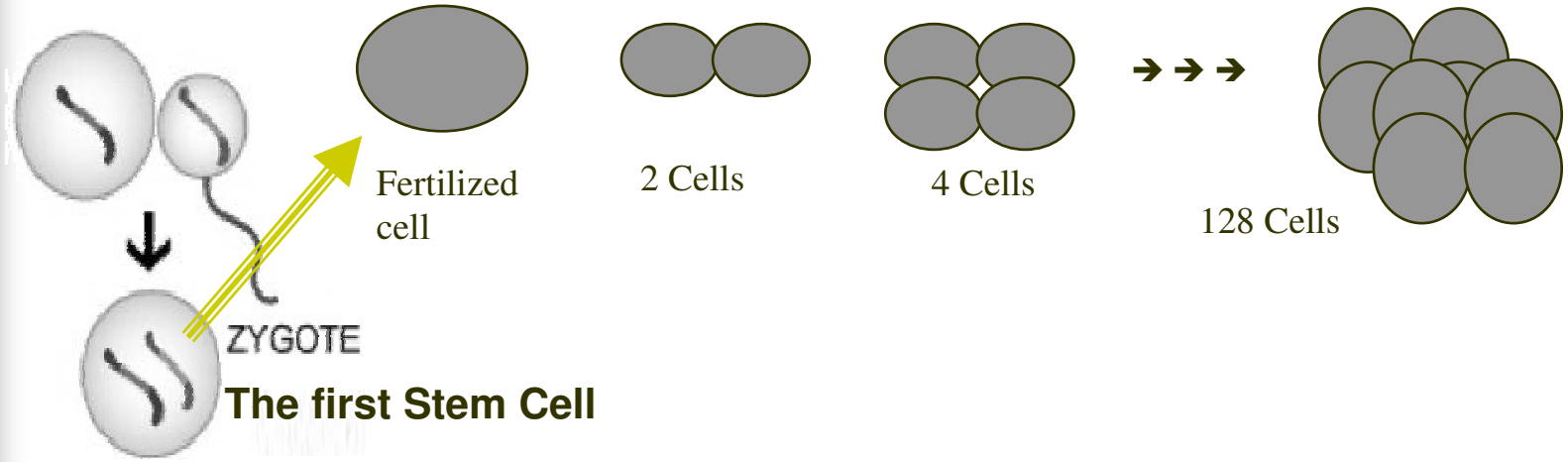

Stem Cell Therapy
THE DARK AND BRIGHT ASPECTS
of Stem Cell Therapy

Stem Cells… Our last Weapon?

- The last weapon in the medical armamentarium?
- Bye the way.. ***What IS a last weapon?***
- I don't know about today, but the last weapon in the 4th World War will be …….

Introducing Stem cells - 1

- When a Paternal sex cell and a Maternal sex cell, each with half the genetic quota, unite, the resultant fused “zygote” cell is the first Stem Cell.
- It then goes on doubling itself till the 128 (or so) cell stage. If any portion separates away at this stage, that is when you get identical twins.
- These are the Totipotent Stem cells that can allow cloning to take place, and hence are virtually banned worldwide from clinical usage.



