

VGTI

F L O R I D A



Infectious Diseases

Cancer

Center for Diseases of Aging

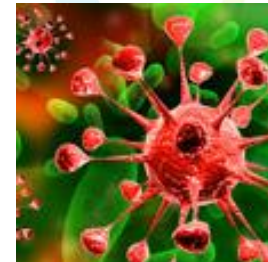
Translating Research into Health®



VACCINE & GENE THERAPY INSTITUTE

VGTI Florida[®]: At a Glance

- Independent, non-profit biomedical research institute
- 100,000 sq ft facility with active research groups in place
- ~70% of space dedicated to pure research activities
- Awarded nearly \$40M in grant funding (NIH, amfAR, corporate, etc.) in last four years



VGTI Florida[®]: Leadership

- 25+ years as PI, Professor, Program Director, Department Chair, Associate Director for Basic Research, Cancer Center Deputy Director, Director of Research Institute
- Recently at the Beckman Research Institute at City of Hope
- NIH funded research in areas of: tumor virology; molecular oncology; cytokine signaling; targeted therapeutics; and translational research



Richard Jove, Ph.D.
Institute Director

VGTI Florida®: A Center of Excellence in Immunotherapeutics

VGTI Florida is conducting discovery research and developing innovative, immune-based therapies for the treatment and prevention of :

- Cancers
- Infectious Diseases
- Diseases Associated with Aging

VGTI^{FL} Core Resources

- Dedicated technical resources available to all research groups
- Centralized leadership and advisory steering committee to meet research needs
- Dedicated highly trained staff using SOP driven workflows
- Standardized technical platforms for data consistency and integration
- Collaborative research centers (assist with study design, grant applications, publications)

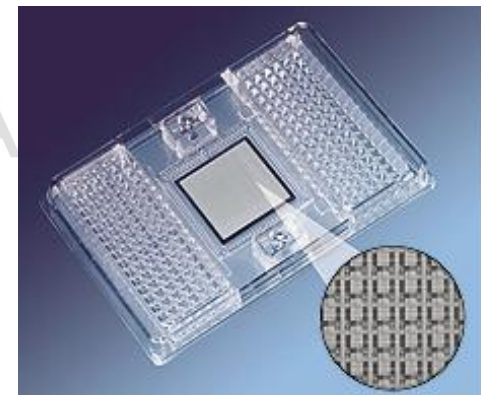
Collaborative Genomics Center

- Illumina CsPro certified lab
- GCLP certified SOPs and workflows
- Microarray, NGS Genomic DNA, mRNA, miRNA, Exome, epigenetics, SNP analysis
- Fluidigm platform for 96x96 digital QPCR with dedicated staff for gene panel design
- Small scale genomics (200 cells in bulk and single cell applications)
- Fully integrated with Bioinformatics for data analysis

ILLUMINA HiSeq 2500

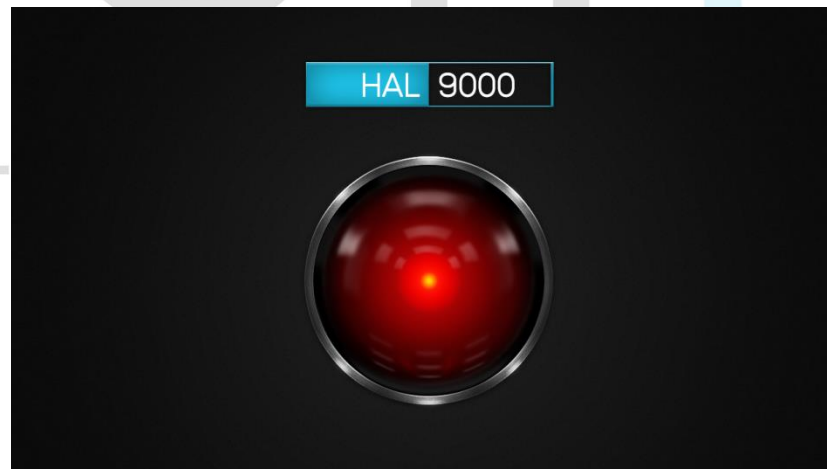


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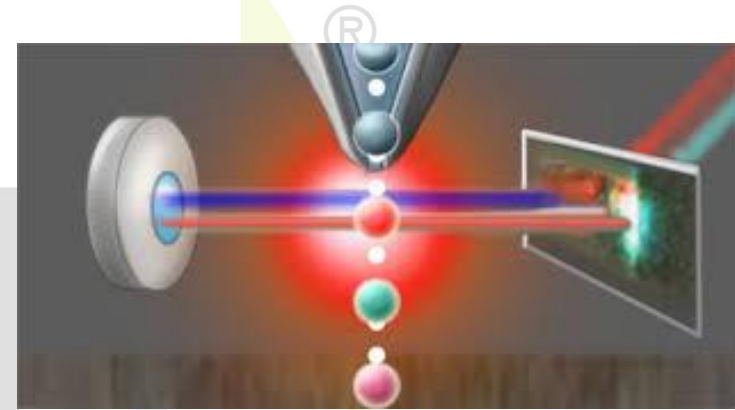
Bioinformatics Core

