## ANTIGEN UPTAKE
### Monday, July 6

### M.14. The TNF Superfamily Cytokine RANKL Provides the Critical Signal Responsible for Switching on Differentiation of M Cells from Epithelial Precursors

Kathryn Knoop[1], Nachiket Kumar[1], Betsy Butler[1], Senthil Kumar Sakthivel[1], Rebekah Taylor[1], Tomonori Nochi[2], Hisaya Akiba[3], Hideo Yagita[3], Hiroshi Kiyono[2], Ifor Williams[1]
*[1]Emory University, Atlanta, GA; [2]University of Tokyo, Tokyo, Japan; [3]Juntendo University, Tokyo, Japan*

M cells are specialized epithelial cells located in Peyer's patches (PP) and other mucosal lymphoid tissues that avidly take up particulate antigens. Subepithelial stromal cells beneath PP domes selectively express RANKL. We used two experimental approaches to determine whether RANKL is involved in M cell differentiation. First, we characterized M cell development in RANKL null mice. Overall, these mice had less than 2% of wild type levels of M cells detected by UEA-I lectin or an M cell-specific monoclonal antibody (NKM 16-2-4). Loss of M cells was associated with markedly diminished uptake of 200 nm diameter fluorescent beads from isolated intestinal loops into PP. These M cell deficits in the PP of RANKL null mice were corrected by systemic administration of exogenous RANKL. The second approach was acute neutralization of RANKL in BALB/c mice by treatment with IK22-5 anti-RANKL monoclonal antibody. After 4 days, most PP M cells were gone. After 8 days, M cell depletion was nearly total, even in the most distal PP that had some residual M cells in RANKL null mice. We conclude that M cells arise where RANKL is locally available to induce the differentiation of M cells from RANK-expressing intestinal epithelial precursors.