From Bench to Bedside Via Veterinary Radiation Oncology: **The Dog as a Model of Human Cancer**

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Similarities between species

- We do not only look alike
- Live in same domestic environment
- Developed together over the last 10,000 – 15,000 years
- Receive preventative and health care

http://fearlessmen.com/when-dogs-look-like-their-owners/

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Dog in US society

- 70-80, 000, 000 dogs in the United States
- ~37% of US households have at least one dog
- 63.2% of households consider their dog a family member
- Many dogs now living to middle and geriatric age

AVMA 2012 Pet Ownership and Demographics Sourcebook

Dogs as a model

- Inbreeding has led to many breed predilection of disease
  - Many of these seen in humans
  - Allows smaller number of individuals to identify
    - Less background noise
- Many dogs are geriatric allowing for natural development of disease of aging – such as cancer
  - ~45% of dogs >6 years in the US

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Comparative medicine

- After humans most diverse and known disease occurrence
- ~400 inherited disease in dogs with human counterparts have been identified
- Affected by many of the same infectious diseases
- Affected by similar cancers

The dog as a model?

- Important to distinguish between laboratory animals and pets
- Toxicity testing in a "Large Animal" model
- Very different than dogs with spontaneous disease

Its in the DNA

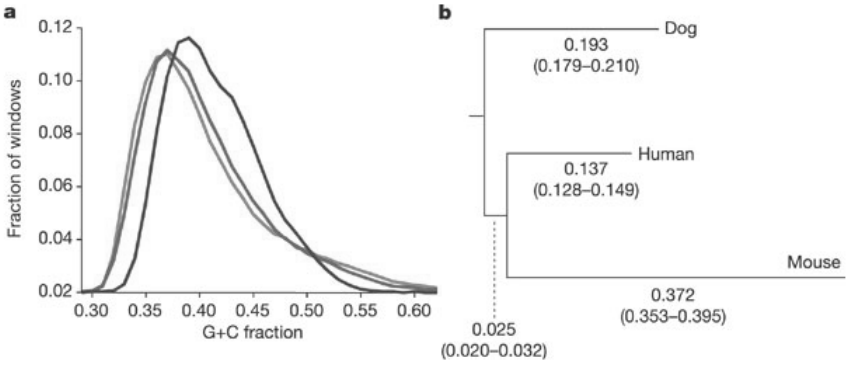
- Share 650 Mb of shared ancestral DNA with humans
- Have closer DNA and protein sequences with humans than mice

Lindblad-Toh, K. et al. (2005) Genome sequence, comparative analysis and haplotype structure of the domestic dog. Nature 438, 803–819

Its in the DNA

- Share
- Have
  mice

than



Lindblad-Toh, K. et al. (2005) Genome sequence, comparative analysis and haplotype structure of the domestic dog. Nature 438, 803–819

Dogs informing human disease

- Genetic studies

J Neuropathol Exp Neurol
Vol. 75, No. 7, July 2016, pp. 700–710
doi: 10.1093/jnen/nlw042

OXFORD

ORIGINAL ARTICLE

Chromosomal Aberrations in Canine Gliomas Define Candidate Genes and Common Pathways in Dogs and Humans

Peter J. Dickinson, BVSc, PhD, Dan York, BA, PhD, Robert J. Higgins, BVSc, PhD, Richard A. LeCouteur, BVSc, PhD, Nikhil Joshi, MS, and Danika Bannasch, DVM, PhD

Cancer types similar between species

- Lymphomas (NHL) and Leukemias
- Multiple Myeloma
- Soft Tissue Sarcoma
- Osteosarcoma (up to 75 x more common than in humans)
- Some forms of mammary cancer
- Melanoma
- Brain tumors (meningioma, glial)
- Bladder tumors

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What is missing in mouse models?