- Dedicated staff for data analysis, consultation and pipeline development
- Integrated data analysis and visualization approach
- Dedicated compute cluster 66 cores ~800GB RAM



Flow Cytometry core

- Multiparametric flow analysis and cell sorting
- BSL-3 level sorting
- Index sorting for single cell “omics” analysis
- Dedicated staff with SOP driven workflows



Vivarium and BSL-3 labs

- Animal facility for specific pathogen free rodent studies
- Humanized mouse models for immune system study
- Large capacity for ferret biology studies
- Select agent and BSL-3 dedicated spaces (CDC and USDA certified)
- AAALAC certified facility



Additional Resources

- Clinical trials core (protocol development, IRB, clinical resource alignment)
- In house development of Intellectual property
- Cell Therapy Core (large scale clinical grade production CD34+ stem cells, RPE cells, Cardiac stem cells, T and NK cell expansion)
- Imaging suite for confocal and live cell imaging
- Seahorse XP for kinetic cellular metabolic monitoring
- Immune monitoring suite (ELISpot, Luminex, high throughput ELISA)

The Global Impact of Vaccines

In the last century, vaccines have saved more lives than any other health intervention. It is estimated that every year, more than two million deaths are prevented worldwide due to immunization.



World Health
Organization

Science

20 December 2013 | \$18

Breakthrough of the Year

Cancer Immunotherapy

T cells on the attack

AAAS



VGTI Florida[®] Research Programs: Cancer Vaccines & Immune Therapies

- Former Director of Cancer Immunotherapy at Mayo Clinic
- Developing vaccines for primary & secondary prevention of cancers
- Breast, Ovarian and Brain
- Innovative immune-based approaches to destroy and eliminate progressive disease



Keith Knutson, Ph.D.
Director, Cancer
Programs

Taking Aim at Preventing Breast & Ovarian Cancers

- Active Immunotherapy vaccines® for the prevention of breast & ovarian cancers is a reality
- Active versus passive
 - Triggers durable, long-lasting immunity
- VGTI Florida® is accelerating next-gen cancer vaccines from bench to patients



VGTI Florida® Research Programs: Cancer Vaccines & Immune Therapies

- Advancing the use of oncolytic vaccine vectors
- Genetically modified viruses that specifically target and destroy tumor cells (HSV, Reo, Vaccinia, Measles, VSV)
- Spares healthy cells
- Researching this approach in multiple tumor types including CLL, prostate cancer and lung cancers



John Hiscott, Ph.D.

VGTI Florida® Research Programs: HIV and Immune function

Major Discoveries Leading to Curative Approaches:

- Identification of mechanisms of immune dysfunction in chronic viral diseases and cancer
- Identification of the role of negative immune regulators that suppresses the body's immune response to HIV



Elias Haddad, Ph.D.



Lydie Trautmann, Ph.D.

VGTI Florida® Research Programs: Vaccines & Viral Immunity

Universal Flu Vaccine Programs:

- Next-gen vaccines capable of protecting against all strains of seasonal flu
- VLP Technology
- Boosting immunity in the young and elderly



Ted Ross, Ph.D.

Emerging Viral Threat Programs:

- Dengue, Rift Valley Fever, West Nile Virus, Ebola, Marburg
- State-of-the-Art BSL-3 Labs

Center for Diseases of Aging

AT VGTI FLORIDA®



**Karolinska
Institutet**

CDA (Ctr. Diseases of Aging)

- State funded collaborative venture with VGTIFL and Karolinska Institutet[®]
- 3 KI laboratories currently operating at VGTIFL
- Collaborative studies integrating immune therapies with regenerative medicine
- Bringing KI scientists and clinical trials to the US market

