

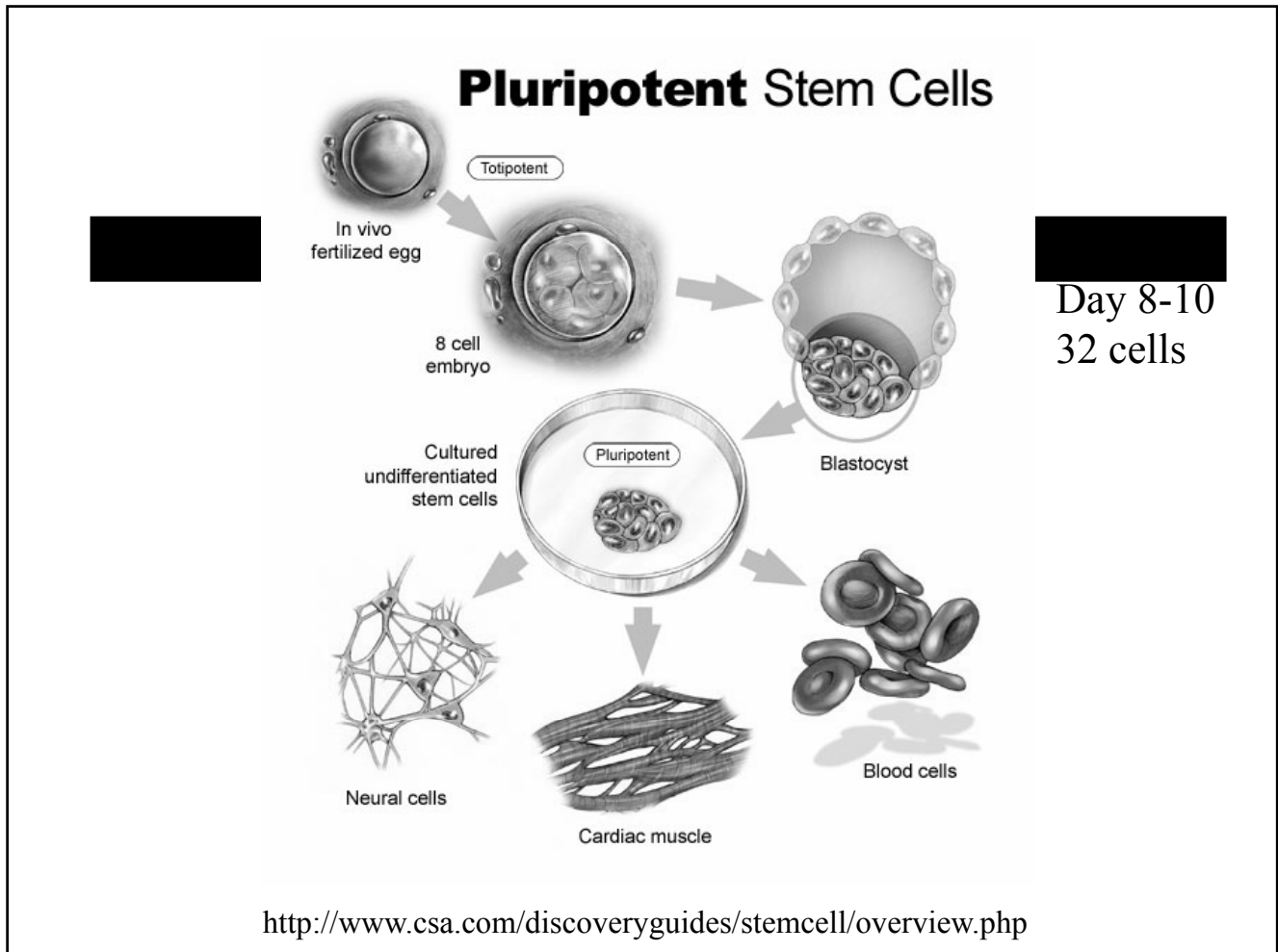
Hematopoietic Stem Cell Transplantation in MS



