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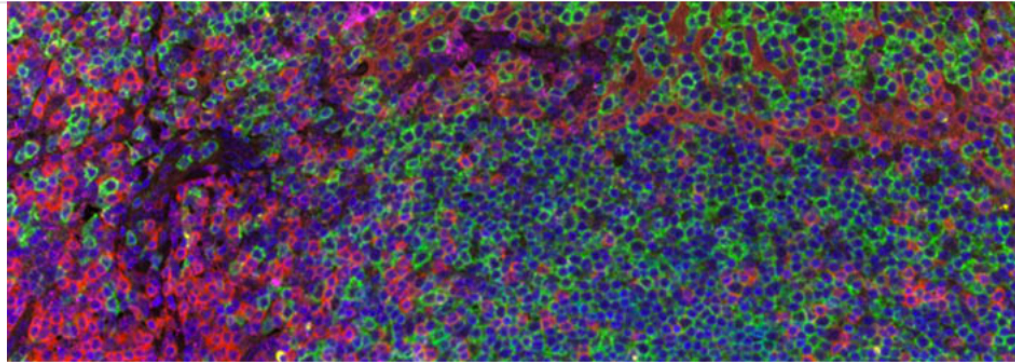
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Meet the Team

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Human Immunology & Immunotherapy Initiative (HI³)

After decades of investigation establishing principles in animal models, it has recently become possible to treat and cure some diseases in humans by interventions that target immunological functions. Immunotherapy, described by Science magazine as the Breakthrough of the Year in 2013, has led to major changes in the standard of care for some diseases and is particularly useful in infectious disease, autoimmunity, allergy/asthma, and especially cancer.

SUPPORT

ucdenver.edu/HumanImmunology

The **mission** of the **Human Immunology and Immunotherapy Initiative (HI³)** is to develop the infrastructure to create an all-inclusive facility that provides experimental models for the preclinical testing of new candidate therapeutics, reliable immunotherapeutic production, consistent clinical trials research support, and organized immune monitoring capabilities. In addition, the HI3 will train future scientific leaders within the realm of immunotherapy and recruit exemplary faculty to the CU Anschutz medical campus that will complement and enhance existing strengths.

The **ultimate goal** of the HI3 is to establish preeminence in human immune system-targeted therapies on the CU Anschutz medical campus.

Visit the
HI3
website





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Human Immunology and Immunotherapy Initiative Fund

To provide support to the HI3 initiative in the School of Medicine on the University of Colorado Anschutz Medical Campus.

Campus: **CU Anschutz**

Keywords: **School of Medicine**

Allocation Code: **0222914**

Interest: **Science, Research & Innovation**

The screen that you will see when you click on the

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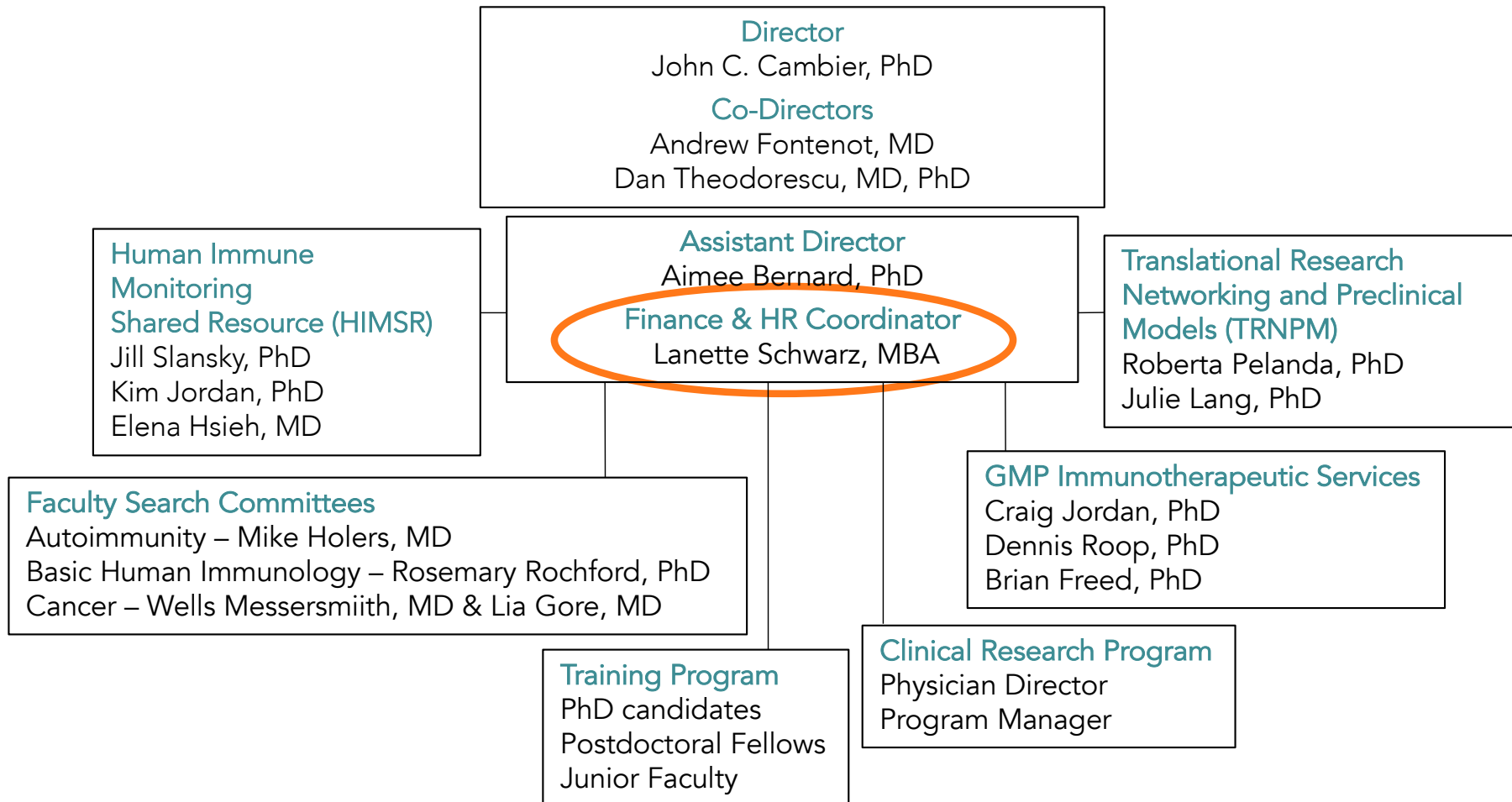


