Stem cell therapy of autoimmune disease

Alan Tyndall
Professor für Rheumatologie
Felix Platter-Spital und Unispital Basel

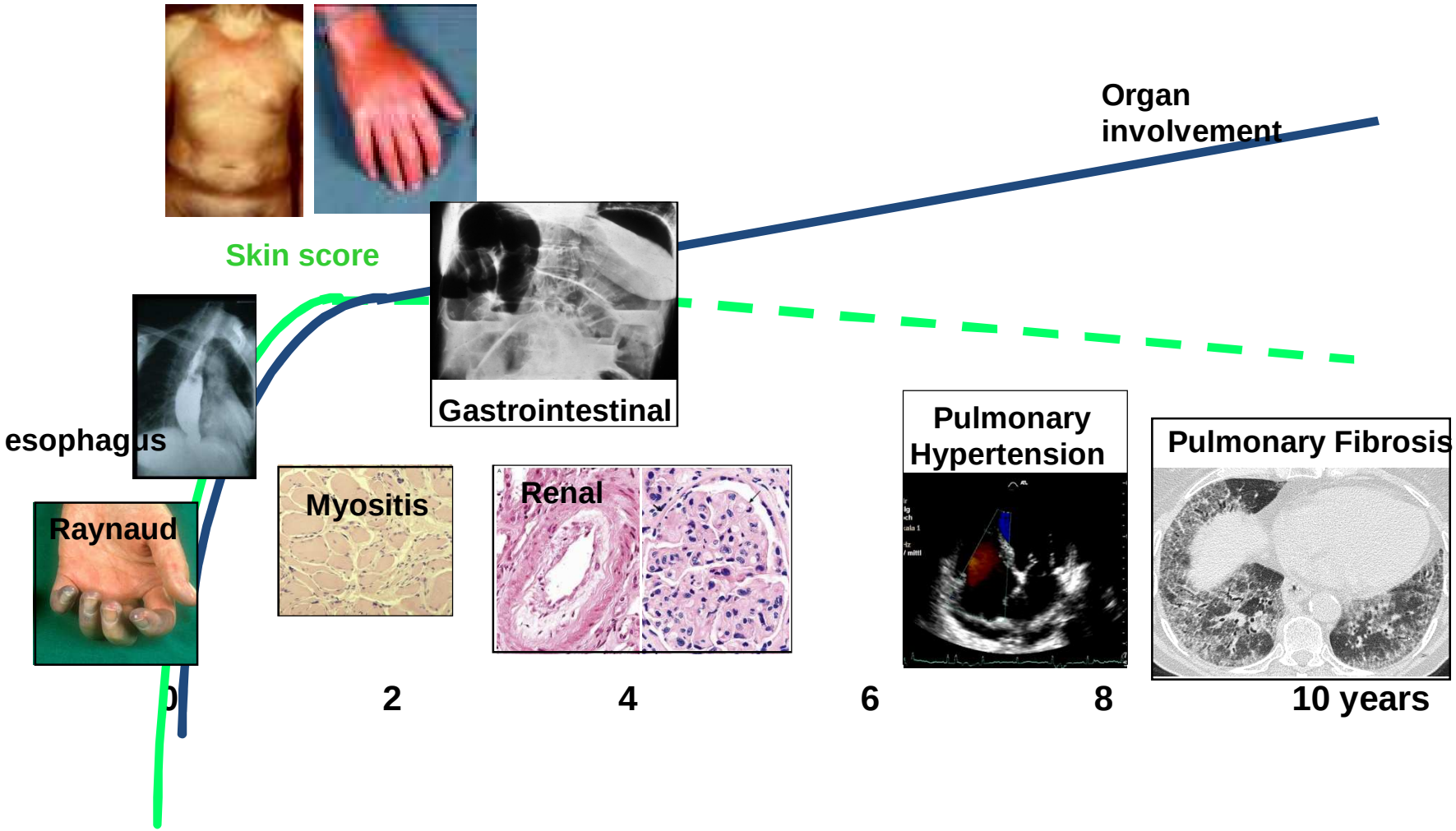
Outline of the Lecture

- Autoimmune disease
- Hematopoietic stem cell transplantation
- Mesenchymal stem cell transplantation

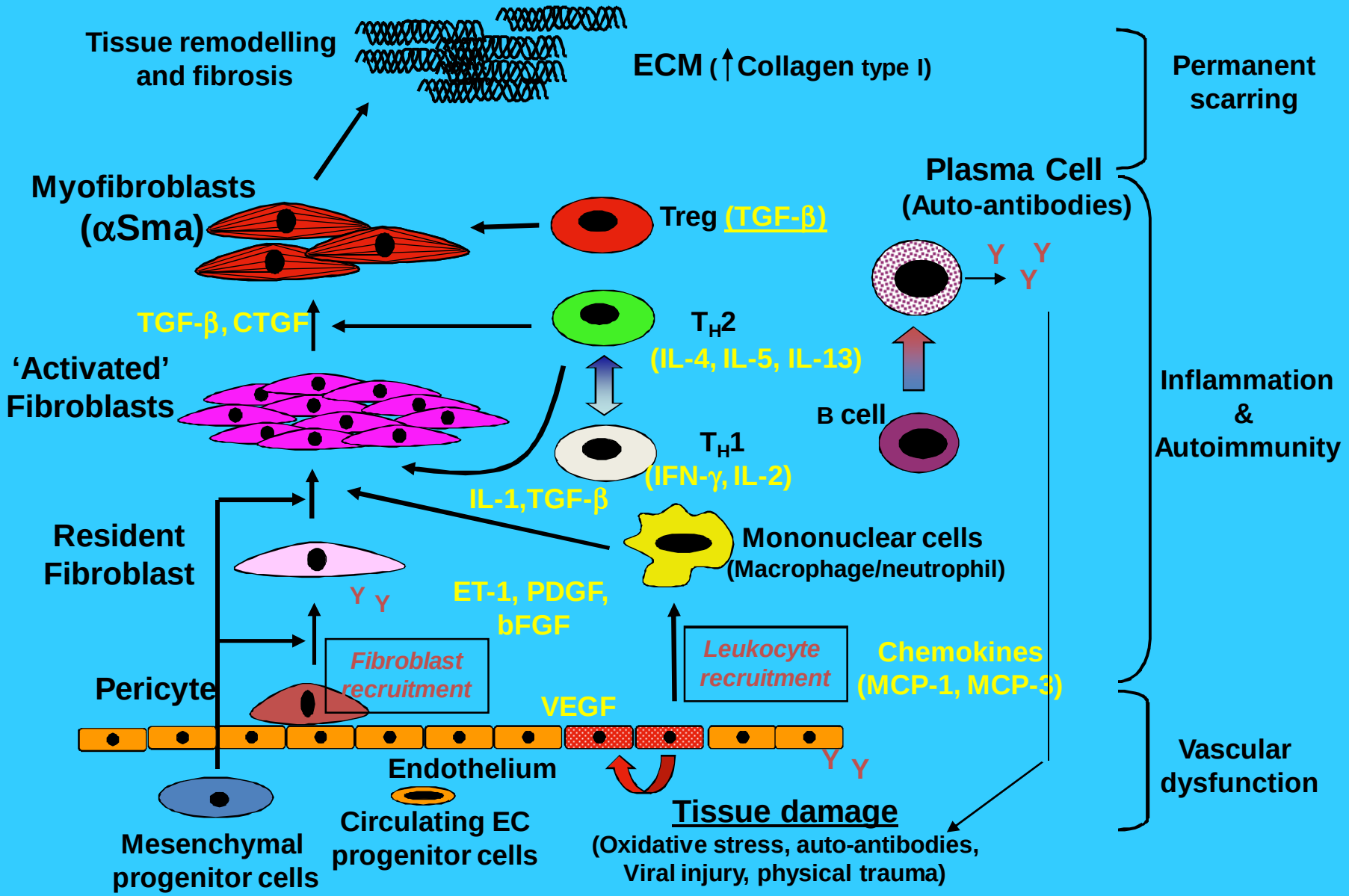
Autoimmune disease

SCLERODERMA

Systemic sclerosis evolves through phases, early vascular, inflammatory, later fibrotic..

