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T-cell vaccination: from basics to the clinic

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The 1st International Workshop on T-cell Vaccination was held at Mizpe Hayamim, Israel from 20–24 May 2001.

Up in the hills overlooking the Sea of Galilee, the International Center for T-Cell Vaccination convened a workshop that brought together scientists studying the fundamental mechanisms of immune regulation and clinicians engaged in clinical trials of T-cell vaccination (TCV). Some time ago, it was discovered that vaccinating experimental animals with antigen (Ag)-specific T-cell lines or clones provides resistance to induced or spontaneous autoimmune diseases[1]. The success of TCV using T-cell clones reactive to myelin basic protein (MBP) in the treatment of experimental autoimmune encephalomyelitis (EAE)[2], a rodent model of multiple sclerosis (MS), has led to clinical trials in human autoimmune conditions[3,4]. The main theme of the workshop was to review the basic mechanisms of T-cell receptor (TCR)-based regulation and discuss its application in the planning of new and improved clinical trials of TCV in MS (Table 1). The workshop also established a TCV website (http://www.T-cell-vaccination.org) for the use of clinical investigators, basic researchers and any other individuals with an interest in MS. Although MS patients did not attend the workshop, we were reminded of their needs by the presentation of some inspiring art work (A. Achiron, Israel).

Results from initial trials of TCV in MS patients are encouraging and warrant further investigations into establishing the most effective protocol. Following vaccination with irradiated, autologous, myelin-reactive T cells, the frequency of myelin-reactive T-cell precursors decreased, accompanied by some clinical improvement, including a reduced relapse rate, delayed time to progression, and improvement and/or stabilization of brain-lesion activity (J. Zhang, Houston, TX, USA). However, there are unresolved issues relating to the selection of myelin Ags, the phenotype of the T cells [e.g. $CD4^+$ versus $CD8^+$ and T helper 1 (Th1) versus Th2], and the dosage and frequency of vaccination, all of which are crucial to the development of an effective TCV protocol.

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

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

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

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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 (T_{reg}), respectively. The $CD8^+$ T_{reg} 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[5–7]. 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 T_{reg} cells have been shown to be involved in the physiological control of potentially pathogenic, autoreactive T cells, such as the MBP-reactive T cells that mediate EAE (Ref. 8). The combined action of the

 1471-4906/01/$ – see front matter PII: S1471-4906(01)02020-8

T_{reg} cells results in the destruction of activated, MBP-reactive Th1 clonotypes, 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 also to disappear following TCV in humans. Interestingly, $CD4^+$ T_{reg} 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 $CD8^+$ T_{reg} 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 T_{reg} 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 T_{reg} 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 T_{reg} cells. Alternatively, activated T cells displaying the TCR-derived-peptide–MHC complexes on their cell surface could directly prime $CD8^+$ T_{reg} 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–Jβ) gene segments was used to study the dynamics of a dominant, type 1 T-cell clonotype, referred to as a 'driver' (E. Sercarz, La Jolla, CA, USA). The appearance of these cells in the central nervous system correlates with disease. T cells reactive to multiple myelin Ags, 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 T_{reg} 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 pathological conditions, including autoimmune diseases and transplantation.

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