- Long latency periods
- Genomic instability
- Tumor heterogeneity
- Microenvironment heterogeneity
- Metastatic patterns
- Often young mice used
- Often lean mice used
- Often immunocompromised mice used
- Differences in the immune system

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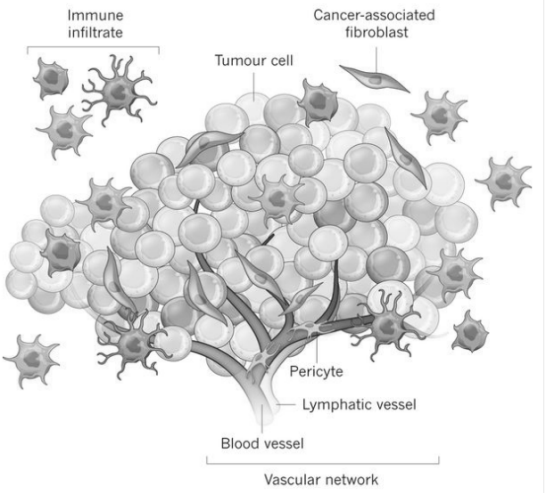
Tumor microenvironment

- Tumor cells
- Stromal cells
- Immune cells
- Vasculature



Junttila MR, de Sauvage FJ. Influence of tumour micro-environment heterogeneity on therapeutic response. Nature. 2013 Sep 19;501(7467)

Immune system similarities to human

- Canine immune systems are genetically and developmentally much more similar to humans than rodent models
  - Eg. TLR8 non functional in rodent
    - Unlike humans and dogs
- Tumors develop in spontaneous dog model in the face of intact immune system
  - Chronic inflammation
- Complexity of tumor immunity and suppression replicated
  - CD8+ T cells, Tregs, NK cells, APCs, Dendritic cells etc

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Of Mice and Men……

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

SUMMARY

Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation.

N Engl J Med 2006;355:1018-28.

- Anti-CD28 humanized monoclonal ab
- Designed to induce T-cells
- Rodent models
  - Expanded T-cells without acute inflammatory reactions
- Biological differences between species

Advantage of a mouse model

- Short gestation
- Small in size
- Can manipulate individual genes
  - Organism
  - Particular tissues
- Immunocompromised variants
  - Nude mouse (athymic – T-cell deficient)
  - NSG mice models (T cell, B cell, NK cells, complement absent, defective macrophages & Dendritic cells)

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Advantages of dog models

- Spontaneous tumor development
- Similar tumor microenvironment
- Intact immune systems
- Larger Size
  - Development of medical procedures
    - Limb sparing surgeries
  - Radiotherapy Trials
  - New Device and Drug Delivery Trials

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Can't we just build a better mouse model?

- Orthotopic xenografts
  - Better simulation of natural tumor environment
- Genetically engineered mouse models (GEM)
  - Often lack tumor heterogeneity
- Patient derived xenograft models (PDX)
  - Immunocompromised, mouse stroma
- Very good at discerning new mechanisms

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Translational canine melanoma study

