Frederick National Laboratory for Cancer Research

The Basic Research Program
Frederick National Laboratory for Cancer Research

Mary Carrington

FNLAC Presentation

Oct 24, 2019

Basic Research Program

Frederick National Laboratory for Cancer Research

The mission of the BSP is to conduct investigator-initiated research in immunology, genetics/epigenetics, cell biology, and computational biology to gain a more thorough understanding of processes involved in human disease, with emphasis on cancer and HIV disease.

The BSP is closely integrated within the Center for Cancer Research (CCR) of the NCI

Frederick National Laboratory for Cancer Research

- **There are 80 full time employees within the Basic Science Program**
  - 6 BSP Principal Investigators whose research laboratories are embedded within CCR Laboratories or Programs:

    Dr. Stephen Anderson, Cancer and Inflammation Program (Dr. Giorgio Trinchieri)

    Dr. Mary Carrington, Cancer and Inflammation Program

    Dr. Jonathan Keller, Mouse Cancer Genetics Program (Dr. Leno Tessarollo)

    Dr. Kathrin Muegge, Mouse Cancer Genetics Program

    Dr. Ruth Nussinov, Cancer and Inflammation Program

    Dr. Cheryl Winkler, Basic Research Laboratory (Dr. Joel Schneider)
  - 17 FTEs working in support of PI research goals
  - 48 FTEs embedded within CCR labs providing research support to CCR's research goals
  - 8 FTEs providing operational, purchasing, and logistical support to BSP FNL employees and CCR gov't employees

Funding and review processes of BSP staff

Frederick National Laboratory for Cancer Research

- All staff members of the BSP are reviewed annually, according to the review cycle of FNLCR.
- Every 4 years, the BSP PIs are reviewed along with their CCR Laboratory/Program colleagues.
- Funding of the BSP PI laboratories (including staffing and budget) is provided by CCR and is dependent on the results of the site visit reviews.

The Basic Science Program Office

Frederick National Laboratory for Cancer Research

The mission of the BSP Program Office is to provide operational and logistical support to the BSP and to provide purchasing support to the both the BSP and CCR

Primary responsibilities:
Purchasing, travel for FNLCR employees, facilitation of several seminar series

- Processed 20409 orders since implementation of the Purchasing Support Request System in Dec., 2018

The group consists of a program manager (Tammy Eyler) and 7 staff members

Stephen K. Anderson, Ph.D.

