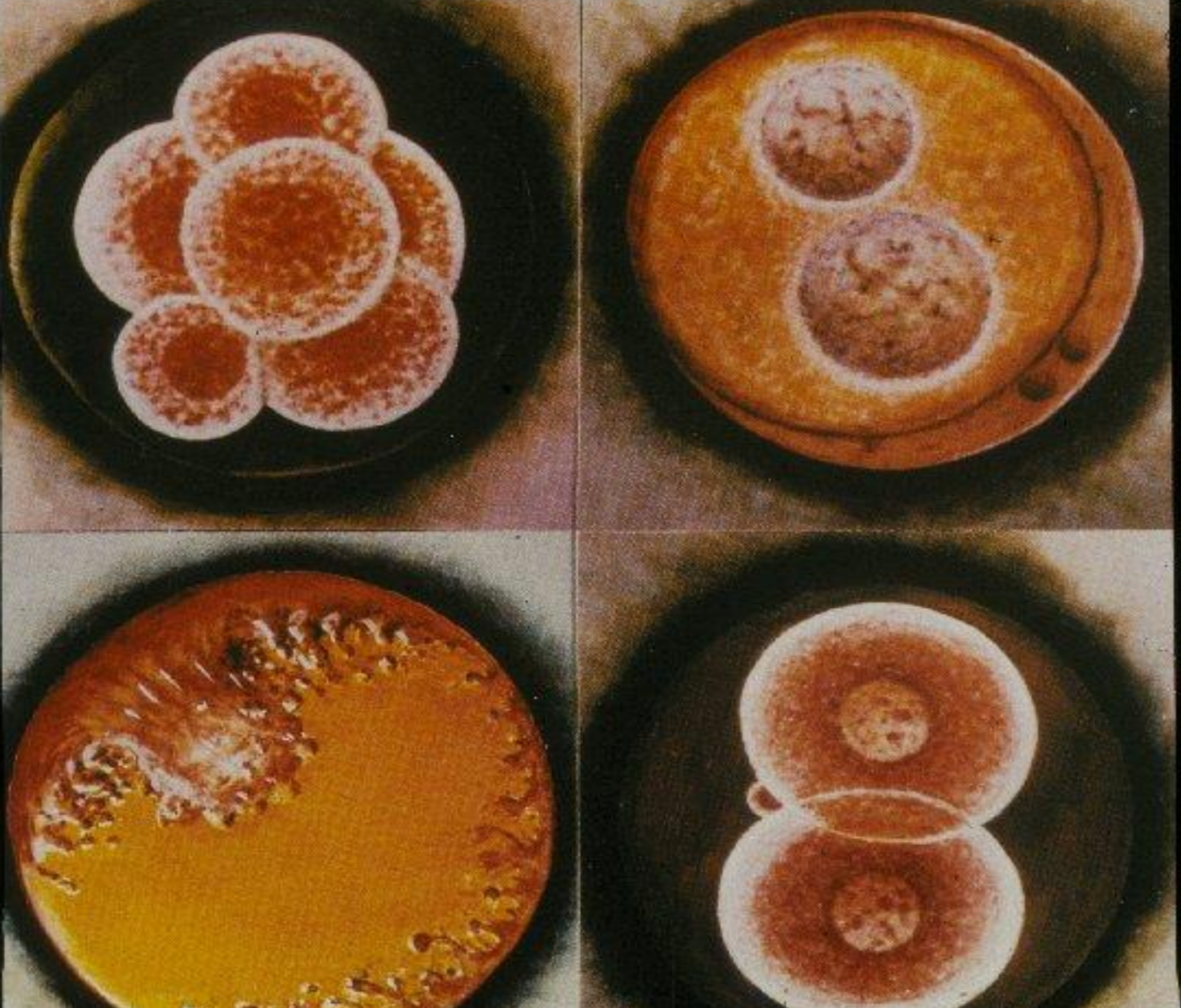
2006: Gewinnung von Stammzellen

Shinya Yamanaka verwandelt Körperzellen einer Maus zurück in Stammzellen.

1. Wichtige Gene für die Funktion von Stammzellen werden identifiziert.
2. Gene werden in Hautzellen einer Maus injiziert
3. Die Hautzellen werden zu induzierten pluripotenten **Stammzellen** (iPS-Zellen), aus denen sich alle Arten von Körperzellen und sogar ein vollständiges Tier entwickeln können.



Quelle: Nobel-Komitee



Stammzelle

1. Totipotente

2. Embryonale
   -Pluripotent

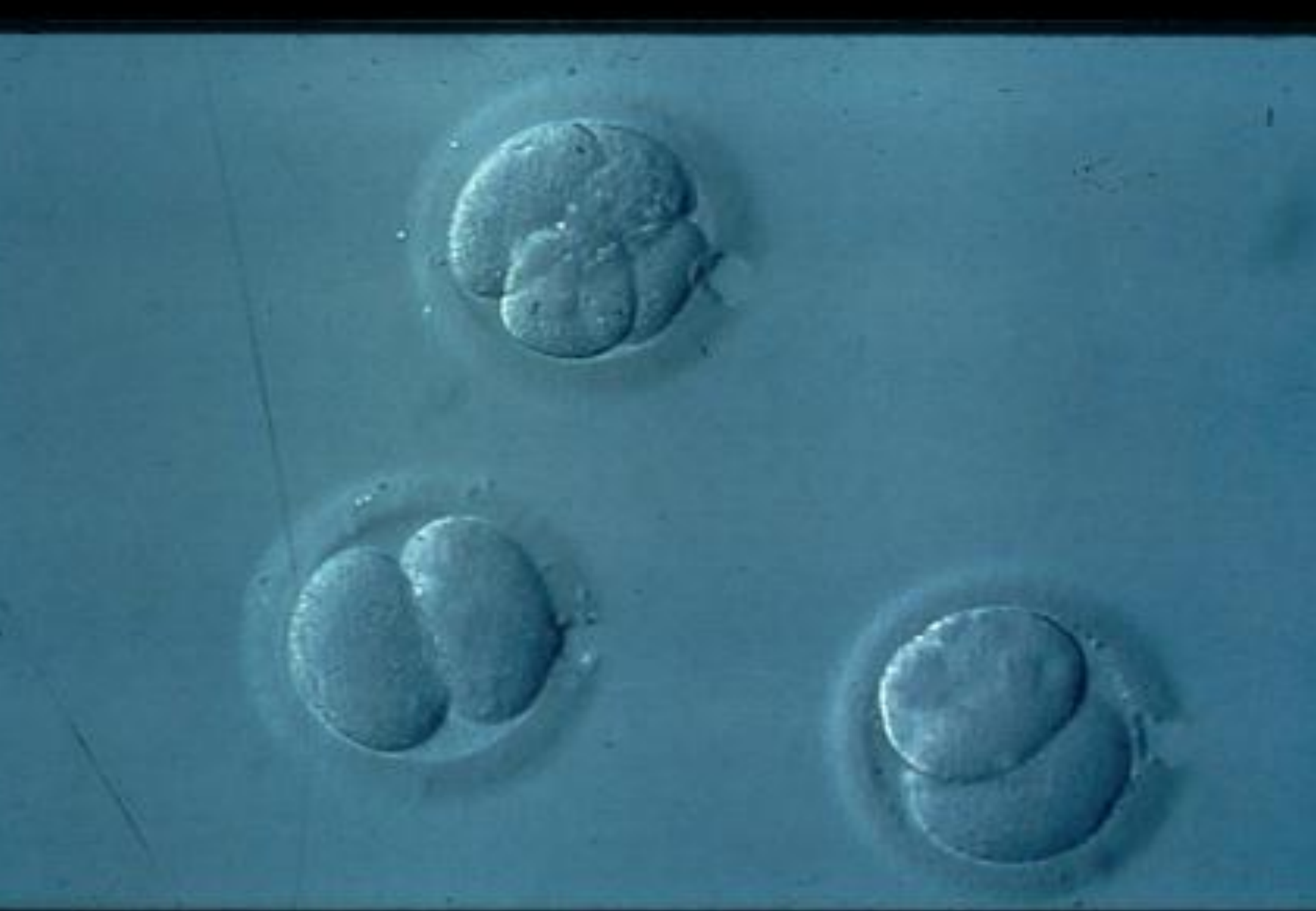
3. Hämato-
   poietische

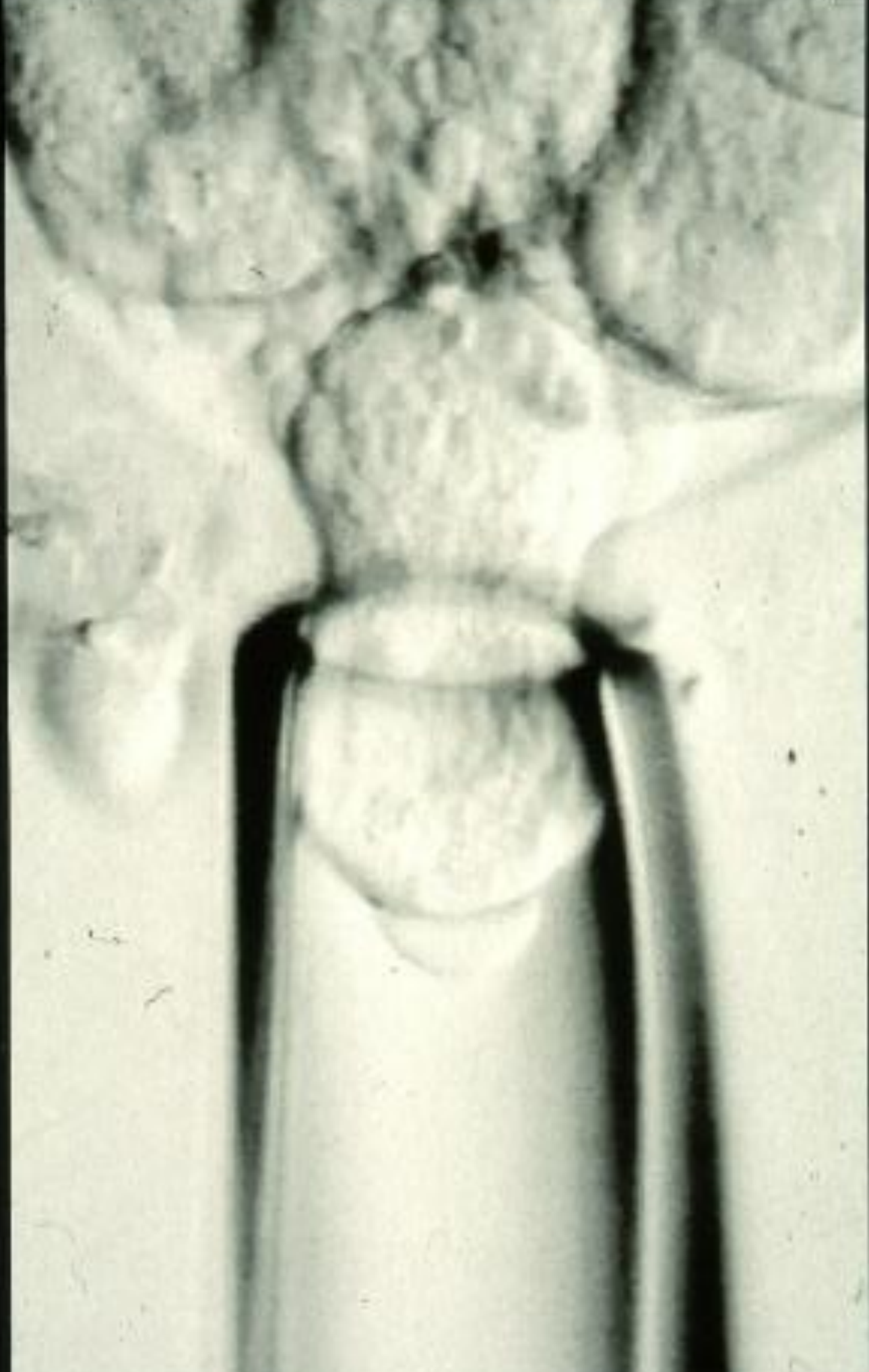
   (etabliert i
   der onkol.
   Behandlun