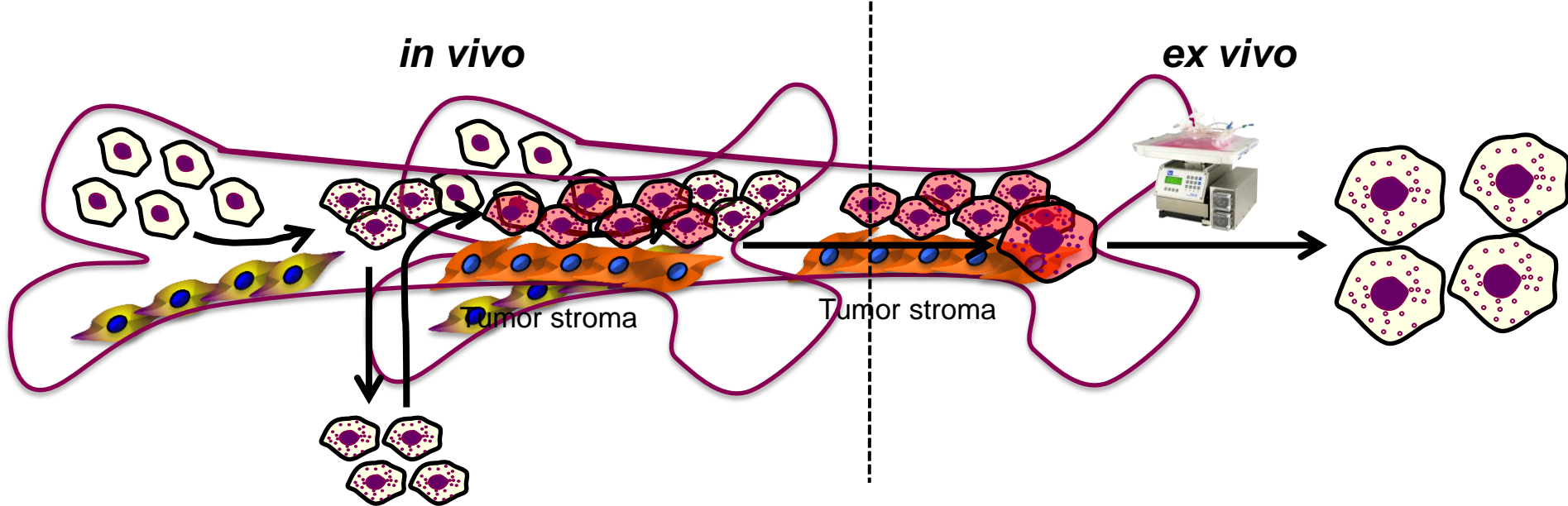
Targeting Age-Related Diseases

- **Infectious diseases**
 - Flu, HIV, Hantavirus, Dengue, etc
- **Cancer**
 - Breast, ovarian, prostate, melanoma, brain, etc
- **Neurodegenerative diseases**
 - Parkinson's, Alzheimer's, ALS, etc
- **Cardiovascular diseases**
 - Heart attack, stroke, birth defects, etc
- **Others**
 - Diabetes, macular degeneration, multiple sclerosis, etc



NK cells and Multiple Myeloma

Evrin Alici
Adil Doganay Duru
Cell and Gene Therapy Group
HERM
Karolinska Institutet

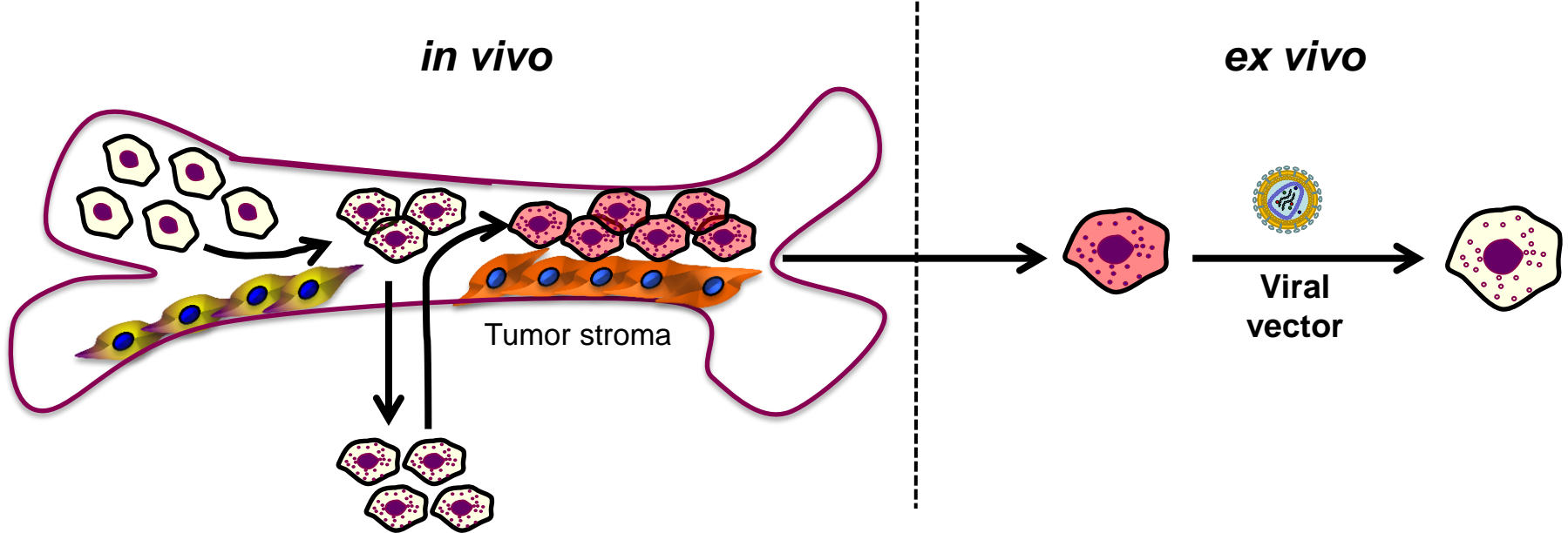


Natural Killer cells

- **Ex vivo NK cell expansion**
 - Clinical trial
 - Developing NK cell culture medium
 - Optimization
- **Genetic modification of NK cells**
 - Improving gene delivery
 - IL-2/IL2ER
 - Genetic screening
- **NK cell-derived exosomes**
- **NK cell phenotyping and genotyping**

Multiple Myeloma

- **Impact of chromosomal abnormalities on disease progression**
- **Effects of Immunomodulatory drugs on myeloma cells and Lymphocytes**
- **Developing alternative treatments**
 - Immunotherapy
 - Cell therapy