Human Immunology & Immunotherapy Initiative (HI³)

SCHOOL OF MEDICINE

UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

HI3 Org Chart & Activities





Human Immunology & Immunotherapy Initiative (HI³)

SCHOOL OF MEDICINE

UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

A c t i v i t i e s

- Faculty Recruitment
- Human Immune Monitoring Shared Resource (HIMSR)
- GMP Immunotherapeutic Production
- Training Program
- Clinical Research Program
- Translational Research Networking & Preclinical Models (TRNPM)



HI3 Faculty Recruitment UPDATE

- **Basic Human Immunology**

- ✓ 6 candidates interviewed fall 2016-spring 2017
- ✓ Resume search fall 2017

- **Autoimmunity**

- ✓ HI3 Autoimmunity Program Director (might change title to 'Autoimmunity & Immune Dysregulation Program Director to cast a wider net)
- ✓ 1 interview April 2017, additional interview(s) anticipated late 2017

- **Cancer**

- ✓ Terry Fry, MD (NCI) – verbal acceptance January 2017 and proposed start January 2018
- ✓ Lei Zheng, MD (Hopkins) declined the offer

- **Data Scientist/Bioinformatician**

- ✓ 3 candidates interviewed spring 2017
- ✓ Offer and negotiations in progress



Human Immune Monitoring Shared Resource (HIMSR) UPDATE

- **HIMSR Team Members**

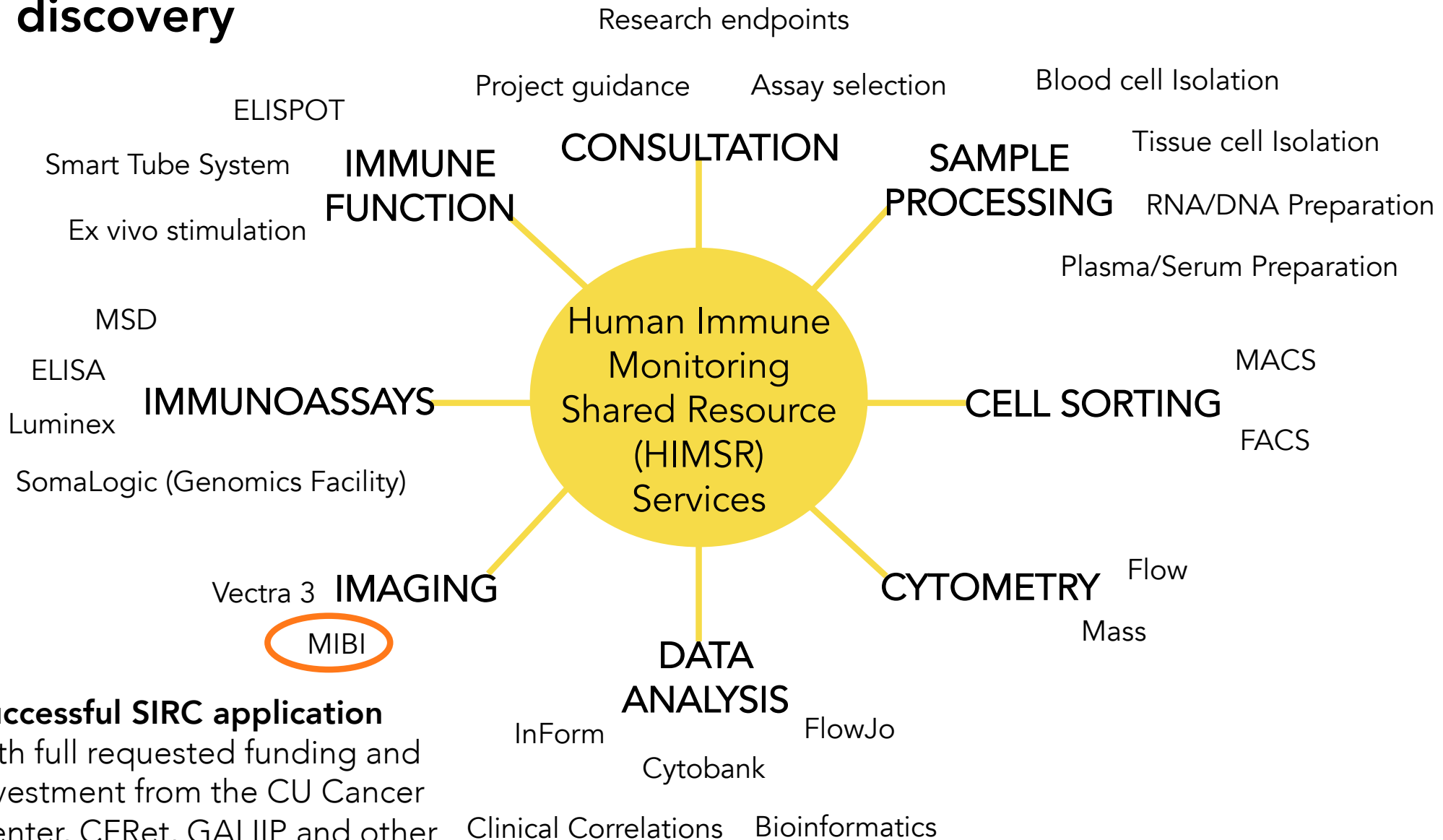
- Director: Jill Slansky, PhD
- Assistant Director: Kim Jordan, PhD
- Experimental Design Consultant: Elena Hsieh, MD
- Flow cytometry/protein purification specialist: Jennifer McWilliams, PhD
- Sr. PRA/Histology Specialist: Angela Minic, MS
- Immuno&Micro Flow Facility Manager: Erin Kitten, BS

- **Rate changes coming soon**

- Since the opening of the HIMSR in November 2016, initial rates were set at a loss to foster growth. Now that the HIMSR is running at full capacity, moving forward, HIMSR rates will begin to increase to allow for continued growth and sustainability of this shared resource.

Human Immune Monitoring Shared Resource (HIMSR) Services

- To facilitate and support human immunology research and discovery



Successful SIRC application
with full requested funding and
investment from the CU Cancer
Center, CFRet, GALIIP and other
colleagues across campus



Human Immunology & Immunotherapy Initiative (HI³)

SCHOOL OF MEDICINE

UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

HI3 GMP Immunotherapeutic Production UPDATE

- **Collaborate with CU AMC GMP facilities toward the production of clinical grade biological reagents and cell-based immunotherapeutic products**
 - ✓ Provide \$250,000 to Drs. E. Purev and C. Jordan for CAR-T cell process development in collaboration with Clinimmune and the Gates Center
- **Facilitate the use of campus CLIA labs for monitoring patient responses and clinical decision-making**
 - ✓ Exsera BioLabs - complement and autoimmune diagnostics
 - ✓ Colorado Molecular Correlates Laboratory (CMOCO) – anatomic pathology
 - ✓ Clinimmune – flow cytometry, cell sorting, histocompatibility



HI3 Training Program UPDATE

- **Develop and establish training programs across the training continuum at the pre-doctoral, post-doctoral, and junior faculty level**
 - ✓ Establish fellowships to support training and research for future leaders in immunotherapy starting in year 3 of initiative – 1-2 PhD candidates, 1-2 post-doctoral fellows, 1 junior faculty
 - ✓ Work with selected faculty and established campus services to provide educational resources
- **Form a Training Program Subcommittee to play a role in the design and structure of the program**
 - ✓ Assemble subcommittee in fall 2017 with structured schedule to roll out training program in fall 2018



Human Immunology & Immunotherapy Initiative (HI³)

SCHOOL OF MEDICINE

UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

HI3 Clinical Immunology Research Program UPDATE

- **HI3 Clinical Immunology Research Program Director**

- ✓ Physician scientist (MD) to develop and oversee program
- ✓ Establish structure (personnel structure, clinical research space, processing and storage)

- **Clinical Immunology Core**

- ✓ Provide ready access to high quality clinical data and biospecimens from subjects who are highly relevant to autoimmune and other immune-system related diseases, individuals at high-risk for disease (e.g. relatives, others with high-risk biomarkers) and healthy controls
- ✓ Goal to improve our understanding of autoimmune and other immune-system related diseases to advance scientific discovery, therapeutic innovation and, ultimately, prevention

