Basic research at hospitals: the keystone to boost the travel from bench to clinical practice

Dr Diego Clemente

Neuroimmuno-Repair Lab

Research Unit

National Hospital for Paraplegics

Toledo (Spain)

Diego Clemente, Ph.D.

EDUCATION

B.Sc. in Biological Sciences; **Ph.D. in Biology (Neurosciences).** University of Salamanca (Spain)

Extraordinary Ph.D. Award

PREVIOUS POSITIONS

2004-2006.- Postdoc fellow. Cajal Institute-CSIC (Spain; Carmen Guaza)

2006-2015.- Senior postdoc fellow. National Hospital for Paraplegics (Spain; Fernando de Castro)

CURRENT POSITION

2015- .- **Principal Investigator** of the Neuroimmuno-Repair Group. National Hospital for Paraplegics (Spain)

2019- .- Honorary Professor at the Universidad Autónoma de Madrid

2021- .- Member of the Executive Board of the Spanish Society of Neuroscience

RESEARCH SUMMARY

41 papers; H index: 23; 1,804 citations; P.I. 13 MS grants; 2 patents; 4 industrial research agreements

MY EXPERTISE

Innate immune system: valuable tool for the control of NEUROINFLAMMATION and NEURAL REPAIR, and as BIOMARKER for MULTIPLE SCLEROSIS

Neuroimmuno-Repair Group (GNIR)

Diego Clemente, Ph.D. (Principal Investigator)

María Cristina Ortega, Ph.D.

Mari Paz Serrano, Ph.D.

Leticia Calahorra, Ph.D.

Celia Camacho-Toledano, M.Sc.

Isabel Machín-Díaz, B.Sc. (Lab Manager)

Inmaculada Alonso García (Lab technician)

Jennifer García-Arocha (Lab technician)

Young Research Lab. Funded in 2015

Members of the Spanish Network of MS (Coordinator: Dr L.M. Villar)

Leaders on the study of MYELOID-DERIVED SUPPRESSOR CELLS (MDSCs) in MS:

1) immunodulatory agents to control adaptive immune response

2) myelin repair

3) biomarkers of disease progression in HUMANS

One third of the published papers in the field comes from our group.

National Hospital for Paraplegics

Spanish reference hospital fully dedicated to <u>spinal cord injury (SCI) patients</u>

- - Inaugurated in 1974
- - 211 beds
- - Aproximmately 20% of our patients have SCI from an inflammatory origin

<u>GOALS</u>

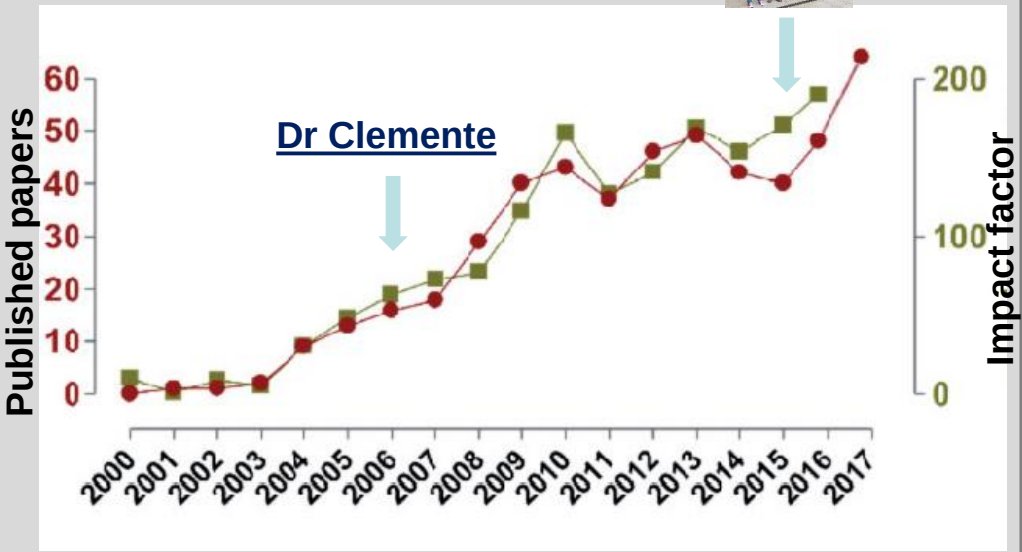
Health improvement and <u>holistic rehabilitation</u>

<u>Neuroscience Research</u> totally focused on the search of efficacious treatments for **neuroinflammation** and **neural repair**

Research Unit of the HNP (UDI-HNP)

Since 2013, we have a new building fully dedicated to **RESEARCH AND INNOVATION**

Research activity organized in the **Research Unit**



GNIR: Research lines

-Myeloid-derived suppressor cells as potentiating agents of myelin repair in MS.