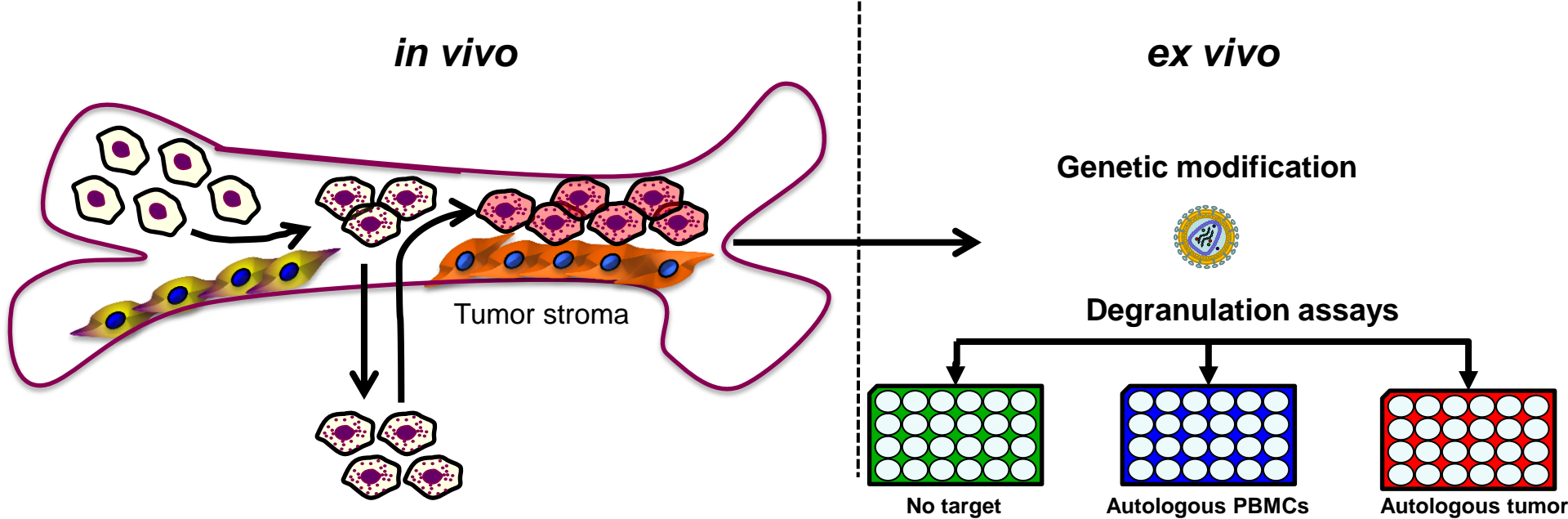


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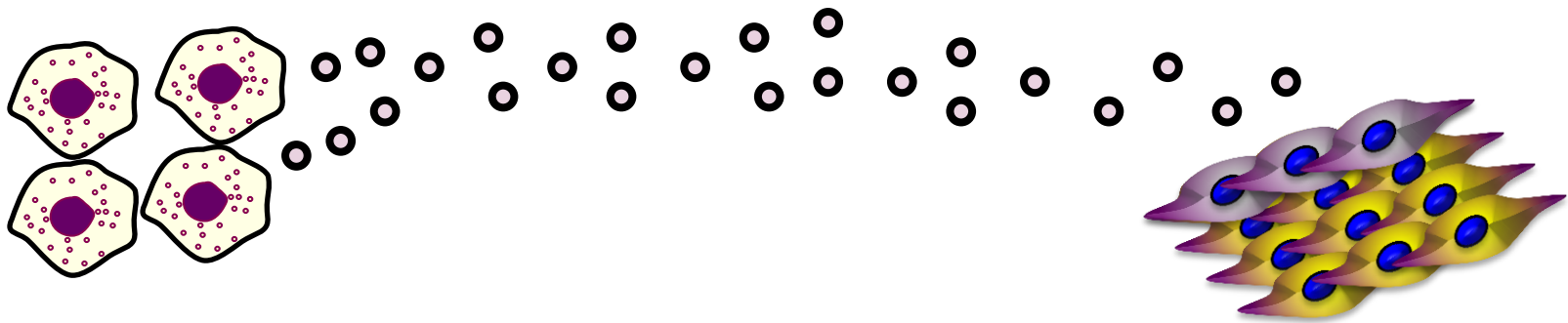


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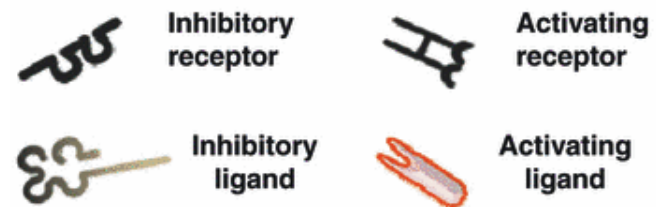
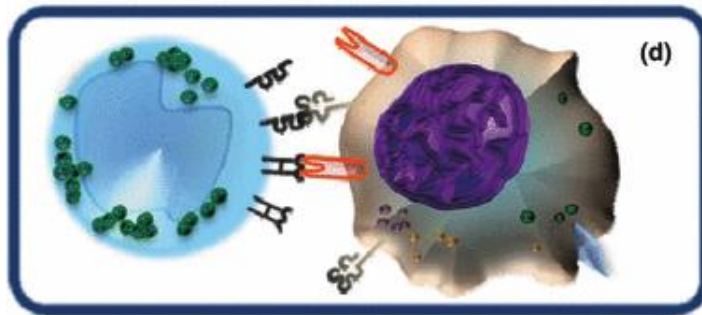


