서울대학교 시스템면역의학연구소

제 3회 국제 학술 대회

The 3rd International Symposium of
Wide River Institute of Immunology

Frontiers in Immune Regulation

- 일시: 2016년 10월 7일 (금) 13:30~18:00
- 장소: 서울대학교 시스템면역의학연구소 볼룸
  강원도 홍천군 화촌면 답연밭길 101

주최

서울대학교 시스템면역의학연구소

The 3rd International Symposium of Wide River Institute of Immunology

Frontiers in Immunology and Immunotherapy

Friday, October 7, 2016

Wide River Institute of Immunology, Ballroom

Seoul National University College of Medicine

인 사 말

안녕하십니까?

서울대학교 시스템면역의학연구소의 개소 2주년을 기념하며 개최하는 제3회 국제 학술대회에 참석하여 주신 여러분께 깊은 감사의 말씀을 전합니다. 또한 강의를 수락하여 훌륭한 강의를 준비해주신 연자 분들께도 특별한 감사의 말씀을 드립니다.

서울대학교 시스템면역의학연구소는 종양 및 다양한 면역 질환의 기전 및 치료법에 대한 연구를 수행해 왔습니다. 또한 의생명과학 분야 여러 핵심 기술들을 지원하는 Lab on a Cloud를 구축하여 지난 두해 동안 국내외 40여 팀과 공동협력 연구를 진행하였습니다. 활발한 협력 연구를 통해 건강한 미래사회를 구현하기 위해 최선의 노력을 다하겠습니다. 앞으로도 아낌없는 격려와 관심 부탁드립니다.

이번 국제학술대회에서는 암를 비롯한 다양한 염증성 질환의 발병 원인이나 그 경과에 관여하는 여러 면역세포들의 역할과 관련된 최신 연구를 소개하는 자리를 마련하였습니다. 본 학회를 통하여 모든 참석자분들의 학문증진 및 상호 교류를 유도하여 연구의 결실이 보다 풍성하게 무르익을 수 있기를 기원합니다.

제3회 국제학술대회가 성공적으로 마무리 될 수 있도록 여러분의 적극적인 성원을 부탁드리며 다시 한 번 감사의 말씀을 드립니다.

서울대학교 시스템면역의학연구소 소장 성승용

Dear Colleagues,

It is my great pleasure and honor to invite all of you to the 3rd International Symposium of Wide River Institute of Immunology hosted by Seoul National University College of Medicine on October 7, 2016, in Hongcheon. I specially appreciated all speakers and audiences attending the conference.

Our institute has been studying on the mechanisms of cancer and immune disease progression and therapeutic targeting of those diseases. We set up the "Lab on a Cloud" providing the essential technology for biomedical research and have been collaborated more than 40 research teams for last two years. We'll continue further collaboration for contributing to make healthy society in future..

In this conference, we will provide special lectures by six world class leaders in the field of immunology studying on the cause and progression of inflammatory diseases including cancer and roles of various immune cells regulating those diseases. I wish this meeting will be an excellent opportunity to exchange scientific ideas on current and emerging discoveries and share research findings through active participation and discussions.

I sincerely hope that this conference will be productive for the establishment of new collaborations among scientists and develop a new vision for the future of immunology.

Seong-Yong Seong, M.D., Ph.D.

Director of Wide River Institute of Immunology,

Seoul National University College of Medicine, Korea

The 3rd International Symposium of Wide River Institute of Immunology

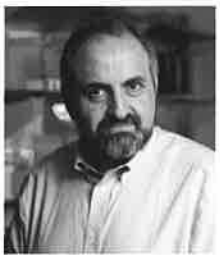
Frontiers in Immunology and Immunotherapy

SCIENTIFIC PROGRAM

12:30~13:30	Registration
13:30~13:40	Opening remark Seung-Yong Seong (Seoul National University, Korea)
13:40~14:20	Myeloid-derived cells are coming to age. Dmitry I. Gabrilovich (Wistar Institute, USA)
14:20~15:00	Designing effective cancer vaccines by mimicking viral infections Esteban Celis (Augusta University, USA)
15:00~15:40	Expansion of immune suppressive myeloid cells in Cancer Je-In Youn (Seoul National University, Korea)
15:40~16:00	Break
16:00~16:40	Molecular control of T cell function in immunity Chen Dong (Tsinghua University, China)
16:40~17:20	Immune regulation via immune checkpoint PD-1 expressed on regulatory T cells during cancer progression Sang-Jun Ha (Yonsei University, Korea)
17:20~18:00	Regulation of innate immune response in the intestine during colitis Sang-Uk Seo (Seoul National University, Korea)
18:00	Closing

Curriculum Vitae

Dmitry I. Gabrilovich



Position/Address The Wistar Institute

3601 Spruce Str. Philadelphia, PA, 19104-4265

USA

E-mail: dgabrilovich@wistar.org

Education:

1984 MD, Kabardino-Balkarian State University Medical School, Nalchik, Russia

1989 PhD, Immunology, Central Institute for Epidemiology, Moscow, Russia.

Professional Backgroud:

08/2005 – 04/2013 Professor, Department of Molecular Medicine, University of South Florida, Tampa, FL

03/2007 – 04/2013 Senior Member and Head, Section of Dendritic Cell Biology, H. Lee Moffitt Cancer Center and Research Institute

01/2008 – 04/2013 Robert Rothman Endowed Chair in Cancer Research, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

05/2013-present Christopher M. Davis Professor in Cancer Research, Program Leader, Translational Tumor Immunology, The Wistar Institute, Philadelphia, PA

04/2014-present Professor, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Recent publications:

1. Gabrilovich D, Nefedova Y. ROR1C Regulates Differentiation of Myeloid-Derived Suppressor Cells. Cancer Cell. 2015 Aug 10;28(2):147-9.

2. Condamine T, Mastio J, Gabrilovich DI. Transcriptional regulation of myeloid-derived suppressor cells. J Leukoc Biol. 2015 Dec;98(6):913-22.

3. Ramachandran IR, Condamine T, Lin C, Herlihy SE, Garfall A, Vogl DT, Gabrilovich DI, Nefedova Y. Bone marrow PMN-MDSCs and neutrophils are functionally similar in protection of multiple myeloma from chemotherapy. Cancer Lett. 2016 Feb 1;371(1):117-4. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. Trends Immunol. 2016 Feb 5.

5. Kumar V., Cheng P., Condamine T., Mony S., Languino, LR., McCaffrey JC., Hockstein N., Guarino, M., Masters G., Penman E., Denstman F., Xu X., Altieri DC, Du H., Yan C., Gabrilovich DI. CD45 Phosphatase Inhibits STAT3 Transcription Factor Activity in Myeloid Cells and Promotes Tumor-Associated Macrophage Differentiation. Immunity, 44, 303–315, 2016

6. Bronte V, Brandau S, Chen SH, Colombo MP, Frey AB, Greten TF, Mandruzzato S, Murray PJ, Ochoa A, Ostrand-Rosenberg S, Rodriguez PC, Sica A, Umansky V, Vonderheide RH, Gabrilovich DI. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun. 2016 Jul 6;7:12150

7. Sayeed A, Lu H, Liu Q, Deming Ii D, Duffy A, McCue P, Dicker AP, Davis RJ,Gabrilovich D, Rodeck U, Altieri DC, Languino LR. β1 integrin- and JNK-dependent tumor growth upon hypofractionated radiation. Oncotarget. 2016 Jul 11.

8. Condamine, T., Dominguez, GA., Youn, JI, Kossenkov, AV., Mony, S., Alicea-Torres, K., Tcyganov, E., Hashimoto, A., Nefedova, Y., Lin, C. Partlova, S., Garfall, A., Vogl, DT., Xu, X., Knight, SC, Malietzis, G., Lee, GH., Eruslanov, E., Albelda, SM., Wang, X., Mehta, JL., Bewtra, M., Rustgi, A. Hockstein, N., Witt, R., Masters, G., Nam, B., Smirnov, D., Sepulveda, MA., Gabrilovich, DI. Lectin-type oxidized LDL receptor 1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. 2016. Science Immunol. 1, aaf8943.

Myeloid-derived cells are coming to age

Dmitry I. Gabrilovich

The Wistar Institute, USA

Myeloid-derived suppressor cells (MDSC) are one of the major components of the tumor microenvironment. The main feature of these cells is their potent immune suppressive activity. They are directly implicated in the promotion of tumor metastases by participating in the formation of pre-metastatic niche, promoting angiogenesis and tumor cell invasion. MDSC are generated in the bone marrow, and in tumor-bearing hosts, migrate to peripheral lymphoid organs and the tumor to contribute to the formation of the tumor microenvironment. Accumulation of MDSC is governed by a network of transcriptional regulators that could be combined into two partially overlapping groups: factors promoting myelopoiesis and preventing differentiation of mature myeloid cells, and factors promoting pathological activation of MDSC. There is now sufficient information demonstrating that the function and fate of MDSC in the tumor and peripheral lymphoid organs are different. Therapeutic targeting of MDSC has emerged as attractive option to enhance clinical response to immunotherapy.

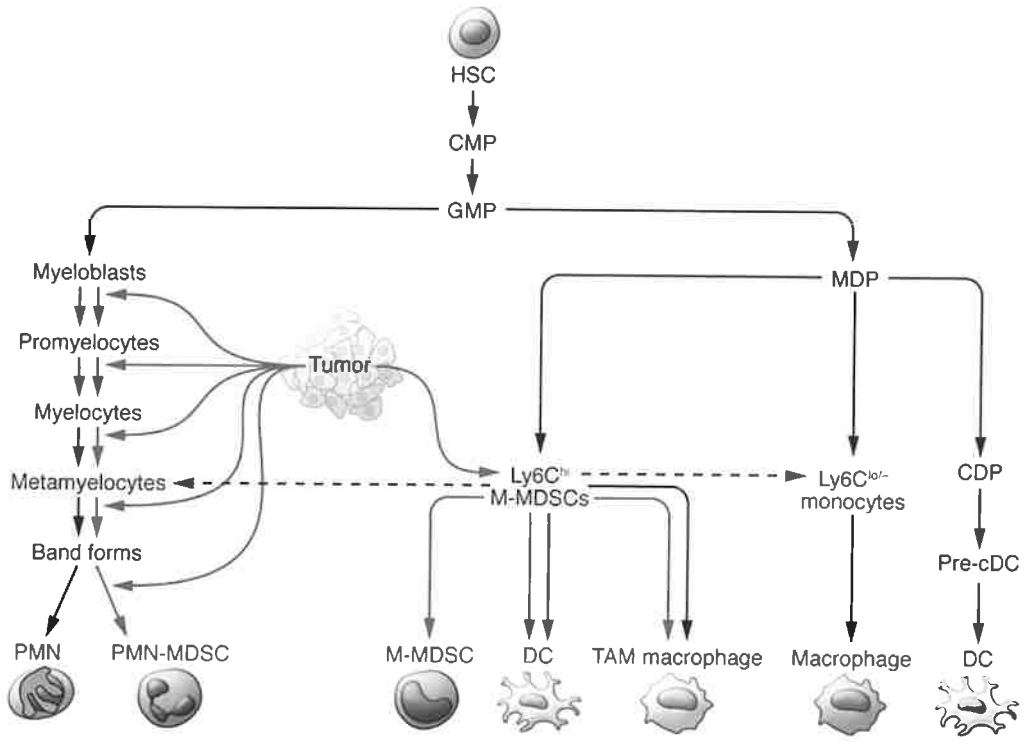
Myeloid-derived suppressor cells coming to age

Dmitry Gabrilovich

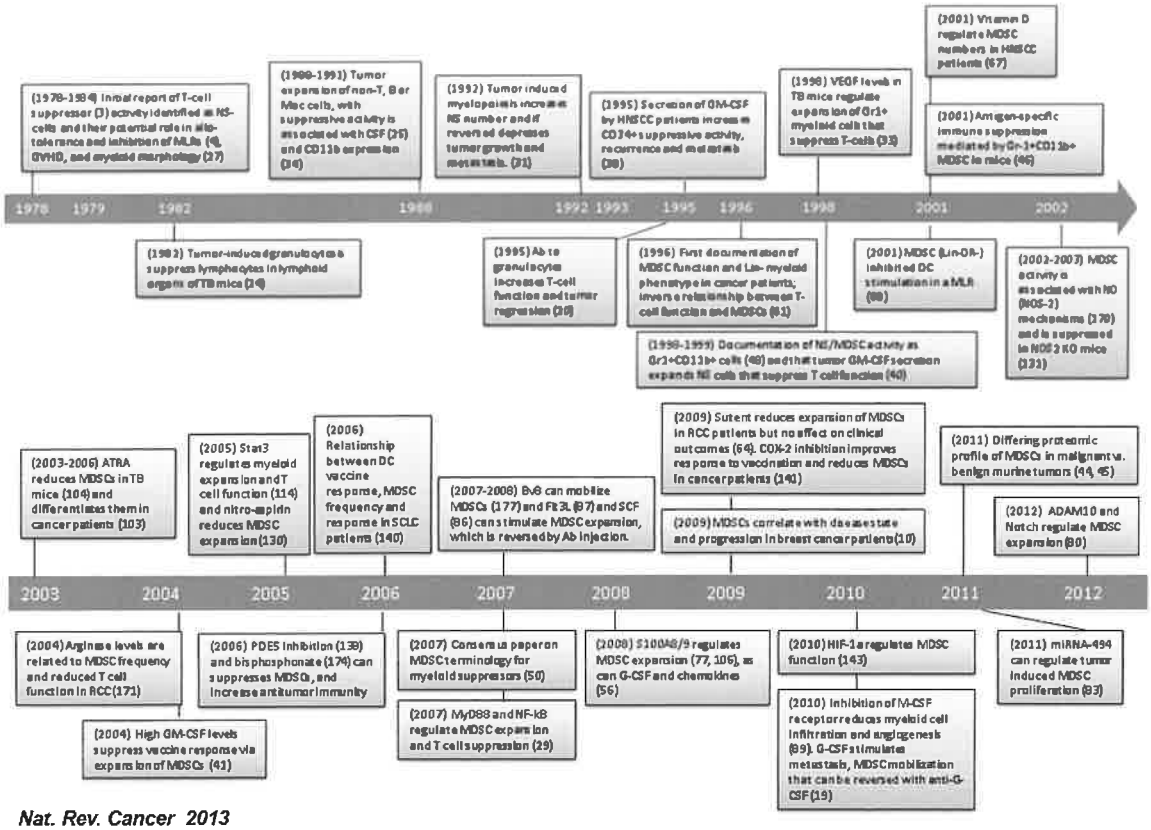
The Wistar Institute, Philadelphia, PA

1894

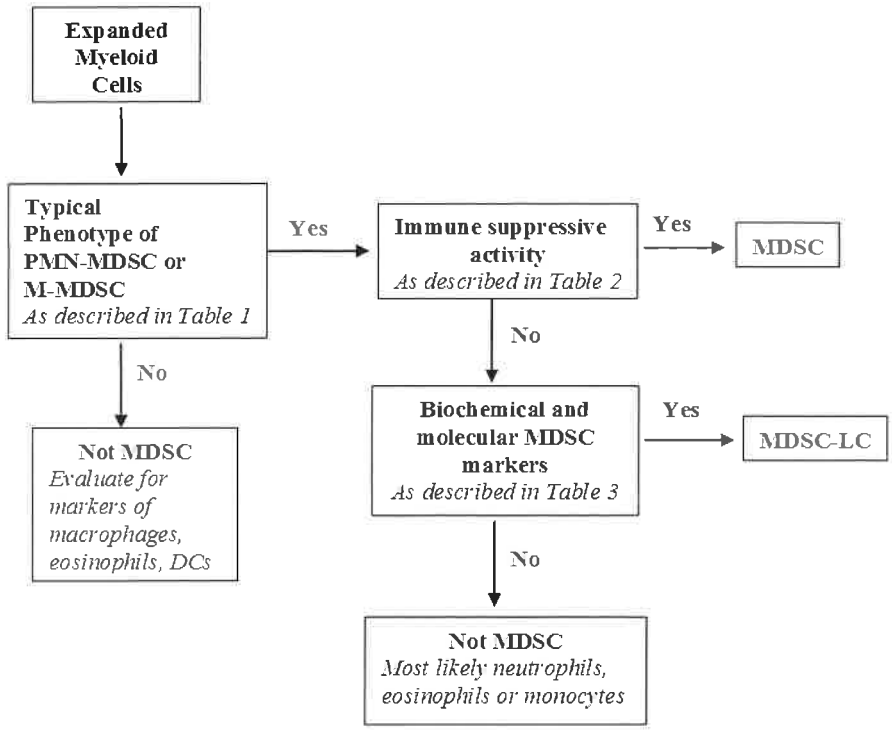
2014



J. Clin. Invest. 2015, 125, 3356-3364



Nat. Rev. Cancer 2013

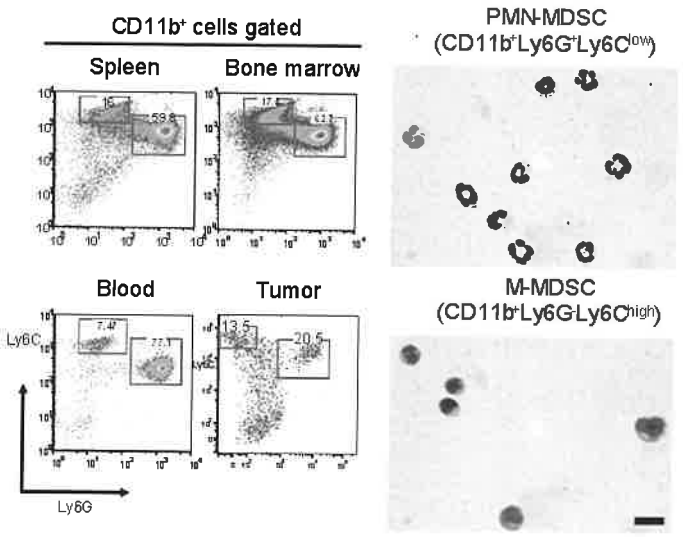


Nat Commun. 2016 Jul 6;7:12150.

Class of biomarkers	Biomarker	Detection technology	Mainly found in
Transcription factors and epigenetic regulators	IRF8 *	FC, P	MDSC
	STAT3 *	FC, ELI	MDSC
	cEBP/β *	ELI, P, T	MDSC
	S100A8/9 *	ELI, FC, IHC, P, T	MDSC
	RB	IF, P, T, FC	M-MDSC
	NF-κB	FC, ELI, P	MDSC
	STAT5	FC, IHC, P, T	MDSC
	ROR/RORC1	FC, P	PMN-MDSC
	VEGF	FC, IHC	MDSC
	cFLIP	P, T	M-MDSC
	sXBP, CHOP	P, T	MDSC
Cytokines and receptors	IL-10 *	ELI, FC, T	MDSC
	TGF/β *	ELI, FC, T, WB	M-MDSC
	IL-6 *	ELI, FC, IF, T, WB	M-MDSC
	IL-1R *	T	MDSC
	IL-4R (CD124) *	FC, T	M-MDSC
	GM-CSF	ELI, T	MDSC
	G-CSF	ELI, T	PMN-MDSC
	M-CSF	ELI, T	M-MDSC
	IL-13	FC	M-MDSC
	IL-1	ELI	MDSC
Genes and molecules contributing to the immune regulatory activity	ARG1 *	E, FC, IHC, P, T	M-MDSC
	NOS2/NO *	FC, IF, IHC, P, T	M-MDSC
	NOX2/ROS *	E, FC, P, T	PMN-MDSC
	PNT/RNS *	PTM (IHC), E, FC	MDSC
	PGE_2	ELI	M-MDSC
	PD-L1	FC, P, T	MDSC
	IDO1	P	M-MDSC

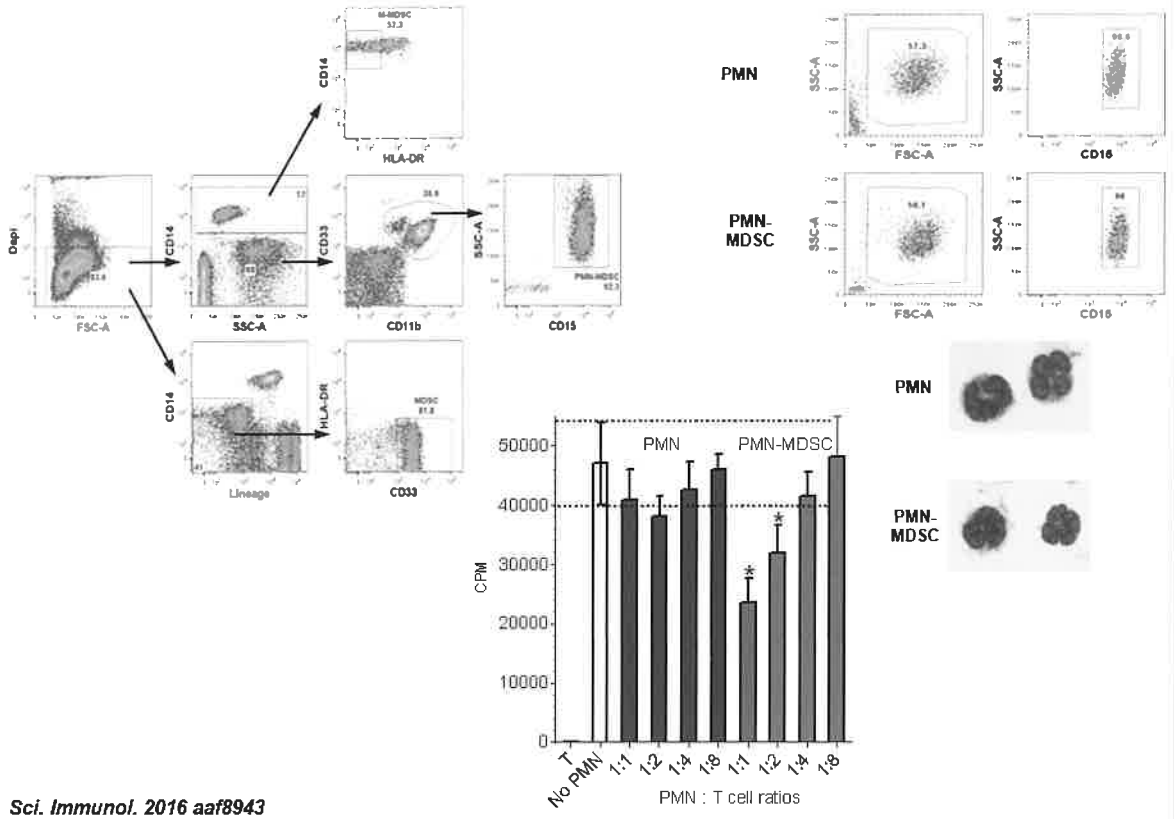
Nat Commun. 2016 Jul 6;7:12150.

