

BRUNO KYEWSKI

Current Research

B. Kyewski's group's research is concerned with the structure-function relationship of the thymic microenvironment with respect to differentiation and selection of the T-cell repertoire with special reference to the role of thymocyte-stromal-cell interactions. The laboratory currently focuses on the analysis of the cellular and molecular mechanisms underlying the phenomenon of promiscuous gene expression by thymic epithelial cells and its relevance for self-tolerance, autoimmunity and tumor immunity. Thymic epithelial cells have the unusual and unique property of expressing a large array of tissue-restricted antigens in an ectopic manner, a phenomenon termed "promiscuous gene expression". Immunological, cell biological and molecular approaches are applied to study this phenomenon in mice and man.

Other areas of interest include the molecular mechanisms of T-cell lineage commitment during positive selection and the dissection of the microenvironment of lymphoid organs.

Future Projects and Goals

Current and future efforts are directed at the following aspects of central T cell tolerance. I) Characterization of promiscuous gene expression in mice and humans, i.e., defining the scope at the mRNA level by gene arrays and at the protein level in single cells. II) Characterization of the cellular and molecular regulation of promiscuous gene expression. III) Presentation of and tolerance induction by tissue-restricted antigens, including tumor antigens. IV) Assessing the role of promiscuous gene expression in the patho-physiology of human autoimmune

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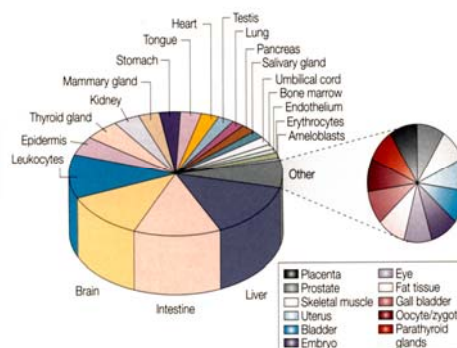
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diseases (Type 1 Diabetes mellitus, Myasthenia gravis) and in tumor immunity. Thus, our topics encompass both basic and translational research aspects.

Selected Publications

1. Derbinski J, Schulte A, **Kyewski B**, Klein L. Promiscuous gene expression in medullary thymic epithelial cells mirrors the peripheral self. *Nat Immunol* 2001;2:1032-9.
2. Derbinski J, Gabler J, Brors B, Tierling S, Jonnakuty S, Hergenahn M, Peltonen L, Walter J, **Kyewski B**. Promiscuous gene expression in thymic epithelial cells is regulated at multiple levels. *J Exp Med* 2005;202:33-45.
3. **Kyewski B**, Klein L. A central role for central tolerance. *Annu Rev Immunol* 2006;24:571-606.
4. Giraud M, Taubert R, ... **Kyewski B**, Garchon H-J. An IRF8-binding promoter variant and AIRE control CHRNA1 promiscuous expression in thymus. *Nature* 2007;448:934-7.
5. Derbinski J, Pinto S, Rösch S, Hexel K, **Kyewski B**. Promiscuous gene expression patterns in single medullary thymic epithelial cells argue for a stochastic mechanism. *Proc Natl Acad Sci USA* 2008;105:657-62.



Tissue representation in thymic epithelial cells