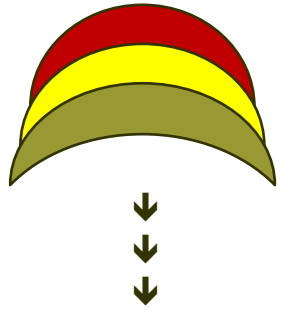
Introducing Stem cells – 2

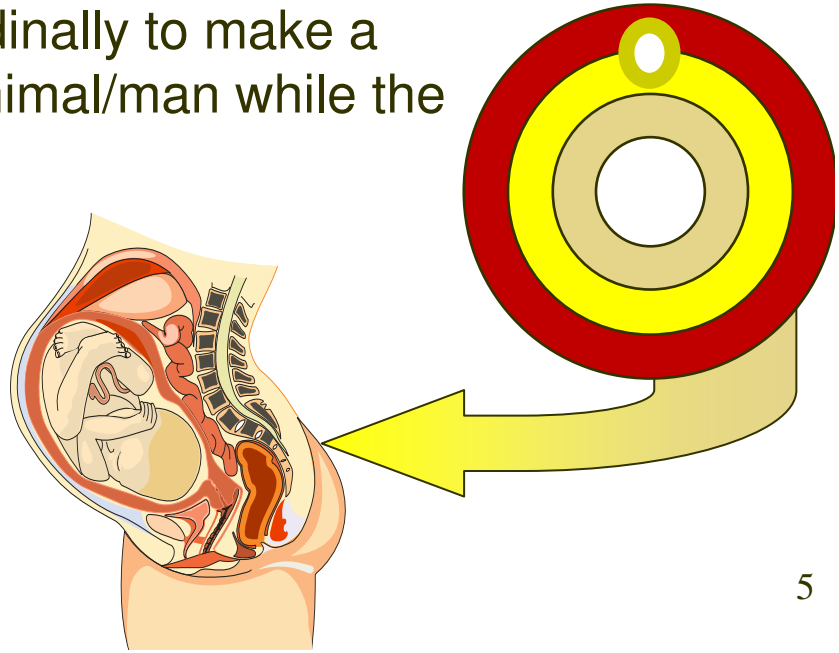
- Called Master Cells of the body.
- Stem cells are distinguished from other cell types by two important characters
  - Stem cells are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity.
  - Undifferentiated cells that have the ability to divide & differentiate into 200 other cell types.
- Under certain physiologic or experimental conditions, they can be induced to become tissue or organ specific cells with special functions, like cartilage, tissue of liver, heart muscle, pancreas, nerve, blood cells, etc.

Sell, S. (2004) Stem cells. Stem Cell Handbook, Humana Press, edited by Sell, S.

Stem Cell Stages - 1

- The first stem cells differentiate into three layers:
  - Outer **Ectoderm** that in future will make skin, hair, enamel of teeth, brain and nerves.
  - Middle **Mesoderm** that in future will make muscles, skeleton, cartilage, connective tissues.
  - Inner **Endoderm** that will in go on to make GI Tract, liver, lungs, etc
- The three layers fold longitudinally to make a tube that will be the future animal/man while the skin at the back folds and is pushed into the body to make another tube that will grow into the nervous system.