Translational Research Networking & Preclinical Models (TRNPM)

- **TRNPM Team Members**

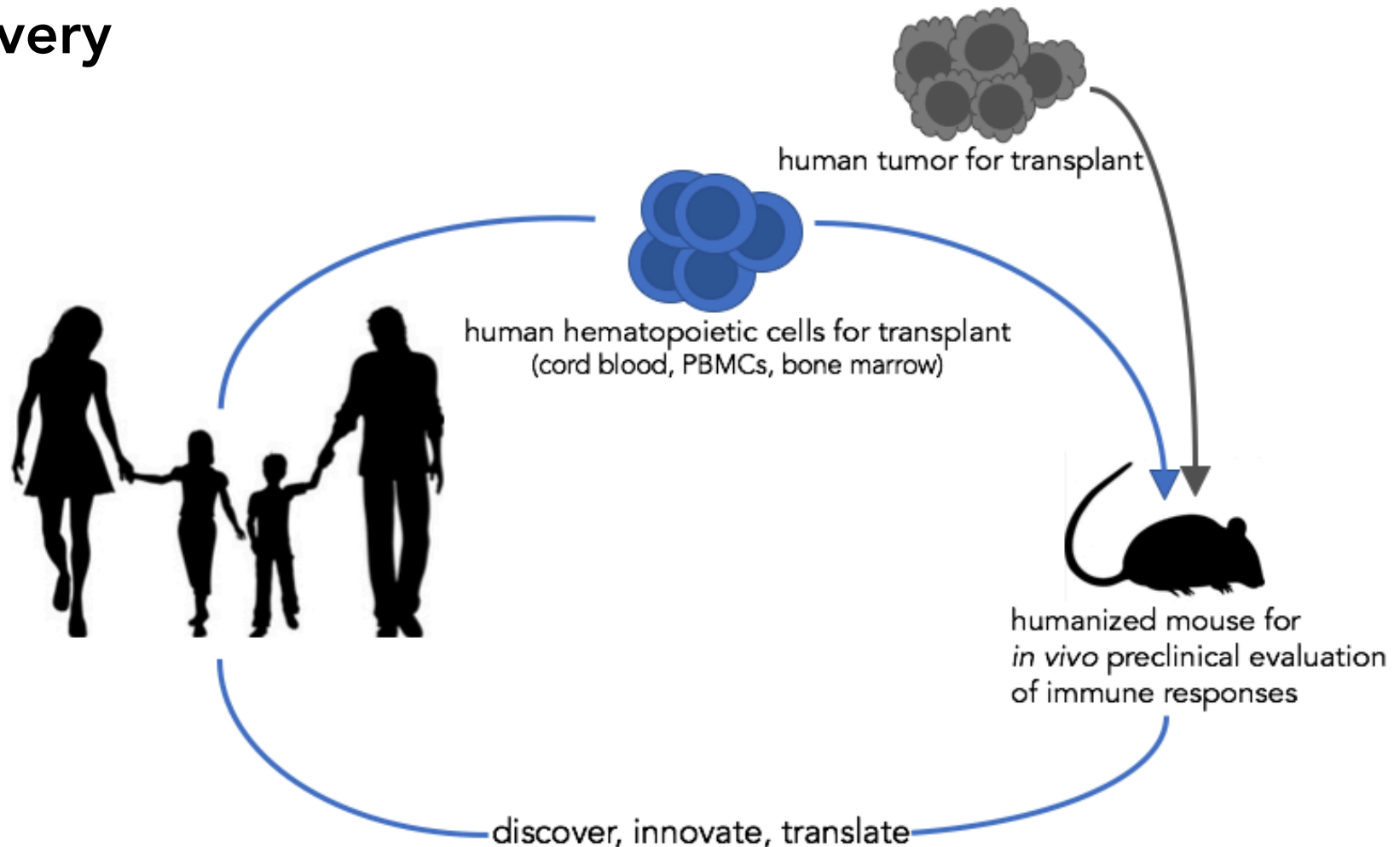
- Director: Roberta Pelanda, PhD
- Manager, H13 Humanized Mouse Core: Julie Lang, PhD
- Sr. PRA: Jessica Barkow, PhD
- PRA: Jacob Barbee, BS

Services include:

- ✓ **Enabling and promoting collaboration among investigators** along the continuum of basic-clinical-translational research by networking and/or matchmaking clinicians, clinician/scientists, and basic scientists with shared interests
- ✓ Establishing mechanisms that ensure **availability of human tissue** for research (umbrella COMIRB protocol)
- ✓ Developing and maintaining **preclinical mouse models** for testing of candidate therapeutics (e.g. humanized mice or hu-mice)

Translational Research Networking & Preclinical Models (TRNPM)

