

Curriculum vitae

PERSONAL INFORMATION

Family name, First name: Matarese, Giuseppe

Researcher unique identifier (ORCID): 0000-0001-9429-0616; Date of birth: August 23rd 1970

Nationality: Italian - URL for personal web site: www.matareselab.it

• EDUCATION and TRAINING

- 05/03/2004 PhD in Scienze Endocrinologiche e Metaboliche, thesis titled: “*Role of leptin in autoimmunity*” (Supervisor: Prof. Serafino Zappacosta);
- 2001-2003 PhD Program in Scienze Endocrinologiche e Metaboliche, Dipartimento di Biologia e Patologia Cellulare e Molecolare (DBPCM), Università di Napoli “Federico II” (UNINA), Napoli, Italy;
- 18/10/1999 Specialist in Clinical Pathology (*summa cum laude*);
- 1994-1999 Medical Resident Program in Clinical Pathology (*summa cum laude*), Clinical Pathology Section, DBPCM, UNINA, Napoli, Italy (Supervisors: Prof. Serafino Zappacosta and Prof. Vincenzo Macchia);
- 1997-1998 Research Associate, Department of Immunology, Hammersmith Hospital, Imperial College School of Medicine, London, UK (Supervisor: Prof. Sir Robert I. Lechler);
- 1995 Visiting Scientist, HLA Tissue Typing Laboratory, Royal Post-Graduate Medical School, Hammermith Hospital, London, UK (Supervisor: Dr. Nick Davey);
- 23/09/1994 MD Degree “*summa cum laude*”, Università di Napoli “Federico II”, School of Medicine & Surgery, Napoli, Italy;
- 1993 Research Trainee in Immunology, Department of Medicine, University California San Diego (UCSD), La Jolla, CA, USA (Supervisor: Prof. Salvo Albani);
- 1988-1994 Medical research internship, Laboratory of Immunology, DBPCM, UNINA (Supervisor: Prof. Serafino Zappacosta);
- 1983-1988 Liceo Classico (High school, Latin/Ancient Greek), Salesiani College, Napoli, Italy.

• CURRENT POSITION

From 2015 Full Professor of Immunology, Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Faculty of Medicine & Surgery, Università di Napoli “Federico II”, Napoli, Italy; Director Laboratory Immunogenetics of Transplants and National Bone Marrow Regional Registry (IBMDR), Dipartimento di Medicina di Laboratorio e Trasfusionale, AOU Federico II Hospital; Head of Treg Cell Lab, Istituto per l’Endocrinologia e l’Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (IEOS-CNR), Napoli, Italy

• PREVIOUS POSITIONS

- 2011 – 2015 Full Professor of Immunology, Faculty of Medicine & Surgery, Università di Salerno, Salerno, Italy; Head of Clinical Immunopathology Service, Ruggi D’Aragona Hospital, Salerno; Head of Treg Cell Lab, IEOS-CNR, Napoli, Italy;
- 2010 – 2011 Qualification as Full Professor of Immunology, Faculty of Medicine & Surgery, Università di Bari “Aldo Moro”, Bari, Italy; Head of Treg Cell Lab, IEOS-CNR, Napoli, Italy;
- 2007 – 2011 CNR Research Director and Head of Treg Cell Lab, IEOS-CNR, Napoli, Italy;
- 2005 – 2007 CNR First Class Researcher at IEOS-CNR, Napoli, Italy;
- 2001 – 2005 CNR Researcher at IEOS-CNR, Napoli, Italy.

• FELLOWSHIPS AND AWARDS

- 2019 Accademia dei Lincei Prize “Antonio Feltrinelli” for Immunology and Pathology
- 2013-2016 Honorary Professor, William Harvey Research Institute, QMUL, London, UK;
- 2013-2018 ERC- Grant – Consolidator Track (ERC call 2012), *menTORingTregs*, n. 310496;
- 2008-2011 ERC- Grant – Starting Track (first ERC call 2007), *LeptinMS*, n. 202579;
- 2005 Rita Levi Montalcini Prize, as Top Italian scientist in field of Multiple Sclerosis;
- 2004 Harlan Prize for Immunology from Italian Society of Immunology (SIICA);
- 2000-2001 Fellowship from the European Union Social Fund, DBPCM, UNINA, Napoli, Italy;
- 1999 Roche Prize for Immunology from Italian Society of Immunology (SIICA);
- 1994-1999 Resident-Clinical Pathology Fellowship, DBPCM, UNINA, Napoli, Italy;
- 1994 Fellowship from the CNR, IEOS-CNR, Napoli, Italy.