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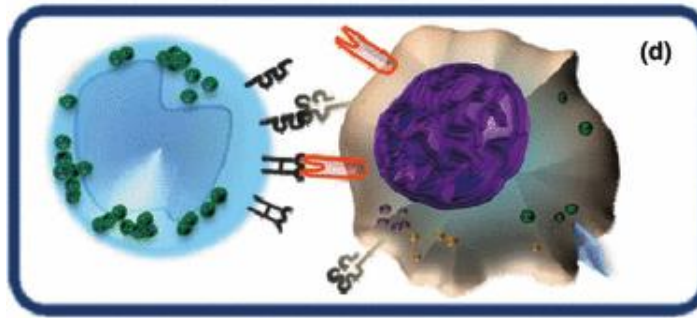


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Multiple Myeloma

Impact of chromosomal abnormalities on disease progression

Effects of Immunomodulatory drugs on myeloma cells and lymphocytes

Developing alternative treatments

Immunotherapy
Cell therapy

A New Strategy of Immune Modulation

Matthias Corbascio MD PhD

Associate Professor of Cardiothoracic
Surgery

Dept of **Cardiothoracic Surgery** and
Anesthesiology

Karolinska University Hospital, Stockholm
Sweden

Successful transplantation of Stem cells or Islet Cells must overcome immune rejection

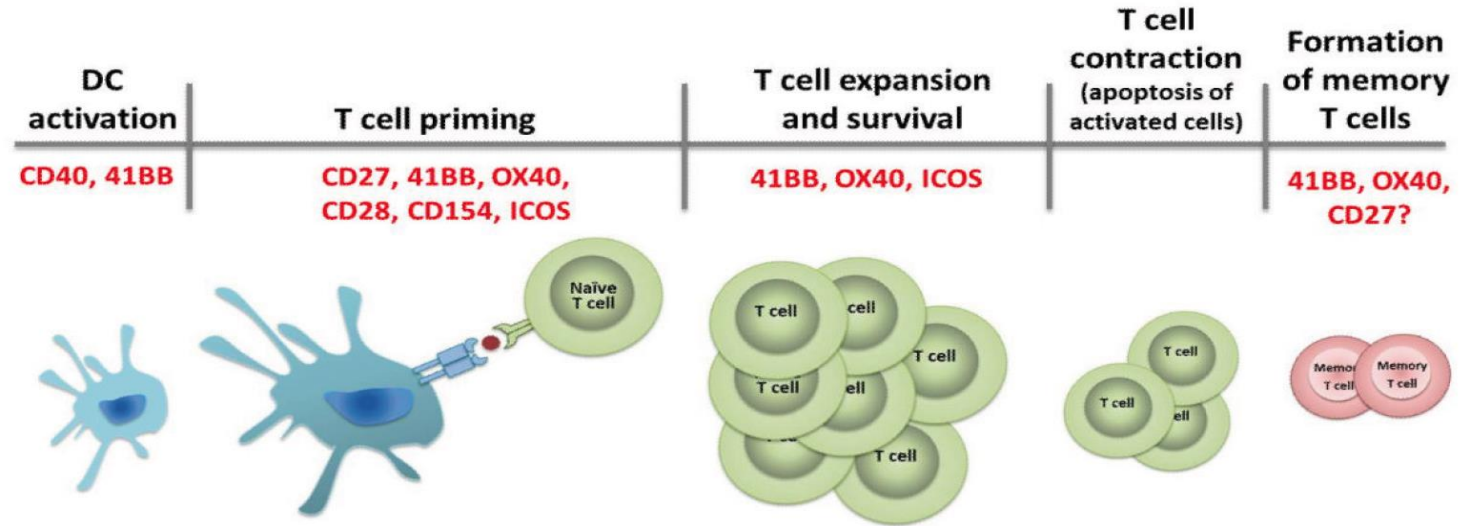


Figure 1.

Diversity of costimulatory molecules in the different stages on the immune response.

Transplantation. 2013 February 27; 95(4): 527–535.