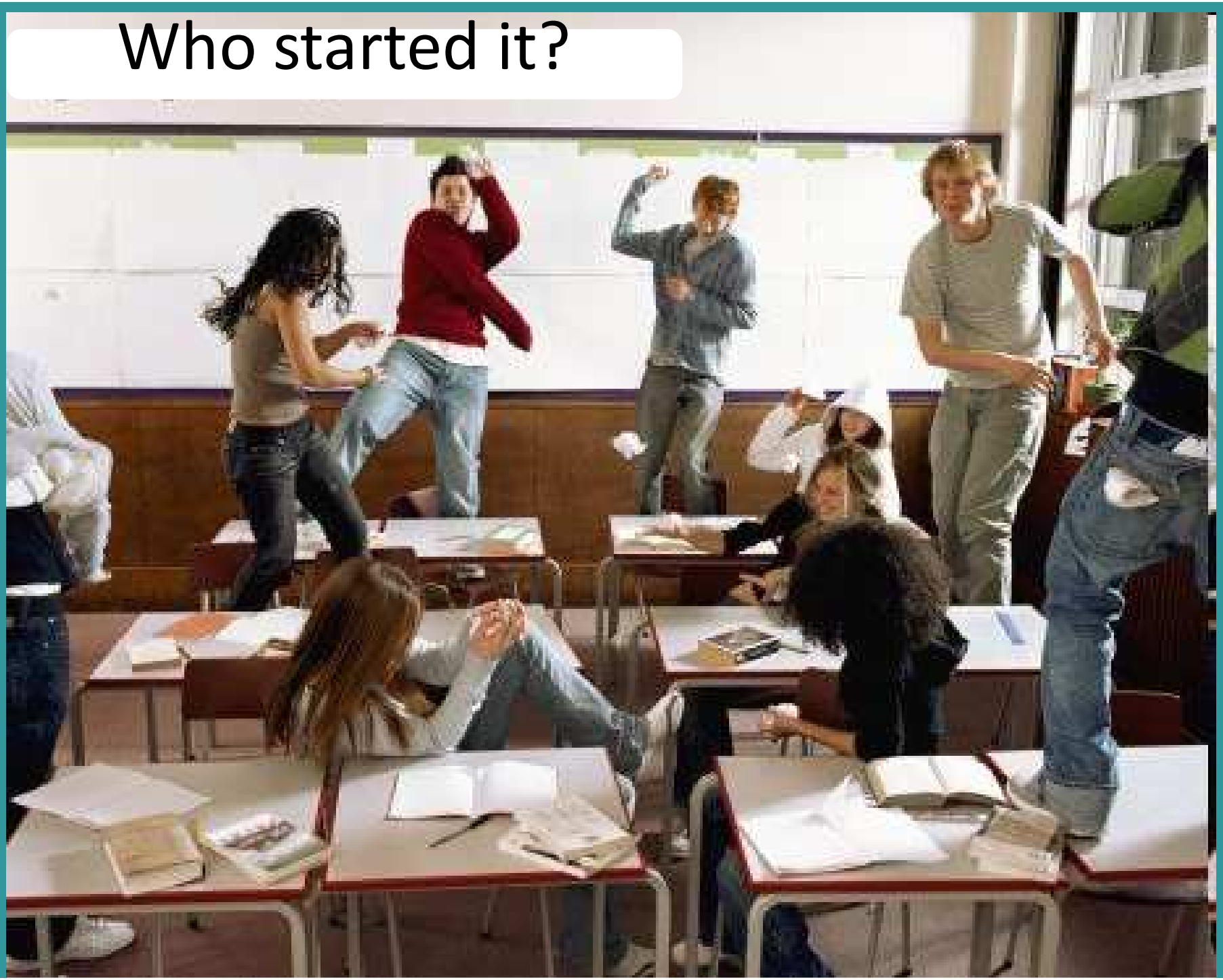


Which cell to target?

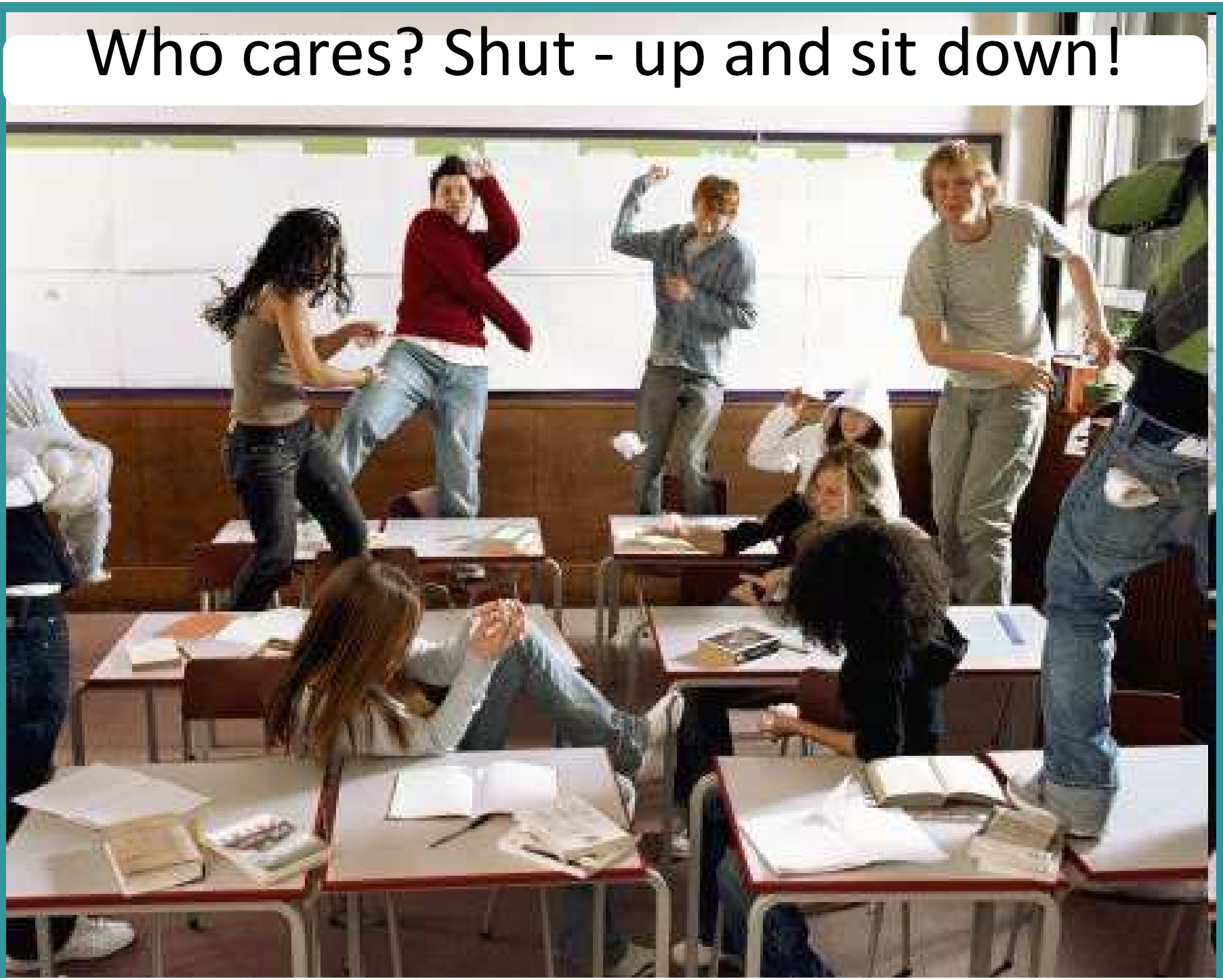


Modified from: Denton C, *et al. Nature Clin Pract Rheum* 2006.

