

Towards Optimized DC-based Cancer Therapies:

Targeting the Induction and Effector Phase of Cancer Immunity

Pawel Kalinski, MD, PhD

Surgery, ImmunoTransplantation Center

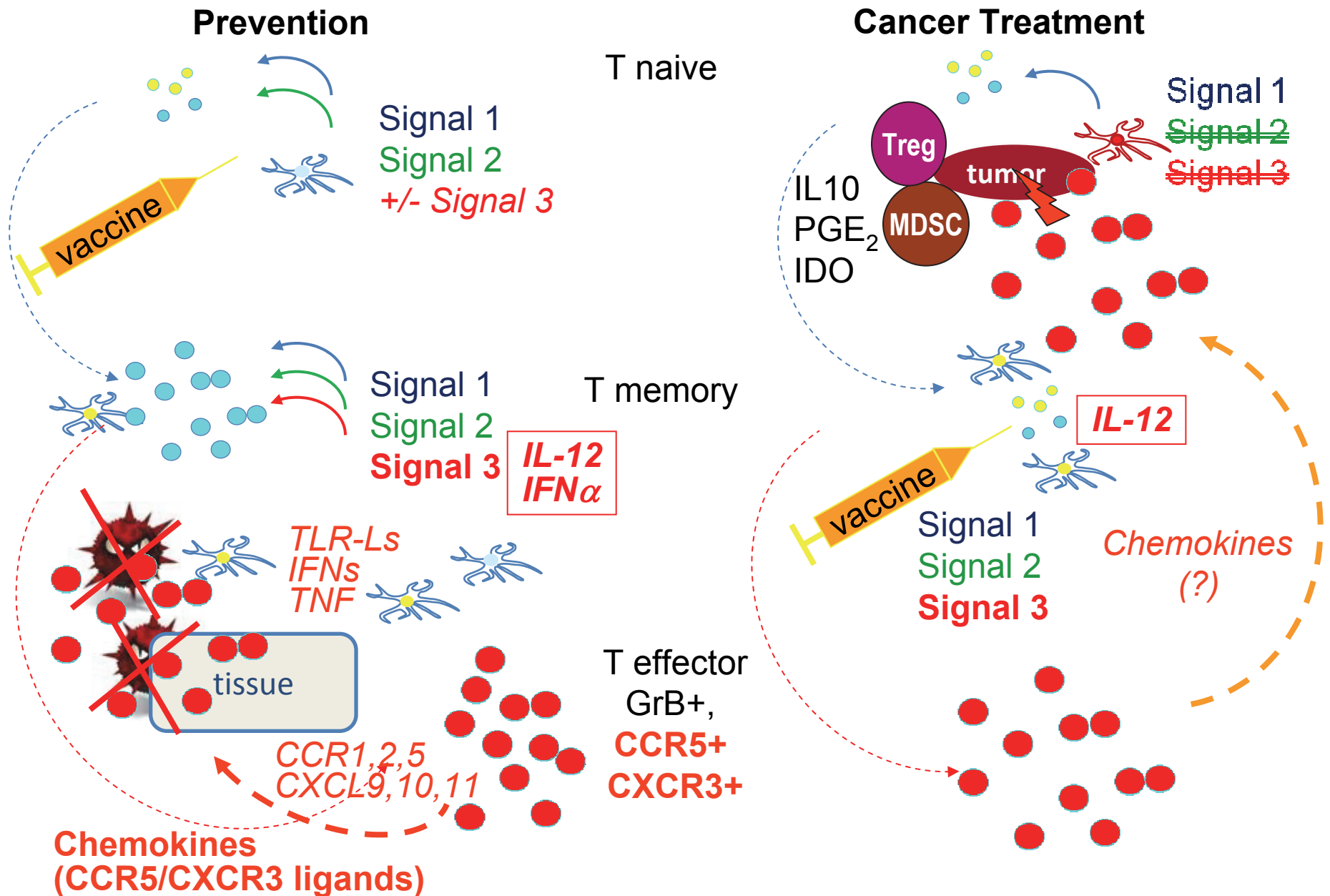
University of Pittsburgh Cancer Institute

No Financial Disclosures

*aDC1s, one of the DC types discussed in this presentation ,
is a subject to issued and pending patent applications*



Preventive versus Therapeutic “Vaccination”

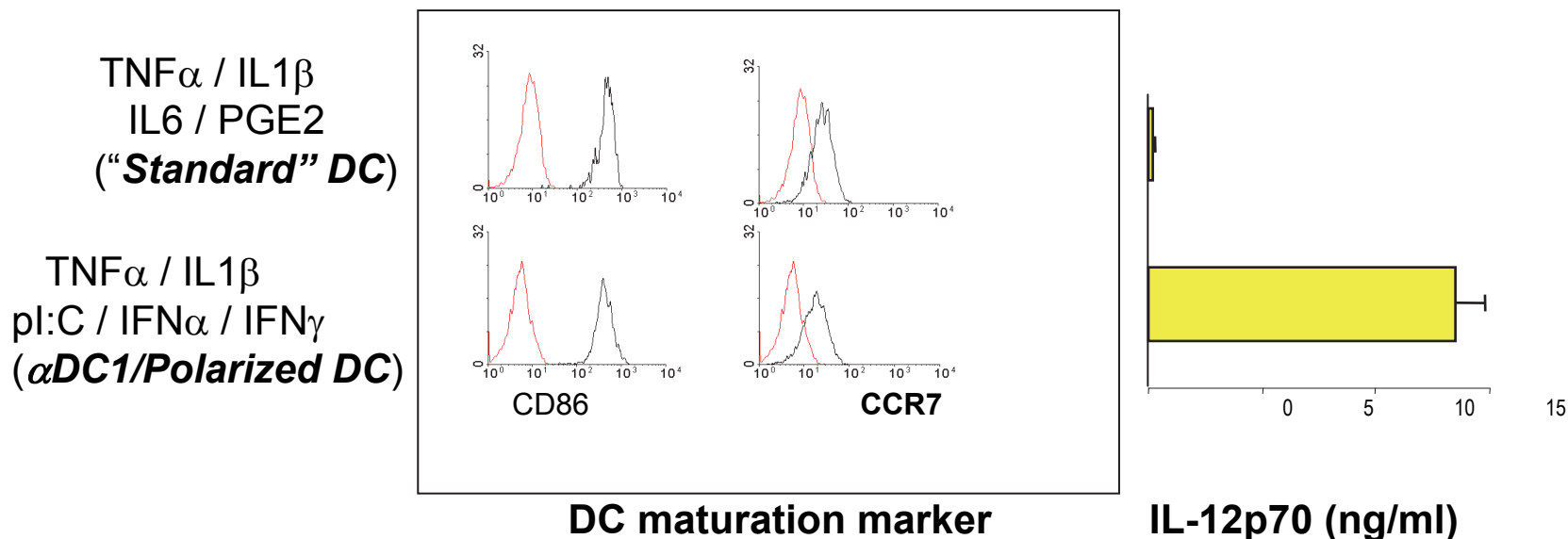


Targeting the Induction and Effector Phases of Immunity in Cancer Immunotherapy

*Suppressive environment of cancers a) promotes the development of **inappropriate forms** of immune response, and b) **excludes the desirable killer cells and suppresses their antitumor function by** preferential attraction and activation of suppressive cells*

1. Instruct dendritic cells (DC) to induce killer-type immune cells (type-1 immunity; CTLs, TH1 and NK cells)
2. Condition cancer microenvironment to become permissive to immune attack
 - a. Promote the attraction of CTLs, Th1 and NK cells
 - b. Counteract the accumulation & function of Tregs and MDSCs

