A surprising and dramatic neuroendocrine-immune phenotype of mice deficient in Growth Hormone-Releasing Hormone (GHRH)

K. FAHRAT, G. BODART*, C. RENARD*, C. DESMET[1], M. MOUTSCHEN[2], Y. BEGUIN[3], F. BARON[3], R. SALVATORI[4], V. GEENEN* & H. MARTENS**

[*]University of Liege, GIGA-I[3], Laboratory of Immunoendocrinology, Liege, Belgium
[1]University of Liege, GIGA-I[3], Laboratory of Cellular and Molecular Immunology, Belgium
[2]Clinical Immunology and Infectiology, University Hospital of Liege, Belgium
[3]University of Liege, GIGA-I[3], Laboratory of Hematology, Liege, Belgium
[4]Division of Endocrinology, Johns Hopkins University, Baltimore, USA

In the framework of close interactions between the immune and neuroendocrine systems, Growth Hormone (GH) has been proposed to exert significant effects on the immune system, but there is not yet a consensus about GH immunomodulatory properties.
These studies investigated the immune and anti-infectious response of dwarf *Ghrh*$^{-/-}$ mice presenting a severe deficiency of the GHRH/GH/IGF-1 axis.
In basal conditions, thymic parameters and T-cell responses of *Ghrh*$^{-/-}$ mice were not severely affected but a constant B-cell lymphopaenia was observed. Thus, we investigated vaccine and anti-infectious responses of *Ghrh*$^{-/-}$ mice toward *Streptococcus pneumonia,* a B-dependent pathogen,
Ghrh$^{-/-}$ mice were unable to trigger production of specific IgM and IgG against serotype 1 pneumococcal polysaccharide (PPS) after vaccination with either native PPS (Pnx23) or protein-PPS conjugate (Prev-13) vaccines. These vaccines both include the serotype 1 (our *S.pneumoniae* strain) and provide an effective protection in mice. A short GH supplementation to *Ghrh*$^{-/-}$ mice (1 daily injection of 1 mg/kg GH for 4 weeks) restored IgM and IgG response to Pnx23 vaccine but not to Prev-13. This suggests that GH could exert distinct impacts upon spenic areas.
Furthermore, after intranasal instillation of a non-lethal dose (defined by the full clearance by WT C57BL/6 mice after 24h) of serotype 1 *S.pneumoniae*, *Ghrh*$^{-/-}$ mice exhibited a dramatic susceptibility. This was proved by a marked time-dependent increase in pulmonary bacterial, a septicemia already 24h after infection and a survival limit of 72h. We also observed a dramatic decrease in lung B- and T-cell populations and an increase in proportion of inflammatory macrophages. By contrast, wild-type and heterozygote mice completely cleared *S.pneumoniae* infection after 24h.
In conclusion, our data show without ambiguity that the somatotrope GHRH/GH/IGF-1 axis plays an important and unsuspected role in defense against *S.Pneumoniae*.