Who started it?



Who cares? Shut - up and sit down!



Hematopoietic Stem Cells and Autoimmune Diseases

Hematopoietic stem cell transplantation for severe autoimmune disease

Concept

- Replaces ablated immune (and hematopoietic) system allowing deep immunosuppression.

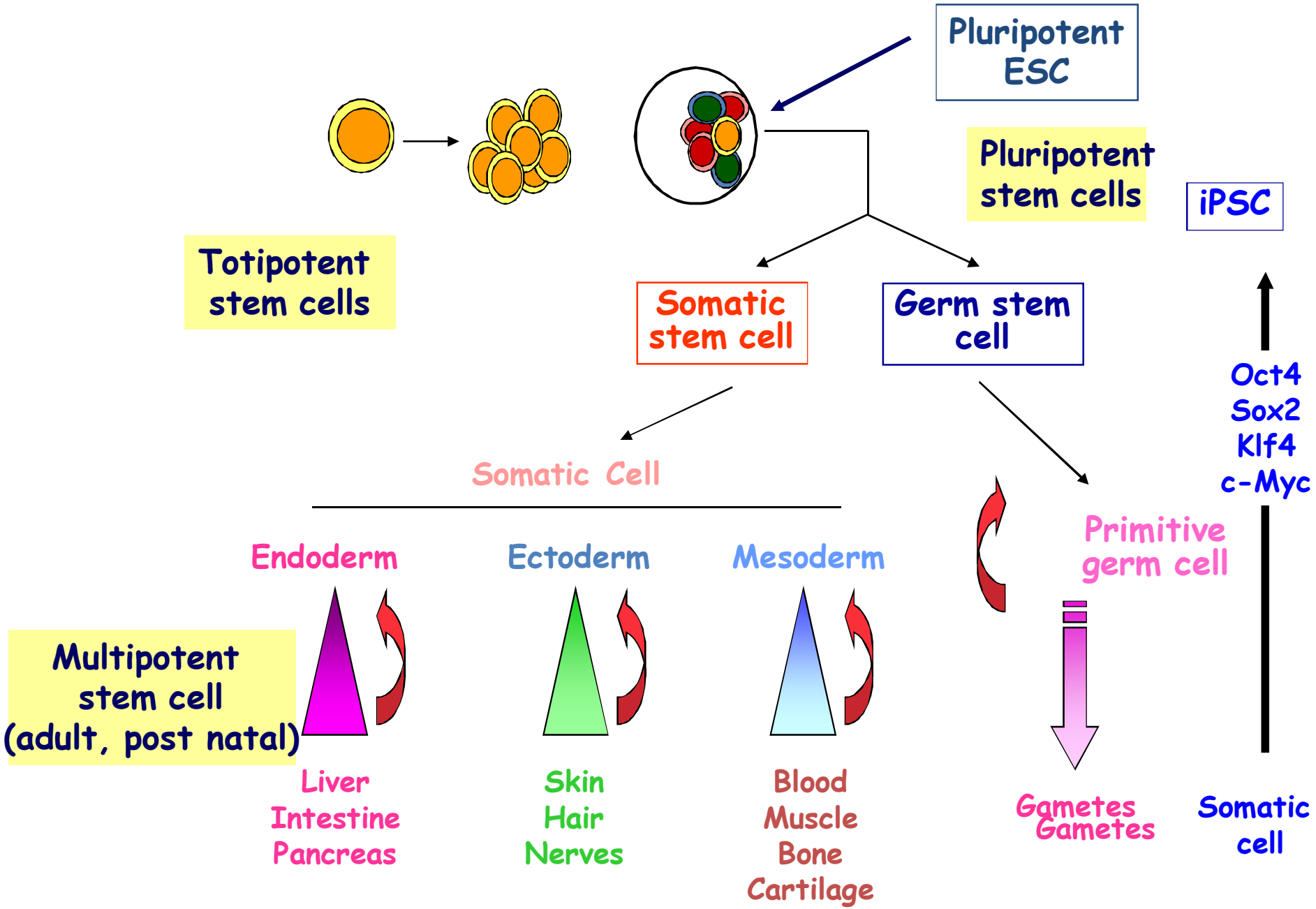
- „Resetting“ of autoaggressive immune system?

Evolution of the concept

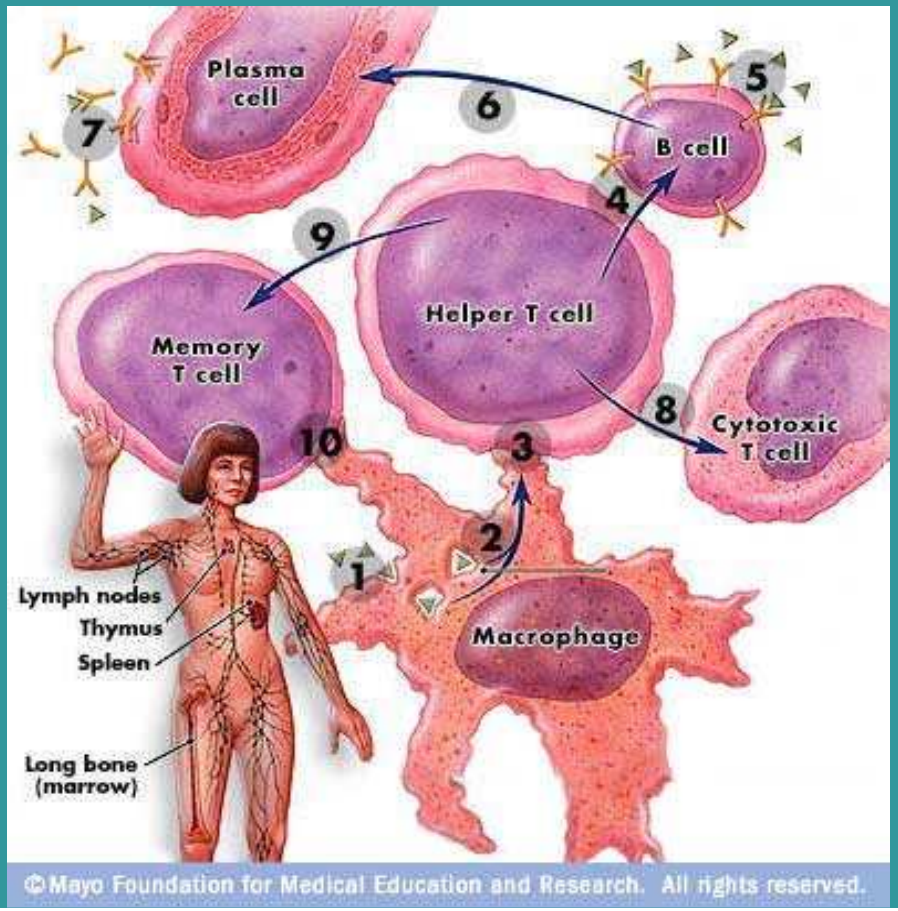
- Coincidental improvement of AD in patients undergoing transplant for other reasons.
  (Jacobs P et al, BMT 1986)

