JIPMER SCIENTIFIC SOCIETY

Reg. no. 474 of 2017 (Reg. Act no. XXI of 1860),
Registrar of Companies, Puducherry, INDIA
Jawaharlal Institute of Postgraduate Medical Education & Research,
Puducherry, India

Dear all,

The second JSS monthly scientific meeting for the year 2019-20 will be held on **22.08.2019 (Thursday)** at **3:15 PM** in SSB Conference Hall, 3rd floor, SSB.
Following is the programme schedule.

Invited talk (3:15 to 3.40 pm) (20+5 minutes)

"Using Health economics to guide Healthcare decisions"

Dr Rakesh Aggarwal
Director, JIPMER

Guest lecture (3.40 to 4.05 pm) (20+5 minutes)

"miRNA control of neuroinflammation in multiple sclerosis"

Dr Murugaiyan Gopal
Assistant Professor of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Paper presentations

Short papers/ Case reports: (4.05 to 4.23 pm) 2 X (7+2minutes)

"An Unusual Presentation of Upper Gastrointestinal Bleeding"
Sakthivel C K, Ashok Kumar sahoo, Gaurav Sharma, Loganathan J, Vijayakumar C, Sudharsanan S, Bhawana Ashok Badhe, Vishnu Prasad N R
Department of General Surgery

"Posterior urethral valve with prostatic utricle cyst and urethra-ejaculatory duct reflux – a case report"
Ravindar Kashyap, Subathra Adithan, S Kumaravel
Departments of Radiodiagnosis and Paediatric Surgery

Regards,
Dr. Subathra Adithan,
Secretary, JSS

BIOGRAPHICAL SKETCH/CURRICULUM VITAE

NAME: Murugaiyan Gopal

POSITION TITLE/ADDRESS: Assistant Professor of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bharathidasan University, Trichy, India	B.Sc.	05/1999	Chemistry&Microbiology
Annamalai University, Chidambaram, India	M.Sc.	05/2001	Biochemistry
National Centre for Cell Science, Pune Univ, India	Ph.D.	05/2007	Biotechnology
Brigham and Women's Hospital and Harvard Medical School, Boston, USA	Post-doc	03/2010	Autoimmunity

A. Personal Statement

My passions for science and health led me to pursue my doctoral degree in basic science and to perform translational disease-focused research. As a postdoctoral fellow at Harvard Medical School, I studied how dendritic cells regulate inflammatory and regulatory T cells in MS and EAE. However, now that we and others have published much about the specific transcription factors and cytokines regulating inflammatory and regulatory T cells, I have expanded my research to include the role of microRNAs (miRNAs) in modulating inflammatory and regulatory T cell subsets. My current research focuses on how miRNAs modulate innate and adaptive immunity in MS, with the goal of discovering potential new therapeutic targets. As a part of these studies, we have identified the role of miR-155 and miR-21 in inflammatory Th1 and Th17 cell differentiation and function in MS and its animal model, EAE. Additionally, we have shown silencing miR-155 and miR-21 with specific inhibitors can have therapeutic benefit in EAE.

B. Positions and Honors

Positions

2006- 2011 Research Fellow, Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham Women's Hospital,
2006-2011 Research Fellow in Neurology, Harvard Medical School, Boston, MA.
2011-2015 Instructor in Neurology, Ann Romney Center for Neurologic Diseases, Harvard Medical School, Boston, MA.
2011-2015 Assistant Scientist, Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham Women's Hospital, Harvard Medical School, Boston, MA.
2015- Assistant Professor in Neurology, Ann Romney Center for Neurologic Diseases, Harvard Medical School, Boston, MA.
2015- Associate Scientist, Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham Women's Hospital, Harvard Medical School, Boston, MA.

Honors

2002-2005 Junior Research Fellowship Award, Department of Biotechnology, Government of India. New Delhi, India.
2005-2006 Senior Scholarship Award, Lady Tata Memorial Trust (LTMT), Mumbai, India.
2009-2012 Postdoctoral Fellowship Award, National Multiple Sclerosis Society, New York, USA.
2011-2013 Junior Faculty Award, Nancy Davis Foundation for MS, USA.
2019-2020 Careers in Immunology Fellowship Award, American Association of Immunologists (AAI), USA.

Other Experience and Memberships

2009- Member, International Society for Dendritic cell and Vaccine Science
2012- Member, American Association of Immunologists (AAI)

2013- Member, International Society for Interferon and Cytokine Research
2013- Editorial Board Member, Frontiers in Physiology
2017- Ad-hoc member, CNBT study section, NIH
2018- Ad-hoc member, BDCN study section, NIH
2018- Full-Member, Cancer Immunology Program, Dana-Farber/Harvard Cancer Center
2018- Faculty member, Harvard Medical School (HMS) Immunology Program
2019- Full-Member, Harvard Initiative for RNA Medicine

C. Contributions to Science

My previous work has identified a major role for dendritic cell (DC)-expressed co-stimulatory molecule CD40 in the regulation of immune response to tumors. My recent major contributions have been towards the identification of cytokine pathways in DCs that control newly identified inflammatory Th17, Th9, and regulatory Tr1 cells both in humans and mice. Most recently, I have also discovered specific microRNA pathways that control inflammatory Th1 and Th17 cell development and demonstrated that targeting specific microRNAs can have therapeutic benefit against Th1 and Th17 cell-mediated autoimmunity.