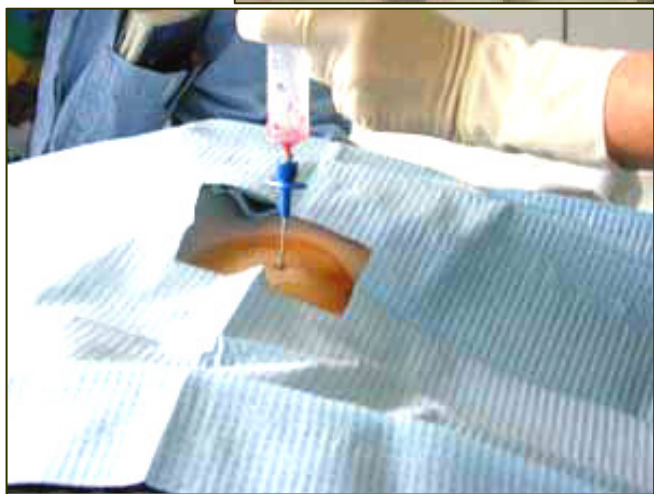


Stem Cell Stage – 2

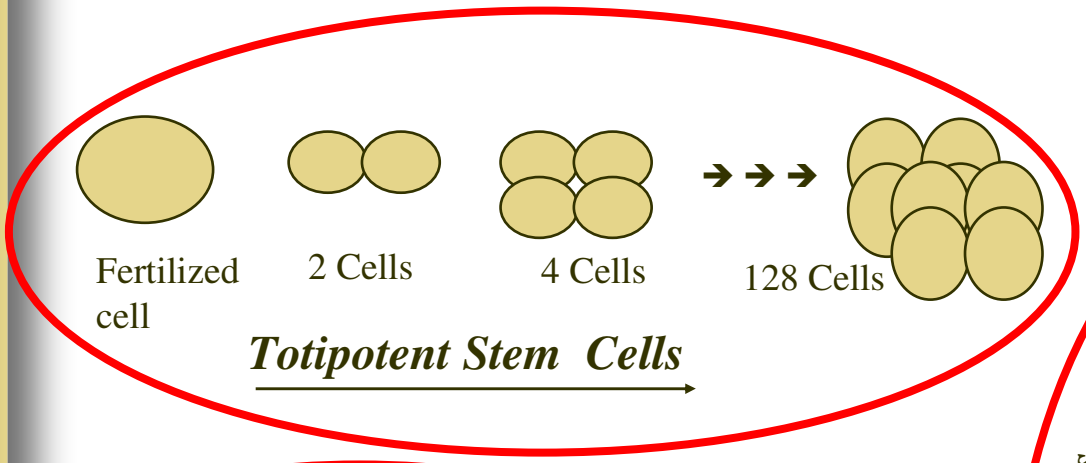
- The embryo is packed with highly active "**Pluripotent**" Stem Cells that help the child to grow to the stage fit for birth.
- Collecting these Embryonic Stem Cells practically means killing that embryo to get at its store of stem cells
- Embryonic stem cells are highly potent and can transform into virtually any tissue or organ, with the right stimulus.
- About 1% cases may develop tumor after 4-5 years
- Status: in primary clinical trial stage

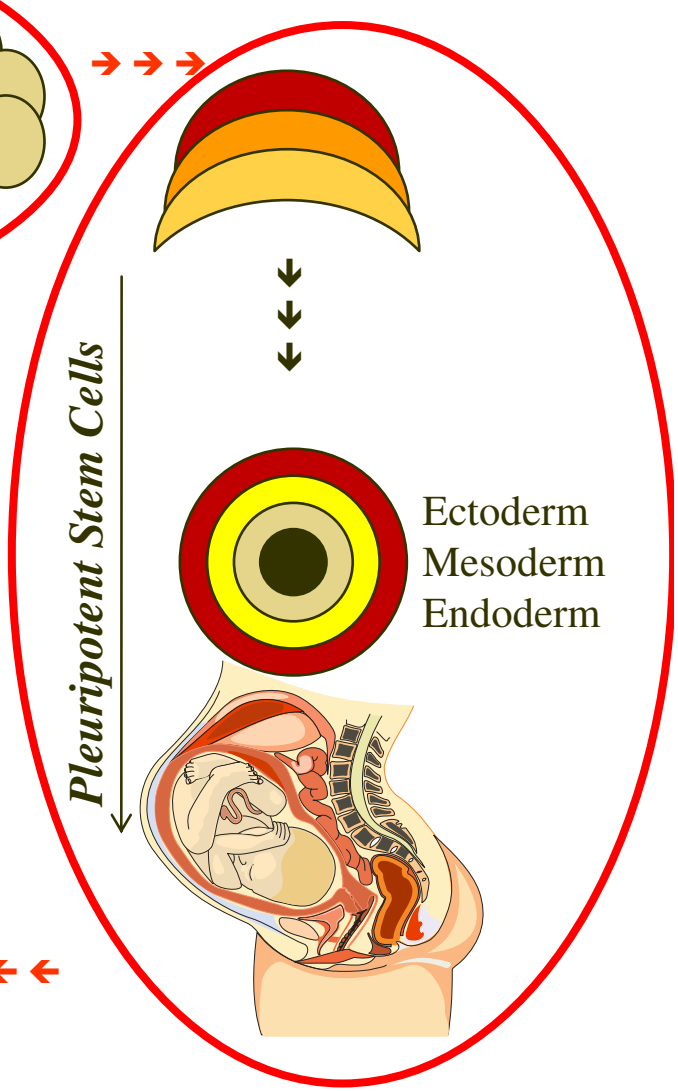
Stem Cell Stage 3

- Once the child is born, the remaining stem cells in every body tissue are the primarily means for repair and regeneration (after apoptosis) of that and a small number of other tissues.
- These much-safer-to-use "Multipotent" stem cells have limited functionality and are called "Adult Human [Somatic / Stromal] Stem Cells or AHSSc
- Status: in Phase II-III Trials