- Confirmatory animal data; allogeneic and autologous
  (Knaan-Shanzer S et al. BMT 1991

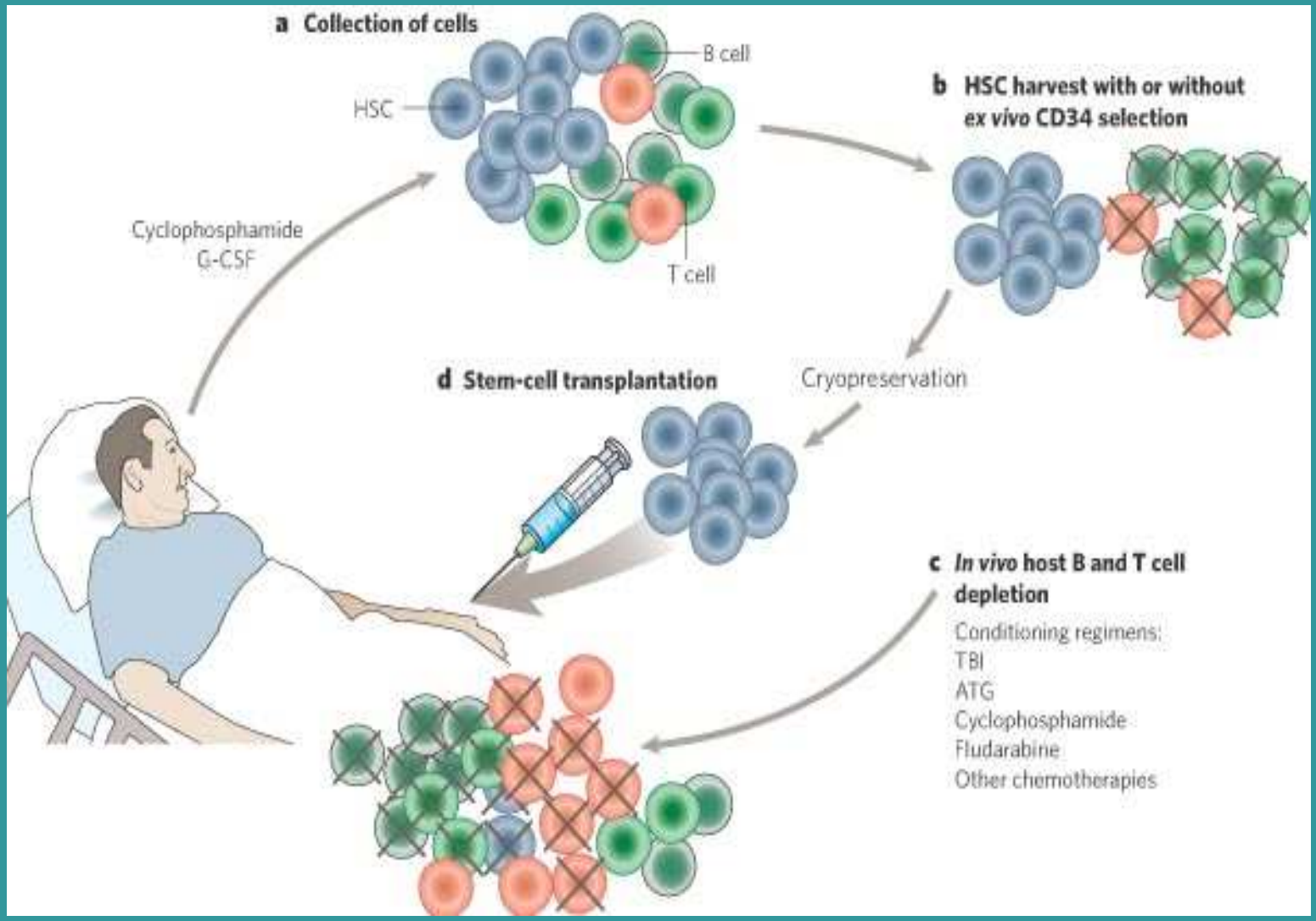

International Meeting
Haemopoietic stem cell therapy
in autoimmune diseases
Basel/Switzerland
26–28 September 1996
EBMT
eular
Alois
Fritz
➢To establish through prospective randomised clinical trials the role of HSCT in treating autoimmune disease
➢ To study immune reconstitution


Pluripotent ESC
Pluripotent stem cells
iPSC
Totipotent stem cells
Somatic stem cell
Germ stem cell
Oct4
Sox2
Klf4
c-Myc
Somatic Cell
Endoderm
Ectoderm
Mesoderm
Primitive germ cell
Multipotent stem cell (adult, post natal)
Liver
Intestine
Pancreas
Skin
Hair
Nerves
Blood
Muscle
Bone
Cartilage
Gametes
Gametes
Somatic cell

Resetting the Immune system



How is it done?