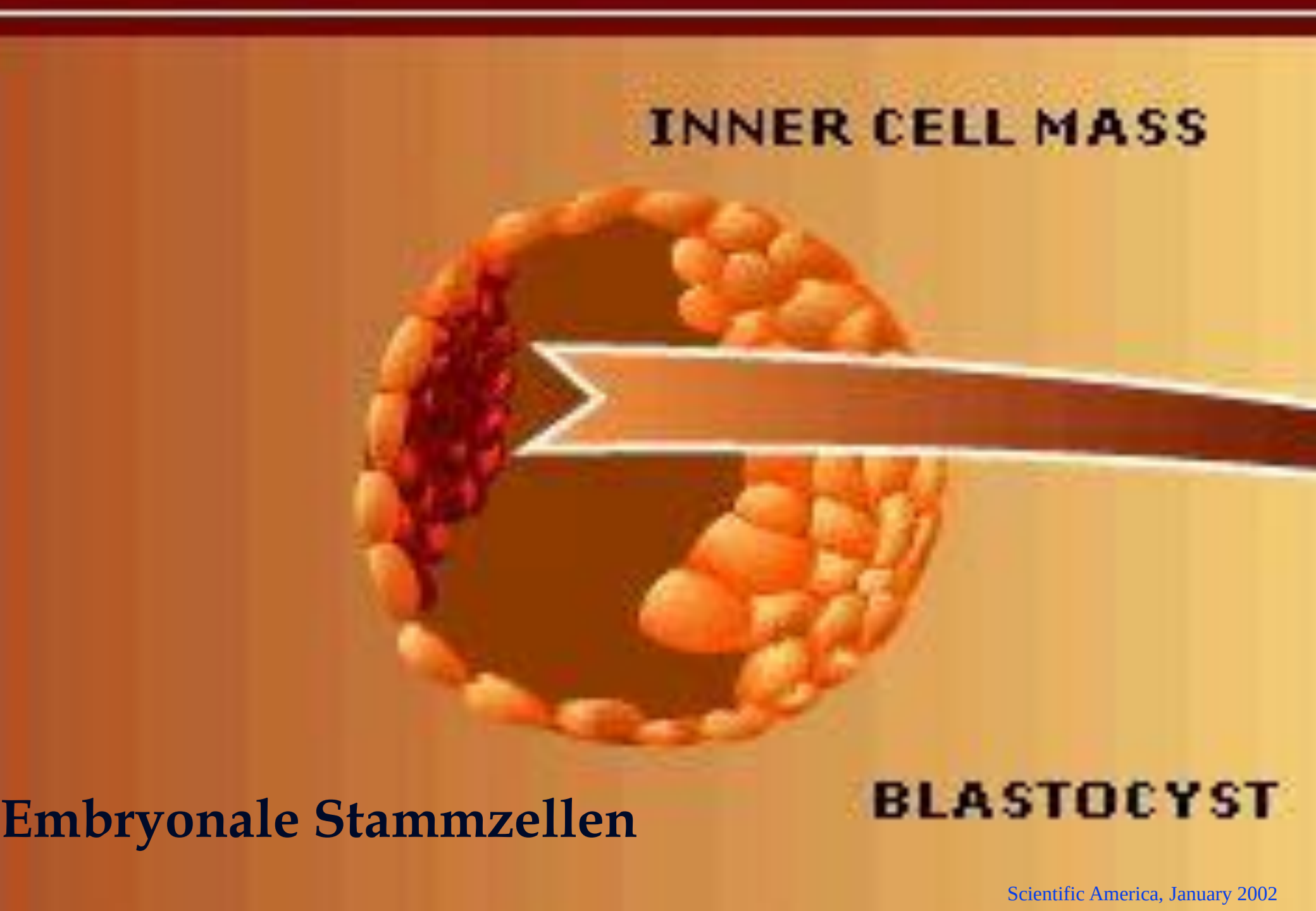
Autolog vs.
Allogen

4. In utero
   Therapie

5. IPS Zellen

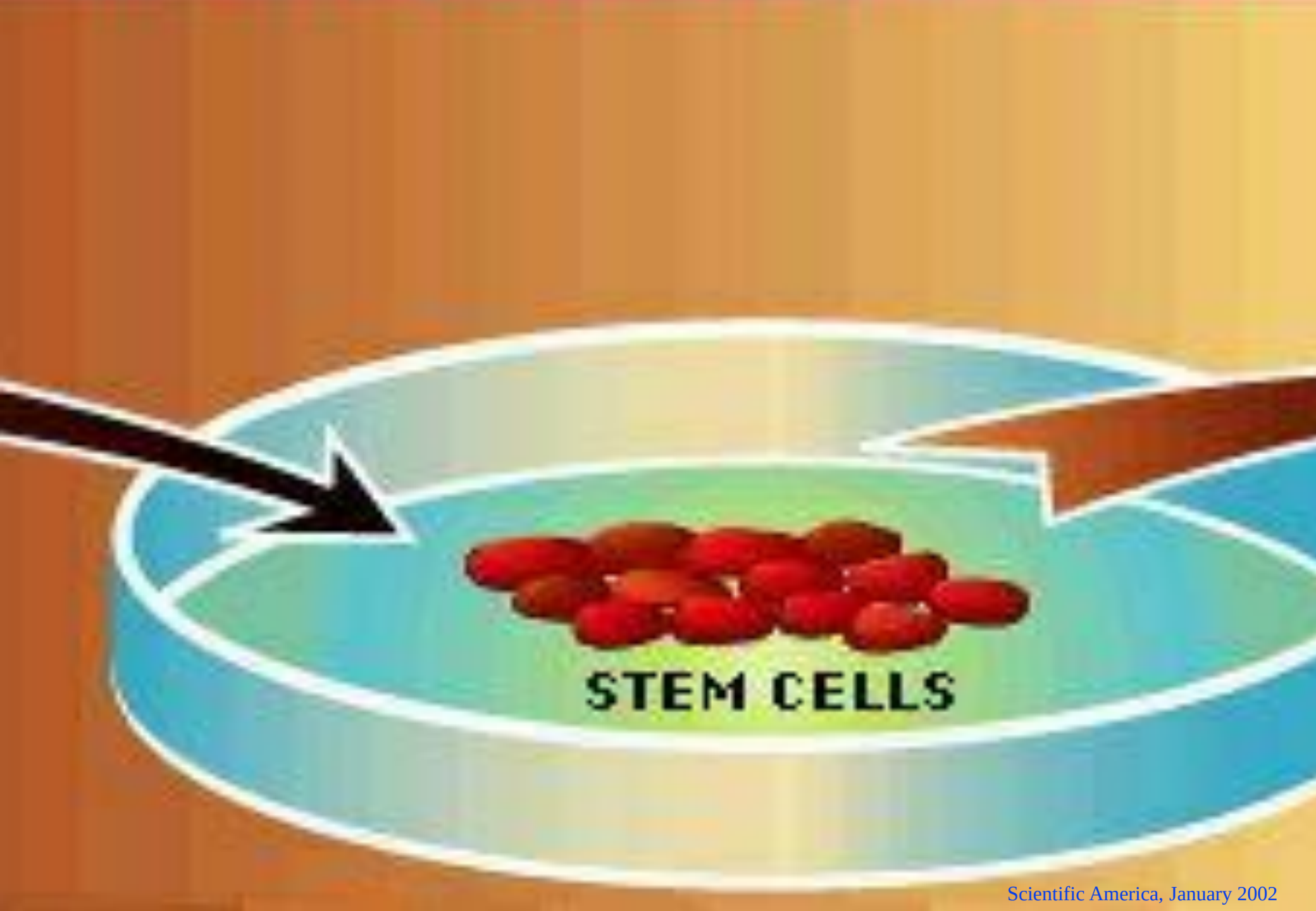




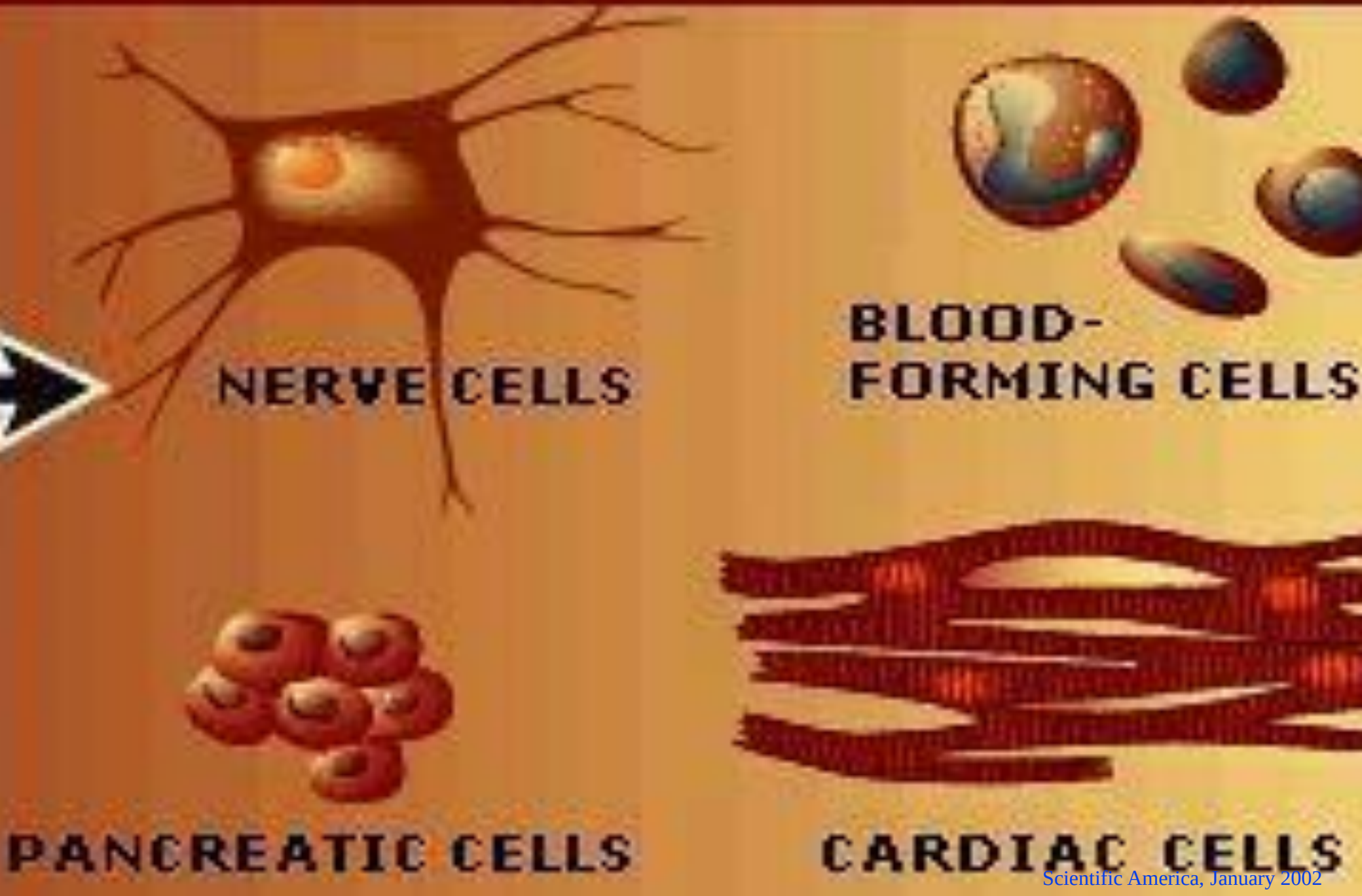


Embryonale Stammzellen

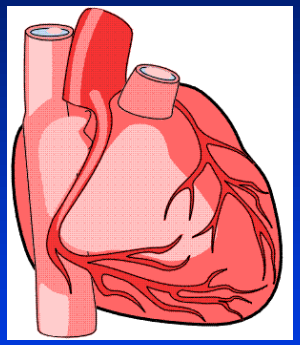
Scientific America, January 2002



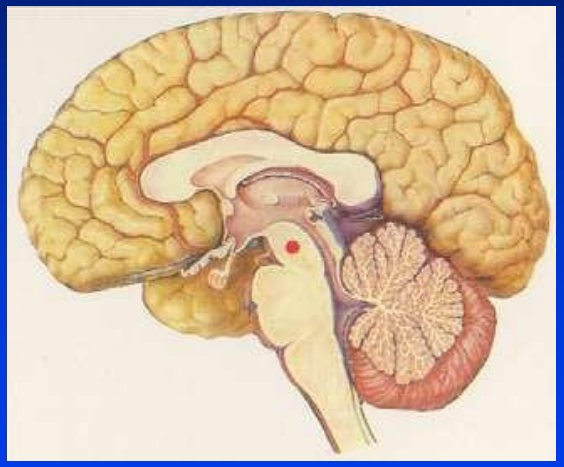
Scientific America, January 2002



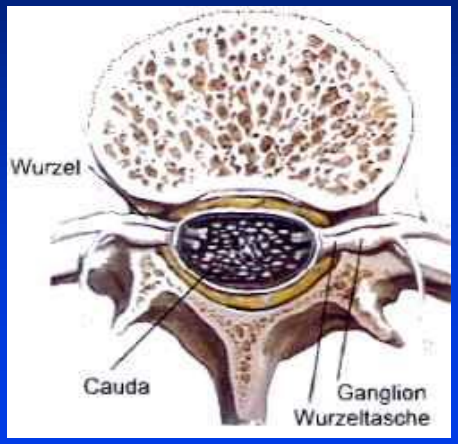
Degenerative, congenitale Erkrankungen etc.



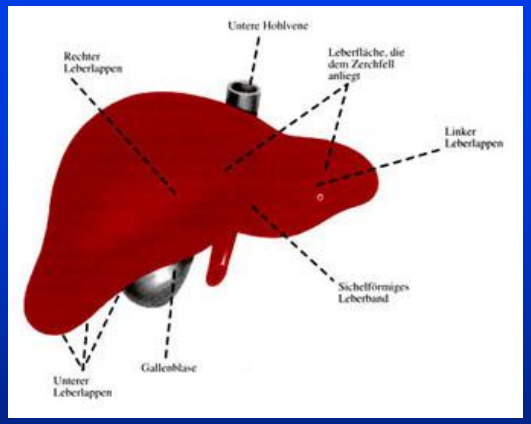
Herzinfarkt



Parkinson



Paraplegie



Leberzirrhose

Diabetes

Osteogenesis imperfecta

MENSCHENWÜRDE

Stürmische Dankbarkeit

Mit seinem Patent-Urteil hat der Europäische Gerichtshof die entscheidende Frage nicht beantwortet: Fängt die Würde des Menschen in der Petrischale an?

Für die Fundamentalisten christlichen Lebensschutzes ist Europa seit Dienstag vergangener Woche sittlich geeint. Da verkündete der Europäische Gerichtshof in Luxemburg sein Urteil über das Patent des deutschen Forschers Oliver Brüstle, der embryonale Stammzellen im Labor nutzen will, um neue medizinische Hilfsmittel gegen Krankheiten wie Parkinson und Alzheimer zu entwickeln.

Das Verbot solcher Patente begründeten die EU-Richter mit einem Verweis auf die Menschenwürde. Damit lösten sie stürmische Dankbarkeit bei den Politikern und Publizisten aus, die schon stets das Grundgesetz mobilisierten, um befruchtete Eizellen in der Petrischale vor dem Zugriff der Medizin zu schützen.

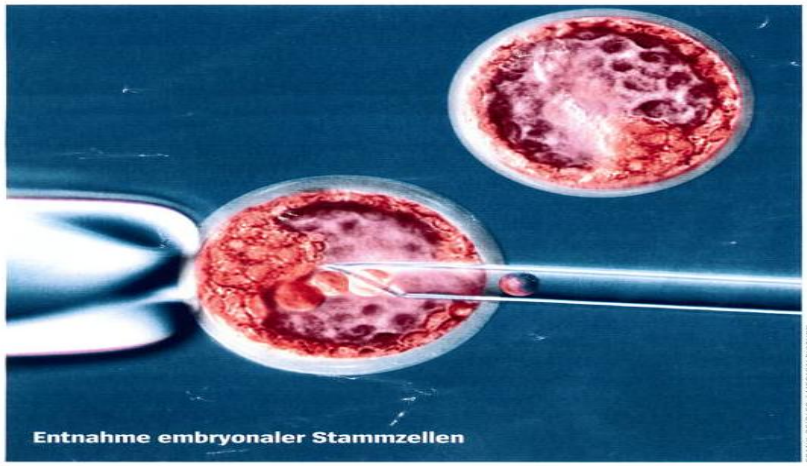
Das letzte Wort im Patent-Streit, so heißt es in der „Frankfurter Allgemeinen“, sei ein „Markstein“, eine „Wegweisung“. Ab sofort gelte die „Würde des Menschen“ für jeden Zellklumpen „vom Moment der Befruchtung an“, in jeder Petrischale Europas.

Das wäre tatsächlich etwas fundamental Neues. Ob es Menschenwürde in der Petrischale gibt, ob tatsächlich jede im Labor befruchtete Eizelle den Schutz der unbeschränkten und uneinschränkbaren Menschenwürdegarantie des deutschen Grundgesetzes und der Europäischen Grundrechte-Charta genießen soll, ist eine so schwierige Gewissensfrage, dass sich selbst das Bundesverfassungsgericht bisher nicht an ihre Beantwortung gewagt hat.

Und die Abgeordneten des Deutschen Bundestags zerstritten sich erst in diesem Jahr monatelang über ein Gesetz zur Frage, ob an solchen künstlich befruchteten Zellhaufen vor der Einpflanzung in den Mutterleib Untersuchungen angestellt werden dürften, um werdendes Leben mit beschädigtem Erbgut gar nicht erst werden zu lassen. In einem Kompromissgesetz mieden sie eine klare Antwort auf die Frage: Gibt es Menschenwürde in der Petrischale?

Die Frage bleibt offen. Das Urteil hat nichts Neues gebracht – ja, weniger als nichts.

Wiederholt haben die Richter bei Urteilen über Biopatente die Frage offengelassen, ob und, wenn ja, ab wann früheste Formen menschlichen Lebens den Schutz der Grundrechte genießen. Und so war es auch dieses Mal.



Entnahme embryonaler Stammzellen

FRANK GEISLER / MEDICALPICTURE

MARTIN ATHENSTÄDT / DPA

Stammzellenforscher Brüstle: *Wegweisung aus Luxemburg?*

Das Gericht hatte im Brüstle-Streit über die Rechtsfrage zu befinden, ob befruchtete Eizellen in vitro als „Embryo“ im Sinne der europäischen Patent-Richtlinie zu betrachten sind. Wenn ja, dann sind Patente nach Brüstle-Art auch nach europäischer Lesart in Deutschland und anderswo verboten.

Bei der Auslegung von Rechtsvorschriften schaut jeder Jurist nach, was sich die Autoren dabei gedacht haben. So taten es auch die Luxemburger. Die Autoren, berichten die Richter, hätten „jede Möglichkeit der Patentierung ausschließen“ wollen, „sobald die der Menschenwürde geschuldete Achtung dadurch beeinträchtigt werden könnte“.

Die Information darüber, was sich der europäische Gesetzgeber wohl beim Verbot der „Verwendung von menschlichen Embryonen zu industriellen oder kommerziellen Zwecken“ gedacht haben könnte, hat nichts damit zu tun, was sich die Richter denken – und schon gar nichts damit, wie sie über den Schutz der Menschenwürde urteilen.

Die Definition des menschlichen Embryos, so hob das Gericht ausdrücklich hervor, „sei ein Thema, das in vielen Mitgliedstaaten gesellschaftspolitisch sehr sensibel und von deren unterschiedlichen Traditionen und Werthaltungen geprägt ist“. Das Gericht sei „nicht dazu aufgerufen, auf Fragen medizinischer oder ethischer Natur einzugehen“. Nichts haben die Juristen zum ethischen oder verfassungsrechtlichen Schutz des Lebens gesagt.

Weniger als nichts: Die Richter haben sich vor einem dringend gebotenen klärenden Wort zum Menschenwürdeschutz in der Europäischen Union gedrückt. Sie tun so, als ständen nicht auch sie unter dem Recht der Europäischen Grundrechte-Charta, die nahezu gleichlautend mit dem Grundgesetz die Menschenwürde schützt und das Thema der Bioethik in mehreren Spezialvorschriften für jeden Richter, ja für die ganze Europäische Union, verbindlich macht. Kein Wort davon im Urteil. Menschenwürde scheint man in Luxemburg nur vom Hörensagen zu kennen.

„Entseelt“ und „handwerklich äußerst dürftig“ nennt der Göttinger Europarechtsexperte Frank Schorkopf diese Art von richterlicher Zurückhaltung: „Mit dieser Entscheidung hat der Gerichtshof gezeigt, dass er Grundrechtsschutz nicht kann.“

„Unteilbar und universell“, so verspricht feierlich die Europäische Grundrechte-Charta, sollen „das sittliche Erbe“ Europas und mit ihm die „Menschenwürde“ über die Grenzen aller Staaten hinweg verwirklicht werden.

Diesmal ist es misslungen. Man weiß gar nicht, ob man so unglücklich darüber sein muss.

THOMAS DARNSTÄDT, DIETMAR HIPP

Daily Mail, 17.11.2010

Stroke victim given stem cell injection to repair his brain

By **Fiona MacRae**
Science Reporter

A BRITON has had millions of stem cells injected into his brain in a pioneering attempt to repair the damage caused by a stroke.

Another 11 patients will be treated with cells from an aborted baby from next month, as part of the world's first neural stem cell trial for the debilitating condition.

The revolutionary treatment could be in widespread use in as little as three years.

Incredibly, one 12-week-old foetus could generate enough cells to treat hundreds of thousands, if not millions, of patients.

But pro-life campaigners insist it is wrong to use an unborn child's life as a factory for spare medical parts.

More than a quarter of a million Britons live with a severe disability caused by stroke but there has been no way of healing the damage caused to the brain.

'Unethical trade-off'

Doctors at Glasgow's Southern General Hospital and scientists at Surrey-based biotech firm ReNeuron believe the answer may lie in stem cells. These are 'blank' cells capable of acting as a repair kit for the body by replacing worn-out tissue.

It is thought that a single jab could mend much of the damage caused by strokes, improving speech and walking and easing memory problems.

Last weekend, a truck driver in his 60s was given an injection of stem cells to the brain, as part of a preliminary trial to assess the safety of the procedure.

The man, who suffered a stroke 18 months ago, has been discharged and doctors say he is doing well. He is part of the first commercial stem cell trial to be held in the UK, in which four groups of three men aged 60-plus will receive progressively higher doses of the cells.

Doctors will monitor them for two years to see if the stem cells have started to repair their brains and if their condition has improved.

If the treatment is deemed safe and shows promise, larger-scale trials will follow. In tests on rats, the stem cells restored movement in animals left disabled by strokes.

Dr Keith Muir, the Glasgow University expert leading the trial, said: 'We are pleased that the first patient in the trial has undergone surgery successfully.'

Some 150,000 Britons suffer a stroke, or interruption in the blood supply to the brain each year.

Josephine Quintavalle, of Comment on Reproductive Ethics, said: 'This is a profoundly unethical trade-off. We share the dream of seeking cures for strokes and all the other conditions which beset modern man, but the realisation of that dream cannot depend on the taking of life of other human beings, no matter how early in development those tiny lives may be.'

ReNeuron says it would be unethical not to treat those who are suffering. They add that it might be possible in the future to sidestep the ethical concerns by creating stem cells suitable for injection from a sliver of the patient's skin.

HOW TUMMY FAT CAN TREAT A HEART ATTACK

STEM cells taken from waistline fat could be used as a treatment for heart attacks.

Scientists injected the cells into the hearts of coronary patients, resulting in reduced levels of damage, increased blood flow and improvement in pumping ability.

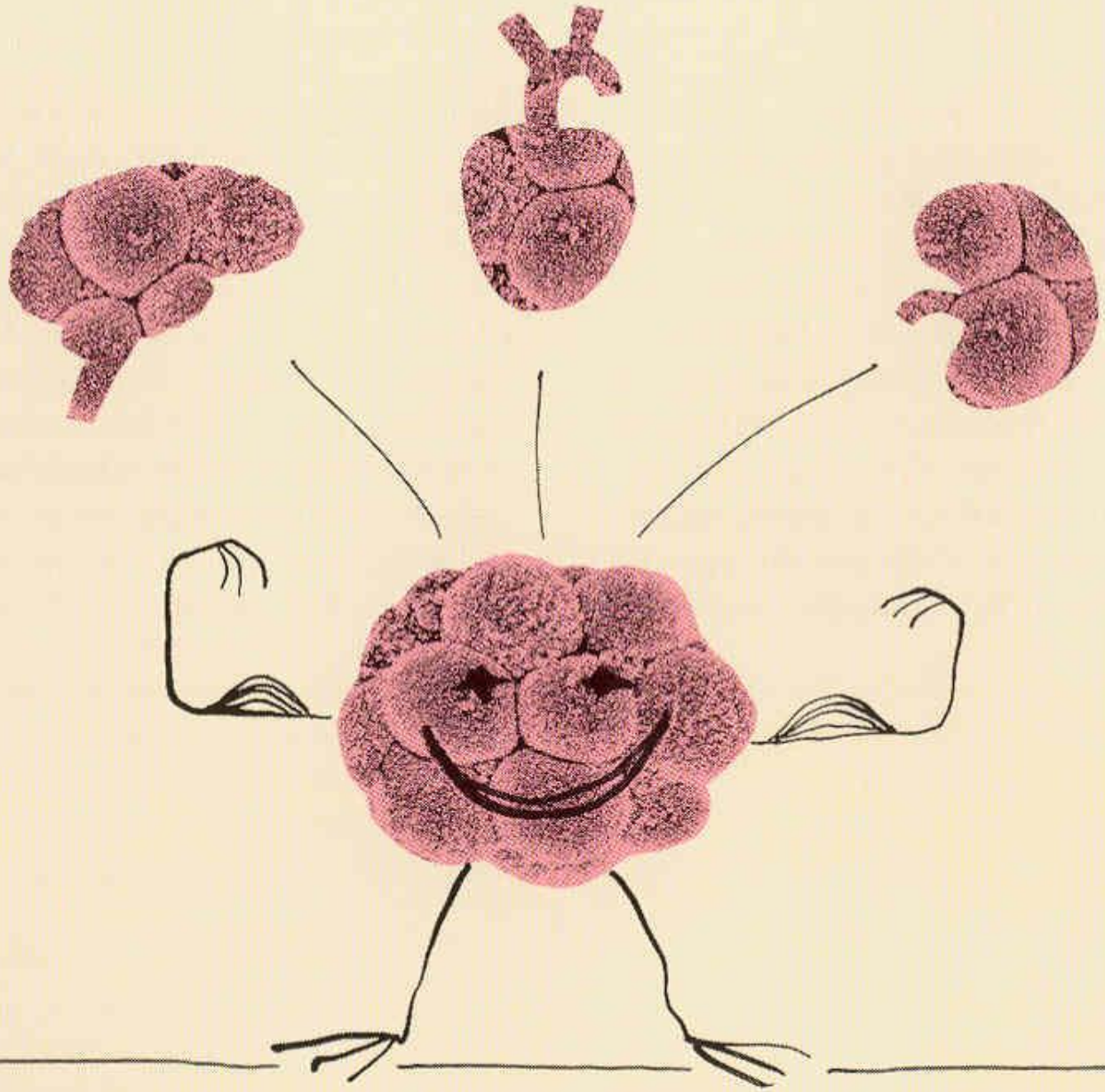
Eleven men and three women who had suffered recent heart attacks took part in the study. Ten were treated with stem cells while four received a dummy, or placebo, infusion.