Morphology of MDSC subsets in mice



Nat. Immunol. 2013; 14: 211-220

Phenotype, morphology, and function of MDSC subsets in humans



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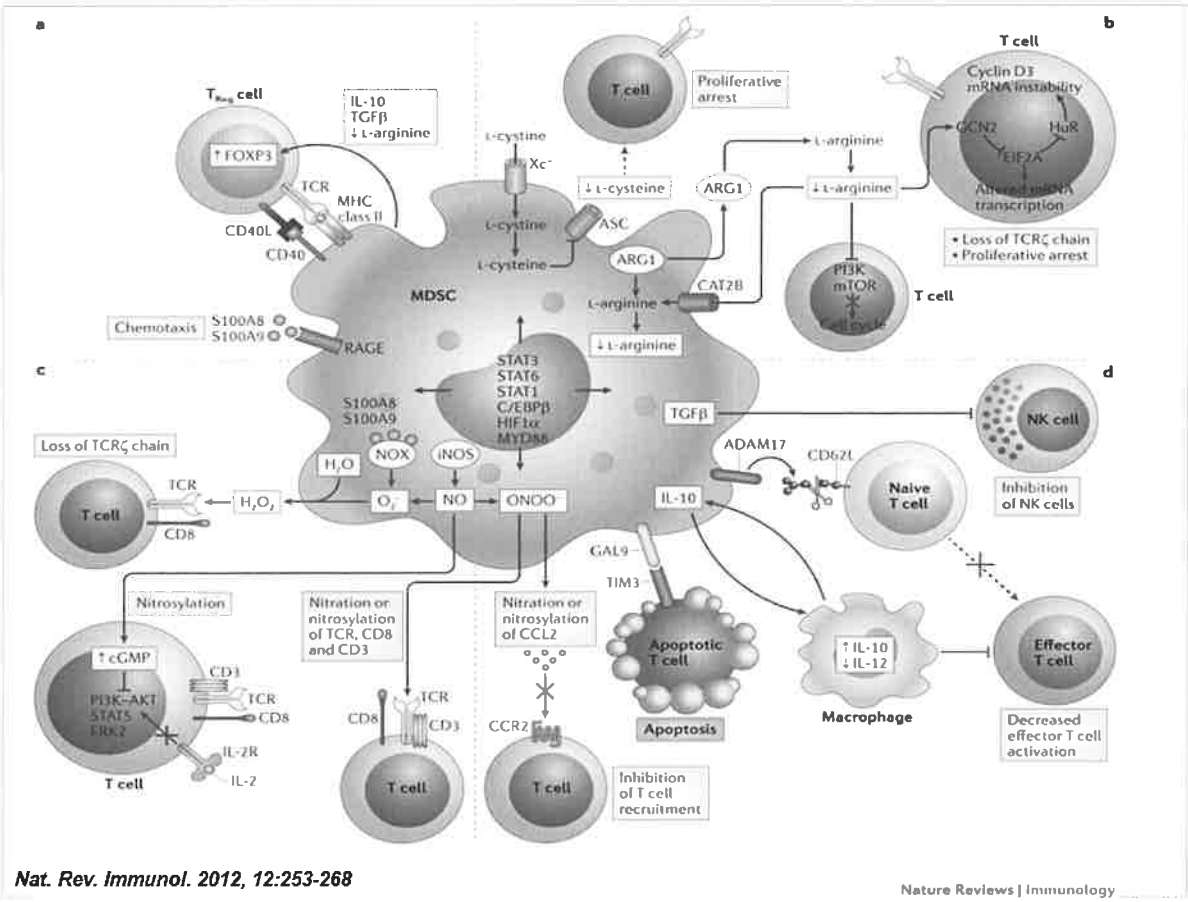

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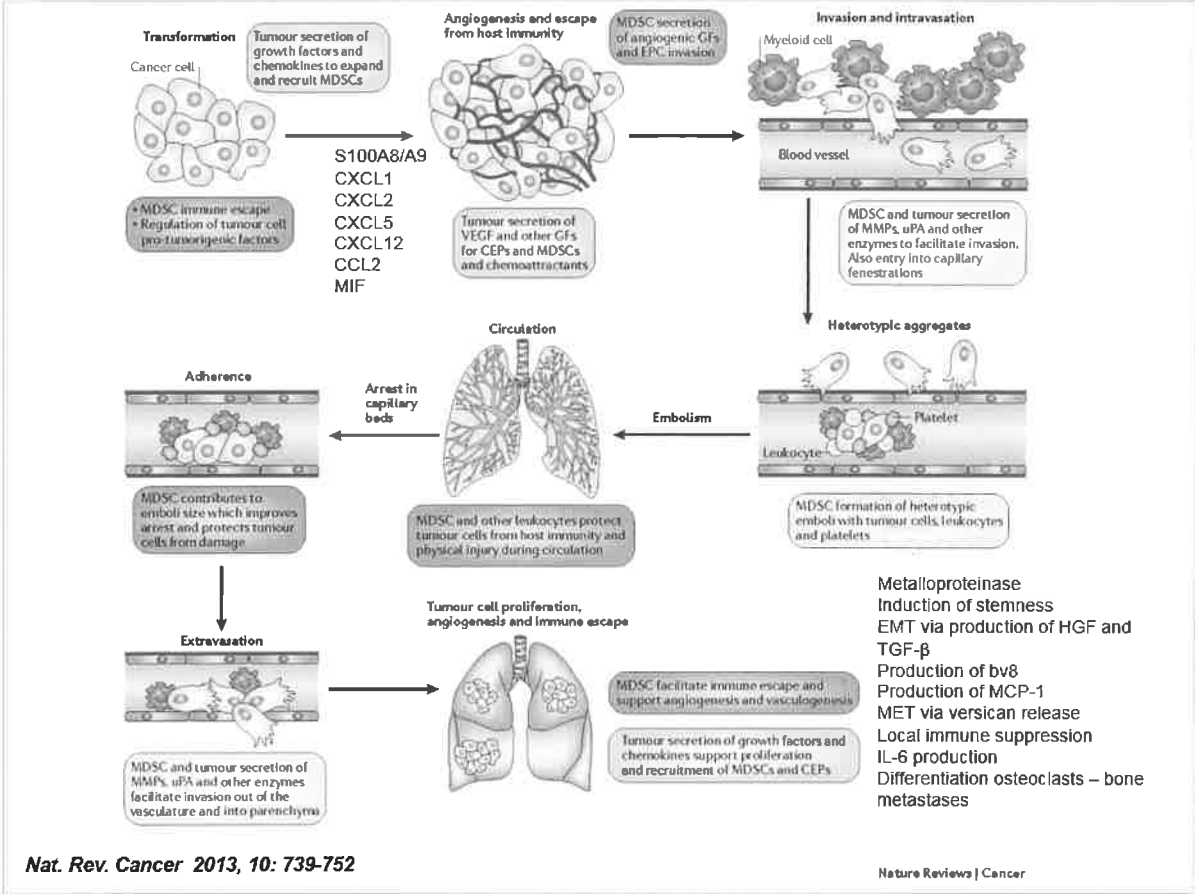

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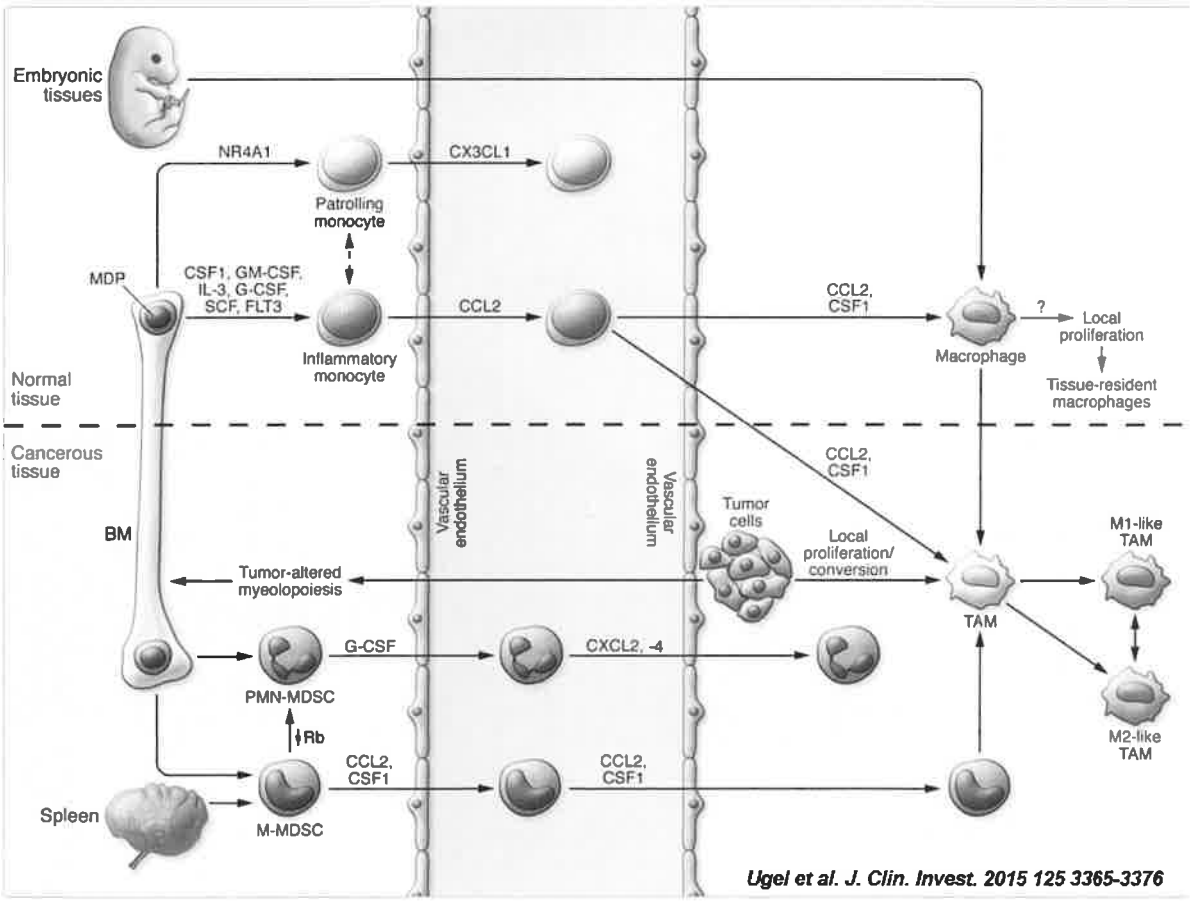

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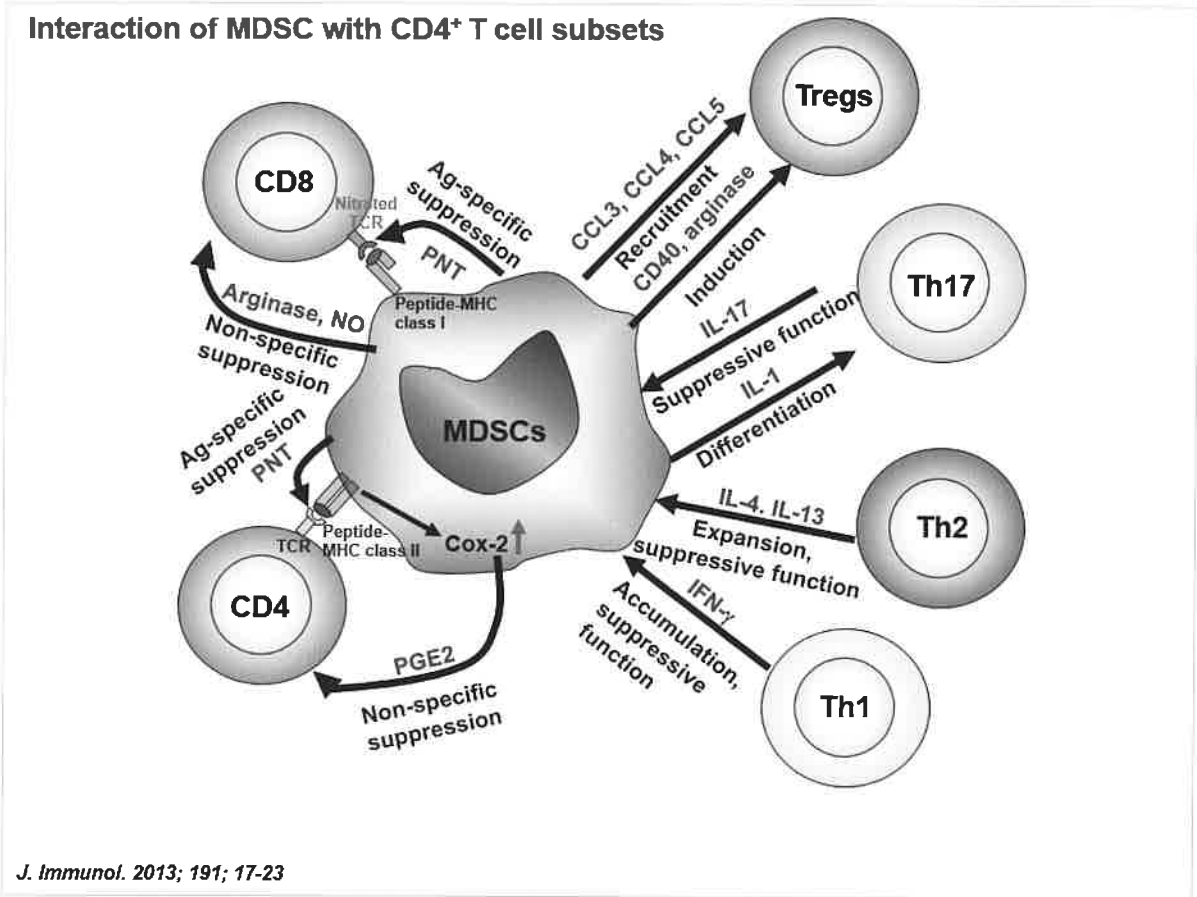

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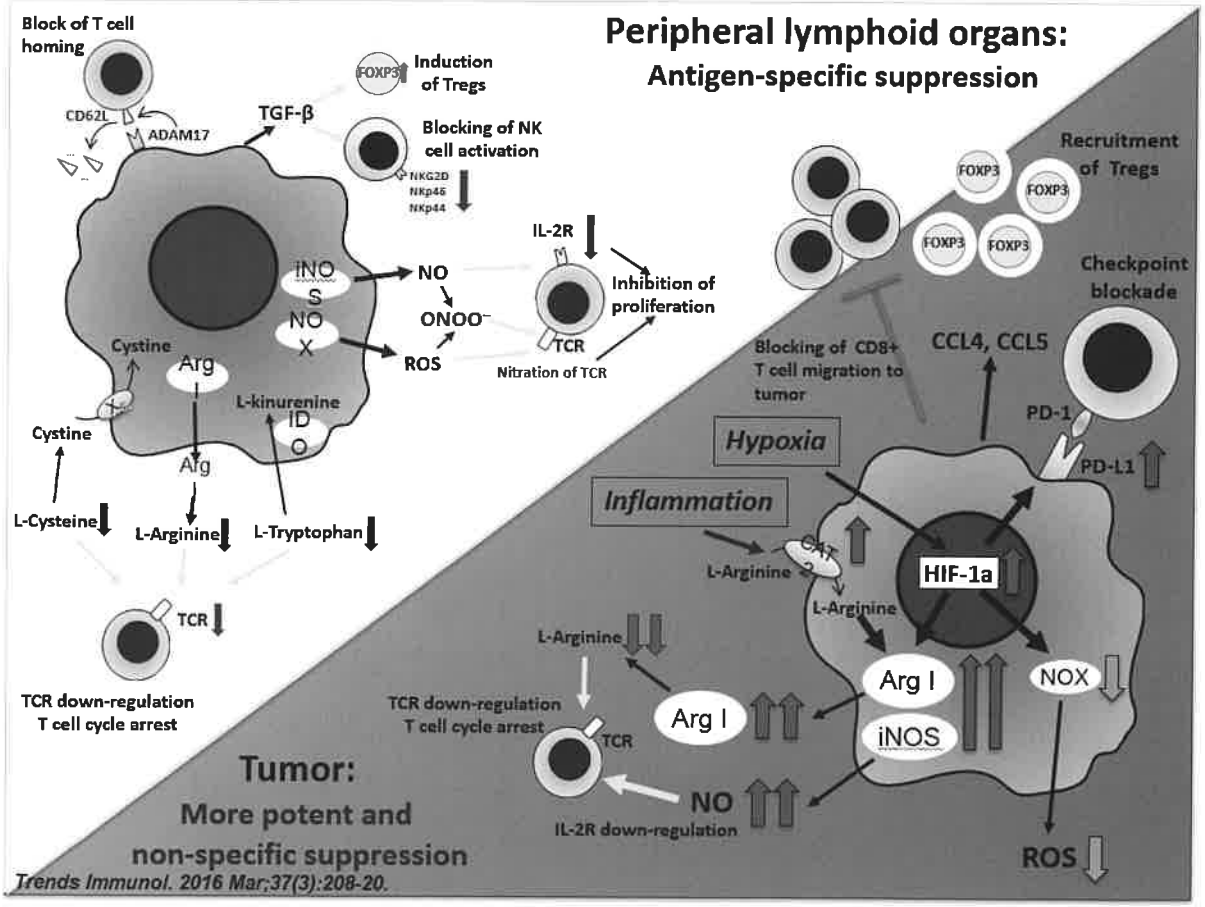

Trends Immunol. 2016 Mar;37(3):208-20.

Curriculum Vitae

Esteban Celis

Position/Address Medical College of Georgia, Augusta University

1410 Laney Walker Blvd., CN4121, Augusta,

GA 30912, USA

E-mail: ecelis@augusta.edu

Education:

1976 M.D., Medicine, National University of Mexico, Mexico

1977 M.Sc, Basic Biomedical Research, National University of Mexico, Mexico

1980 Ph.D., Basic Biomedical Research, National University of Mexico, Mexico

Professional Backgroud:

1992-1997 Director, Tumor Immunology,

Project Leader, Tumor Vaccine and Ex Vivo CTL Therapy Programs

Cytel Corporation/Epimmune, San Diego, CA

1997-2004 Professor, Department of Immunology, Mayo Clinic, Rochester MN

2/2005-11/2013 Professor, Department of Immunology, Moffitt Cancer Center and Research Institute, Tampa FL.

Professor, Department of Molecular Medicine, University of South Florida College of Medicine

12/2013-present Professor of Medicine, Medical College of Georgia, Augusta University

Director (Interim), Cancer Immunology Inflammation and Tolerance Program (CIT), Georgia Cancer Center

Recent publications:

1. Kumai, T., Matsuda, Y., Ohkuri, T., Oikawa, K., Ishibashi, K., Aoki, N., Kimura, S., Harabuchi, Y., Celis, E., and Kobayashi, H. (2015). C-Met is a novel tumor associated antigen for T-cell based immunotherapy against NK/T cell lymphoma. Oncommunology Mar 6;4(2):e976077. eCollection 2015 Feb. PMID: 25949874.

2. Wang, Z., Celis, E. (2015). STING activator c-di-GMP enhances the anti-tumor effects of peptide vaccines in melanoma-bearing mice. Cancer Immunol. Immunother. 64:1057-1066. PMID: 25986168.

3. Cho, H.I., Jung, S.H., Sohn, H.J., Celis, E., and Kim, T.G. (2015). An optimized peptide vaccine strategy capable of inducing multivalent CD8+ T cell responses with potent antitumor effects. Oncoimmunology. 4(11), e1043504, doi: 10.1080/2162402X.2015.1043504. PMID: 26451316.

4. Kumai, T., Ohkuri ,T., Nagato, T., Matsuda, Y., Oikawa, K., Aoki, N., Kimura, S., Celis, E., Harabuchi, Y., and Kobayashi, H. (2015). Targeting HER-3 to elicit antitumor helper T cells against head and neck squamous cell carcinoma. Scientific Reports. 5:16280-16292. PMID: 26538233.

5. Sharma, M.D., Shinde, R., McGaha, T.L., Huang, L., Holmgaard, R.B., Wolchok, J.D., Mautino, M.R., Celis, E., Sharpe, A.H., Francisco, L.M., Powell, J.D., Yagita, H., Mellor, A.L., Bruce R. Blazar, B.R, and Munn, D.H. (2015). The PTEN pathway in Tregs is a critical driver of the suppressive tumor microenvironment. Science Advances. 1(10), e1500845. doi: 10.1126/sciadv.1500845. PMID: 26601142.

6. Raber, M.D., Sierra, R.A., Thevenot, P.T., Shuzhong, Z., Wyczechowska, D.D., Kumai, T., Celis, E., and Rodriguez, P.C. (2016). T cells conditioned with MDSC show an increased anti-tumor activity after adoptive T cell based immunotherapy. Oncotarget. doi: 10.18632/oncotarget.8197. [Epub ahead of print] PMID: 27007050.

7. Sultan, H., Fesenkova, V.I., Addis, D., Fan, A.E., Kumai, T., Wu, J., Salazar, A.M., and Celis, E. (2016). Designing therapeutic cancer vaccines by mimicking viral infections. Cancer Immunol. Immunother.

Designing effective cancer vaccines by mimicking viral infections

Esteban Celis, M.D., Ph.D.

Augusta University, USA

Numerous CD8 cytotoxic T lymphocyte (CTL) epitopes have been identified allowing the development of epitope-based cancer immunotherapies such as the use of synthetic peptide-based vaccines. However, peptide vaccines have been notoriously weakly immunogenic, providing suboptimal therapeutic effects. In contrast, as a response to viral and bacterial infections, the immune system can produce massive numbers of antigen-specific CTLs eliminating disease and providing memory responses to prevent future infections. Our strategy to optimize peptide vaccines is to design immunization strategies that mimic infections by providing the necessary immune activation signals together with the appropriate immunogenic peptides. Furthermore, it has been proposed that minimal peptide epitopes are poorly immunogenic because they are presented to T cells by non-professional APCs. Therefore, it is suggested that using long peptides vaccines will improve immunogenicity by forcing antigen presentation by professional APCs. Using several mouse tumor models, we observe that peptide composition (hydrophobicity, amphipathicity), adjuvant and route of administration are more critical than peptide size for generating strong CTL responses that limit tumor growth. Two separate events are required for peptides to generate huge CTL responses, similar to those observed during acute infections: 1) Peptide priming mediated professional APCs, where CD40 activation and TLR signals are critical; 2) T cell expansion, which can be mediated by either professional and non-professional APCs and where type-I interferon induced by retinoic acid-inducible (RIG-I)-like receptor stimulation by poly-IC plays a critical role. Effective anti-tumor CTL responses were accomplished by 2 systemic injections (i.v. or i.m. 5-7 days apart) of peptide/poly-IC. Lastly, in some instances even in the presence of huge numbers of tumor-reactive CTLs anti-tumor effects remained suboptimal, but could be significantly enhanced by implementing PD1 blockade. Resulting in complete tumor eradication. After 15 years we are learning how to motivate the immune system to reject tumors.

Designing Effective Cancer Vaccines by Mimicking Viral Infections

Esteban Celis, M.D., Ph.D.
Cancer Immunology Program

In vitro immunization with predicted CD8 T cell epitopes from TAAs

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 2105–2109, March 1994
Immunology

Induction of anti-tumor cytotoxic T lymphocytes in normal humans using primary cultures and synthetic peptide epitopes

(major histocompatibility complex antigen-binding peptides/tumor-specific cytotoxic T cells/MAGE antigens/melanoma immunity)

ESTEBAN CELIS*†, VAN TSAI*, CLAIRE CRIMI*, ROBERT DEMARS‡, PEGGY A. WENTWORTH*, ROBERT W. CHESNUT*, HOWARD M. GREY*, ALESSANDRO SETTE*, AND HORACIO M. SERRA*

*Cytel, 3525 John Hopkins Court, San Diego, CA 92121; and ‡University of Wisconsin-Madison, Laboratory of Genetics, Madison, WI 53706

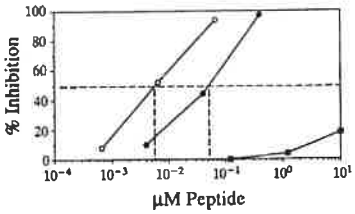

FIG. 1. HLA-A1 binding of synthetic peptides from MAGE-1, -2, and -3. The MAGE peptides were tested in a dose titration for the inhibition of the binding of the ^{125}I-labeled standard peptide YLEPAIAKY to purified HLA-A1 molecules. ●, MAGE-1 peptide EADPTGHSY; ■, MAGE-2 peptide EVVPISHLY; ○, MAGE-3 peptide EVDPIGHLY. Dotted lines are used to calculate the 50% inhibitory dose for each peptide.