-Analysis of the inflammatory lesion environment in MS.

-Screening for molecular and cellular biomarkers of MS severity.

- New therapeutic targets for neuroprotection in MS.

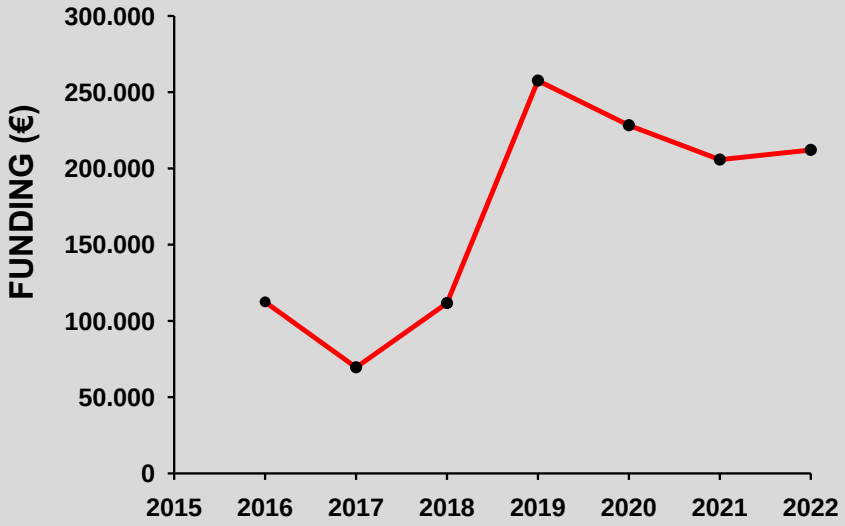
GNIR: Funding

Global funding (Grants): 1,336,187 €

Spanish Ministry of Science and Innovation

Marie Curie Actions-FP7;European Union

Regional Government of Castile-La Manche



Merck Serono EMB

Bristol Myers Squibb

French Foundation for the Research on Multiple Sclerosis

Spanish Society of Multiple Sclerosis (MS patients)

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Instituto de Salud Carlos III
UNIÓN EUROPEA
Fondo Europeo de Desarrollo Regional
"Una manera de hacer Europa"