(Sykes et al , Nature Med 200

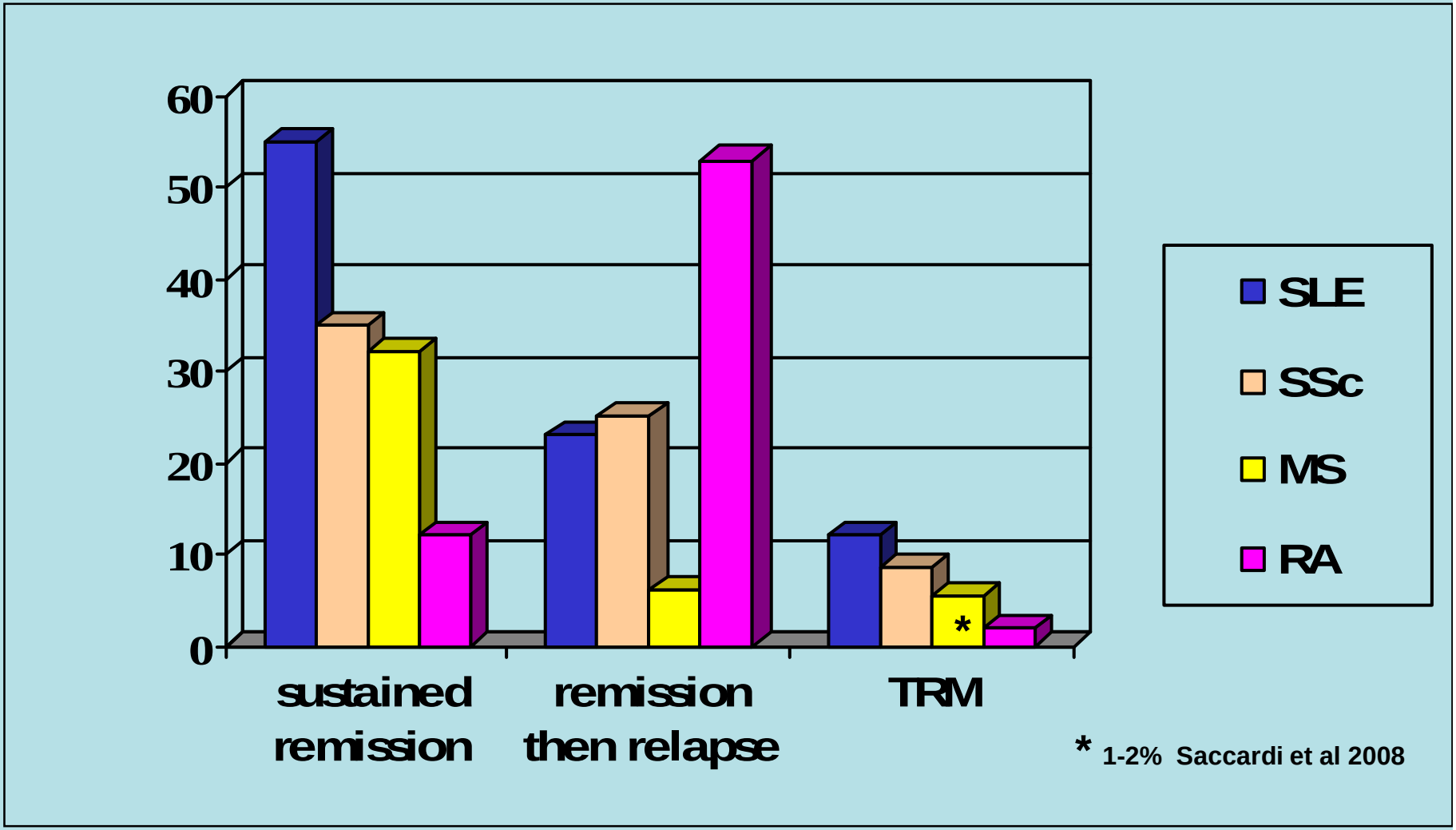
Number of HSCT: 1357- EBMT Registry

September 2011*

*All transplants not yet registered for 2011

MULTIPLE SCLEROSIS	**476**
CONNECTIVE TISSUE D.	**427**
SSc	283
SLE	102
PM-DM	18
Sjogren	3
Antiphosph. syndrome	3
Other/Unknown	15
ARTHRITIS	**163**
Rheumatoid arthritis	80
Juvenile chronic arthritis :	
- Systemic JIA	49
- Other JIA	18
- Polyarticular JIA	10
Psoriatic arthritis	3
Other	4
INFLAMMATORY BOWEL	**79**
Crohn's disease	68
Ulcerative colitis	4
Other	7
HAEMATOLOGICAL	**80**
ITP	26
Evans'	19
AIHA	18
Other	17
VASCULITIS	**41**
Wegener's	10
Behcet's	8
Takayasu	2
Microscopic poly. nodosa	3
Classical poly. nodosa	1
Churg-Strauss	2
Other/Unknown	14
OTHER NEUROLOGICAL	**38**
Myasthenia gravis	5
Other/Unknown	33
INSULIN DEPENDENT DIABETES	**10**
OTHER/UNKNOWN/MISSING	***29***

The European Group for Blood and Marrow Transplantation



Tyndall A, van Laar J. Rheumatology 2006

Systemic Sclerosis (Scleroderma)

ASTIStrial

•Autologous•Stemcell•Transplantation•
•International•Scleroderma•Trial•

patients with severe systemic sclerosis

Immunoablation + SCT =

1. **Mobilisation (CYC 2x2 g/m^2,G-CSF 10 mg/kg)**
2. **Leukapheresis/CD34-selection**
3. **Conditioning (CYC 200 mg/kg, rbATG 7.5 mg/kg)**
5. **Reinfusion CD34+ cells**

Control treatment =

12x monthly
i.v. pulse CYC 750 mg/m^2

PI: J van Laar, Newcastle
Co- investigators: D Farge, Paris
A Tyndall, Basel
Study coordinator: S Hales, Newcastle

ASTIS trial March 2001 - June 2009:
156 patients randomized in 25 centers - COMPLETED
No unexpected toxicity (independent DSMB)

Leeds (3)
Amsterdam (7)
Leiden (24)
Nijmegen (10)
Leuven (1)
Lille (1)
Paris* (24)
Strasbourg (4)
Bordeaux (1)
Clerm Ferr (1)
Grenoble (2)
Toulouse (2)
Marseille (1)

Herne-Bochum (4)
Frankfurt (1)
Tübingen (2)
Würzburg (1)
Freiburg (1)
Basel-Bern -Geneva(5
Vienna (3)
Ferrara (1)
Florence (10)
Thessaloniki

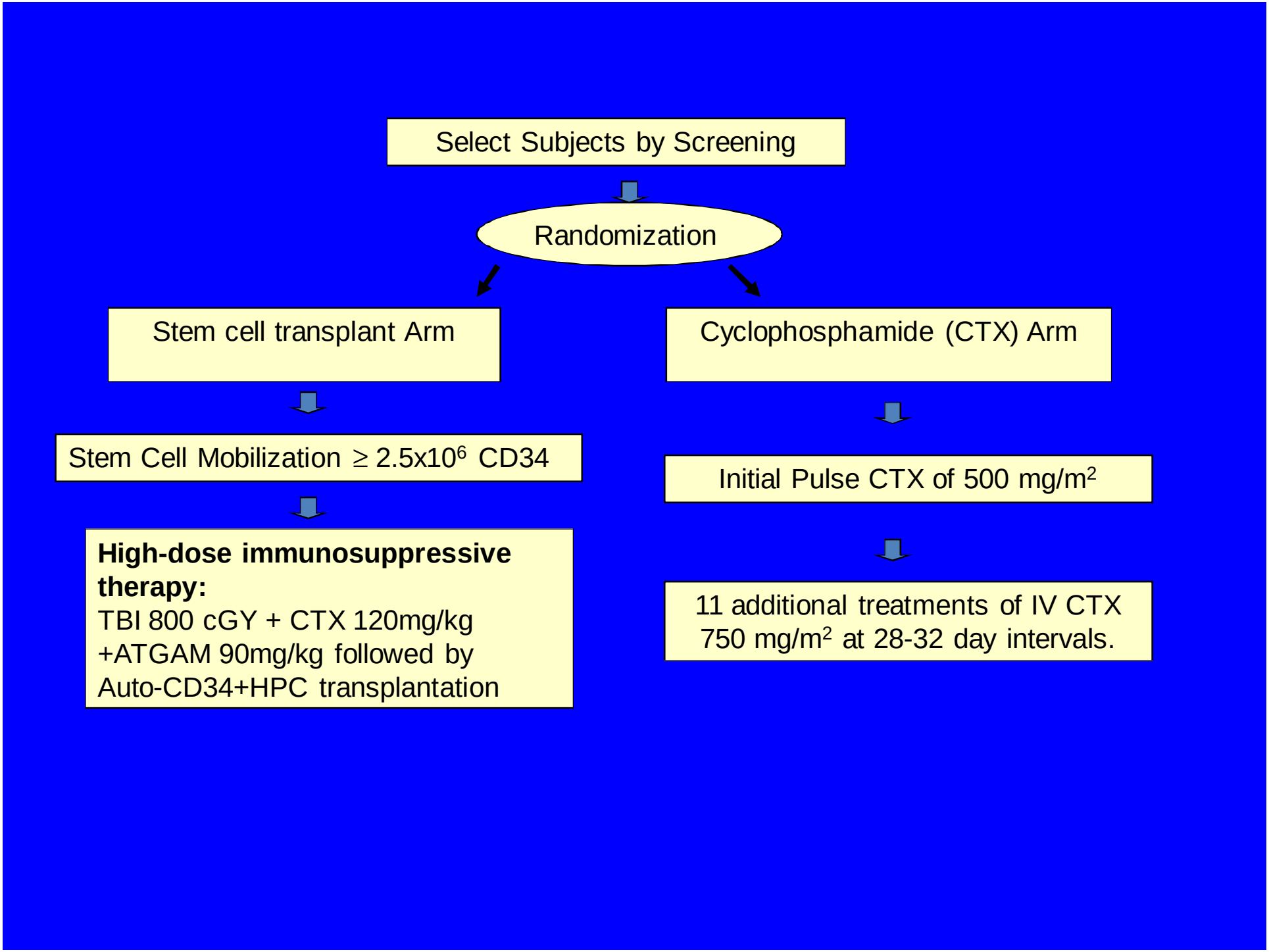
** includes Martignique, Poitiers*

Montreal (1

Scleroderma: Cyclophosphamide Or Transplantation

Sponsored by:

National Institutes of Health (NIH) through its Division of Allergy, Immunology and Transplantation (DAIT) in the National Institute of Allergy and Infectious Diseases (NIAID)


Select Subjects by Screening
Randomization
Stem cell transplant Arm
Cyclophosphamide (CTX) Arm
Stem Cell Mobilization ≥ 2.5x10^6 CD34
Initial Pulse CTX of 500 mg/m^2
High-dose immunosuppressive therapy:
TBI 800 cGY + CTX 120mg/kg +ATGAM 90mg/kg followed by Auto-CD34+HPC transplantation
11 additional treatments of IV CTX 750 mg/m^2 at 28-32 day intervals.