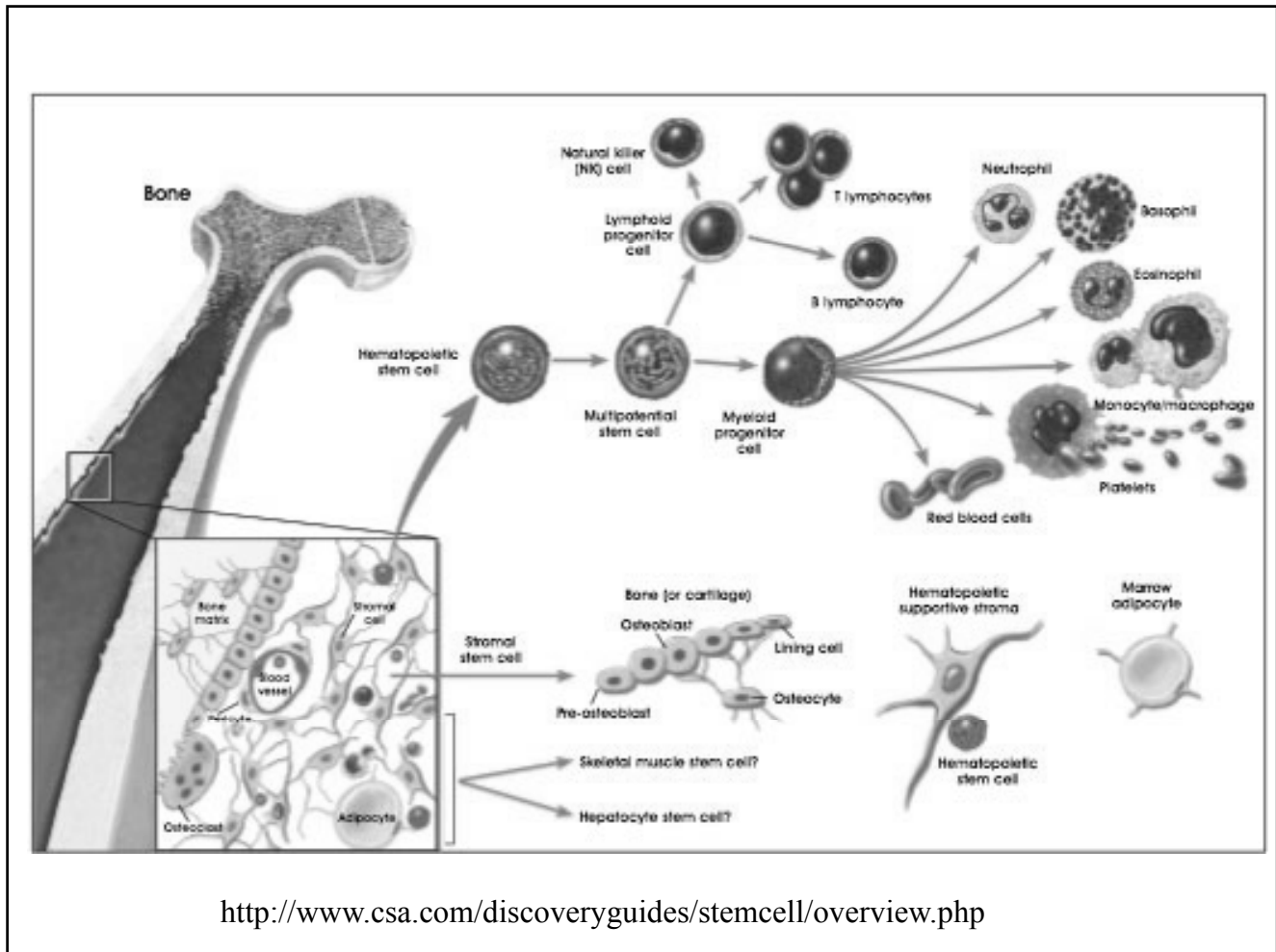
James Bowen, MD
MS Center at Evergreen
Kirkland, WA