Molecular Immunology Section, CIP

Frederick National Laboratory for Cancer Research

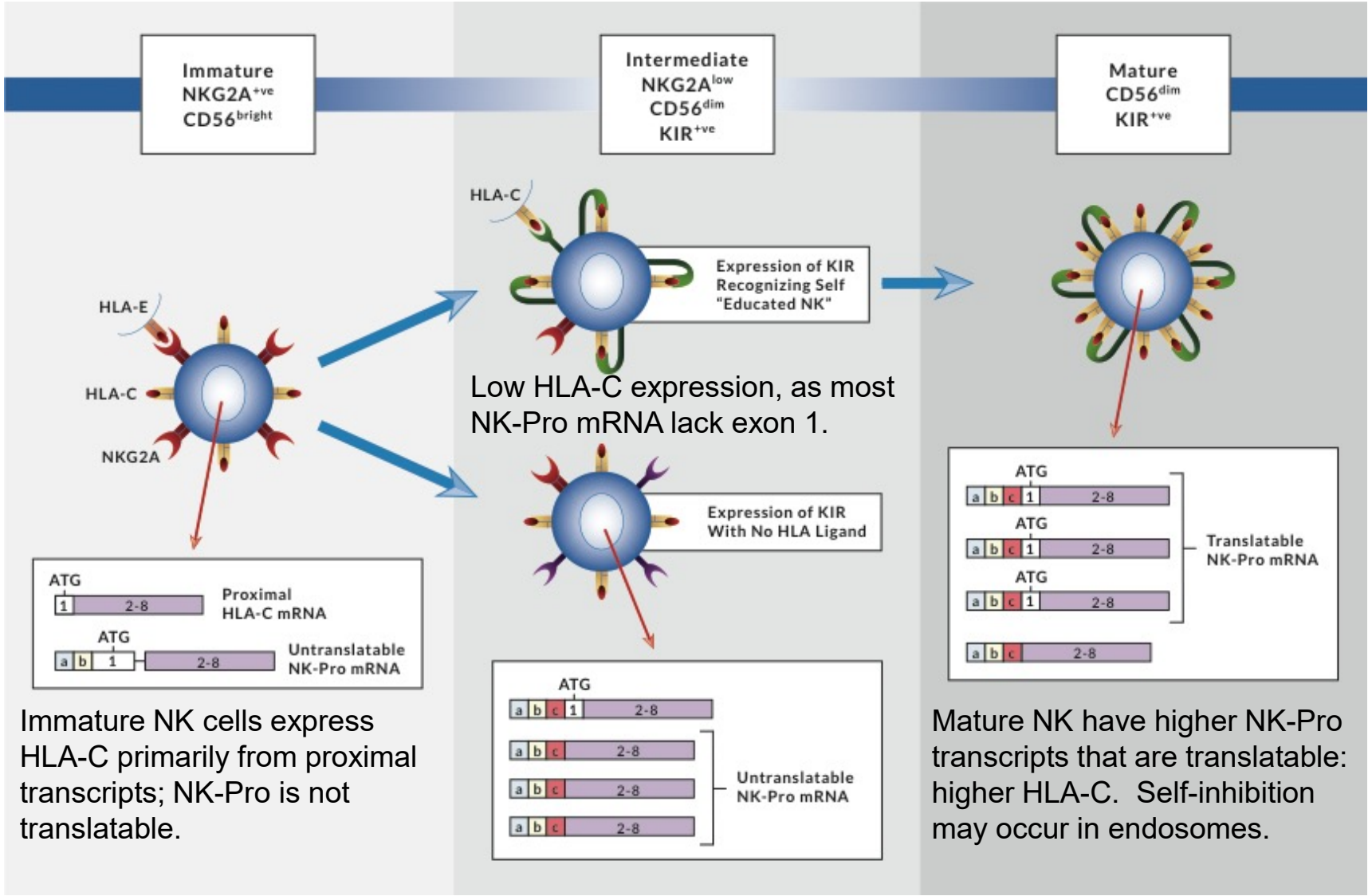
- Dr. Anderson's lab is focused on unraveling the mechanisms controlling the stochastic process whereby MHC class I receptors are expressed by subsets of NK cells. Their discovery of probabilistic promoter switches in the separately evolved KIR and Ly49 gene families produced a novel paradigm for the selective activation of genes. This paradigm has important implications for the control of stem cell fate, and the possibility of modifying differentiation outcomes in various systems.
- **Primary Goal: Delineate gene regulation in the immune system**
  - Particular emphasis on major histocompatibility genes and their receptors expressed by natural killer (NK) cells.
  - Decision-making processes of lineage-defining transcription factors
- Dr. Anderson supervises four full time staff members

Recent publications:

Anderson SK, *HLA* 2018; **92**:271-278 *
Li H, *PLoS Genet* 2018; **14**:e1007163 *
Forero A, *Immunity* 2019; **51**(3):451-64

The HLA-C transcript profile varies across distinct stages of NK cell differentiation

Frederick National Laboratory for Cancer Research



Low HLA-C expression, as most NK-Pro mRNA lack exon 1.

Immature NK cells express HLA-C primarily from proximal transcripts; NK-Pro is not translatable.

Mature NK have higher NK-Pro transcripts that are translatable: higher HLA-C. Self-inhibition may occur in endosomes.