Cancer Therapy: Clinical

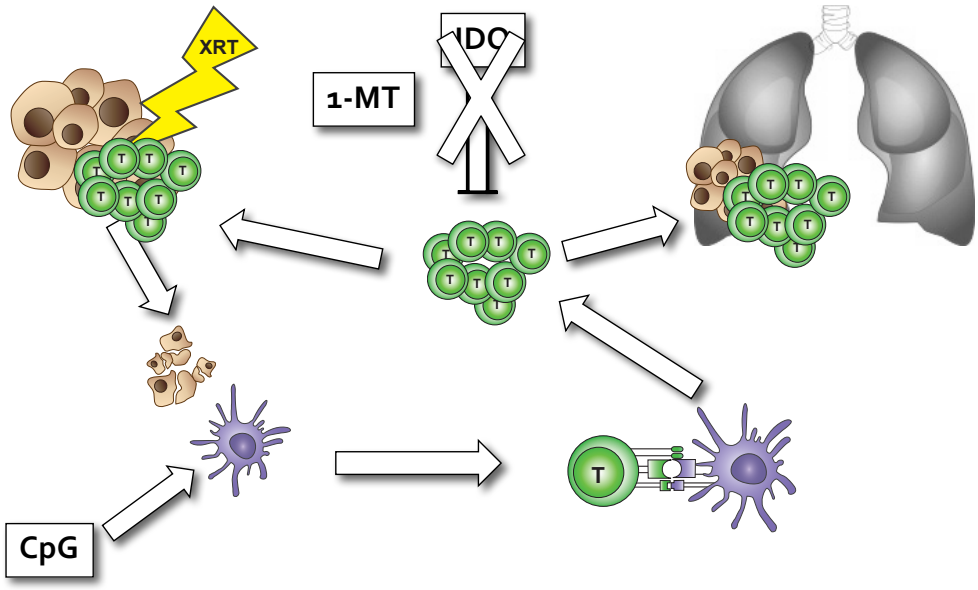
Clinical Cancer Research

Blocking Indolamine-2,3-Dioxygenase Rebound Immune Suppression Boosts Antitumor Effects of Radio-Immunotherapy in Murine Models and Spontaneous Canine Malignancies

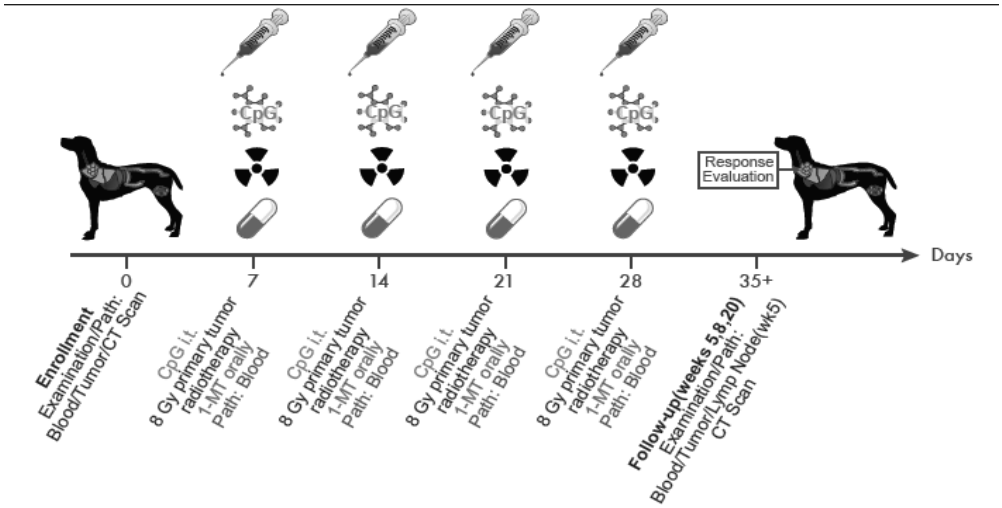
Arta M. Monjazeb[1], Michael S. Kent[2], Steven K. Grossenbacher[3], Christine Mall[3], Anthony E. Zamora[3], Annie Mirsoian[3], Mingyi Chen[4], Amir Kol[5], Stephen L. Shiao[6], Abhinav Reddy[1], Julian R. Perks[1], William T.N. Culp[2], Ellen E. Sparger[2], Robert J. Canter[7], Gail D. Sckisel[3], and William J. Murphy[3,8]

- Radiotherapy to create tumor antigens
- CpG
  - Prokaryotic DNA sequences
  - Potent immune stimulation via TLR9
- Indolamine 2,3-Dioxygenase (IDO)
  - Immunosuppresive Enzyme
  - Inhibited by 1-Methyl-D-tryptophan (1-MT)