Stem Cells



Hematopoietic Stem Cell Transplantation in Multiple Sclerosis
James Bowen, MD





Immunology of
immunosuppression

Immunology of immunosuppressive treatments



- Short-term immediate effects
 - RBC, leukocytes, platelets recover in 14-21 days
 - Lymphocyte counts recover within 3 months
- Long-term changes in lymphocyte subtypes

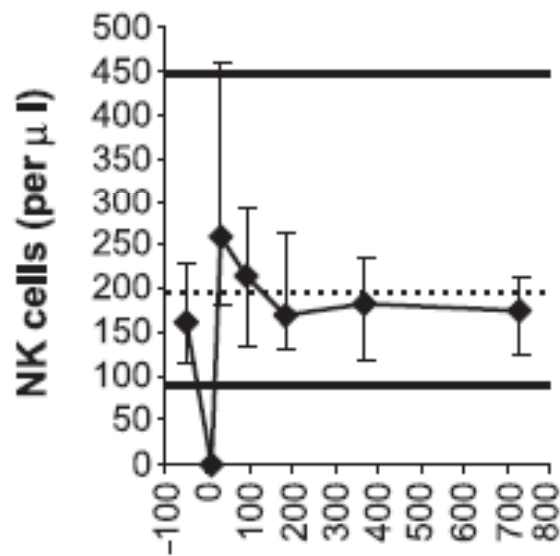
Mackall CL Stem Cells 2000;18:10-18

Effects of Immunosuppression

- NK cells normal immediately
- Total B cells normal within 1-3 months (often with overshoot)
- CD8+ 3-6 months (often with overshoot)
 - This is mostly the CD8+CD28- subset (suppressor cells). These recover over 1 year.
- CD4+ prolonged loss (enhanced with age)