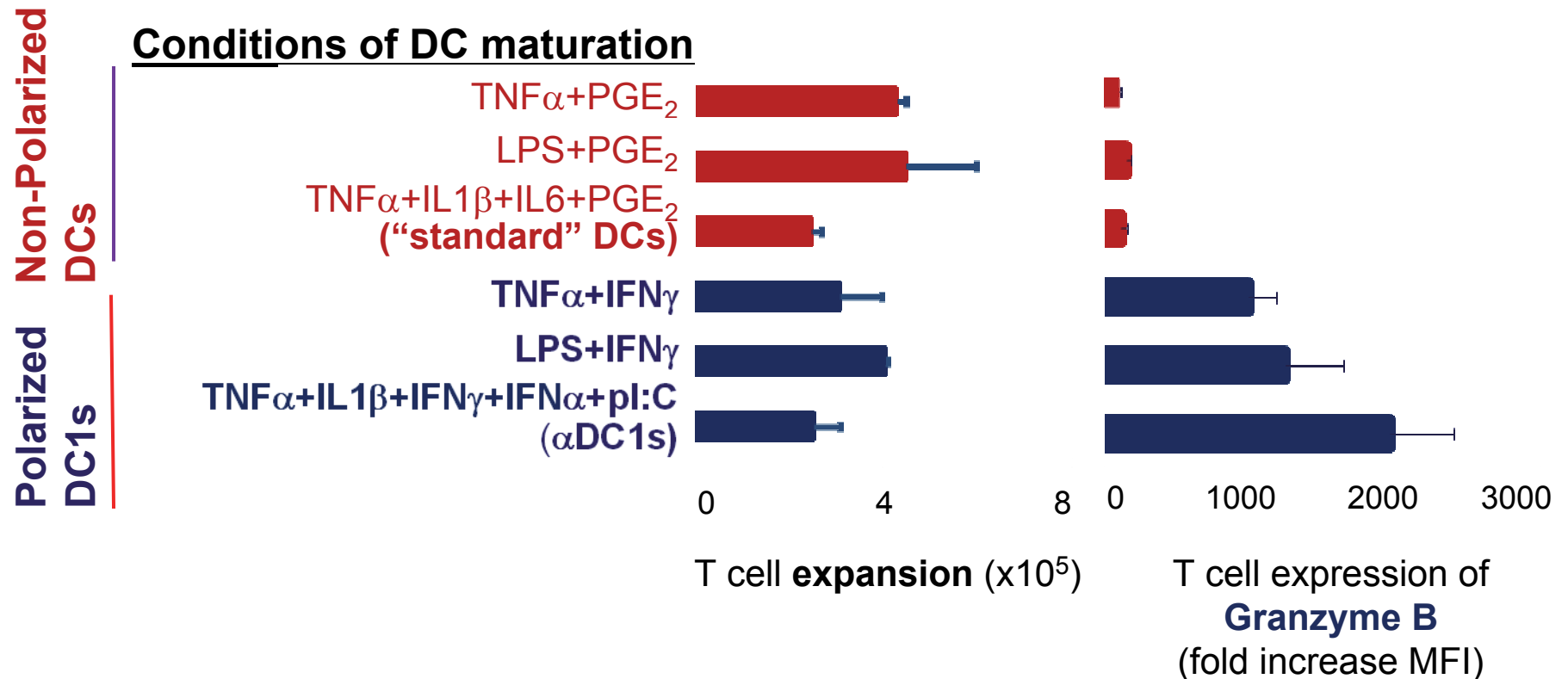
α DC1: High-IL-12-producing Mature DCs Induced by Mediators of Anti-Viral Immunity



Mailliard, Kalinski et al. *Canc. Res.* 2004, 64: 5934

- IL-12 production by DCs is needed for the **induction of tumor-specific CTLs *ex vivo*** (Mailliard R.B., *Canc. Res.* 2004, Butterfield L.H., *J. Immunother.* 2008 ; Watchmaker P., *J.I.* 2010; DeBenedette M.A., *J. Immunother.* 2011)
- IL-12 producing DC needed for **activation of NK cells** (Gustafsson K., *Canc. Res.* 2008)
- IL-12 producing DC needed for **Th1 cell induction** (Kalinski P., *J.I.* 1997, Wesa A. *J.I.* 2007)
- DC-produced IL-12 **predicts prolonged TTP in cancer patients** (Okada H., *JCO* 2011)

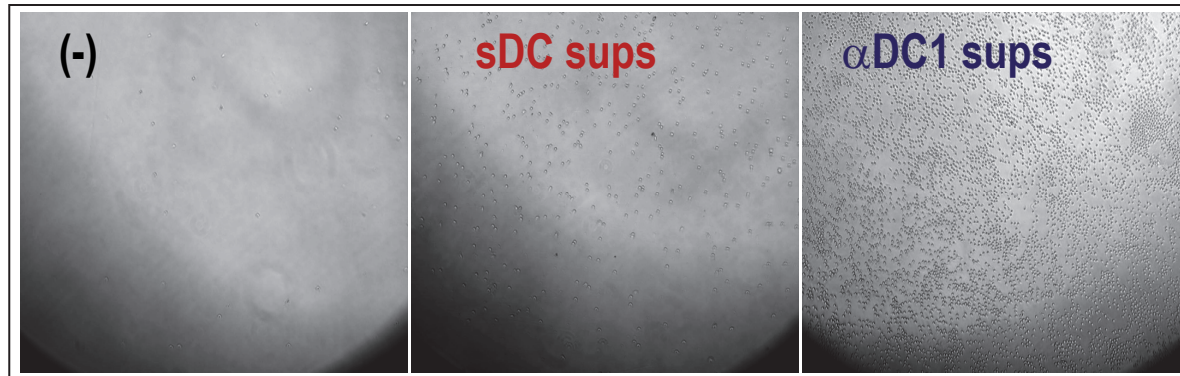
Polarized DC1s Induce GrB^{high} Effector CTLs



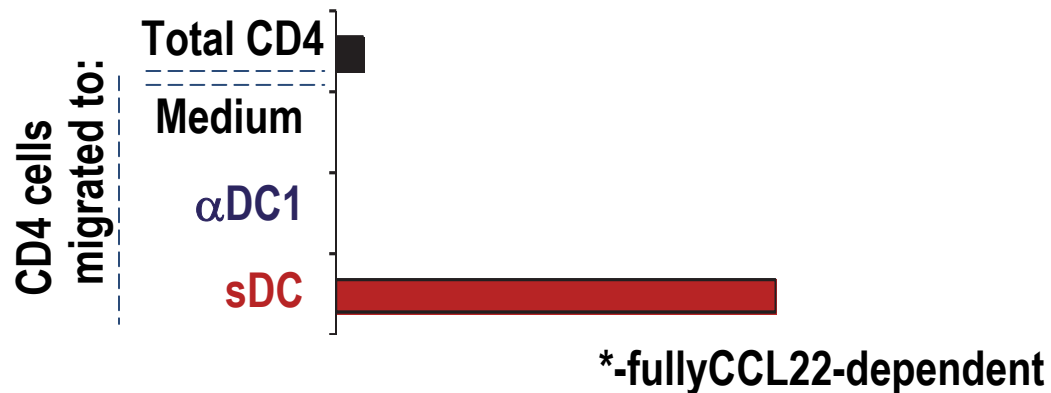
Watchmaker, Berk et al. 2010; J. Immunol. 184: 591-597
 Berk, Watchmaker, et al. in preparation

α DC1 Vaccines: Preferential Interaction with Naïve, Effector and Memory Cells, but not Tregs

