T-cell vaccination: from basics to the clinic

Vipin Kumar, Eli Sercarz, Jingwu Zhang and Irun Cohen

Table 1. Clinical trials of T-cell vaccination in MS (undertaken or planned)*

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial (no. of patients)</th>
<th>Vaccinogen - T-cell lines specific for:</th>
<th>Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992–1995</td>
<td>Phase I (8)</td>
<td>MBP</td>
<td>Diepenbeek, Belgium</td>
</tr>
<tr>
<td>1996–1999</td>
<td>Phase II (54)</td>
<td>Peptides of MBP</td>
<td>Baylor, Houston, TX, USA</td>
</tr>
<tr>
<td>Ongoing</td>
<td>Phase I and II (80)</td>
<td>Whole bovine myelin</td>
<td>USC, Los Angeles, CA, USA</td>
</tr>
<tr>
<td>Ongoing</td>
<td>Phase I and II (20)</td>
<td>Peptides of MBP, PLP and MOG</td>
<td>Shbea Medical Center, Israel</td>
</tr>
<tr>
<td>Planned</td>
<td>Phase I and II for recent onset MS (ND)</td>
<td>Peptides of MBP, PLP and MOG</td>
<td>Shbea Medical Center, Israel</td>
</tr>
<tr>
<td>Planned</td>
<td>Dose-escalation (9–18)</td>
<td>Peptides of MBP, PLP and MOG</td>
<td>Baylor, Houston, TX, USA</td>
</tr>
</tbody>
</table>

*Abbreviations: MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; ND, not decided; PLP, proteolipid protein.

It is becoming clear that the clinical manifestation of autoimmunity involves not only activation of a dominant, self-reactive T-cell population but also, failure of the peripheral immune regulatory mechanisms that normally control these cells. One important regulatory mechanism is centered on the recognition of TCR-derived peptides in the context of class I and class II MHC by regulatory CD8+ and CD4+ T cells (Treg), respectively. The CD8+ Treg cells can recognize TCR-derived peptides complexed with classical MHC class I molecules or nonclassical molecules, such as Qa-1 in mice or HLA-E in humans. The expression of Qa-1 and HLA-E is upregulated on activated T cells and these molecules are unique in their ability to bind to the extremely hydrophobic leader peptides (H. Jiang and L. Chess, New York, NY, USA). The Treg cells have been shown to be involved in the peripheral control of potentially pathogenic, autoreactive T cells, such as the MBP-reactive T cells that mediate EAE (Ref. 8). The combined action of the...
CD8+ Treg cells results in the destruction of activated, MBP-reactive Th1 clone(s), causing a 'global' deviation of the immune response and protection from EAE (V. Kumar, La Jolla, CA, USA). In confirmation of the animal studies, MBP-reactive T cells have been shown to also disappear following TCV in humans. Interestingly, CD4+ Treg cells must secrete pro-inflammatory cytokines, for example, interferon-γ (IFN-γ), for effective TCR-based regulation (V. Kumar). Accordingly, Th1 clones, but not Th2 clones, can be used to vaccinate successfully against EAE. Consistent with this, a CD8+ Treg hybridoma has been shown to recognize the Th1 version but not the Th2 version of a clone (H. Jiang).

"...the display of TCR-derived-peptide-MHC complexes on a professional Ag-presenting cell...is crucial for the priming of Treg populations."

These studies suggest that, contrary to some expectations, T-cell lines used for vaccination should be of the Th1 phenotype. Thus, pro-inflammatory cytokines might be required for the effective recruitment of CD8+ T cells. Furthermore, it appears that the display of TCR-derived-peptide-MHC complexes on a professional Ag-presenting cell (APC), following uptake of an apoptotic T cell or its contents, is crucial for the priming of Treg populations. Because Th2 cells are less susceptible to apoptosis than Th1 cells, vaccination with Th2 cells might not load APCs for the effective priming of Treg cells. Alternatively, activated T cells displaying the TCR-derived-peptide-MHC complexes on their cell surface could directly prime CD8+ Treg cells.

An important issue in TCV is identifying the relevant T-cell clones or lines for constructing vaccines. In the B10.PL mouse, length analysis of complementarity determining region 3 or spectratyping of TCR variable-joining (Vβ-μ Jβ) gene segments was used to study the dynamics of a dominant, type 1 T-cell clone, referred to as a 'driver' (E. Sercarz, La Jolla, CA, USA). The appearance of these cells is in the central nervous system correlates with disease. T cells reactive to multiple myelins, such as MBP, proteolipid protein and myelin oligodendrocyte glycoprotein, are thought to be involved in the development of MS in the human population, and effective use of them is necessary for making vaccines. TCV is an individualized immunotherapy; therefore, it will be crucial to define the relevant genes encoding Ag-reactive TCR-α or -β, whose use can be monitored during or after disease or vaccination, in each individual patient. Hopefully, the use of the relevant clones in the vaccine for each Ag, to engage specific Treg populations, will make it possible to ignore or overcome the effects of determinant spreading. An interesting strategy combining cell-sorting and anchored and/or real-time PCR could potentially be used for the relative quantification of myelin-reactive T cells during the course of the disease following TCV (D. Douek, Bethesda, MD, USA).

The collaboration between clinical and pre-clinical researchers exemplified at this meeting is aimed not only at uncovering the basic principles of immune regulation, but also, at improving strategies for TCV. The stage is now set for the delivery of TCR variable-region domains (Vα and/or Vβ), by providing relevant T cells or proteins (or plasmid and/or viral DNA vectors encoding them), in clinical trials for intervention in T-cell-mediated pathologic conditions, including autoimmune diseases and transplantation.

References
8 Kumar, V. (1998) TCR-peptide-reactive T cells and peripheral tolerance to myelin basic protein. Res. Immunol. 149, 827–834

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