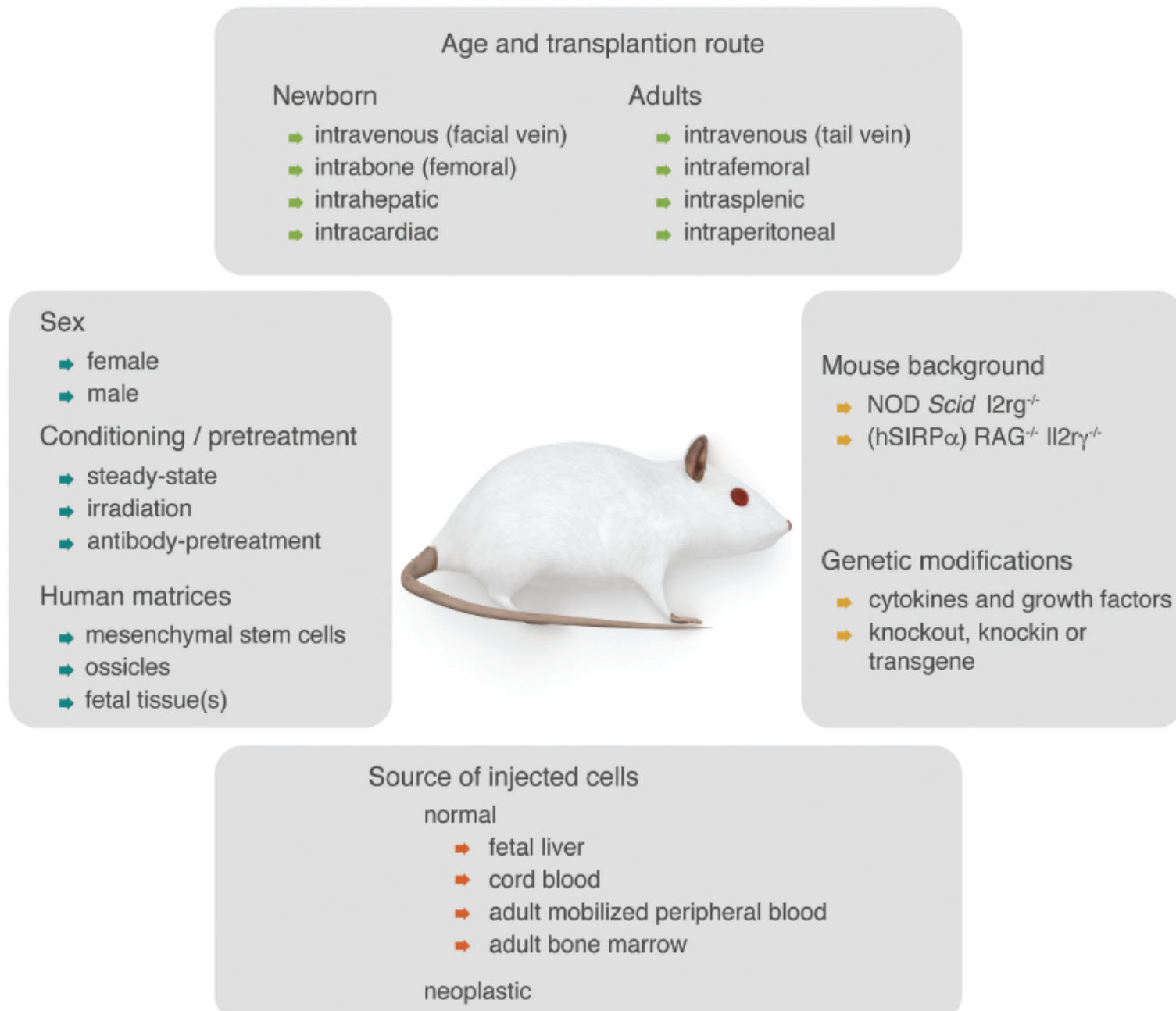
- To facilitate and support human immunology research and discovery



