Continuation/Research Progression Projects Form (7)

Required for projects that are a continuation/progression in the same field of study as a previous project.

This form must be accompanied by the previous year's abstract and Research Plan/Project Summary.

Student's Name(s) Daniel Khaykin

To be completed by Student Researcher: List all components of the current project that make it new and different from previous research. The information must be on the form; use an additional form for previous year and earlier projects.

Components	Current Research Project	Previous Research Project: Year: 2018
1. Title	SETD8 and P53 Correlations in Multiple Myeloma	Bone Marrow Morphologic, MyPRS, and Mutation Correlations in Multiple Myeloma
2. Change in goal/ purpose/objective	The goal of this study is to see the effects SETD8 and P53 on the progression of myeloma tumors.	The goal of this study was to see what type of mutation correlations as well as genetic were associated with high risk myeloma.
3. Changes in methodology	I applied SETD8 and P53 to smear samples of myeloma and then recorded the effects, rather then look through myeloma data and form correlations.	I looked through databases of de-identified myeloma data and recorded any possible correlations. I then conducted chi square tests and statistical analysis to ensure significance of such correlations.
4. Variable studied	Tumor progression	Genetic expression, mutations
5. Additional changes		

Attached are:

☑ Abstract and Research Plan/Project Summary, Year 2018

I hereby certify that the above information is correct and that the current year Abstract & Certification and project display board properly reflect work done only in the current year.

Daniel Khaykin	Daniel Khaykin	1/8/2020
Student's Printed Name(s)	Signature	Date of Signature (mm/dd/yy)

Abstract 2018-2019

Bone Marrow Morphologic, My PRS, and Mutation Correlations in Multiple Myeloma

Multiple myeloma is a malignant neoplasm of plasma cells with clinical and genetic heterogeneity. Recent work has shown that molecular subtypes and the 70-gene prognostic risk score (MyPRS) significantly correlate with prognosis in myeloma patients. Here, the correlation of bone marrow histology and genetic alterations with MyPRS gene expression are investigated. 774 multiple myeloma cases (325 patients) were collected from 01/2017 to 05/2018. Histologic features were evaluated and samples were analyzed for MyPRS risk score, molecular subtype and virtual karyotype through gene expression profiling. Translocation and mutation data were obtained from targeted next-generation sequencing studies (FoundationOne Heme). Among the 7 molecular subtypes, poor prognostic types were closely associated with high-risk group, whereas good prognostic types are associated with low-risk group (p=0.0001). Compared to low-risk cases, high-risk ones show higher marrow cellularity (p=0.0005), higher percentage of tumor cells (p=0.0155) and higher histological stage (p=0.0001). Diffuse sheet growth patterns were more associated with high-risk cases (62.8%). It was shown that bone marrow histologic features, including high plasma cell volume, diffuse growth pattern, immature cell morphology, high mitotic index, and increased fibrosis, significantly correlate with MyPRS high risk disease. Furthermore, the association between MyPRS risk stratification and specific genetic alterations is proven by the results.

Work Cited

Hanamura, I. (2006). Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: Incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood,108*(5), 1724-1732. doi:10.1182/blood-2006-03-009910

Huang, J., Yu, J., Li, J., Liu, Y., & Zhong, R. (2012). Circulating microRNA expression is associated with genetic subtype and survival of multiple myeloma. *Medical Oncology, 29*(4), 2402-2408. doi:10.1007/s12032-012-0210-3

Lendvai, N., Gnjatic, S., Ritter, E., Mangone, M., Austin, W., Reyner, K., . . . Cho, H. (2009). Cellular immune responses against CT7 (MAGE-C1) and humoral responses against other cancer-testis antigens in multiple myeloma patients. 1-9.