nEUROinflammation

Castilla-La Mancha

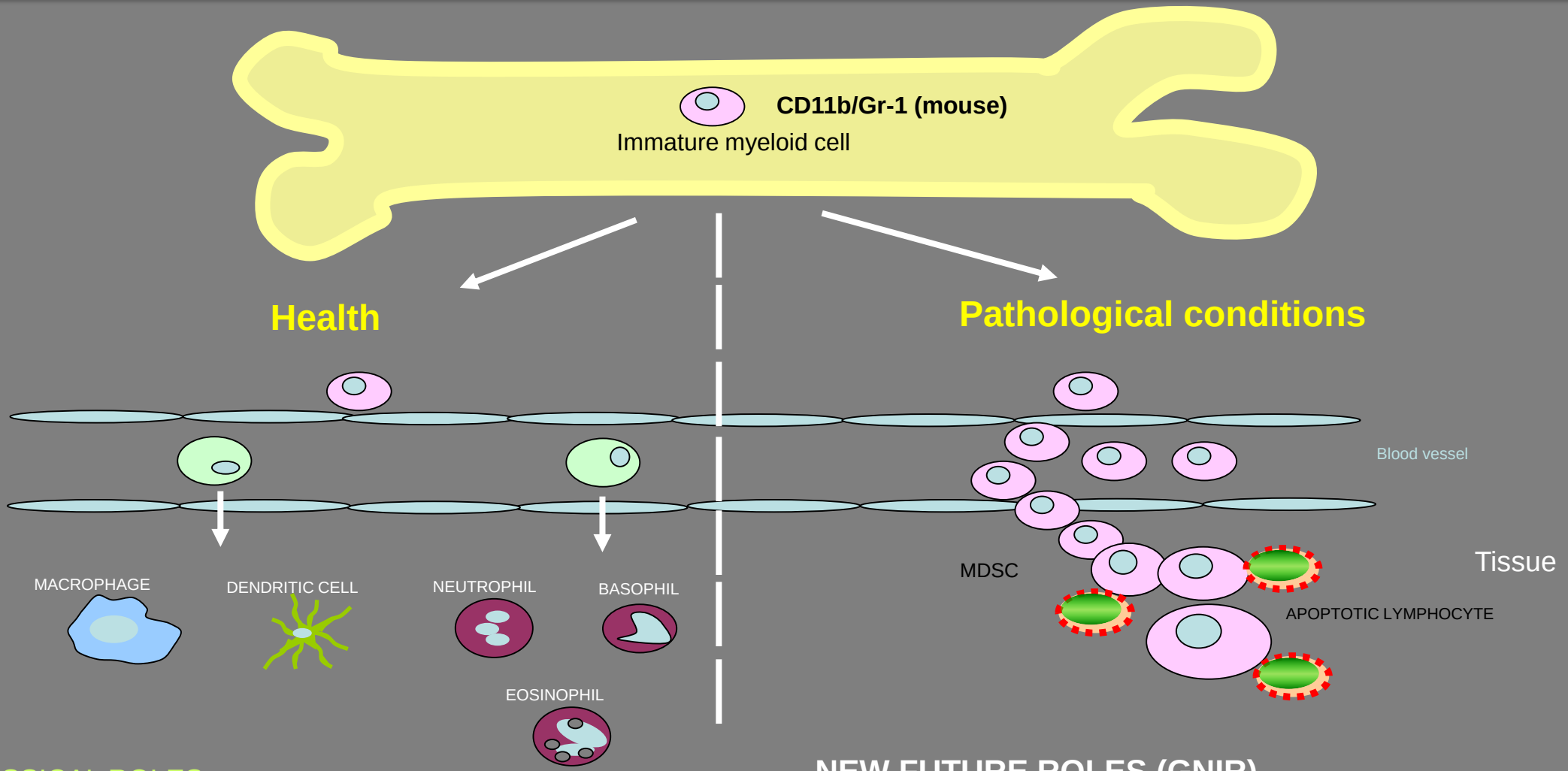
Bristol Myers Squibb

Esclerosis Múltiple España

MERCK

arsep fondation

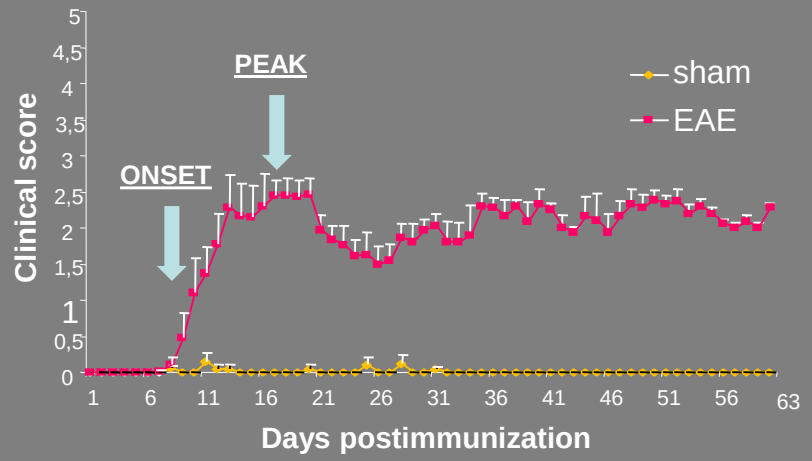
What are MDSCs?