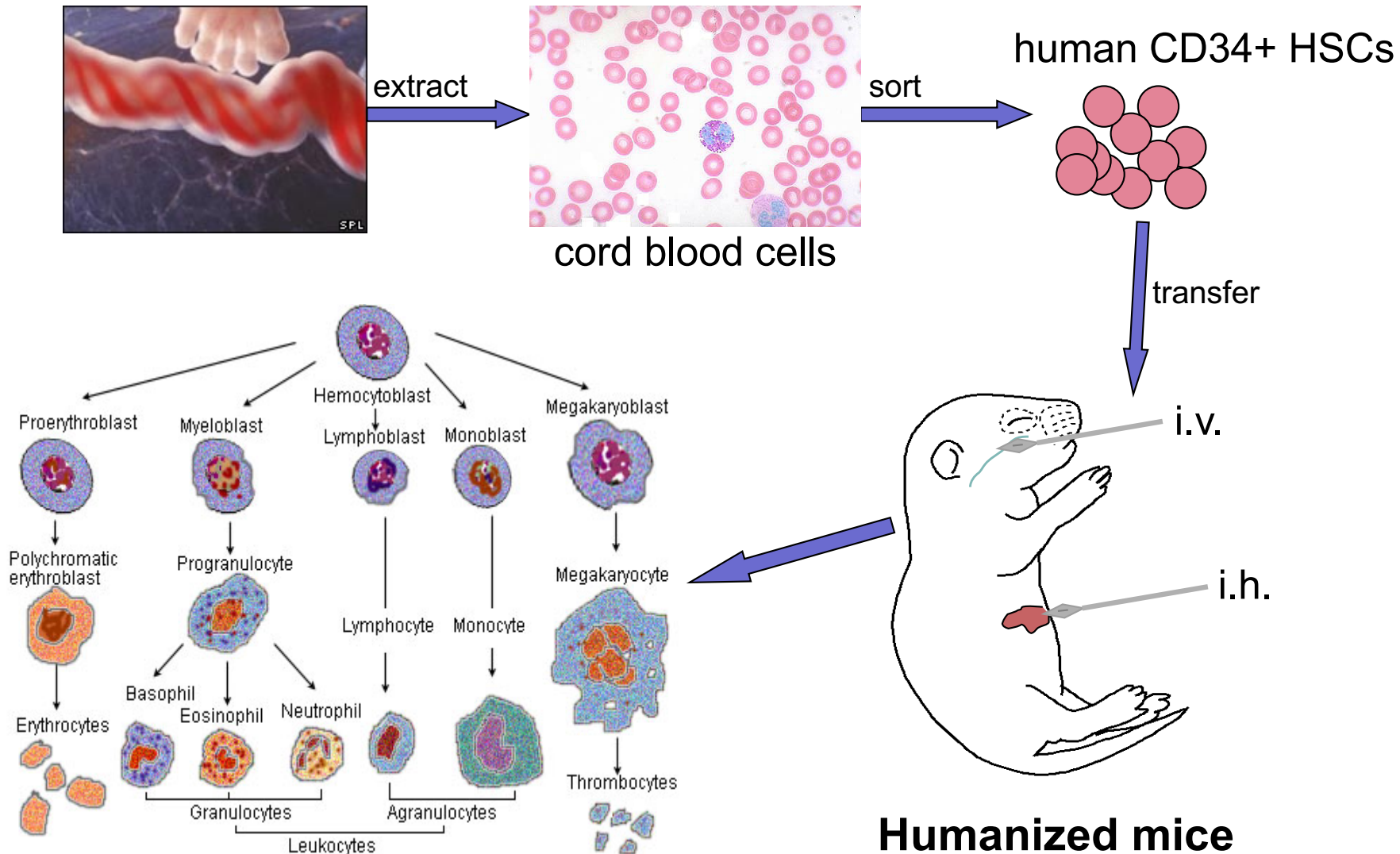
Utilization of humanized mouse models for preclinical testing

NOTE: UNPUBLISHED DATA HAS BEEN REMOVED FROM THE ONLINE VERSION OF THIS PRESENTATION

Various parameters for the engraftment of HSCs



Hematopoietic humanized mice in the Pelanda lab (TRNPM:CD34-CB-BRGS)



**NOTE: UNPUBLISHED DATA HAS BEEN
REMOVED FROM THE ONLINE VERSION OF
THIS PRESENTATION**

Humanized mice
BALB/c-Rag2^{null}-IL2r^{null}
(BRG/S)
Traggiai et al, Science 2004

General features of hematopoietic hu-mice

- **B cells** develop robustly in BM and exit to spleen and blood. Most B cells are initially immature but mature B cells are observed with time and T cell numbers.
- **T cells** enter the lymphoid and peripheral tissue after 3 months and increase in all organs to dominate the lymphocytes by 26 wks.
- Immune system reaches a **quasi-homeostatic state** with T and B cells in the spleen, lymph node and blood that lasts approximately 3 months.
- **Lymph nodes** develop late (~4 mo) and correlate with presence of serum IgM/IgG and mature B cell population.
- **Myeloid lineage** is inconsistently generated – some animals have clear populations, others do not.

Rationale for studying human immunotherapy in hu-mice

- ❖ Offers both a mouse capable of accepting human tumors (aka nude, SCID) but in the presence of a (suppressed) human immune system
- ❖ **The humanized mouse is a model with an immunosuppressive environment similar to a tumor microenvironment**
- ❖ Can study PDX tumors in vivo – not limited to cell lines
- ❖ Provides a preclinical in vivo model for human immunotherapies
 - Test human reagents on human immune cells
 - Platform to study combination therapies to improve responsiveness of tumors to PD1 therapies
- ❖ Investigate mechanisms of tumor killing