Stem Cells Summary





Which cell type to choose for Stem Cell Rx?

- **Toti-potent (Initial cells after fertilization)**

X

  - Can become any type of cell in the body
  - If split in early stage, develops identical monozygotic twins

- **Pluri-potent (Embryonic cells)**

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  - Can become almost any kind of cell in the body (fetal cells)

- **Multi-potent (Post-delivery stem cells)**

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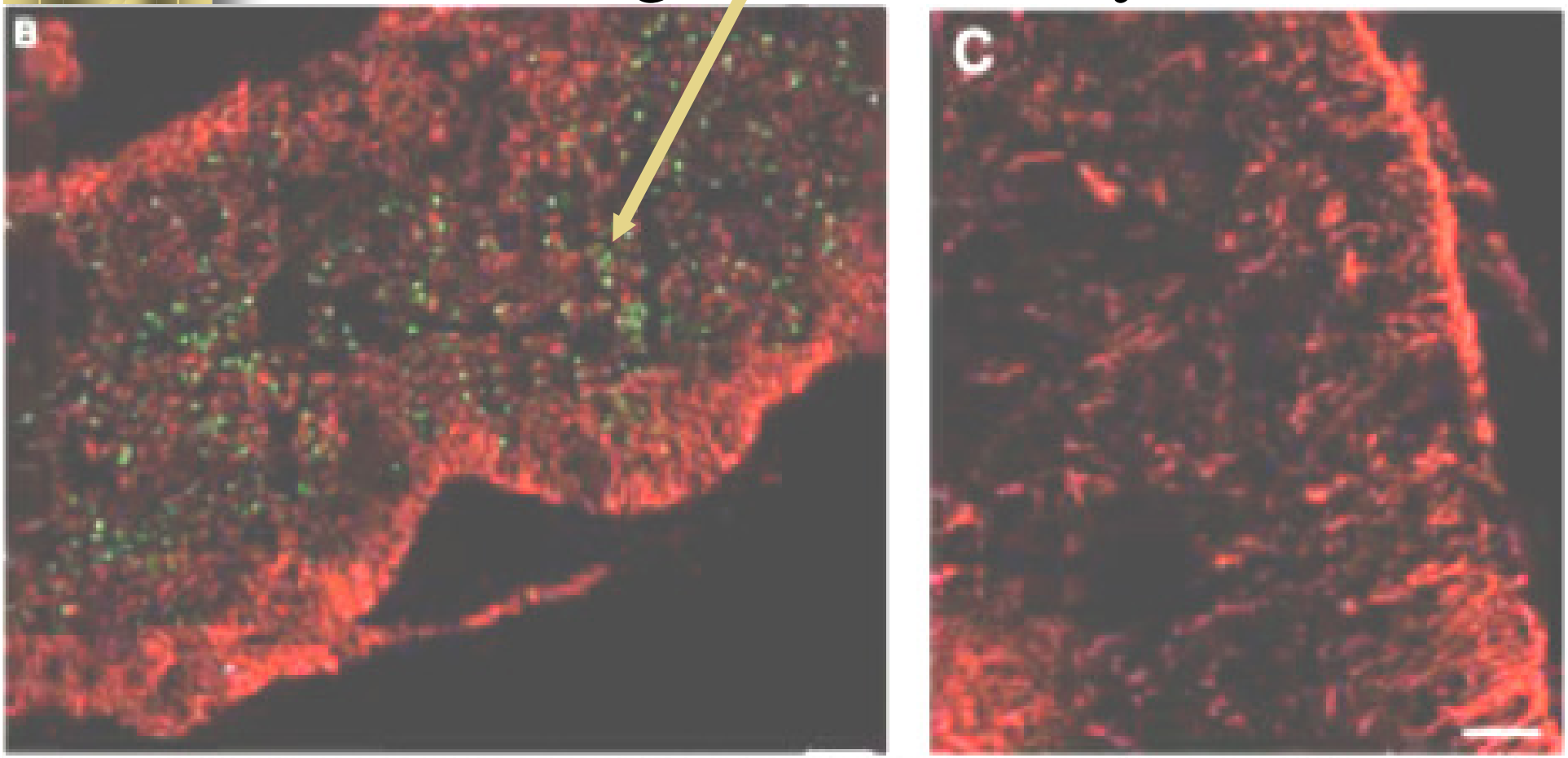
  - Can differentiate into only a limited range of cell types (examples include umbilical cord and adult stem cells)
  - May be from self (autologous) or donor (allogenic)

