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The Milieu Intérieur study — An integrative approach for study of human immunological variance☆

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Abbreviations: AbdoCM, abdominal circumference; ALP, alkaline phosphate; ALT, alanine aminotransferase; ANSM, Agence Nationale de sécurité du médicament et des produits de santé; AST, aspartate aminotransferase; BASO, basophil; β-HCG, beta-human chorionic gonadotropin; BILI, bilirubin; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; CLT, clinical laboratory test; CMV, cytomegalovirus; CREAT, creatinine; CRF, case report form; CRO, clinical research organization; CRP, C-reactive protein; CVD, cardiovascular disease; df, degree of freedom; DYSBP1, diastolic blood pressure; EBV, Epstein–Barr virus; ECG, electrocardiogram; eCRF, electronic case report form; EOS, eosinophil; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; GLUC, glucose; HAS, human serum albumin; HBV, hepatitis B virus; hCG, human chorionic gonadotropin; HCO3, bicarbonate; HCT, hematocrit; HCV, hepatitis V virus; HDL, high density lipoprotein; HGB, hemoglobin; HIV, human immunodeficiency virus; HSA, human serum albumin; HTLV, human T cell lymphotropic virus; IgA, Immunoglobulin A; IgE, Immunoglobulin E; IgG, Immunoglobulin G; IgM, Immunoglobulin M; INSEE, Institut National de la statistique et des études économiques; IQR, interquatile range; K, potassium; LabEx, Laboratoire d'Excellence; LDL, low density lipoprotein; LYMPH, lymphocyte; MAMP, microbial-associated molecular pattern; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; mM, glucose level; MONO, monocyte; Na, sodium; NEUTR, neutrophil; P, phosphorus; PBMC, peripheral blood mononuclear cells; PCA, principal component analysis; PHOS, phosphorus; PLT, platelet; RBC, red blood cell; RT, room temperature; SNP, single nucleotide polymorphisms; SOPs, standard operating procedures; SYSBP1, systolic blood pressure; TCHOL, total cholesterol; TG, triglyceride; TPROT, total protein; TRIGLY, triglyceride; UA, urinalysis; UAC, uric acid; V0, visit 0; V1, visit 1; V2, visit 2; WBC, white blood cell.

☆ One sentence summary: This report presents the first demographic data from the *Milieu Intérieur* Consortium, which has established a 1000-person healthy population-based study, for assessing the genetic and environmental determinants of human immunologic variance.

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Abstract The *Milieu Intérieur* Consortium has established a 1000-person healthy population-based study (stratified according to sex and age), creating an unparalleled opportunity for assessing the determinants of human immunologic variance. Herein, we define the criteria utilized for participant enrollment, and highlight the key data that were collected for correlative studies. In this report, we analyzed biological correlates of sex, age, smoking-habits, metabolic score and CMV infection. We characterized and identified unique risk factors among healthy donors, as compared to studies that have focused on the general population or disease cohorts. Finally, we highlight sex-bias in the thresholds used for metabolic score determination and recommend a deeper examination of current guidelines. In sum, our clinical design, standardized sample collection strategies, and epidemiological data analyses have established the foundation for defining variability within human immune responses.

1. Introduction

Susceptibility to infections, disease severity, and response to medical therapies or vaccines are highly variable from one individual to another. Medical practices and public health policies typically take a 'one size fits all' model for disease management and drug development. This approach ignores individual heterogeneity in immune responses that likely impacts the response to therapy or the efficiency and development of side effects secondary to vaccine or treatment administration. Due to the complexity of immune responses at the individual and population level, it has been challenging thus far to define the borders of a healthy immune system as well as the parameters (genetic, epigenetic, and environmental) that drive its naturally-occurring variability. In particular, such assessments require large sample sizes, consensus for defining "healthy", and standardized protocols for sample recruitment. In this context, the *Milieu Intérieur* Consortium initiated in September 2012 a cross-sectional healthy population-based study called *"Genetic & Environmental Determinants of Immune Phenotype Variance: Establishing a Path Towards Personalized Medicine (ID-RCB Number: 2012-A00238-35)"*.

The overall aim of the *Milieu Intérieur* study is to assess the factors underlying immunological variance within the general healthy population. The primary objective is to

[§] co-coordinators of the Milieu Intérieur Consortium. Additional information can be found at: http://www.pasteur.fr/labex/milieu-interieur.