Conclusions: Humanized Mice and Immunotherapy

- ❖ Offers a system to test turning off “immunological breaks” in the tumor immunosuppressive environment
 - The Immunosuppression is reduced with Immunotherapy - more leukocytes infiltrate the tumors, more functional T cells (IFN γ) and lower tumor burden
 - Possible autoimmune side-effects – colitis? Unknown (mouse didn't tell me)
 - The specificity of the response is unknown (mouse, allo, tumor-specific?)
- ❖ Provides an experimental system to study combination therapies
 - Easy readout for a change of immune reactivity to tumor
 - **Collect data on numerous mice with same tumor and treatment**
- ❖ System to study mechanisms of immune system alterations as a result of therapy
 - Can study lymph organs and tumor infiltrating cells
 - Changes in immune system are most pronounced within tumor relative to LN or spleen

Humanized Mouse Facility Services

- ❖ Provide Humanized mice for Immune system/Immunotherapy/Autoimmunity Studies
 - Chimerism (>25%) guaranteed by bleeds at 10 and 15 weeks post reconstitution
- ❖ Provide expertise for experiments
 - Experimental Design
 - Immunological Expertise (flow panels, humanized mouse nuances/specifics)
 - Harvest of mouse tissues, flow cytometry, ELISAs, prep tissue for histology
 - Data analysis
 - Report

HI3 website – TRNPM Services and Fee Structure

Translational Research Networking and Preclinical Models (TRNPM) Services and Fee Structure for users within the CU system. Prices below are subsidized by the Human Immunology and Immunotherapy Dean's Transformation Initiative (CU School of Medicine). Further reduced rates are available for preliminary data that will be used in future grant applications, please inquire if your study qualifies.

Users outside the CU system, please inquire about non-academic, non-subsidized pricing.

CONSULTATION

	description	service fee	internal
Initial project consultation	Discussion of research project needs, a high-level view of experimental design and timeline, and associated analyses and services	FREE	
Experimental Design	Design of experiment including number of mice, treatments, time-course and flow cytometry panel design for analysis of humanized mouse lymph tissue	NA	\$295

HI3 website – TRNPM mice currently available

MICE

	description	unit	internal
BRGS	BRGS (BALB/c Rag2 ^{-/-} IL2R γ ^{-/-} SIRP α NOD mice)		
CD34-CB-HSC BRGS	Humanized mice generated from CD34 ⁺ HSCs from cord blood at birth and verified by two bleeds to be >25% human, > 15 weeks	per mouse	\$265
Hu-PBMC BRGS	Humanized mice generated from peripheral blood mononuclear cells (PBMC) from adult blood or cord blood and injected into adult BRGS immunodeficient mice. Human chimerism verified at 2 weeks post injection. Mice develop GVHD and should be used between 2-4 weeks and typically reconstitute with a predominate activated T cell population and approximately 15% B cells.	per mouse	\$200
Hu-CBMC BRGS	Immunodeficient mouse humanized by injection with human cord blood (CB) mononuclear cells (MCs).	per mouse	\$200

Humanized Mouse Work Flow - Logistics

- ❖ Interested investigators contact us – via email (julie.lang@ucdenver.edu or roberta.pelanda@ucdenver.edu) **or** request services through iLabs
- ❖ Set up initial (free) consult to discuss feasibility of project and timeline
- ❖ We provide quote (through iLabs), estimated timeline
- ❖ Investigator needs to add us and our mice to their Animal Protocol
- ❖ Humanized mice, guaranteed to be >25% chimeric at 10 and 15 weeks, are transferred to investigator's Animal Protocol at the start of the experiment

Humanized Mouse Work Flow - Experiment

- ❖ Mice are housed in a BSL2 room (investigators need to revise their animal protocol, possibly obtain their own BSL2 space, and acquire training and access to BSL2)
- ❖ Investigators or our TRNPM Core can perform manipulations (tumor transplant, drug treatment, measurements, etc.)
- ❖ TRNPM Core can perform/help with harvest at end of experiment
 - Flow Cytometry
 - Histology (w/HIMSR)
 - ELISA
 - Data Analysis
 - Report

Humanized Mouse Core Objectives I

Increase Understanding of Model

❖ VECTRA Analysis

- Optimize panel for humanized mouse tumors (including mouse Ab)
- Use flow to analyze tumors with best TILs

❖ Time course of effect of treatment and/or tumor on human immune system

- Use TNBC MDA-231 model
- Look at D0, D11 and D21 to detect infiltration into tumor of HIS
- Isolate RNA from TIL for transcriptome analysis

❖ Unbiased approach to analyze human immune system (CyTOF)

- Help guide us for future experiments
- Use TNBC line

❖ Study the reactivity of human immune system from Hu-mice to tumors

- In vitro
- Incucyte

Humanized Mouse Core Objectives II

Provide Alternative Models

- Improved T cell Selection
- Improved T cell Match for Tumor
- Reduced T cell Activation

Develop PDX models in BRGS models and transplant at early passage

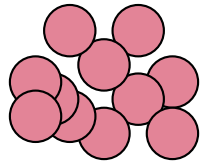
- Reduce “foreign” mouse stroma
- Help maintain more normal architecture of tumor