Blocking immune activators to facilitate transplantation

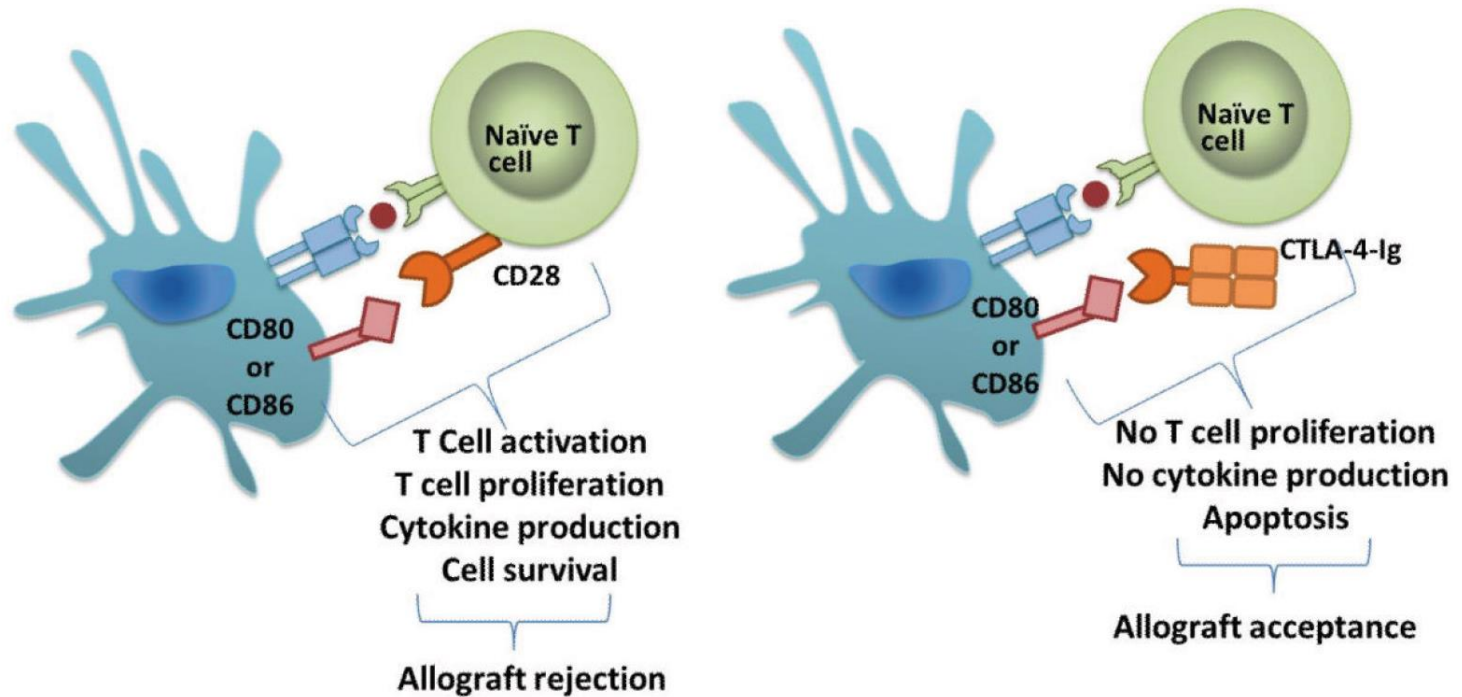
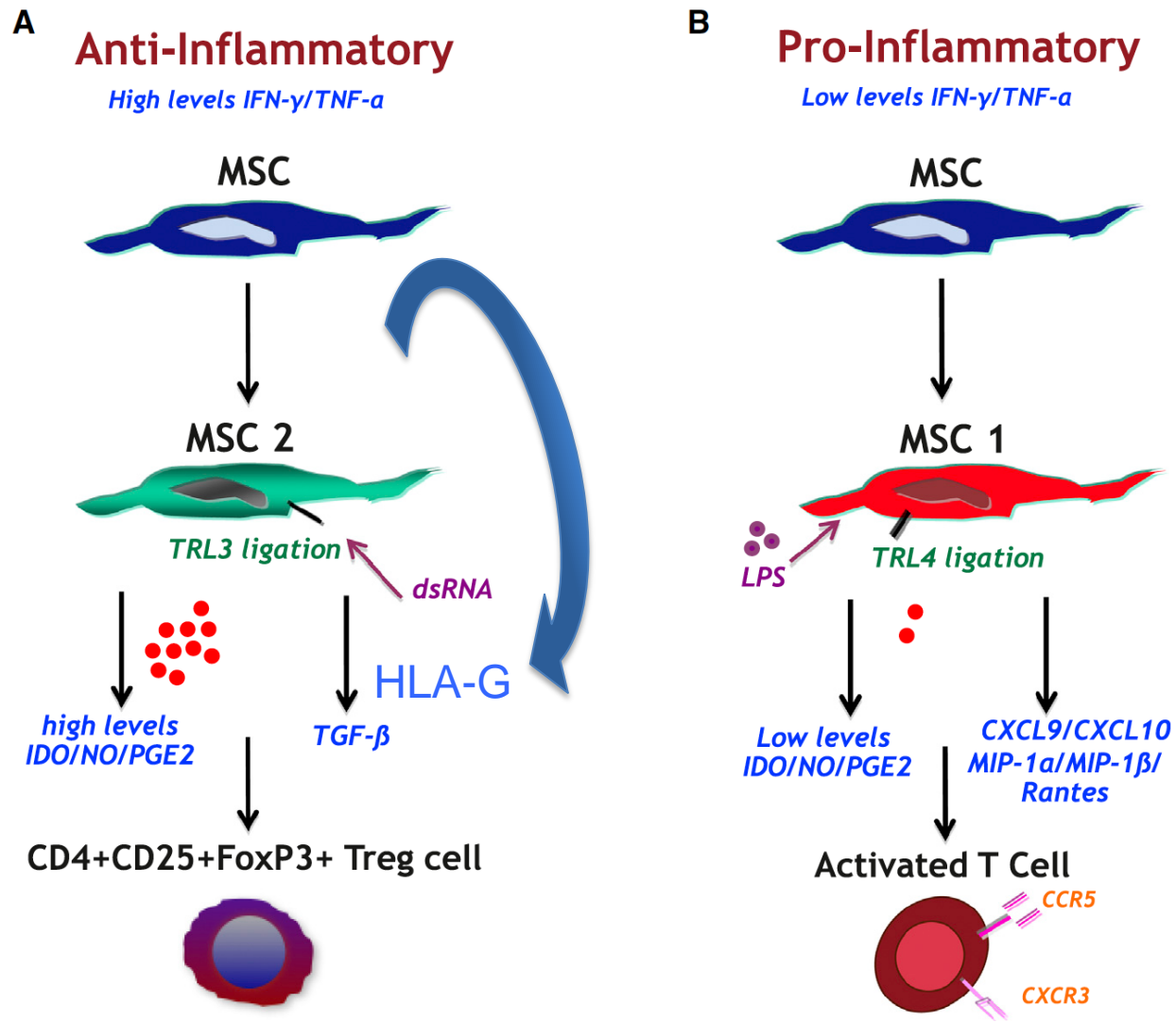


