AHSCT in MS and autoimmune diseases: how does it work?

Paolo A. Muraro, MD, PhD, FRCP
Department of Medicine, Imperial College London
CONFLICT OF INTEREST
DISCLOSURES

Honoraria for speaking and travel support from Merck Serono, Biogen, Bayer, Novartis, Merck
Outline

- MS as prototype of organ-specific inflammatory disease
- The concept and requisites of immune resetting
- Highlights of evidence in MS, SLE, Systemic Sclerosis
- Conclusions
Pathophysiology of MS – from inflammation to neuronal injury

Adapted from Compston and Coles, Lancet 2008 and Noseworthy et al. NEJM 2000
Initiation of CNS inflammation by antigens derived from the CNS

- Soluble antigen
- Antigen taken up by APCs in the subarachnoid space or choroid plexus

1. Primary virus infection of CNS
2. Induction of autoimmunity due to 'aberrant' leakage of CNS antigens into the draining lymph nodes

Initiation of CNS inflammation by non-CNS antigens

Aberrant homing of T cells to the CNS instead of peripheral tissues

1. Secondary spread of virus infection from the periphery to the CNS
2. Induction of autoimmunity due to cross-reactivity with peripheral antigens or molecular mimicry

Evidence required to support “immune resetting”

- Replacement/ renewal of the immune system
- Reduction of inflammatory cell or molecule expression
- Increased regulatory cell frequency/function
- Normalization of gene expression profiles
Evidence required to support “immune resetting”

Replacement/ renewal of the immune system (adaptive – T and B)

- Reduction of inflammatory cell or molecule expression
- Increased regulatory cell frequency/function
- Normalization of gene expression profiles
Recent Thymic Emigrants have:

- Naïve phenotype
- High TREC levels
Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients

Paolo A. Muraro,1 Daniel C. Douek,4 Amy Packer,1 Katherine Chung,1 Francisco J. Güenaga,4 Riccardo Cassiani-Ingoni,1 Catherine Campbell,2 Sarfraz Memon,5 James W. Nagle,1 Frances T. Hakim,5 Ronald E. Gress,5 Henry E McFarland,1 Richard K. Burt,6 and Roland Martin1

1. **TREC assay** (Douek)

2. **Phenotype-based Enumeration** (CD45RA+RO-CD31+)

![Diagram showing TREC assay](image_url)

![Box plot showing median TREC values](image_url)

<table>
<thead>
<tr>
<th>pre-Tx</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
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<tbody>
<tr>
<td>848</td>
<td>790</td>
<td>6689</td>
<td>4602</td>
</tr>
</tbody>
</table>

\[ P = 0.01 \text{ (RM-ANOVA)} \]

\[ P = NS \text{ (pre-Tx and 6 mo)} \]

\[ P = 0.028 \text{ (24 mo vs. other time points)} \]

\[ P = 0.01 \text{ (24 mo vs. other time points)} \]

*J. Exp. Med. (2005) 201: 805-816*
Recovery of CD4+ T-cell subsets over time in SLE patients treated by immunoablation and ASCT versus levels in age-matched healthy controls.

% Memory of all CD4+ T

% RTE of all CD4+ T

Naïve CD4+ T

Memory CD4+ T

RTE CD4+ T, Absolute

### Trend toward improved T cell diversity in patients with SSc with favorable outcome after HSCT

**Table 3.** T cell repertoire diversity, thymic function analysis by quantification of T cell receptor rearrangement excision circles (TRECs), and phenotypes after hematopoietic stem cell transplantation (HSCT)*

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>At inclusion</th>
<th>6–8 months after HSCT</th>
<th>10–12 months after HSCT†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group A</td>
</tr>
<tr>
<td>Polyclonal BV families, %</td>
<td>70.30 ± 19.85</td>
<td>43.17 ± 7.84</td>
<td>59.06 ± 12.01</td>
<td>22.50 ± 15.58</td>
</tr>
<tr>
<td>Skewed BV families, %</td>
<td>22.80 ± 20.02</td>
<td>39.78 ± 2.25</td>
<td>33.33 ± 9.29</td>
<td>58.25 ± 13.20</td>
</tr>
<tr>
<td>Negative BV families, %</td>
<td>6.90 ± 7.81</td>
<td>37.53 ± 35.71</td>
<td>7.33 ± 2.89</td>
<td>19.25 ± 14.70</td>
</tr>
<tr>
<td>TRECs/μg CD3+ cell DNA</td>
<td>694 ± 776.85</td>
<td>50.75 ± 51.05</td>
<td>117.33 ± 19.73</td>
<td>112.75 ± 180.68</td>
</tr>
</tbody>
</table>