Li H, *PLoS Genetics*, 2018; **14**(1):e1007163 *

Jonathan Keller, Ph.D.
Hematopoiesis and Stem Cell Biology Section
Mouse Cancer Genetics Program

Frederick National Laboratory for Cancer Research

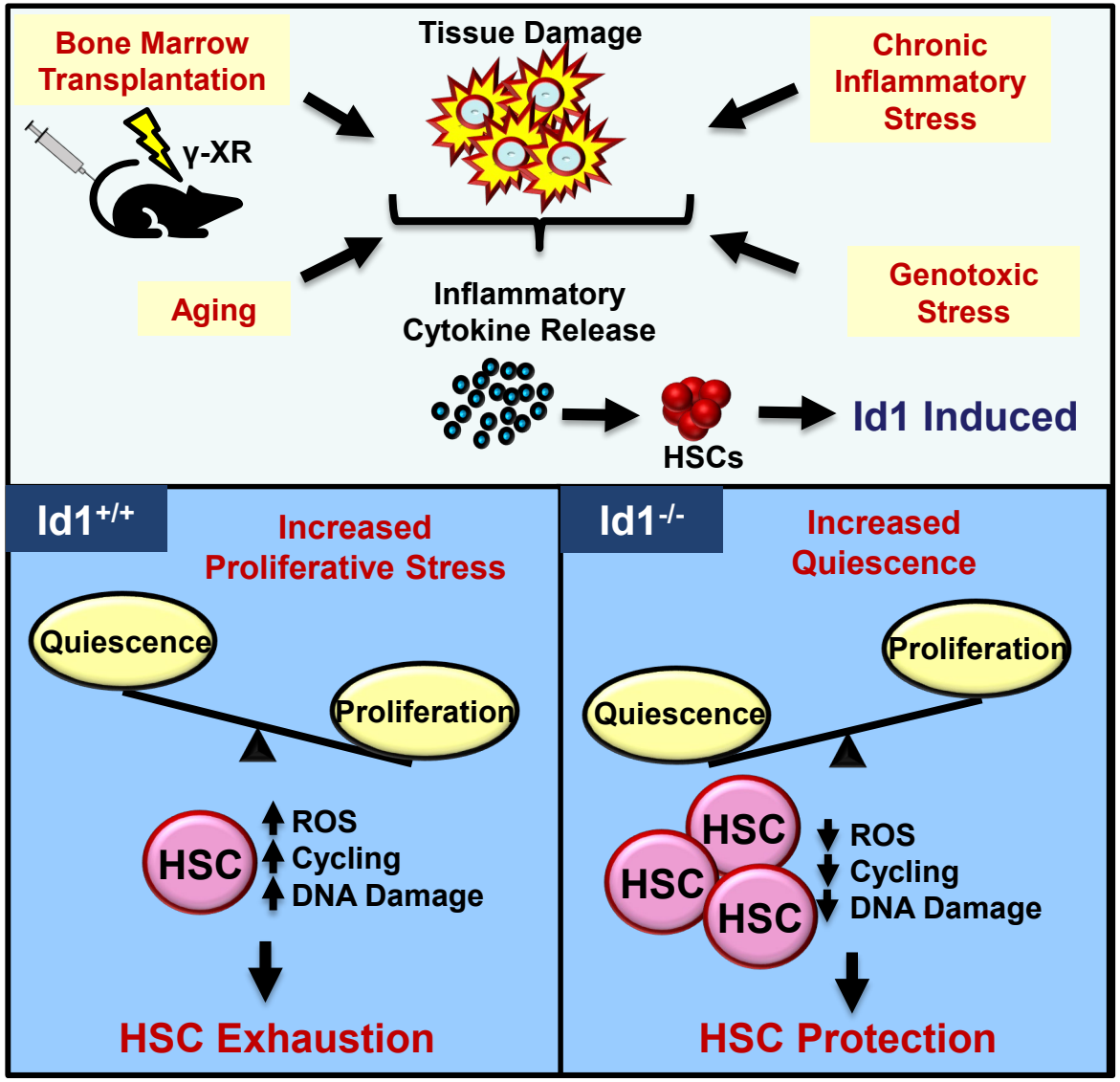
- Dr. Keller's laboratory is focused on understanding the cellular and molecular regulation of hematopoietic stem cell (HSC) quiescence, survival, self-renewal, and cell fate, as regulated by transcription factors and epigenetic regulators recruited to DNA. This ultimately leads to activation or repression of gene expression. His group is studying the physiological function of the inhibitor of DNA binding (Id) family of proteins in self-renewal, quiescence and cell fate determination with the aim to develop novel therapeutic agents.
- **Primary Goal: Identify and Define the Molecular and Cellular Pathways that Regulate Hematopoietic Stem Cell Quiescence, Self-Renewal, and Differentiation.**
- **Determine the role of inhibitor of DNA binding (Id) proteins in normal and malignant hematopoiesis**
- Dr. Keller supervises 5 full-time employees.

