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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		The influence of the microbiome on outcomes of bone marrow transplantation
Name		Dr Kate Markey
Award Received		2018 RACP Research Establishment Fellowship
Report Date		15 January 2020
Chief Investigator / Supervisor		Dr Marcel van den Brink
Administering Institution		Memorial Sloan Kettering Cancer Center
Funding Period	Start Date:	1 January 2018
	Finish Date:	31 December 2018

PROJECT SUMMARY

Allogeneic bone marrow transplantation is employed as curative therapy for blood cancers. Unfortunately, transplant-related complications are common, and mainly take the form of severe infections and a problem known as 'graft-versus-host' disease, where the new donor immune system attacks the patients' body- most commonly the gut, skin, and liver.

This project examines the relationship of the bacteria living inside the gut (the microbiome) with transplant outcomes.

PROJECT AIMS / OBJECTIVES

The aims of the proposed research program were as follows:

1. Compare 16S-based sequencing of paired blood and stool samples from post-transplant patients with and without a) severe infectious complications, b) GVHD and c) relapsed disease in order to identify immunomodulatory elements of the microbiome that translocate into the systemic circulation. These samples have already been collected, sub- cohorts can be created from the large existing biobank.

I have completed a study in collaboration with Kari us (a biotech company) comparing blood and stool samples in a small group of patients (n = 20) and healthy controls (n = 100). We are working on a validation cohort for these findings (n = 100 further patients) and we plan to submit the manuscript to Nature Medicine when the validation samples are complete.

2. Perform the same comparisons using specific samples collected at the time of onset of suspected sepsis. Samples will be prospectively collected specifically for this study in New York,

and are already being prospectively collected in Brisbane (Royal Brisbane Hospital and QIMR Berghofer). This will facilitate a multi-centre collaborative project across the two institutes.

This work is ongoing, and will form part of a further paper.

3. Assess the role of specific microbial metabolites (acetate and butyrate) in GVHD, leukemia relapse, and responses to infection using well established mouse models, and new tools (e.g. mice deficient in the GPR43, a short-chain fatty acid receptor required for acetate and butyrate signaling).

I have pursued a clinical project examining the relationship between the GI microbiome and chronic graft-versus-host disease. This paper is currently in the final revision stage at Blood. The key finding of this paper is that the short chain fatty acids butyrate and propionate circulate (in blood) at higher levels in patients who do not develop cGVHD. This suggests that these metabolites may have an immunomodulatory protective role and I am now pursuing a follow up project further examining these findings in the mouse models.

4. In parallel to targeted examination of these lead candidate immunomodulators, I will use unbiased metabolomics and lipidomics approaches with the unique bank of clinical samples to identify novel microbiome-derived systemic immunomodulators, and then examine the mechanisms underlying their role inpatients using mouse models.

As noted above regarding aim 3, I have a very promising series of clinical results relating to chronic GVHD and circulating short chain fatty acids. To attain this data, I have run in the order of 200 patient samples (from 3 transplant centers) on untargeted metabolomics platform, yielding an enormous dataset that is now available for hypothesis generation re: controllers of the late complications of transplantation.

SIGNIFICANCE AND OUTCOMES

This research project has the capacity to uncover new pathways for immunomodulation after BMT and translate these into therapies that will directly improve patient outcomes for thousands of patients each year who undergo allogeneic bone marrow transplantation. The findings are likely to have much broader relevance, in the setting of immunocompromised patients, but also those suffering from autoimmune conditions where the microbiome has clearly been implicated.

I am continuing my project work in this field as a physician-scientist and junior faculty member at Memorial Sloan Kettering Cancer Center.

PUBLICATIONS / PRESENTATIONS

1. Oral presentation at the ASH meeting 2018.
2. Poster presentations at: ASBMT 2018, the Cold Spring Harbor Microbiome meeting 2019, ASH 2019
3. Markey et al, Manuscript currently in revision at Blood.
4. Blair, ... Markey (senior author), Manuscript currently in preparation for submission to Nature Medicine.

In addition to these outputs specific to my project, I have published the following papers during the period since the award was granted:

5. Peled JU, Gomes LC, Devlin SM, Littmann ER, Taur Y, Sung AD, Weber D, Hashimoto D, Slingerland AE, Slingerland JB, Maloy M, Clurman AG, Stein-Thoeringer CK, Markey KA. Docampo MD, Burgos da Silva M, Khan N, Gessner A, Messina JA, Romero K, Lew M, Bush A, Bohannon L, Brereton DG, Fontana E, Amoretti LA, Wright RJ, Armijo GK, Shono Y,

Sanchez-Escamilla M, Castillo Flores N, Tomas A, Lin RJ, Yanez San Segundo L, Shah GL, Cho C, Scordo M, Politikos I, Hayasaka, Yuta Hasegawa K, Gyurkocza B, Ponce DM, Barker JN, Perales M-A, Giralt SA, Jenq RR, Teshima T, Chao NJ, Holler E, Xavier JB, Pamer EG, van den Brink, MRM. Microbiota as a Predictor of Mortality in Allogeneic HCT. New England Journal of Medicine. Accepted 1/10/20.