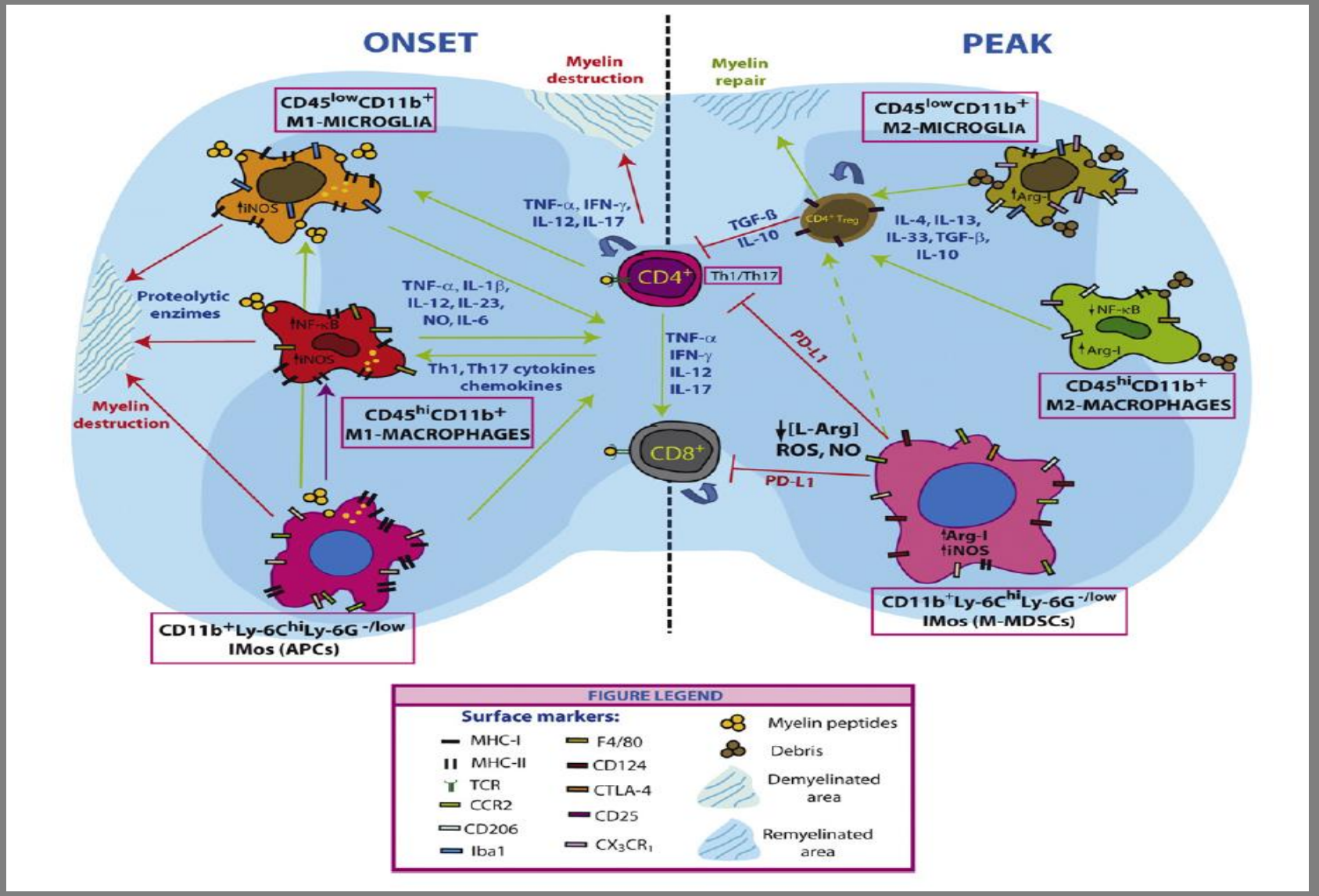


CLASSICAL ROLES
T CELL ANERGY
INDUCTION OF T CELL APOPTOSIS
INDUCTION OF Treg

NEW FUTURE ROLES (GNIR)
TARGETS FOR DMTs
CELL THERAPY
BIOMARKERS OF MS
INDUCTOR OF MYELIN REPAIR

What is the role of MDSCs in MS?





Melero-Jerez et al., 2016; Biochim. Biophys. Acta-Mol Basis Dis. 1862: 368-380

MDSC markers

Disease /Species	EAE/MS (peak)[1]		Glioma[2]		Uveits[3]	SCI[4]	Ageing[5]
	G-MDSCs	M-MDSCs					
MOUSE	**CD11b^{high}** **Gr-1^{+++}** **Ly-6C^{int}** **Ly-6G^{high}** MHC-II^{-} F4/80^{-} **Arg-I^{+}** **iNOS^{-}** CD11c^{-}	**CD11b^{high}** **Gr-1^{+}** **Ly-6C^{high}** **Ly-6G$^{-/low}$** MHC-II$^{-/low}$ CD124^{+} F4/80^{+} **Arg-I^{+}** **iNOS^{+}** CD115^{+} CD11c$^{-/low}$ CD62L^{+} CCR2^{+}	**CD11b^{+}** **Ly-6C^{low}** **Ly-6G^{high}** **Gr-1^{+}** Arg-I^{+} CD124^{+} IL-10^{+} PD-L1^{+}	**CD11b^{+}** **Gr-1^{+}** **Ly6C^{high}** **Ly6G^{-}** iNOS^{+} Arg-1^{+}	CD11b^{+} CD45^{+} Gr-1^{+} Ly-6C^{+} Ly-6G^{-} CCR2^{high} iNOS^{+} Arg-I^{+}	**CD11b^{+}** **Gr-1^{+}** CD115^{+}
HUMAN	**CD15^{+}** **CD33^{+}** **HLA-DR^{low}** CD14^{-} PD-L1^{+}	**CD15^{-}** **CD33^{+}** **HLA-DR$^{-/low}$** **CD14^{+}**	G-MDSCs: CD33^{+} HLA-DR^{-} CD15^{+} CD14^{-} M-MDSCs: CD33^{+} HLA-DR^{-} CD15^{-} CD14^{+}		*Not determined*	**CD11b^{+}** **CD115^{+}** **CD33^{+}** **HLA-DR^{-}**	CD11b^{+} CD14^{low} PD-L1^{high} CD33^{+} LIN^{-} HLA-DR^{-} B7-H1^{high}

1) Ioannou et al., 2012; Moliné-Velázquez et al., 2011; Moliné-Velázquez et al., 2014; Yang et al., 2014; Yi et al., 2012; Zhu et al., 2007; Zhu et al., 2011.

