2012 JMNMF RSA Photo & Summary

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Pictured Left to Right: Taha Merghoub, PhD, Assistant Attending Biologist, Melanoma-Sarcoma Service, MSKCC; Denise Safko, JMNMF Secretary & RSA Committee Member; Judith Murphy, JMNMF RSA Recipient; Greg Safko, JMNMF President; and, Jedd Wolchok, MD, PhD, Director, Immunotherapy Clinical Trials, Department of Medicine, Memorial Sloan-Kettering Cancer Center.

SUMMARY: Investigation of the Role of the GITR Pathway in Tumor Immunity and Anaphylasix

The incidence of metastatic melanoma, which accounts for approximately 80% of deaths from skin cancer, has risen significantly in recent decades**.** Conventional chemotherapy and radiotherapy are typically ineffective at treating this disease. A recently approved immunotherapy, called ipilimumab, was shown to be the first drug to prolong survival of patients with metastatic melanoma. Immunotherapies such as ipilimumab act by helping "killer T cells" to recognize and kill tumor cells more effectively. Our laboratory has demonstrated in preclinical studies that other new immunotherapy drugs also have significant antitumor potential. A single dose of one of these drugs, called "anti-GITR," has been shown to eradicate tumors in 60% of rodents with melanoma. We hypothesized that administering several doses of anti-GITR would improve the survival benefit to 100%. However, it became apparent that three or more doses of anti-GITR caused a fatal anaphylactic reaction in about 10% of the rodents receiving this therapy. This reaction was characterized by increased blood levels of two proteins involved in the inflammatory response, TNF and IL-6. Additionally, rodents undergoing anti-GITR-induced anaphylaxis became severely hypothermic. The research put forward in this grant aims to understand the cellular and molecular causes of anti-GITR-induced anaphylaxis. This is of critical importance for the design of clinical trials using anti-GITR. Understanding the cause of and preventative actions against this severe side effect will enable anti-GITR to be administered to patients in the safest way possible while still maximizing the antitumor potential of this therapy.