Recent publications:

Singh SK. *Cell Stem Cell* 2018; **23**(2):252-65 *
Gudmundsdottir B, *Cell reports* 2018; **23**(11):3236-48 *

Id1 Ablation protects hematopoietic stem cells from stress-induced exhaustion and aging

Frederick National Laboratory for Cancer Research



XR conditioning for bone marrow transplants, aging, chemotherapy, or chronic inflammatory stress results in tissue damage and release of pro-inflammatory cytokines. Receptors for these ligands are present on HSCs resulting in increased proliferation and differentiation of HSCs.

Id1 inhibits E proteins, which regulate p21 and p27, proteins that induce growth arrest. Thus, presence of Id1 promotes HSC proliferation and absence of Id1 reduces chronic proliferative stress.

Targeting Id1 may improve HSC survival and function during chronic stress and aging.

Singh SK, *Cell Stem Cell* 2018 *

Kathrin Muegge, M.D.

Epigenetics Section, Mouse Cancer Genetics Program

Frederick National Laboratory for Cancer Research

- Dr. Muegge studies molecular mechanisms that alter chromatin structure and function during murine development. She discovered several links between chromatin modifiers, including nucleosomal remodeling and DNA methylation. Her work focuses on chromatin changes during normal cellular differentiation. Her studies provide insights into how stable gene expression is achieved, how cells maintain a proper phenotype, and how this process may be disturbed in disease pathogenesis, including cancer.
- **Primary goals: Delineate the impact of epigenetic changes on mammalian development**
  - Identify the effect of DNA methylation changes on gene expression, recombination and DNA repair, and determine the role of chromatin remodeling in allowing access to DNA
- **Determine the role of Lymphoid Specific Helicase homolog, a chromatin remodeler, in the human Immune Deficiency Centromeric Instability Facial Anomalies (ICF)4 syndrome**
  - Determine how it regulates transcription factor binding, immunoglobulin switch recombination, and replication fork protection
- Dr. Muegge supervises 4 full-time employees

Recent publications:

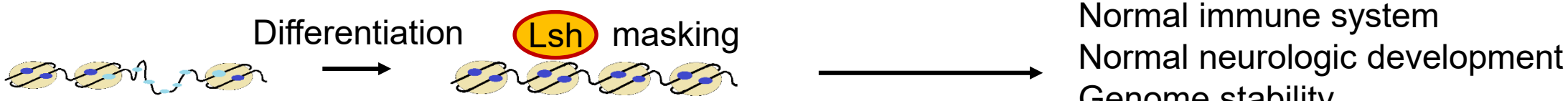
Ren J, *Epigenetics* 2019; **14**:277-293 *
Ren J, *Epigenetics* 2018;**13**(2):173-181 *
Han Y, *Sci Rep* 2017; **7**(1):1136 *

Lsh regulates nucleosome occupancy and chromatin accessibility during development