6. Stein-Thoeringer CK, Nichols KB, Lazrak A, Docampo MD, Slingerland AE, Slingerland JB, Clurman AG, Armijo G, Gomes ALC, Shono Y, Staffas A, Burgos da Silva M, Devlin SM, Markey KA, Bajic D, Pinedo R, Tsakmaklis A, Littmann ER, Pastore A, Taur Y, Monette S, Arcila ME, Pickard AJ, Maloy M, Wright RJ, Amoretti LA, Fontana E, Pham D, Jamal MA, Weber D, Sung AD, Hashimoto D, Scheid C, Xavier JB, Messina JA, Romero K, Lew M, Bush A, Bohannon L, Hayasaka K, Hasegawa Y, Vehreschild MJGT, Cross JR, Ponce DM, Perales MA, Giralt SA, Jenq RR, Teshima T, Holler E, Chao NJ, Pamer EG, Peled JU, van den Brink MRM. Lactose drives Enterococcus expansion to promote graft-versus-host disease. Science. 2019 Nov 29;366(6469):1143-1149.

Other work from my previous projects in Brisbane that has been published since the fellowship was awarded are as follows:

7. Mohamed A, Collins J, Jiang H, Molendijk J, Stoll T, Torta F, Wenk MR, Bird RJ, Marlton P, Mollee P, Markey KA,* Hill MM. Concurrent lipidomics and proteomics on malignant plasma cells from multiple myeloma patients: Probing the lipid metabolome. PloSOne. 2020 Jan 8;15(1):e0227455. *Shared senior author
8. Vuckovic 5, Minnie SA, Smith D, Gartlan KH, Watkins TS, Markey KA, Mukhopadhyay P, Guillerey C, Kuns RD, Locke KR, Pritchard AL, Johansson PA, Varelias A, Zhang P, Huntington ND, Waddell N, Chesi M, Miles JJ, Smyth MJ, Hill GR. Stem cell transplantation generates T celldependent myeloma immune equilibrium. Journal of Clinical Investigation. Nov 19. pii: 98888.
9. Minnie SA, Kuns RD, Gartlan KH, Zhang P, Wilkinson AN, Samson L, Guillerey C, Engwerda C, MacDonald KPA, Smyth MJ, Markey KA. Vuckovic 5, Hill GR. Myeloma-escape after stem cell transplantation is a consequence of T cell exhaustion and is prevented by TIGIT inhibition. Blood. 2018 Oct 18;132(16):1675-1688.
10. Catchpoole EM, Thirunavukarasu CE, Varelias A, Schlebusch S, Olver S, Zomerdijk N, Osland E, Kennedy GA, Tey SK, Hill GR, Markey KA. Early Blood Stream Infection after BMT is Associated with Cytokine Dysregulation and Poor Overall Survival. Biol Blood Marrow Transplant. 2018 Mar 5. pii: S1083-8791(18)30111-3.
11. Markey KA. Gartlan KH, Kuns RD, Lane SW, Hill GR. Conventional dendritic cells are required for the cross-presentation of leukemia specific antigen in a model of AML relapse post-BMT. Bone Marrow Transplantation. 2018 Jun;53(6):800-803.
12. Liang F, Browne DJ, Gray MJ, Gartlan KH, Smith DD, Barnard RT, Hill GR, Corrie SR, Markey KA. Development of a multiplexed microsphere PCR for rapid, culture-free detection and Gram-typing of bacteria in human blood samples. ACS Infectious Diseases. 2018 May 11;4(5):837-844.
13. Markey KA, Kuns RD, Browne DJ, Gartlan KH, Robb JR, Martins JP, Henden AS, Minnie SA, Cheong M, Koyama M, Smyth MJ, Steptoe RJ, Belz GT, Brocker T, Degli-Esposti MA, Lane SW, Hill GR. Flt-3L expansion of recipient cosa.+ dendritic cells deletes alloreactive donor T cells and represents an alternative to post- transplant cyclophosphamide for the prevention of GVHD. Clinical Cancer Research. 2018 Apr 1;24(7):1604-1616.

As a res1,1lt of my move to MSKCC, I have been a contributing author to a number of other publications arising from the van den Brink laboratory,

the two most prominent are below:

I have written a first-author review paper for Cell Host and Microbe that is currently:in the final stages of revision and slated for publication in their February 2020 issue (Markey, van den Brink, Peled, *Therapeutics targeting the gut microbiome: rigorous pipelines for drug development*, Cell Host and Microbe 2020).

ACKNOWLEDGEMENTS

- Oral presentation at the ASH meeting 2018.
- Poster presentations at: ASBMT 2018, the Cold Spring Harbor Microbiome meeting 2019, ASH 2019
- Markey et al, Manuscript currently in revision at Blood.
- Blair, ... Markey (senior author), Manuscript currently in preparation for submission to Nature Medicine.