• **SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS**

From 2001 7 Postdocs, 10 PhD Students, 20 Master Students, 1 CNR Technician, 2 Postdocs from international programs (Sheffield University and Cambridge University, UK).

• **TEACHING ACTIVITIES**

From 2015 Teaching of Immunology at the Faculty of Medicine and Surgery, UNINA, Napoli, Italy;

From 2005 Teaching of Immunology at the PhD program in Cellular and Molecular Pathology, UNINA, Napoli, Italy;

2011 – 2015 Teaching of Immunology at the Faculty of Medicine and Surgery, UNISA, Salerno, Italy;

2010 – 2011 Teaching of Immunology at the Faculty of Medicine and Surgery, UNIBA, Bari, Italy;

2005 – 2010 Teaching of Immunology at the Faculty of Biological Sciences, UNINA, Napoli, Italy.

• **ORGANISATION OF SCIENTIFIC MEETINGS**

2008 XVIII Congress Italian Society of NeuroImmunology (AINI), 8-11 October 2008, Napoli;

2014 XXIV Congress Italian Society of NeuroImmunology (AINI), 1-4 October 2014, Sorrento;

2015 EFIS-EJI Course for the “Ceppellini School of Immunology” 5-6 November entitled: “Treg cell biology and metabolism”, Napoli (Co-Director with Fiona Powrie and Giovanna Lombardi);

2018 EFIS-EJI Course for the “Ceppellini School of Immunology” 12-15 October entitled: “T cell memory”, Capri Island (Organizing Committee);

INSTITUTIONAL RESPONSIBILITIES

Member of the Committee for final PhD exams:

2005 Seconda Università di Napoli, Napoli, Italy. Coordinator: Prof. Migliaccio;

2006 Università di Napoli “Federico II”, Napoli, Italy. Coordinator: Prof. Avvedimento;

2012 Université Claude Bernard Lyon-1, Lyon, France. Coordinator: Prof. Christine Delprat;

2013 Università “La Sapienza”, Roma, Italy. Coordinator: Prof. Angela Santoni;

2013 Università di Napoli “Federico II”, Napoli, Italy. Coordinator: Prof. Paolo De Girolamo;

2015 Università Vita-Salute San Raffaele, Milano, Italy. Coordinator: Prof. Fabio Grohovaz.

Member of the Committee for Positions:

6 CNR Fellowships at IEOS-CNR, Napoli, Italy;

7 CNR Postdoc Fellowships at IEOS-CNR, Napoli, Italy;

2 Permanent positions as Researcher at IEOS-CNR, Napoli, Italy;

2 Associate Professor (1 in Medical Genetics, Salerno University and 1 in General Pathology, Sapienza University)

3 Full Professors (1 in General Pathology, Federico II University, Napoli; 2 in General Pathology, Sapienza University, Roma)

2019-2020 National Board for Research (Piano Nazionale della Ricerca - PNR)

• **REVIEWING ACTIVITIES, EDITORIAL BOARD & SCIENTIFIC ADVISORY BOARD**

Ad hoc Reviewer for the following Grants Agencies: European Research Council; National Research Council (CNR, Italy); Agencie de Richerché Medicale, ANR (France); Inflammatory Bowel Disease Foundation (USA); Israeli Science Foundation (Israel); University of Sheffield Grants for Research Programs (UK); Juvenile Diabetes Research Foundation (UK); Fondazione Italiana Sclerosi Multipla (FISM-Italy); National Swiss Science foundation (Geneve); Arthritis Foundation (UK);

Ad hoc Reviewer for the following Journals: Science, Science Translational Medicine, Immunity, Cell Metabolism, Cell Reports, Nature Immunology, Nature Medicine, Nature Communications, Nature Reviews Immunology, New Engl J Medicine, J Clin Invest, J Exp Med, J Biol Chem, J Immunol, J Leuk Biol, J Clin Immunol, Clin Endocrinol, Endocrinology;

Editorial Board for the following Journals: Molecular Metabolism (2012-1017); Metabolism – Clinical & Experimental; The Journal of Biological Chemistry; Cytokines & Growth Factors Reviews;

Member of the Board of Directors of: EFIS-EJI Advanced School of Immunology Ruggero Ceppellini (www.ceppellini.it);

Scientific Advisory Board of the Italian Foundation for Multiple Sclerosis (FISM); Scientific and Advisory board Cluster ALISEI.