*Refers to residue number of the first position of the peptide in relation to the sequence of the entire gene product.
†Concentration of the peptide necessary to inhibit 50% binding of the radiolabeled test peptide to purified HLA-A1 molecules.

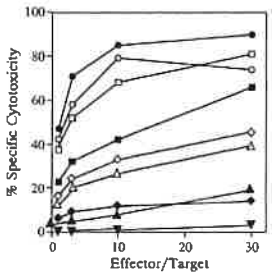

FIG. 4. Cytotoxic activity of MAGE-3-specific CTLs toward various tumors. The MAGE-3 specific CTLs were tested for their ability to kill breast and prostate HLA-A1⁺ tumor lines previously treated or not treated with γ-IFN. Cytotoxic responses were measured against mel-397 (MAGE-3⁺) (●), mel-397 plus γ-IFN (○), HBL-100 (HLA-A1/10, -B7/8 MAGE-3⁺) (■), HBL-100 plus γ-IFN (□), BT-20 (HLA-A1, -B16.MAGE-3⁺) (▲), BT-20 plus γ-IFN (△), PC3 (HLA-A1/9) (◆), PC3 plus γ-IFN (◇), and mel-888 plus γ-IFN (MAGE-3⁻) (▼).

Human Immunology 59, 1–14 (1998)

The Multi-epitope Approach for Immunotherapy for Cancer: Identification of Several CTL Epitopes from Various Tumor-Associated Antigens Expressed on Solid Epithelial Tumors

Ichiro Kawashima, Stephen J. Hudson, Van Tsai, Scott Southwood, Kazutoh Takesako, Ettore Appella, Alessandro Sette, and Esteban Celis

From the Cytel Corporation, San Diego, California 92121USA (I.K., S.J.H., V.T., S.S., A.S., E.C.), Takara Shuzo Co., Ltd., Biotechnology Research Laboratories, Otsu, Shiga, Japan (I.K., K.T.) and Laboratory of Cell Biology, National Cancer Institute, Bethesda, MD 20892, USA (E.A.).

Address reprint requests to: Dr. Esteban Celis, Department of Immunology, Mayo Clinic, Guggenheim 4, Rochester MN 55905, USA; Tel: (507) 284-0124; Fax: (507) 284-1637; E-Mail: celis@mayo.edu.

TABLE 2 List of HLA-A2.1 binding peptides from CEA

Peptide[a]	Sequence	A*0201 Binding[b] IC_{50} (nM)	No. of cultures containing CTL reactive with:[c] Peptide	Tumor cells
CEA[$10_{[illegible]}$]	YLWWVNNQSL	26.3	0	0
CEA[$9_{[illegible]}$]	YLSGANLNL[d]	27.8	9	1
CEA[$10_{[illegible]}$]	YLWWVNGQSL	33.3	NT[e]	NT
CEA[$10_{[illegible]}$]	GIMIGVLVGV	56.8	NT	NT
CEA[$9_{[illegible]}$]	IMIGVLVGV	68.5	10	1[e]
CEA[$9_{[illegible]}$]	LLTFWNPPT	178.6	0	0
CEA[$9_{[illegible]}$]	VLYGPDTPI	200.0	2	0
CEA[$10_{[illegible]}$]	IMIGVLVGVA	227.3	NT	NT
CEA[$10_{[illegible]}$]	VLYGPDAPTI	454.5	NT	NT

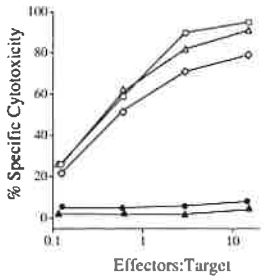

FIGURE 5 Recognition of various tumor types by a CEA specific CTL clone. The CEA[$9_{[illegible]}$] specific CTL clone was tested for its lytic activity against following target cell lines: ○, .221A2.1 pulsed with CEA[$9_{[illegible]}$]; ●, .221A2.1 without peptide; △, KATO-III (gastric Ca, $A2^+$, CEA^+); ◇, SW403 (colon Ca, $A2^+$, CEA^+); ▲, HT-29 (colon Ca, $A2^-$, CEA^+).

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Int. J. Cancer 78, 518–524 (1998)

IDENTIFICATION OF GP100-DERIVED, MELANOMA-SPECIFIC CYTOTOXIC T-LYMPHOCYTE EPITOPES RESTRICTED BY HLA-A3 SUPERTYPE MOLECULES BY PRIMARY *IN VITRO* IMMUNIZATION WITH PEPTIDE-PULSED DENDRITIC CELLS

Ichiro Kawas

Identification of New HER2/*neu*-Derived Peptide Epitopes That Can Elicit Specific CTL Against Autologous and Allogeneic Carcinomas and Melanomas[1]

Yung Rong
Kristina E
Olle Larsso
Rolf Kiessl

[CANCER RESEARCH 61, 5223–5227, September 15, 2001]

Use of Two Predictive Algorithms of the World Wide Web for the Identification of Tumor-re

[CANCER RESEARCH 61, 4773–4778, June 15, 2001]

Jun Lu and F

Tumor-reactive T Helper Lymphocytes Recognize a Promiscuous MAGE-A3 Epitope Presented by Various Major Histocompatibility Complex Class II Alleles[1]

Hiroya Kobayashi, Yongsheng Song, Dave S. B. Hoon, Ettore Appella, and Esteban Celis[2]

Department of Immunology, Mayo Graduate School, and Mayo Cancer Center, Mayo Clinic, Rochester, Minnesota 55905 [H.K., E.C.]; National Cancer Institute, NIH, Bethesda, Maryland 20892 [Y.S., E.A.]; and John Wayne Cancer Institute, Santa Monica California 90404 [D.S.B.H.]

[CANCER RESEARCH 61, 7577–7584, October 15, 2001]

Identification of Helper T-Cell Epitopes That Encompass or Lie Proximal to Cytotoxic T-Cell Epitopes in the gp100 Melanoma Tumor Antigen[1]

Hiroya Kobayashi, Jun Lu, and Esteban Celis[2]

Department of Immunology and Cancer Center, Mayo Clinic and Mayo Graduate School, Rochester, Minnesota 55905

$gp100_{175-189}$: GR**AMLGTHTMEV**TV

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Now that we had CD8 T cell epitopes for TAA, what did we do?

Journal of Immunotherapy
22(5):401–409 © 1997 Lippincott Williams & Wilkins, Inc., Philadelphia

A Phase I Trial of an HLA-A1 Restricted MAGE-3 Epitope Peptide with Incomplete Freund's Adjuvant in Patients with Resected High-Risk Melanoma

Jeffrey S. Weber, Flora L. Hua, Lucy Spears, Verna Marty, Catherine Kuniyoshi, and *Esteban Celis

*Department of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, and *Cytel Corporation, San Diego, California, U.S.A.*

TABLE 4. *Cytolysis by MAGE-3 peptide stimulated CTL pre- and postvaccine*

Cohort/ Patient #	Prevaccine unpulsed	Postvaccine unpulsed	Prevaccine MAGE-3 pulsed	Postvaccine MAGE-3 pulsed
100 μg				
10024	7	11	16	46
10025	2	2	8	22
10073	1	0	0	4
300 μg				
10081	0	0	4	23
10083	0	0	9	2
10084	0	0	14	5
1,000 μg				
10095	4	0	22	6
10102	21	30	10	28
2,000 μg				
10103	20	30	18	72
10104	4	13	0	0
10105	25	20	19	13
10106	1	1	1	2
10108	28	28	4	4
10109	2	1	4	14

TABLE 5. *Cytokine release data from patients receiving the MAGE-3/PADRE vaccine with IFA*

Patient # pre/post	Effectors alone	Effectors/ 221.A1 unpulsed	Effectors/ 221.A1 MAGE-3	SEB control
10073	72	0	1	>1024
10085	64	0	15	>1024
10097	0	0	0	240
10105	0	0	0	286
10103	90	50	40	>1024
10112	210	140	>1024	>1024
10104	560	345	340	>1024
10110	210	100	99	>1024
10105	59	590	57	>1024
10116	70	28	580	>1024
10106	20	510	480	>1024
10114	12	230	225	>1024
10108	645	400	512	>1024
10119	59	165	170	>1024
10118	140	145	200	>1024
10125	172	180	178	>1024

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Now that we had CD8 T cell epitopes for TAAs, what did we do?

Peptide Vaccination of Patients With Metastatic Melanoma

Improved Clinical Outcome in Patients Demonstrating Effective Immunization

Svetomir N. Markovic, MD, PhD, Vera J. Suman, PhD, James N. Ingle, MD, Judith S. Kaur, MD, Henry C. Pitot, MD, Charles L. Loprinzi, MD, Ravi D. Rao, MBBS, Edward T. Creagan, MD, Mark R. Pittelkow, MD, Jakob B. Allred, Wendy K. Nevala, and Esteban Celis, MD

American Journal of Clinical Oncology • Volume 29, Number 4, August 2006

MART-1_{27}, $gp100_{209}$ & Tyr_{368} in Montanide ISA 51 ± GM-CSF

Overlapping Human Leukocyte Antigen Class I/II Binding Peptide Vaccine for the Treatment of Patients With Stage IV Melanoma

Evidence of Systemic Immune Dysfunction

CANCER July 1, 2007 / Volume 110 / Number 1

Melanoma Study Group of the Mayo Clinic Cancer Center[1]
Esteban Celis, MD, PhD[2]

[1] Mayo Clinic Cancer Center, Rochester, Minnesota.

[2] H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida.

$gp100_{175-189}$ (GRAMLGTHTMEVTV)
in Montanide ISA 51 + GM-CSF

GRAMLGTHTMEVTV = DR53, DQ6
MLGTHTMEV = HLA-A2
AMLGTHTMEV = HLA-A2

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So is there any future for peptide vaccines to treat cancer?

- Vaccines that induce T cell responses
  - *Promising results but no homeruns*
  - *Suboptimal immune responses (quantity and quality of T cells)*
  - *Tumor-generated immunosuppression (PDL1, MDSCs, Tregs)*
- Adoptive cell therapy (ACT)
  - *Some homeruns and many good hits*
  - *Achieves huge numbers of tumor-reactive T cells*
  - *Technically challenging, not very cost effective*
  - *Toxic adjunct therapies (lymphodepletion, high dose IL-2)*

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Working Hypothesis

It may be possible to design a simple, cost-effective vaccine that achieves what ACT does, w/o so much toxicity by mimicking a <u>systemic</u> acute infection

- Magnitude of response : > 10% of all T cells
- Duration of response: until disease is eradicated and more (memory CD8 T cells)
- Capable of overcoming immune suppressive activities (tolerance and tumor-related immunosuppression)

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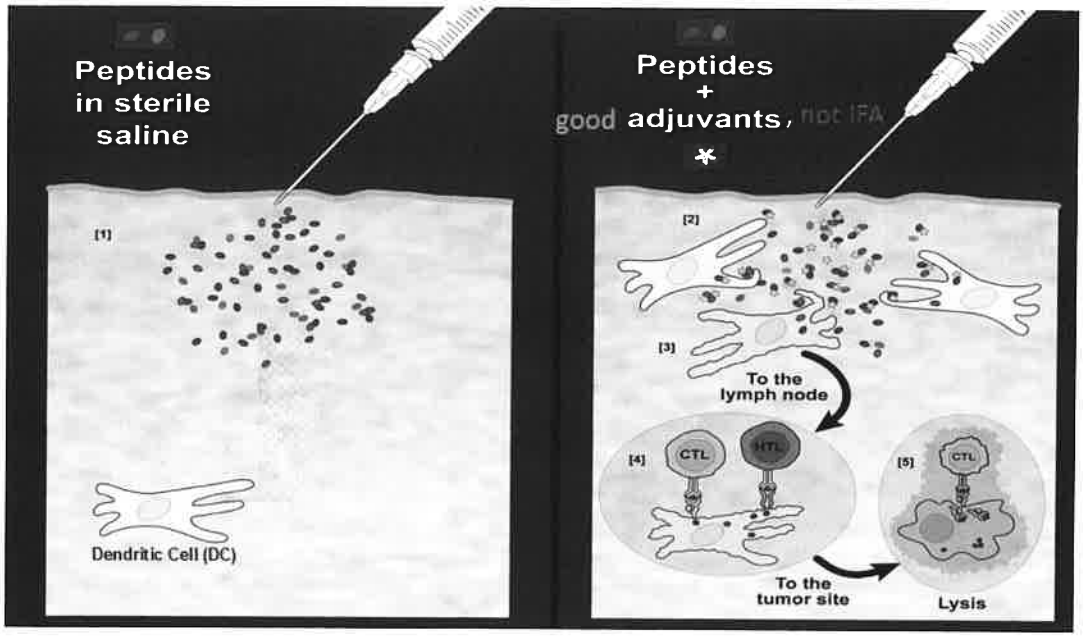
Peptides are in general poor immunogens



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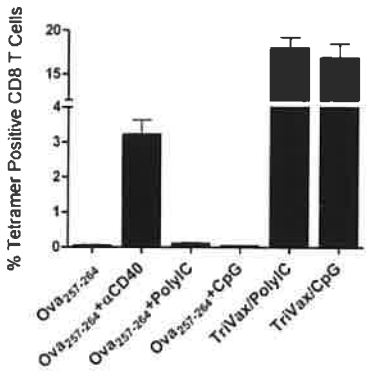
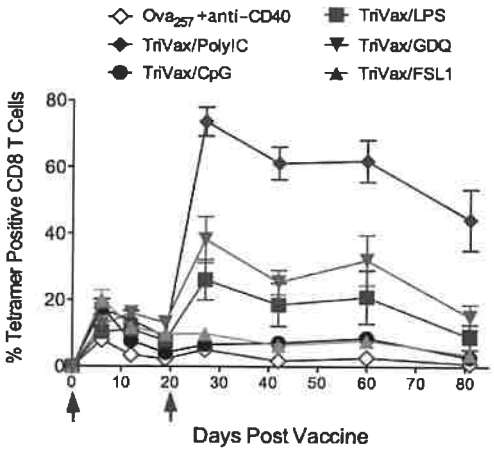
Some soluble (minimal epitope) peptides can be highly immunogenic in mice when given with the right adjuvants





- One single *i.v.* injection of Ova_{257} (SIINFEKL) in PBS
- TriVax: peptide + TLR-L + αCD40 mAb
- Responses measured in blood 6 days post-vaccination

Q: So what's so special about poly-IC that allows a substantial boost?

A: Poly-IC can stimulate TLR3 (endosomes) & MDA5, a RIG-I-like receptor (cytoplasmic)

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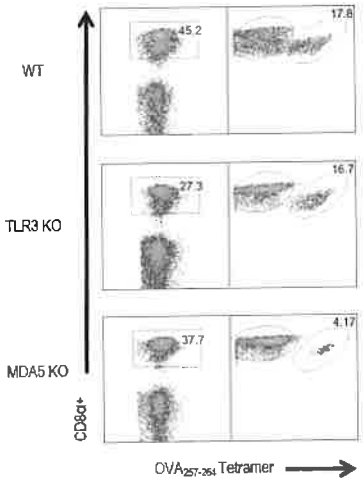
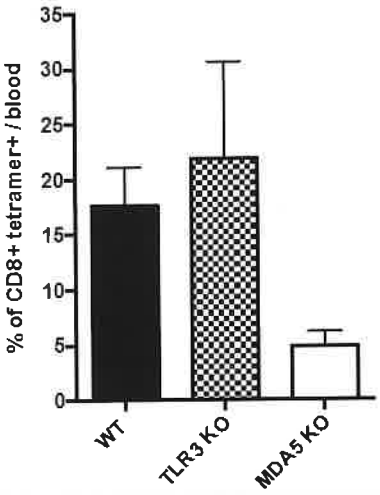
Role of TLR3 and MDA5 in T cell priming and expansion





Prime/boost 5 days apart using Pam_2-Ova peptide + poly-IC w/o αCD40mAb

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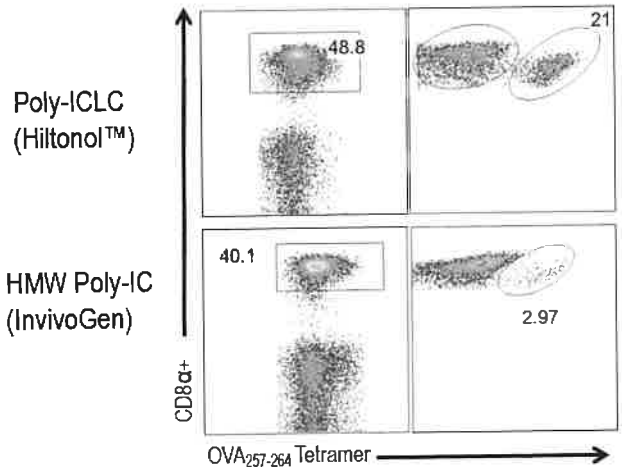
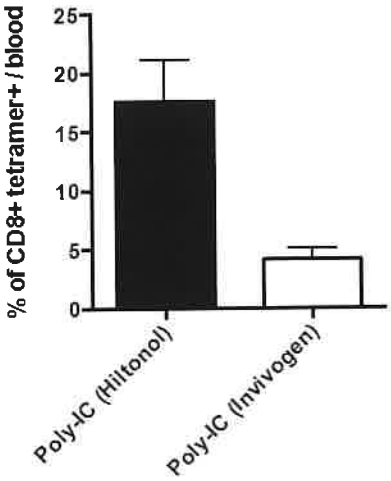
But not all poly-ICs are the same...





To stimulate RIG-I-like receptors, poly-IC must go to the cytoplasm

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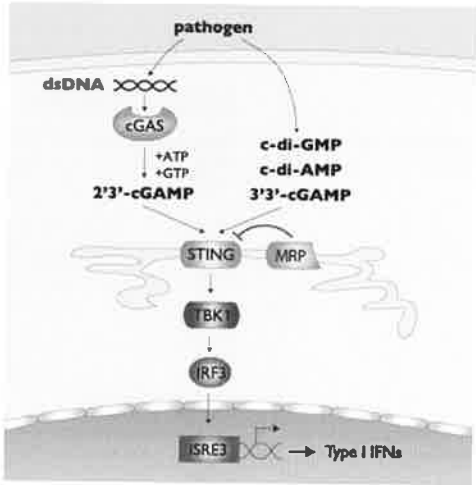
Second Hypothesis

To mimic a systemic acute infection, non-professional APCs can present antigen and danger signals derived from cytoplasmic PRRs (e.g., RNA helicases, STING)



Can a STING agonist enhance immune responses to peptide vaccines?

Can concurrent TLR3/MDA5 and STING enhance peptide vaccines?

Model system:

Peptides: hgp100 (KVPRNQDWL) or Pam-hgp100 ($[Pam]_2$-KMFVKVPRNQDWL)
Adjuvants: Anti-CD40 mAb, poly-IC ± c-di-GMP
Tumor: Mouse B16 melanoma, expressing mgp100 (EGSRNQDWL)

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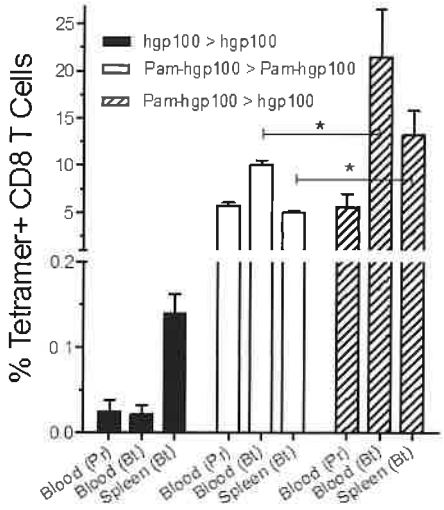
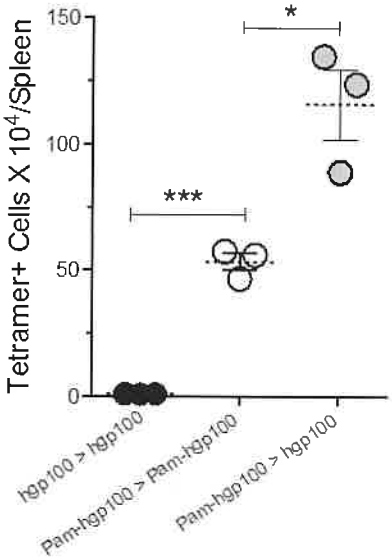
Heterologous Pam-hgp100 prime, hgp100 boost is superior to homologous vaccines





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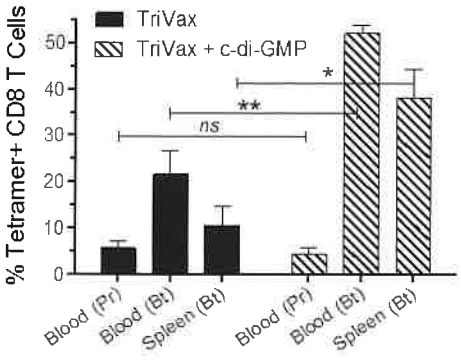
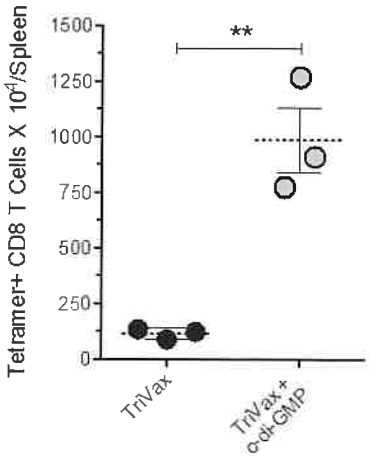
c-di-GMP increases immune responses to hgp100 TriVax





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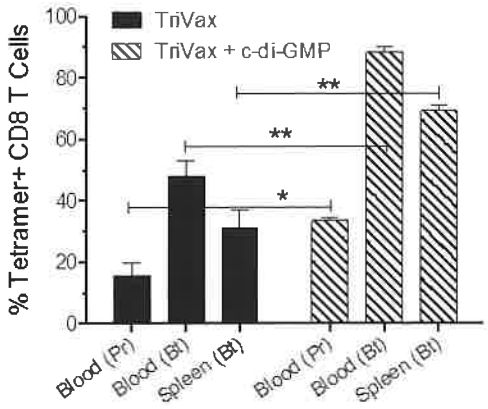
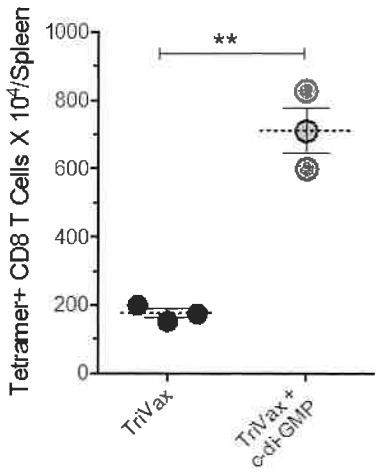
c-di-GMP increases immune responses to Ova TriVax