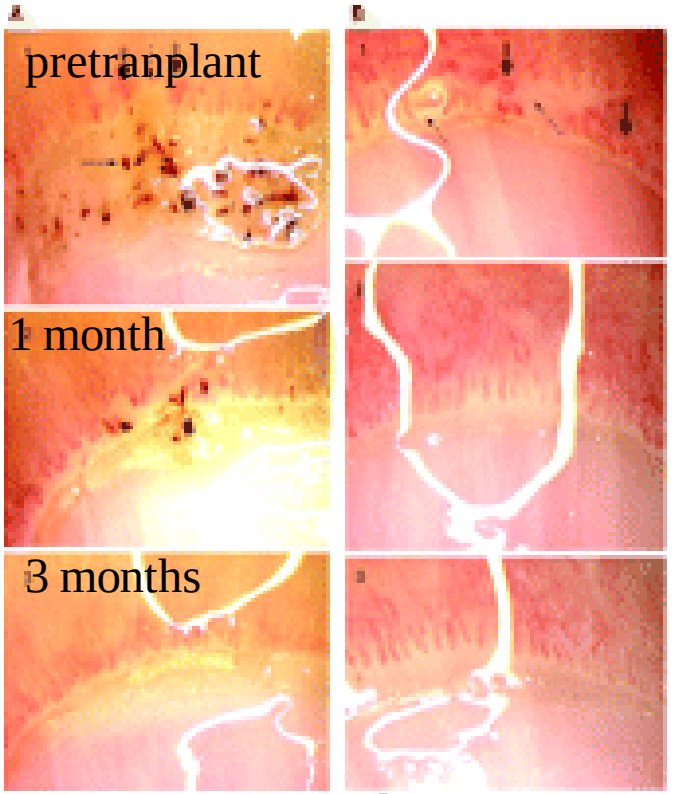
ASSIST

American Scleroderma Stem Cell versus Immunosuppression Trial

- 19 pts : 10 transplanted (CY 200mg/kg + ATG and methyl pred 5 g)
  9 controls (monthly CY 1g/m2 x6)
- 1° end point: mRSS and /or lung improved at 12 months
  - achieved
- Toxicity : no deaths
- Relapse : 2 after 12 months

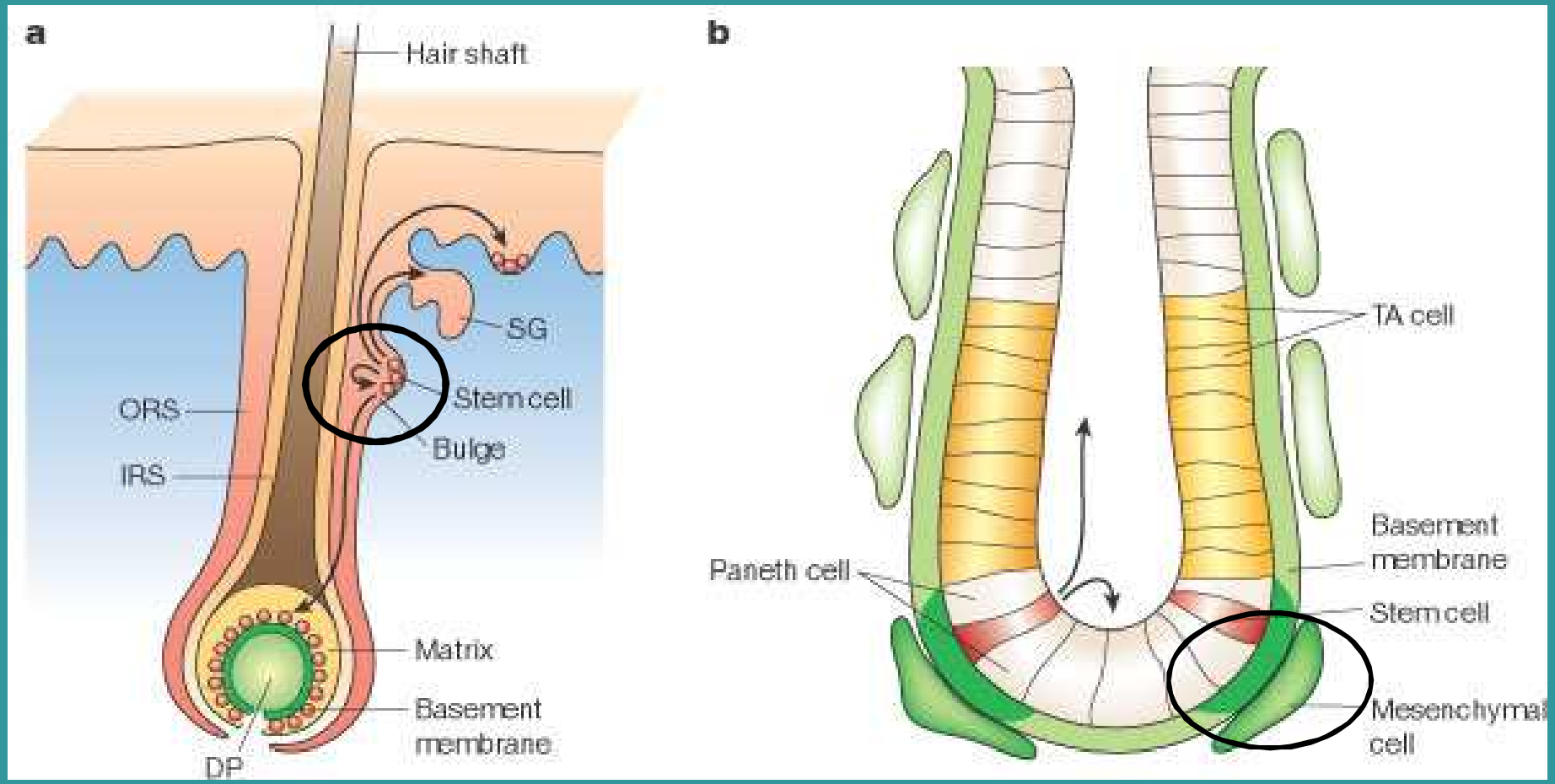
(Burt et al , Lancet 2011)

Pre transplant . Thickened , shiny and hyperpigmented skin. Flexion contracture of the elbows.
Transplant in 2007. Normal skin texture and pigmentation. No joint contractures (patient of Indian origin)



Two patients showing normalisation of microvasculature 3 months after transplantation

Stem cell niche in the skin and gut



Mesenchymal Stem Cells and Autoimmune Diseases

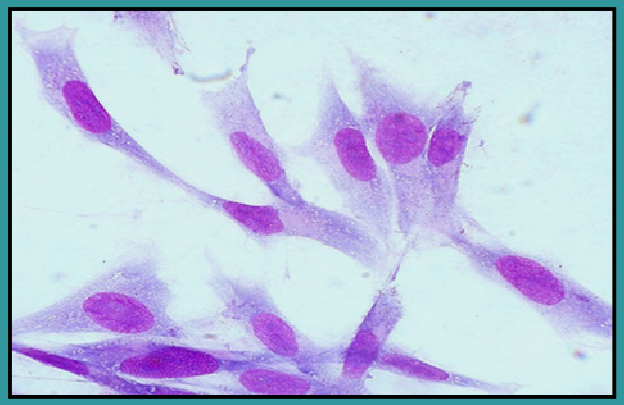
Mesenchymal stem cell transplantation for severe autoimmune disease

Concept

- Homing to inflammed tissue then antiinflammatory effect

- Repair of damaged tissue??