1. Role of CD40 in the regulation of immune response to tumors

The CD40-CD40L interaction is crucial for IL-12-dependent, IFN-γ- and cytotoxic T cell (CTL)-mediated immunity against cancer. Due to these features, agonistic CD40 antibody has been used as a systemic cancer therapeutic agent; however, these CD40-induced immune responses have achieved only partial success. We demonstrated that this failure is due to a functional dichotomy of CD40 whereby it self-limits its anti-tumor functions by inducing the pro-tumor cytokine IL-10 from DCs (**a**). DC-mediated priming of $CD8^+$ T cells in the presence of IL-10 rendered them functionally tolerant. Infusion of antigen-pulsed IL-10-deficient, but not wild-type, DCs back into syngenic mice results in successful therapeutic vaccination against tumors. In addition, we demonstrated that the CD40-induced T cell response is a function of its expression levels (**b**). Furthermore, we found that during the tumor progression, CD40 expression is reduced on DCs and that the T cells primed in the presence of lower CD40 signaling led to IL-10-mediated suppression of tumor regressing CTLs that were less effective at fighting off cancer cells (**c**). A number of anti-CD40 antibodies with diverse biological functions are under clinical development for treatment of cancer as a result of these findings. Most recently, we have shown that anti-LAP antibody, which targets the LAP/TGF-β complex on innate and adaptive immune cells, enhances anti-tumor immune responses and reduces tumor growth in models of melanoma, glioblastoma and colorectal carcinoma (**d**). As a result of this finding, an anti-LAP antibody is under clinical development for treatment of cancer.

a. **Murugaiyan G**, Agrawal R, Mishra GC, Mitra D, Saha B. (2006). Functional dichotomy in CD40 reciprocally regulates effector T cell functions. **J Immunol**, 177, 6642-6649. Not Federally Funded
b. **Murugaiyan G**, Agrawal R, Mishra GC, Mitra D, Saha B. (2007). Differential CD40/CD40L expression results in counteracting antitumor immune responses. **J Immunol**, 178, 2047-2055. Not Federally Funded
c. **Murugaiyan G**, Martin S, Saha B. (2007). Levels of CD40 expression on dendritic cells dictate tumour growth or regression. **Clin. Exp. Immunol**, 149,194-202. Not Federally Funded
d. Gabriely G, da Cunha AP, Rezende RM, Kenyon B, Madi A, Vandeventer T, Skillin N, Rubino S, Garo L, Mazzola M, Kolypetri P, Lanser A, Moreira T, Faria AM, Lassmann H, Kuchroo V, **Murugaiyan G** and Weiner HL (2017). Targeting latency-associated peptide promotes anti-tumor immunity. **Science Immunology**, May 19;(2)11, pii: eaaj1738. Free full text

2. Dendritic cell control of inflammatory and regulatory T cells in EAE and MS.

Osteopontin (OPN) is a proinflammatory cytokine that has been shown to play an important role in MS and its animal model EAE. We have shown that OPN expression is elevated in DCs during the course of autoimmune inflammation (both in EAE and MS) and that DC-expressed OPN induces Th17 cells while inhibiting IL-10-producing Tr1 cells in both humans and mice (**a**). Contrary to the function of OPN, IL-27 is another DC-derived cytokine known to have anti-inflammatory functions. We have shown that IL-27 induces IL-10-producing Tr1 cells while inhibiting Th17 differentiation in humans (**b**). Furthermore, we have identified the regulatory mechanisms in DCs that control these two (Th17 and Tr1) cell types. We found that IFN-γ induces IL- 27 while inhibiting OPN from DCs, and that engagement of DC IFN-γR leads to suppression of Th17 cells while inducing IL-10 from T cells (**c**). Recently, we also found that IFN-γ limits Th9-mediated autoimmune inflammation through DC modulation of IL-27 (**d**). Together, our results identify a previously unknown mechanism by which IFN-γ limits Th17/Th9-mediated autoimmune inflammation through DC modulation of OPN and IL-27. Following these publications, several others have documented the pathogenic

role of OPN-IL-17 axis and/or protective role of IL-27 in other inflammatory disorders, including cancer.