Differentiation of Stem Cells: Many opinions. *Limited* Trial Data

- Bone Marrow
  - Marrow, Blood Cells
  - Heart Muscle
  - Bone & Cartilage
  - Tendon & Muscle
  - Fat
  - Liver
  - Brain / Nerves
- Adipose Tissue
  - Bone & Cartilage
  - Muscles & Nerves
  - Brain/Spinal Cord cell
- Peripheral Blood
  - Bone Marrow
  - Blood Cells
  - Nerves
- Umbilical Bl./Cord
  - Various Tissues
- Placenta/Wharton's jelly
  - Bone & Cartilage
  - Marrow & Bl. Cells
  - Nerves and Neurons
  - Muscle & Tendon

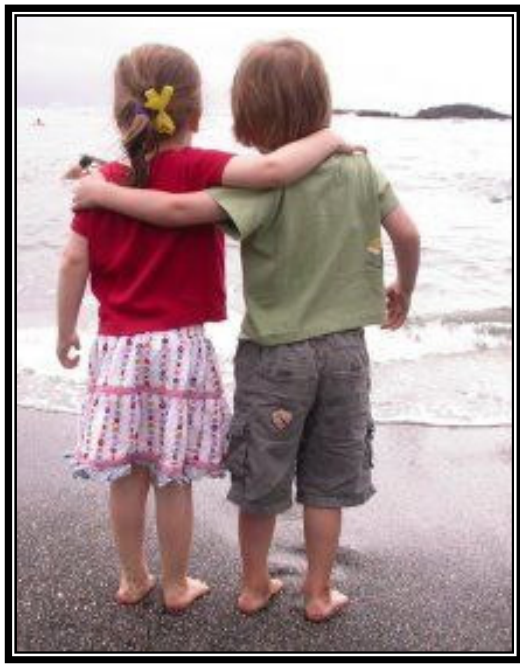
[Representative incomplete list]

Chemotaxis of Stem Cells homing in to damaged tissue only



B. HLA-DR positive mononuclear cells (green) are located within a scaffold of GFAP positive astrocytes (red) in the area of the hypoxic-ischemic lesion. C. Non-lesioned parts of the brain are devoid of human cells. *Meyer et al. Pediatr Res. 2006 Feb;59(2):244-9*

Action of Stem Cells in Brain



- Stem Cells support existing injured neurons by attaching to them. This type of “cell fusion” may be more efficient than creating new neurons in cases where neurons may have hundreds of synapses already established.
- Help balance the immune system and autoimmune disorders.
- Adult stem cells release Vascular Endothelial Growth Factor (VEGF) and Nerve Growth Factor to assist growth of new neurons and nerves for repair of injured brain tissue.
- Relax the artery walls which promotes improved blood flow.