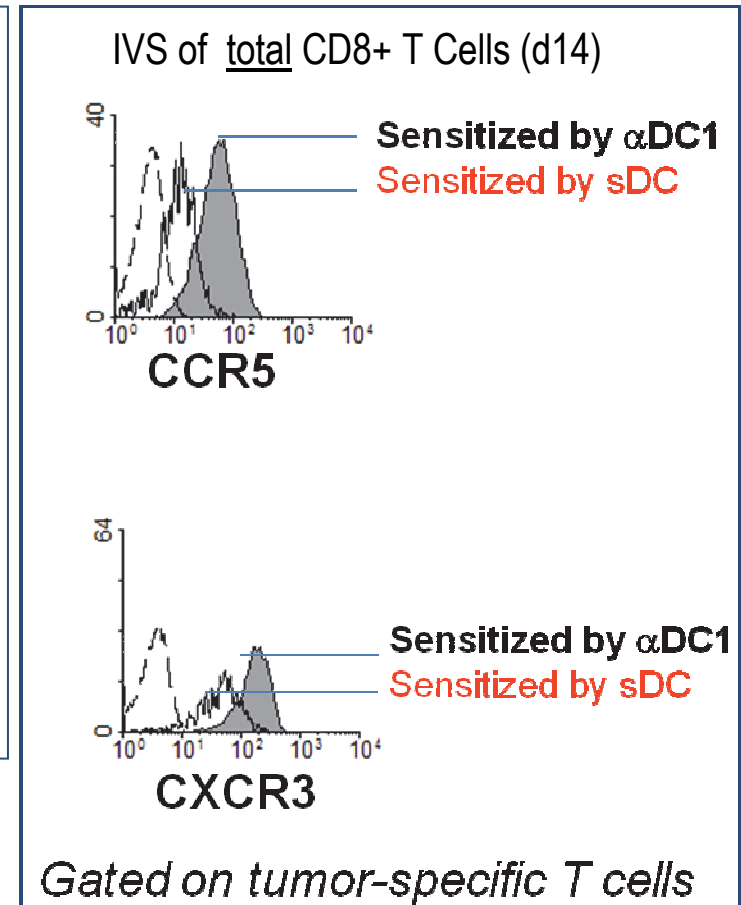
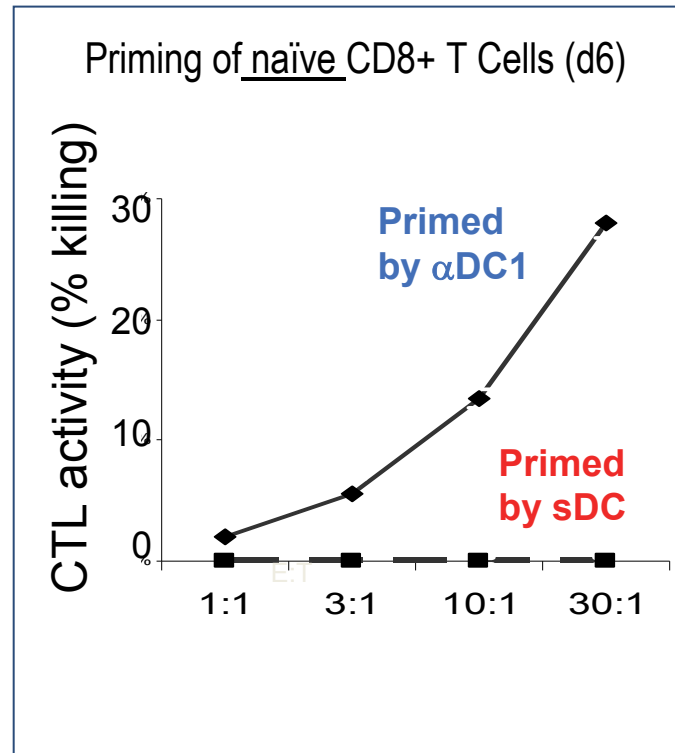
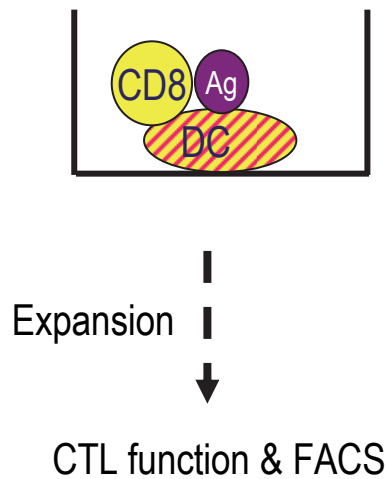
Chemotaxis of blood-isolated CD4⁺ T cells



FOXP3 expression in migrated T cells



α DC1-induced CTLs Express High Levels of CCR5 & CXCR3



Watchmaker, Berk et al. 2010; J. Immunol. 184: 591-597
Berk, Watchmaker, et al. in preparation

UPCI 05-115 (H. Okada): Phase I/II Study in Recurrent High-Grade Glioma (22 patients)

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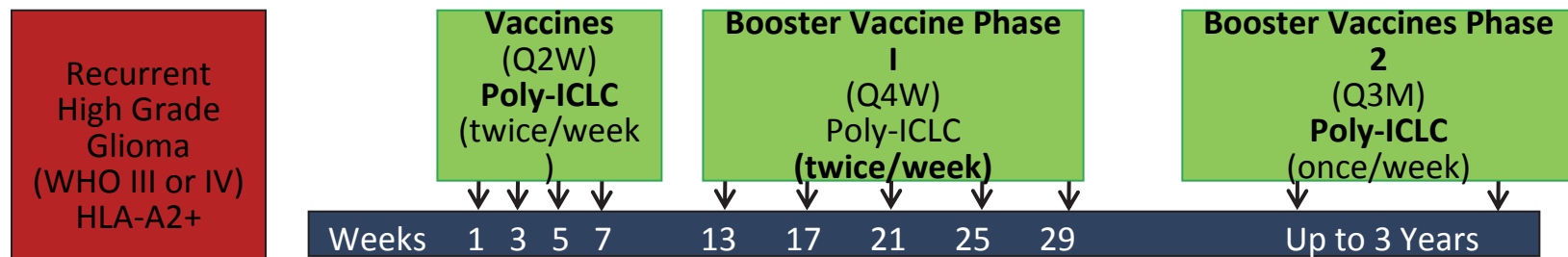
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Induction of CD8⁺ T-Cell Responses Against Novel Glioma-Associated Antigen Peptides and Clinical Activity by Vaccinations With α -Type 1 Polarized Dendritic Cells and Polyinosinic-Polycytidylic Acid Stabilized by Lysine and Carboxymethylcellulose in Patients With Recurrent Malignant Glioma

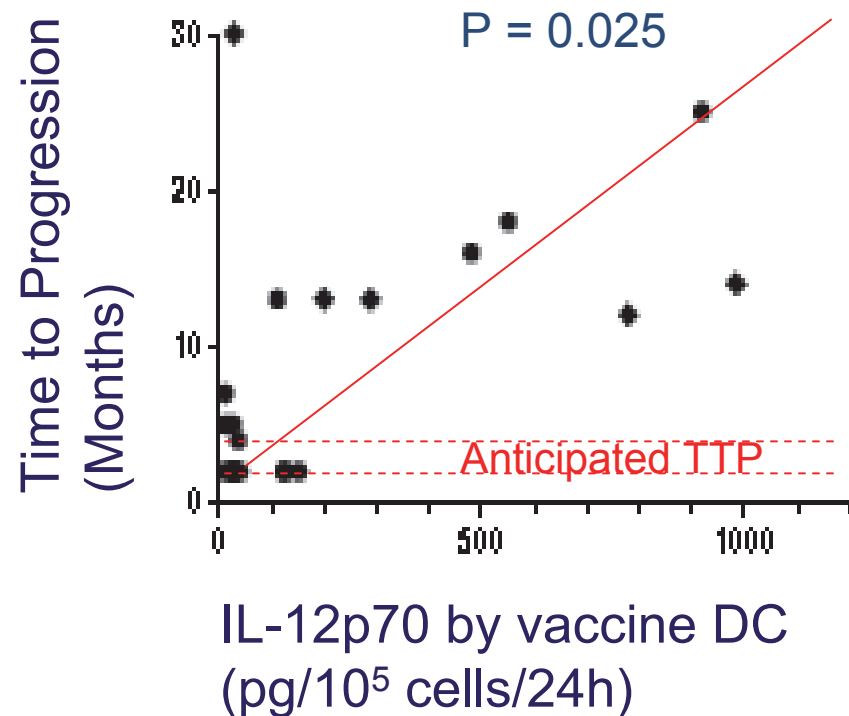
Hideho Okada, David Kufe, Ryo Ueda, Aki Hagi, Gary Kohlenstein, Teresa E. Doolan, Andre H. Mouton, Johnathan A. Engh, David L. Bartlett, Charles K. Brown, Herbert Loh, Matthew D. Hollman, Todd A. Brenner, Thomas L. Whiteside, Lisa M. Butterfield, Ronald L. Hamilton, Douglas M. Jetter, Jon F. Peck, Andrew M. Salner, and Frank J. Longman

- i.n. injections of aDC1s (1 or 3 x 10⁷ per dose) loaded with IL-13Ra2_{345-353:1A9V}, gp100_{209-217:2M}, EphA2₈₈₃₋₈₉₁ and YKL-40₂₀₁₋₂₁₀
- i.m. injections of poly-ICLC (20 mcg/kg; Twice/week)