Figure 3.
Proposed model of the mechanism action of CTLA-4-Ig.

Mesenchymal Stem Cells alter immune environment



The model

- Balb/c islets + C57BL6 Bone Marrow **MSCs** injected intraportal into MHC-mismatched diabetic C57BL6 mice
- Treated with **CTLA4Ig** or **CTLA4Ig+anti-CD40L** for the first ten days.
- Follow blood glucose and harvest grafts at 100 days

Clinical Implications

3396 clinical trials register in [ClinicalTrials.gov](https://clinicaltrials.gov) with MSC
Most have an immunological or inflammatory target

CTLA4Ig is FDA approved for kidney transplantation and rheumatoid arthritis

Anti-CD40 highly effective in liver, kidney and islet transplantation in non-human primates and in Phase 1 clinical trials

MSC + Costimulation blockade = good for transplant,
autoimmunity, regenerative medicine

NK cell based immunotherapy against solid tumors

Andreas Lundqvist
Dept. of Oncology-Pathology
Karolinska Institutet

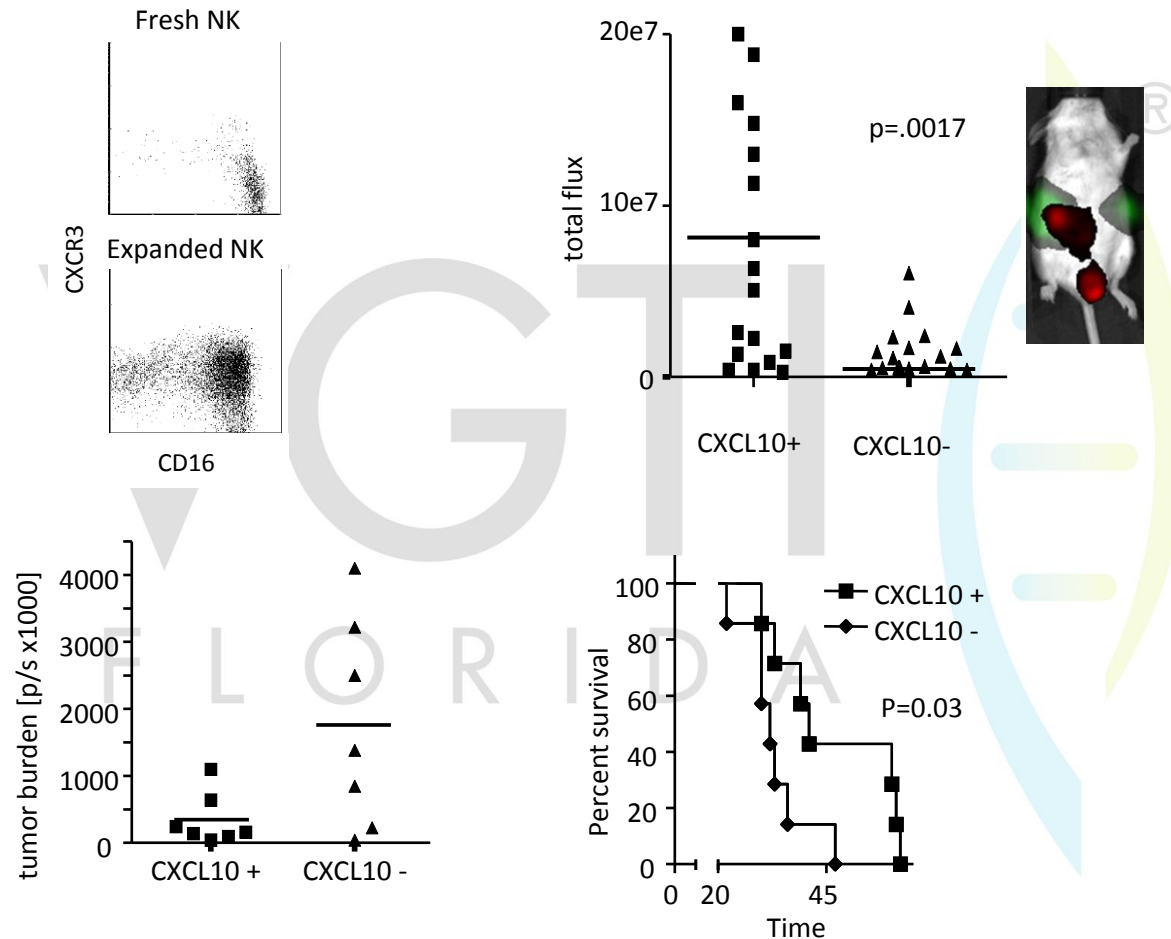
NK Cells and Cancer

- Expansion of peripheral blood NK cells correlates with clinical outcome in cancer patients receiving IL-2 and IFN α
- Tumor-infiltrating natural killer cells play a crucial role in the generation of anti-tumor T lymphocytes.
- Low peripheral blood NK cell activities have been related to the poor prognosis in patients with a number of different cancers
- Peripheral blood NK cell count is associated with clinical outcome in patients with diffuse large B-cell lymphoma

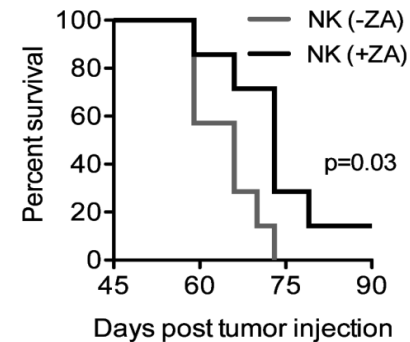
