

University of Maryland Baltimore Graduate School

Announcement of Doctoral Dissertation Defense*

Candidate: Kim Graulich-Hankey

Date, Time, and Place: July 3, 2007; 9:00am; Bressler Research Building 9th Floor Conference Room

Dissertation Title: Thymic Contribution to the Generation and Maintenance of the Peripheral T-cell Pool in Healthy and Lympho-depleted Subjects

Dissertation Abstract**:

The ability of the T-cell population to recognize and respond to a wide array of antigens is created in the thymus during thymocyte differentiation when the assortment of T-cell receptor gene segments, encoding the different parts of the TCR α and β chains, are assembled in a variety of combinations to form the TCR. T-cell receptor excision circles (TRECs), stable by-products of this process, are extra-chromosomal DNA fragments that do not replicate during cell division and therefore are used as a marker of thymic origin. We quantified the percentage of TRECs in CD4+, CD8+, and CD4+CD25+ peripheral blood T-cells of healthy newborns and adults in order to test the hypothesis that the thymus contributes equally to the formation and maintenance of these T-cell subsets. We find that the thymus and post-thymic proliferation equally contribute to the generation of the newborn T-cell repertoire and confirm the inverse association of thymic activity and age. Interestingly, when compared to CD4+ T-cells, the frequency of TRECs in CD4+CD25+ T-cells is significantly lower in both newborn and adults. In the newborn, this appears to be due proliferative expansion of the CD4+CD25+ T-cells as approximately 4.5 times more CD4+CD25+ cells express the memory marker, CD45RO, than do CD4+ T-cells. When applying regression modeling to our data, we find the rate of T_{reg} TREC loss to be significantly faster than loss in the other T-cell subsets consistent with the notion that this subset of T-cells is highly proliferative and can also originate from TREC poor CD4+ memory T-cells upon antigen-induced activation. To evaluate thymic reconstitution of T-cells in lymphodepleted subjects, we monitored TREC levels in five Multiple Myeloma patients following autologous hematopoietic stem cell transplantation (aHSCT). One year post-transplant, the numbers of TREC in CD4+ T-cells returned to baseline in 4 of the 5 patients but only 1 patient experienced TREC CD8 T-cell TREC restoration. Interestingly, the 1-year post-aHSCT CD4+CD25+ TREC levels in 2 subjects were higher than baseline quantity. Although T_{reg} TREC level did not return to baseline in the remaining 3 patients, the content in this T-cell subset was higher than in CD8+ T-cells.

Dissertation Committee Chair: Dr. Dean L. Mann, M.D.

Dissertation Committee Members (names and titles): Dr. Alan S. Cross, M.D.
Dr. Thomas J. MacVittie, Ph.D.
Dr. Martin F. Flajnik, Ph.D
Dr. Aaron P. Rapoport, M.D.

The Open Presentation is open to the university community and invitees of the candidate. Any member of the Graduate Faculty may observe the Final Examination. Only committee members may vote. For more information, see **Procedures for*

Examination of the Doctoral Dissertation.

***You must type your abstract on this form in the space provided.*

Updated: February 24, 2006