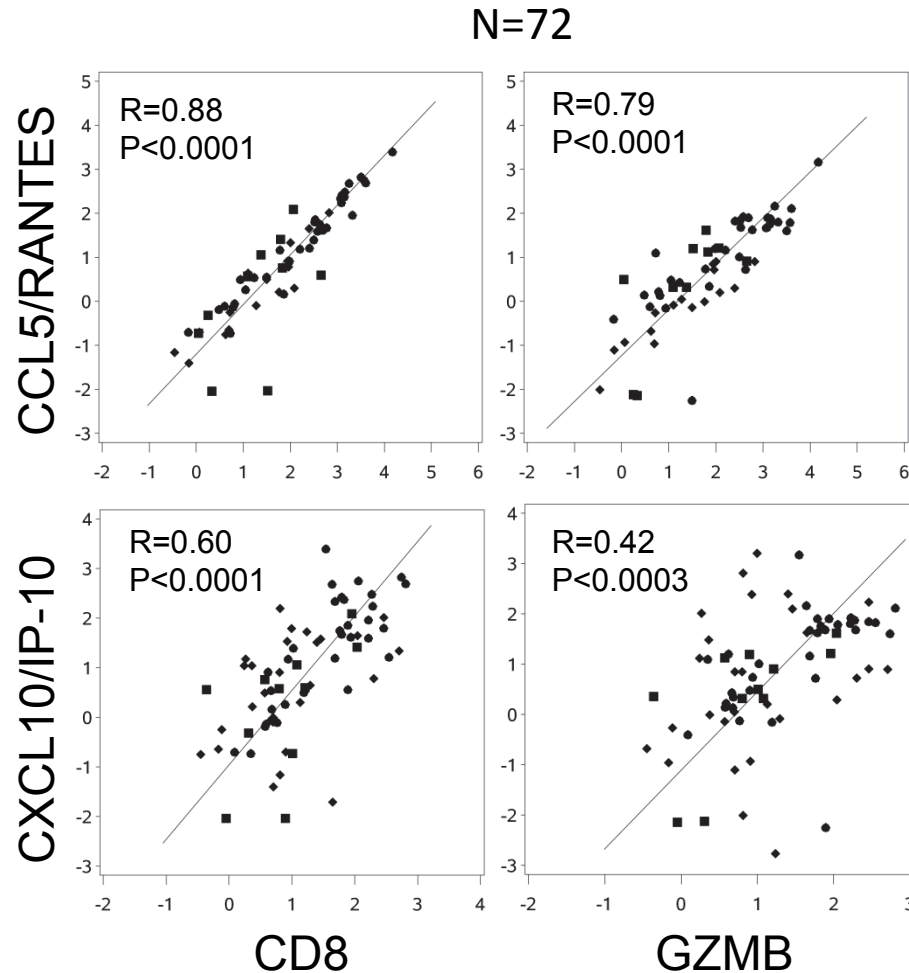


α DC1-produced IL-12 Predicts Delayed Time to Progression in α DC1-Vaccinated Patients

Patient #	TTP (Months)	IL-12
1	7	10
2	<2	25
3	5	25
4	<2	<10
5	<2	26
6	>30	27
7	25	919
8	16	480
9	<2	24
10	5	<10
14	18	551
11	<2	38
12	13	111
13	<2	151
15	4	35
16	>14	985
17	<2	123
18	<2	125
19	>13	199
20	>13	287
21	<2	27
22	>12	779



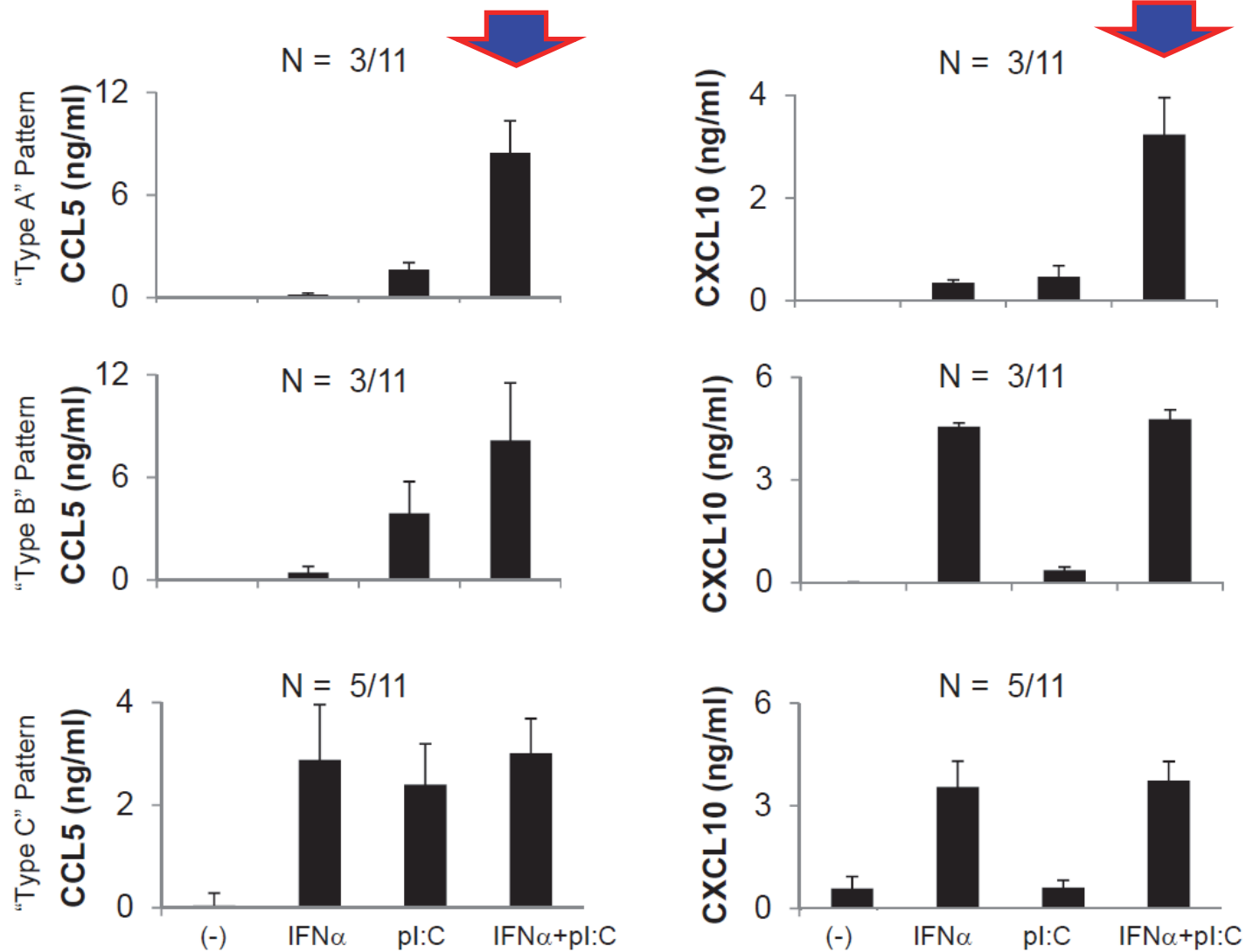
Directing CTLs to Tumors: Intra-Tumoral CXCL10 & CCL5 Levels in Metastatic CRC Correlate with CTL Infiltration