2) Fujita et al., 2011; Gielen et al., 2015; Kohanbash et al., 2013; Raychaudhuri et al., 2015; Zhu et al., 2011.

3) Lee et al., 2015; Rodrigues et al., 2010; Tu et al., 2012.

4) Saiwai et al, 2012.

5) Eniuontina et al., 2011; Hertzenberg et al., 2013; Verschoor et al., 2013.

Graft versus host disease

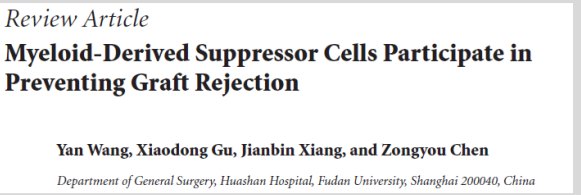
Human Immunology 71 (2010) 1061–1066

Contents lists available at ScienceDirect

Myeloid-derived suppressor cells: Natural regulators for transplant tolerance

Peter Boros [a,*], Jordi C. Ochando [b], Shu-Hsia Chen [b], Jonathan S. Bromberg [a,b]

[a] Recanati/Miller Transplantation Institute, Mount Sinai School of Medicine, New York, New York, USA
[b] Department of Gene and Cell Medicine, Mount Sinai School of Medicine, New York, New York, USA



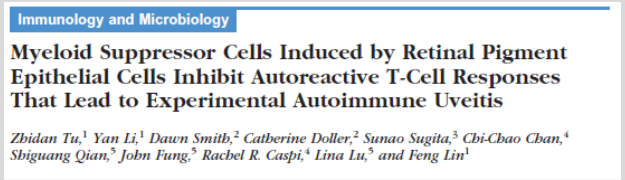
Review Article

Myeloid-Derived Suppressor Cells Participate in Preventing Graft Rejection

Yan Wang, Xiaodong Gu, Jianbin Xiang, and Zongyou Chen

Department of General Surgery, Huashan Hospital, Fudan University, Shanghai 200040, China

Uveitis

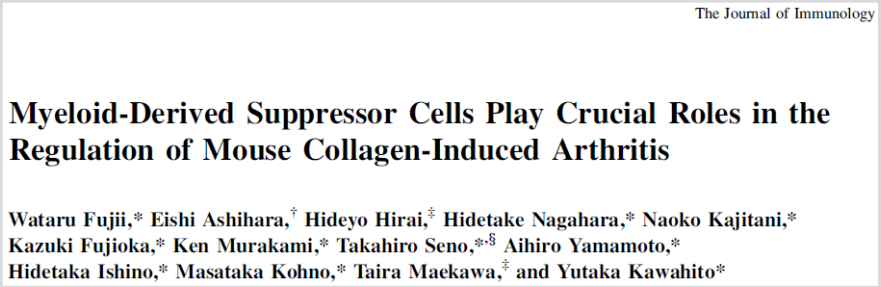


Immunology and Microbiology

Myeloid Suppressor Cells Induced by Retinal Pigment Epithelial Cells Inhibit Autoreactive T-Cell Responses That Lead to Experimental Autoimmune Uveitis

Zhidan Tu,[1] Yan Li,[1] Dawn Smith,[2] Catherine Doller,[2] Sunao Sugita,[3] Chi-Chao Chan,[4] Shiguang Qian,[5] John Fung,[5] Rachel R. Caspi,[4] Lina Lu,[5] and Feng Lin[1]

Arthritis



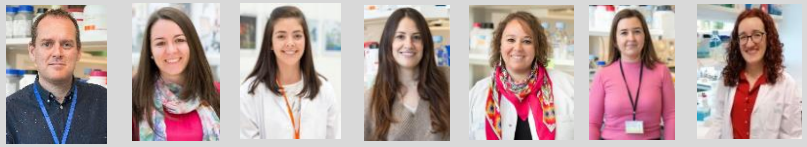
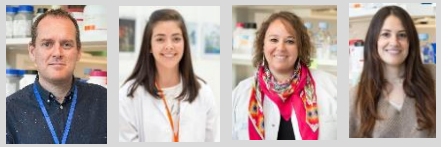
The Journal of Immunology