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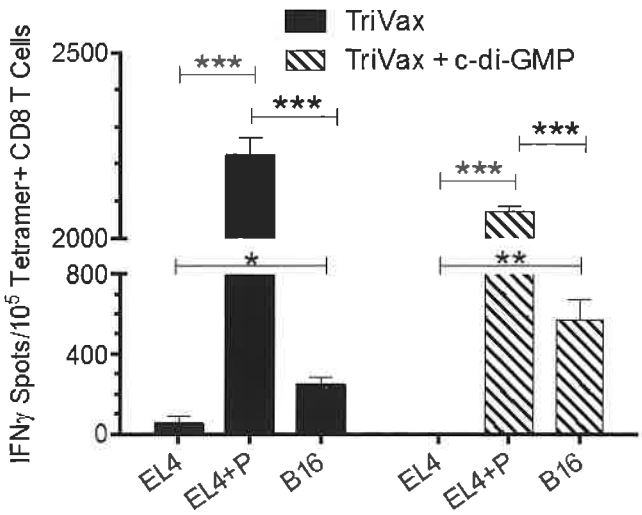
Tumor recognition by T cells



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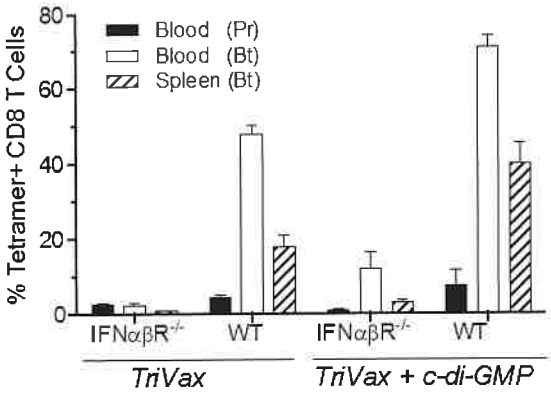
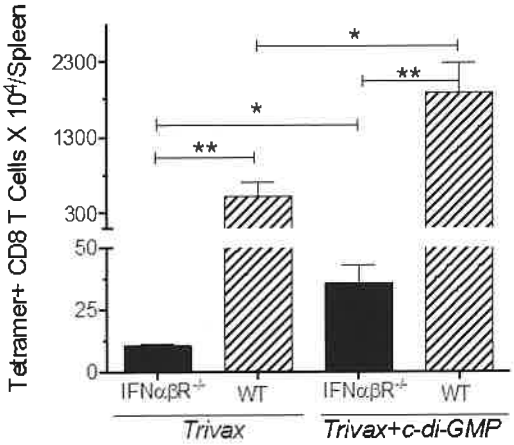
Type-I IFN requirements





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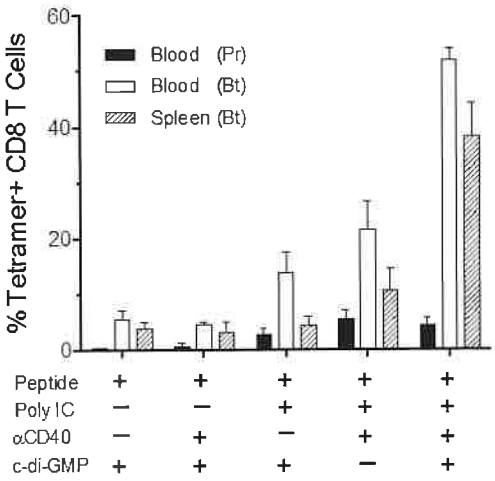
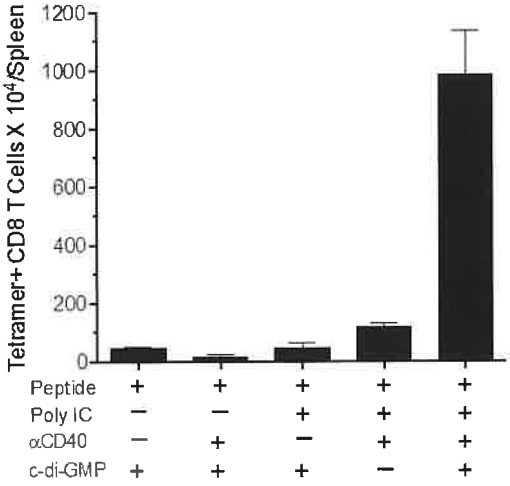
Synergism between poly-IC and c-di-GMP





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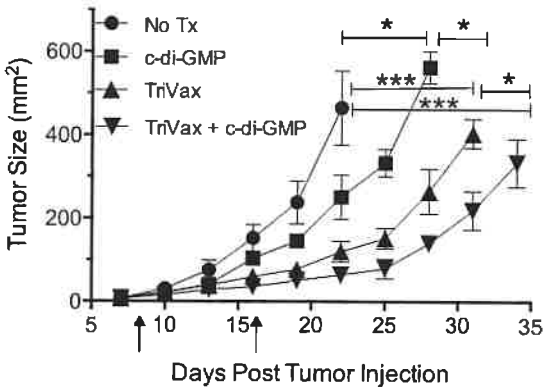
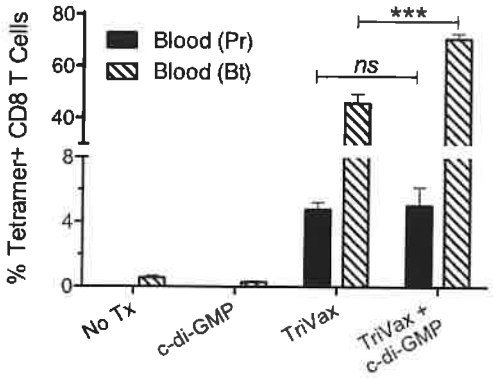
Anti-tumor effects of vaccination





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Reassessing the use αCD40 mAb

- αCD40 mAbs may generate severe lethal toxic effects
  - Enhance cytokine cascade
  - Activation on MØs
  - Increase production of IFNγ (which may decrease vaccine efficacy)
- Clinical development of agonistic human αCD40 mAbs was suspended by Pfizer (now being developed by Roche)
- Will peptide plus poly-IC (BiVax) provide sufficient immune responses to control tumor growth?

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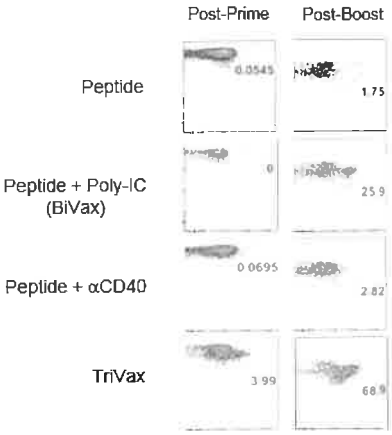
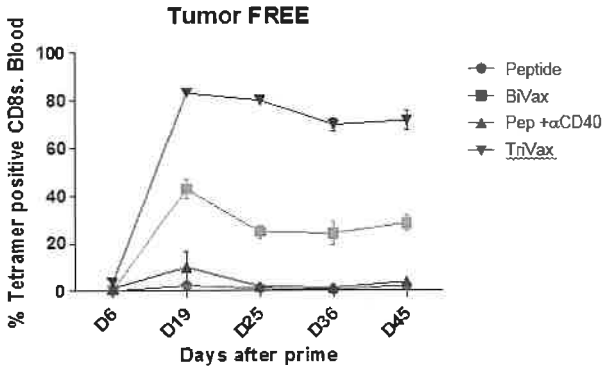
HPV mouse tumor model

Experiments using HPV16-E7$_{49}$ (RAHYNIVTF) H-2D^b epitope





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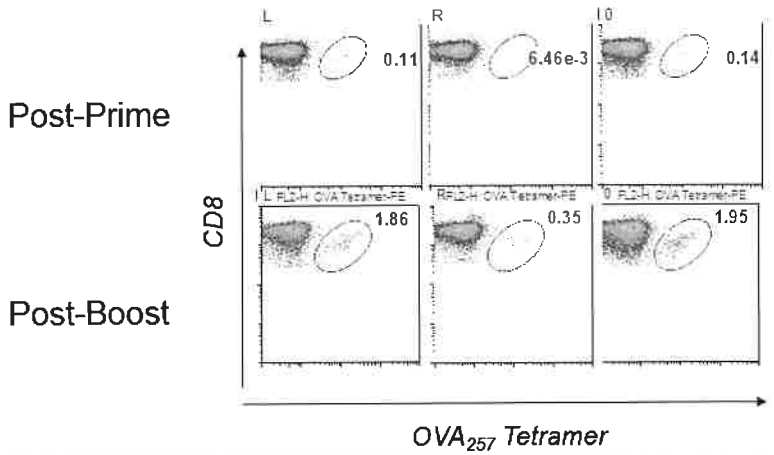
Ova$_{257}$ BiVax fails to induce substantial T cell responses

SIINFEKL



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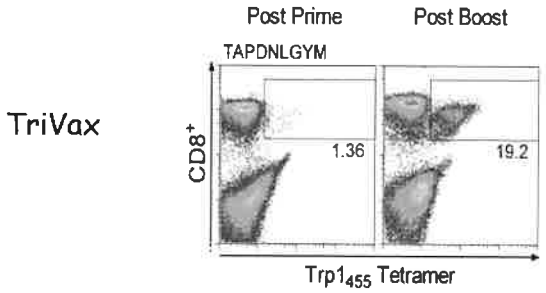
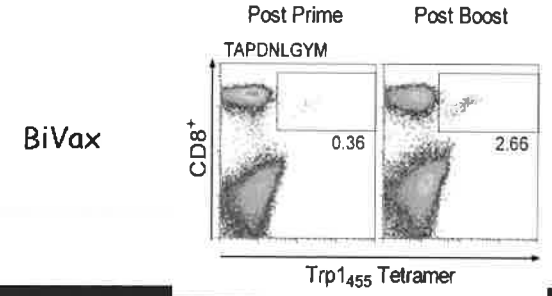
T cell responses to $Trp1_{455-463/9M}$





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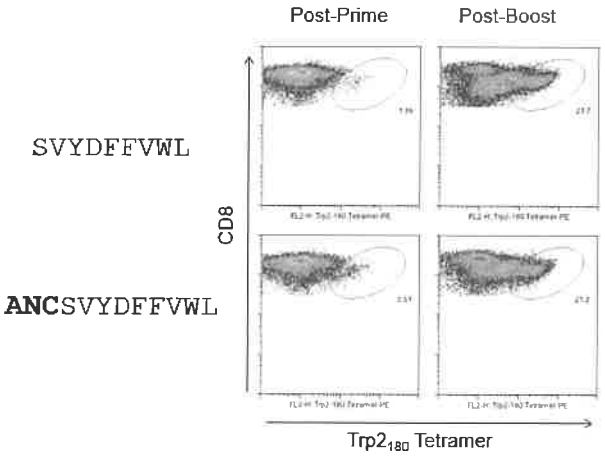
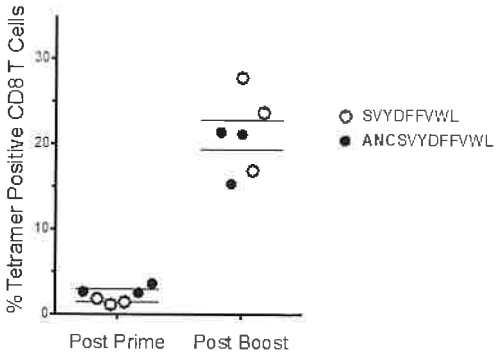
T cell responses to $Trp2_{180-188}$ with BiVax immunization





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Peptide composition may affect immunogenicity in BiVax

Amino Acid Hydrophobicity

Residue Type	kdHydrophobicity*
Ile	4.5
Val	4.2
Leu	3.8
Phe	2.8
Cys	2.5
Met	1.9
Ala	1.8
Gly	-0.4
Thr	-0.7
Ser	-0.8
Trp	-0.9
Tyr	-1.3
Pro	-1.6
His	-3.2
Glu	-3.5
Gln	-3.5
Asp	-3.5
Asn	-3.5
Lys	-3.9
Arg	-4.5

Sequence	kd Hydrophobicity
RAHYNIVTF	-0.1
SIINFEKL	+3.9
TAPDNLGYM	-3.5
SVYDFFVWL	+11.3
ANCSVYDFFVWL	+12.1

* A simple method for displaying the hydropathic character of a protein, Kyte J, Doolittle RF. *J Mol Biol*. 1982 May 5;157(1):105-32.

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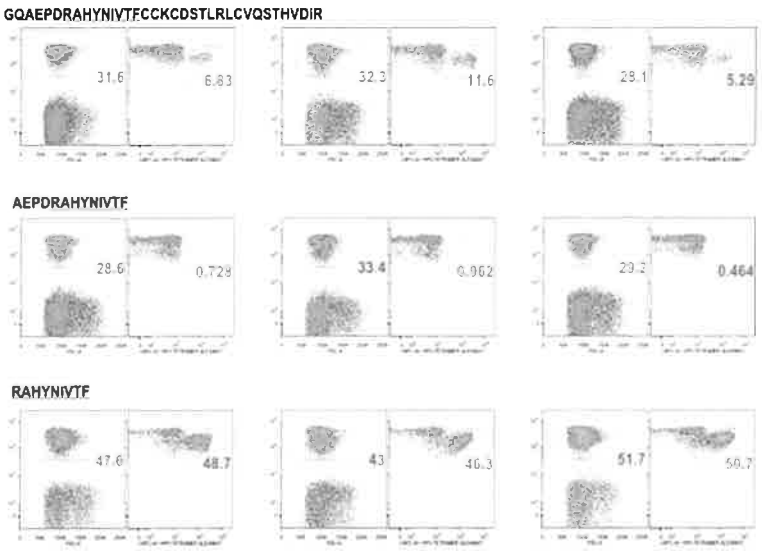
Simply elongating peptides does not increase immunogenicity



Immune responses in blood 6 days after BiVax boost

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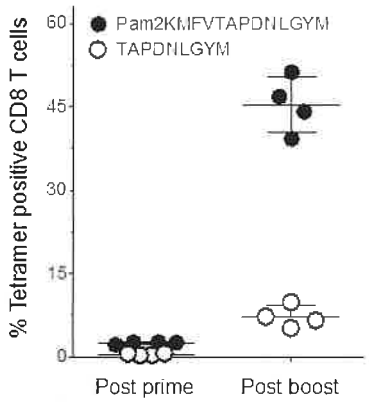
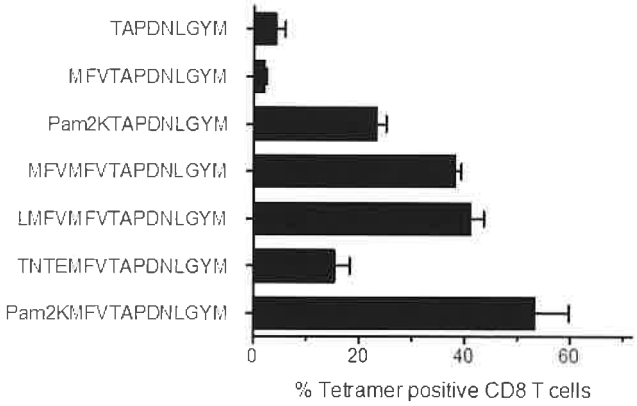
Increasing amphipathicity enhances BiVax efficacy





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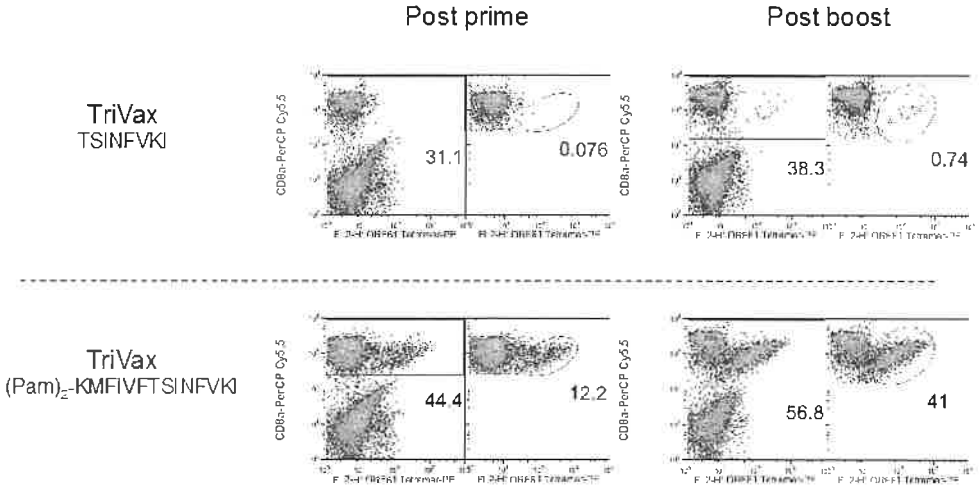
Increasing amphipathicity enhances TriVax efficacy



Murine Gammaherpesvirus (MHV)-68 H-2K^b T cell epitope

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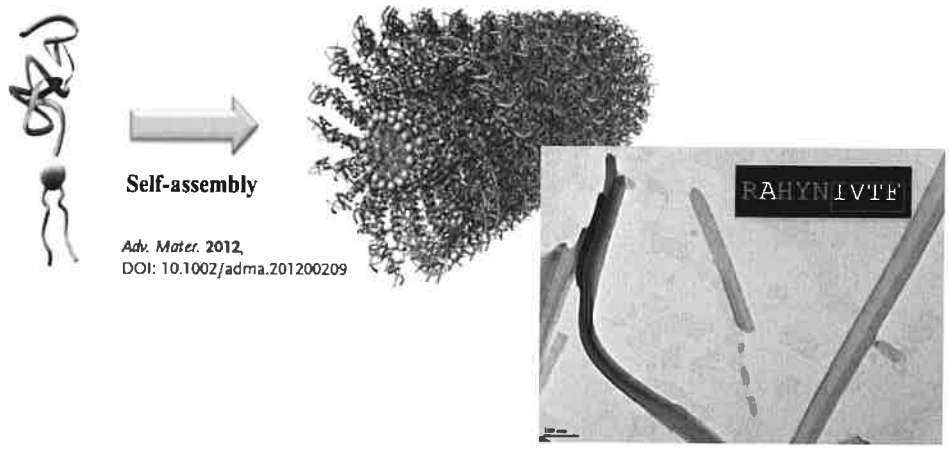
Peptides amphiphiles can assemble into tubular micelle structures (VLPs?)



Adv. Mater. **2012**,
DOI: 10.1002/adma.201200209

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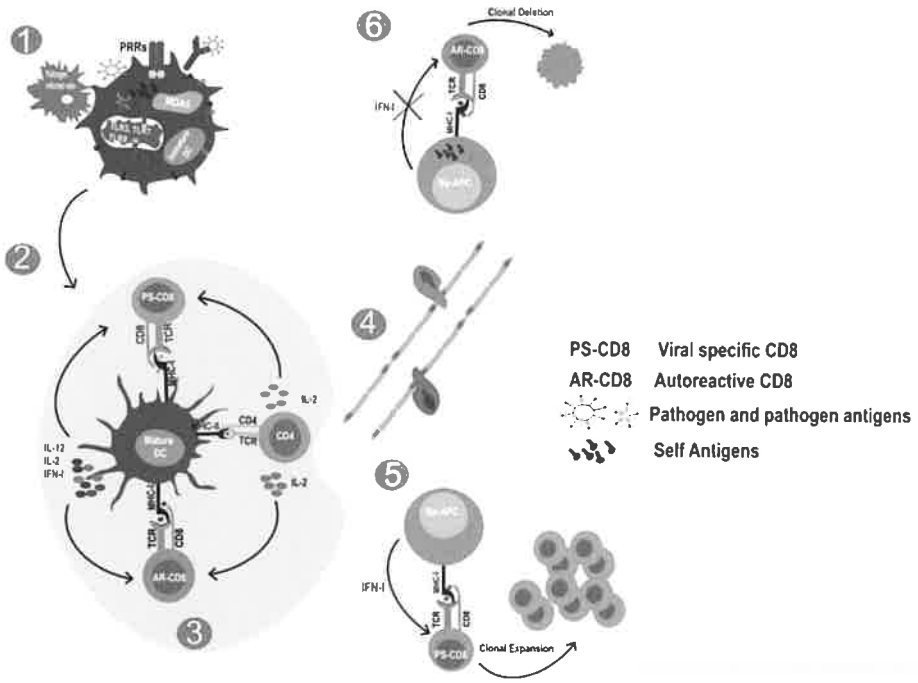

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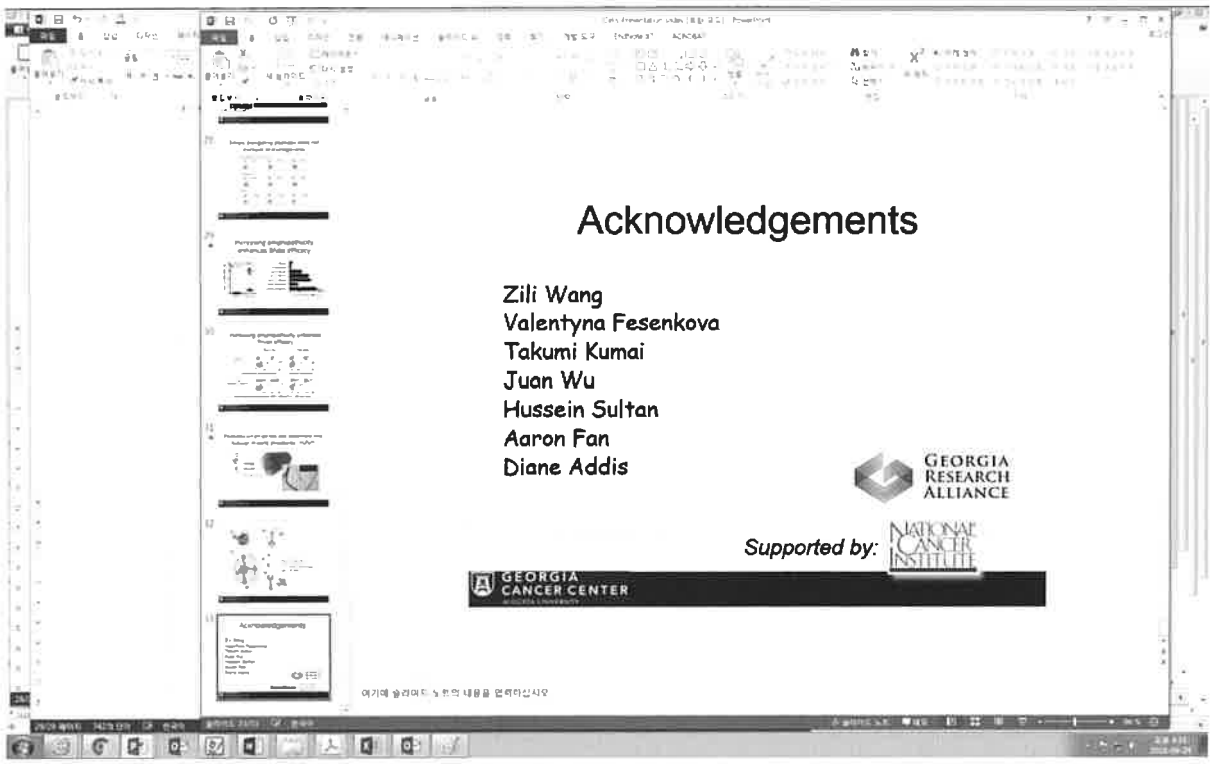
Acknowledgements
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Aaron Fan
Diane Addis
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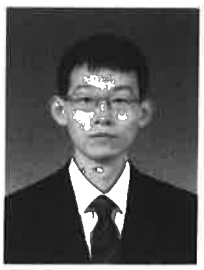
Curriculum Vitae

Je-In Youn



Position/Address Department of Biomedical Sciences,

Wide River Institute of Immunology,

Seoul National University College of Medicine

E-mail: jiyoun@snu.ac.kr

Education:

2003 B.S., Department of Life Science, POSTECH, Pohang, Korea

2005 M.S., Department of Molecular and Life Science, POSTECH, Pohang

2011 Ph.D., Cancer Biology program, University of South Florida, Florida, USA.

Professional Backgroud:

8/2005-7/2006 Researcher, Department of Molecular and Life Science, POSTECH, Pohang, Korea

02/2011-4/2013 Postdoctoral Fellow, Department of Immunology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

4/2013-2/2014 Associate Staff Scientist, The Wistar Institute, Philadelphia, Pennsylvania, USA

4/2014-present Assistant professor, Department of Biomedical Sciences, Wide River Institute of Immunology, Seoul National University College of Medicine

Recent publications:

1. Yang M, Youn JI, Kim SJ, Park JY. Epigenetic modulation of Chlorella (Chlorella vulgaris) on exposure to polycyclic aromatic hydrocarbons. Environ Toxicol Pharmacol. 2015 Nov;40(3):758-63

2. Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. Regulation of tumor metastasis by myeloid-derived suppressor cells. Annu Rev Med. 2015 Jan 14;66:97-110.