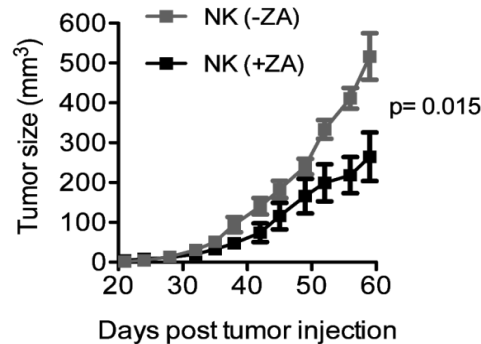
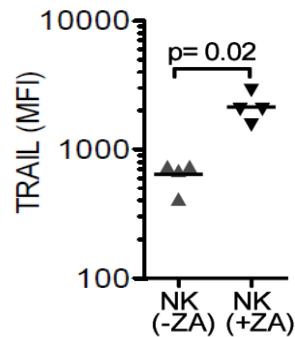
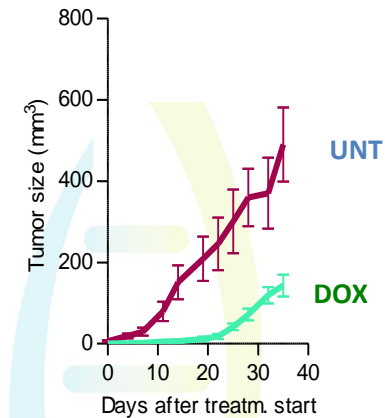
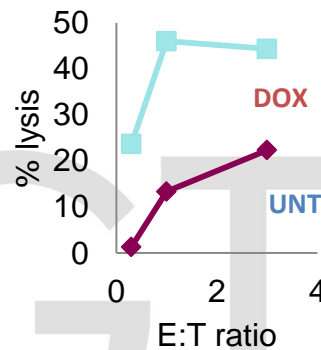
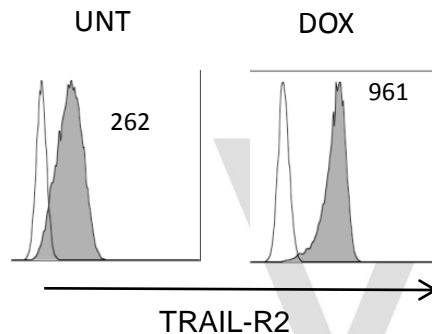
Rate limiting factors for successful clinical outcome of adoptive NK cell therapy

- How to make infused NK cells reach the tumor?
- How to make NK cells kill tumor cells as effectively as possible?
- How to make NK cells survive in the tumor microenvironment?

How to make infused NK cells reach the tumor?



Engineering NK cells to kill tumor cells more effectively



Other CDA projects

- Stem cell transplants for repair of macular degeneration and cardiac damage[®]
- Define mechanisms to overcome stem cell transplant rejection
- Integration of VGTIFL cores and technologies with KI projects in the CDA for novel therapies and clinical trials

Potential interactions with FAU

- VGTIFL Principal Investigators hold adjunct appointments with FAU (training of grad students, committee service)
- Collaborative research efforts (joint grant applications)
- Shared resources available to FAU scientists
- Summer Undergraduate Research Fellowship (SURF) program:
<http://www.vgtifl.org/internships>

Acknowledgments

- Dr. Jove President and Director VGTIFL
- Dean of KI Hans-Gustaf Ljunggren
- State and local legislators
- CDA scientists
 - Dr. Alici
 - Dr. Lundqvist
 - Dr. Carbascio
 - Dr. Grinnemo
 - Dr. Hovatta
- VGTI investigators
 - Dr. Ross
 - Dr. Hiscott
 - Dr. Haddad
 - Dr. Trautmann
 - Dr. Knutson
- VGTI core staff