Liposuction was used to remove up to 250 cubic centimetres of fat from their bellies. From each sample, researchers extracted 20million stem cells.

It took nine to ten minutes to infuse the stem cells into a patient's heart.

Six months later, the amount of damaged heart muscle in the treated patients was halved from 31.6 to 15.4 per cent.

In the untreated group, levels of heart damage remained the same.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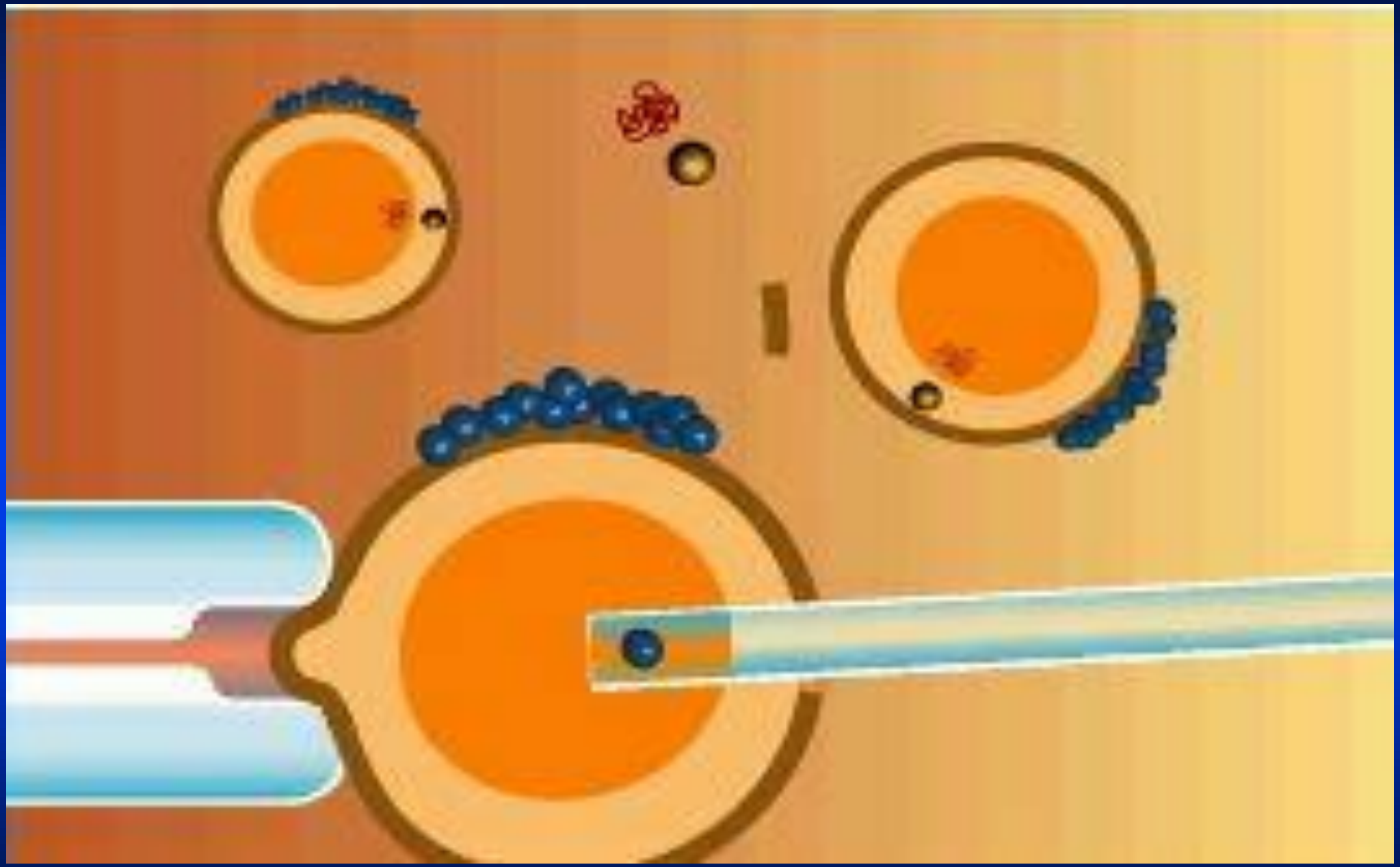


Scientific America, January 2002

1997

Dolly kloniert von

Euterzellen

Kapp et al

Foto [M]: Steph

sity ins Rampenlicht der Weltöffentlichkeit katapultiert haben.

Hwang traf in Berlin auch auf den deutschen Stammzellforscher Hans Schöler. Der Direktor am Münsteraner Max-Planck-Institut für molekulare Medizin ist mit Hwang gut bekannt und lächelte ein bisschen verlegen, als er vom Klonkönig als *»best friend from Germany«* angesprochen wurde. Ob diese Freundschaft Bestand hat, ist derzeit offen. Und das hat mit der unbequemen Frage zu tun, die Hwang sich nach seinem Vortrag von einer Journalistin gefallen lassen musste: Ob es wahr sei, dass Frauen aus seinem Team für sein Forschungsprojekt eigene Eizellen gespendet hätten?

machen müssen. Andererseits war er nach koreanischem Ehrenkodex gezwungen, seine Untergebenen unter allen Umständen zu schützen und ihre Privatsphäre zu wahren. Hwang entschied sich für das Zweite, erst für das Schweigen, dann für die Lüge – und brüskierte damit viele seiner westlichen Kollegen. Allerdings betonen auch sie unisono, dass Hwang nur formal die Verantwortung für den Missbrauch trage. Sie befürchten vor allem, der Skandal könnte die ohnehin umstrittene Klonforschung beschädigen und auch die Arbeit an embryonalen Stammzellen erschweren. Deren Kritiker nämlich würden nun auf den Koreaner zeigen und sagen: »Der hat unethische Dinge geduldet, er

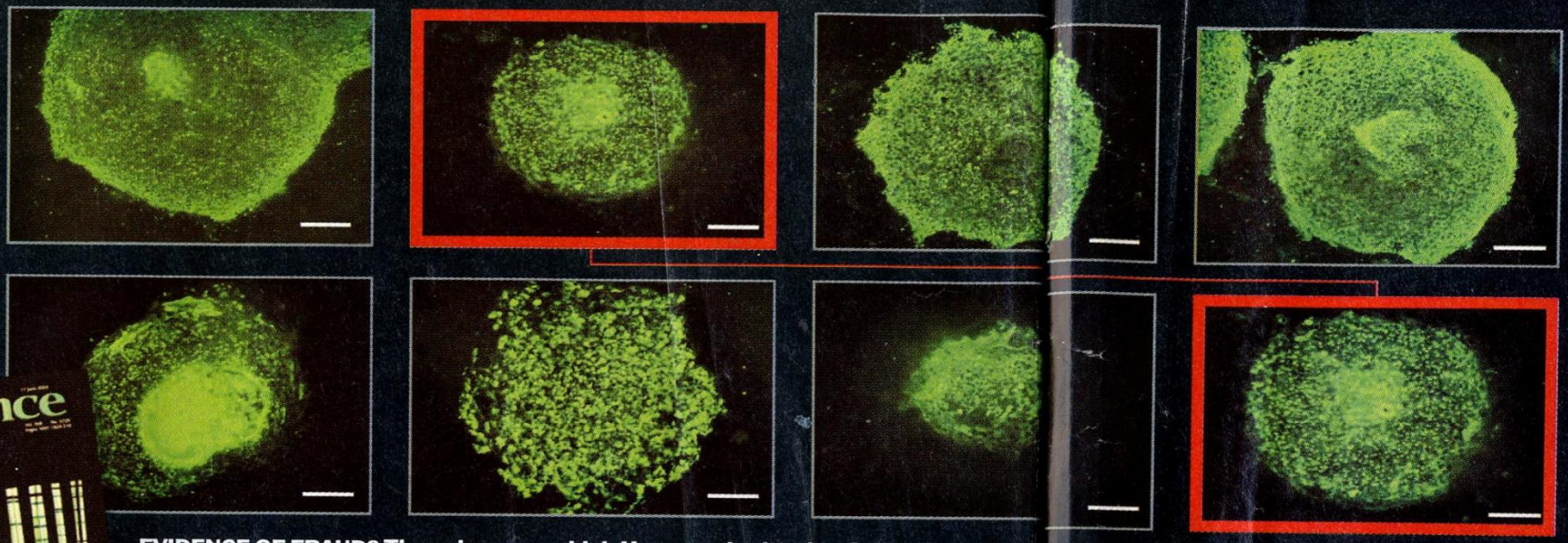
Der Mensch …

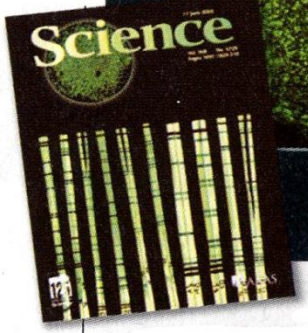
Hwang Woo-Suk ist Professor für Tiermedizin an der Seoul National University. Schon als Kind faszinierten ihn Tiere, vor allem Kühe. Der katholische Spross einer armen Familie konvertierte später zum Buddhismus. Heute arbeitet er täglich 16 Stunden, auch an Feiertagen. Hwang meditiert regelmäßig und lebt nach dem Motto: »Hebe dein Herz in den

In seiner Jugend war Hwang pra
Katholik, doch er litt darunter, wegen
ren Armut nie etwas zur Kollekte beitra
nen. Als er von seinem Priester deswege
gelt wurde, brach er mit dem Christe
Glücksfall, sagt man in Korea, denn sei
schung wäre kaum mit dem katholisch
zu vereinbaren gewesen. Heute ist H
zeugter Buddhist und meditiert täglic
ten. Nicht seine Begabung – in Biolog
tenfalls mittelmäßig gewesen sein – s
te, disziplinierte Arbeit seien der Sch
nem Erfolg, sagt Hwang.

Die Regierung dürfte es sich kaum

Would You Have Spotted the Duplicates?





EVIDENCE OF FRAUD? These images, which Hwang submitted to *Science*, were (in rows) of stem cells from four patients (in columns). But the images outlined in red are pictures of the same cells supposed to represent two distinct colonies

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JANUARY 26, 2006

Beyond Fraud — Stem-Cell Research Continues

Evan Y. Snyder, M.D., Ph.D., and Jeanne F. Loring, Ph.D.

The developments in the laboratory of Woo Suk Hwang of Seoul National University in South Korea are profoundly disappointing to all scientists — not solely stem-cell biologists, although we are the most immediately affected

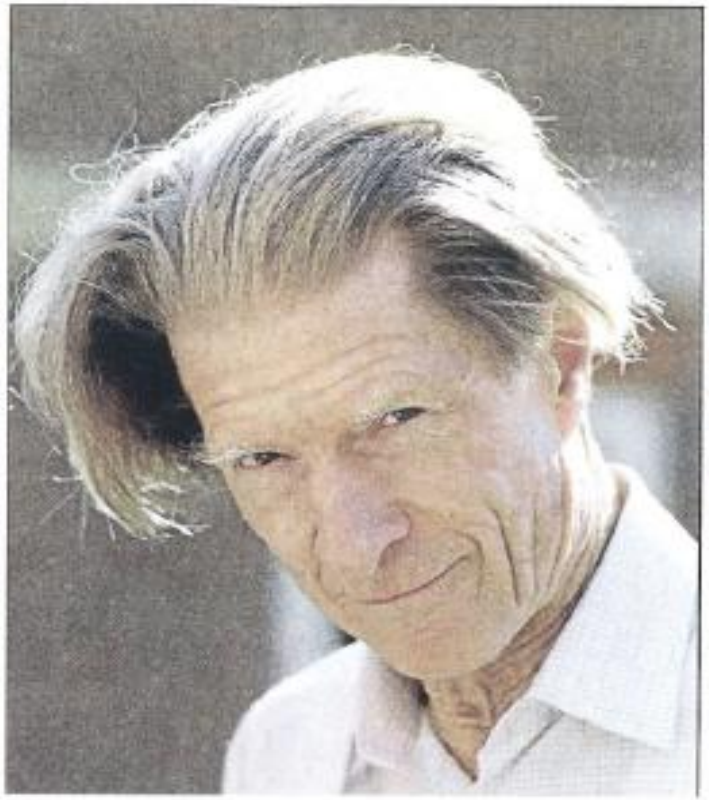
file identical to that of the donor

as the earlier research had used 242 oocytes to generate a single stem-cell line, by 2005 the research team had reportedly learned to perform the procedures with remarkable efficiency, generating 11 patient-specific stem-cell lines

Auf dem Weg zum Jungbrunnen

Medizin-Nobelpreis geht an zwei Forscher für die Entwicklung von ethisch unumstrittenen Stammzellen

OLM. Forscher haben ei-
ungbrunnen entwickelt:
-n eines Menschen wer-
ungen Nervenzellen um-
t. Aus Schwanzzellen ei-
s entsteht ein komplett
er. Dazu programmieren
haftler die Zellen zu-
eine Art Embryonalzu-
ück und lenken ihre Ent-
dann in die gewünschte
Grundlage dafür ist die
sechs Jahren veröffent-
chnik des diesjährigen
Nobelpreisträgers Shinya
a (50) von der japani-
iversität Kyoto. Er stützt
Erkenntnisse des Briten
don (79) von der Univer-
bridge, der die hohe Aus-
g ebenfalls erhält.
rjüngten Zellen sollen
verschlissenes Gewebe
oder als Versuchsobjekte
Forschung dienen. Eine
von Patienten ist aber
entfernt.
steckt vor mehr als ei-
en Jahrhundert das Erb-
ausgewachsenen Zelle in
ernte Frosch-Eizelle – mit
bnis, dass die entstande-
embryonale Eigenschaf-
962 beweist Gurdon auf
se, dass erwachsene Zel-
re Eigenschaften behal-
wenn sie etwa als Zellen



Ausgezeichnet: Die beiden Forscher Shinya Yamanaka aus Japan (links) und der Brite John Gurdon teilen sich in diesem Jahr den Nobelpreis für Medizin. FOTO: AP/DPA

in Haut oder Haaren ausgebildet sind, können sie zurück in eine Art Embryonalstadium gelangen. Zudem klonte Gurdon erstmals ein Tier: einen Frosch.

Die Klontechnik beim Menschen ist ethisch umstritten und in vielen Ländern – auch Deutschland – verboten. Im Jahr 2006 gelingt es Yamanaka zusammen mit dem Japaner Kazutoshi Takahashi, diese Technik zu umgehen. Nach vielen Versuchen findet er vier Kontrollgene namens Oct3/4, Sox2, c-Myc und Klf4, die er in Mäusezellen einschleust. Diese setzen eine Kaskade von Reaktionen in Gang, so dass die Zellen sich verjüngen. Das Ergebnis nennt er induzierte pluripotente Stammzellen (iPS-Zellen). Allerdings ist der Einsatz von Genen in das Erbgut immer mit einem Krebsrisiko verbunden, das Gen c-Myc galt sogar als krebsverdächt
Forschung entwickelt
Schritt für Schritt kön
scher auf ein Kontr
dem anderen verzich
iPS-Zellen herzustell
ruar 2009 präsentiert
raner Prof. Hans Sch
len von Mäusen, die e
fe eines Kontrollgens
stammzellen gewonn
de April 2009 nutzt
amerikanisches Fo
darunter Schöler, nu
trolleiweiße (Protein
Hautzellen von Mäu
zuprogrammieren.
nennt sein Produkt
(protein-induced plur
cells). Damit ist das
Krebsrisiko ausgesch
beim Einsatz von n
besteht.

Im September 20
chinesische Forscher
len einer Maus so
Nachkommen. 2011
Jürgen Hescheler (Köl
Ludwig Laugwitz (Mü
Zellen von Patienten
generkrankung zu gew

Doch die Forscher w
vor Euphorie. „Wiss
voller Überraschunge
manaka. „Die iPS-Zel
steckt weiterhin in
schuhen."

Generation of germline-competent induced pluripotent stem cells

Keisuke Okita[1], Tomoko Ichisaka[1,2] & Shinya Yamanaka[1,2]

We have previously shown that pluripotent stem cells can be induced from mouse fibroblasts by retroviral introduction of Oct3/4 (also called Pou5f1), Sox2, c-Myc and Klf4, and subsequent selection for *Fbx15* (also called *Fbxo15*) expression. These induced pluripotent stem (iPS) cells (hereafter called Fbx15 iPS cells) are similar to embryonic stem (ES) cells in morphology, proliferation and teratoma formation; however, they are different with regards to gene expression and DNA methylation patterns, and fail to produce adult chimaeras. Here we show that selection for *Nanog* expression results in germline-competent iPS cells with increased ES-cell-like gene expression and DNA methylation patterns compared with Fbx15 iPS cells. The four transgenes (*Oct3/4*, *Sox2*, *c-myc* and *Klf4*) were strongly silenced in Nanog iPS cells. We obtained adult chimaeras from seven Nanog iPS cell clones, with one clone being transmitted through the germ line to the next generation. Approximately 20% of the offspring developed tumours attributable to reactivation of the *c-myc* transgene. Thus, iPS cells competent for germline chimaeras can be obtained from fibroblasts, but retroviral introduction of c-Myc should be avoided for clinical application.