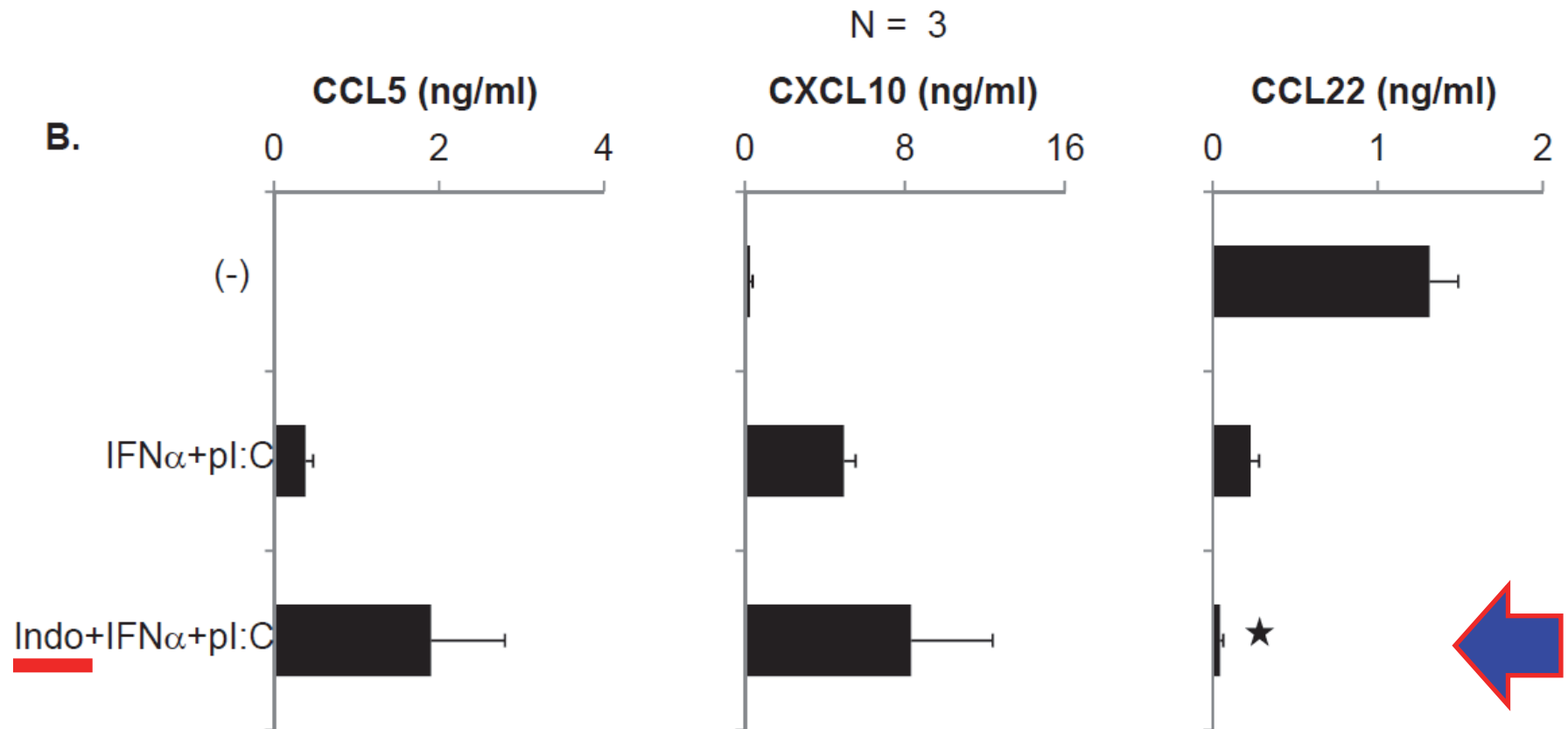
**Muthuswamy R. 2012;
Canc.Res. 272:3735
+ POSTER 205**

Variable Response of Different Cancer Lesions to *Individual* Factors & **Uniform Response to Combination** Treatment

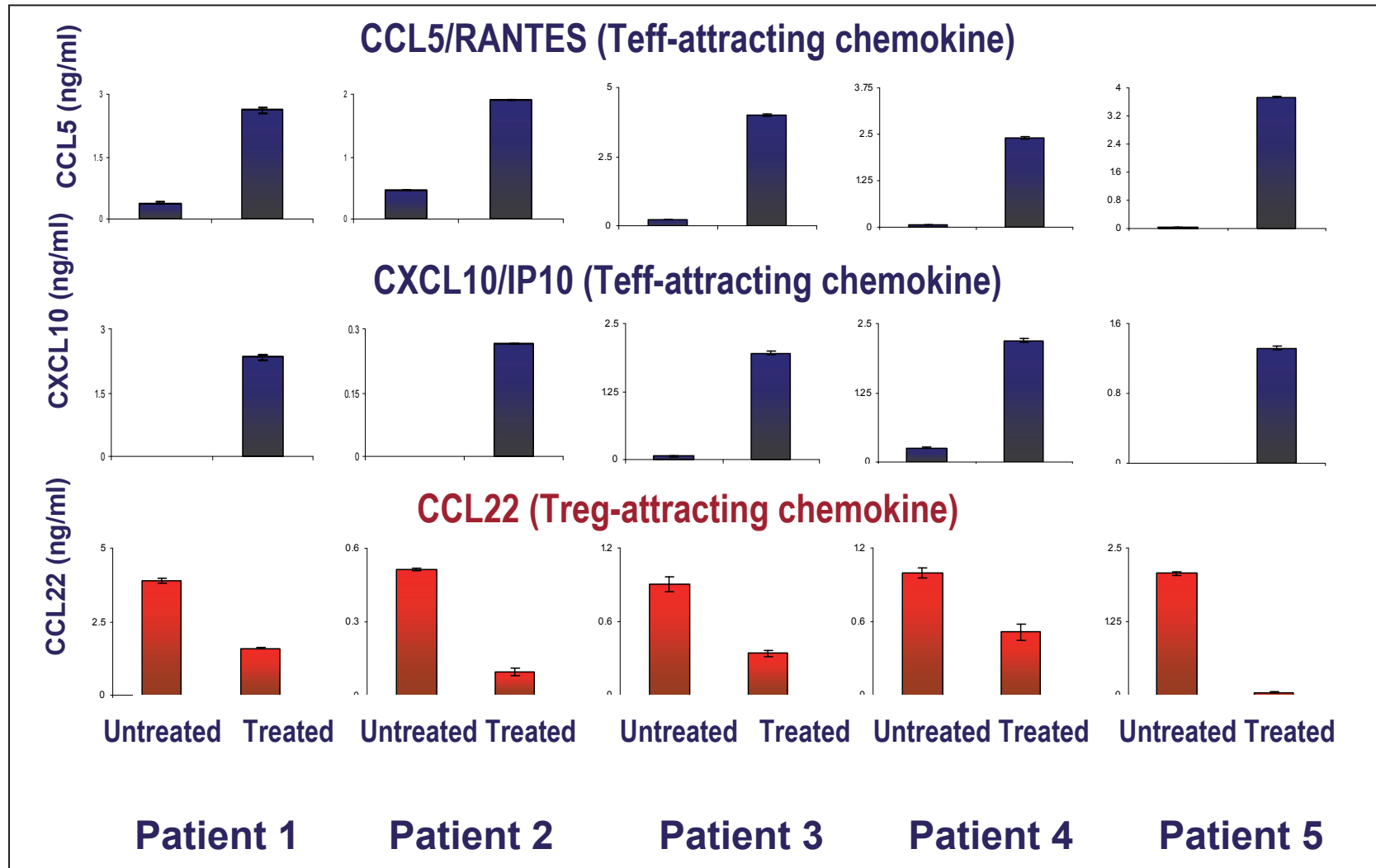
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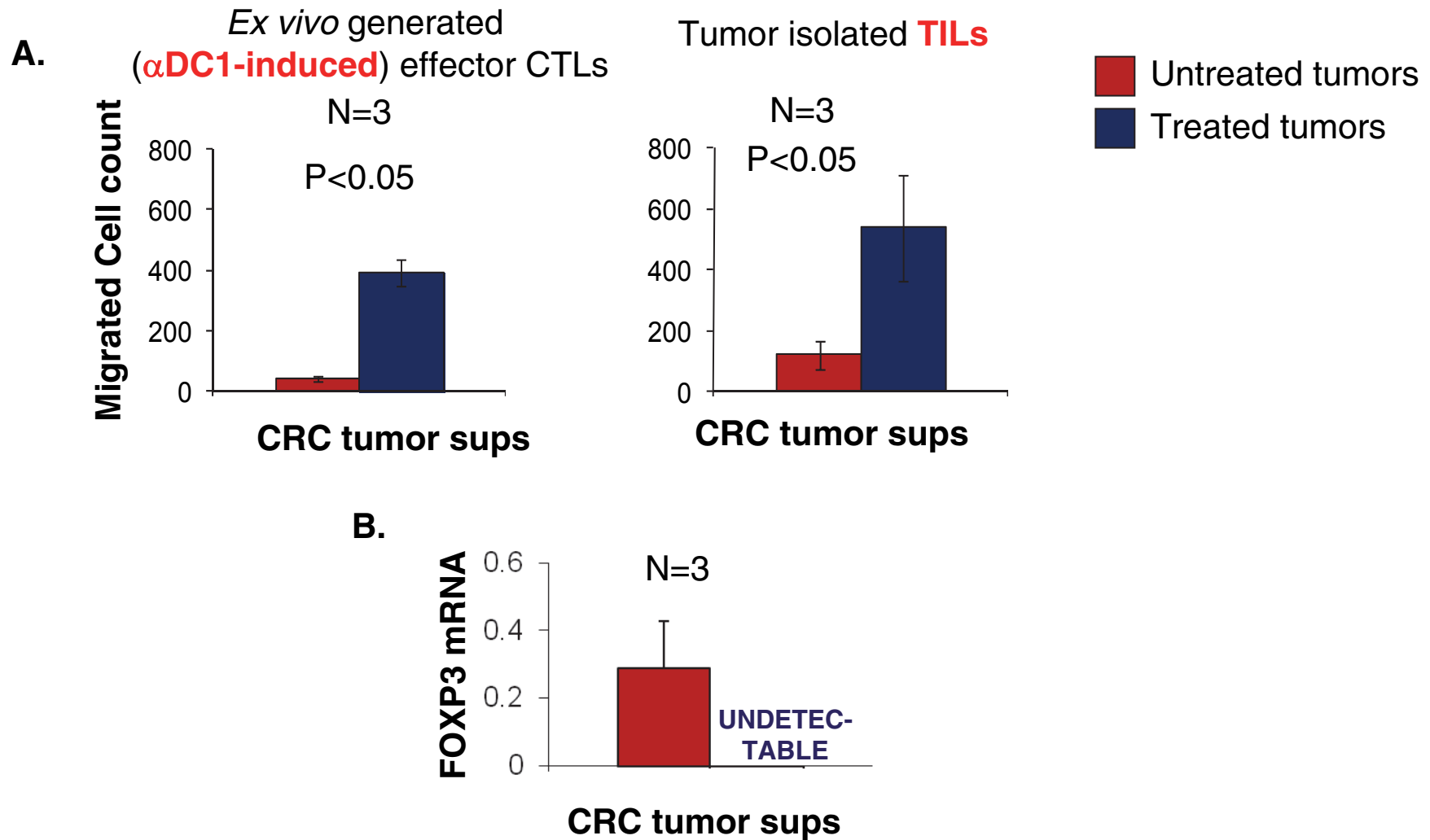
COX Inhibition Helps to Optimize the Chemokine Production Patterns in Tumor Tissues