Myeloid-Derived Suppressor Cells Play Crucial Roles in the Regulation of Mouse Collagen-Induced Arthritis

Wataru Fujii,* Eishi Ashihara,† Hideyo Hirai,‡ Hidetake Nagahara,* Naoko Kajitani,* Kazuki Fujioka,* Ken Murakami,* Takahiro Seno,*[,§] Aihiro Yamamoto,* Hidetaka Ishino,* Masataka Kohno,* Taira Maekawa,‡ and Yutaka Kawahito*

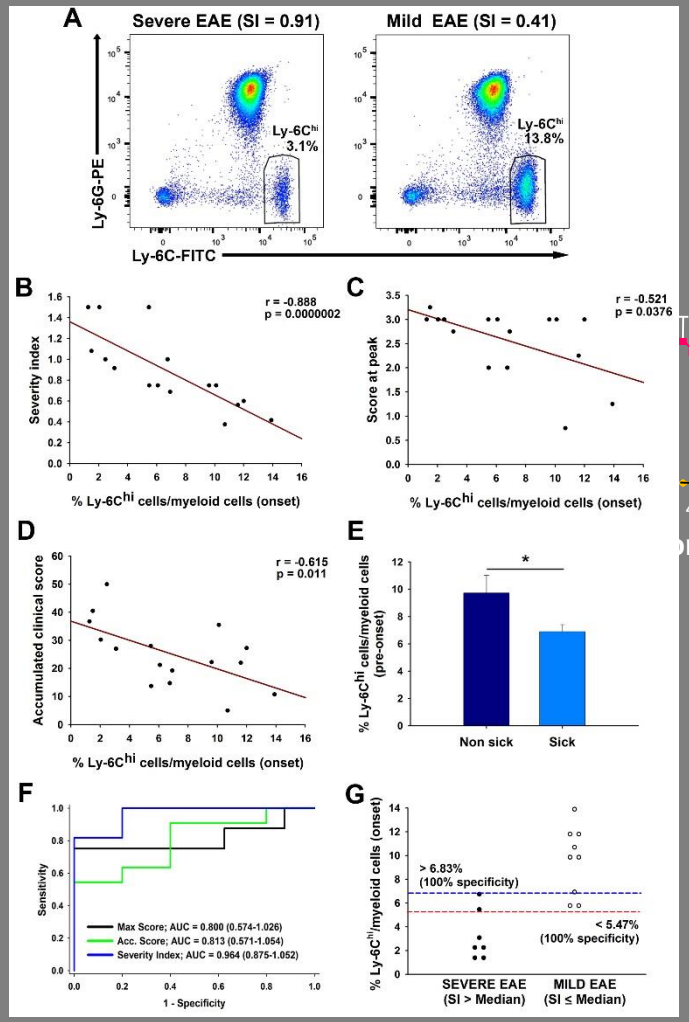
Modified from Melero-Jerez et al., 2016; Biochim. Biophys. Acta-Mol Basis Dis. 1862: 368-380

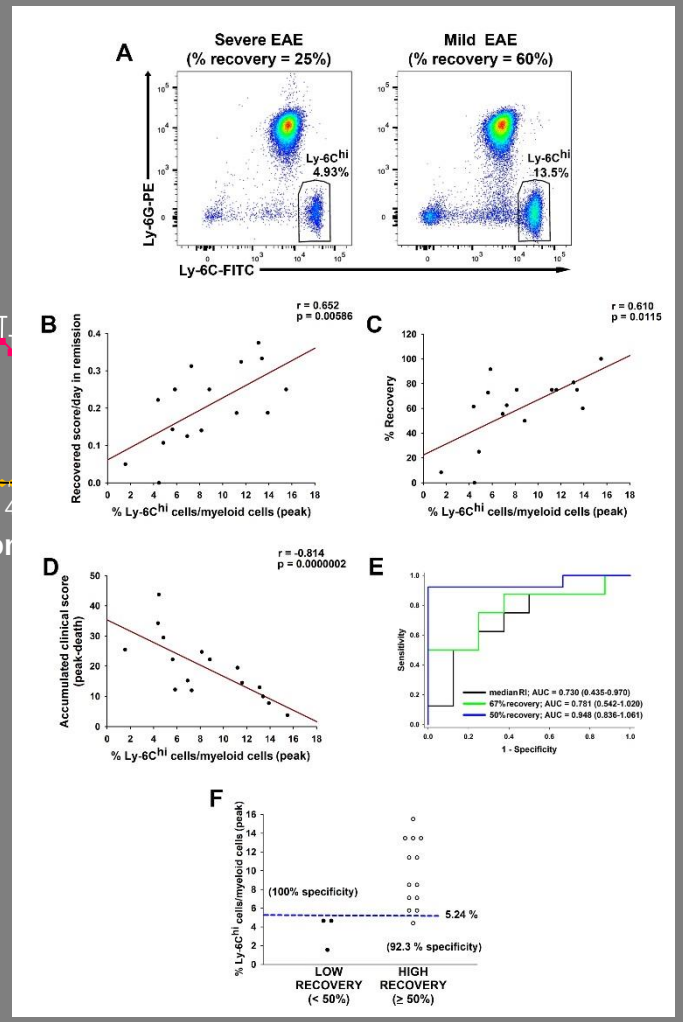
Research lines = Open Clinical Questions