Although ES cells are promising donor sources in cell transplantation therapies[1], they face immune rejection after transplantation and there are ethical issues regarding the usage of human embryos. These concerns may be overcome if pluripotent stem cells can be directly derived from patients' somatic cells[2]. We have previously

for GFP, but became negative when differentiation was induced (not shown). By introducing these ES cells into blastocysts, we obtained chimaeric mice and then transgenic mice containing the Nanog-GFP-IRES-Puro^r reporter construct. In transgenic mouse blastocysts, GFP was specifically observed in the inner cell mass (Fig. 1b). In

Nature 2007

nature

Vol 448|19 July 2007|doi:10.1038/nature05944

ARTICLES

In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state

Marius Wernig[1]*, Alexander Meissner[1]*, Ruth Foreman[1,2]*, Tobias Brambrink[1]*, Manching Ku[3]*, Konrad Hochedlinger[1]†, Bradley E. Bernstein[3,4,5] & Rudolf Jaenisch[1,2]

Nuclear transplantation can reprogramme a somatic genome back into an embryonic epigenetic state, and the reprogrammed nucleus can create a cloned animal or produce pluripotent embryonic stem cells. One potential use of the nuclear cloning approach is the derivation of 'customized' embryonic stem (ES) cells for patient-specific cell treatment, but technical and ethical considerations impede the therapeutic application of this technology. Reprogramming of fibroblasts to a pluripotent state can be induced *in vitro* through ectopic expression of the four transcription factors Oct4 (also called Oct3/4 or Pou5f1), Sox2, c-Myc and Klf4. Here we show that DNA methylation, gene expression and chromatin state of such induced reprogrammed stem cells are similar to those of ES cells. Notably, the cells—derived from mouse fibroblasts—can form viable chimaeras, can contribute to the germ line and can generate live late-term embryos when injected into tetraploid blastocysts. Our results show that the biological potency and epigenetic state of *in-vitro*-reprogrammed induced pluripotent stem cells are indistinguishable from those of ES cells.

Epigenetic reprogramming of somatic cells into ES cells has attracted

contributed to the germ line. Our results establish that somatic cells

nature news

Published online 23 July 2009 | Nature | doi:10.1038/460560a

News

Mice made from induced stem cells

Technical feat shows that the different route to stem cells can indeed make a full mammal body.

David Cyranoski

Two teams of Chinese researchers have created live mice from induced pluripotent stem (iPS) cells, answering a lingering question about the developmental potential of the cells.

Since Shinya Yamanaka of Kyoto University in Japan created the first iPS cells[1] in 2006, researchers have wondered whether they could generate an entire mammalian body from iPS cells, as they have from true embryonic stem cells. Experiments reported online this week in *Nature*[2] and in *Cell Stem Cell*[3] suggest that, at least for mice, the answer is yes.

For the first study, animal cloners Qi Zhou of the Institute of Zoology in Beijing and Fanyi Zeng of Shanghai Jiao Tong University started by creating iPS cells the same way as Yamanaka, by

Generation of Retinal Pigment Epithelial Cells from Small Molecules and *OCT4* Reprogrammed Human Induced Pluripotent Stem Cells

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Key Words. Retina • Induced pluripotent stem cells • Differentiation • Small molecules • Stem cell transplantation • Aging

ABSTRACT

Autologous retinal pigment epithelium (RPE) grafts derived from induced pluripotent stem cells (iPSCs) may be used to cure blinding diseases in which RPE dysfunction results in photoreceptor degeneration. Four-, two-, and one-factor-derived iPSCs (4F-, 2F-, and 1F-iPSCs, respectively) were differentiated into fully functional cuboidal pigmented cells in polarized monolayers that express RPE-specific markers. 1F-iPSC-RPE (1F-iPS-RPE) strongly resembles primary human fetal RPE (hfRPE) based on proteomic and untargeted metabolomic analyses, and using novel in vivo imaging technology coupled with electroretinography, we demonstrated that 1F-iPS-RPE mediate anatomical and functional rescue of photoreceptors after transplantation in an animal model of RPE-mediated retinal degeneration. 1F-iPS-RPE cells were injected subretinally as a suspension and formed a monolayer dispersed between host RPE cells. Furthermore, 1F-iPS-RPE do not simply provide trophic support to rescue photoreceptors as previously speculated but actually phagocytose photoreceptor outer segments in vivo and maintain visual cycling. Thus, 1F-iPS-RPE grafts may be superior to conventional iPS-RPE for clinical use because 1F-iPS-RPE closely resemble hfRPE, mediate anatomical and functional photoreceptor rescue in vivo, and are generated using a reduced number of potentially oncogenic reprogramming factors. STEM CELLS TRANSLATIONAL MEDICINE *2012;1:96–109*

NATURE | ARTICLE

n

Reprogramming *in vivo* produces teratomas and iPS cells with totipotency features

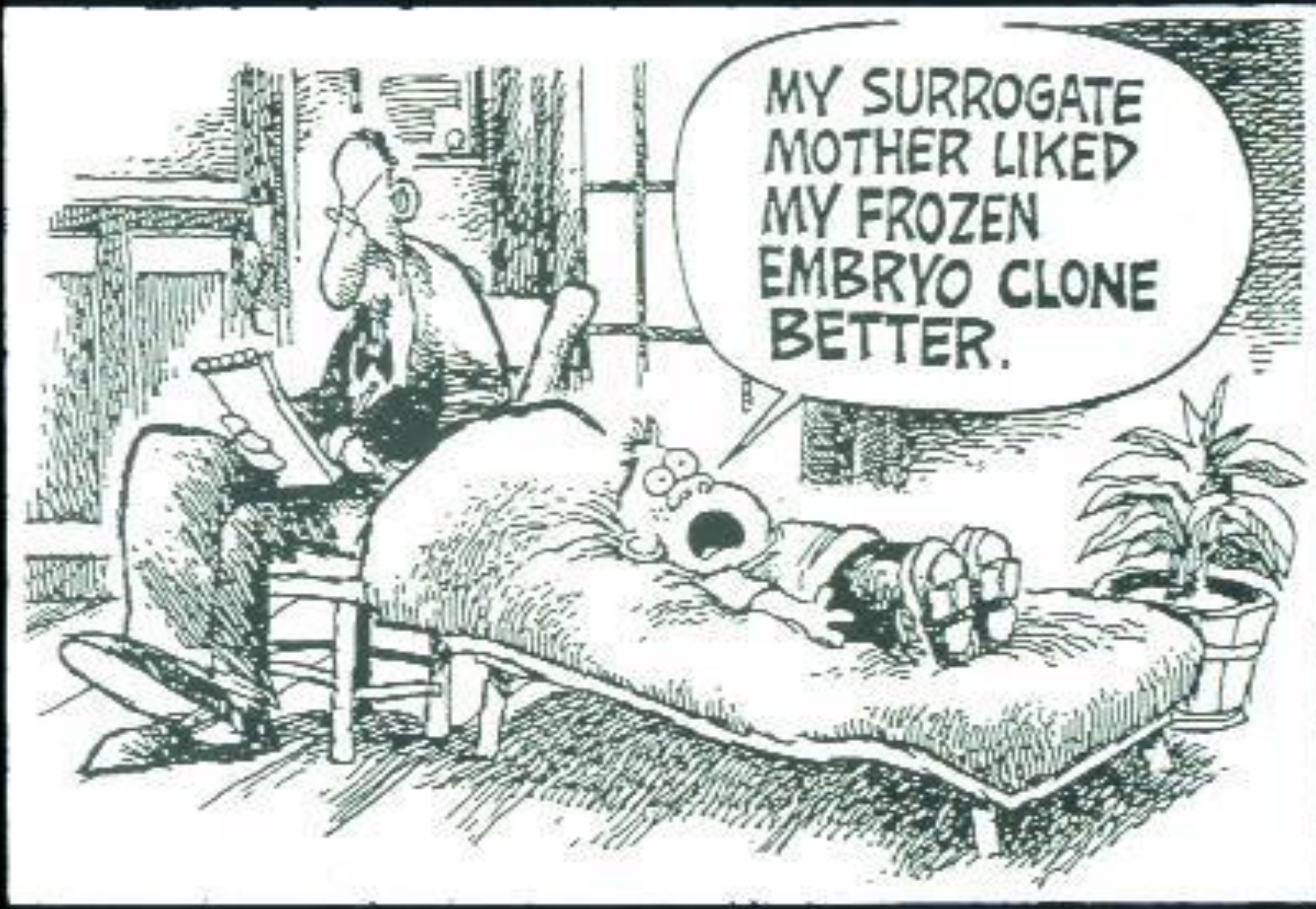
María Abad, Lluc Mosteiro, Cristina Pantoja, Marta Cañamero, Teresa Rayon, Inmaculada Ors, Osvaldo Graña, Diego Megías, Orlando Domínguez, Dolores Martínez, Miguel Manzanares, Sagrario Ortega & Manuel Serrano

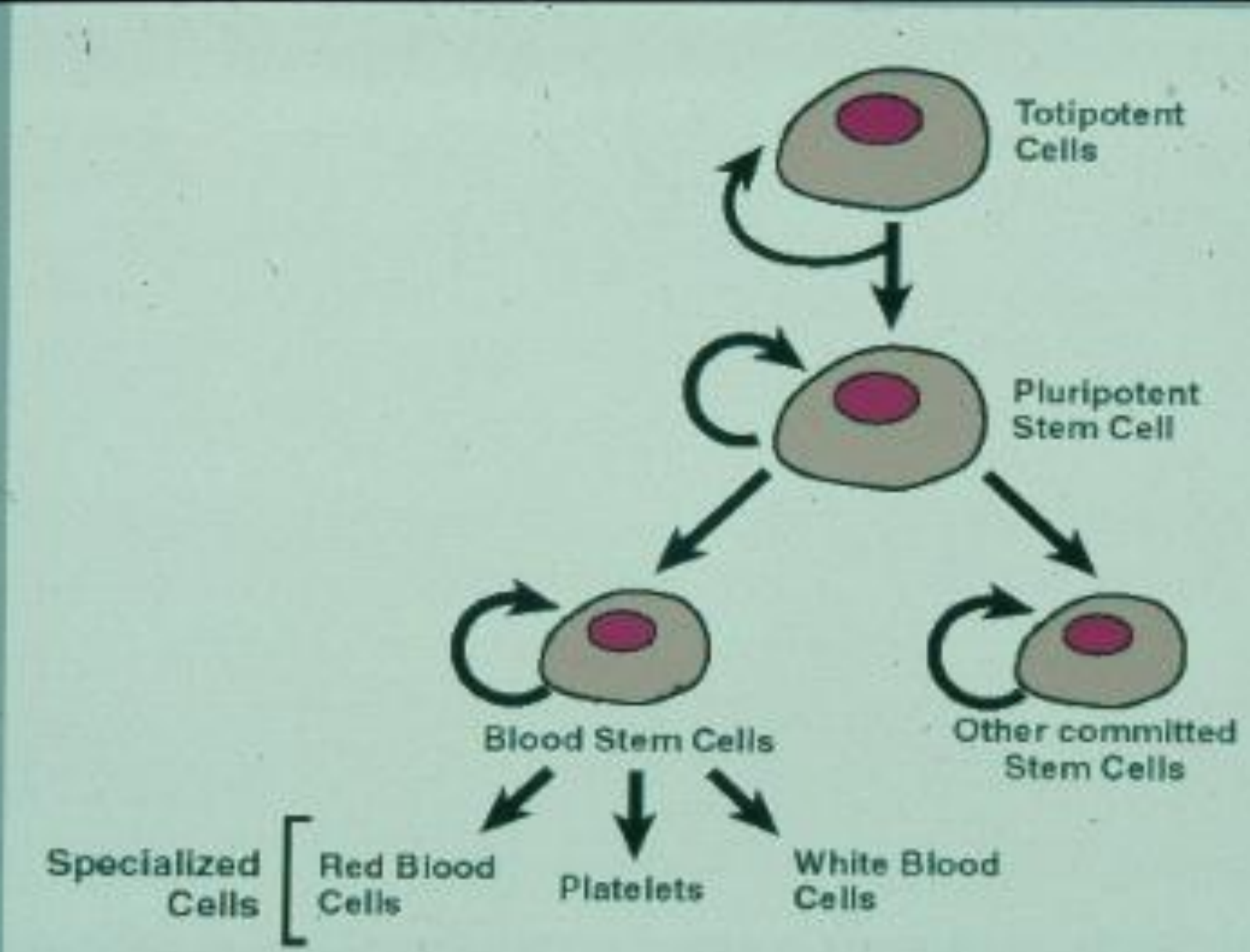
Nature (2013) doi:10.1038/nature12586

Received 04 March 2013 Accepted 23 August 2013 Published online 11 September 2013

Abstract

Reprogramming of adult cells to generate induced pluripotent stem cells (iPS cells) has opened new therapeutic opportunities; however, little is known about the possibility of *in vivo* reprogramming within tissues. Here we show that transitory induction of the four factors *Oct4, Sox2, Klf4* and *c-Myc* in mice results in teratomas emerging from multiple organs, implying that full reprogramming can occur *in vivo*. Analyses of the stomach, intestine, pancreas and kidney reveal groups of dedifferentiated cells that express the pluripotency marker NANOG, indicative of *in situ* reprogramming. By bone marrow transplantation, we demonstrate that haematopoietic cells can also be reprogrammed *in vivo*. Notably, reprogrammable mice present circulating iPS cells in the blood and, at the transcriptome level, these *in vivo* generated iPS cells are closer to embryonic stem cells (ES cells) than standard *in vitro* generated iPS cells. Moreover, *in vivo* iPS cells efficiently contribute to the trophectoderm lineage, suggesting that they achieve a more plastic or primitive state than ES cells. Finally, intraperitoneal injection of *in vivo* iPS cells generates embryo-like structures that express embryonic and extraembryonic markers. We conclude that reprogramming *in vivo* is feasible and confers totipotency features absent in standard iPS or ES cells. These discoveries could be relevant for future applications of reprogramming in regenerative medicine.

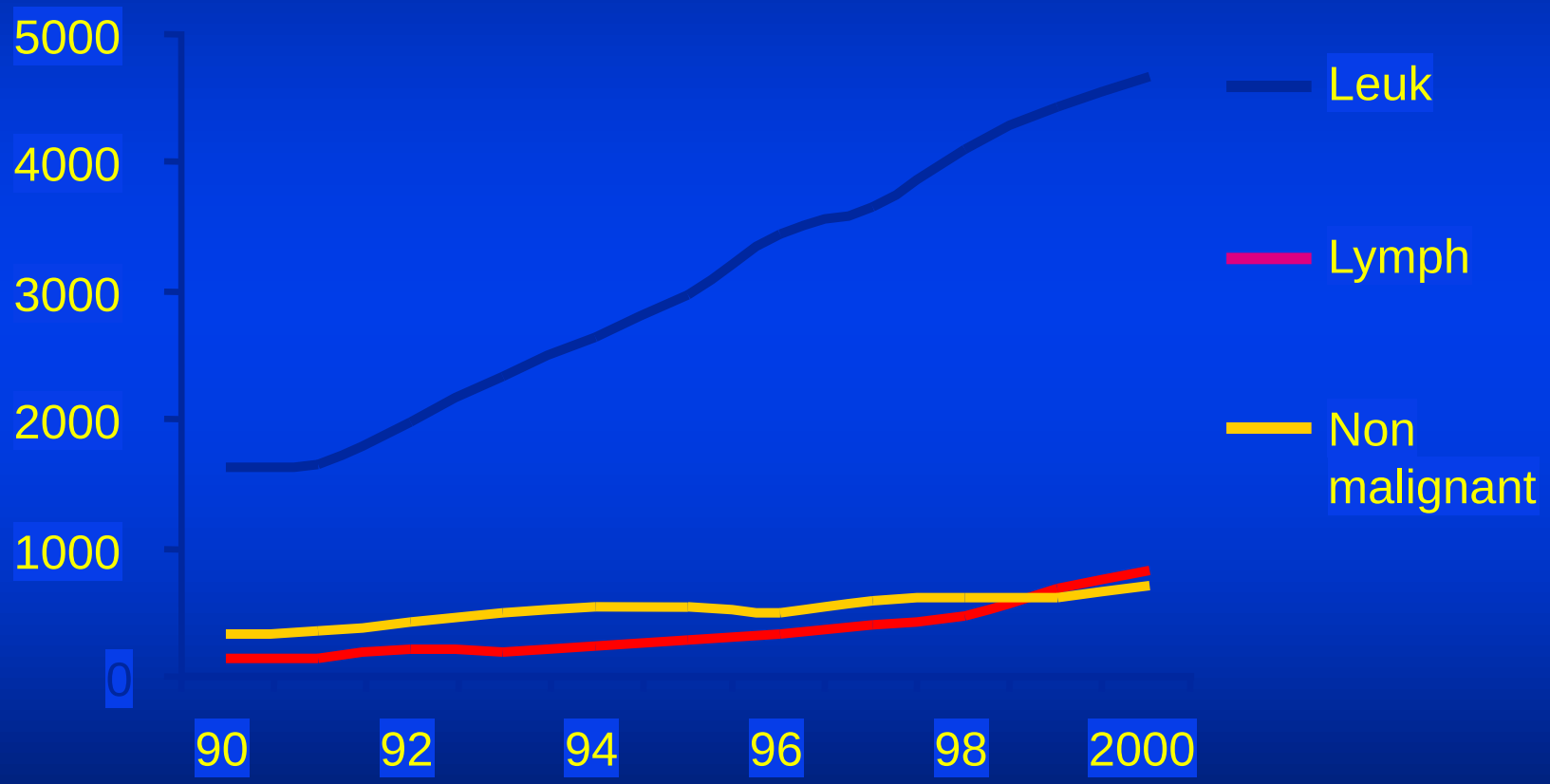

MY SURROGATE MOTHER LIKED MY FROZEN EMBRYO CLONE BETTER.


Totipotent Cells
Pluripotent Stem Cell
Blood Stem Cells
Other committed Stem Cells
Specialized Cells
Red Blood Cells
Platelets
White Blood Cells

1967 First Successful Bone Marrow Transplantation

E.D. Thomas: Nobel Prize for Physiology und Medicine, 1990

Allogenic stem cell transplantation in Europe 1990 - 2000



Marh 2002

EBMT

Blutkrebs! Raissa Gorbatschow geht es immer schlechter

● Deutsche Ärzte suchen jetzt Knochenmark-Spender

Wer schenkt ihr neues Leben?

Kämpft seit über drei Wochen gegen den heimtückischen Blutkrebs: Raissa Gorbatschow (67).

Betet für das Leben seiner Frau: Ex-Sowjet-Staatschef Michail Gorbatschow (68).

onnerstag, 192/33
August 1999, 70 Pf
Bild

Raissa Gorbatschow (67) ringt mit dem Tod!

Schon seit über drei Wochen kämpfen deutsche Krebsspezialisten der Uni-Klinik Münster um das Leben der Frau von Ex-Sowjet-Staatschef **Michail Gorbatschow** (68). Die niederschmetternde Diagnose: „akute Leukämie" – **Blutkrebs!**

Jetzt schließen die Krebsärzte auch eine Knochenmark-Transplantation bei Raissa nicht mehr aus. Doch wie so schnell einen geeigneten Spender finden? Krebsspezialist **Prof. Thomas Büchner**: „Wir sind für jeden dankbar, der sich zur Verfügung stellt." Gorbatschow verzweifelt: „Ich bete, daß meine Raissa geholfen wird."

Der dramatische Kampf um Raissa, wer schenkt ihr neues Leben? Seite 8.