Embryonic Stem Cells

- Embryonic: **DO IT AT YOUR OWN RISK.**
  - LONG TERM safety unknown; though potency very good.
  - Source questionable plus many social/ ethical/ regulatory/ religious issues.
  - Donor to host tissue match rarely done as GVHD rarely seen but what may happen at micro level is not conclusively known;
  - Tissue matching not required unless cultured > 3 passages
  - Small but established risk of tumor formation after 4 years
- Small stock.
  - Needs repeated Culturing and often Cell Manipulation to obtain therapeutic dose.
  - In culture, after about ≥ 3 passages, Genetic Micro-Array changes noticed.
    - Long term effect unknown.
- Legally, STRICTLY, CLINICAL TRIAL PHASE II-III only. Choose this at your own risk.

Autologous Umbilical Cord Blood Stem Cells

- If used in same child, safe and effective.
- Small stock. Must be cultured to get optimum quantity. Micro-array genetic changes not yet studied fully.
- Long term viability issues. Longest stored cord blood is now 16 years and > 40% loss of viability reported so far.
- Legally, in CLINICAL TRIAL PHASE II or III in India

- Permitted in US under stringent quality controlled clinical trials

Allogenic Umbilical Cord Blood Stem Cells

- Low stock. Many rounds of cultures needed ➔ genetic micro-array changes after 2nd culture.
- HLA match recommended by regulatory authorities but rarely done except in Clinical Trials.
  - Sterility and genetic safety to be tested as it is obtained from Hospital Labor Room waste.
  - Extent / severity of in-vivo Graft Versus Host Reaction (GVHR) not established after 2nd round of culture.
  - Risk in spite of all tests, as living cells can't be sterilized & there is no 100% foolproof test to guarantee infection-free status.
  - 1st dose usually accepted well. Subsequent doses may cause reaction 2 weeks after 1st dose.
- Legally, in CLINICAL TRIAL PHASE II or III in India
- Permitted in US under stringent quality controlled clinical trials

Peripheral Blood Stem Cells

- Peripheral Blood has Stem Cells but the pool is very small.
- Their population may be enhanced by specific cell stimulants and bone marrow inducing agents, so that much more stem cells get released into peripheral blood. HBOT has a similar effect on bone marrow.
- Effect of Micro-array genetic changes after 3 passages on culture not yet studied.
- Long term safety/efficacy needs more data.
- Status of peripheral SCT uncertain.

Bone Marrow Stem Cells

- Autologous, unmanipulated bone marrow derived mononuclear cells (fair % of Stem cells) with no chemical added, is known to be effective and safe.
- Allogenic marrow stem cells to replace marrow after its destruction by Radiation / Chemotherapy in Leukemia, carries > 5 decades of safety with efficacy data.
- Marrow transfusion as above legally permitted.
- Adequate stock available. No need for culture.
- No infection, allergy, or GVHD when done with due precautions, in cases with Leukemia.
- Other uses/routes.
  - If doctor extracts in OT, separates stem cells without culturing, and injects it, then it cannot be called a drug as it is similar to Packed RBCs as used in Anemia or Platelets as used in Dengue.`
- Usage under Para 35 of Helsinki Protocol

Major Types & Action of Stem Cells

- **CD 34+** : hemopoietic stem cells
  - Can release Glial Derived Neurotrophic Factor (GDNF). GDNF can rescue neurons from a lack of oxygen and help stimulate the repair of white matter in the brain.
  - Releases Neurotrophin 3 (NT-3) (NGF) Nerve Growth Factor and Brain Derived Neurotrophic Factor (BDNF) to stimulate the growth of new neurons and nerves.

- **Mesenchymal Cells**: almost as potent as embryonic stem cells but safer.

