Bernard MALLISEN, PhD
Marie MALLISEN, PhD

Group leaders: Genetic and structural analysis of T cell interactions

Background

Bernard and Marie MALISSEN have contributed to the molecular and structural analysis of the TCR transduction cassette, the molecular basis of T cell development and the genetic dissection of T cell and dendritic cell functions. Using knock-in mice and proteomic approaches, they systematically dissected the proximal elements of the TCR transduction cassette.

Bernard MALISSEN is supervising the development of the Center for Immunophenomics, a novel infrastructure that will boost phenogenomics approaches in a concerted manner with the teams of CIML.

Awards

Bernard MALISSEN

Grand Prix INSERM

Silver Medal of CNRS

Bronze medal of CNRS

Prize of the "Fondation B. Halpern"

Prize "Ville de Paris" of the "Ligue Nationale Contre le Cancer"

Behring-Metchnikoff Prize

Marie MALISSEN

Silver Medal of CNRS

Membership

Bernard MALISSEN

Member of the French Academy of Sciences

EMBO member

Honorary Member of the American Association of Immunologists

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Main achievements

During the past twenty years, the primary objective of our team has been to decipher the architecture of the signaling cassette operated by the T cell receptor (TCR). After deciphering the structure of human and mouse MHC genes in the laboratory of Bertrand Jordan (CIML) and Leroy Hood (Caltech), we demonstrated that the transfer of TCR and CD8 molecule is necessary and sufficient to confer to a “naïve” T cell the ability to recognize a specific peptide/MHC class I complex. The possibility to reprogram a T cell with 5 different genes allowed us to establish the concept of CD3 "signaling modules". Based on the exon-intron organization of the transduction motifs (ITAMs) found in the cytoplasmic tail of most of the polypeptides associated with antigen receptors or Fc receptors, we showed that the present-day ITAMs stem from on a common primordial building block made of two exons. In parallel studies, we provided the first direct evidence for the existence of chromosomal inversion during TCR gene rearrangements. In the course of these studies, we also unexpectedly found that T cells can express two functional TCR αlpha chains and thus apparently violate the main tenet of the clonal selection theory that is at the basis of adaptive immunity.

More recently, we developed mice harbouring specific deletion and modification in genes coding for components of TCR transduction cassette, and contributed to work out the organization of the pre-TCR, a key molecular sensor used by developing T cells to control the outcome of early TCR gene rearrangements. Analysis of an allelic series involving the LAT adaptor, a key “hub” of the TCR signalling cassette, revealed that there exists a pathology proper to defective LAT signalosomes. This pathology is characterized by a lymphoproliferative disorder involving polyclonal Th2 effectors that belong to the alpha/beta or gamma/delta T cell lineage, and results in fulminant hypergammaglobulinemia E and G1. This pathological condition, emphasizes that the LAT adaptor constitutes a key signalling node controlling T cell homesostasis and terminal differentiation.

We also elucidated the first three dimensional structure of an intercellular recognition complex involving an alloreactive TCR. Alloreactivity occurs when an organ is transplanted into an MHC-mismatched host and results in acute rejection. These results provided a definitive structural explanation for the basis of this important clinical phenomenon. The resolution of the crystal structure of a second alloreactive TCR in its free and bound states allowed us to revisit at the molecular level whether TCRs bind to their ligands according to a "lock-and-key" or to an "induced fit" mechanism, and to propose the first molecular explanation for the degeneracy of T cell recognition.

Finally, in the process of tackling the dynamics and function of Langerhans cells, a dendritic cell subset that resides in the epidermis, we discovered a novel subset of dermal dendritic cells that excels in cross-presenting antigens that are expressed in keratinocytes.

Selected publications

- Henri, S., Poulin, L.F., Tamoutounour, S., Ardouin, L., Guilliams, M., de Bovis, B., Devilard, E., Viret, C., Azukizawa, H., Kissenpfennig, A., et al. (2010). CD207+ CD103+ dermal dendritic cells cross-present keratinocyte-derived antigens irrespective of the presence of Langerhans cells. *J Exp Med* 207, 189-206.
- Mazza, C., Auphan-Anezin, N., Gregoire, C., Guimezanes, A., Kellenberger, C., Roussel, A., Kearney, A., van der Merwe, P.A., Schmitt-Verhulst, A.M., and Malissen, B. (2007). How much can a T-cell antigen receptor adapt to structurally distinct antigenic peptides? *Embo J* 26, 1972-1983.
- Mingueneau, M., Roncagalli, R., Gregoire, C., Kissenpfennig, A., Miazek, A., Archambaud, C., Wang, Y., Perrin, P., Bertosio, E., Sansoni, A., et al. (2009). Loss of the LAT adaptor converts antigen-responsive T cells into pathogenic effectors that function independently of the T cell receptor. *Immunity* 31, 197-208.
- Mingueneau, M., Sansoni, A., Gregoire, C., Roncagalli, R., Aguado, E., Weiss, A., Malissen, M., and Malissen, B. (2008). The proline-rich sequence of CD3epsilon controls T cell antigen receptor expression on and signaling potency in preselection CD4+CD8+ thymocytes. *Nat Immunol* 9, 522-532.

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- Poulin, L.F., Henri, S., de Bovis, B., Devilard, E., Kissenpfennig, A., and Malissen, B. (2007). The dermis contains langerin+ dendritic cells that develop and function independently of epidermal Langerhans cells. *J Exp Med* 204, 3119-3131.
- Prinz, I., Sansoni, A., Kissenpfennig, A., Ardouin, L., Malissen, M., and Malissen, B. (2006). Visualization of the earliest steps of gammadelta T cell development in the adult thymus. *Nat Immunol* 7, 995-1003.