**Group A:** patients with sustained major or partial response  
**Group B:** patients with no response or with relapse of disease

Recovery of CD19+ B-cell subsets over time in SLE patients treated by immunoablation and ASCT versus levels in healthy controls.

Recent Thymic Emigrants
Highly diverse TCR repertoire
Extensive clonotypic renewal within the T cell repertoire.


CDR3 spectratyping

Pre-transplant

6 months

1 year

2 years

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Increased percentage of polyclonal TCR-Vβ in patients with SSc at long-term after aHSCT

Renewal of T cell repertoires (CD4>CD8) in patients with MS who underwent AHSCT in HALT-MS trial

Cerebrospinal fluid and peripheral blood T cell repertoires are substantially renewed long-term in patients with MS treated with HSCT.
Evidence required to support “immune resetting”

- Replacement/ renewal of the immune system
- Reduction of inflammatory cell or molecule expression
  - Increased regulatory cell frequency/function
  - Normalization of gene expression profiles
Diminished Th17 responses after AHSCT

Radical depletion post-AHSCT of CD8+CD161 high, IFN-γ and IL-17 producing, Mucosal Associated Invariant T (MAIT) cells

Evidence required to support “immune resetting”

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Phenotypic analysis of FoxP3+ Treg levels in 5 patients after ASCT compared with those in healthy controls and conventionally treated SLE patients.

Surge of Treg and NK cell proportions in patients with MS after AHSCT

**A**

**FoxP3**^+^ CD4^+^

<table>
<thead>
<tr>
<th></th>
<th>PreTx</th>
<th>6 mo</th>
<th>1 yr</th>
<th>2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>% FoxP3^+^CD4^+^</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreTx</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6 mo</td>
<td>5</td>
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<td>5</td>
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<td>1 yr</td>
<td>5</td>
<td>5</td>
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</tr>
<tr>
<td>2 yrs</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*P* < .001

**B**

**CD56**^high^ NK

<table>
<thead>
<tr>
<th></th>
<th>PreTx</th>
<th>6 mo</th>
<th>1 yr</th>
<th>2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CD56^high^CD3^-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreTx</td>
<td>0.1</td>
<td>5.1</td>
<td>1.0</td>
<td>3.2</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.1</td>
<td>5.1</td>
<td>1.0</td>
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*P* = .001

Successful autologous HSCT leads to a renewed and more diverse Treg TCR repertoire in blood of patients with refractory autoimmunity (JIA or DM)

Evidence required to support “immune resetting”

- Replacement/renewal of the immune system
- Reduction of inflammatory cell or molecule expression
- Increased regulatory cell frequency/function
- Normalization of gene expression profiles
Normalization of differentially expressed genes on CD8+ T cells of MS patients after AHSCT

Sousa et al. *Clinical Science*. 2015. 128 (2) 111-120;
Autologous hematopoietic SCT normalizes miR-16, -155 and -142-3p expression in MS patients

Compared with healthy donors, MS patients showed higher miRNA expression at baseline, which decreased and normalized after AHSCT

Arruda et al. Bone Marrow Transplantation (2014), 1–10
Conclusions
Key steps of immune reconstitution and mechanisms of AHSCT

Nature Reviews Neurology
88: 306-15
Conclusions on AHSCT – how does it work?

- Immune regeneration in the T (and some in the B) cell compartment includes:
  - Clonal renewal and diversification of repertoire
  - Depletion of proinflammatory cells
  - Enhanced immune regulation
  - Normalization of gene and micro RNA expression

- Evidence of correlation with clinical outcome is still limited
Key acknowledgments:
People in my group: Sofia Abrahamsson, Alessandra Sousa
Collaborators: Richard Burt, Julio Voltarelli, Riccardo Saccardi