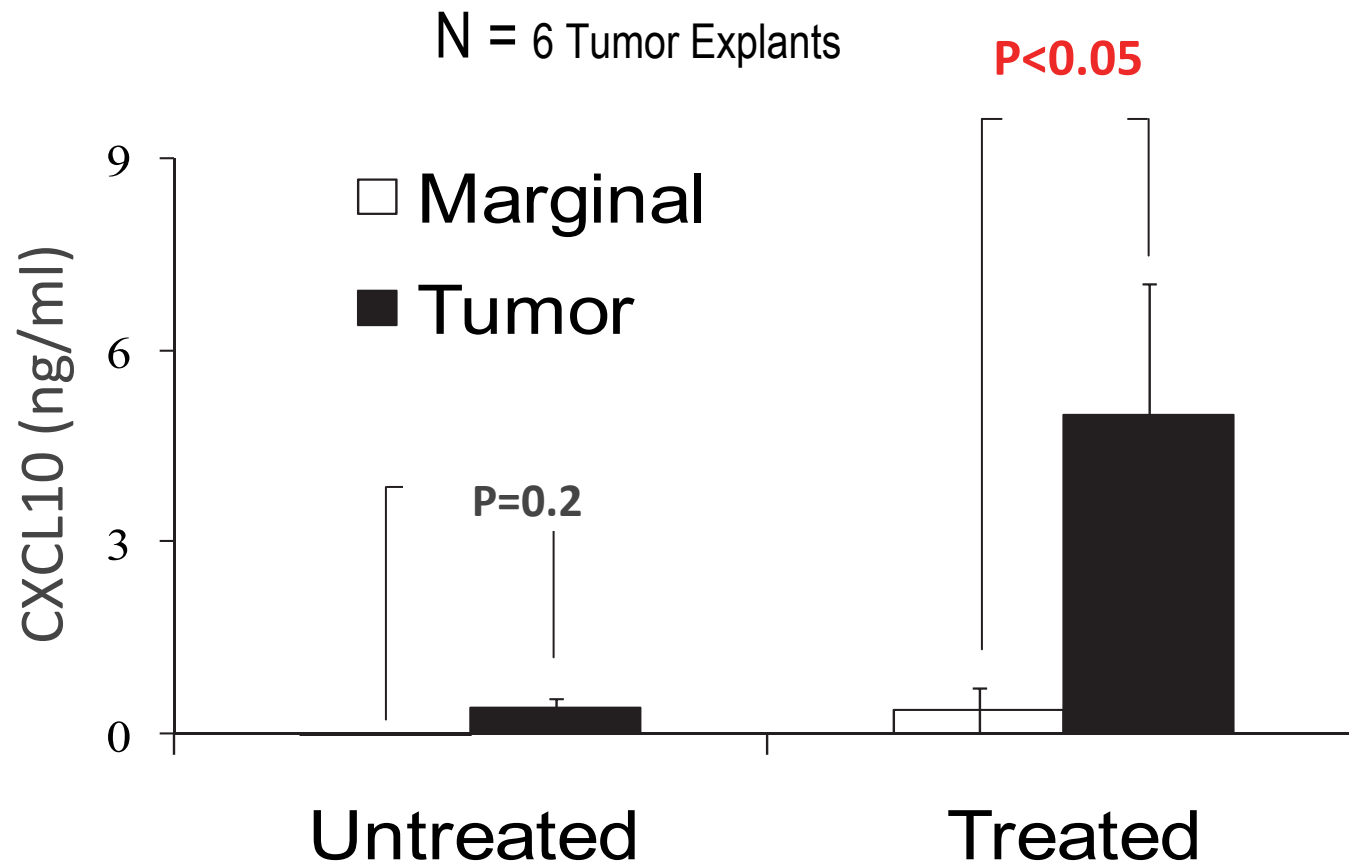
Combination of IFN α , Poly-I:C & COX2 Blockade
Uniformly Induces CTL-attracting CCL5&CXCL10, Blocks
T_{reg}-attracting CCL22 in Tumor Lesions



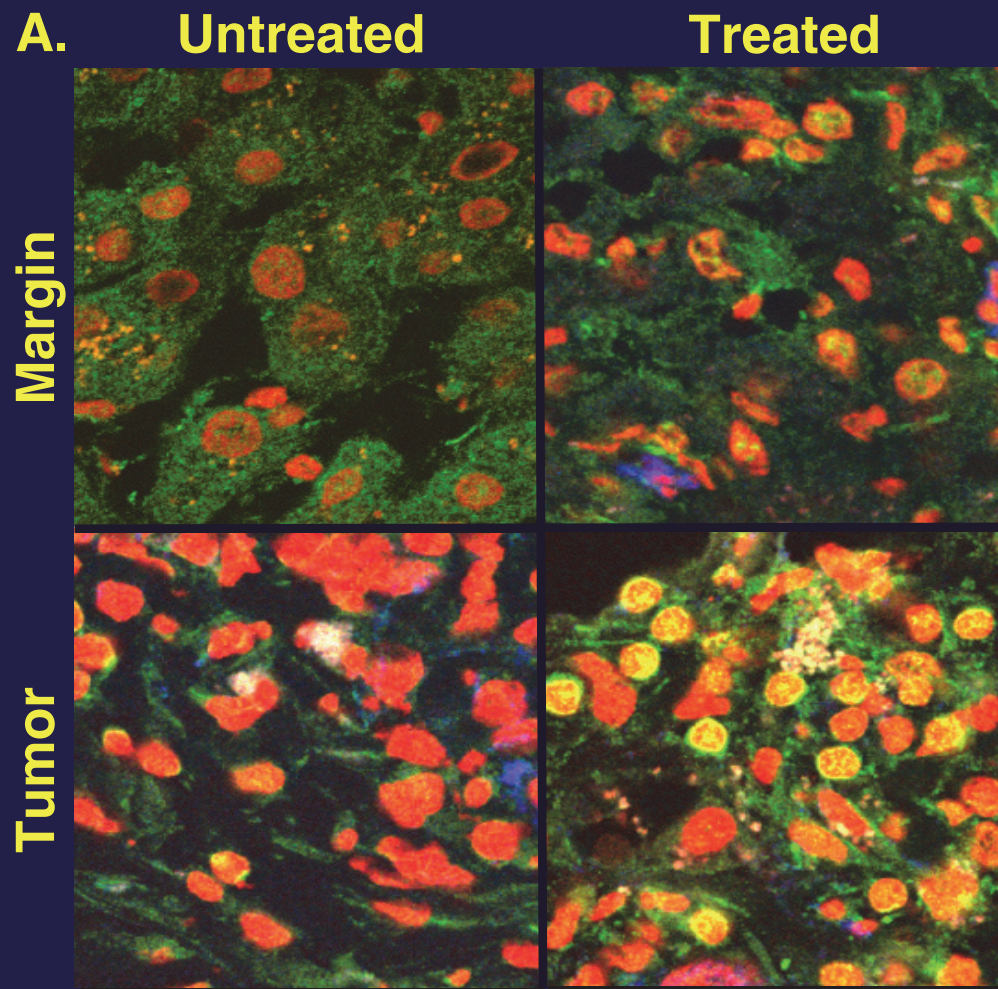
“Conditioned” Tumors *Selectively* Attract α DC1-induced CTLs and Spontaneously Arising TILs and, but Not Tregs