MS is highly heterogeneous		Biomarkers to predict disease severity and regenerative ability
How can I choose the good medication for MS?		Biomarkers to predict the response to treatments
Highly severe MS patients remain reluctant to treatments		Cell-based therapy to avoid disability advance
There is a lack for regenerative treatments		New agents to improve remyelination
New therapeutic targets (progressive MS)		New molecules for the progressive forms of MS

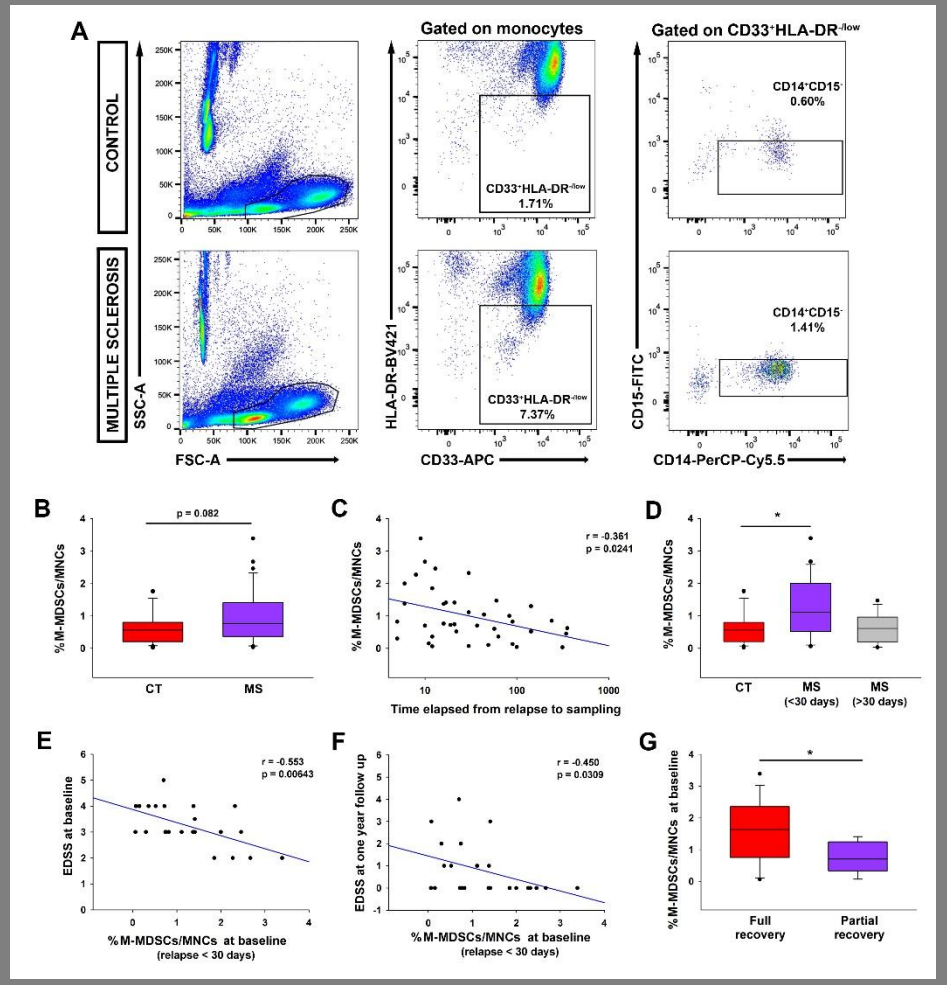
MDSCs as prognostic biomarkers

PRECLINICAL STUDY





CLINICAL STUDY



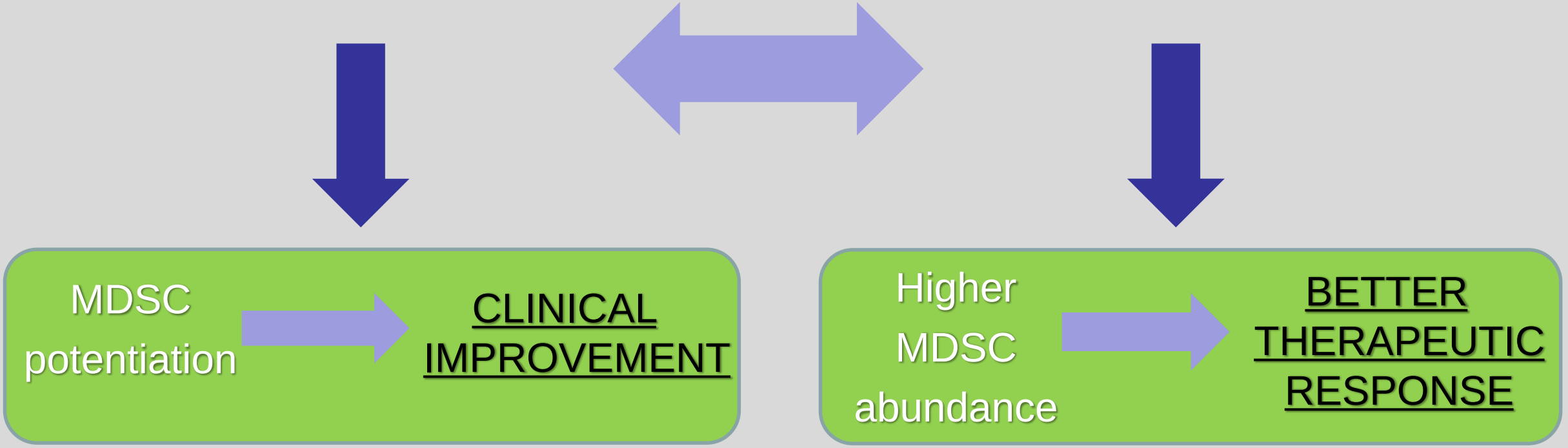
Collaborative work with industry

Collaborative question 1

MDSCs as new targets for DMTs

Collaborative question 2

MDSCs as biomarkers of response to DMTs



Collaboration with industry: research

NOVARTIS

FINGOLIMOD

Material transfer agreement

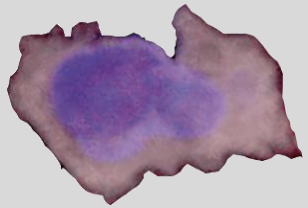
MERCK

EVOBRUTINIB

Collaborative agreement (200 k€)

Collaboration with industry: research

NOVARTIS +  sescam Servicio de Salud de Castilla-La Mancha + MERCK



MDSCs

Control of T and B cell activity

↓

IMMUNE SYSTEM CONTROL

↓

STOP DISEASE PROGRESSION

Promotion of myelin production

↓

NEURO-REGENERATION

Conclusions

Clinical investigators should be more interested on research activity, improving their scientific formation.