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8. Youn JI, Gabrilovich DI. New roles of Rb1 in expansion of MDSCs in cancer. Cell Cycle. 2013 Apr 11;12(9).

9. Youn JI, Kumar V, Collazo M, Nefedova Y, Condamine T, Cheng C, Villagra A, Antonia S, McCaffrey JC, Sarnaik A, Sotomayor E, Gabrilovich DI. Epigenetic silencing of retinoblastoma gene regulates pathologic differentiation of myeloid cells in cancer. Nature Immunology. 2013 Mar;14(3):211-20.

Expansion of immune suppressive myeloid cells in Cancer

Je-In Youn, Ph.D.

Seoul National University, Korea

Myeloid-derived suppressor cells (MDSC) are a group of myeloid cells comprised of precursors of macrophages, granulocytes, dendritic cells (DC) and myeloid cells at earlier stages of differentiation with potent immune suppressive activity. These cells accumulate at many pathologic conditions especially in cancer and play a major role in regulation of immune responses. These cells were reported to exert a profound inhibitory activity on both tumor-specific and nonspecific T lymphocytes but also aid tumor development by providing molecules and factors essential for tumor growth and neovascularization. MDSC consists of two distinct populations: monocytic MDSC (M-MDSC) and polymorphonuclear MDSC (PMN-MDSC). A large proportion of M-MDSC, in tumor-bearing mice, acquired phenotypic, morphological and functional features of PMN-MDSC. This effect was caused by soluble tumor-derived factors and mediated by transcriptional silencing of the retinoblastoma (Rb) gene. Through the proteomic analysis, we selected candidate proteins which are detected at the high levels in the group of tumor bearing mice compared to tumor free mice in the plasma and tumor explant supernatant. Treatment of stress induced protein promoted the differentiation of MDSC from bone marrow progenitor cells in vitro. The results suggest that the stress induced protein has a crucial role in MDSC expansion in cancer.

Expansion of immune suppressive myeloid cells in Cancer

Cancer Immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

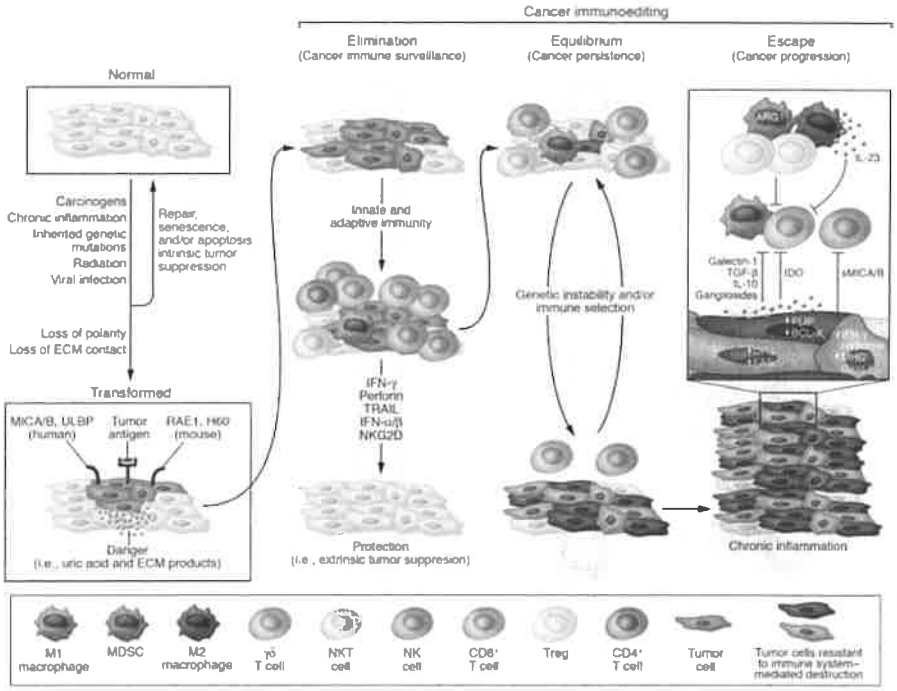
The NEW ENGLAND JOURNAL of MEDICINE

JUNE 28, 2012

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

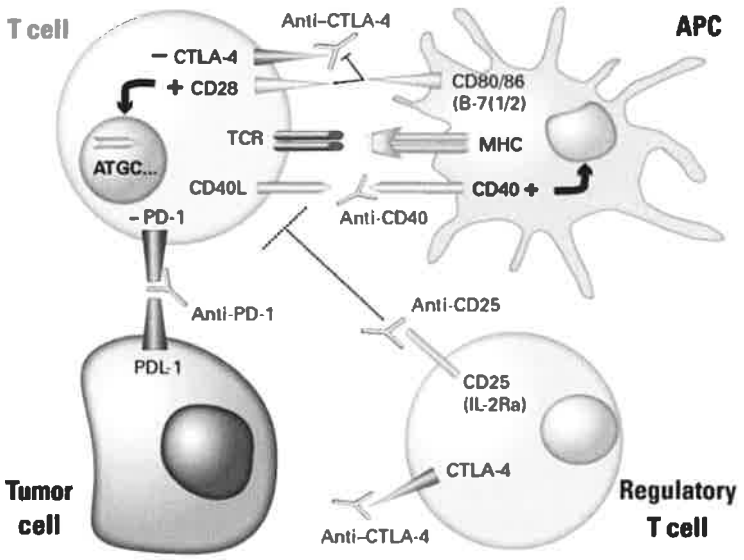
Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leisha Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Mary Jarosek Kuiken, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., George D. Kelly, Ph.D., Ashish Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

Cancer Immunoediting



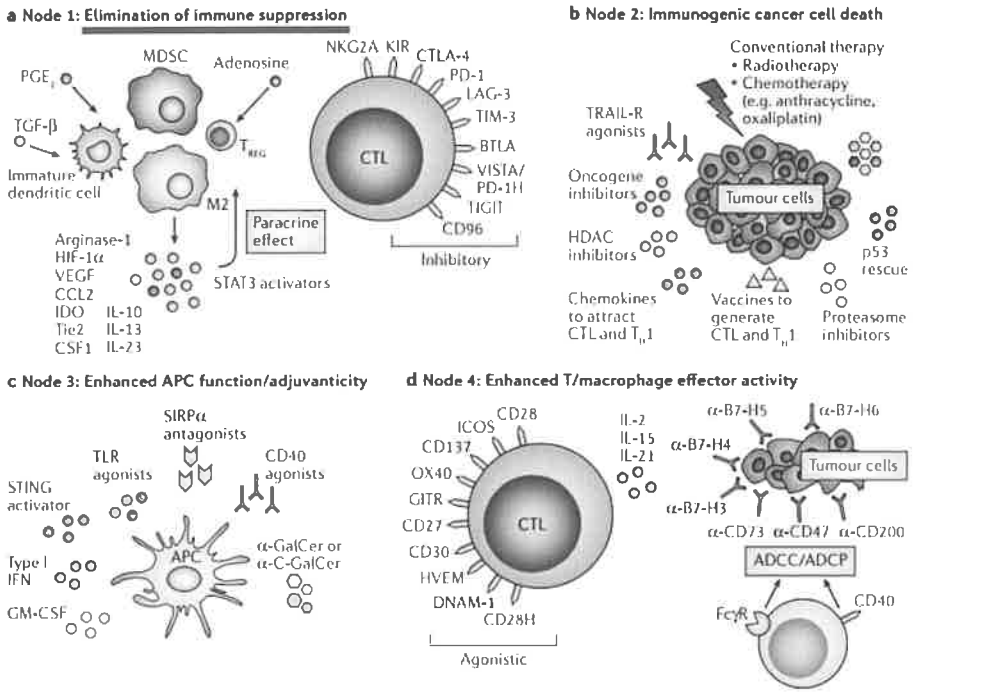
Swann et al, J. Clin. Invest. 2007

Immune checkpoint blockade



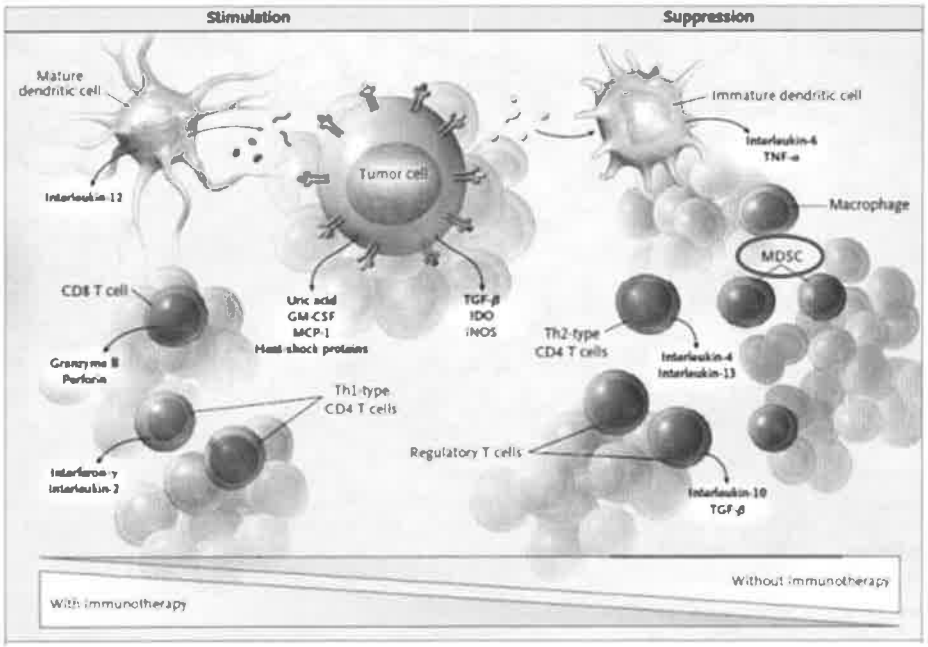
Kandalaft et al, J. Clin. Oncol, 2010.

Four Targets for inducing anti-tumor immunity



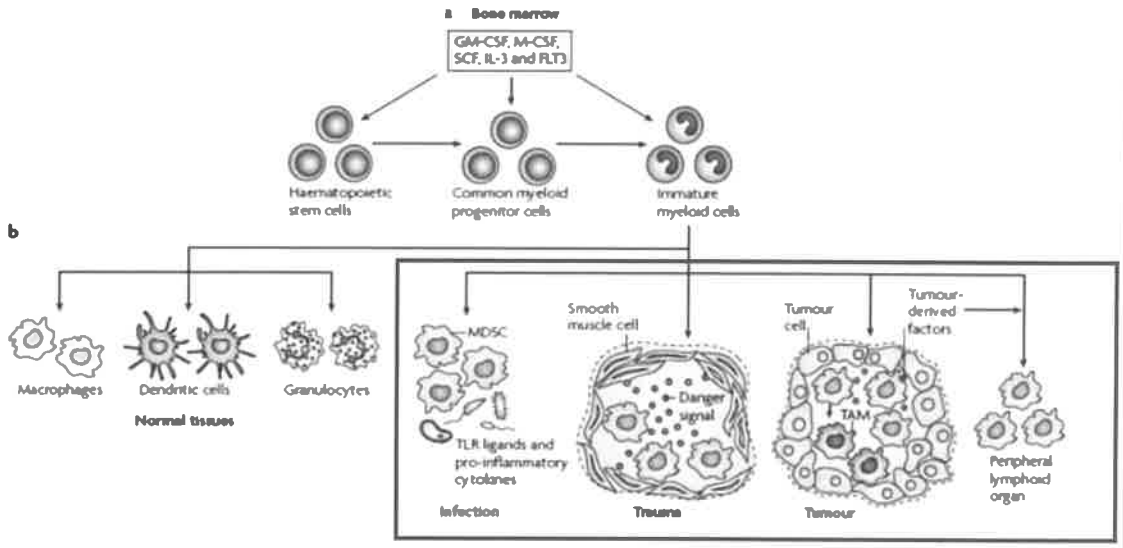
Smith MJ, NAT. REV CLIN ONCOLOGY 2016

Immune suppressions in Cancer and Myeloid-derived suppressor cells (MDSC)



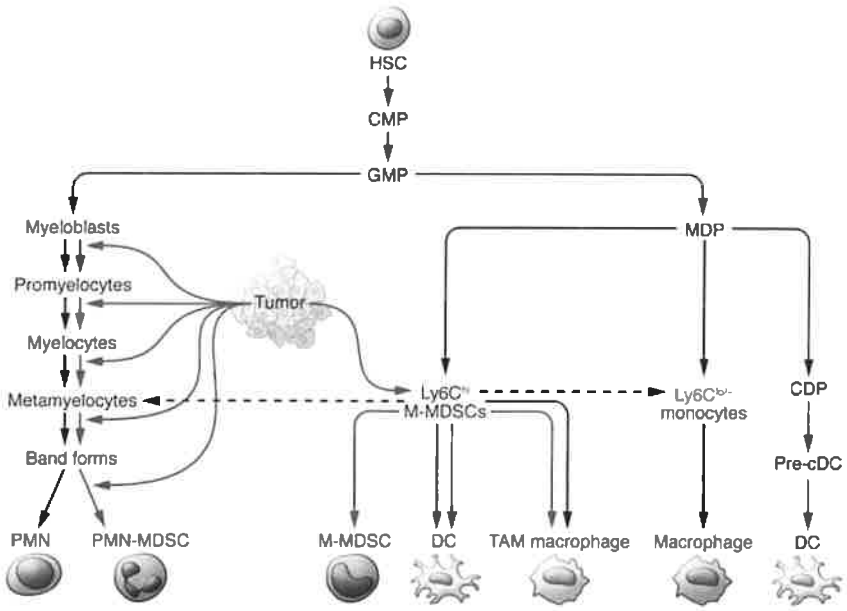
Finn OJ, *N Engl J Med.* 2008

Expansion of MDSC



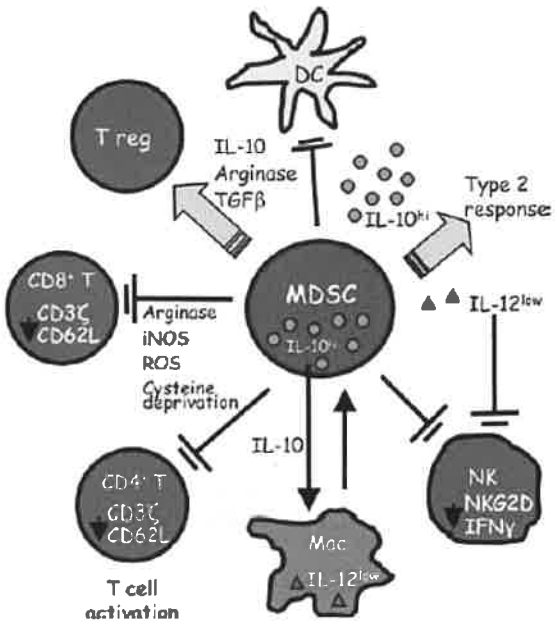
Gabrilovich and Nagaraj. *Nat Rev Immunol.* 2009

Expansion of MDSC in Cancer



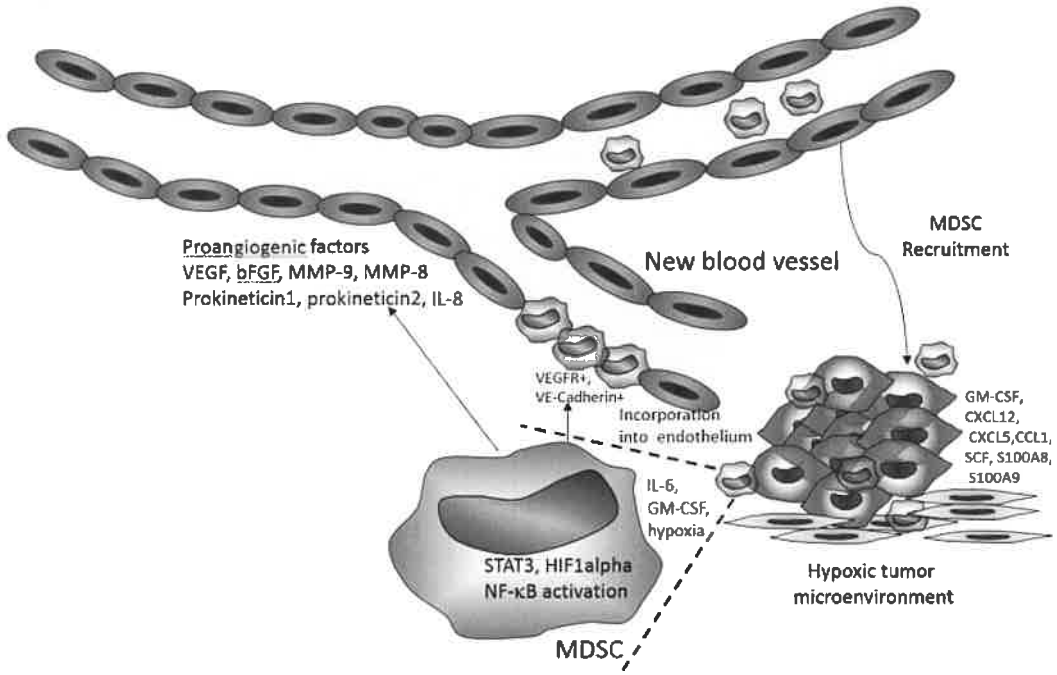
J. Clin. Invest. 2015, 125, 3356-3364

Immune suppression mechanisms of MDSC



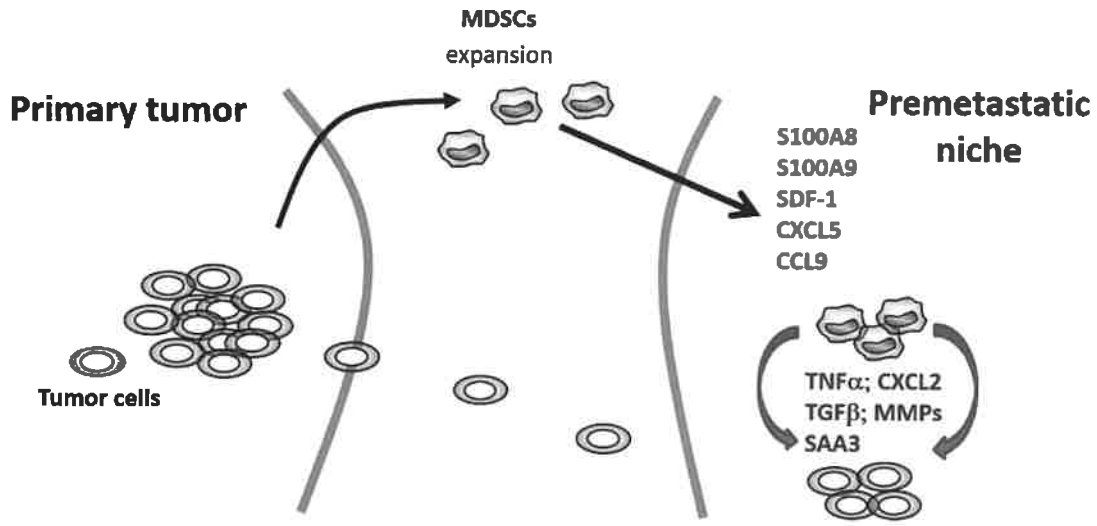
Ostrand-Rosenberg et al. *J. Immunol.* 2009

MDSC promote angiogenesis



Condamine et al, Annu Rev Med. 2015

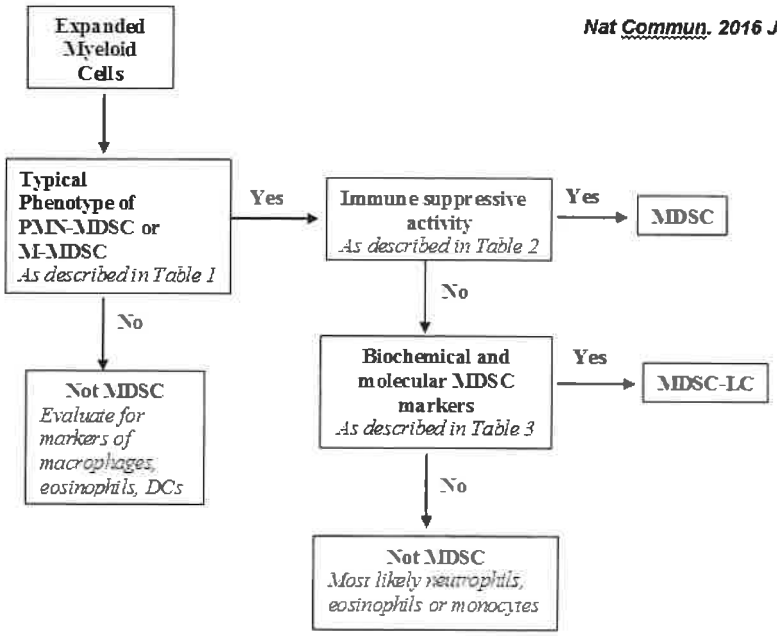
MDSC promote metastasis



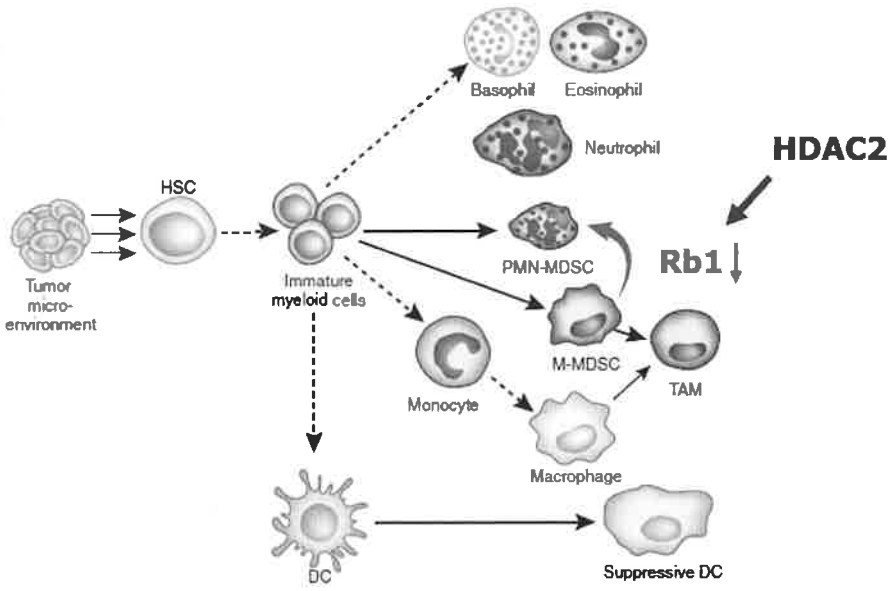
Condamine et al, Annu Rev Med. 2015

Algorithm for identification of cells as MDSC

Nat Commun. 2016 Jul 6;7:12150.