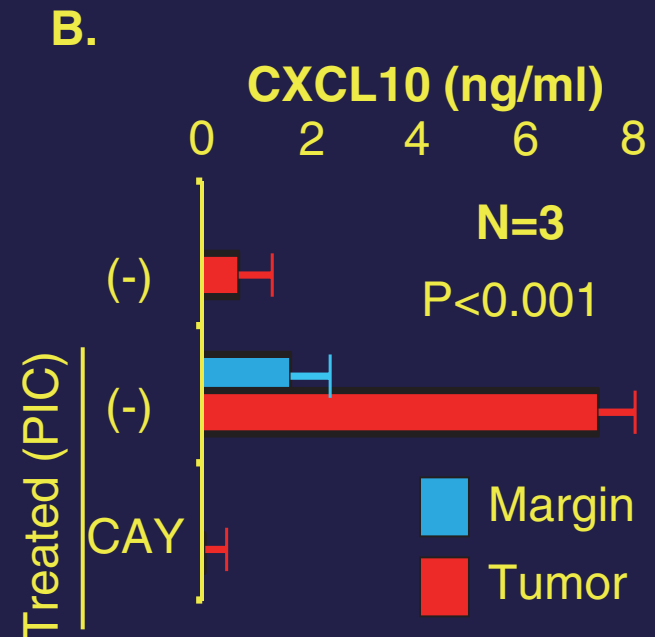
Tumor-*selectivity* of the Pharmacologic Induction of Teff-attracting Chemokines



Tumor-selectivity of the Pharmacologic Modulation of Teff-attracting Chemokines: Role of $\text{NF-}\kappa\text{B}$