Definition of a Multipotent Mesenchymal Stromal Cell (MSC)



Adherent (CFU-F)

Fibroblast- like morphology

Positive adhesion molecules, CD73, CD 90, CD105

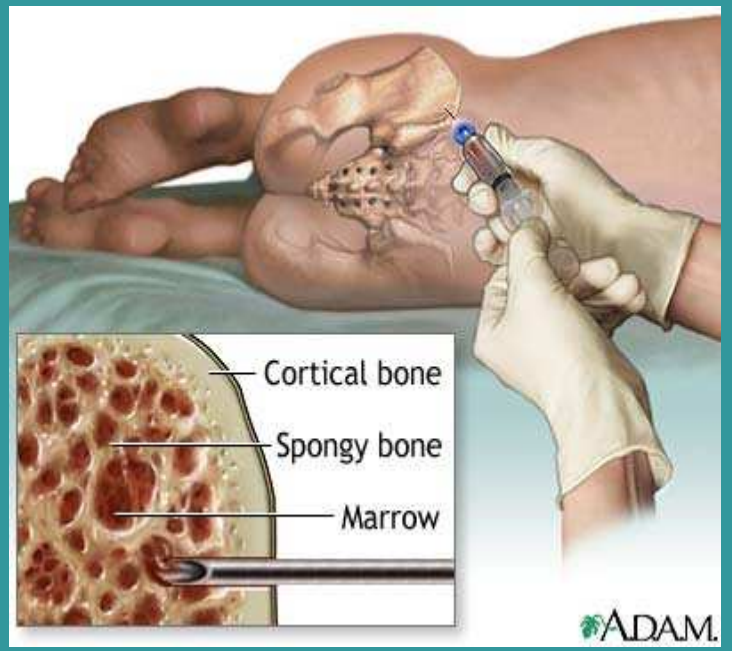
Negative hematopoietic cell markers CD14 or 11a, CD 34 and CD 45

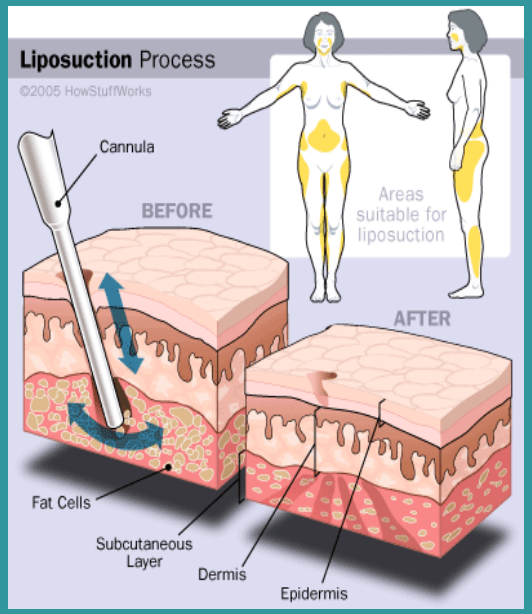
CD 19, HLA-class II

Tripotential for differentiation into: osteo. adipo and chondrogenic.
(Horwitz et al ,Cytotherapy, 2006)

Sources of MSC

- Bone marrow
- Fat
- Umbilical cord
- Placental membranes
- Amniotic fluid epithelial
- Synovial membrane
- teeth
- ?





Immunomodulation and tissue protection: *in-vivo* models

- Skin graft
- EAE (multiple sclerosis)
- Arthritis
- GvHD
- Ischemia: renal, cerebral, myocardial, limb
- Fibrosis: lung, hepatic
- Radiation injury

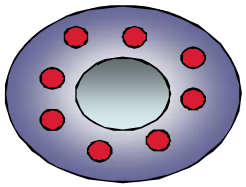
Tissue injury : *in-vivo* models

- Human MSC injected one day after transient global ischemic in mouse hypocampus.
- Improved function and reduced neuronal cell death.
- Persisted < 7 days (also in SCID variant).
- Did not proliferate.
- Ischemia upregulated 586 mouse genes.
- hMSC down regulated > 10% of these (inflammation/ immune response).
- In mouse microglia/ macrophages increased protein :
  Ym1 (neuroprotective, IGF-1 (cell survival), galectin-3, MHC II, Th2 cytokines
- In hMSC , 170 genes upregulated, 54 downregulated. *(Ohtaki H et al PNAS 2008)*

MSC impact on effector functions of immunocompetent cells

natural killer cells

•Inhibition of proliferation
•Partial inhibition of cytolysis
•NK cells can lyse MSC

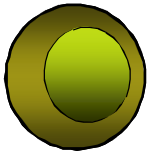


macrophage

•Reprogrammed to IL-10 secreting via MSC derived PGE2
•Macrophage secreted TNFα (plus MSC TLR4activation) drives PGE2 secretion.

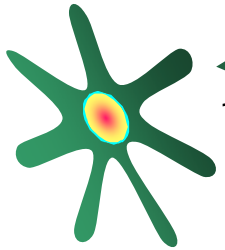
T cells

•Inhibition of proliferation
•Inhibition of cytokine production
•Impairment of their encephalitogenic potential
•Increased Tregs
•Enhancement of MSC immunosuppressive activity by T cell derived cytokines

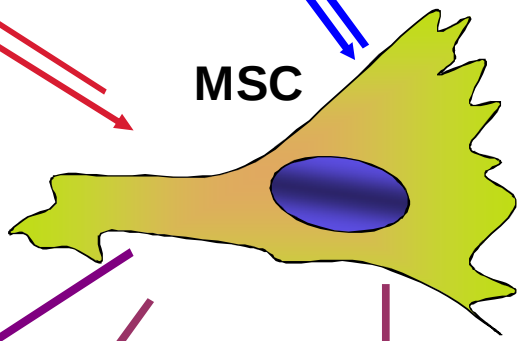


dendritic cells

•Inhibition of activation
•Inhibition of maturation

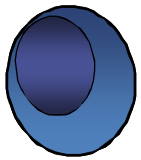


MSC



B cells

•Inhibition of proliferation
•Inhibition of differentiation to plasmacells
•Impairment of chemotaxis
•Activated B cells enhance the suppressive effect of MSC mediated by soluble factors



monocytes

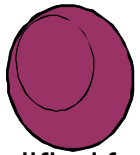
•Inhibition of maturation

Neutrophils

•Protected from apoptosis
•Decreased vessel egress (via macrophage)

T reg

•Recruit
•Expand
•Maintain



(modified from Uccelli A, Moretta L, Pistoia V, Eur J Immunol,

Immunomodulation: clinical

- > 1,000 patients have received MSC therapeutically

  (Martin I, Tissue Engineering Part A 2011)

- Around 120 running clinical trials

- Early termination of Crohns (no difference in one treatment arm and placebo) and failed primary end point acute GvHD (too stingent?)