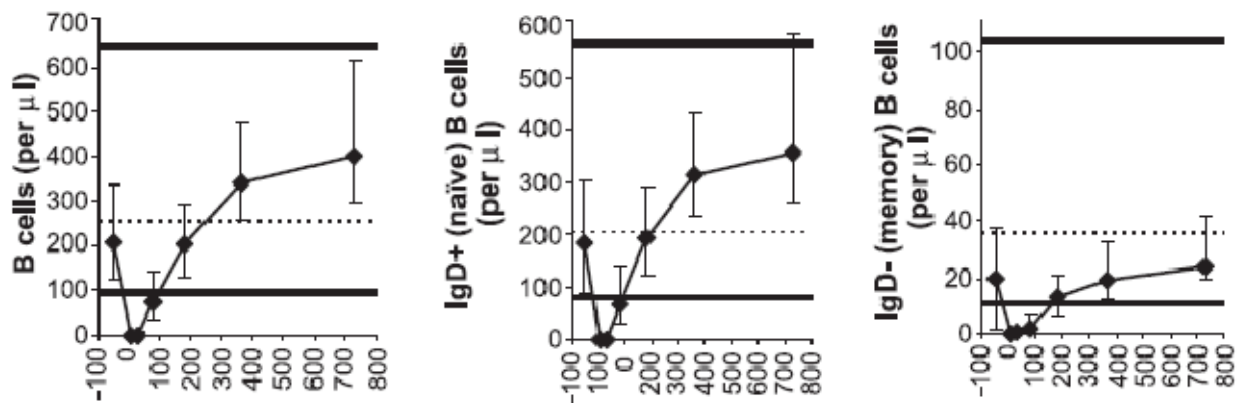
Mackall CL Stem Cells 2000;18:10-18

NK Cells



Storek J. Clin Immunol 2004;113:285-98

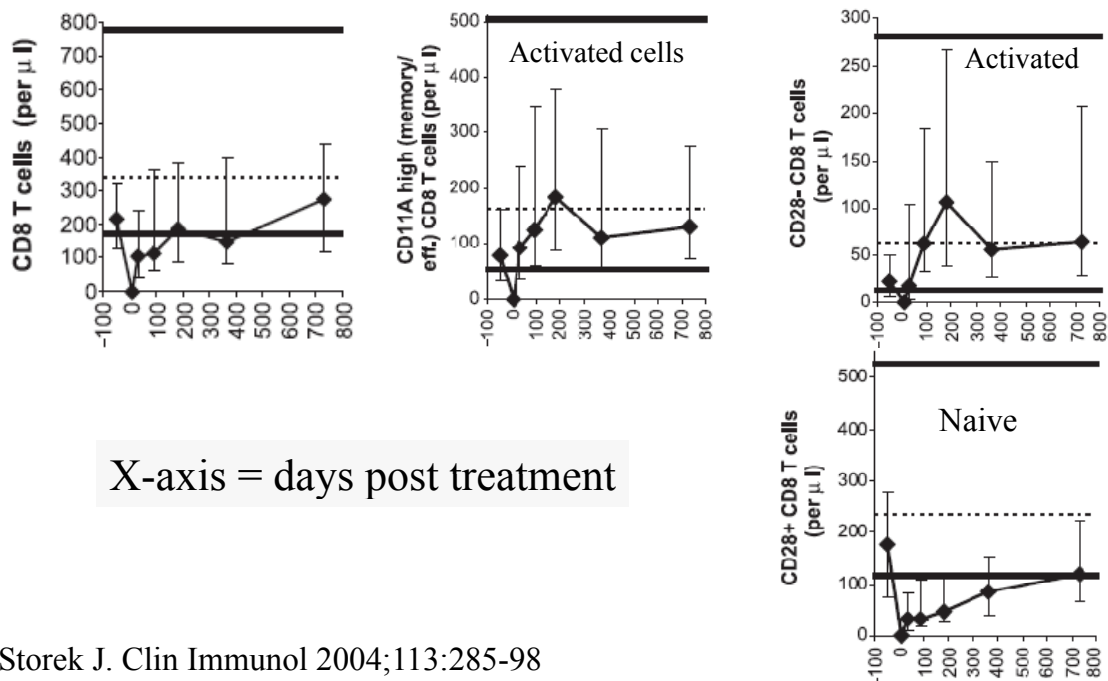
B cells



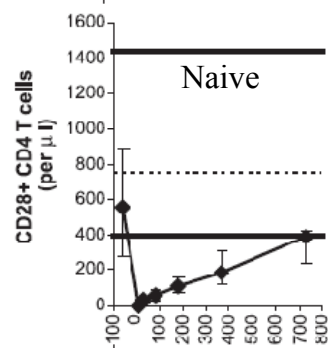
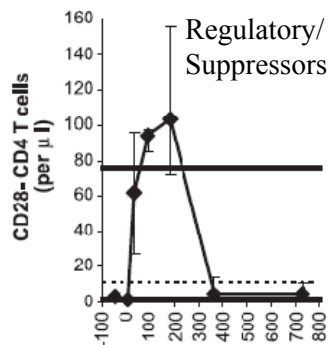
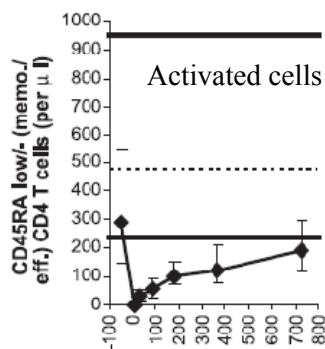
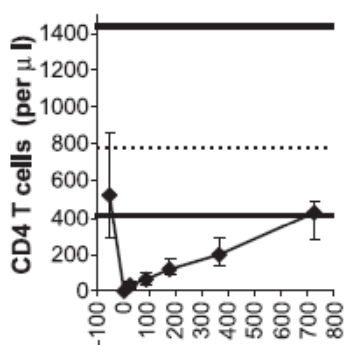
X axis = days post treatment

Storek J. Clin Immunol 2004;113:285-98

CD8+ Cells



CD4+ Cells



X-axis = days post treatment

Storek J. Clin Immunol 2004;113:285-98

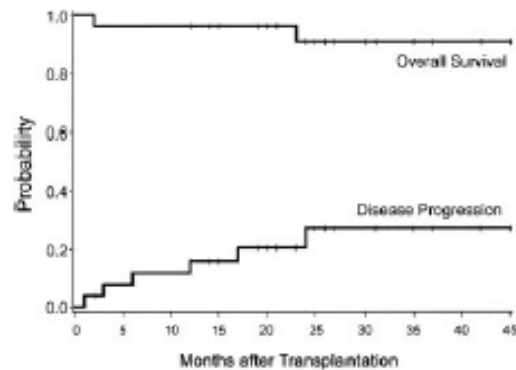
Immunosuppressive Treatments

- Mitoxantrone
- Cyclophosphamide
- Methotrexate
- Azathioprine
- Mycophenolate
- Rituxumab