Basic researches at hospitals should addapt their scientific questions to the clinical neccesities.

Basic/preclinical research at hospitals could are useful to accelerate the transition to clinical practise.

Hospital and profesional networks are optimal environments for traslational research.

Basic/preclinical research at hospitals can be also attractive to private funding, specially from pharmaceutical companies.

Grupo de Neuroinmuno-Reparación (GNIR)

MIEMBROS DE GNIR

Dr. Diego Clemente López
Dra. Mª. Cristina Ortega Muñoz
Dra. Mª Paz Serrano Regal
Dra. Leticia Calahorra Melero
Isabel Machín Díaz
Celia Camacho Toledano
Jennifer García Arocha
Inmaculada Alonso García

COLABORACIONES

H V Salud

I.P. Molina

HGUGM

J.M.Gª. Domínguez

H La Princesa

V. Meca

H R U Málaga

Ó. Fernández

CEMCAT/ VHIR

M. Comabella

C. Espejo

Biodonostia

D. Otaegui

HNP/SESCAM

M. Nieto-Díaz

J. Rosa

Instituto Cajal/CSIC

C. Guaza

F. de Castro

ICCM/CSIC

C. Serrano

CIC-CSIC

S. Blanco

U. SALAMANCA/INCYL

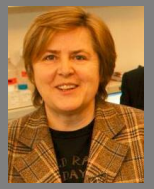
E. Weruaga

D. Díaz

INSERM

F. Docagne

Nencky I.



B. Kaminska

Queen's U. Belfast

D. Fitzgerald

FINANCIACIÓN

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AELEM

ADEM-TO · Asociación de Esclerosis Múltiple de Toledo

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