Hypothesis



Canine clinical trial: schema



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Clinical trial: Results

Age	Sex	Breed	Primary Disease	Systemic Disease	Best Primary Response (WHO)	Best Systemic Response (irRC)	Survival (months)	Toxicity
10	Female	Husky	Melanoma - lingual	Lung	PR	Lung – irSD	9.2	Mucositis – Grade 2
8	Female	Labrador	Soft Tissue Sarcoma – body wall	LN, Lung	PR	LN – irPR Lung – irSD	2.8	Skin – Grade 1
11	Male	Mixed	Melanoma-buccal	Lung	PR	Lung – irPD	3.2	Mucositis – Grade 1
12	Female	Terrier	Melanoma -buccal	Lung	CR	Lung – irCR	5.6	Mucositis – Grade 1
11	Male	Mixed	Melanoma-maxillary	Lung	PR	Lung – irPR	6	Mucositis – Grade 1
Canine melanoma median survival after development of metastatic disease: This Study: 5.8 months (95% CI: 3.2-9.2 months) Previously published historical controls treated with radiotherapy alone: 2 months (95% CI: 1-4 months)								

Clinical trial: Patient 1

- Alaskan Husky with rapidly progressive metastatic melanoma

Pre-Treatment

Post RT/Immunotherapy

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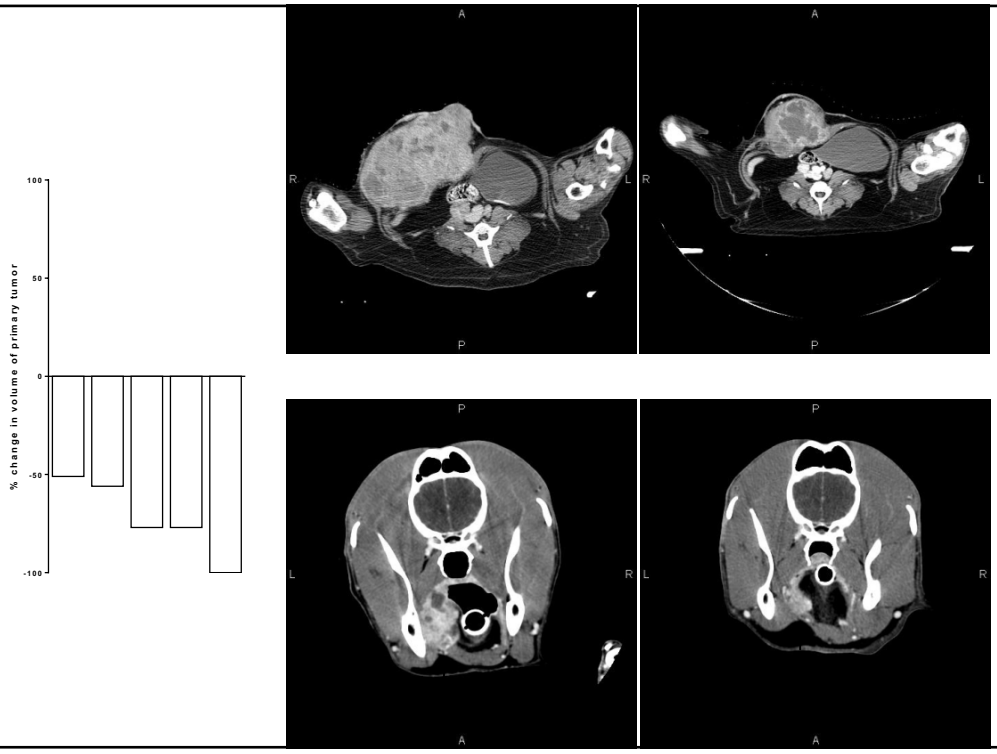
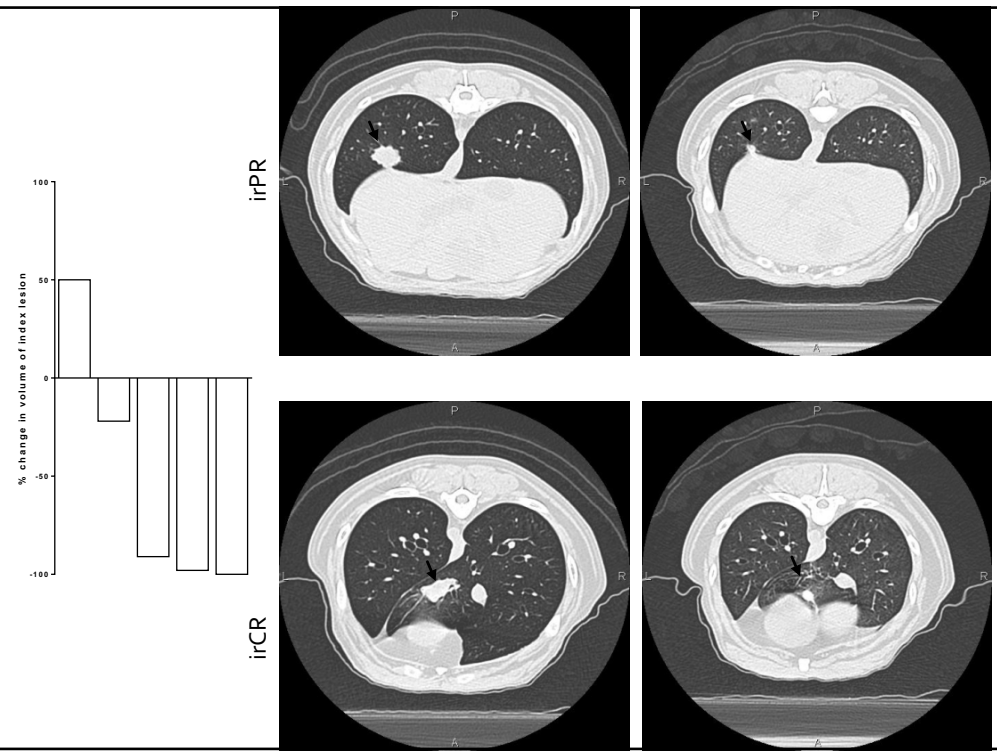
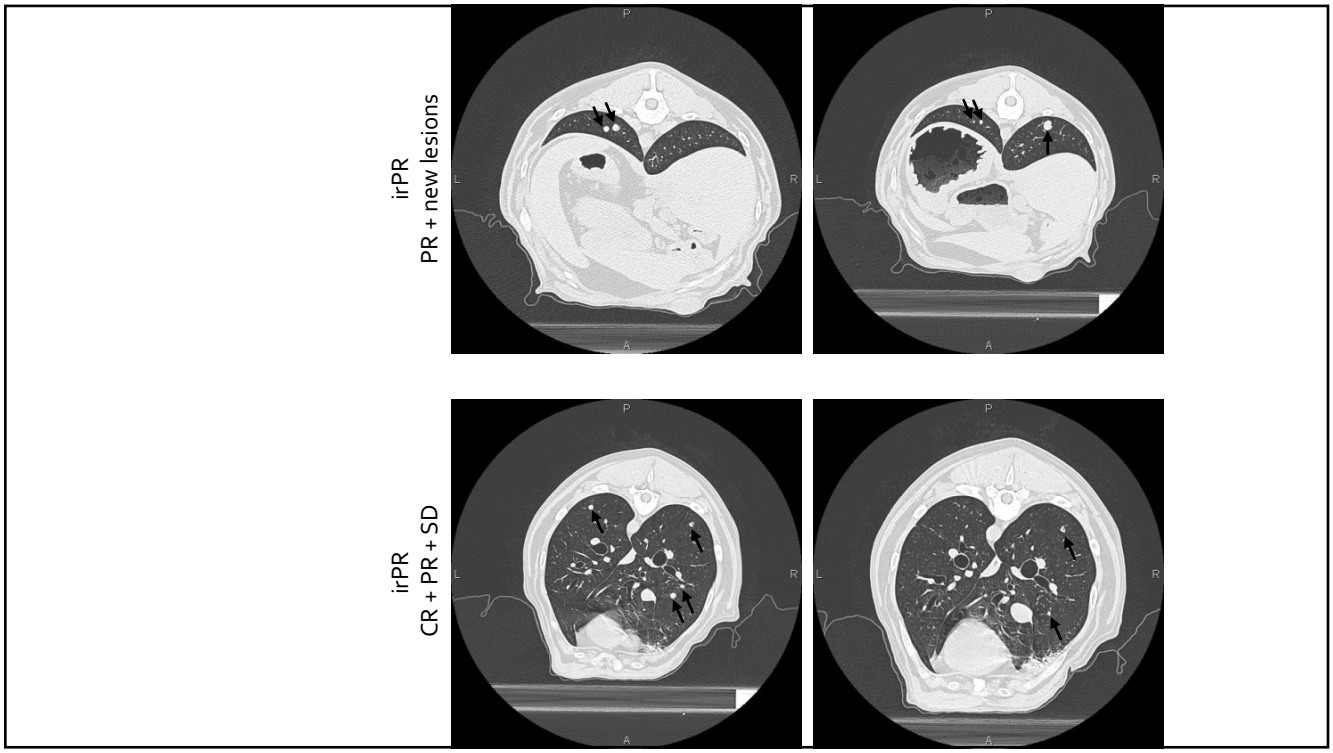
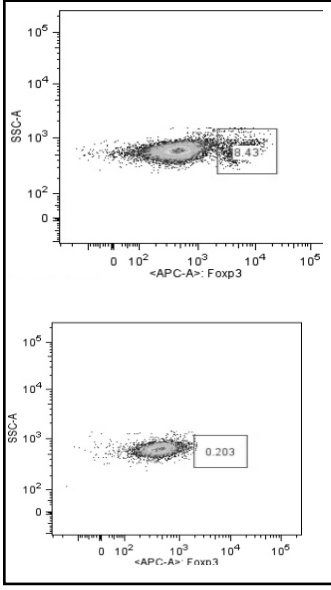
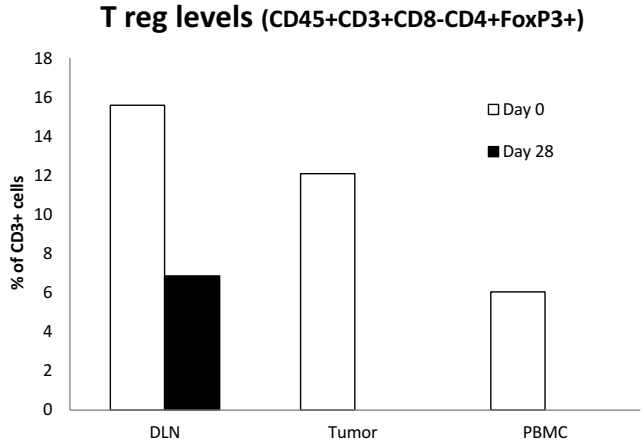