National Collaborative Study of SCT for Autoimmune Diseases

26 pts
EDSS 5-8 mean = 7
8 PPMS, 17 SPMS, 1 RRMS

At 2 yrs
6 worse by ≥ 1 point
3 worse by $\frac{1}{2}$ point
2 better by $\frac{1}{2}$ point
14 stable



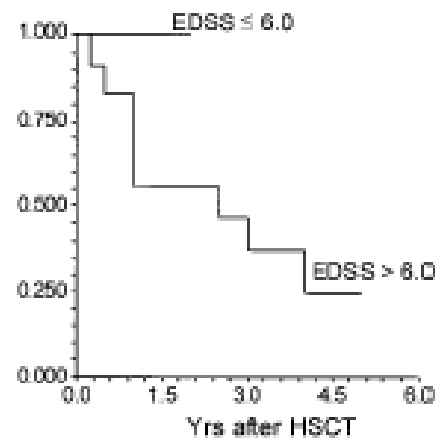
Nash, RA Blood. 2003;102:2364

Northwestern University

21 patients
EDSS 3.5-8 mean = 6.3
14 SPMS, 1 RRMS, 6 PRMS

If EDSS \leq 6: 6 worse by $\frac{1}{2}$ point
1 better by 2.5 points
2 no change

If EDSS $>$ 6: 8 worse by 1 point
2 worse by $\frac{1}{2}$ point
2 no change



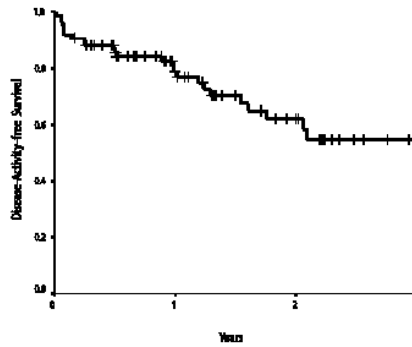
Burt RK, Blood. 2003;102:2373

EBMT Database

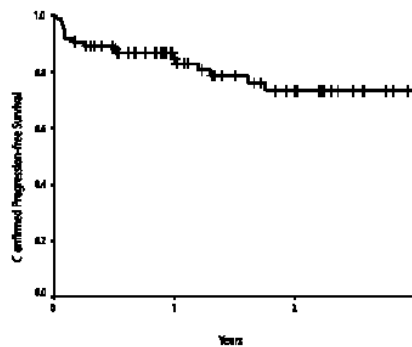
85 pts
EDSS 4.5-8.5 median 6.5
RRMS 4%
SPMS 70%
PPMS, 26%