Can cord blood be used?

David C. Linch and Leslie Brent

NATURE - VOL 340 - 31 AUGUST 1989

HEMATOPOIETIC RECONSTITUTION IN A PATIENT WITH FANCONI'S ANEMIA BY MEANS OF UMBILICAL-CORD BLOOD FROM AN HLA-IDENTICAL SIBLING

ELIANE GLUCKMAN, M.D.,
HAL E. BROXMEYER, PH.D.,
ARLEEN D. AUERBACH, PH.D.,
HENRY S. FRIEDMAN, M.D.,
GORDON W. DOUGLAS, M.D.,
AGNÈS DEVERGIE, M.D., HÉLÈNE ESPEROU, M.D.,
DOMINIQUE THIERRY, PH.D., GÉRARD SOCIE, M.D.,
PIERRE LEHN, M.D., SCOTT COOPER, B.S.,
DENIS ENGLISH, PH.D., JOANNE KURTZBERG, M.D.,
JUDITH BARD, AND EDWARD A. BOYSE, M.D., F.R.S.

New Engl J Med 1989; 321: 1174-8

„History“ of stem cells from cord blood

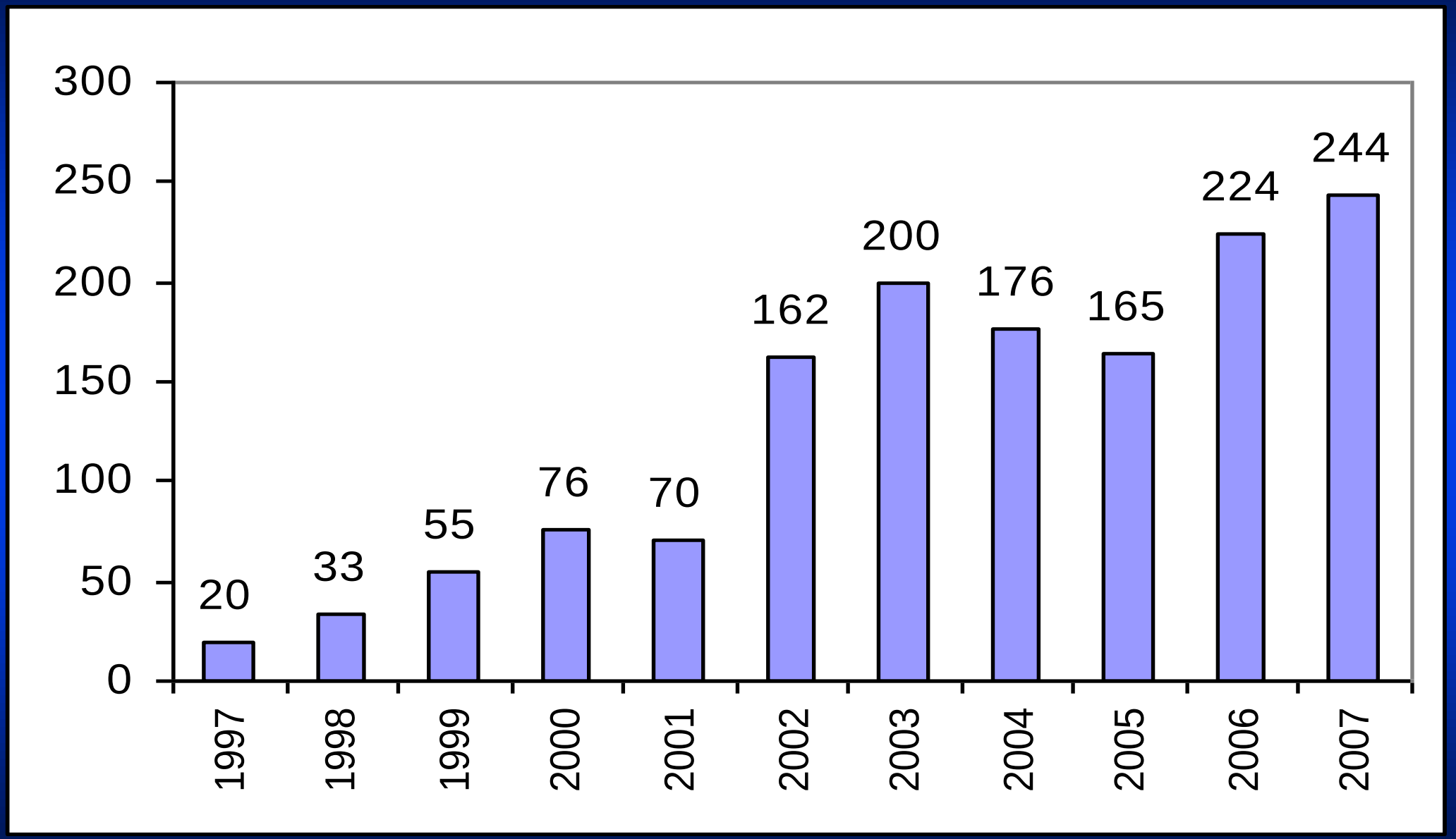
1988 E.Gluckman, H.Broxmeyer et al.: First transplantation Fanconi anemia

1997 500 Transplantations

2002 > 1000 Transplantations

2o14 >50000 banked

Nabelschnurblut- Bank für allogene SCT am Universitätsspital Basel



Erfolgreich auf der Bühne und im Kampf gegen die Leukämie: José Carreras.

Diseases Treated with Cord Blood

Leukemias and lymphomas, including:
- Acute myelogenous leukemia
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia

Multiple myeloma and other plasma cell disorders
- Severe aplastic anemia
- Fanconi anemia

Hemoglobinopathies, including:
- Beta thalassemia major
- Sickle cell disease

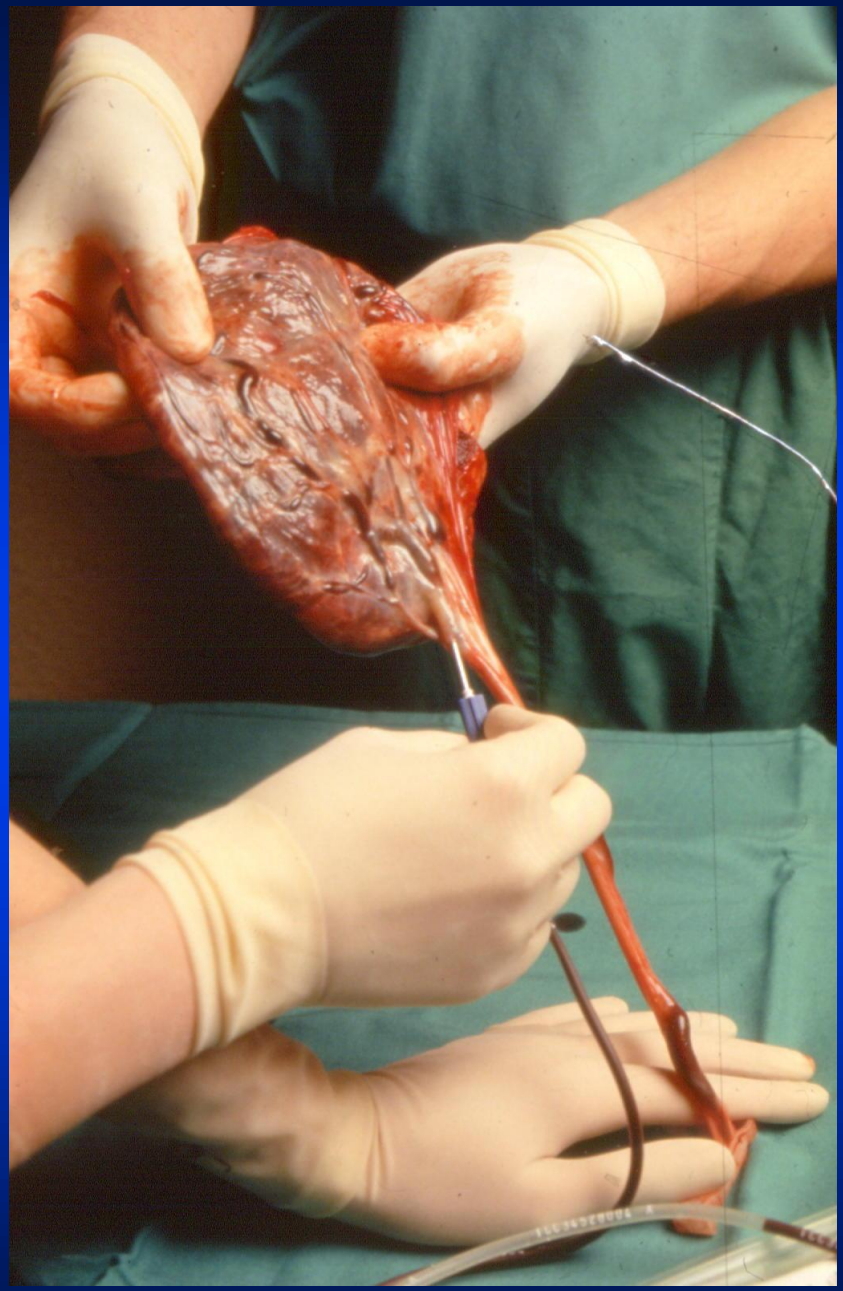
Inherited metabolic disorders
- Hurler's syndrome (MPS-IH)
- Krabbe disease

Myelodysplastic and myeloproliferative disorders
- Refractory anemia (all types)
- Chronic myelomonocytic leukemia

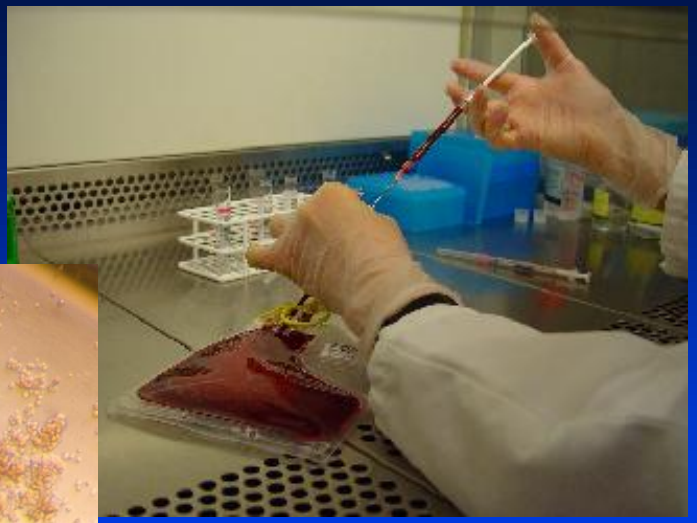
Lymphoproliferative Disorders
- Non-hodgkins lymphoma
- Hodgkin's disease

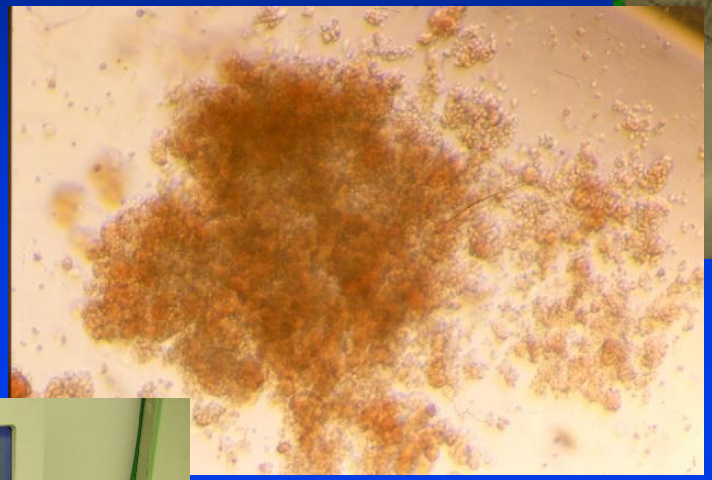
Histiocytic Disorders
- Histiocytosis-X

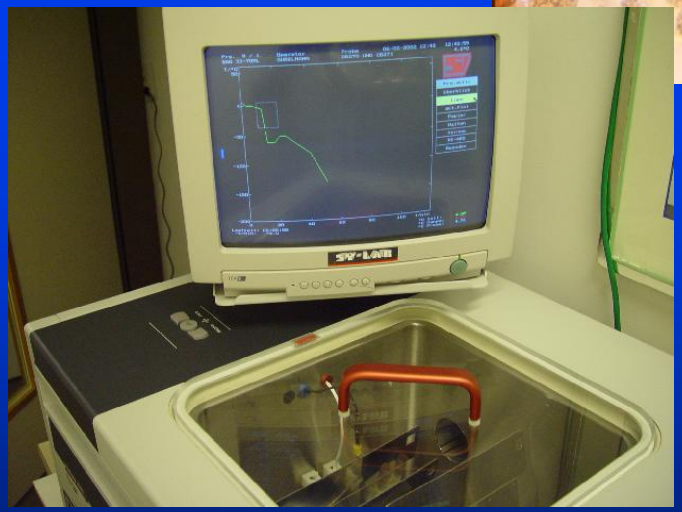
SCID and other inherited immune system disorders
- Severe combined immunodeficiency (SCID, all sub-types)
- Wiskott-Aldrich syndrome

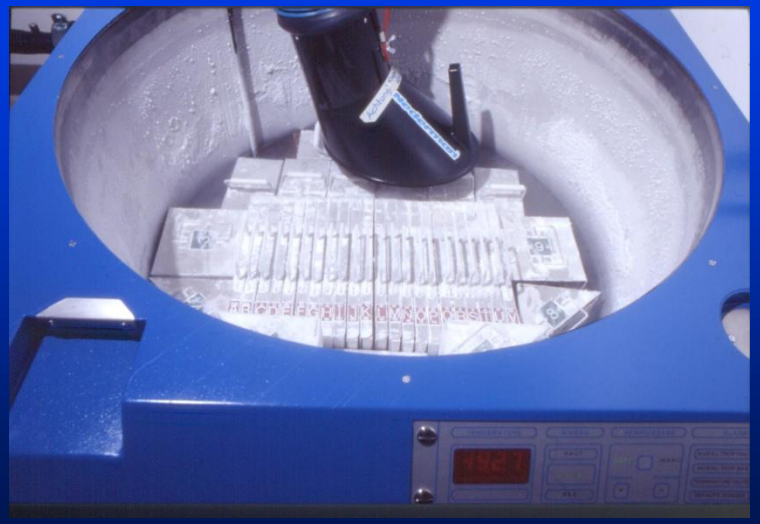


Sollen wir allogenes oder autologes Nabelschnurblut einfrieren?

