We found earlier that monocyte-derived macrophages from human neonates are hyporesponsive to activation by IFN-γ, a finding that cannot be attributed to lower expression of IFN-γR or decreased affinity of these receptors to their natural ligand on neonatal cells. We have recently found that this phenomenon was linked to a marked deficiency in phosphorylation of the IFN-γR-associated STAT-1. STAT-1 is a convergent point for immunologic stimuli in a macrophage proinflammatory response and the strength of signal through the IFN-γR may influence immune responsiveness. Therefore, these findings suggest the possibility that there are important differences in the way newborns and adults use STAT-1 to modify immune response to pathogens. During pregnancy there may be a bias towards a Th2 type response and placental-derived Th2 cytokines antagonize Th1 responses that could otherwise be harmful to the fetus. In early life, the diminished production of IFN-γ, IL-12/IL-23, and IL-18 by neonatal cells may result from the abundance of Th2 cytokines. The impaired production of the most critical Th1-type cytokines, together with the impaired Th1-type response of neonatal macrophages are likely to associate with the high susceptibility of newborns to infectious diseases in which type-1 differentiation is needed to combat the pathogen. Based on our research we propose that a decreased STAT-1 phosphorylation and activation may represent developmental immaturity and may contribute to the unique susceptibility of neonates to infections by intracellular pathogens.

Genetically-determined human models for Toll-like receptor (TLR) deficiencies provided valuable information to understand the molecular basis of innate cellular immunity in neonates better. We have recently identified a 6-year-old Hungarian patient with genetic IRAK-4 deficiency (Eur. J. Immunol., submitted). The immunological phenotype in this patient includes a seriously impaired production of inflammatory cytokines (IL-1β, IL-6, IL-12, TNF-α, and IFN-γ) upon stimulation with TLR agonists of blood cells. In addition, this patient failed to mount an efficient antibody response to polysaccharide antigens. Neonates do not mount an adequate antibody response to polysaccharide antigens and have an increased susceptibility to encapsulated bacteria such as S. pneumoniae. In contrast, protein antigens are able to elicit antibody response from neonates as well as from our patient with IRAK-4 deficiency. The overlapping immunological phenotype in newborns and our patient with genetic defects of NF-κB-mediated immunity in terms of cytokine profiles, antibody responses, and susceptibility to infections by encapsulated bacteria is striking. Polysaccharides are thymus-independent antigens the antibody response to which requires Th1-type cytokines provided by T cells and macrophages. Neonatal macrophages are qualitatively different from adult macrophages in that they are defective in secretion of a variety of Th1-type cytokines and, as a consequence, they have an intrinsic inability to promote B cells to respond to polysaccharide antigens. In particular, the defect of mononuclear phagocytes to secrete IL-1β, IL-6, IL-12, TNF-α, and IFN-γ in newborns is the typical cellular phenotype described in our patient with IRAK-4 deficiency. These findings suggest that the defects in inflammatory cytokine production in concert with the impaired polysaccharide antibody response in newborns are related to defects in expression and function of TLR-mediated immunity.

In collaboration with French scientists we described a new molecular form of hyper IgM syndrome (HIGM) which we designate as HIGM-4. In contrast to HIGM-2 (activation-induced cytidine deaminase deficiency) featured by the lack of generation of somatic hypermutation (SHM) and class switch recombination, B cells in HIGM-4 patients are characterized by preserved SHM.

. We have described a new disease-causing, SH2D1A mutation in X-linked lymphoproliferative syndrome. We have reported that the p.G16D mutation resulted in a defect in protein folding as manifested by moderately reduced half-life compared to that of wild type SH2D1A. Furthermore, the G16D protein was defective in binding to its

physiological ligands (SLAM and 2B4). These results suggest that defects in protein folding and ligand binding collectively contribute to the loss of function of the SH2D1A protein in patients carrying p.G16D mutation.

We reported earlier that macrophages from patients with type I Gaucher disease (GD) have a decreased capacity to generate superoxide anion (O_2^-) on stimulation with opsonized *S. aureus* or formyl-methionyl-leucyl-phenylalanine. During this research period we unveiled that assembly of the respiratory burst oxidase of mononuclear phagocytes may be a possible target of the pathologic actions of glucocerebrosid accumulating in macrophages of patients with GD.