Frederick National Laboratory for Cancer Research

Lsh in normal development:

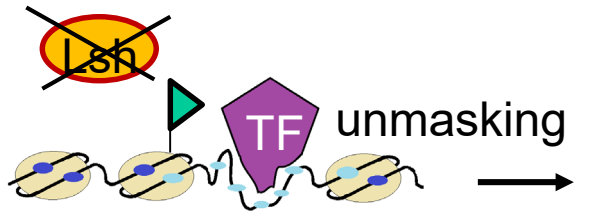
- Regulates nucleosome density
- Masks transcription factor binding sites
- Protects nascent DNA
- Critical role in hematopietic and neurological development



Normal immune system
Normal neurologic development
Genome stability

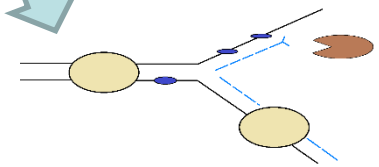
Lsh malfunction (mutation):

- Chromatin structure altered
- Access to transcriptional reg. sites changes
- DNA at replication fork changed
- Defects in recomb. of immunoglobulins
- Defects in DNA repair
- Genomic instability
- Immunodeficiency
- Insights to ICF syndrome



DNA access,
IgG switch
recombination

Chromatin Changes



Genomic Instability,
Tumor development

ICF syndrome

Replication fork protection

Ruth Nussinov, Ph.D.

The Structural Biology Section, CIP

Frederick National Laboratory for Cancer Research

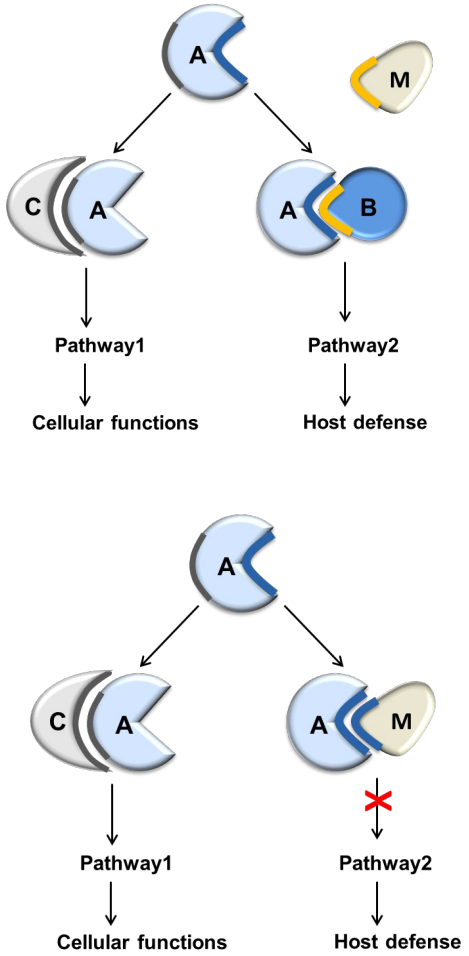
- Dr. Nussinov's section uses modelling to obtain insight into molecular structure, function and signaling. Her studies unveiled the key role of allostery under normal conditions and in disease, and the principles of allosteric drug discovery. She is interested in the structural basis of protein oncogenic transformation and cancer signaling. Her research focuses on key signaling proteins in the cellular network, Ras, its activators, its major effectors, their signaling pathways and allosteric structural regulation.
- **Primary Goal: Unraveling KRas4B oncogenic signaling at the membrane, focusing on the detailed mechanisms of activation of PI3K, Raf, RASSF5 tumor suppressor, MAPK and PI3K/Akt signaling pathways as well as other signaling proteins involved in these pathways.**
- **Goal: Unraveling how microbes alter host signaling and evade immune surveillance through protein cross-talk**
  - The section developed the first computational structural method to predict how microbiota can hijack host signaling and revealed that oncoviruses can drive cancer by rewiring signaling.
- Dr. Nussinov supervises 5 full-time employees

