Role of Prostaglandin E-major Urinary Metabolite Levels in Identifying The Phenotype of Pachydermoperiostosis

M. Iliehj3,1, Y. Oza2, Y. Yoshikawa1, N. H. Sueizki2 and K. Kahunbishi1 1 Dermatology, Kyoto University, Kyoto, Japan; 2 Dermatology, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan and 3 Dermatology, National Center for Child Health and Development, Tokyo, Japan

Pachydermoperiostosis (PDP) is an autosomal recessive hereditary disease, but has three diagnostic features: digital clubbing, periostosis, and pachydermia including cutis verticis gyrata (CVG). CVG is a condition in which folds of the hypertrophic scalp skin create a cerebellar appearance. The phenotypic spectrum of PDP has been categorized to the complete and incomplete form depending on presence or absence of CVG. Two causative genes: HPGD and SLC22A1 have been identified. Prostaglandin E2 (PGE2) is metabolized by HPGD and in PDP complete phenotype in blood and skin. We found that LPS-induced NF-kB phosphorylation in type-2 dendritic cells (DC) before therapy, significantly correlated with lack of clinical response to adalimumab after 12 weeks (r2=0.573, FDR<10-10). In vitro DC maturation and frequency of circulating IL-17+ T cells were increased in PASI75 non-responders before therapy. Moreover, lesional skin of non-responders contained more activated dermal DC and increased numbers of IL-17+ T cells. Finally, we clinically validated LPS-induced NF-kB phosphorylation at baseline as a predictive biomarker of non-response to adalimumab (93.3% accuracy, 100% sensitivity and 90.1% specificity) in an independent cohort of an additional 15 patients. Our study has uncovered key molecular and cellular players in adalimumab’s mechanism of action in pachydermia and identified a blood biomarker for predicting clinical outcome before commencement of therapy.