UPR/MDACC Partnership 2022 Call for Pilot Research Projects received by February 25, 2022

UPR	MD Anderson	Title of the Project	Aims of the Project	Abstract
Jose A. Lasalde-Dominicci, PhD, Professor of Biochemistry	**Phyu P. Aung, MD, PhD**, Associate Professor of Pathology **Leomar Y. Ballester, MD, PhD**, Assistant Professor of Pathology	The Role of Acetylcholine Receptors in Merkel Cell Polyoma Virus-induced Merkel Cell Carcinoma from Various Ethnicities	• **Aim 1**. Evaluate the MCPyV-status of a large existing cohort of 100 MCC cases from various ethnicities. It is expected that ~80% of cases will be MCPyV related. • **Aim 2**. Characterize the expression nicotinic acetylcholine receptors (a-5, a-7, a -9) in a large cohort (n=100) of MCC. • **Aim 3**. To correlate the expression pattern of nicotinic acetylcholine receptors with clinical and demographic characteristics including survival, race, MCPyV status, and molecular characteristics (e.g., immunoprofile, and epigenetic signatures) characteristics in MCC.	Merkel cell carcinoma (MCC) is a rare but aggressive cutaneous malignancy. At least one-third of patients experience local or distant recurrence with 5-year survival rates of approximately 14% in patients presenting with distant metastases. MCC tends to occur in sun-damaged skin in the elderly population, with a male to female ratio of 8:1. Various mechanisms drive MCC development: either integrated Merkel cell polyoma virus (MCPyV) in approximately 80% of cases, or high ultraviolet light–induced somatic mutational burden specific to MCPyV-negative MCCs. There is controversy surrounding the cell of origin of MCC but it has been postulated that possible cells of origin include dermal pluripotent stem cells or neural crest cells. Neural crest derived tissues express acetylcholine receptors (AChRs) (PMID: 7649378). These receptors are critical for migration of neural crest derived cells to their corresponding tissues during development. In fact, recent reports demonstrate neural crest derived melanoma and numerous non-Merkel cell neuroendocrine tumors express AchRs. In particular nicotinic AChR a-9 and a -5 have been proposed to play a role in other cutaneous malignancies (i.e., melanoma) (PMID: 33120929). However, the role of

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				AchRs in MCC has not been explored, although a pilot study with 15 patients demonstrated expression of muscarinic AchRs in MCC (PMID: 18645305). AchRs have been linked to cell proliferation and cell migration and may serve as potential therapeutic targets in MCC. For this study, we will build on our previous work on MCC (PMID: 26818033, 29601841, 30636696, 30808776) and utilize and existing cohort of 100 MCC cases diagnosed at MD Anderson. We hypothesize that an integrated evaluation of MCC including, clinical and histopathologic parameters, MCPyV status, epigenetic signatures, and immune infiltrates, and nicotinic acetylcholine receptor expression, will increase our understanding of this tumor and reveal potential novel prognostic factors and therapeutic targets.
Stephanie Dorta Estremera, PhD, Assistant Professor, Microbiology and Medical Zoology Department **Filipa Godoy-Vitorino, PhD,** Associate Professor, Microbiology and	**Jagannadha K. Sastry, PhD**, Department of Thoracic-Head and Neck Medical Oncology, virologist, and immunologist **Lauren Colbert, MD** Department of Radiation Oncology, radiation oncologist	Immune and microbial signatures associated to cervical cancer progression and treatment outcomes among Puerto Rican and US Hispanics.	Identify unique immune and microbial signatures in Hispanics, especially differentiating Puerto Ricans from US Hispanics with cervical cancer and as a response to treatment	Cervical cancer is the most common human papillomavirus-related malignancy and its incidence rate varies among racial and ethnic groups. In the United States, cervical cancer is more prevalent in Hispanic and African American women compared to other races or ethnicities; in addition, these racial groups have a higher mortality rate than non-Hispanic whites. Among these racial groups, Puerto Rican Hispanics have the highest incidence of cervical cancer with an age-

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Medical Zoology Department				adjusted incidence increases in the last decade from 9.2 to 13 per 100,000 person-years (Ortiz,AP JAMA Oncol 2021). Among the reasons accounting for this disproportionate burden of cervical cancer, are challenges in implementing effective cervical cancer screening in these populations especially in the Caribbean. We hypothesize that changes in immune and microbiome composition, due to genetic, behavioral, dietary, and environmental factors may also play a role in the increase in cervical cancer incidence in US and Caribbean Hispanics. Immune responses are shaped by microbial cells and therefore the presence of different microbial populations in tumors and/or surrounding tissues may modulate tumor-specific immune responses. Increasing evidence shows crosstalk between immune, microbial, and tumor cells, suggesting that their interplay may modulate tumor development and treatment responses. Many studies have characterized the microbiome present in the gut and the correlation of these microbial communities with tumor development and responses to cancer therapies. In addition, the presence of specific types of bacteria in the cervix has been associated with increased levels of proinflammatory cytokines and invasive cervical cancer (Łaniewski P, Sci Rep 2018). Our team at UPR-MSC which advanced the