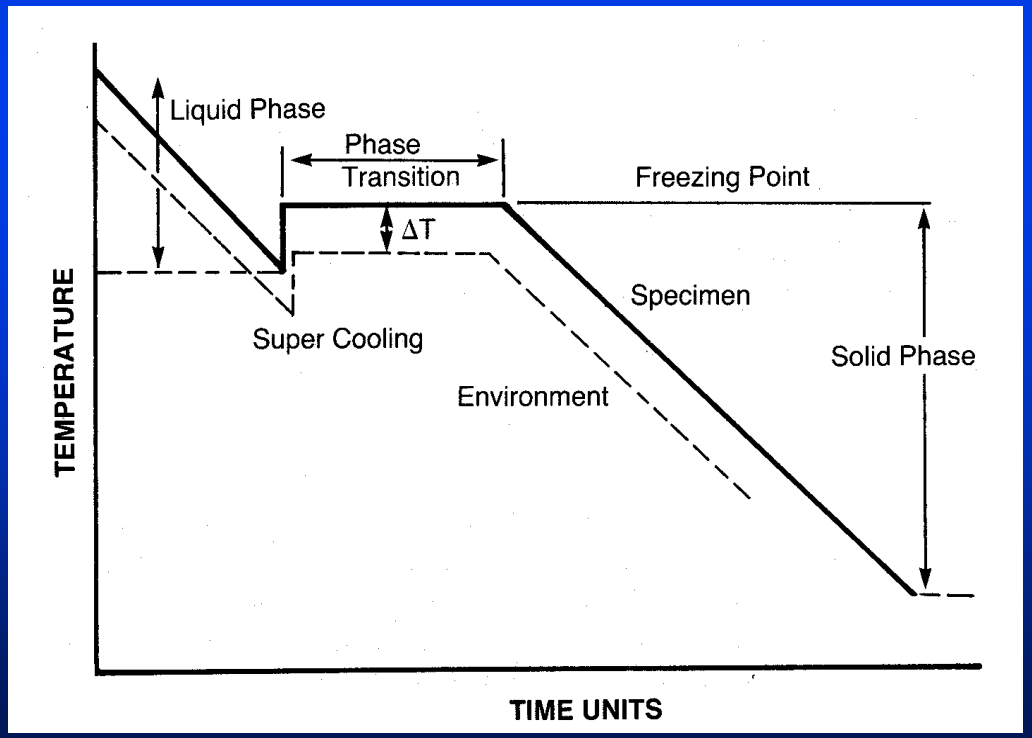




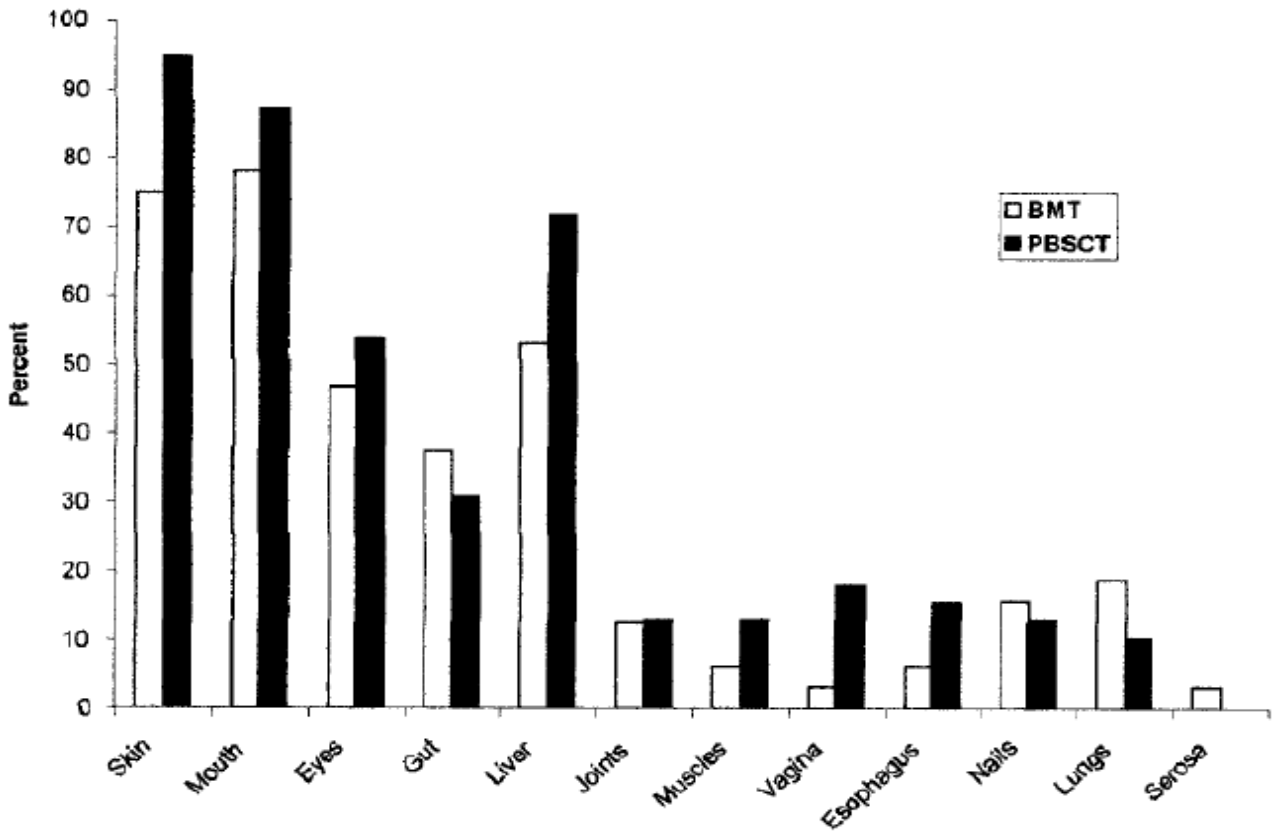




Control-rate freezing

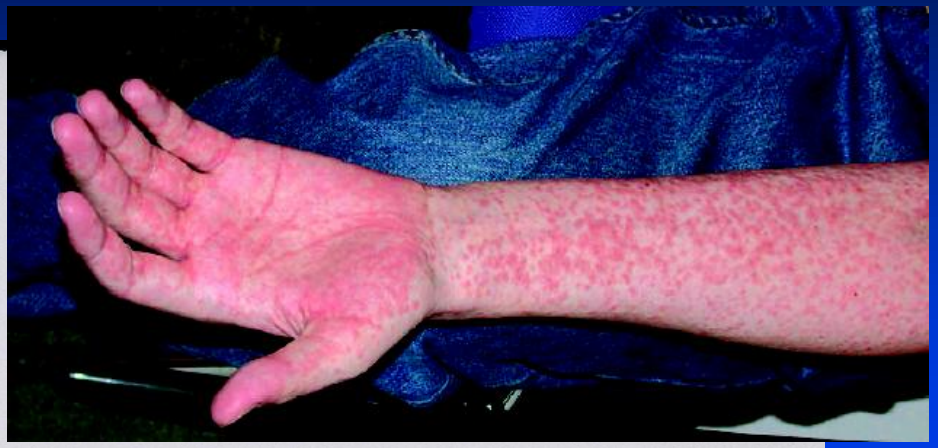


Chronische GvHD



Flowers et al., Blood 2002

GvHD after Related CB (n=113) vs. BM (n=2052) Transplantation



Rocha et al, *N Engl J Med* 2000; 342: 1846-54

Advantages and Disadvantages of Cord Blood

Advantages

- Limitless supply
- Available on short notice for transplant
- No donor attritution compared with bone marrow registry
- Ethnic diversity easier to achieve
- Painless collection of stem cells
- Higher proliferative capacity
- Lower rate of acute graft-vs-host disease

Disadvantages

- Unable to obtain additional "donor" cells for leukocyte infusion or second transplant
- Fewer total HPCs due to small volumes

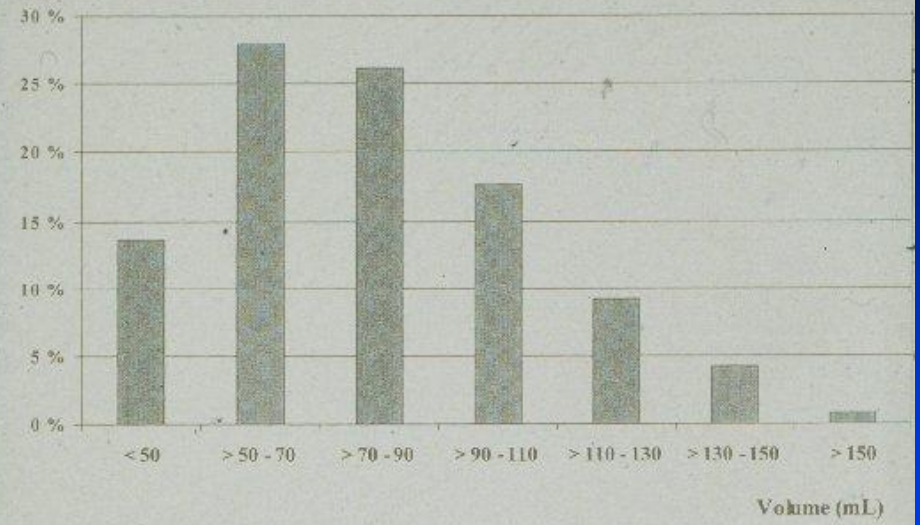


Fig. 1. Distribution of cord blood volume (n=400)

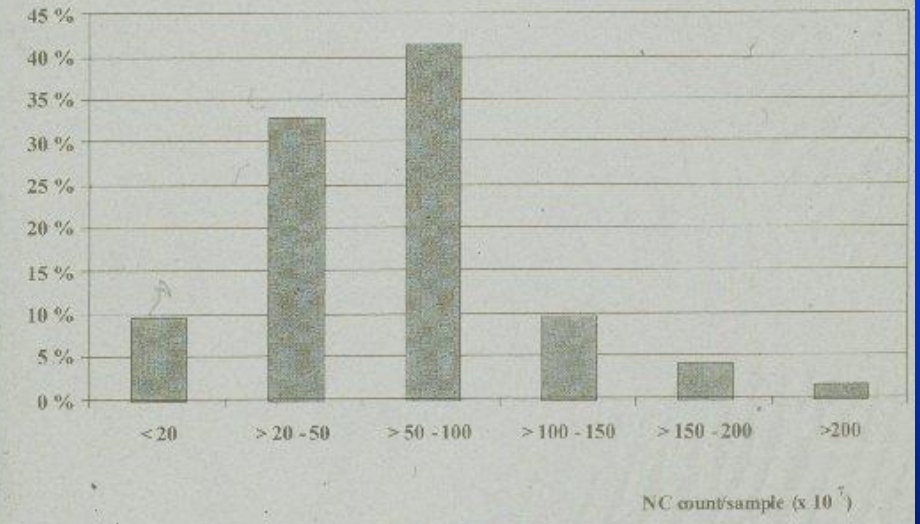
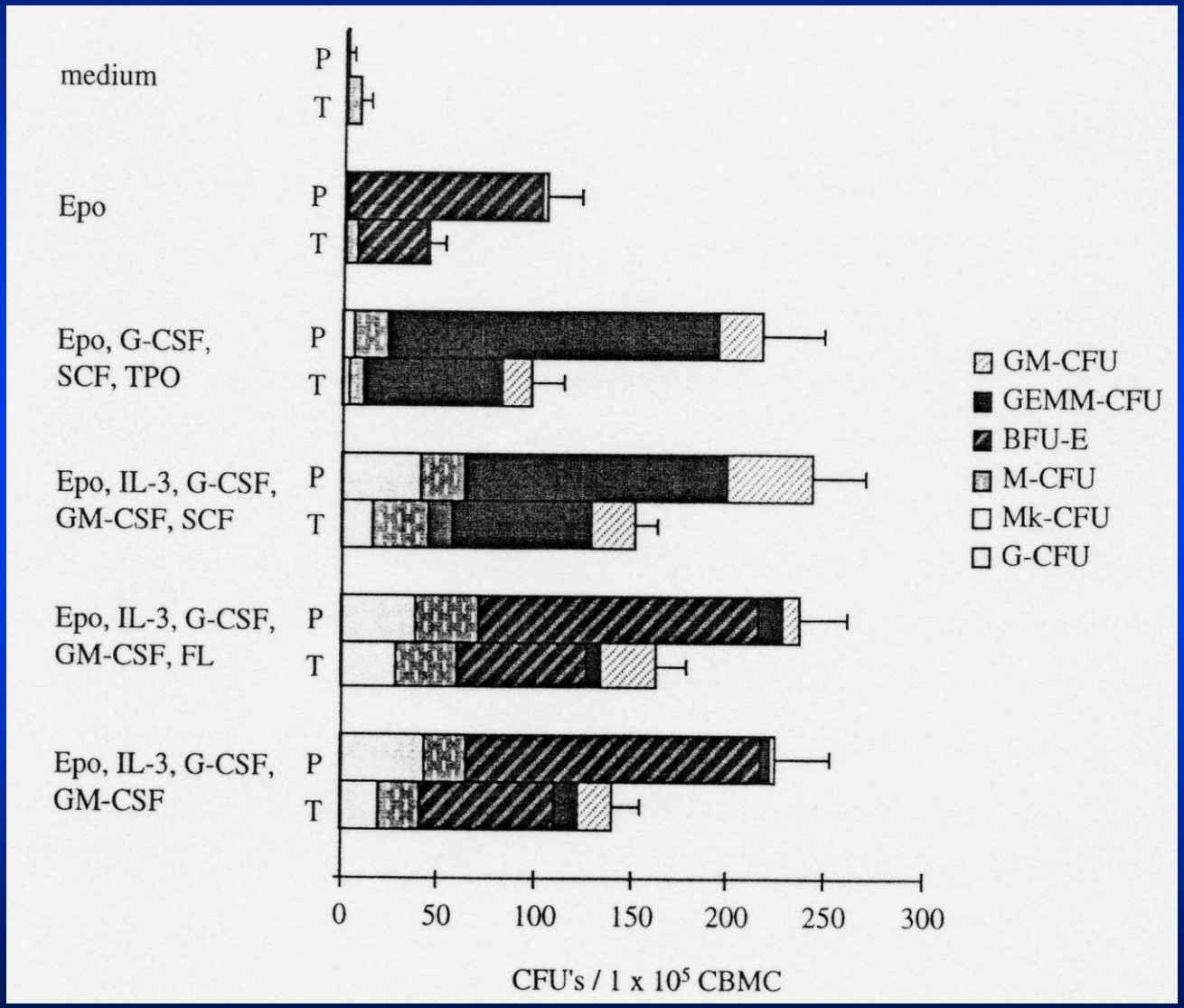


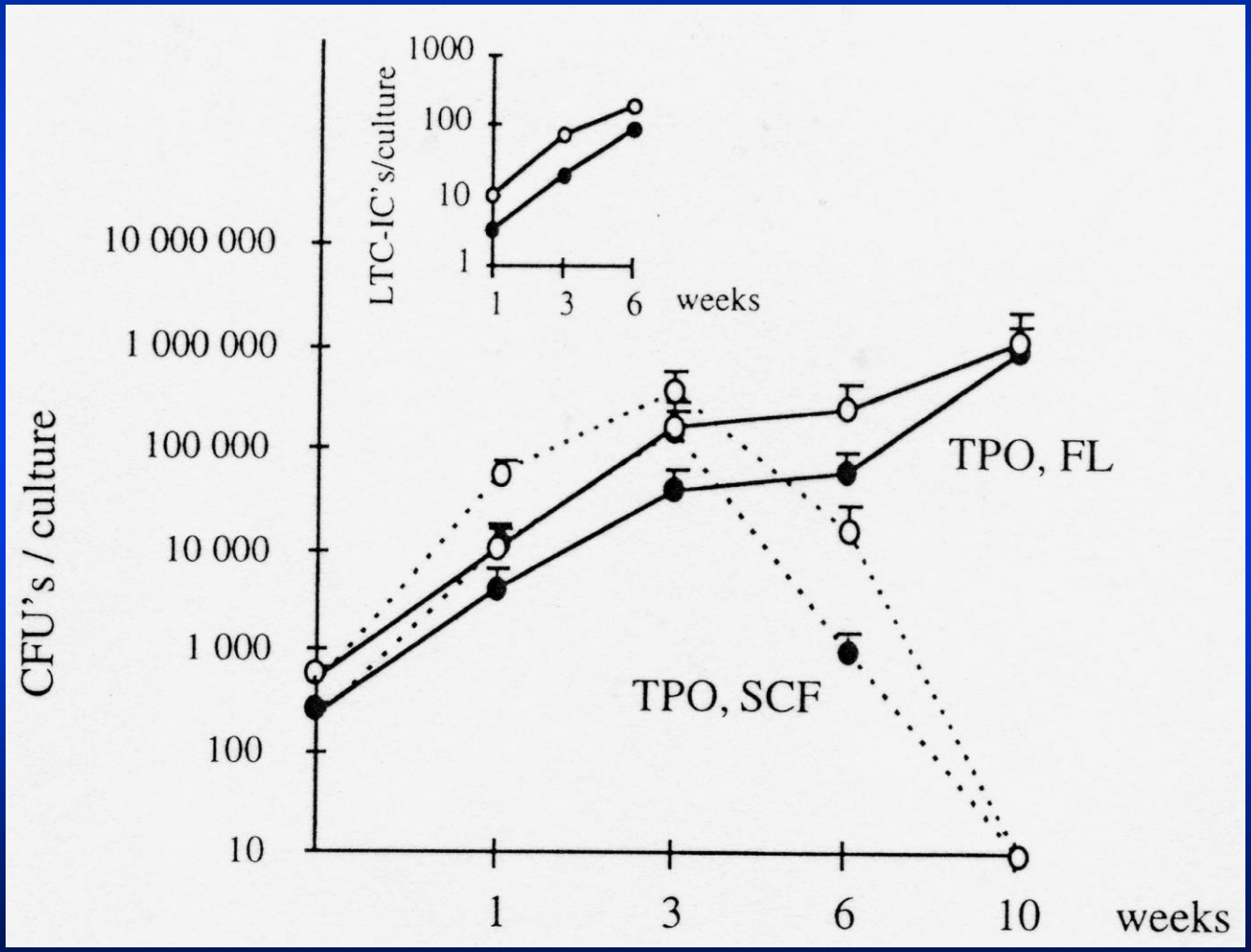
Fig. 2. Distribution of nucleated cell (*NC*) count (n>300)

E. Wunder
in W. Holzgreve, M. Lessl, Springer, 2000

Content of CFU's in fetal blood



Long-term liquid culture expansion

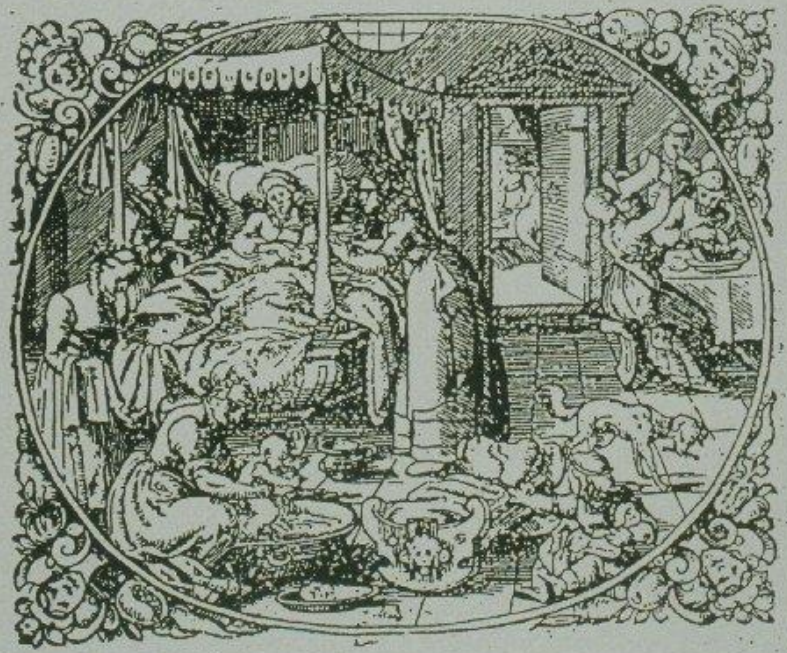


Albertus Magnus/

Daraus man alle Heimligkeit deß

Weiblichen geschlechts erkennen kan/ Deßgleichen von jhrer Geburt/ sampt mancherley artzney der Kreuter/ auch von tugendt der edlen Gestein vnd der Thier/ mit sampt einem bewehrten Regiment für das böse ding.

Jetzund aber auffs new gebessert/ vnd mit schönen Figuren gezieret/ dergleichen vor nie außgangen.



Getruckt zu Franckfurt am Mayn/ M. D. LXXXI.


PRIVATE
BANKING

First Report of Autologous Cord Blood Transplantation in the Treatment of a Child With Leukemia

Ammar Hayani, MD[a], Eberhard Lampeter, MD[b,c], David Viswanatha, MD[d], David Morgan, MD[e], Sharad N. Salvi, MD[a]

Sections of [a]Pediatric Hematology/Oncology and [e]Radiation Oncology, Advocate Hope Children's Hospital and Christ Medical Center, Oak Lawn, Illinois; [b]VITA34 International AG, Leipzig, Germany; [c]CorCell Inc, Philadelphia, Pennsylvania; [d]Department of Pathology, Mayo Clinic, Rochester, Minnesota

Financial Disclosure: Dr Lampeter works for CorCell Inc, a private cord blood–banking laboratory. The other authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

We present the case of a 3-year-old girl with acute lymphoblastic leukemia who developed isolated central nervous system relapse while receiving chemotherapy 10 months after diagnosis. The child achieved a second remission on retreatment with systemic and intrathecal chemotherapy. She then underwent myeloablative chemotherapy and radiation therapy followed by infusion of her own umbilical cord blood, which the parents had saved after her delivery. She is now doing well and is in complete remission 20 months after cord blood transplantation. In this first report of autologous cord blood transplantation for treatment of childhood leukemia, we discuss the safety and feasibility of this procedure as well as some of the uncertainties surrounding autologous cord blood collection and usage.