• **MEMBERSHIPS OF SCIENTIFIC SOCIETIES**

American Association of Immunologists (AAI); Società Italiana di Immunologia, Immunologia Clinica ed Allergologia (SIICA); Società Italiana di NeuroImmunologia (AINI); European Association for the Study of

Diabetes (EASD); EFIS-EJI Advanced School of Immunology Ruggero Ceppellini.

• MAJOR SCIENTIFIC COLLABORATIONS

Prof. Tamas Horvath, Yale University, New Haven, USA; *Neural control of peripheral immunometabolism*;
Prof. Christos Mantzoros, Harvard University, Boston, USA; *Clinical trials with human metreleptin*;
Prof. Antonio La Cava, UCLA, Los Angeles, USA; *Effects of leptin on pathogenesis of autoimmunity and Lupus*;
Prof. Triantafyllos Chavakis, Dresden University, Dresden, Germany; *Effects of Del-1 on Treg cell function*;
Prof. Mihai Netea, Radboud University, Radboud, Netherland; *Role of trained immunity in induction of Treg cells (part of the INTRIM Network)*.

Research lines, Grants and Personal Achievements

Prof. Matarese, about 20 years ago, was among the first which opened a novel area of investigation that links nutritional status/metabolism to immune responses, currently known as “immunometabolism”. His paper that initiated the field and was published in *Nature* (1998), has been cited so far more than 2274 times. In that paper, Matarese and co-workers showed for the first time that leptin, the adipocyte-derived hormone that inhibits food intake and increases basal metabolism, can influence T helper 1 (Th1) immune responses. After that work, Prof. Matarese and co-workers went on demonstrating that leptin could influence susceptibility to multiple sclerosis (MS) and its animal model of experimental autoimmune encephalomyelitis (EAE) through the secretion of inflammatory cytokines (Matarese et al., *Ji*, 2001; Sanna et al., *JCI*, 2003; Matarese et al., *PNAS*, 2005; De Rosa et al., *JCI*, 2006) and through the control on regulatory T (Treg) cell proliferation, suggesting for the first time a link between adipose tissue biology and Treg cell function (De Rosa et al., *Immunity*, 2007). Prof. Matarese also identified a novel link between “oscillations” of intracellular energy metabolism regulated by mTOR and the proliferation of Treg cells (Procaccini et al., *Immunity*, 2010) and the survival of effector T cells (Galgani et al., *J. Immunol.*, 2010). In addition, Prof. Matarese showed that mTOR overactivation is responsible for the impaired proliferative potential *in vivo* and *in vitro* of human *ex vivo* isolated peripheral Treg cells from MS patients (Carbone et al., *Nat Med.* 2014). More recently, Prof. Matarese and co-workers identified a new mechanism of Foxp3 regulation linking engagement of glycolysis by Tconv cells in the generation of inducible (i)Treg cells through the enolase-1 enzyme (De Rosa et al. *Nat. Immunol.* 2015). This evidence has suggested for the first time that Treg cells not only rely on fatty acid metabolism, as generally thought, but also on glycolysis. Prof. Matarese confirmed the involvement of glycolysis in Treg cell immunobiology at the proteomic level (Procaccini et al. *Immunity* 2016), in the migration of Treg cells in peripheral tissues (Kishore et al. *Immunity* 2017), and in Treg cell expansion during tumour progression (Pacella et al. *PNAS* 2018). In the field of leptin biology and its use in human diseases, Prof. Matarese significantly contributed to the characterization of the effect of leptin in controlling food intake, metabolism and immune functions in humans (Farooqi et al. *JCI* 2002), in reconstituting CD4 T cell numbers (Matarese et al. *PNAS* 2013), and in restoring disturbed neuro-endocrine function in women with hypothalamic amenorrhoea (Chan et al. *PNAS* 2006; Chou et al. *PNAS* 2011). Further, Prof. Matarese contributed to the FDA and EMA approval of metreleptin (MYALEPT[®], Aegerion Pharmaceuticals) for its use in humans in rare lipodystrophic subjects. He currently acts for the Advisory Committee in the strategic planning for the use of metreleptin in human diseases and the study of its immunogenicity.