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				field of microbiome-induced carcinogenesis in Hispanics, has demonstrated the role of the cervicovaginal microbiome and the metabolic environment in high-grade cervical disease in patients with high-risk HPV types (Godoy-Vitorino, Front Microbiol 2018). Also, the partner team at MDACC has determined that increased gut microbial diversity correlated with increased activation of T cells in cervical cancer (Simms TT Commun Biol 2021). However, a comprehensive study of the cervical microenvironment, including immune cells, soluble factors, metabolites, and microbial communities that are involved in tumor development and treatment response in Hispanics has not been performed yet.
Cornelis P. Vlaar, PhD, Department of Pharmaceutical Sciences, School of Pharmacy *Collaborator:* **Magaly Martinez-Ferrer, PhD**, Associate Professor, Department of Pharmaceutical Sciences, School of Pharmacy &	**Faye Johnson, MD, PhD,** Professor Department of Thoracic-Head & Neck Med Oncology, Division of Cancer Medicine. *Collaborator:* **Niki M. Zacharias Millward, PhD**, Assistant Professor, Department of Thoracic-Head & Neck Med Oncology,Division of Cancer Medicine.	Development of TRIP13 Inhibitors for Treatment of HPV+ Cancers	The goal of the proposed research is to develop novel inhibitors of (TRIP13) and further elucidate the synergistic effect by which Aurora kinase and TRIP13 inhibition kills HPV+ squamous cancer cells while sparing normal cells. Our collaboration is important for the development of novel treatment options for HPV+ penile, cervical, and head and neck cancers.	Our research demonstrated that the combination of an Aurora kinase inhibitor with depletion of the AAA-ATPase Thyroid hormone receptor interactor 13 (TRIP13) led to considerable apoptosis, specifically in HPV+ cancer cells. The goal of the proposed research is to develop novel inhibitors of (TRIP13) and further elucidate the synergistic effect by which Aurora kinase and TRIP13 inhibition kills HPV+ squamous cancer cells while sparing normal cells. Our collaboration is important for the development of novel treatment options for HPV+ penile, cervical, and head and neck cancers.

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Filipa Godoy-Vitorino, PhD, Associate Professor, Microbiology and Medical Zoology Department	**Candelaria Gomez-Manzano, MD**, Department of Neuro-Oncology, Division of Cancer Medicine	The Gut microbiome as a therapeutic strategy for modulating the efficacy of viroimmunotherapy against malignant glioma	To evaluate the systemic molecular and immunological underpinnings associated with the survival of glioma-bearing animal models. We also aim to define gut microbial and metabolic biomarkers modulating the efficacy of viroimmunotherapy by coupling in-depth microbiome and metabolomic approaches. Finally, fecal transplants from responders to germfree mice will define the role of gut microbiota signatures as viroimmunotherapy modifiers.	Glioblastoma (GBM) is the most frequent and aggressive primary brain tumor. Despite treatment with surgery, radiotherapy, and chemotherapy, GBM invariably recurs. Therefore, strategies for finding potential novel therapeutics are urgently needed. Oncolytic adenoviruses are a promising therapeutic strategy for GBM (JCO 2018; NEJM 2018; NEJM 2021; Lancet Oncol 2021). In a clinical trial developed at MDACC, 20% of GBM patients treated with the intratumoral injection of the oncolytic adenovirus Delta-24-RGD showed complete response and survivals longer than three years (JCO 2018). To increase the percentage of responders, the team developed a third-generation oncolytic adenovirus termed Delta-24-RGDOX that includes the T cell activator OX40-ligand (OX40L), which in preclinical studies has been shown to induce a potent T cell-mediated antitumor effect in GBM murine models and is being tested in a clinical trial in patients with recurrent malignant gliomas (NCT03714334) and another trial in patients with liver metastases (NCT04714983). Accumulating evidence from pre-clinical animal models strongly suggest a role for gut microbes in modulating the response to cancer

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				immunotherapy. Furthermore, numerous trials are testing to which extent the modulation of the gut microbiota may enhance clinical responses to immunotherapy. Thus, the role that the gut microbiome plays in the response of cancer patients to immunotherapy was first suggested in two preclinical studies (Science 2018). Several clinical studies subsequently demonstrated a robust connection between the gut microbiome and response to immunotherapy in several types of tumors. While it is well documented that the gut microbiome is a robust biomarker of response to immunotherapy, studies on preclinical models have also shown that manipulation of the gut microbiome resulted in an enhanced therapeutic response, supporting a role for the manipulation of the gut microbiome as an interventional therapy when combined with immunotherapy. Oncolytic viruses are a particular case of immunotherapy that utilizes viral agents, such as Delta-24-RGDOX adenovirus, to produce an antitumor immune response in cold tumors, including gliomas. The UPR team, experts in microbial ecology, has generated promising preliminary data using fecal pellets collected from the glioma-bearing mice and has identified significant differences in the structure and composition of the gut bacterial communities, specifically an

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				increase in Bifidobacterium in the responders and those animals with higher survival. Based on this rationale and our preliminary results, we hypothesize that manipulating the gut microbiome will significantly enhance the effect of viroimmunotherapy in GBM.