Despite the improvement of survival in childhood acute lymphoblastic leukemia (ALL), relapse in the central nervous system (CNS) remains a challenging problem. Early CNS relapse carries a high risk of addi-

10^9/L, hemoglobin at 100 g/L, and platelets at 15 × 10^9/L. Bone marrow examination showed 94% lymphoblasts with L-1 morphology. The lymphoblasts expressed CD45, CD10, CD19, CD20, HLA-DR, and terminal de-

Reimann,G. und G. Kögler Frauenarzt 49, Nr. 9, 2008:

Einsatzwahrsch. 0,001-0,04%

„… erklären Sie Ihnen, dass ihrem Kind durch eine Spende nichts Verloren geht.“

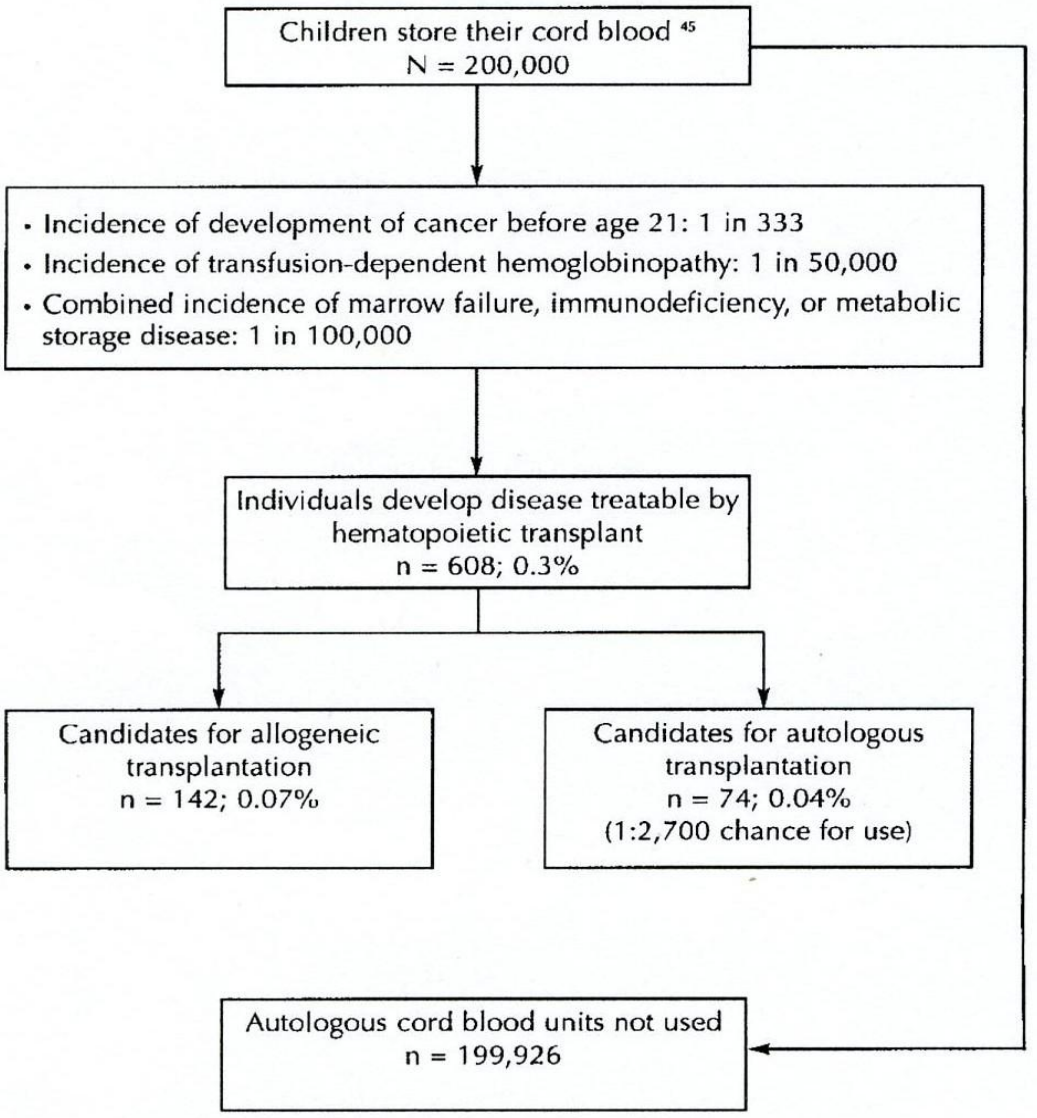


Fig. 3. Flow diagram for potential future autologous use of stored umbilical cord blood.

Moise. Umbilical Cord Blood. Obstet Gynecol 2005.

K.J.Moise Jr, Obstetrics & Gynecology 106,6,1393-1407, 2005

JOURNAL OF MEDICINE

Research Communications
Westbury, NY 11590-0966 USA

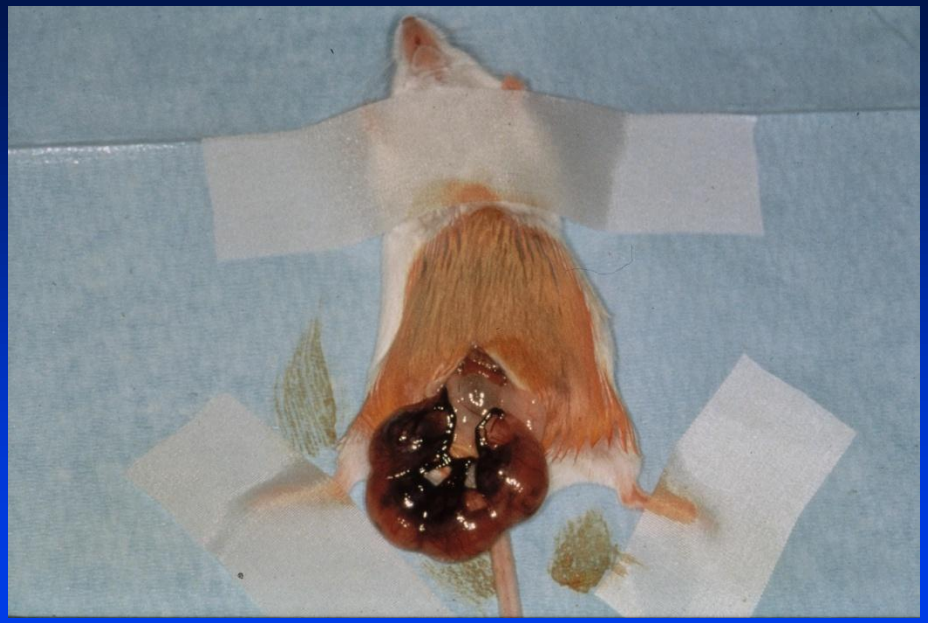
HUMAN UMBILICAL CORD BLOOD CELLS AMELIORATE ALZHEIMER'S DISEASE IN TRANSGENIC MICE

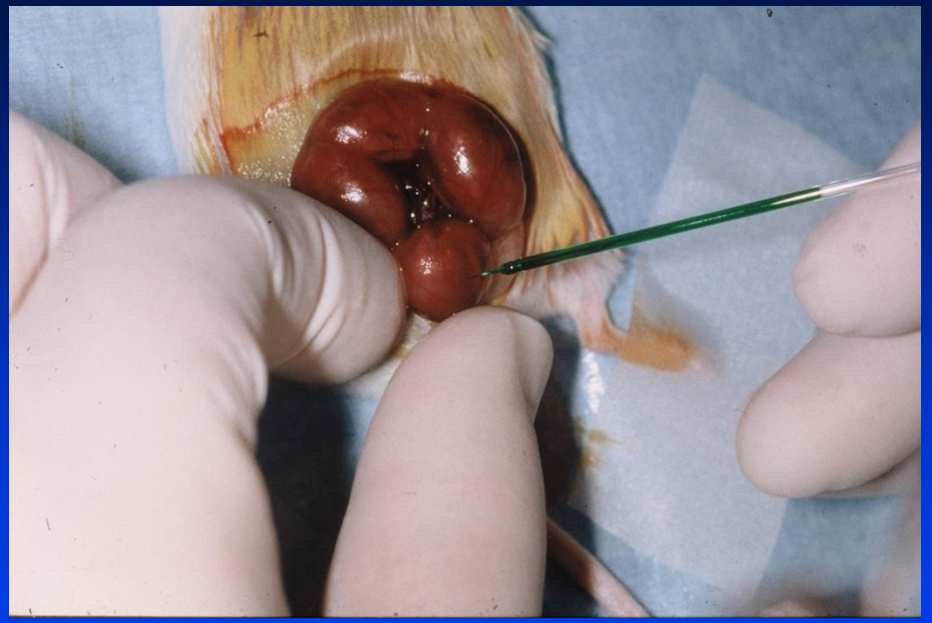
A BRIEF REPORT

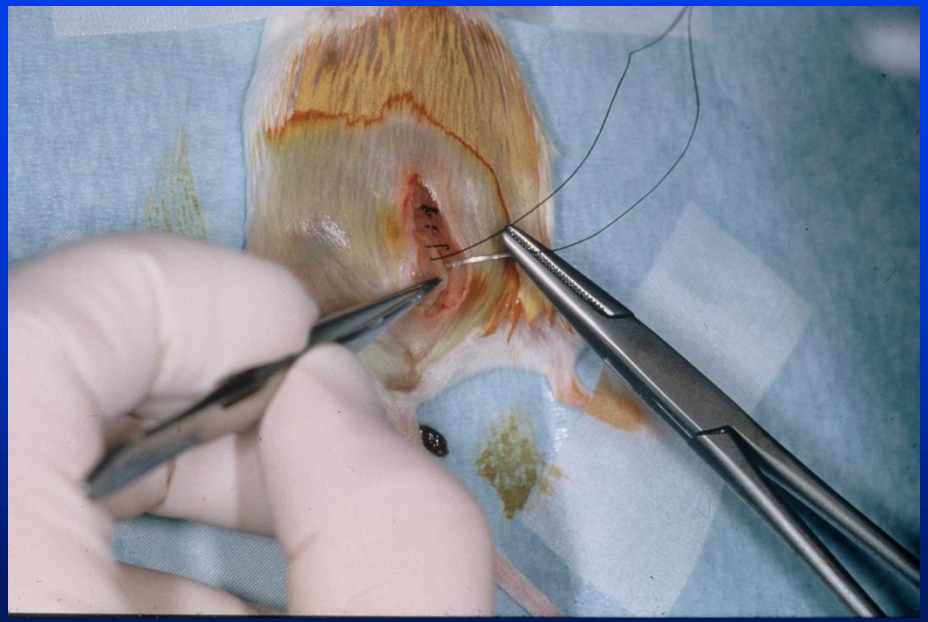
Norman Ende, Ruifeng Chen and David Ende-Harris

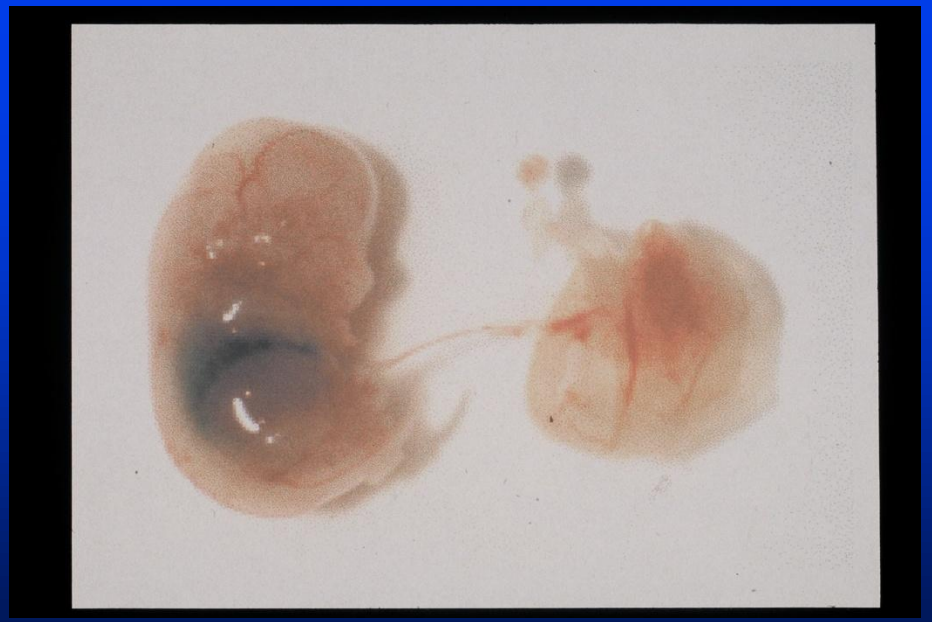
Department of Pathology and Laboratory Medicine,
University of Medicine and Dentistry of New Jersey, New Jersey
Medical School, 185 South Orange Avenue, Newark, NJ 07103

Key Words: Alzheimer's disease, human umbilical cord blood; transgenic mice.
Subjects: Transgenic mice.
Abbreviations: APP = Amyloid precursor protein, SOD1 = amyotropic lateral sclerosis mice, HUCB = human umbilical cord blood, Hdexon1 = Huntington's disease mice, MNC = mononuclear cells.



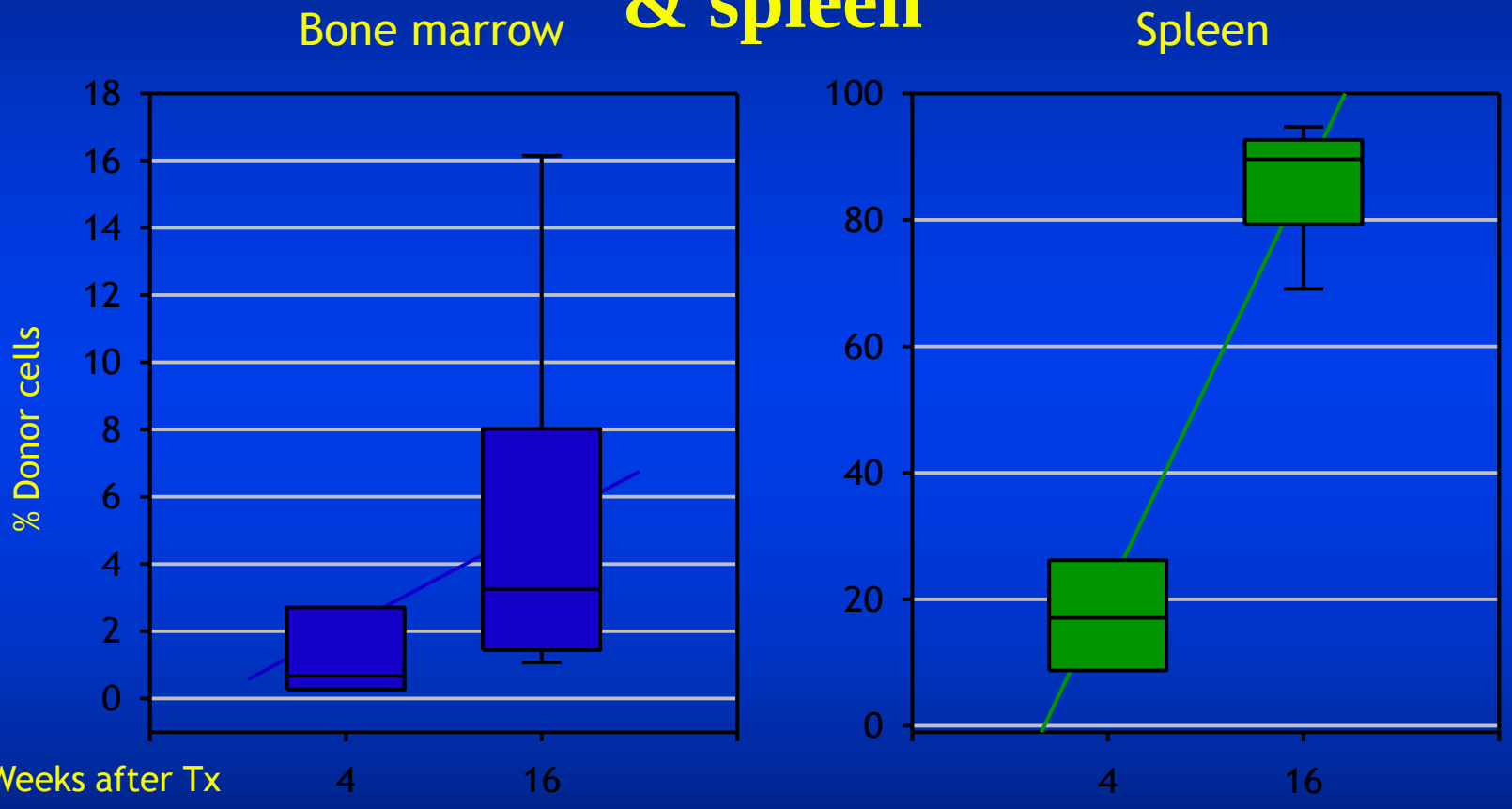




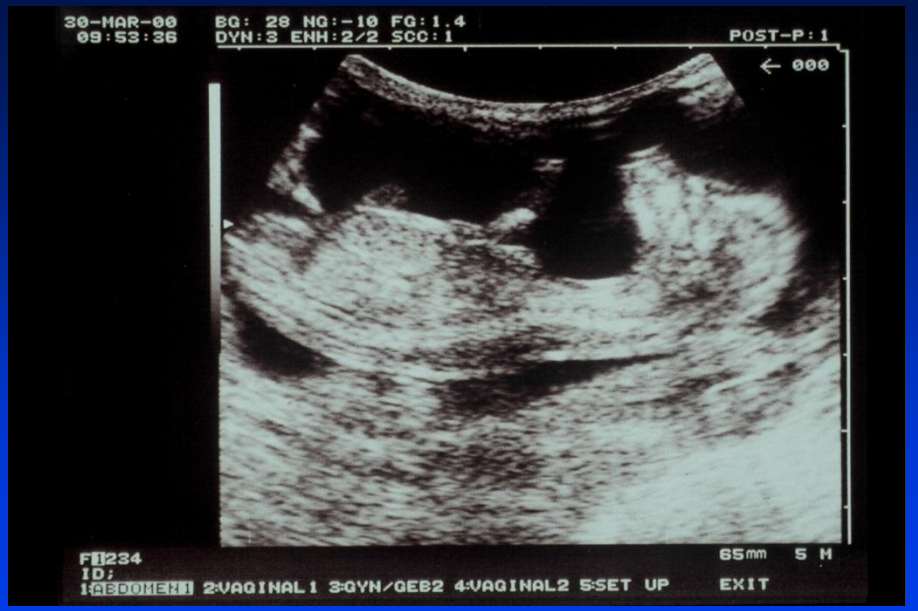


60-70 % successful injections

Postnatal engraftment after Tx of allogeneic fetal liver cells: bone marrow & spleen



	Bone marrow		Spleen	
n	8	9	8	9
Mean (%)	2.1	5.2	21.1	86.2
SD (%)	3.6	5.0	16.4	8.8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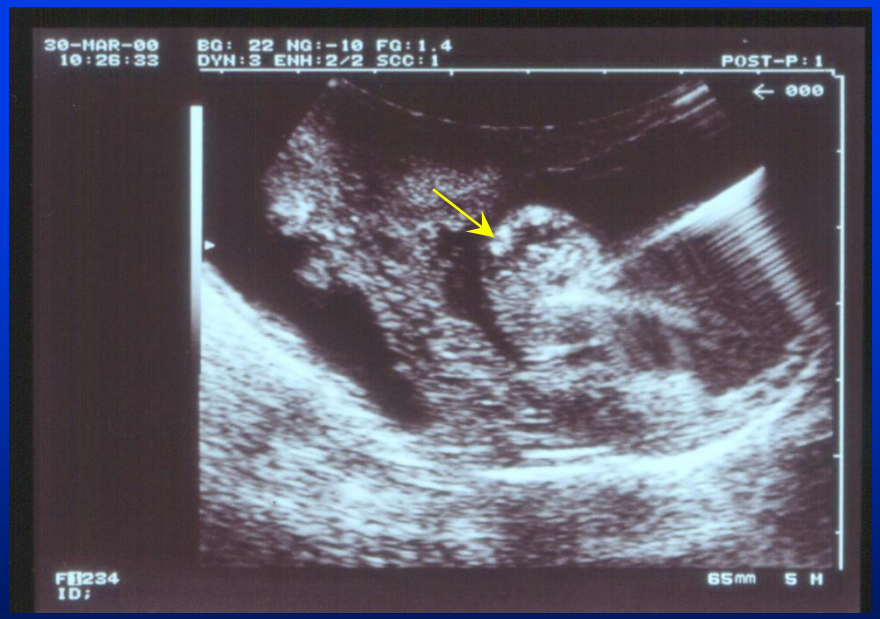
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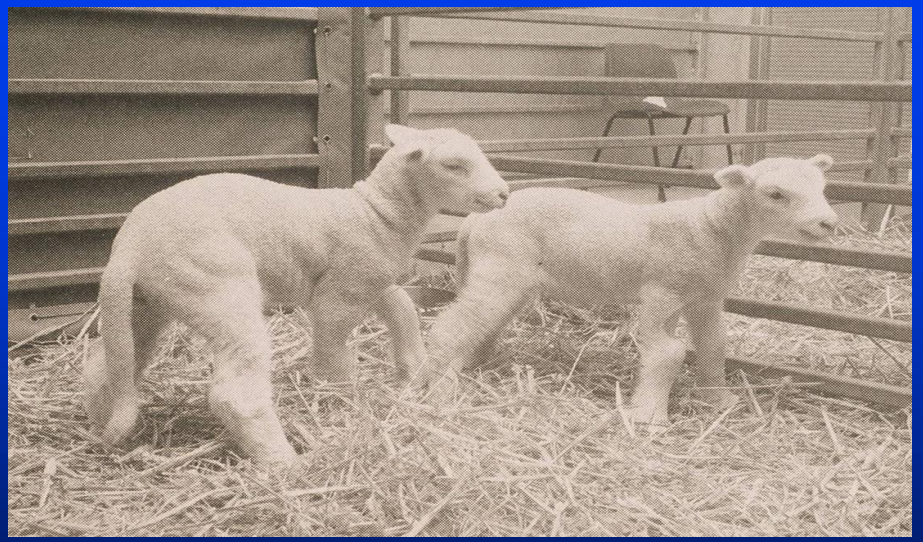