Confirmed
progression-free survival
at 3 yrs = 74%
PPMS 66%
SPMS 78%

Fassas A. J Neurol 2002;249:1088

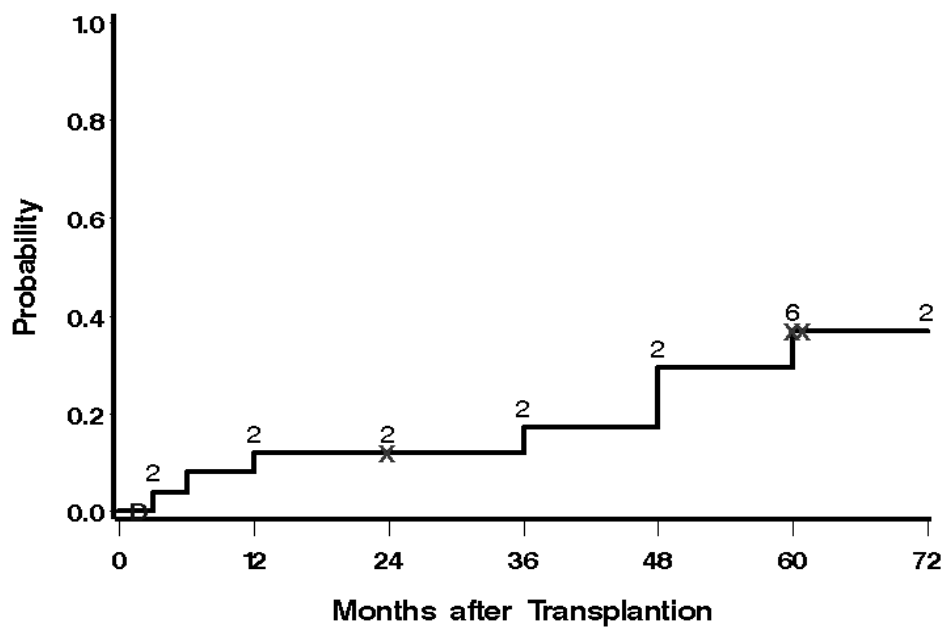


All Activity
EDSS, attacks,
death



Confirmed
progression free

National Collaborative Study of SCT for Autoimmune Diseases



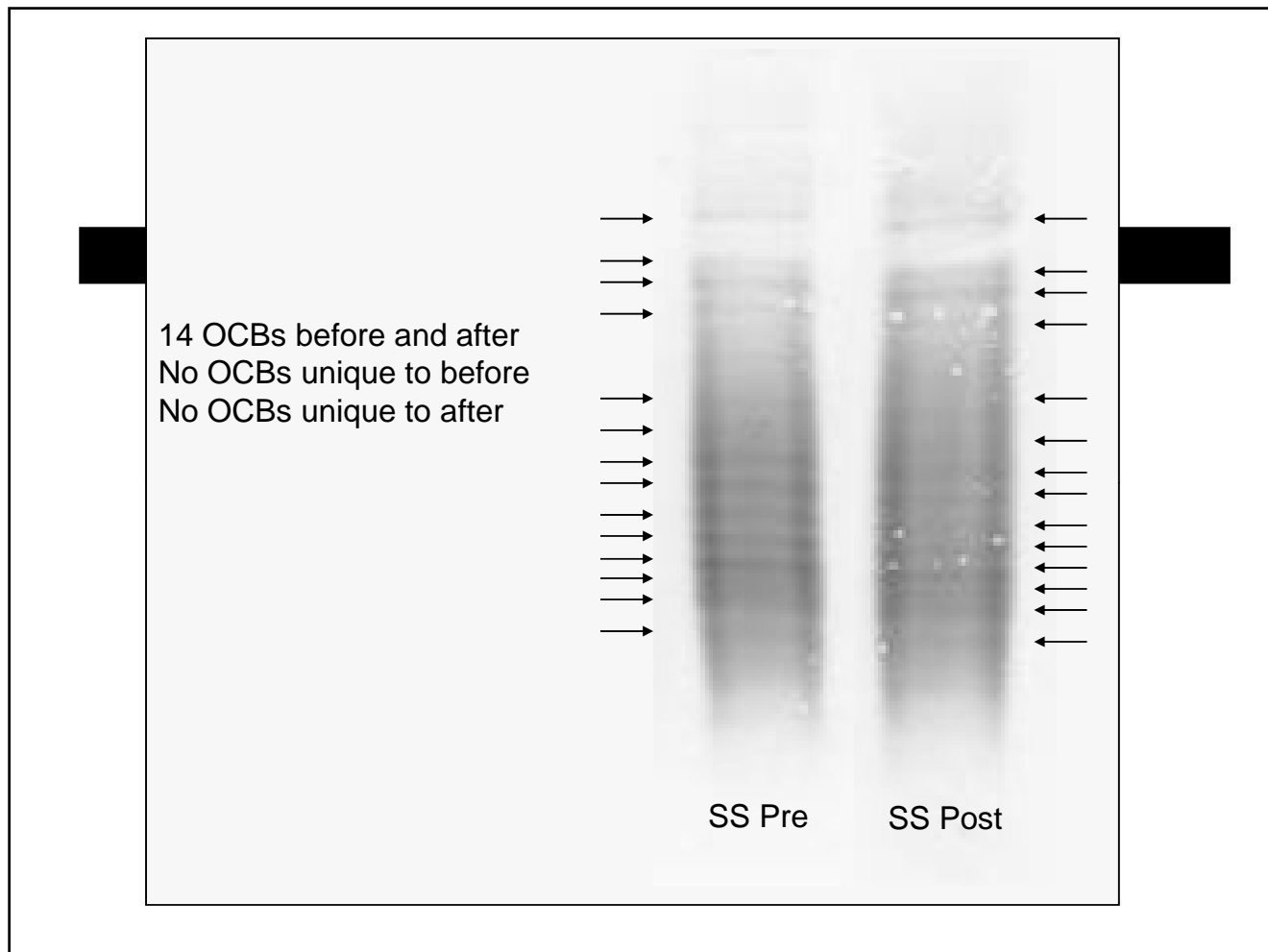
Time to worsening of EDSS by ≥ 1 point on 2 consecutive measures