Regulation of MDSC differentiation by Rb1



Wynn TA , *Nat Rev Immunol.* News and views, 2013

Molecular control of T cell function in immunity

Chen Dong, Ph.D.

Tsinghua University, China

CD4+ T lymphocytes play important regulatory roles in the adaptive immunity. Upon activation, naïve CD4+ helper T (TH) cells differentiate into effector subsets with different cytokine expression profiles and immune regulatory function. Effector TH cells have been classified into TH1 and TH2 lineages: TH1 cells express IFNg, and TH2 cells produce IL-4, -5 and -13. More recently, several other subsets of TH cells, including TH17 and Tfh cells have been identified and may play important roles in autoimmune diseases. I will discuss our recent work on the molecular regulation of TH17 and Tfh cell development and function. The knowledge from our work may benefit targeting these cells in autoimmune diseases.

Curriculum Vitae

Sang-Jun Ha

Position/Address Department of Biochemistry,

College of Life Science & Biotechnology

Yonsei University, Korea

E-mail: sjha@yonsei.ac.kr

Education:

1996 B.S., Department of Biochemistry, Yonsei University, Seoul, Korea

1998 M.S., Department of Life Science, POSTECH, Pohang,

2001 Ph.D., Division of Molecular and Life Sciences, POSTECH, Pohang, Korea

Professional Backgroud:

2001 – 2004	Post-doctoral fellow, POSTECH, Pohang, Korea
2004 – 2007	Post-doctoral fellow, Emory University School of Medicine, Atlanta, US
2007 – 2009	Research Associate, Emory University School of Medicine, Atlanta, US
2009 – 2014	Assistant Professor, Yonsei University, Seoul, Korea
2014 – Present	Associate Professor, Yonsei University, Seoul, Korea

Recent publications:

1. Lee BR, Jeong SK, Ahn BC, Lee BJ, Shin SJ*, Yum JS*, Ha SJ*. (* equal contribution) Combination of TLR1/2 and TLR3 ligands enhances CD4+ T cell longevity and antibody responses by modulating type I IFN production. Scientific Reports 2016 [In press]

2. Kim WS, Kim H, Kwon KW, Im SH, Ha SJ*, Shin SJ*. (* equal contribution) Cisplatin induces tolerogenic dendritic cells in response to TLR agonists via the abundant production of IL-10, thereby promoting Th2- and Tr1-biased T-cell immunity. Oncotarget 2016 [Epub ahead of print]

3. Park HJ, Oh JH, Ha SJ. Phenotypic and functional analysis of activated regulatory T cells isolated from chronic lymphocytic choriomeningitis virus-infected mice. Journal of Visualized Experiments 2016 Jun 22;112:e54138

4. Park HJ, Lee A, Lee JI, Park SH, Yoo S, Ha SJ*, Jung KC*. (* equal contribution) Effect of IL-4 on the development and function of memory-like CD8 T cells in periphery. Immune Network 2016 Apr;16(2):126-133

5. Baek KH, Zhang H, Lee BR, Kwon YG, Ha SJ*, Shin I*. (* equal contribution) A small molecule inhibitor for ATPase activity of Hsp70 and Hsc70 enhances the immune response to protein antigens. Scientific Reports 2015 Dec 3;5:17642

6. Lee A, Park SP, Park CH, Kang BH, Park SH, Ha SJ*, Jung KC*. (* equal contribution) IL-4-induced innate CD8+ T cells control persistent viral infection. PLoS Pathogens 2015 Oct 9;11(10):e1005193

7. Kim HR, Park HJ, Ha SJ. PD-1: dual guard for immunopathology. Oncotarget 2015 Sep 8;6(26):21783-21784

8. Park HJ, Park JS, Jeong YH, Son J, Ban YH, Lee BH, Chen L, Chang J, Chung DH, Choi I, Ha SJ. PD-1 upregulated on regulatory T cells during chronic virus infection enhances the suppression of CD8+ T cell immune response via the interaction with PD-L1 expressed on CD8+ T cells. Journal of Immunology 2015 Jun 15;194(12):5801-5811

9. Jeong YH, Hur YG, Lee H, Kim S, Cho JE, Chang J, Shin SJ, Lee H, Kang YA, Cho SN, Ha SJ. Discrimination between active and latent tuberculosis based on the ratio of antigen-specific and mitogen-induced IP-10 production. Journal of Clinical Microbiology 2015 Feb;53(2):504-510

10. Shin JI, Ha SJ. Regulatory T cells: another important target of immune checkpoint in cancer immunotherapy. Nature Reviews Clinical Oncology 2014 Jun;11(6):307

Immune regulation via immune checkpoint PD-1 expressed on regulatory T cells during cancer progression

Sang-Jun Ha, Ph.D.

Yonsei University, Korea

For more than 100 years, cancer immunotherapy has played an ever-increasing role in the understanding and treatment of cancer even though there are not many approved drugs and regimens. Activating the immune system for therapeutic benefit in cancer has long been a goal in immunology and oncology. After repetitive failures, the tide has finally changed due to the success of recent proof-of-concept clinical trials using antibodies to blockade immune checkpoint molecules such as CTLA-4 and PD-1. These successes suggest that tolerance raised by tumor microenvironment is a major obstacle for immunotherapy and therefore, blocking the tolerance is the first step to rejuvenate tumor-specific T cell immune responses. Herein, we show that PD-1 is upregulated in tumor-infiltrating regulatory T (Treg) cells as well as CD8+ T cells in tumor microenvironment. Tumor-infiltrating Treg cells displayed greater suppressive capacity for inhibiting CD8+ T cells proliferation and subsequent cytokine production than Treg cells isolated outside tumor microenvironment. A contact between Treg cells and CD8+ T cells was necessary for the potent suppression of CD8+ T cell immune response. More importantly, the suppression required cell-specific expression and interaction of PD-1 on Treg cells and PD-1 ligand on CD8+ T cells. Our study defines PD-1 upregulated on Treg cells and its interaction with PD-1 ligand on effector T cells as one cause for the potent T cell suppression and proposes the role of PD-1 on Treg cells, in addition to that on exhausted T cells, in tumor microenvironment.

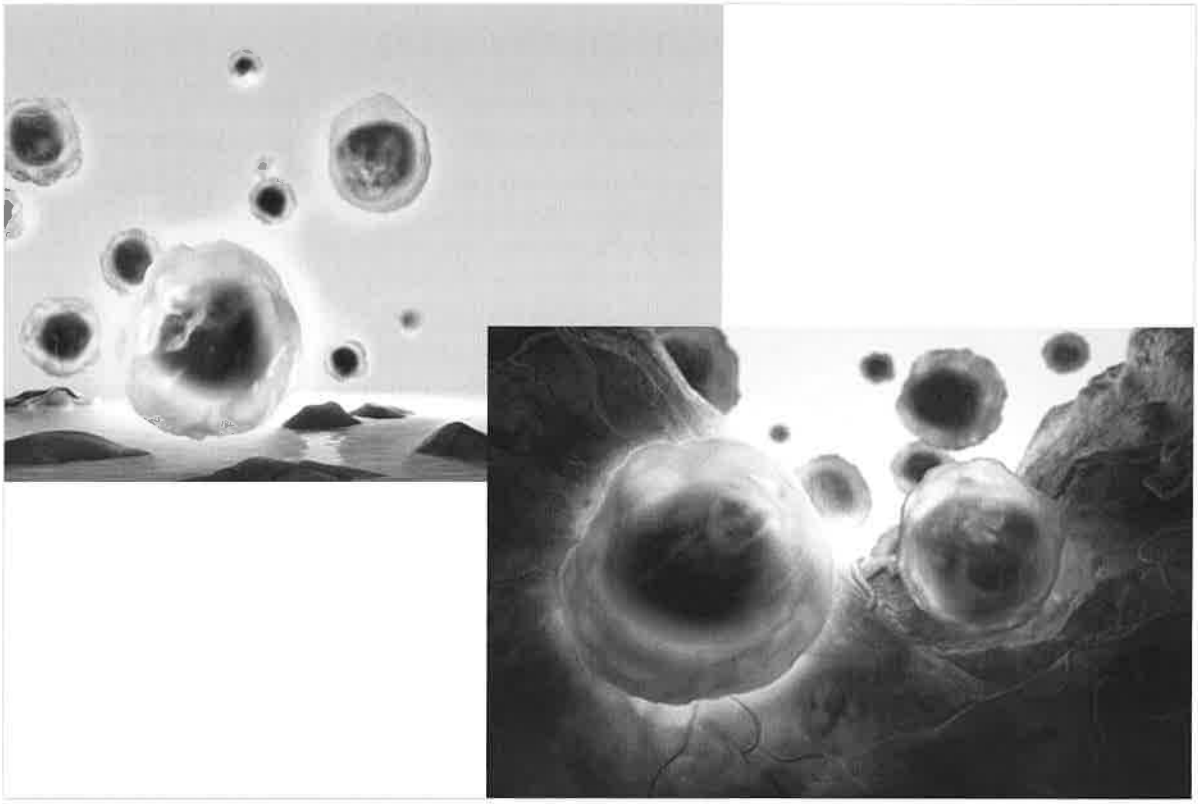
Immune regulation via immune checkpoint PD-1 expressed regulatory T cells during cancer progression

Sang-Jun Ha

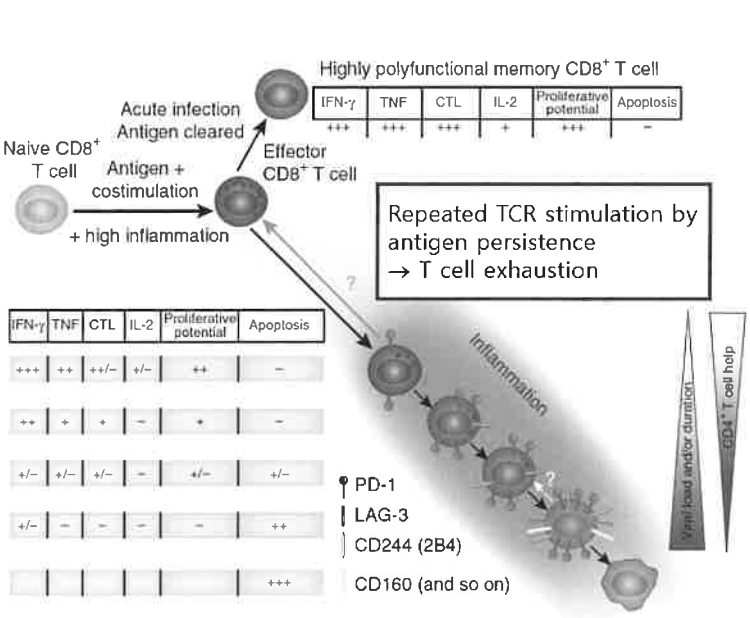
Department of Biochemistry
College of Life Science and Biotechnology
Yonsei University

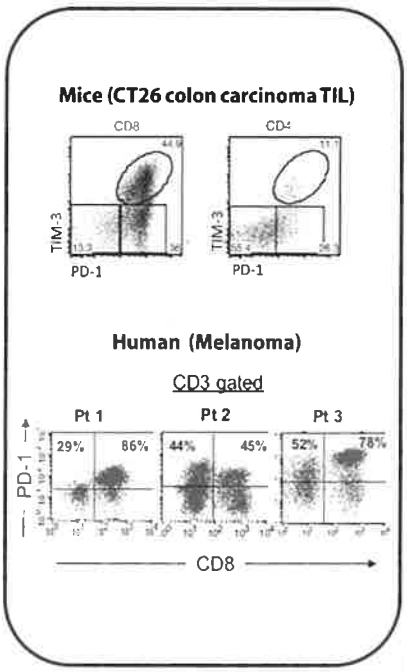
Question

Why cannot our immune system treat efficiently chronic infection and cancer ?

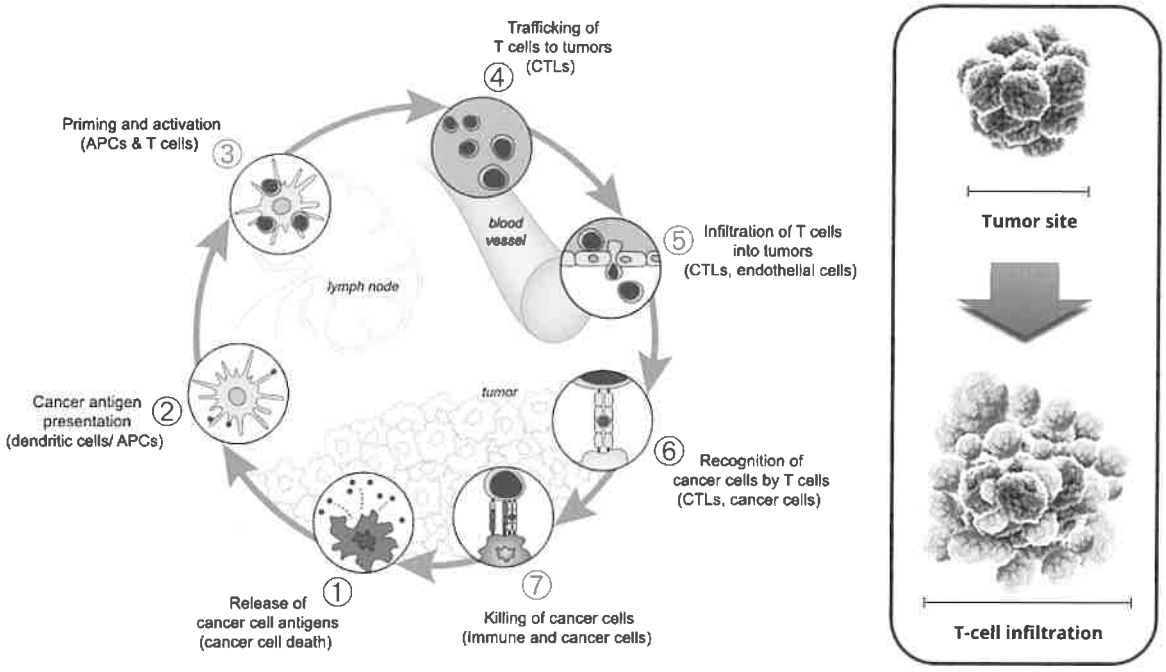


T cell exhaustion under cancer microenvironment



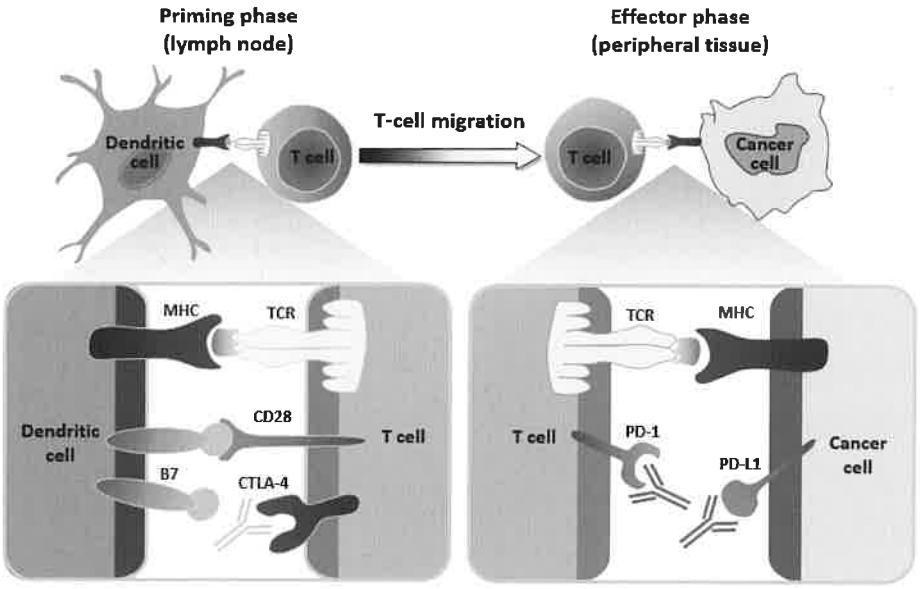


Cancer-immunity cycle



Chen DS & Mellman I. ***Immunity*** 2013 39:1

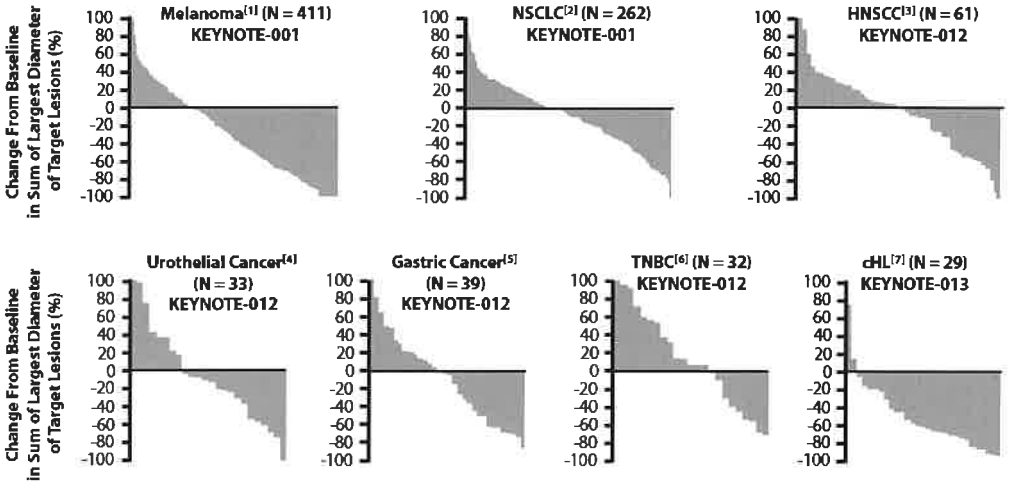
CTLA-4/B7-1 and PD-1/PD-L1 checkpoint blockade for cancer treatment



Adapted from Ribas A. ***N Engl J Med*** 2012 366:2517

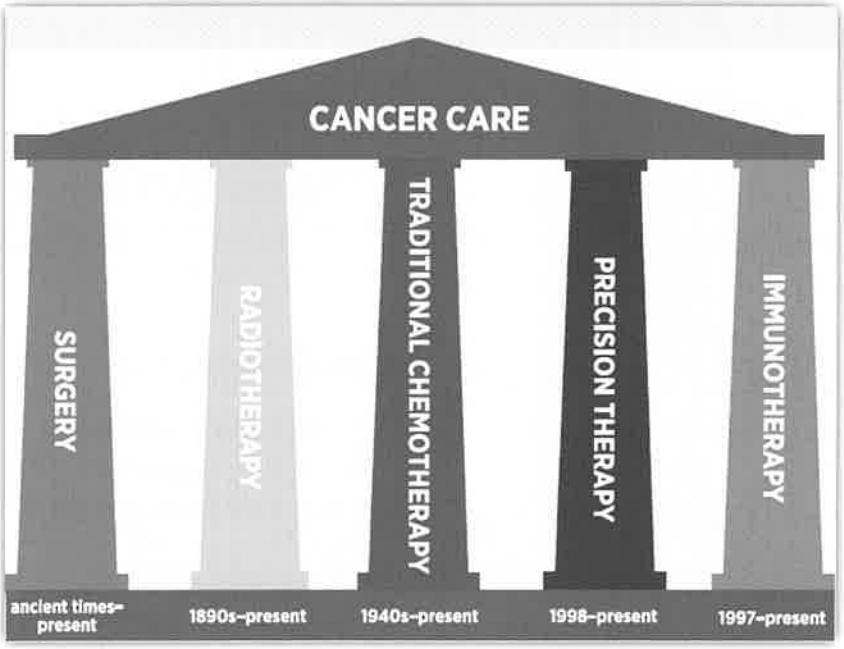
Why do we need more checkpoint blockers?

Pembrolizumab antitumor activity (Merck)

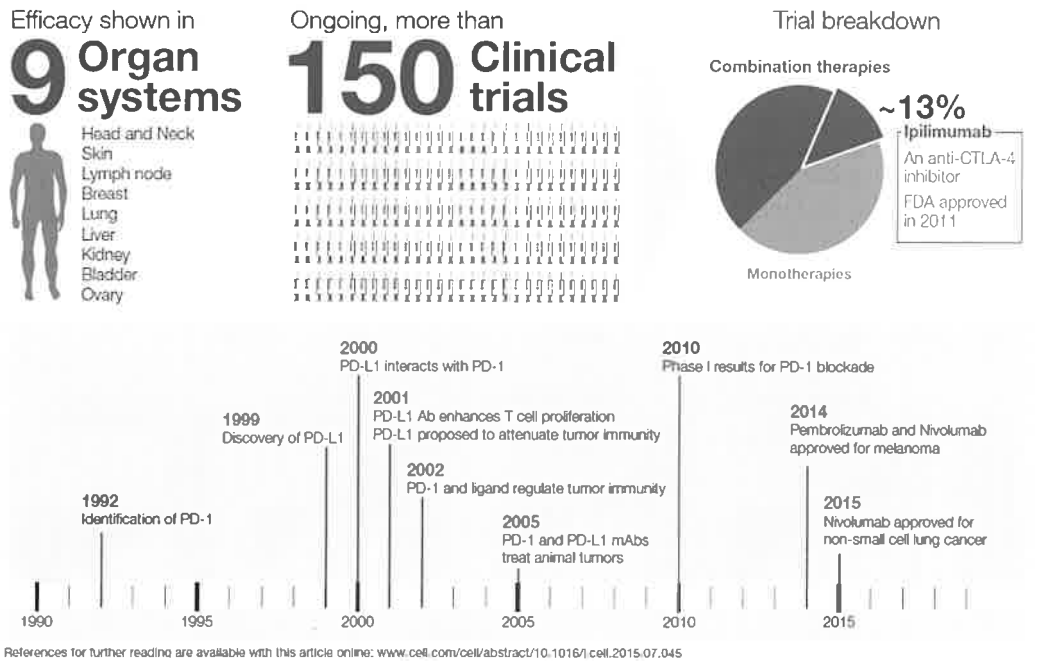


1. Robert C, et al. Lancet. 2014;384:1109-1117. 2. Garon EB, et al. ESMO 2014. LBA43. 3. Chow LQ, et al. ESMO 2014. LBA31. 4. O'Donnell P, et al. ASCO GU 2015. Abstract 296. 5. Muro K, et al. ASCO GI 2015. Abstract 03. 6. Nanda R, et al. SABCS 2014. Abstract S1-09. 7. Moskowitz C, et al. ASH 2014. Abstract 290.