% change in volume of primary tumor
100
50
0
-50
-100
A
P
R
L


% change in volume of index lesion
100
50
0
-50
-100
irPR
irCR
P
A
R
L

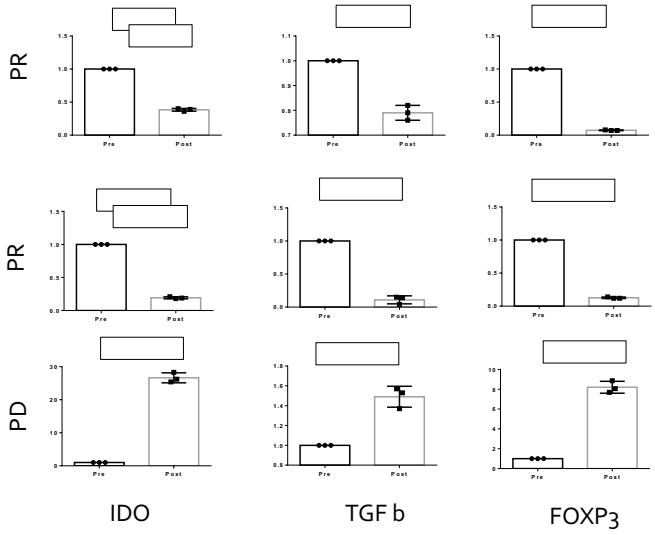


Decreased Tregs Post Treatment





Tumor Microenvironment Response



mRNA Expression by qPCR

Questions?

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