Grant Training Center

1901 N Fort Myer Drive
Suite 1016
Arlington, VA 22209

NIH Grant

NIH Specific Aims Page

The development of the mammalian immune system is typically thought to occur in a linear fashion, from immaturity to maturity as a function of antigen exposure. Previous findings in birds and in mice, however, indicate that this view is oversimplified. Thus, in these species, the developing immune system appears to be "layered" in a manner that is independent of antigen exposure, beginning as a multilineage fetal system that is replaced by an anatomically and biologically distinct multilineage system after birth. If so, then developmentally ordered and unique hematopoietic stem/progenitor cells (HSPC) could give rise to distinct lymphocyte lineages at different stages of development.

In ongoing experiments, we have found that such immune system "layering" occurs in humans. Our preliminary data show that a vigorous human fetal immune response to exogenous antigens can be actively suppressed by antigen-specific Tregs, that these fetal Tregs are derived from a fetal-specific lineage of T cells, and that this lineage is generated by an HSPC that is distinct from that found in adults. These data suggest that the human immune is comprised of two distinct waves: one generated from a "fetal" HSPC that exists in utero in the fetal liver and bone marrow, and another generated from a superseding "adult" HSPC that resides in the bone marrow at later time points. The former gives rise to an immune system that is prone to deliver a to lerogenic response to foreign antigens. The latter gives rise to an immune system that is more likely to generate an immunoreactive responses (e.g.,one including cytotoxic T cells and neutralizing antibodies).

Given these findings, we hypothesize that physiologic layering of immune system ontogeny leads to a normal range in the ratio of fetal- to adult-type T cells at birth, with some neonates exhibiting a higher fraction of fetal T cells than others; and that those with a high ratio of fetal/adult T cells will generate predominant Th2 responses to routine childhood immunizations.

These hypotheses will be addressed in the experiments of the following Specific Aims:

> **Specific Aim 1. To determine the normal range of fetal to adult T cells in the umbilical cord blood of the full term neonate.**
> In these experiments, comprehensive phenotypic, transcriptional, and functional analyses will be carried out on umbilical cord blood (UCB) mononuclear cells from a total of 200 normal full-term deliveries, obtained over an 18-month time frame from the Human Cord Blood Bank of the UCSF Clinical and Translational Sciences Institute, from

1901 N Fort Myer Drive
Suite 1016
Arlington, VA 22209

Dr. Elizabeth Shpall of the University of Texas M.D. Anderson Cancer Center, and as part of a prospective study to be carried out with Dr. Shannon Thyne of the Child Health Center at San Francisco General Hospital (SFGH). Naïve T cells in these samples will be studied to determine the ratio of fetal/adult T cells (TF/TA) and the relationship of this ratio to naïve T cell function.

<u>Specific Aim 2.</u> To determine whether those full-term neonates with a high ratio of fetal/adult T cells are more likely to generate a Th2-polarized immune response to routine childhood immunizations.
Under the auspices of an existing protocol that has been approved by the UCSF Committee on Human Research protocol and in collaboration with Dr. Shannon Thyne, 50 full-term infants will be followed from birth through 12 months. Cord blood samples obtained from each of these newborns will be examined for the TF/TA ratio and this ratio will be related to the response of the newborn to hepatitis B vaccination.

We anticipate that this study will reveal normal variation in the ratio of fetal to adult T cells at birth and that such variability in this ratio will be directly related to – and possibly causal of – a Th2 skew that results in a poor response to childhood vaccines *and* a heightened predisposition to childhood infections and to atopic disorders. If so, then modalities aimed at changing this ratio more towards the adult lineage at birth may provide benefit to a substantial number of newborns.