  (announced, not published)

Immunomodulation: clinical

Disease	No.	MSC product	Route	Outcome	reference
MS	10	Allo bone marrow	Intrathecal	Mixed	Mohyeddin, 2007
SSc	1	Allo bone marrow	IVI	Improved	Christopeit, 2008
MS	1	Allo umbilical cord	IVI	Improved	Liang, 2009
MS	3	allo / auto fat	Mixed IVI / intrathecal	Improved clinic (not MRI)	Riordan, 2009
MS	10	Auto bone marrow	intrathecal	Some improved (not MRI)	Yamout, 2010
Crohns fist	14	Autologous fat	Intra fistula	71%closure	Garcia 2009
Crohns fistulae	10	Autologous fat	Intra fistula	100% closure (30% partial)	Ciccocioppo,2011
SSc DU	2	Autol blood /bm MNC	Local	Improved	Nevskaya, 2009
SLE nephritis	15	Allo bone marrow	IVI	Reduced SLEDAI /proteinuria	Liang, 2010
SLE nephritis	16	Allo umbilical cord	IVI	Reduced SLEDAI / proteinuria	Sun, 2010
SLE	2	Auto bone marrow	IVI	no change	Carrion 2010,
SLE alv. bleed	1	Allo umbilical cord	IVI	Improved	Liang, 2010
Crohns	10	Auto bone marrow	IVI	some Improved	Duijvestein, 2010
MS	15	Auto bone marrow	Intrathecal + IVI (5)	some stabilised	Karussis, 2010
Type 2 DM	10	Allo placental	IVI x 3	All improved (3 months)	Jiang , 2011

Summary

- MSC antiproliferative *in vitro*
- Home to „distressed“ tissue
- Probably act through multifactorial paracrine mechanisms.
- Acute toxicity appears low – long term safety , especially tumour surveillance required.
- Correct patient selection critical.

Ongoing activities

•Standardisation of:

definition and expansion of MSCs
patient selection
outcome measurement

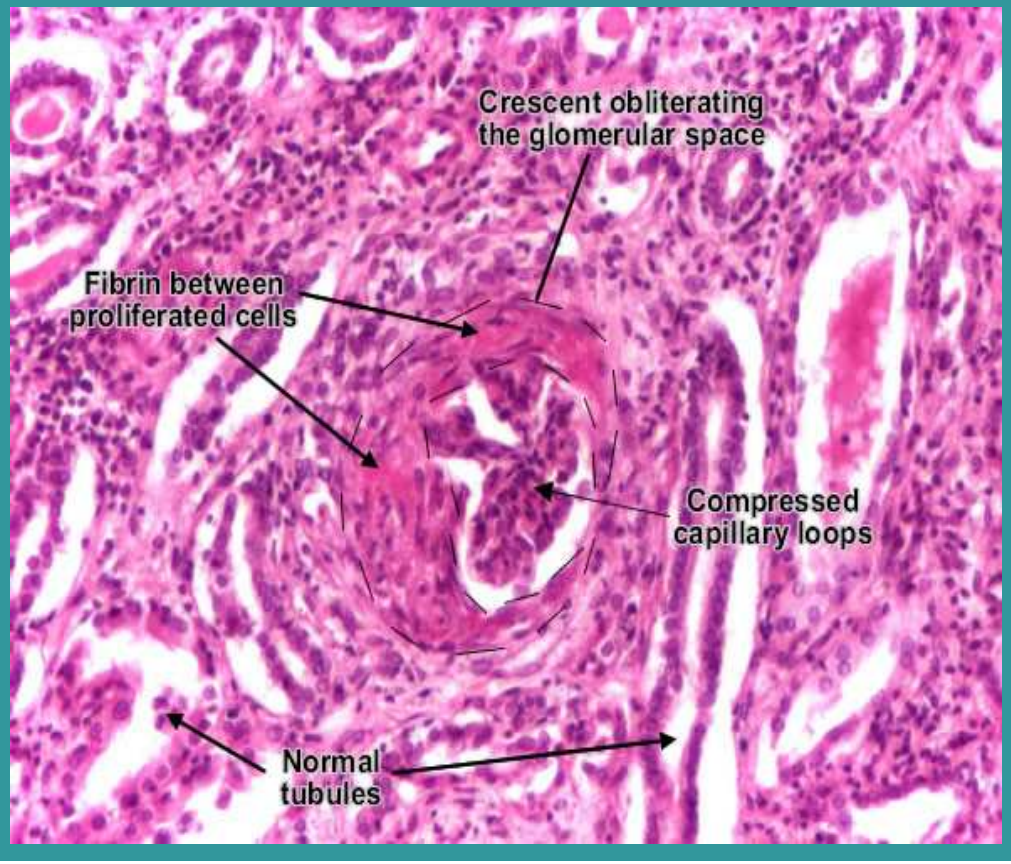
- - EBMT (developmental group)
  - EULAR (stromal cell group – renal lupus)
  - Multiple Sclerosis (Consortium of Multiple Sclerosis Centres)
  - cardiology , tissue engineering, nephrology, diabetology etc

SLEMS (SLE Mesenchymal Stemcell)Study

PI: David Jayne, Cambridge
Alan Tyndall, Basel
Frederic Houssiau, Brussels

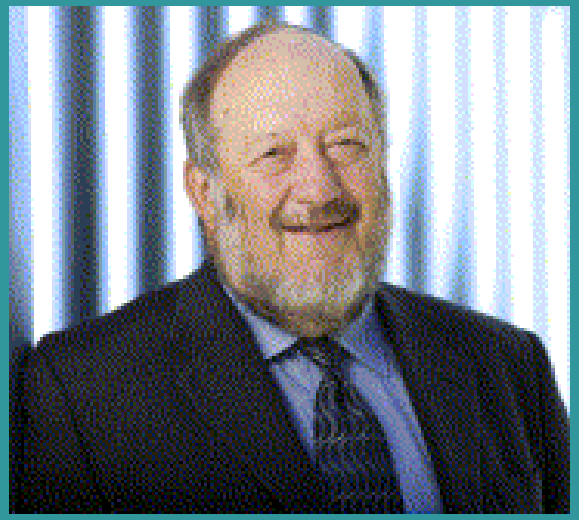
LUPUS NEPHRITIS

Diffuse prolif .GN with crescents



1. Standardised definitions
2. Accessible tissue
3. Rapid clinical readout
4. Validated biomarkers
5. Need for new therapy
6. Mixed pathology-inflammation
   - vascular
   - fibrosis

The ISSCR: who are we and where are we going?



Irving Weissman
President, ISSCR
Director, Stanford Institute of Stem Cell Biology and Regenerative Medicine

The Sad Practice of Unapproved Stem Cell "Therapies"
Every week, I am asked whether a family should take their loved one with an incurable disease to clinics that promise cures with supposed stem cell therapies. Usually, the costs for such therapies are in the tens of thousands of dollars. When I go to the websites of the providers, usually very slick, the therapies are often transplantation of tissue or umbilical cord stem cells for a variety of nonhematopoietic or nonmesenchymal disorders (claiming transdifferentiation), or even claim to be ESC therapies. I tell those that ask that there is no scientific basis for such transdifferentiation to date and no approved therapies using ESCs.

Cell Stem Cell. 2009 Aug 7;5(2):151-3.

Thanks to:

J van Laar, Newcastle

D Farge, Paris

A Gratwohl, Basel

C Bocelli-Tyndall, Basel

G Spagnoli, Basel

I Martin, Basel

F Houssiau, Brussels

A Uccelli, Genua

David Jayne, Cambridge

EULAR, EBMT, Horton Foundation