More options for cancer care

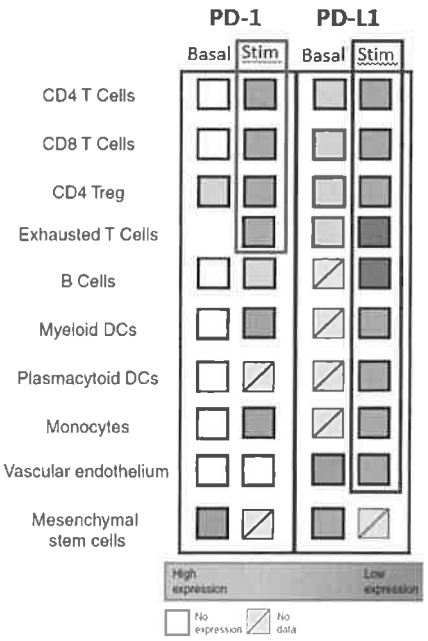


AACR Cancer Progress Report 2015



Wolchok JD. ***Cell*** 2015 162:937

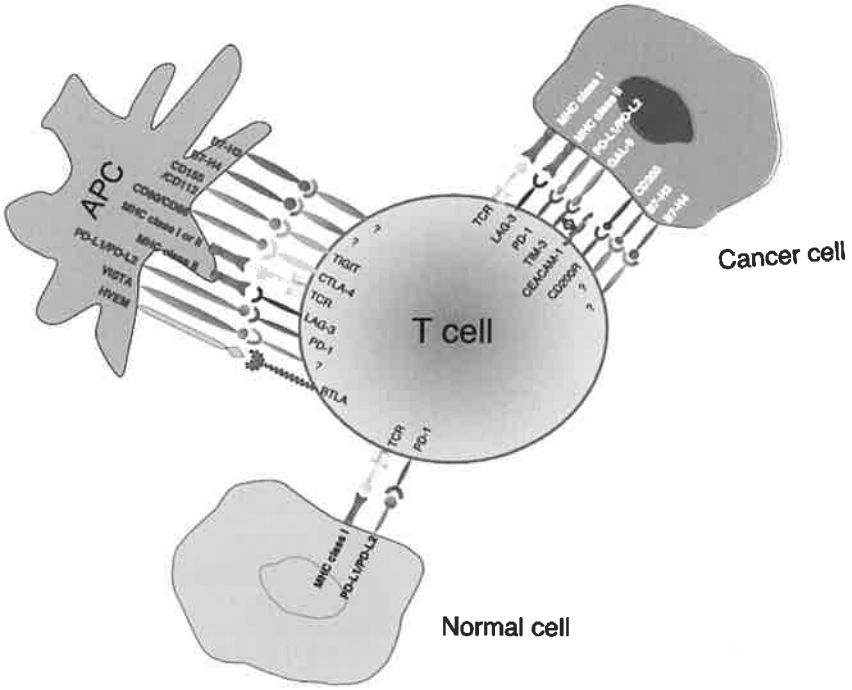
PD-L1 expression in various cells under inflamed environment



- **PD-1** expression
  - Activated/Exhausted T cells
  - Regulatory T cells (T_{reg})
- **PD-L1** expression
  - Inflamed tumor cells
  - Various types of cells under inflamed environment

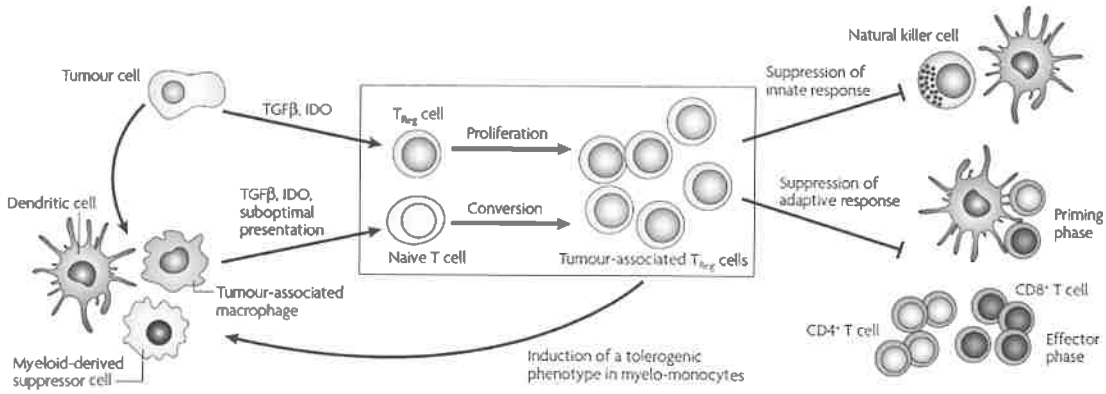
Sharpe AH *et al.* ***Immunol Rev*** 2010 236:219

Immune checkpoints between APC, T cell, cancer, & normal cell



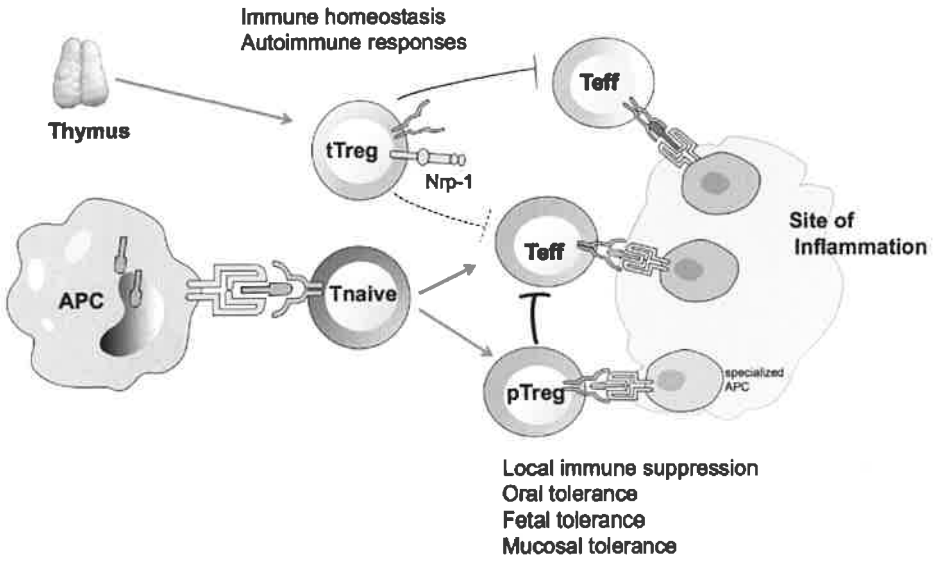
Modified from Shin DS & Ribas A. ***Curr Opin Immunol*** 2015 33:23

Immune suppression by Treg



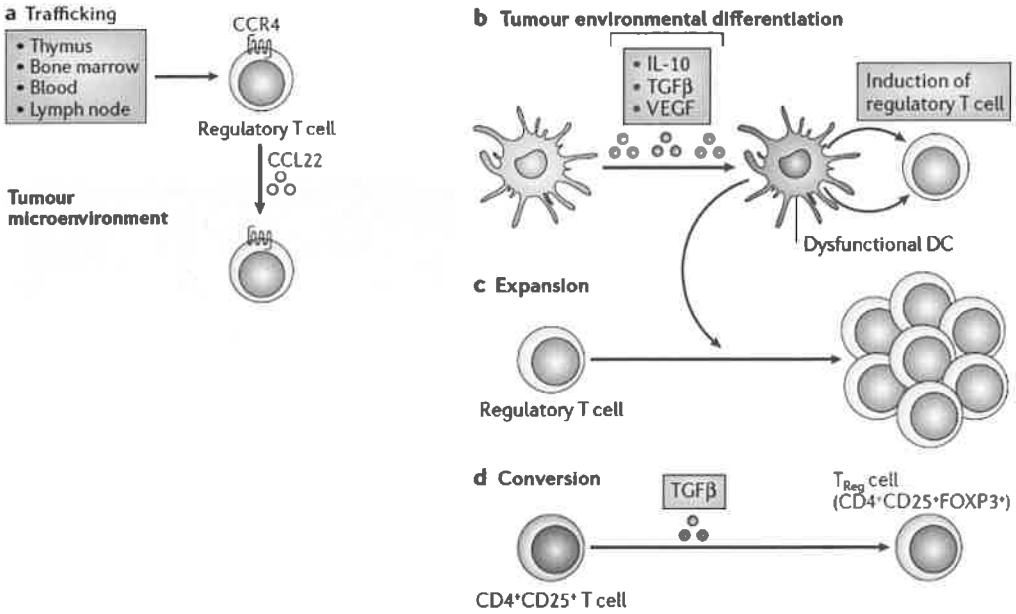
Characteristics of thymic T_{reg} and peripheral T_{reg}

◆ Model depicting the generation and function of tT_{reg} and pT_{reg}



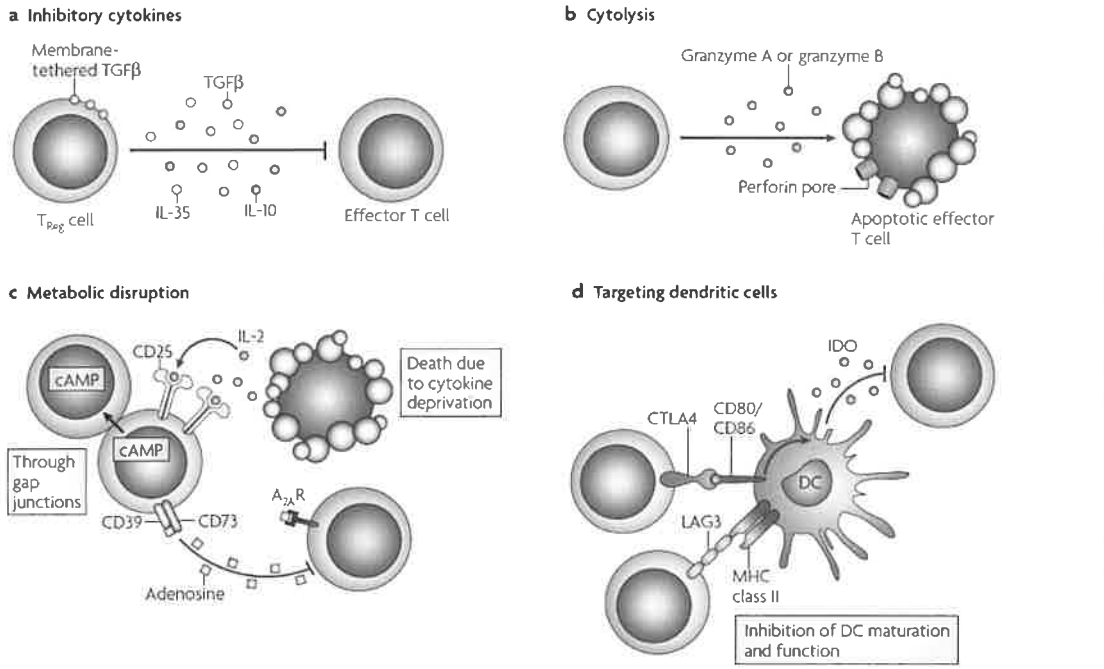
Yadav M *et al.* ***Front. Immunol***. 2013 4:232

T_{reg} in cancer microenvironment



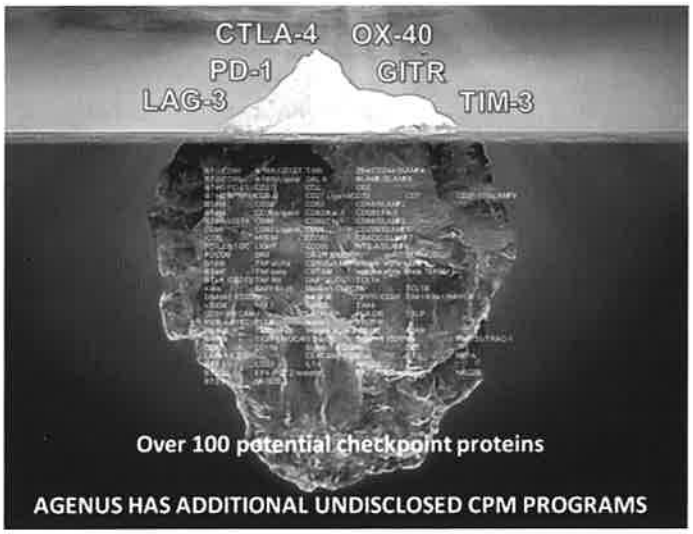
Zou W. ***Nat Rev Immunol*** 2006 6:295

Basic mechanisms used by T_{reg} cells



Vignali DAA et al. ***Nat Rev Immunol*** 2008 8:523

Checkpoints – The Beginning of Understanding



Curriculum Vitae

Sang-Uk Seo

Position/Address Department of Biomedical Sciences,

Wide River Institute of Immunology,

Seoul National University College of Medicine

E-mail: suseo@snu.ac.kr

Education:

2003 B.S., Department of Biotechnology, Yonsei University, Seoul, Korea

2005 M.S., Department of Biotechnology, Yonsei University, Seoul, Korea

2011 Ph.D., Department of Biotechnology, Yonsei University, Seoul, Korea

Professional Backgroud:

03/2008-11/2011 Postdoctoral Fellow, International Vaccine Institute, Korea

12/2011-8/2015 Postdoctoral Fellow, Department of Pathology, University of Michigan, USA

9/2015-present Associate professor, Department of Biomedical Sciences, Wide River Institute of Immunology, Seoul National University College of Medicine

Recent publications:

1. Kim D, Kim YG, Seo SU, Kim DJ, Kamada N, Prescott D, Philpott DJ, Rosenstiel P, Inohara N, Núñez G. Nod2-mediated recognition of the microbiota is critical for mucosal adjuvant activity of cholera toxin. Nat Med, 2016, 22(5):524-530.

2. Yang JY, Kim MS, Kim E, Cheon JH, Lee YS, Seo SU, Lee SH, Kim Y, Shin SH, Choi SS, Kim B, Chang SY, Ko HJ, Bae JW, Kweon MN. Enteric virus ameliorate gut inflammation via TLR3 and TLR7-mediated interferon- production. Immunity, 2016, 44(4):889-900.

3. Seo SU, Kuffa P, Kitamoto S, Nagao-Kitamoto H, Rousseau J, Kim YG, Puente JL, Núñez G, Kamada N. Intestinal macrophages control pathogen infection by activating innate lymphoid cells through caspase-11-mediated IL-1β production. Nat Commun, 2015, 6:8010.

4. Hong EH, Song JH, Shim A, Lee BR, Kwon BE, Song HH, Kim YJ, Chang SY, Jeong HG, Kim JG, Seo SU, Kim H, Kwon Y, Ko HJ. Coadministration of Hedera helix L. extract enabled mice to overcome insufficient protection against influenza A/PR/8 virus infection under suboptimal treatment with Oseltamivir. PLoS One, 2015, 10(6):e0131089.

5. Kamada N*#, Sakamoto K*, Seo SU, Zeng MY, Kim YG, Cascalho M, Vallance BA, Puente JL, Núñez G#. Humoral immunity in the guts selectively targets phenotypically virulent attaching-and-effacing bacteria for intraluminal elimination. Cell Host Microbe, 2015, 17(5):617-627. (*equal contribution) (#corresponding authors)

6. Seo SU, Kamada N, Muñoz-Planillo R, Kim YG, Kim D, Koizumi Y, Hasegawa M, Himpsl SD, Browne HP, Lawley TD, Mobley HL, Inohara N, Núñez G. Distinct commensals induce interleukin-1β via NLRP3 inflammasome in inflammatory monocytes to promote intestinal inflammation in response to injury. Immunity, 2015, 42(4):744-755.

7. Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. Nat Rev Immunol, 2013, 13(5):321-335.

8. Yang H, KO HJ, Yang JY, Kim JJ, Seo SU, Park SG, Choi SS, Seong JK, Kweon MN. Interleukin-1 promotes coagulation, which is necessary for protective immunity in the lung against Streptococcus pneumoniae infection. J Infect Dis, 2013, 207(1):50-60.

9. Seo SU, Kim JJ, Yang H, Kwon HJ, Yang JY, Curtiss III R, Kweon MN. Effective protection against secondary pneumococcal pneumonia by oral vaccination with attenuated Salmonella delivering PspA antigen in mice. Vaccine, 2012, 30(48):6816-6823.

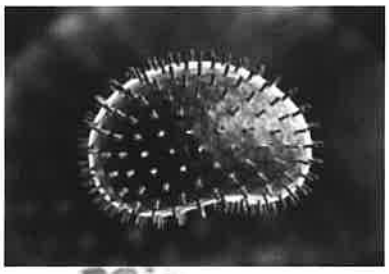
Regulation of innate immune response in the intestine during colitis

Sang-Uk Seo, Ph.D.

Seoul National University, Korea

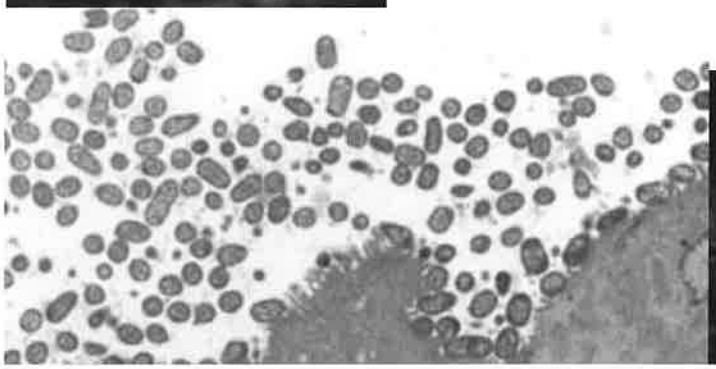
The intestinal immune system is comprised of both innate and acquired defense mechanisms and they are interacting with most complex ecosystem in the body. Because various luminal contents can stimulate immune system, the host has evolved several mechanisms to prevent inappropriate activation of inflammatory response in the intestine. For instance, the intestinal epithelium and resident macrophages are hyporesponsive to bacterial Toll-like receptor ligands such as lipopolysaccharides. In addition, several barriers including the mucus layer and antimicrobial peptides limit the contact between microbes and the host immune system and contribute to gut homeostasis. Once these barriers are breached, innate immune cells play immediate role to react disease condition. However, when innate immune system is overactive, immune cells may enhance pathology associated with inflammation. As a key regulator of innate immune response, major function of innate immune cells includes interaction with its environment and production of immune mediator called 'cytokine'. Recruited innate immune cells, including monocyte and neutrophil, amplify the degree of innate immune response and these cell types are reported to be involved various diseases when uncontrolled. Therefore, study of immune pathways involved in interaction between cells and inflammatory milieu are crucial to understand intestinal disease pathogenesis.

Regulation of innate immune response in the intestine during colitis



Seoul National University
Wide River Institute of Immunology

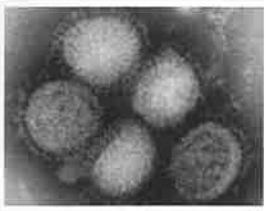
Sang-Uk Seo



Host-Microorganisms (Microbes) interaction

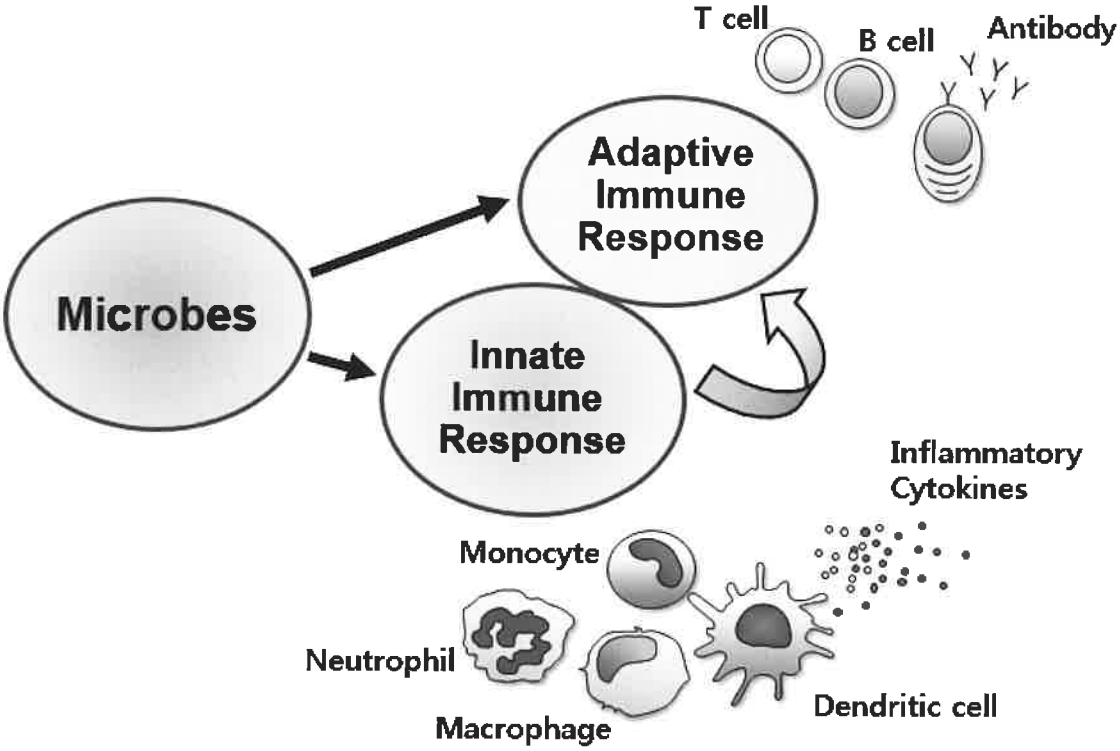
- Microbes; Microscopic & living organism
- Immunity; Host defense mechanism against infection

Virus
Bacteria
Fungi
Protozoa
Algae
Archaea



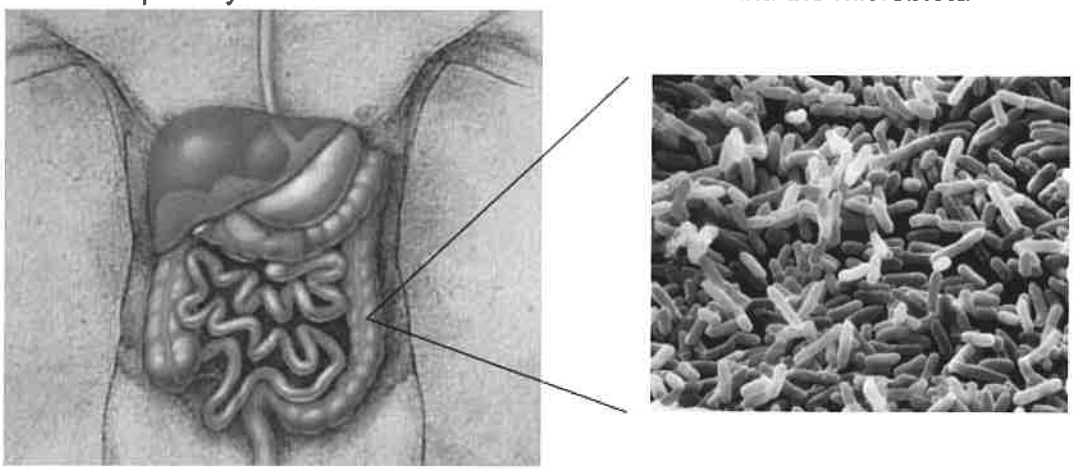
Human body
(Health & Disease)