A challenge will be space in the mouse facility

T cell MHC match in humanized mice

Our model

Cord blood CD34+

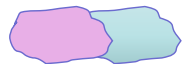
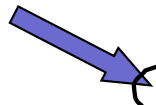
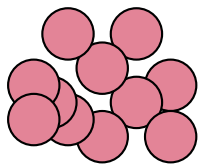


BRG/S

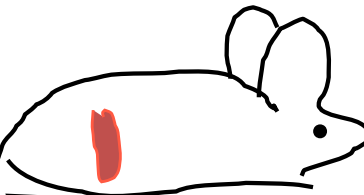
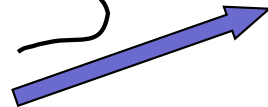
Match: None, possible HIS-Tumor (5/6 frozen CB)

Alternative models

Fetal liver CD34+



Fetal thymus + liver



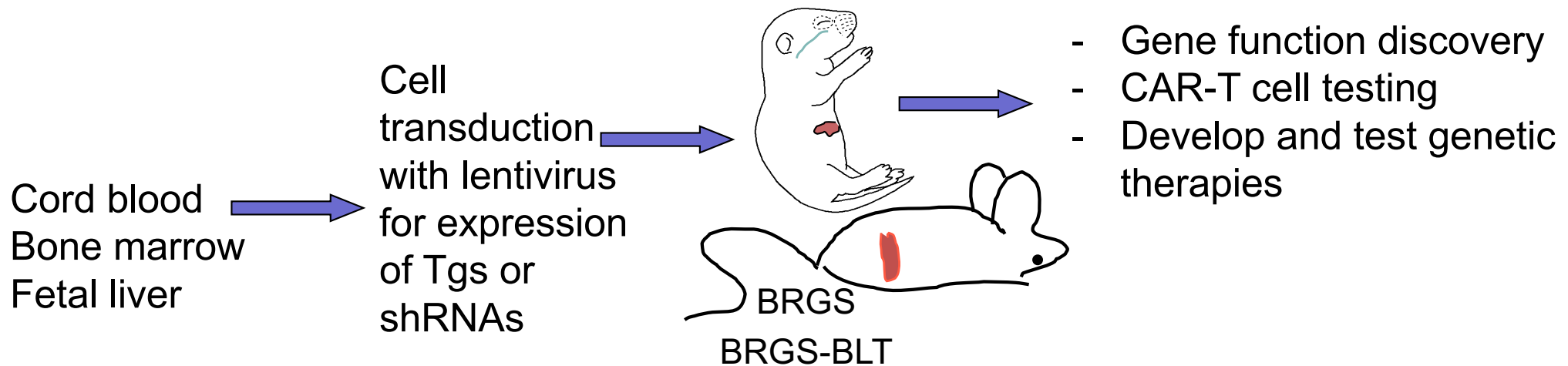
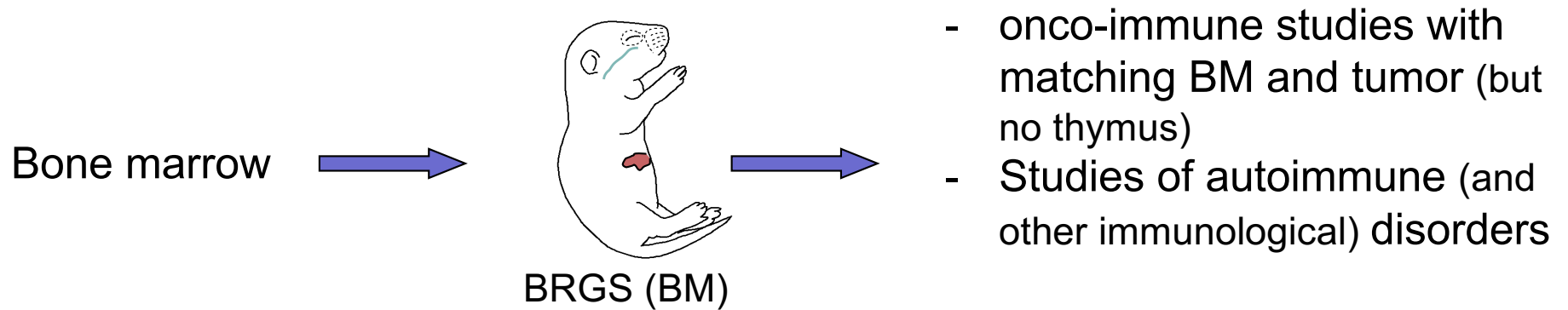
BRGS-
BLT

Match: HIS-Thymus

- Infection studies
- Vaccine studies
- Tumor studies

Generation of a HLA-Tg recipient HLA-A2, HLA-DR2

Models to provide in near future



Check us out! HI3 TRNPM

Website:

ucdenver.edu

HI³/TRNPM

iLabs:

Humanized Mouse
Preclinical Model
Core

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Thanks:

Pelanda Lab

Jessica

Jake

Jacob

Eckhardt Group

Todd

Anna

Wells