For Grants, Prof. Matarese has been awarded an **ERC-Grant (LeptinMS, n. 202579, ERC call 2007)** in the first starting call which is ended in October 2011 (2008-2011, 40 months). Subsequently, Prof. Matarese has been awarded another 5 years **ERC-Grant (mentORingTregs, n. 310496, ERC call 2012)**, which has been recently completed (2013-2018, 60 months; ended in April 2018). Both the awarded ERC-Grants represented a key step in the advancement of his career in the field of immunometabolism. In his career, Prof. Matarese has also received Grants from other National and International Grant Agencies including the Juvenile Diabetes Research Foundation (JDRF)-Telethon, European Foundation for the Study of Diabetes (EFSD), Italian Space Agency (ASI) and Italian Foundation for Multiple Sclerosis (FISM). Prof. Matarese acts as advisor and collaborates with International Pharma Industries such as Merck, Novartis and Biogen Idec, particularly in the context of characterization of the effects of novel drug treatments in multiple sclerosis.

Prof. Matarese has been invited as a speaker and/or chairman to more than 90 international conferences. Among them: Institute Pasteur, “Metabolic regulation of immune response”, Roma, 2018; 2013 (2nd) and 2015 (3rd) Aegean-Nature Medicine “ImmunoMetabolism” Conferences, Rhodes, Greece; Keystone Symposia “Integrating Immunity and Metabolism”, Dublin, 2017; Hans-Fisher TUM Symposium “Metabolic principles of human physiology and disease”, Munich, 2015; Cold Spring Harbor Laboratory (CSHL) Expert Panel, Banbury Centre, 2012; Workshop Endocrine-Immunology, 2nd European Congress of Immunology, Berlin, 2009; 2008 Pennington Meeting, Neuro-Immuno-Endocrine signalling, Baton Rouge, USA, etc.

Finally, Prof. Matarese is an inventor in five patents on the use of leptin antagonists. Patents: 1) Patent on “Use of leptin, its derivatives, agonists and antagonists in modulating immune responses”, UK patent application n. GB9807062.6; 2) Patent on “Leptin antagonist and method for quantitative measurement of leptin”, EU patent n. 04797956.2-2402-EP2004013043. 3) Patent on “Leptin ligand” UK patent application n. GB0605162.7; 4) Patent on “Adjuvant” UK patent application n. GB0605163.5; 5) Patent on “A diagnostic assay for obesity and related disorders” UK patent application n. GB1004058.2 and US patent application n. US61/312,949; Pub. No.: WO/2011/117084, PCT/EP2011/053673.

Publications

Prof. Matarese has authored 189 articles on internationally, peer-reviewed journals; **total citations is 28896; the h-index is 66** (From Scholar); the average number of total citations per year in last 5 years is > 2500. **Below are shown the top articles in the last 10 years (for complete list of publications visit Pubmed or www.matareselab.it):**

1) Procaccini C, Garavelli S, Carbone F, Di Silvestre D, La Rocca C, Greco D, Colamatteo A, Lepore MT, Russo C, De Rosa G, Faicchia D, Prattichizzo F, Grossi S, Campomenosi P, Buttari F, Mauri P, Uccelli A, Salvetti M, Brescia Morra V, Vella D, Galgani M, Mottola M, Zuccarelli B, Lanzillo R, Maniscalco GT, Centonze D, de Candia P, **Matarese G**. Signals of Pseudo-Starvation Unveil the Amino Acid Transporter SLC7A11 as Key Determinant in the Control of Regulatory T Cell Proliferative Potential. *Immunity* 2021 *in press*.