Allogenic multiple umbilical cord derived Wharton's Jelly Stem Cells

- Enough stock. Only 1 to 2 rounds of culture needed to obtain pure stem cell line.
- Genetic micro-array changes not expected.
- HLA match rarely needed as cell markers absent.
- Sterility and genetic safety to be tested as it is obtained from Hospital Labor Room waste.
- Risk in spite of all tests, as living cells can't be sterilized & there is no 100% foolproof test to guarantee infection-free status.
- Usually well tolerated even after multiple doses.
- Legally, in CLINICAL TRIAL PHASE II or III in India
- Permitted in US under stringent quality controlled clinical trial

More details on Adult Human Mesenchymal Stem Cells

- Considered useful in repairing or replacing one tissue type; e.g.:
  - **CNS cells in CP, Stroke**
  - **Spinal Cord Injury repair**
  - **Reduce CNS inflammation in Autism Spectrum Disorder**
  - **Liver in Cirrhosis**
  - **Lung in COPD**
  - **Pancreas in Diabetes**
  - **Muscles in DMD**
  - **Muscle etc. in DM Foot**
  - **Muscle of heart in AMI**
- **Main Sources**: Wharton's Jelly, Fat and Marrow.
- May need 2 passages for desired purity and specificity.
- Effect of ≥ 3 passages on stem cell quality is uncertain.
- Lab should supply Stem Cells as per regulatory authority standards.
- Legal status of minimally manipulated MSC: **gray area**..

Prochymal®: Mesenchymal Cells

- Prochymal is a preparation of mesenchymal stem cells specially formulated for intravenous infusion.
- Prochymal is currently being evaluated in Phase III trials for steroid refractory GVHD, acute GVHD, and Crohn's disease.
- Prochymal has been granted Fast Track status by FDA for all three of these indications.
- Prochymal also obtained Orphan Drug status by FDA and the European Medicines Agency for GVHD.
- Prochymal is being studied in Phase II trials for the treatment of COPD, type 1 diabetes, and acute myocardial infarction. Additionally, the Department of Defense recently awarded Osiris a contract to develop Prochymal as a treatment for acute radiation syndrome

From website of Osiris: manufacturer

Safety

Autologous Stem Cell Transplantation by lumbar puncture:

A safety Follow-up in 870 Patients

February 4th, 2009

Johannes P.J.M de Munter, Director Research and Development

XCell-Center Cologne and Dusseldorf Germany

Title:

Autologous Stem Cell Transplantation by lumbar puncture:
A safety Follow-up in 870 Patients

Report file:

Official Safety Report XCell-Center GmbH Germany 2009: XC20091207RS

Author:

J.P.J.M. de Munter, Director Research and Development XCell-Center GmbH

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February 4th, 2009

Conclusions

Within XCell-Center, the incidence of Post Dural Puncture Headache is estimated as low as 11.9% (103 cases out of 870 patients). There were no reported side effects concerning fever, skin rashes, shock or tachycardia. Therefore, the transplantation of autologous stem cells seems to be safe and the lumbar puncture is a safe and non-invasive procedure to inject the stem cells into the intrathecal space. The Post Treatment Survey is a useful tool to monitor the safety of the procedures.

Routes of administration

- **Local**
- **Intrathecal**
- **Intramuscular or Intravenous**
- **Intraocular or Retrobulbar**
- **Intra-cerebral**
- **Intra-luminal for site specific dosing under video control in Cath Lab.**

CHOICE DEPENDS ON EXPERIENCE, SITE & TYPE OF LESION.

Some other administration choices

- **Will Target Specific routes do better in:**
  - Extensive brain lesions
  - Motor neuron disease,
  - Cardiomyopathy: Ischemic / Congenital
  - Muscular dystrophy,
  - Advanced kidney failure
  - Cirrhosis of liver
  - Diabetes Type I and II
- **Source**: Autologous or Allogenic?
  - Depends on site, severity, availability, role of genetic abnormality in the lesion, age of Patient
- **Precaution**: these are all EXPERIMENTAL.

Stem Cells

Harbinger of Hope
when used judiciously with correct technique.

Pathway to long term future tragedies
if short cuts and injudicious faulty techniques resorted to.

Only time and experience will reveal the truth.