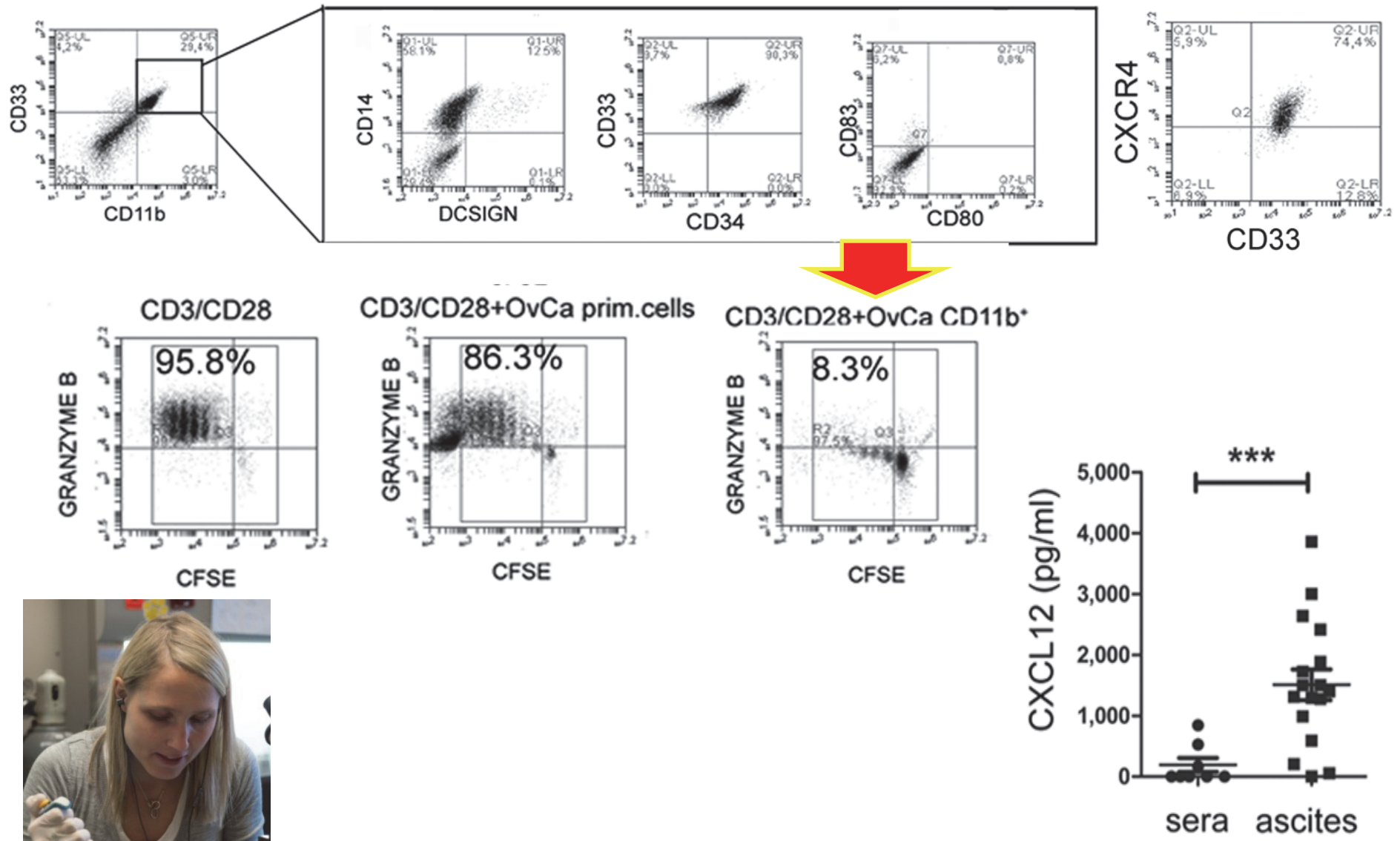


NF- κ B,
DRAQ5



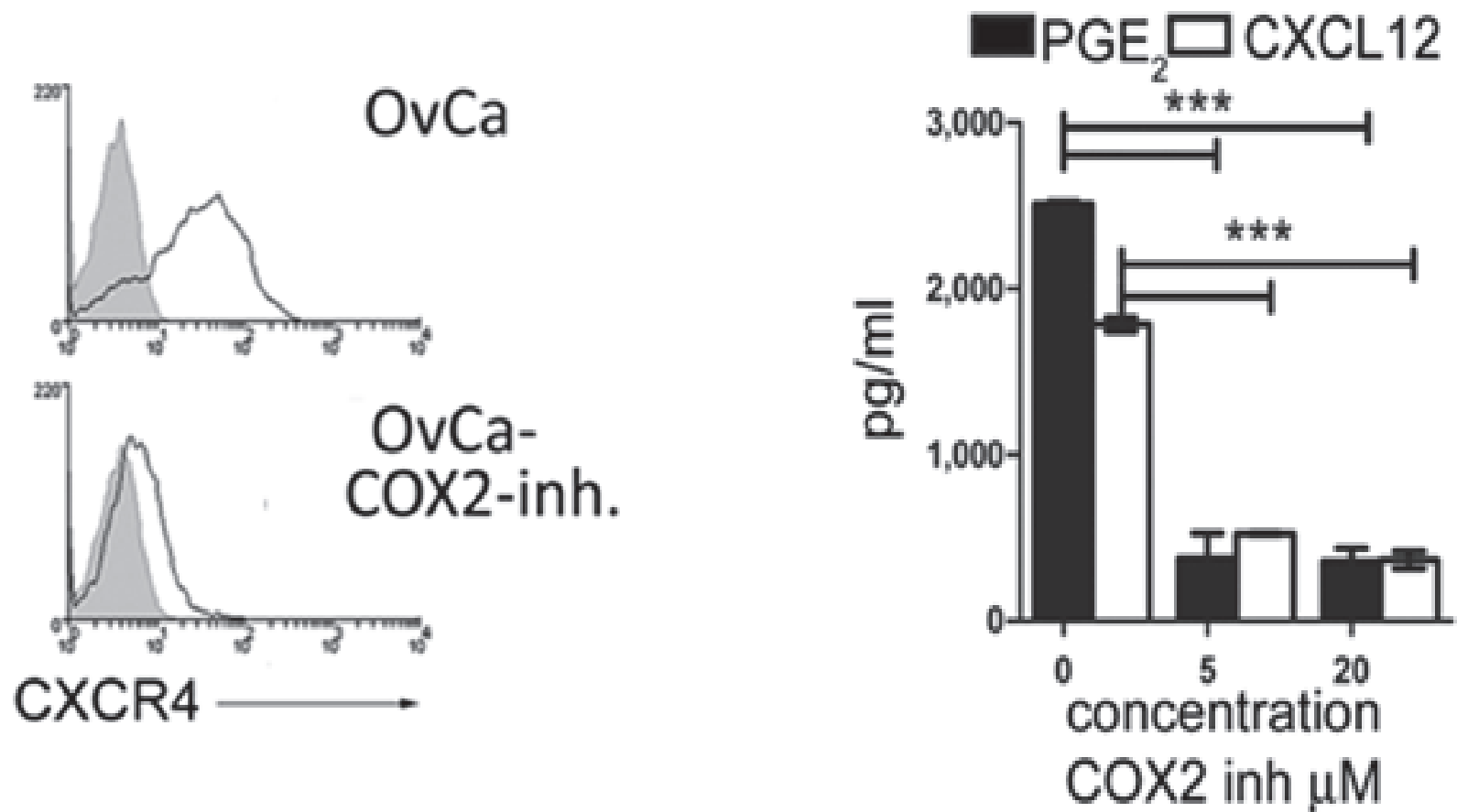
See Poster 205: *STAT-1/IRF1* vs *PKA/pCREB* pathways in the regulation of Teff/Treg chemokines

Phenotype and CTL-Suppressive Function of OvCa-isolated CD11b⁺ MDSCs

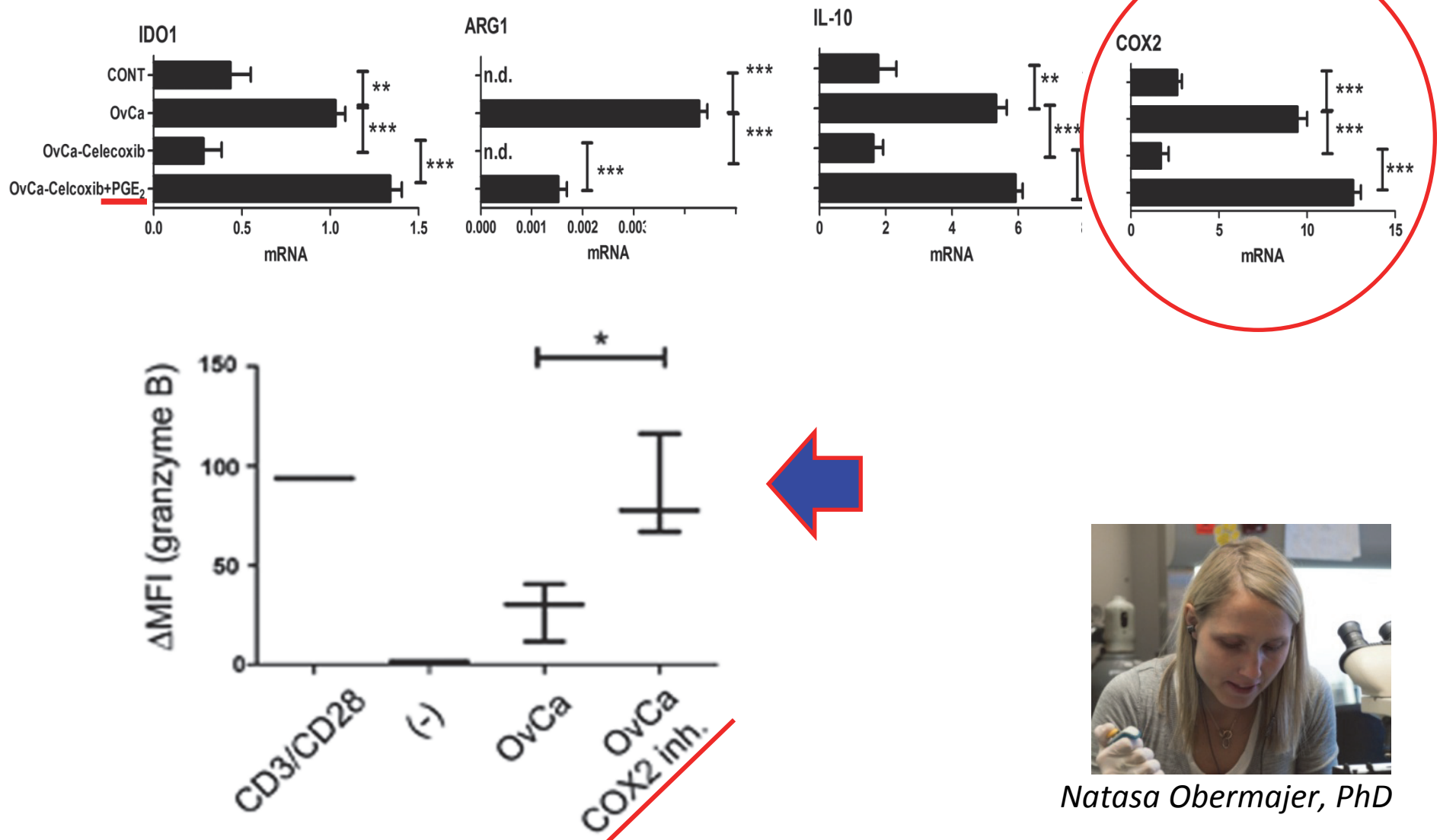


Natasa Obermajer, PhD

PGE₂ Is Needed *Both* for CXCR4 Expression by MDSCs and for Local Production of CXCL12 in Cancer Tissues



Positive Feedback between COX2 & PGE₂ Is Required for Functional Stability of MDSCs in Ovarian Cancer



Natasa Obermajer, PhD

Directing Vaccination-Induced T Cells to Tumors

- *Type-1 DC polarization can be used to preferentially activate naïve, effector and memory T cells (T_{EFF} and T_{MEM}), rather than T_{reg} cells*
- *α DC1s loaded with peptide- or cell-associated Ags induce 20-70 fold more tumor-specific CTLs than non-polarized DCs*
- *α DC1s induce CTL functions and responsiveness to tumor-produced chemokines (CCR5- and CXCR3 ligands) in naïve and memory $CD8^+$ T cells*
- *Combination of IFNs with TLR-ligands and COX2 blockers selectively enhances the production of T_{EFF} -attracting chemokines in tumor lesions and counteracts T_{reg} /MDSC attraction and function*
- *Ongoing and upcoming combination trials in colorectal cancer (UPCI 10-131 and UPCI 11-123) and ovarian cancer (UPCI 11-128)*

Conditioning Tumor Microenvironment for Effective Immune Attack

Ravi Muthuswamy
Natasa Obermajer
Erik Berk
Payal Watchmaker
Eva Wieckowski
Julie Urban
Becky Pazehosky
Robbie Mailliard
Jeffrey Wong
Je-Jung Lee
Yutaro Nakamura
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