a. **Murugaiyan G**, Mittal A, Weiner HL. (2008). Increased osteopontin expression in dendritic cells amplifies IL-17 production by CD4+ T cells in experimental autoimmune encephalomyelitis and in multiple sclerosis. **J Immunol**, 181, 7480-8. PMCID: PMC2653058
b. **Murugaiyan G**, Mittal A, Lopez-Diego R, Anderson DE, Weiner HL. (2009). IL-27 is a key regulator of IL-10 and IL- 17 production from human $CD4^+$ T cells. **J Immunol***,*183, 2435-2443. PMCID: PMC2904948
c. **Murugaiyan G**, Mittal A, Weiner HL. (2010). Identification of an IL-27/osteopontin axis in dendritic cells and its modulation by IFN-γ limits IL-17 mediated autoimmune inflammation. **Proc Natl Acad Sci U S A**, 107, 11495-500. PMCID: PMC2895126
d. **Murugaiyan G**, Beynon V, Pires Da Cunha A, Joller N and Weiner HL. (2012). IFN-γ limits Th9 mediated autoimmune inflammation through dendritic cell modulation of IL-27. **J. Immunol**, 189, 5277-83. PMCID: PMC3504131

3. MicroRNA control of Inflammatory T cells in EAE.

IFN-γ-producing Th1 and IL-17-producing Th17 cells are the key participants in various autoimmune diseases, including MS. Although both of these T cell subsets are known to be regulated by specific transcription factors and cytokines, the role of microRNAs that control these two inflammatory T subsets and whether targeting microRNAs can have therapeutic effects is not yet well explored. We have found that microRNA-155 (miR-155) expression is elevated in $CD4^+$ T cells during EAE, and that miR-$155^{-/-}$ mice have a delayed course and reduced severity of disease, accompanied by decreased inflammation and Th1/Th17 responses in the CNS. Together, these findings identify miR-155 as a potential therapeutic target in MS (**a, d**). More recently, we have used a mouse model with a deletion of microRNA-21 (miR-21) and found that of miR-21 deficiency specifically impairs inflammatory Th17 cell differentiation without affecting differentiation of other T cells subsets. Specifically, we found that miR-$21^{-/-}$ mice have a defect in Th17 differentiation and are resistant to EAE. MiR-21 promotes Th17 differentiation by targeting Smad-7, a negative regulator of TGF-β signaling (**b, c**). Together, these publications document a key role of miR-155 and miR-21 in Th1 and Th17 differentiation and function (**d**).

a. **Murugaiyan G**, Beynon V, Mittal A, Joller N and Weiner HL. (2011). Silencing microRNA-155 ameliorates experimental autoimmune encephalomyelitis. **J. Immunol**, 187, 2213-21. PMCID: PMC3167080
b. **Murugaiyan G***, Pires Da Cunha A, Ajay AK, Joller N, Garo L, Kumaradevan S, Yosef N, Vaidya V, Weiner HL. (2015) MicroRNA-21 promotes Th17 differentiation and mediates experimental autoimmune encephalomyelitis. **J Clin Invest**, 25, 1069-1080. ***Corresponding author.**
c. Garo LP and **Murugaiyan G*** (2016) Use of miRNA antagonists in the alleviation of inflammatory disorders. **Methods Mol Biol**. 1390: 413-425. ***Corresponding author.**
d. Garo LP and **Murugaiyan G*** (2016) Contribution of microRNAs to autoimmune diseases (2016) **Cell Mol Life Sci**. 73: 2041-51. ***Corresponding author.**

4. Mucosal immunology and intestinal inflammation

Oral/mucosal tolerance is an active immunologic process mediated by multiple mechanisms: regulatory T cells (Tregs), anergy, and deletion. We found that oral administration of endogenous aryl hydrocarbon receptor (AHR) ligand ITE promotes the induction of active immunologic tolerance by its direct effects on dendritic and T cells (**a**). Recently, we also have observed that AHR activation via a non-toxic endogenous AHR ligand, ITE, is protective against T-cell driven colitis in humanized mice (**b**). In addition, Th9 cells have been shown to play a key role in intestinal inflammation. However, the regulatory mechanisms that control Th9 cells are not understood well. Recently, we have described the molecular mechanisms by which IL-27 controls Th9 cell differentiation (**c**). Most recently, using DC- and T cell-specific Smad7 knockout mice, we found Smad7 mediates intestinal inflammation by limiting the PDL1/2-PD1 pathway (**d**).

a. Quintana F, **Murugaiyan G**, Farez M, Mitsdoerffer M, Tukpah AM, Burns E, Weiner HL. (2010). The endogenous AHR ligand ITE acts directly on dendritic cells and T cells to suppress experimental autoimmune encephalomyelitis. **Proc Natl Acad Sci U S A**, 107, 20768-20773. PMCID: PMC2996442.
b. GoettelJA, GandhiR, Kenison JE, Yeste A, **Murugaiyan G**, Sambanthamoorthy S, Griffith AE, Patel B, Shouval DS, Weiner HL, Snapper SB, Quintana FJ (2016). AHR activation is protective against colitis driven by T cells in humanized mice. **Cell Reports**, 17, 1318-1329. PMCID: PMC5106873

c. Garo L, Beynon V, **Murugaiyan G***. (**2017**) Flow cytometry assessment of STAT molecules in Th9 cells. **Methods Mol Biol**, 1585; 127-140.