2) Palma C, La Rocca C, Gigantino V, Aquino G, Piccaro G, Di Silvestre D, Brambilla F, Rossi R, Bonacina F, Lepore MT, Audano M, Mitro N, Botti G, Bruzzaniti S, Fusco C, Procaccini C, De Rosa V, Galgani M, Alviggi C, Puca A, Grassi F, Rezzonico-Jost T, Norata GD, Mauri P, Netea MG, de Candia P, **Matarese G**. Caloric Restriction Promotes Immunometabolic Reprogramming Leading to Protection from Tuberculosis. *Cell Metab.* 2021 Feb 2;33(2):300-318.e12. doi: 10.1016/j.cmet.2020.12.016.

3) Li X, Colamatteo A, Kalafati L, Kajikawa T, Wang H, Lim JH, Bdeir K, Chung KJ, Yu X, Fusco C, Porcellini A, De Simone S, **Matarese G**, Chavakis T, De Rosa V, Hajishengallis G. The DEL-1- β 3 integrin axis promotes regulatory T cell responses during inflammation resolution. *J Clin Invest.* 2020 Aug 20;137530. doi: 10.1172/JCI137530.

4) Terrazzano G, Bruzzaniti S, Rubino V, Santopaolo M, **Matarese G*** et al. Type 1 diabetes progression is associated with loss of CD3+CD56+ regulatory T cells that control CD8+ T-cell effector functions. *Nat Metab.* 2020;2(2):142-152. doi:10.1038/s42255-020-0173-1 ***Corresponding authors.**

5) Bruzzaniti S, Bocchino M, Santopaolo M, Cali G, Stanziola AA, D'Amato M, Esposito A, Barra E, Garziano F, Micillo T, Zuchegna C, Romano A, De Simone S, Zuccarelli B, Mottola M, De Rosa V, Porcellini A, Perna F, **Matarese G***, Galgani M*. An immunometabolic pathomechanism for chronic obstructive pulmonary disease. *Proc Natl Acad Sci U S A.* 2019 Jul 15. pii: 201906303. doi: 10.1073/pnas.1906303116. ***Corresponding authors.**

6) Simula L, Pacella I, Colamatteo A, Procaccini C, Cancila V, Bordi M, Tregnago C, Corrado M, Pigazzi M, Barnaba V, Tripodo C, **Matarese G**, Piconese S, Campello S. Drp1 Controls Effective T Cell Immune-Surveillance by Regulating T Cell Migration, Proliferation, and cMyc-Dependent Metabolic Reprogramming. *Cell Rep.* 2018 Dec 11;25(11):3059-3073.e10.

7) Becher J, Simula L, Volpe E, Procaccini C, La Rocca C, D'Acunzo P, Cianfanelli V, Strappazon F, Caruana I, Nazio F, Weber G, Gigantino V, Botti G, Ciccocanti F, Borsellino G, Campello S, Mandolesi G, De Bardi M, Fimia GM, D'Amelio M, Ruffini F, Furlan R, Centonze D, Martino G, Braghetta P, Chrisam M, Bonaldo P, **Matarese G**, Locatelli F, Battistini L, Cecconi F. AMBRA1 Controls Regulatory T-Cell Differentiation and Homeostasis Upstream of the FOXO3-FOXP3 Axis. *Dev Cell.* 2018 Dec 3;47(5):592-607.

8) Pacella I, Procaccini C, Focaccetti C, Miacci S, Timperi E, Faicchia D, Severa M, Rizzo F, Coccia EM, Bonacina F, Mitro N, Norata GD, Rossetti G, Ranzani V, Pagani M, Giorda E, Wei Y, **Matarese G***, Barnaba V*, Piconese S*. Fatty acid metabolism complements glycolysis in the selective regulatory T cell expansion during tumor growth. *Proc Natl Acad Sci USA.* 2018 Jul 10;115(28):E6546-E6555. ***Corresponding authors.**

9) De Rosa V, La Cava A, **Matarese G**. Metabolic pressure and the breach of immunological self-tolerance. *Nat Immunol*. 2017 Oct 18;18(11):1190-1196.

10) Melis D, Carbone F, Minopoli G, La Rocca C, Perna F, De Rosa V, Galgani M, Andria G, Parenti G, **Matarese G**. Cutting Edge: Increased Autoimmunity Risk in Glycogen Storage Disease Type 1b Is Associated with a Reduced Engagement of Glycolysis in T Cells and an Impaired Regulatory T Cell Function. *J Immunol*. 2017 May 15;198(10):3803-3808.