Mohty, B., El-Cheikh, J., Yakoub-Agha, I., Moreau, P., Harousseau, J., & Mohty, M. (2010). Peripheral neuropathy and new treatments for multiple myeloma: Background and practical recommendations. *Haematologica, 95*(2), 311-319. doi:10.3324/haematol.2009.012674

Daniel Khaykin

Research Plan 2018- 2019

A. RATIONAL: Plasma Cell Myeloma (PCM) is the most common lymphoid disorder, with initial morphological grading and histologic classification by Bartl in 1987. High risk myeloma is stratified by a gene expression panel, but no morphologic correlation has been performed so far. A plasmablastic myeloma cell contains a large central nucleus, and has a high nuclear to cytoplasmic ratio, but despite this also lacks a dominant perinuclear hof. When a plasma cell becomes abnormal, the body creates antibodies to fight it off, but this causes blood to thicken, which leads to the bone marrow not making enough healthy plasma cells. Because of this, the human bone, immune system, and kidneys weaken. Using scoring criteria to predict the development of high or low risk Myeloma can help clinicians more easily diagnose and provide treatment for the cancer. High and low risk Myeloma require different intensities of treatment, where immunotherapy is used for low risk and total therapy is used for high risk Myeloma. Being able to begin the correct chemotherapy earlier on can increase the survival rate of Myeloma patients.

B. RESEARCH QUESTIONS: Are there specific scoring criteria to predict high risk and low risk plasma cell myeloma patients that can help drive subsequent ancillary testing on an enlarged cohort? What is the correlation of various ancillary phenotypic assays such as flow cytometry, free light chain, IHC in MM patients?

C. RESEARCH METHODS:

Procedures: To conduct this experiment 1000 multiple myeloma biopsies with available MyPRS risk scores will be collected from clinicians at Mount Sinai Icahn School of Medicine. These biopsy samples were given by Mount Sinai clinicians, where each patient involved had to sign a waiver of consent. Additionally, all data will be de-identified and histological features such as bone marrow cellularity, mitoses/HPF, and genetic alteration rate will be recorded and analyzed. Afterward, Fisher's exact test or Chi square test will be performed for analysis of different distribution in gender, race, molecular subtypes, morphologic features (including Bartl stage, growth pattern, nuclear morphology, fibrosis, mitotic index), light chain restriction, gene mutation and translocation between the two groups (High risk, low risk) of patients. All statistical analyses will be performed using GraphPad Prism. Multi and univariate analyses will also be performed as well as scoring criteria to determine samples for subsequent testing to predict high risk scores.

Data Analysis: After all information is inputted, the data will be statistically analyzed for correlative associations using chi square tests, Fisher's exact test, and statistical analyses.

Risk and Safety: There is not much safety risk involved in the study as it is entirely analyzing biopsy smears under a microscope and inputting histological data in a de-identified password protected excel G-drive. The microscopy, also, will not be used for diagnostics.

D. BIBLIOGRAPHY:

- Bartl R, Frisch B, Burkhardt R, Fateh-Moghadam A, Mahl G, Gierster P, Sund M, Kettner G. Bone marrow histology in myeloma: its importance in diagnosis, prognosis, classification, and staging. *British Journal of Haematology* 1982; 51: 361-375.

- Bartl R, Frisch B, Fateh-Moghadam A, Kettner G, Jaeger K, Sommerfeld W. Histologic Classification and Staging of Multiple Myeloma: A Retrospective and Prospective Study of 674 Cases. *Am J Clin* Pathol 1987; 87(3): 342-355.

- Garand R, Avet-Loiseau H, Accard F, Moreau P, Harousseau JL, Bataille R. t(11;14) and t(4;14) translocations correlated with mature lymphoplasmacytoid and immature morphology, respectively, in multiple myeloma. *Leukemia* 2003; 17: 2032-2035

- NCI Dictionary of Cancer Terms. (n.d.). Retrieved July 11, 2018, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/plasma-cell-myeloma

- Plasma cell disorders and myeloma terminology and classifications. (2017, February 22). Retrieved July 13, 2018, from https://themmrf.org/2017/02/plasma-cell-disorders-and-myeloma-terminology-and-classifications/