Recent Publications:

Zhang M, *Chemical science*. 2019; **10**(12):3671-80 *
Jang H, *Structure* 2019; **27**: 1-13 *
Tsai CJ, *Biophys J*. 2019; **117**, 5–13 *

Host-microbe protein-protein interactions are facilitated via interface mimicry

Frederick National Laboratory for Cancer Research



A host protein (A) has two possible interfaces. Binding to protein C leads to signaling pathway 1. Binding to protein B promotes host defense pathway. A microbial protein (M, cream color) can compete with host protein B since it shares the same interface (yellow) to bind to host protein (A), thereby hijacking host cell defense signaling.

The section developed the first structural method to predict host-microbe interactions through interface mimicry.

Guven-Maiorov E, *PLoS Computational Biology* 2017;13(10):e1005579 *

Cheryl Winkler, Ph.D.
Molecular Genetic Epidemiology Group

Frederick National Laboratory for Cancer Research

- Dr. Winkler's laboratory studies the contribution of host factors that contribute to infectious and other complex diseases such as kidney disease and cancer. The aim is to identify drug targets and improved diagnosis.
- **Primary goal: The Impact of Genetic Variation on Global Health Disparities and Chronic Diseases**
  - Pathogen-selected, African specific genetic variants and their impact on major USA health disparities (*APOL1*, Sickle Cell Trait)
    - Spectrum of *APOL1* disease associations: progressive and end stage kidney disease, cardiovascular disease, HIV-associated nephropathy, preeclampsia
  - Association of African-specific variants on chronic diseases in sub-Saharan Africa

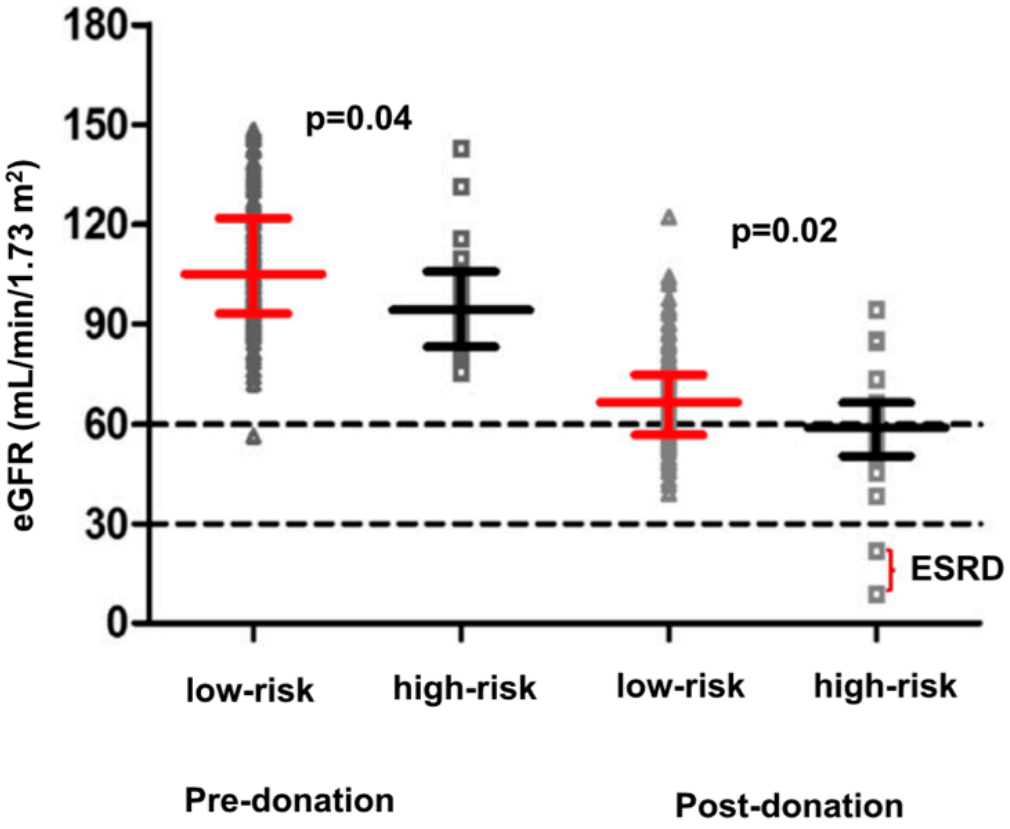
Dr. Winkler supervises 4 full-time employees, 1 part-time employee and 3 guest researchers