d. Garo LP, Ajay AK, Fujiwara M, Beynon V, Kuhn C, Gabriely G, Sadhukan S, Raheja R, Rubino S, Weiner HL and **Murugaiyan G** (2019). Smad7 controls immunoregulatory PDL2/1-PD1 signaling in intestinal inflammation and autoimmunity. **Cell Reports**. In Press.

5. Role of DCs and microRNAs in MS and other neurodegenerative disorders.

I have successfully collaborated with other researchers in our Center to study the role of T cells, DCs and microRNAs in EAE, MS (**a,d**), and ALS (**b, c**), producing peer-reviewed publications from each project.

a. Quintana F, **Murugaiyan G**, Farez M, Mitsdoerffer M, Tukpah AM, Burns E, Weiner HL. (2010). The endogenous AHR ligand ITE acts directly on dendritic cells and T cells to suppress experimental autoimmune encephalomyelitis. **Proc Natl Acad Sci U S A**, 107, 20768-20773. PMCID: PMC2996442

b. Butovsky O, Siddiqui S, Gabriely G, Lanser A, Dake B, **Murugaiyan G**, DoykaN C, Wu P, Reddy G, Berry J, Krichevsky A, CudkowiczM and Weiner HL. (2012). Modulation of inflammatory monocytes with a unique microRNA-gene signature ameliorates ALS in a mouse model. **J Clin Invest**, 122, 3063-3087. PMCID: PMC3428086

c. Butovsky O, Jedrychowski MP, Cialic R, Krasemann S, **Murugaiyan G**, Fanek Z, Greco DJ, Wu PM, Doykan CE, Kiner O, Lawson RJ, Frosch MP, Pochet N, Fatimy RE, Krichevsky AM, Gygi SP, Lassmann H, Berry J, Cudkowicz ME, Weiner HL. (2014). Targeting miR-155 restores abnormal microglia and attenuates disease in SOD1 mice. **Ann Neurol**, 77, 75-99. PMCID: PMC4432483

d. Farez MF, Mascanfroni ID, Méndez-Huergo SP, Yeste A, **Murugaiyan G**, Garo LP, Balbuena Aguirre ME, Patel B, Ysrraelit MC, Zhu C, Kuchroo VK, Gabriel A. Rabinovich, Quintana FJ, Correale J. (2015). Melatonin contributes to the seasonality of multiple sclerosis relapses. **Cell**. 162:1338-1352. PMCID: PMC4570563

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Murugaiyan+g

D. Research Support

Ongoing Research Support

1R01AI127853 (Gopal, PI)
NIH 2/01/17 – 01/31/22
MicroRNA control of inflammatory and regulatory T cells in central nervous system autoimmunity.
The goal of this project is to investigate the role of miR-21 in the regulation of inflammatory and regulatory T cells in CNS autoimmunity.
Role: PI

Completed Research Support

Pilot Grant Award (Gopal, PI)
Brigham and Women's Hospital 03/01/18 – 02/28/19
Contribution of microRNAs to gender differences in susceptibility to MS
The goal is to investigate the contribution of microRNAs in gender differences in MS susceptibility

RG 5074-05164 (Gopal, PI)
National Multiple Sclerosis Society 4/01/16 – 03/31/19
MicroRNA control of inflammatory and regulatory T cells in central nervous system autoimmunity.
The goal of this project is to investigate the role of microRNAs (miR-21) in inflammatory T cells in EAE and MS.
Role: PI

PP-1603-08130 (Gopal, PI)
National Multiple Sclerosis Society 8/01/16 – 07/31/17
MicroRNA Control of myeloid cell functions in EAE
The goal of this project is to investigate the role of miR-146a in the regulation of myeloid cell functions in EAE.
Role: PI

RG 4904A2/1 (Gopal, PI)
National Multiple Sclerosis Society 10/01/13 – 09/30/16
Control of Inflammatory and regulatory T cells in MS
The goal of this project is to investigate the molecular mechanisms by which regulates inflammatory Th1/Th17 and regulatory T cells in patients with MS and how they are affected by treatment.

Role: PI

Pilot Research Grant (Gopal, PI)
Harvard NeuroDiscovery Center 04/01/15 – 03/30/16
MicroRNA Control of Inflammatory Th17 cells in MS
The goal of this project is to investigate the role of microRNA-21 in the regulation of Th17 cells in MS.