A. PROTOCOL SYNOPSIS

Background: Influenza A H1N1/09 is a new virus against which potent adjuvanted influenza A H1N1/09 vaccines have been developed. These novel vaccines provide a unique opportunity to probe, qualify and compare the functional immune competence of patients with variable degrees of immune competence resulting from their age, underlying diseases and/or immunosuppressive treatment.

Primary Objective(s): To assess the influence of age, disease condition and immunosuppression on the acquisition of influenza A H1N1/09 vaccine immunity, in order to identify correlates or markers of immune competence.

Methodology : Prospective, open-label, parallel-cohorts study.

Study groups/Sample size: Six cohorts (n=1500) have been constituted:

1) Adult HIV-infected patients under HAART, at various stages of their disease evolution, as characterized by high or low CD4 T cell counts (n = 200);
2) Adult patients with rheumatic diseases treated by classical DMARDS, TNF inhibitors or B-cell depleting therapies (n=300);
3) Adult patients undergoing treatment for solid or hematologic malignancies, expected to result into minimal, moderate or severe immunosuppression (n = 300);
4) Adult patients at various time after solid organ transplantation (heart, kidney, lung, pancreas, liver) requiring various degrees of immunosuppression (n=250);
5) Pediatric patients at risks because of young age (prematurity) or underlying disease / treatments affecting their immune competence (n= 200).
6) A common healthy control group (n=250) constituted by spouses/partners and health-care-workers from the University Hospitals of Geneva.

Inclusion Criteria: Meeting cohort-specific criteria; medically indicated influenza A H1N1/09 immunization; follow-up in Geneva during 3 months; signed informed consent.

Exclusion Criteria: Refusal to participate; insufficient blood volume.

Intervention: Venous bleeding before and 4-6 weeks after 2 doses of adjuvanted influenza A H1N1/09 vaccine, at 3 weeks interval.

Follow-up: Baseline and post-immunization functional antibodies (inhibition of hemagglutination, microneutralisation) and T cell responses; vaccine adverse events.

Endpoint(s): Primary endpoint: Antibody responses (IH, MN). Secondary endpoints: antigen-specific cytokine-producing T cells, vaccine-induced adverse events.

Statistical Analysis: Comparison of immunogenicity endpoints and confidence bounds of each cohort, group and sub-group (by Chi-square or Fisher exact test, and Wilcoxon's test or Kruskal-Wallis test) within a group, a cohort and across cohorts. The influence of variables will be tested in an univariate way. A logistic model will be constructed to study the factors likely to explain the proportion reaching the primary endpoints. A multivariate analysis (logistic regression) will compare patients and healthy controls, while adjusting for other variables. The goodness-of-fit will be analysed using the Hosmer-Lemeshow' test. Recorded solicited adverse events will be described and compared using non-parametric methods.

Time Frame: 2 years

Budget: Data management (22'000.-), field work (126'000.-), sample preparation (74'000.-), immunological analyses (355'000.-), statistical analyses (32'000.-); study materials and laboratory reagents (100'000): **total CHF 709'000.-**

Demand to the CRC : **CHF 360'000.-**