Jan-Feb-Mar 2009
Volume 10, Issue 1

Targeting Trends

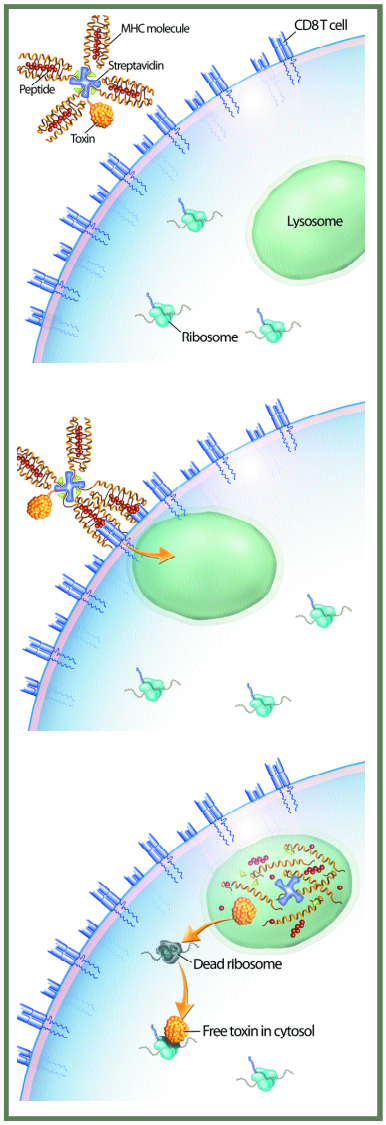
Reporting the latest news in Molecular Surgery

Selective deletion of CD8+ T cells by saporin-coupled MHC class I tetramers

Contributed by Paul R. Hess, Adam S. Buntzman, Sabrina L. Murray, Ellen F. Young, and Jeffrey A. Frelinger; North Carolina State University College of Veterinary Medicine, Raleigh, NC; and University of North Carolina-Chapel Hill School of Medicine, Chapel Hill, NC.

CD8+ T cells constitute important effectors of the adaptive immune response, functioning principally to remove infected cells from the body, which are detected by the display of short peptides (epitopes) derived from microbial proteins within the binding groove of class I major histocompatibility complex (MHC) molecules on the cell surface. When the T cell receptor (TCR) of a primed T cell binds to its cognate peptide-MHC (pMHC) ligand, the T cell is triggered, and induces apoptosis in the infected cell. To anticipate the potential myriad of pathogen-origin peptides that might be encountered over a lifetime, a correspondingly large, diverse TCR repertoire is randomly generated, with each nascent T cell expressing thousands of identical TCRs of a single specificity. During the subsequent selection process that occurs in the thymus, most T cells bearing TCRs that inadvertently bind MHC molecules presenting "self" peptides (i.e., derived from normal proteins) are deleted prior to entering the circulation, to prevent autoimmunity; the minority of these autoreactive T cells that escape elimination are turned off by peripheral tolerizing mechanisms. In some immune-mediated conditions, such as multiple sclerosis and type 1 diabetes mellitus, normal tolerance is disabled, and autoreactive CD8+ T cells are inappropriately activated, leading to organ-specific tissue destruction and clinical signs of disease. Unfortunately, non-specific inhibition of T cell responses with immunosuppressive agents has not been particularly effective for these conditions, and such drugs carry risks of cancer and serious infections. Selective deletion of the pathogenic CD8+ T cells would appear to be an ideal strategy, but, until recently, there has been no efficient means of targeting just the culprits. In 1996, Altman *et al*. showed that CD8+ T cells of known specificity could be discriminated from other T cells in polyclonal populations by the use of soluble complexes, widely known as "tetramers," consisting of four identical pMHC molecules bound to streptavidin.[1] When coupled to a fluorophore, such tetramers permit ready visualization of epitope-specific T cells by flow cytometry.

(continued on page 6)



Artist's conception of an MHC class I toxic tetramer
(illustration: AM Harvey, NCSU-CVM).

Inside this issue:

Newsletter Highlights

- 2008 SfN Poster Award Winner *(page 2)*
- 2008 SfN Poster Award Runners Up *(page 2)*
- Teaser Winners *(page 5)*
- Tumor Cell Line Screening *(page 7)*

Denise Higgins, Editor
Gangsta, Guest Editor

ADVANCED TARGETING SYSTEMS