11) Procaccini C, Carbone F, Di Silvestre D, Brambilla F, De Rosa V, Galgani M, Faicchia D, Marone G, Tramontano D, Corona M, Alviggi C, Porcellini A, La Cava A, Mauri P, **Matarese G**. The Proteomic Landscape of Human Ex Vivo Regulatory and Conventional T Cells Reveals Specific Metabolic Requirements. *Immunity*. 2016 Mar 15;44(3):712.

12) De Rosa V, Galgani M, Porcellini A, Colamatteo A, Santopaolo M, Zuchegna C, Romano A, De Simone S, Procaccini C, La Rocca C, Carrieri PB, Maniscalco GT, Salvetti M, Buscarinu MC, Franzese A, Mozzillo E, La Cava A, **Matarese G**. Glycolysis controls the induction of human regulatory T cells by modulating the expression of FOXP3 exon 2 splicing variants. *Nat Immunol*. 2015 Nov;16(11):1174-84.

13) Carbone F, De Rosa V, Carrieri PB, Montella S, Bruzzese D, Porcellini A, Procaccini C, La Cava A, **Matarese G**. Regulatory T cell proliferative potential is impaired in human autoimmune disease. *Nat Med*. 2014 Jan;20(1):69-74.

14) **Matarese G**, Procaccini C, Menale C, Kim JG, Kim JD, Diano S, Diano N, De Rosa V, Dietrich MO, Horvath TL. Hunger-promoting hypothalamic neurons modulate effector and regulatory T-cell responses. *Proc Natl Acad Sci USA*. 2013 Apr 9;110(15):6193-8.

15) Galgani M, Nugnes R, Bruzzese D, Perna F, De Rosa V, Procaccini C, Mozzillo E, Cilio CM, Elding Larsson H, Lernmark A, La Cava A, Franzese A, **Matarese G**. Meta-immunological profiling of children with type 1 diabetes identifies new biomarkers to monitor disease progression. *Diabetes*. 2013 Jul;62(7):2481-91.

16) **Matarese G**, La Rocca C, Moon HS, Huh JY, Brinkoetter MT, Chou S, Perna F, Greco D, Kilim HP, Gao C, Arampatzi K, Wang Z, Mantzoros CS. Selective capacity of metreleptin administration to reconstitute CD4+ T-cell number in females with acquired hypoleptinemia. *Proc Natl Acad Sci USA*. 2013 Feb 26;110(9):E818-27.

17) Procaccini C, De Rosa V, Galgani M, Abanni L, Cali G, Porcellini A, Carbone F, Fontana S, Horvath TL, La Cava A, **Matarese G**. An Oscillatory switch in mTOR kinase activity sets regulatory T cell responsiveness. *Immunity*. 2010 Dec 14;33(6):929-41.

Pioneering articles in the field of Immunometabolism:

1) De Rosa V, Procaccini C, Cali G, Pirozzi G, Fontana S, Zappacosta S, La Cava A, **Matarese G**. A Key Role of Leptin in the Control of Regulatory T Cell Proliferation. *Immunity*. 2007;26:241-255.

2) De Rosa V, Procaccini C, La Cava A, Chieffi P, Nicoletti GF, Fontana F, Zappacosta S, **Matarese G**. Leptin neutralization interferes with pathogenic T cell autoreactivity in autoimmune encephalomyelitis. *J Clin Invest*. 2006; 116: 447-455.

3) Sanna V, Di Giacomo A, La Cava A, Lechler R, Fontana S, Zappacosta S, **Matarese G**. Leptin surge precedes the onset of autoimmune encephalomyelitis and correlates with the development of pathogenic T cell responses. *J Clin Invest*. 2003;111:241-50.

4) Farooqi S, ***Matarese G**, ***Lord GM**, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F, Fontana S, Lechler RI, De Paoli AM, O'Rahilly S. Beneficial effects of leptin on obesity, T cell hyporesponsiveness and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest*. 2002;110:1093-103. ***Equal contribution.**

5) *Lord GM, ***Matarese G**, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature*. 1998;394:897-901. *Equal contribution. ***Equal contribution.**