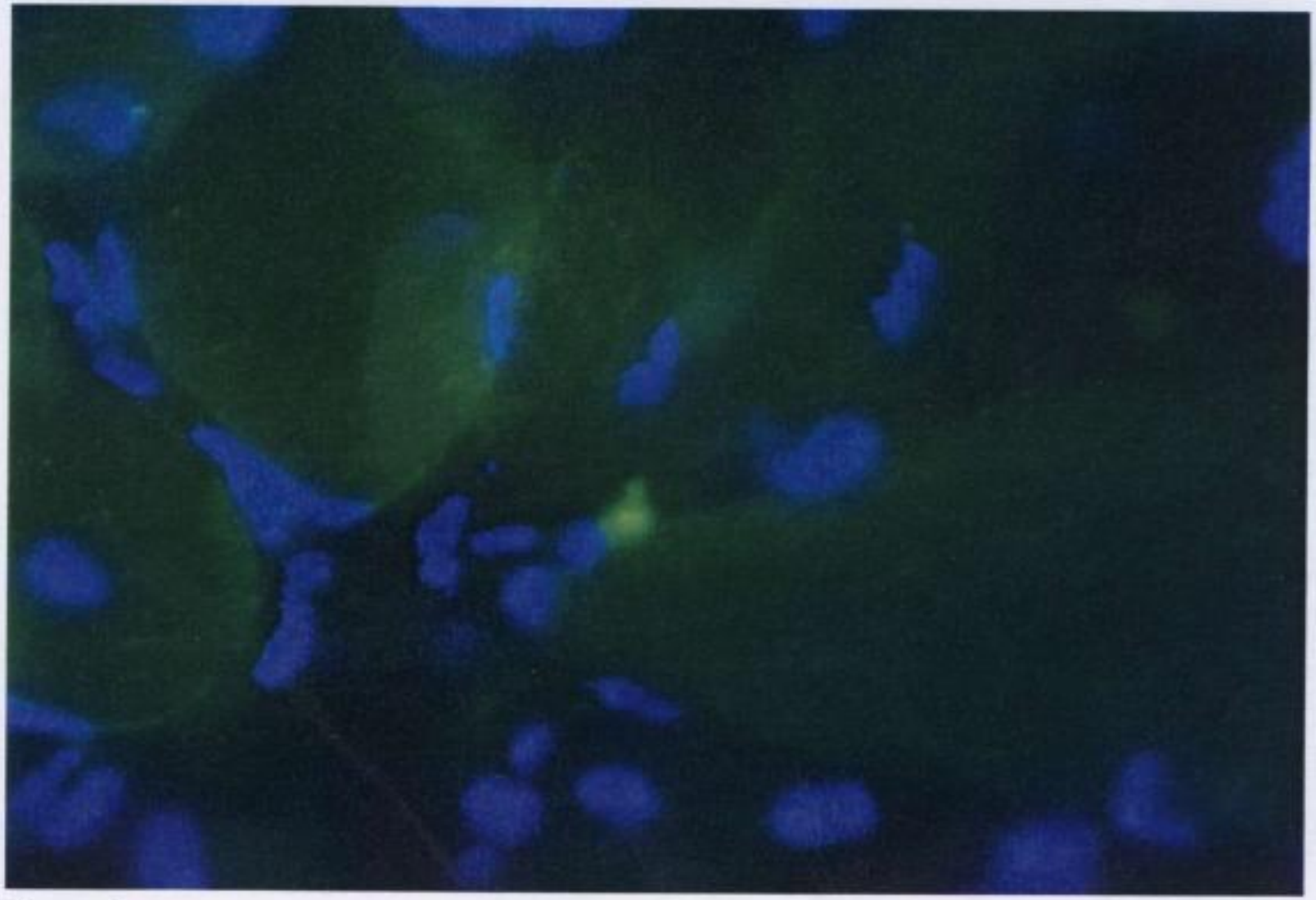

Figure 1

Cryostat section of the maternal scar and muscle tissue of the abdominal wall one week after delivery of pubs who received eGFP+ MSC by in-utero transplantation. Nuclei are stained using DAPI (blue dye). One cell is eGFP positive (green).

Troeger, C., Perahud, I., Holzgreve, W. et al.

SMW 137, 561-2, 2007

S. Hahn, R. Sant and W. Holzgreve, Molec.
Human Reproduction 4 (6), 515-521, 1998

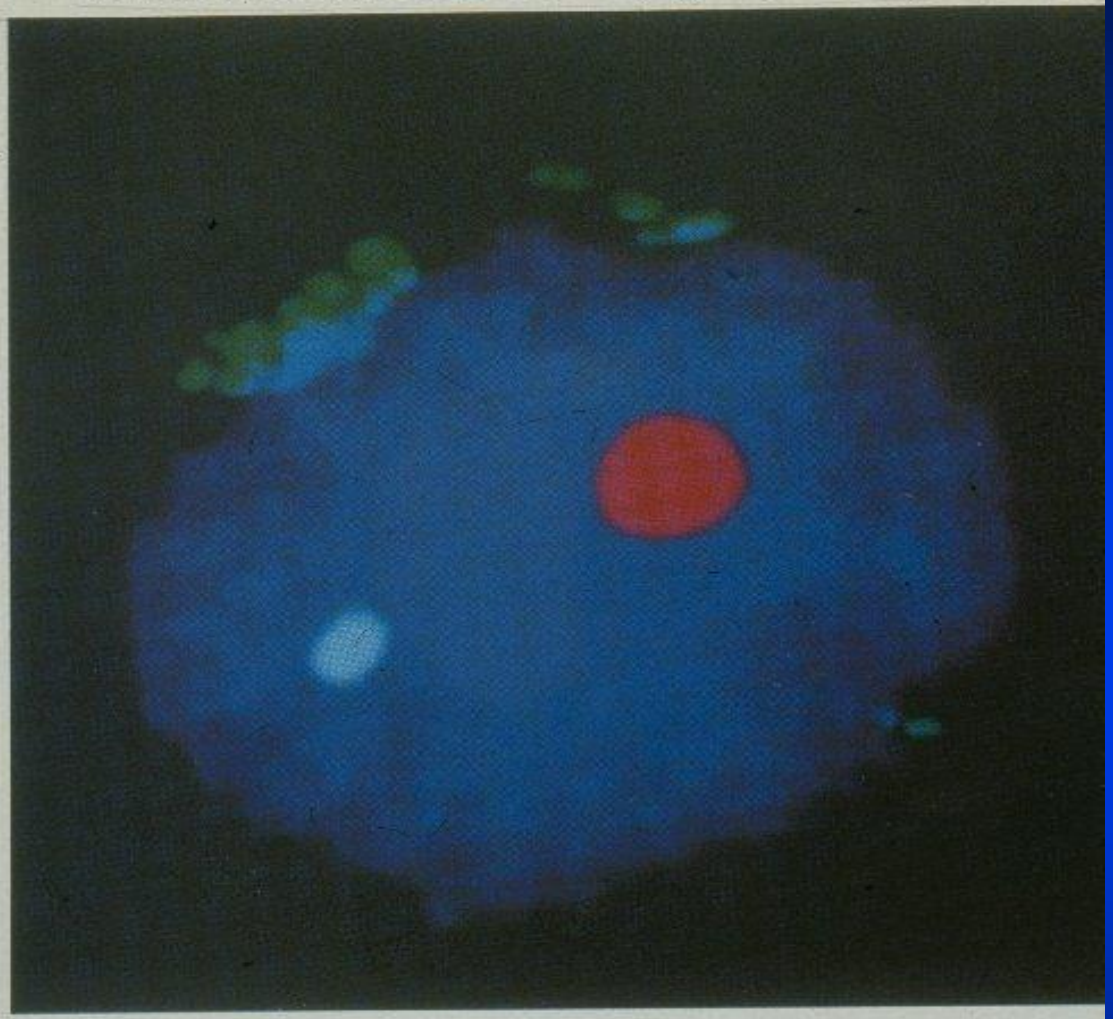

Figure 1. Male fetal cell identified by immunohistochemical staining for fluorescein-conjugated anti-fetal haemoglobin (Europa, Cambridge, UK) and simultaneous fluorescent in-situ hybridization for X (pale blue) and Y (pink) chromosomes (Genzyme Genetics, Framingham, MA, USA), following enrichment with anti-CD71 and MiniMacs.

Cells Exchanged During Pregnancy Live On

Microchimerism, viewed at first as an oddity, has been linked to autoimmune diseases and complications of pregnancy

A mother's love is enduring. But most mothers would be surprised to discover that there's a similarly enduring physical bond: Cells from a fetus can live on in the mother's body for decades after pregnancy, a situation called microchimerism. Likewise, a mother's cells can also survive for many years in her child.

When this phenomenon was first reported in the mid-1990s, scientists scoffed at the notion that these cells could persist for so long, tolerated by their host's immune system. "Everyone said it can't be true," says rheumatologist Michael Lockshin, director of the Barbara Volcker Center for Women and Rheumatic Disease at the Hospital for Special Surgery in New York City. "But now everyone who looks finds it."

In some cases, the cells might be benign guests: self-perpetuating lines of stem cells that can reproduce and even give rise to other types of cells, all without harming their host. But a growing body of research, still preliminary, suggests that the cells might also be at the root of some autoimmune diseases and other conditions.

Indeed, microchimerism might help explain one of the puzzles about autoimmune diseases: why many of them strike more women than men. No one knows how many women carry foreign cells around from past pregnancies, but several studies have shown that women with certain autoimmune diseases are more likely to harbor such cells than healthy women. "When you see that this is a real phenomenon, it gives you a different perspective," says pediatric hematologist William Reed of the Children's Hospital Research Institute in Oakland, California. "You begin to ask yourself whether a disease might have a pathogenesis that you've never considered before."

And it's not only the long-lived cells that might be making mischief. Reproductive biologists have known for some time that fetal cells course through the bloodstream of pregnant women, but in the past 4 years researchers have discovered that this temporary invasion might be implicated in two common complications of pregnancy.

Inner turmoil

Fetal microchimerism was uncovered quite by chance. In 1992, medical geneticist Diana

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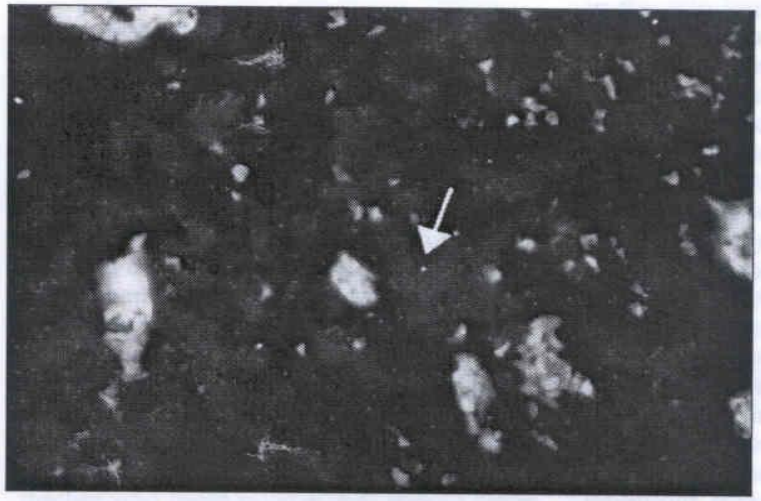
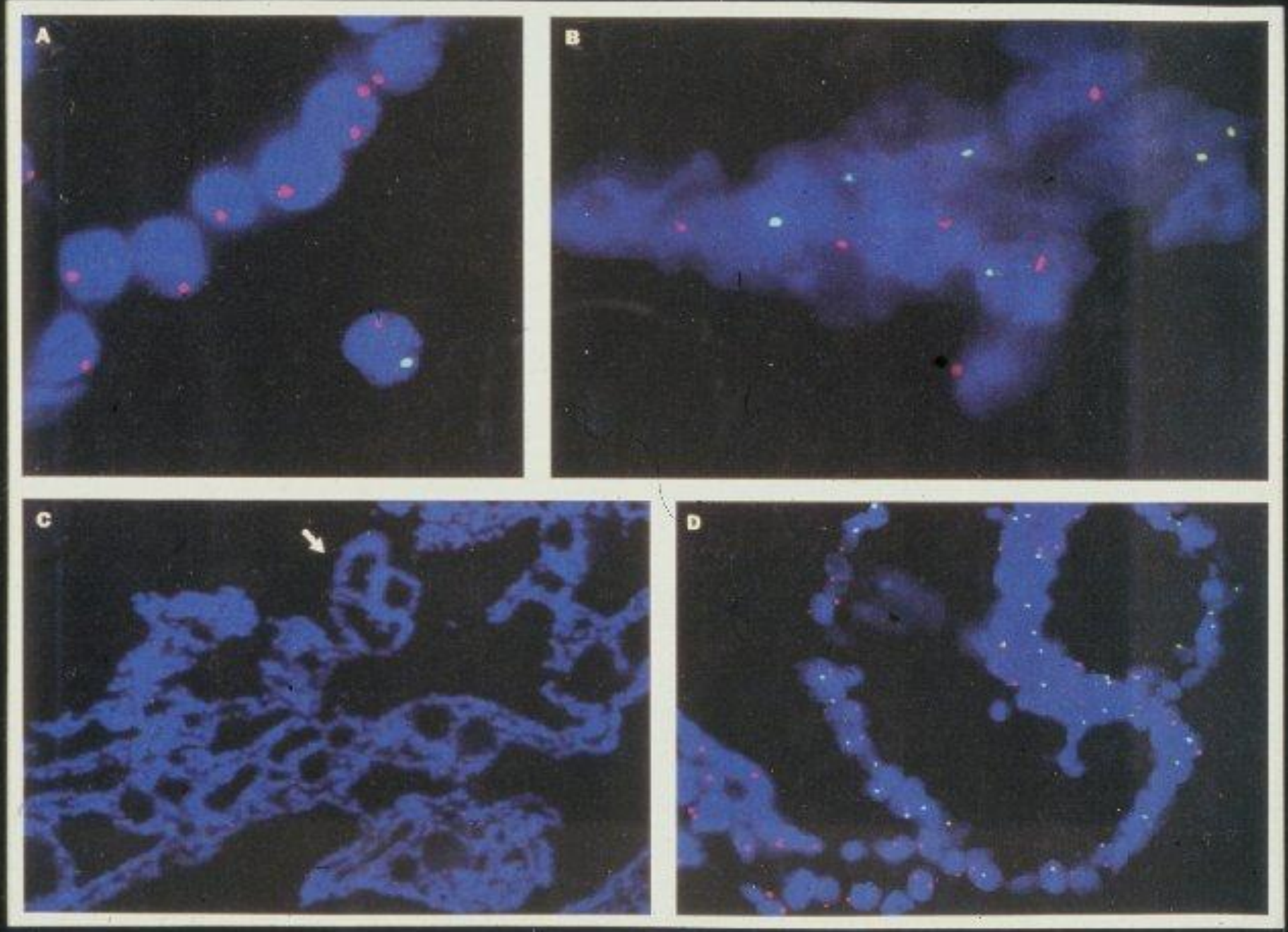


Under mom's skin. A cell with a green-stained Y chromosome, presumably from a son, was found in a skin biopsy from a woman with systematic sclerosis.

D.Bianchi et al.

Lancet 358, 2034-8, 2001



Yang et al. Journal of Translational Medicine 2011, 9:65
http://www.translational-medicine.com/content/9/1/65

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Human umbilical cord blood-derived mononuclear cell transplantation: case series of 30 subjects with Hereditary Ataxia

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Abstract

Background: The differential diagnosis for hereditary ataxia encompasses a variety of diseases characterized by both autosomal dominant and recessive inheritance. There are no curative treatments available for these neurodegenerative conditions. This open label treatment study used human umbilical cord blood derived mononuclear cells (CBMC) combined with rehabilitation training as potential disease modulators.

Methods: 30 patients suffering from hereditary ataxia were treated with CBMCs administered systemically by intravenous infusion and intrathecally by either cervical or lumbar puncture. Primary endpoint measures were the Berg Balance Scale (BBS), serum markers of immunoglobulin and T cell subsets, measured at baseline and pre determined times post-treatment.

Results: A reduction of pathological symptoms and signs was shown following treatment. The BBS scores, IgG, IgA, total T cells and CD3+CD4 T cells all improved significantly compared to pre-treatment values ($P < 0.01$–0.001). There were no adverse events.

Conclusion: The combination of CBMC infusion and rehabilitation training may be a safe and effective treatment for ataxia, which dramatically improves patients' functional symptoms. These data support expanded double blind, placebo-controlled studies for these treatment modalities.

Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Women's Health and Disease*

Umbilical cord blood stem cells: what to expect

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Umbilical cord blood (UCB) is a valuable alternative source of hematopoietic stem cells (HSCs). It has unique advantages of easy procurement, absence of risk to donors, low risk of transmitting infections, immediate availability, greater tolerance of human leukocyte antigen (HLA) disparity, and lower incidence of inducing severe graft-versus-host disease (GVHD). In the last several years, these features of UCB permit the field of UCB transplantation (UCBT) to move at a faster pace for both children and adults with malignancies and nonmalignancies. However, new strategies and novel developments are expected to improve engraftment and reconstitution, and to enable *in utero* transplantation for early therapy, as well as to allow the therapy for a wide spectrum of human diseases.

Keywords: hematopoietic stem cells; umbilical cord blood; human leukocyte antigen disparity