Innate & Adaptive Immunity



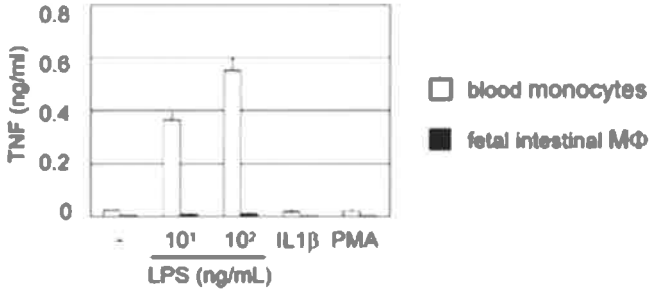
Gastrointestinal Tract

-the primary site of interactions between the host and the microbiota-



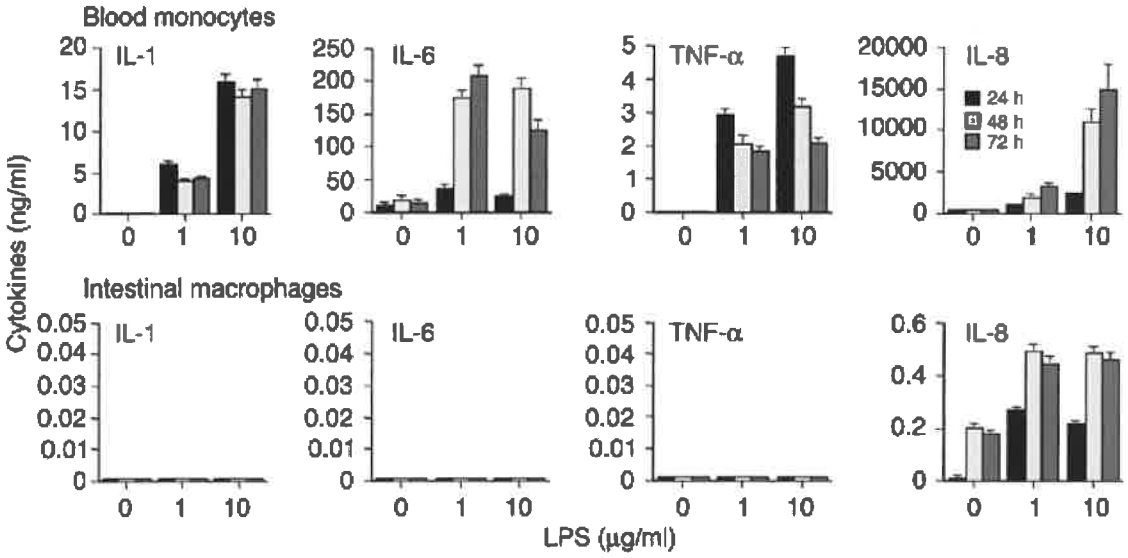
- More than 100 trillion bacteria
- More than 1000 different species

Inflammatory anergy of intestinal macrophage

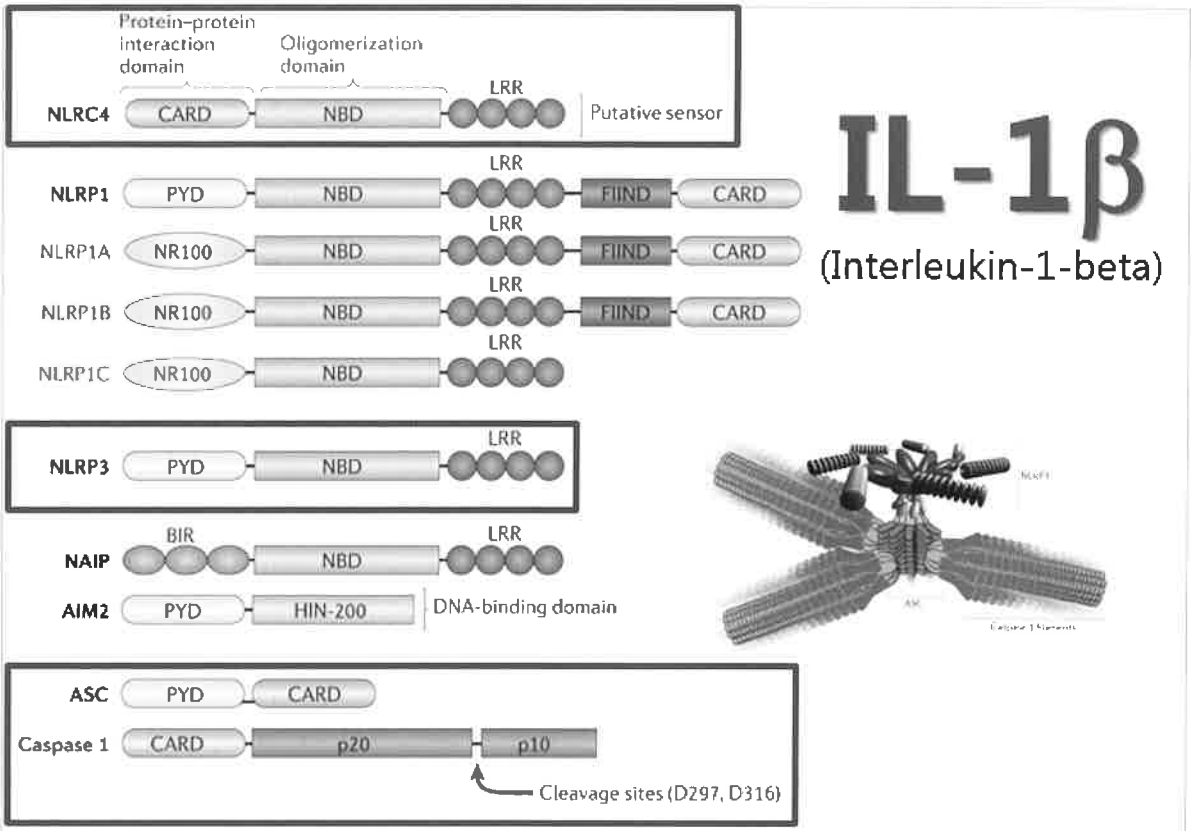


Lotz et al., J Exp Med 2006 203(4):973-84.

Inflammatory anergy of intestinal macrophage



Smythies et al., J Clin Invest 2005 115(1):66-75.



IL-1β

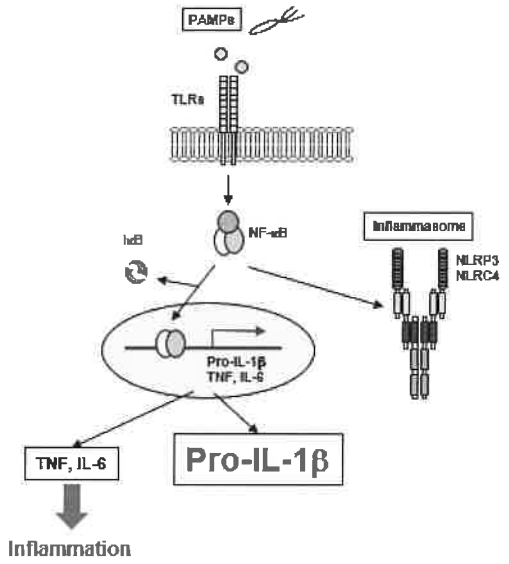
(Interleukin-1-beta)

Walsh et al., Nature Reviews Neuroscience **15**, 84-97.

Leavy, Nature Reviews Immunology **14**, 287.

Inflammasome; 2-step regulation of IL-1β secretion

Signal 1

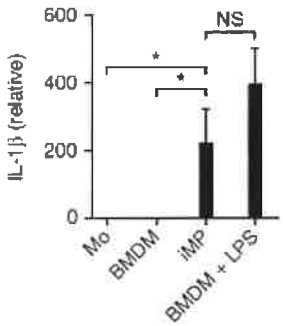


ARTICLES

nature immunology

NLRC4-driven production of IL-1β discriminates between pathogenic and commensal bacteria and promotes host intestinal defense

Luigi Franchi[1,2], Nobuhiko Kamada[1,2], Yuumi Nakamura[1], Aaron Burberry[1], Peter Kuffa[1], Shiho Suzuki[1], Michael H Shaw[1], Yun-Gi Kim[1] & Gabriel Núñez[1]



Signal 1 (= pro-IL-1β) sufficient

ARTICLES

nature immunology

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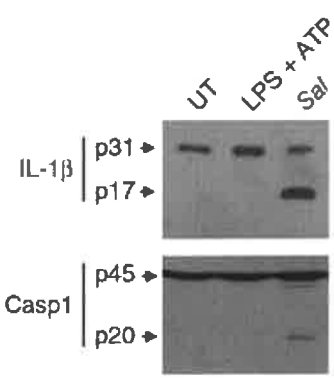
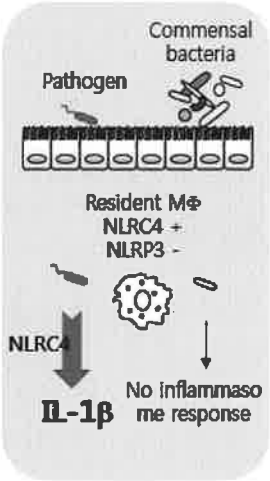


NLRP3 (broad sensor)

NLRC4 (pathogen-specific sensor)



Inflammatory Bowel Disease (IBD)

IL-1β is highly up-regulated in IBD patients.


Role of interleukin 1 in inflammatory bowel disease – enhanced production during active disease


Serum interleukin 1β and interleukin 1 receptor antagonist concentrations in children with active ulcerative colitis and during recovery

Ligumsky M et al. (1990). **Gut** 31, 686-689.
Wedrychowicz A et al. (2003). **Eur J Pediatr** 162, 541-542.

IL-1β is related to various animal colitis model

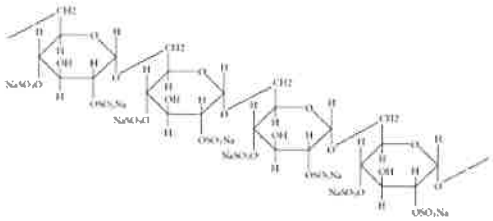

Interleukin-1β (IL-1β) promotes susceptibility of Toll-like receptor 5 (TLR5) deficient mice to colitis

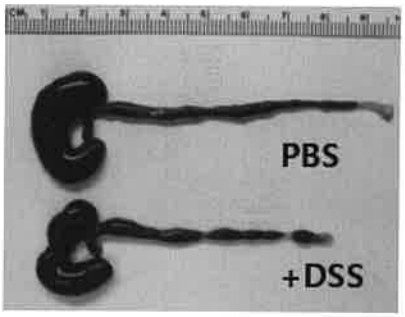
Coccia M et al. (2012). **J Exp Med** 209, 1595-1609.
Carvalhoo FA et al. (2012). **Gut** 61, 373-384.
Ey B et al. (2013). **J Immunol** 190, 5676-5688.
Zhang J et al. (2013). **Mucosal Immunol** 7, 1139-1150.

Dextran sodium sulfate (DSS)-induced colitis

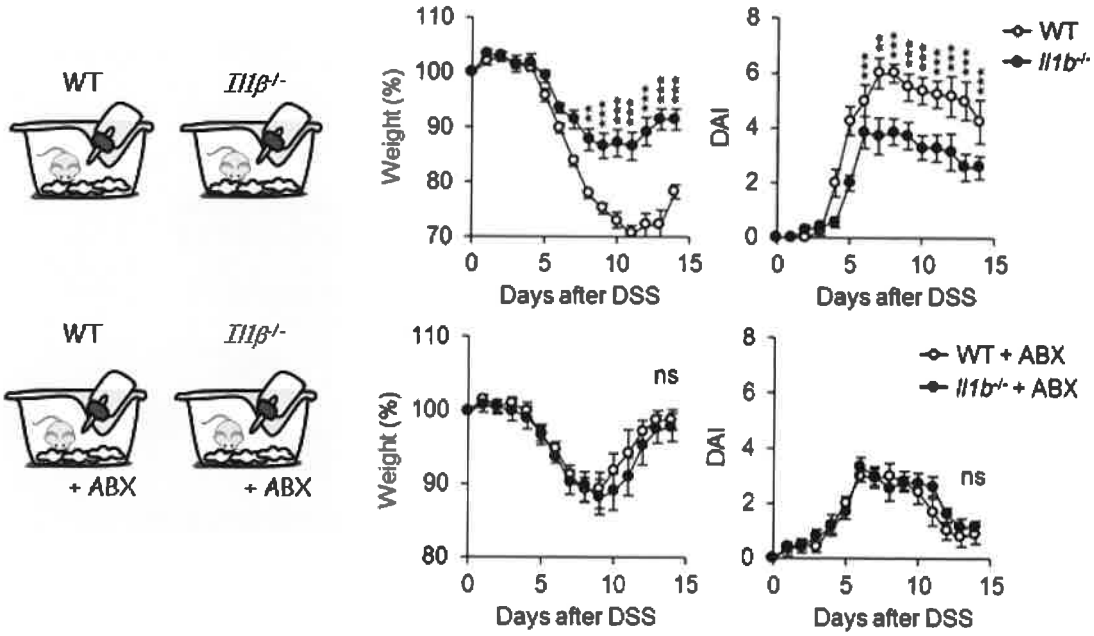
Most frequently used mouse IBD model

- Epithelial cell damage
- Colon inflammation
- Diarrhea
- Rectal bleeding
- Weight loss



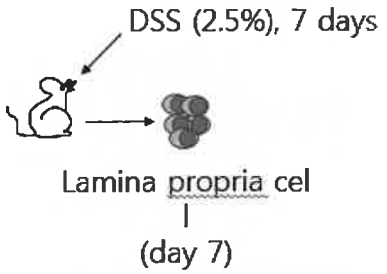


Commensal bacteria induce IL-1β production and contribute to enhance colitis

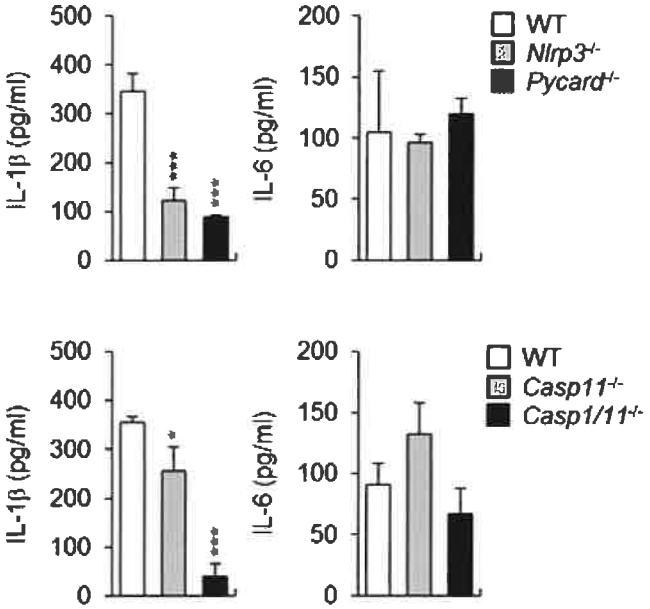


Commensal bacteria-derived IL-1β promotes DSS-induced colitis

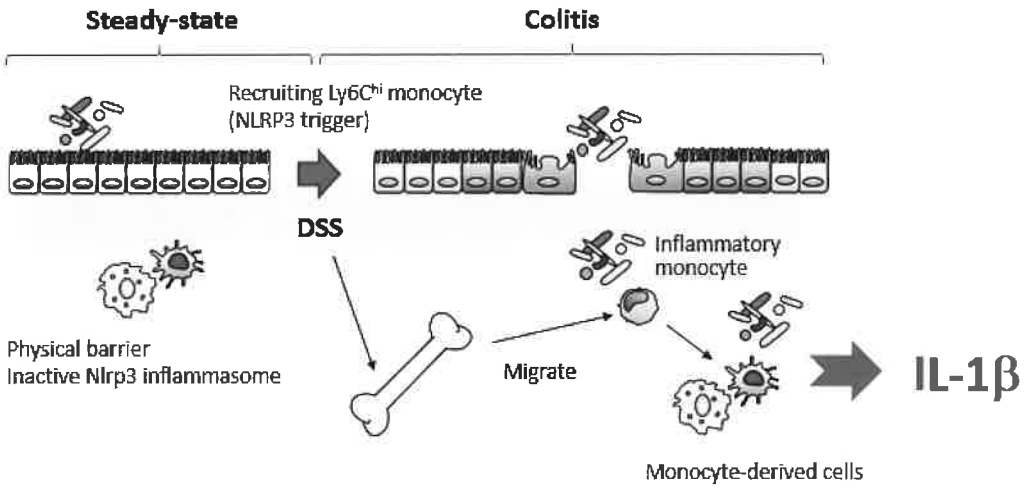
Commensal bacteria induce IL-1β production via NLRP3 -ASC-Caspase-1 pathway.



Ex vivo culture of intestinal LP cells



Inflammatory monocyte recruitment triggers NLRP3 inflammaso me response in intestine



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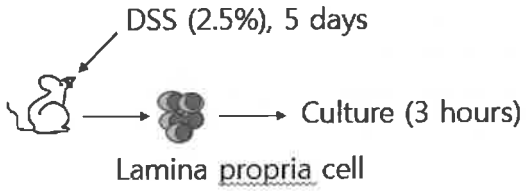

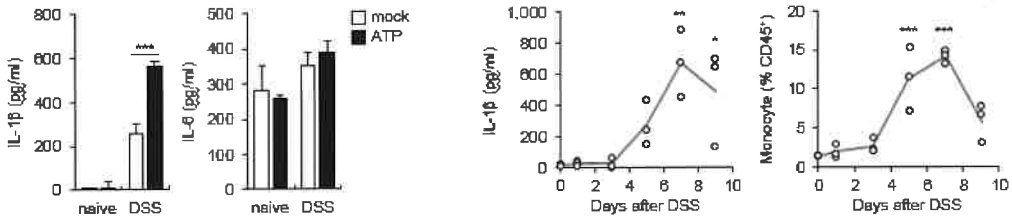

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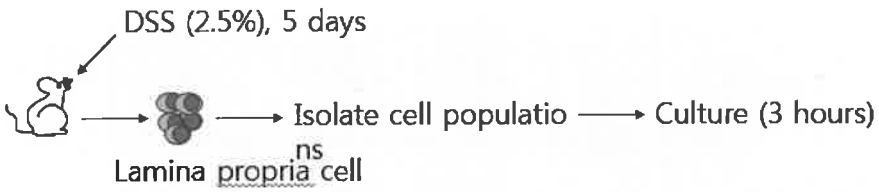
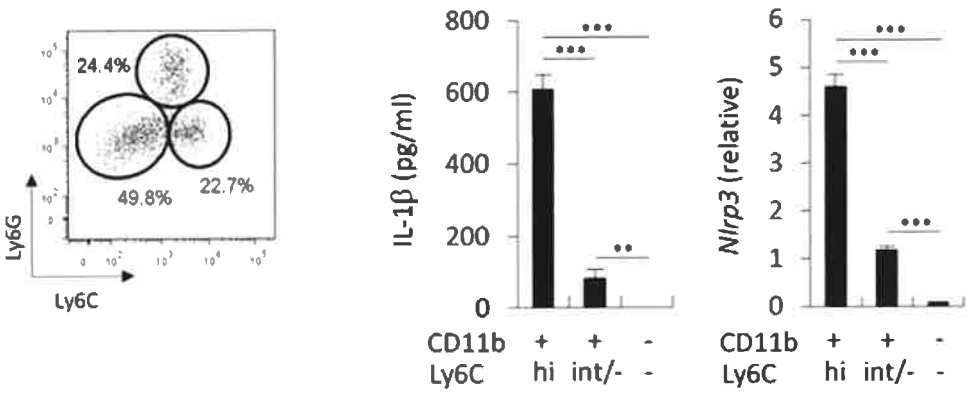


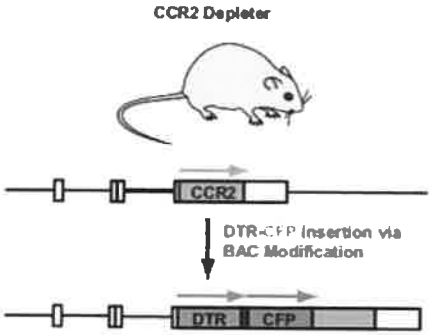


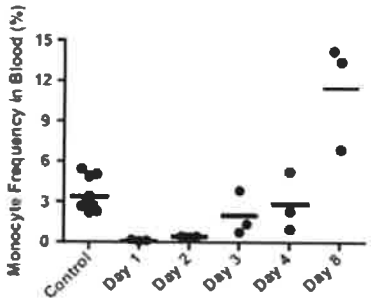
Cell Host & Microbe
Article

Inflammatory Monocytes Facilitate Adaptive CD4 T Cell Responses during Respiratory Fungal Infection

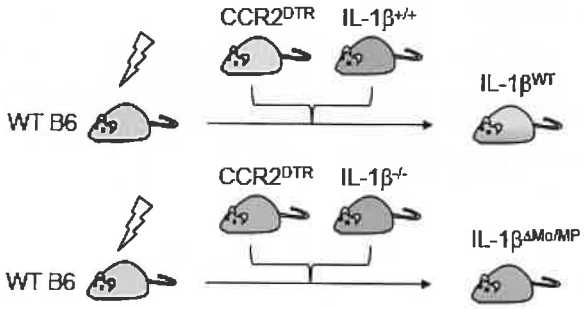
Tobias M. Hohl,[1,3,4,*] Amariliz Rivera,[1,3] Lauren Lipuma,[1] Alena Gallegos,[1] Chao Shi,[1] Mathias Mack,[2] and Eric G. Pamer[1,*]
[1]Infectious Disease Service, Department of Medicine, and Immunology Program, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
[2]Department of Internal Medicine, University of Regensburg, 93053 Regensburg, Germany
[3]These authors contributed equally to this work
[4]Present address: Vaccine and Infectious Diseases Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
[*]Correspondence: thohl@fhcrc.org (T.M.H.); pamere@mskcc.org (E.G.P.)
DOI 10.1016/j.chom.2009.10.007

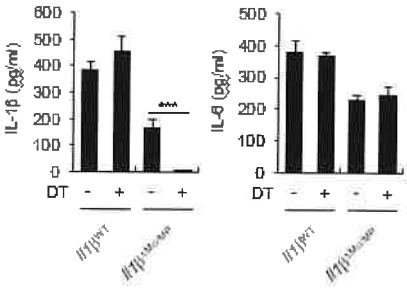
CHM, 2009. 6(5);470-81



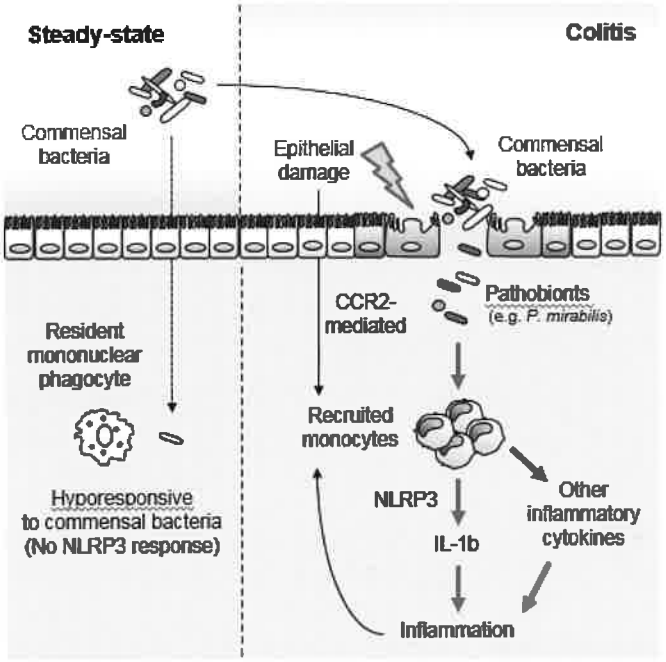


Inflammatory monocyte recruitment triggers NLRP3 infl ammasome response in intestines





Summary


Steady-state
Colitis
Commensal bacteria
Epithelial damage
Commensal bacteria
CCR2-mediated
Pathobionts
(e.g. P. mirabilis)
Resident mononuclear phagocyte
Recruited monocytes
Hyporesponsive to commensal bacteria (No NLRP3 response)
NLRP3
IL-1b
Other inflammatory cytokines
Inflammation

NOTE

NOTE