Summary

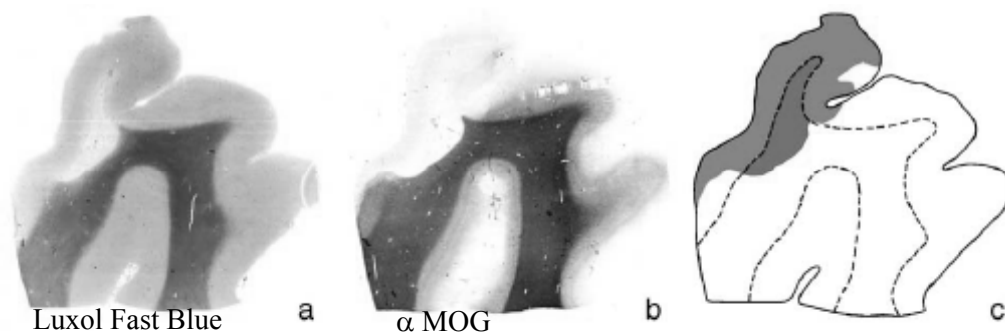
- 75-80% stable at 3 years
- 63% stable at 6 years
- Perhaps more effective earlier in disease
- Perhaps more effective for RRMS
- However, 11/147 deaths (7%)

Why not complete success?

- May not be entirely autoimmune
- May not be immune suppressive enough
 - B cells
- Damage may lead to irreversible loss
 - Treating too late



Cortical and Subcortical Demyelination



White matter demyelination = green
Cortical demyelination = orange

Kutzelnigg and Lassmann. J Neurol Sci 2005;233:55

Allogeneic Stem Cell Transplants



- Only method known to completely eliminate recipient's immune system.
- Graft vs Host eventually eliminates host cells, including memory B cells
- High mortality

Allogeneic Stem Cell Transplants

- 10 Allogeneic patients (all with leukemia)
- 6-144 months post transplant
 - 7 Stable
 - 2 Worse (all with OCB negative)
 - 1 Not evaluated
- Oligoclonal bands
 - 6 absent
 - 2 present
 - 2 not done

**High dose immunosuppression and
AutoLogous Transplantation for Multiple
Sclerosis (**HALT MS**) Study**



- 25 subjects: 18-60 yr old
- RRMS, EDSS 3.0-5.5
- ≥ 2 relapses/18 months on other treatment
- Documented worsening by more than one point on the EDSS during 18 months

**High dose immunosuppression and
AutoLogous Transplantation for Multiple
Sclerosis (**HALT MS**) Study**

- BEAM + rATG
- Autologous CD34+ selected cells
- Followed 5 years
- Clinical endpoints
- MRI endpoints (MTR, MRS)
- Immune reconstitution/mechanistic studies

Conclusions

- High dose immunosuppression may slow MS
- Transplant morbidity has been reduced.
- True immunoablative regimens may be more successful, but data is scant
- Further studies should yield additional information on success rate and mechanisms of action