Recent Publications:

An P, *Front Immunol* 2019; **10**:53 *
Reidy KJ, *Am J Hum Genet* 2018; **103**(3):367-376 *
Doshi MD, *J Am Soc Nephrol* 2018; **29**(4):1309-16

Living kidney donors with APOL1 high-risk genotypes are at greater risk of decreased kidney function and end stage renal disease

Frederick National Laboratory for Cancer Research



- APOL1 high-risk donors had lower pre-donation kidney function (glomerular filtration rate (GFR))
- High-risk donors had lower compensatory rebound in kidney function post-donation
- Low-risk versus high-risk
  - Kidney failure: 0% vs 11%
  - Chronic kidney disease: 36% vs 58%
  - Mean GFR: 67 ml/min vs 57 ml/min
  - Albumin/creatinine ratio: mg/g: 4.9 vs. 8.4 mg/g

Based on this study, African Americans living kidney donors are now screened for APOL1 genotype at most transplant centers.

Doshi MD, *J Am Soc Nephrol* 2018; 29(4):1309-16

Mary Carrington, Ph. D.
HLA Immunogenetics Section

Frederick National Laboratory for Cancer Research

- Dr. Carrington's lab focuses on understanding the impact of genetic variation on resistance or susceptibility to human disease, with emphasis on immune response loci. This is accomplished through a variety of techniques such as whole-genome sequencing, genotyping as well as bioinformatics
- **Goal: Identify immunogenetic polymorphisms that associate with human disease**
  - Primary loci: HLA, KIR, Ig, CCR5
  - Diseases: Infections such as HIV, cancer, immune related disorders, transplantation
- **Goal: Determine the functional significance of these genetic associations**
  - Differential HLA expression levels
  - Allele-specific dependence on the antigen processing pathway
  - Interactions between NK cell receptors and HLA ligands

Dr. Carrington supervises 6 full-time employees, and 3 guest researchers

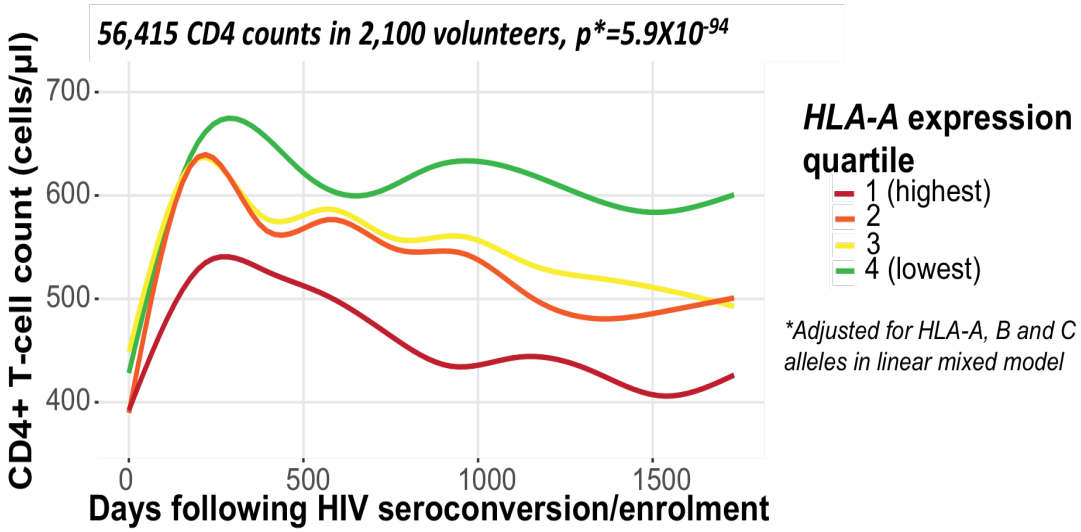
Recent publications:

Kulkarni S, *Nature Immunol* 2019; **20**: 824-834 *
Petersdorf E, *Lancet Haematology* 2019 In Press; *
Ramsuran V, *Science* 2018; 359: 86-90 *

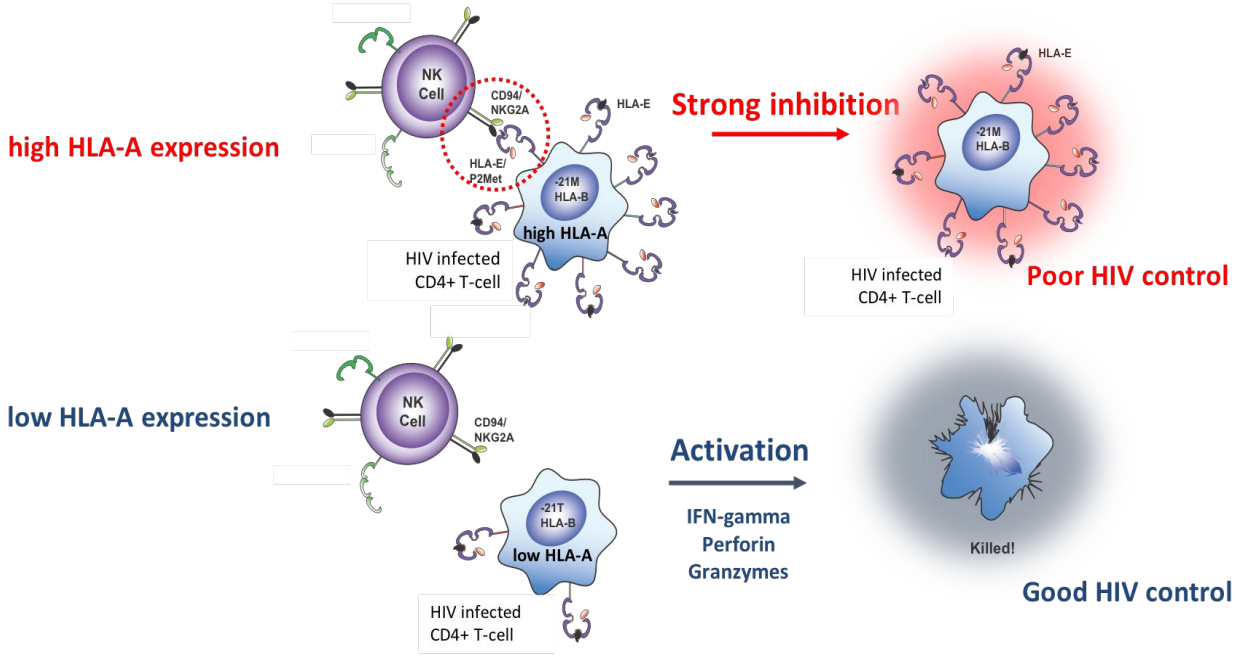
Elevated HLA-A expression levels impair HIV control through inhibition of NKG2A expressing cells

Frederick National Laboratory for Cancer Research

Elevated HLA-A expression associates with lower CD4 counts consistently over time



Higher HLA-A → higher HLA-E→ greater NKG2A-mediated NK cell inhibition



Ramsuran V, *Science* 2018; 359: 86-90 *