The NYU School of Medicine’s new “Curriculum for the 21st Century (C21)” allows students to customize their educations by engaging in research projects designed to build in-depth knowledge in a key biomedical area, foster more student – faculty mentoring opportunities and increase student competitiveness when searching for specialty training. This new opportunity is called a Concentration.

The Department of Pathology currently offers Concentrations in three areas of research under the mentorship of members of our faculty. Project will be developed in partnership with a clinical faculty member whenever possible. Students will spend 12 weeks in a laboratory pursuing basic science, or translational research, or 8 weeks in a laboratory and 4 weeks doing a clinical elective that is linked to the research topic. The structure of 12 week block will be decided through discussions with the proposed mentor(s) depending on the nature of the project, availability of specific opportunity (e.g., status of a pre-clinical project or clinical trial at the time of the rotation), and students preferences.

Application process: Students should contact Dr. Demaria by e-mail (Sandra.demaria@nyumc.org) if they have questions about the program or have an interest in a research area not currently officially available. If they are interested in one of the research areas listed below they can contact the research faculty member directly by e-mail to request a meeting to discuss a suitable project. Once the project is selected the mentor and the student will fill in the “Concentration Project Form”, which includes a brief description of the project and an attestation of mentoring commitment from the mentor (and clinical co-mentor if relevant); the student will forward the signed form to the Office of Medical Education. The Department recommends that students finalize their plans in minimum 3 months prior to the start date of the Concentration project. Students understand that the mentor may require prerequisites, such as readings from the literature, attendance at lab meetings or, in the case of a clinical project, the successful completion of a specific clinical rotation. Students should also be aware that mentors may require attendance at lab meetings, journal clubs, seminars and other lab activities during the concentration itself.

Assessment: At the end of the concentration period, students are required to prepare and submit a written report to their mentor describing their work. Students are also encouraged to present the final report orally in a lab meeting of the mentor’s research group, to the department or at a scientific conference, as stipulated by the project mentor(s). The written work can be written in the form of a paper for publication or a poster for a conference presentation. The student will meet with his/her mentor(s) and at least one other faculty member who has not been engaged in the project and provide an oral defense of the project and its work product. A copy of the written report will also be uploaded by the student to his/her e-portfolio and forwarded to the Office of Medical Education as evidence of completion of the concentration. Grading of the “Concentration” program activities is PASS/FAIL. The mentor will determine the student’s grade after the final report is submitted.

AVAILABLE MENTORS AND RESEARCH AREAS:

Sandra Demaria, M.D.

PARTNERSHIP OF RADIOTHERAPY AND IMMUNOTHERAPY FOR BREAST CANCER TREATMENT: FROM PRE-CLINICAL MODELS TO CLINICAL TRIALS.

Background: Ionizing radiation has been known to have pro-inflammatory and immunomodulatory effects for a long time, but only in the last few years several of the changes that occur in irradiated
tumors have been elucidated at a molecular level, providing the rationale for the counterintuitive observation that local radiotherapy (RT), rather than suppressing anti-tumor immunity, can promote it (Figure 1) (1). In fact, evidence from pre-clinical models and recent clinical reports supports the concept that RT has the potential to render the cancer an in situ, individualized vaccine (2). However, similarly to other cancer vaccines, RT by itself is usually insufficient to generate therapeutically effective anti-tumor immunity (3), due to the presence of multiple barriers that are in place to counteract the priming and effector phase of immune rejection in established tumors (1). We have shown in mouse breast cancer models that the ability of RT to generate an effective anti-tumor immune response requires the targeting of immunosuppressive pathways (4), and depends on the dose and fractionation of radiation used (5).

Figure 1. RT converts the tumor into an in situ vaccine. RT induces an immunogenic tumor cell death characterized by calreticulin (CRT) translocation to the surface of dying cells, and release of HMGB-1 and ATP. CRT allows uptake of dying cells by DC via scavenger receptor(s). HMGB-1 binds to TLR4 and promotes the cross-presentation of tumor antigens, while ATP binds to P2X7 and triggers the activation of the inflammasome. Activated DC migrate to the draining lymph node, where they activate naïve T cells specific for tumor antigens to become cytoltyc T cells (CTL). CTLs traffic to the tumor guided by radiation-induced chemokines. Tumor infiltration by CTLs is facilitated by radiation-induced upregulation of VCAM-1 on the vascular endothelium. Once in the tumor, CTLs interact efficiently with tumor cells expressing increased levels of MHC-I, ICAM-1, NKG2D ligands and Fas that promote the formation of stable immunological synapses between targets and effectors and facilitate the killing of tumor cells by CTLs. Tumor cells killed by CTLs become a source of antigens for cross-presentation thus fueling the process (1).

Current focus of the lab is in three main areas: a) Testing of new immune response modifiers in mouse models for the ability to synergize with local RT and induce therapeutically effective anti-tumor immunity (example: ref.(6)) b) Identification of the immunological mechanisms responsible for the success or failure of the treatment. (example: ref. (7)). c) Translation of the treatment strategies to the clinic in collaboration with medical and radiation oncologists (example: ref. (8)).

Projects available will include training in the use of mouse breast cancer models for the evaluation of new treatments combining radiation with immunotherapy, the pathologic evaluation of breast cancer samples from patients and mice with emphasis on the immune infiltrate, and the approach to clinical translation of experimental treatments involving immunotherapy.

Literature cited
Eva Hernando, PhD

STUDY OF microRNA ALTERATIONS IN MELANOMA PATHOGENESIS.

Melanoma arises from the melanocytic lineage, and is the most aggressive and invasive cancer of the skin. Although melanoma accounts for only 4% of all skin cancers, it is responsible for more than 80% of skin cancer related deaths [1]. Melanoma incidence continues to rise sharply (at a rate of 4% per year) despite better awareness and screening [2,3]. The impact of melanoma on average years of life lost and lifetime earnings lost is greater than other cancers [4].

MicroRNA (miRNA) are small, non-coding RNA that play key roles in development and cancer [5]. miRNA are emerging as key contributors to tumor metastasis because of their ability to regulate multiple targets and thereby alter several functions simultaneously. Our lab is studying the role of miRNA alterations in various steps of melanoma pathogenesis, from initiation to metastasis [6-9], the underlying molecular mechanisms and their crosstalk with other pathways (reviewed in [10]). We are also exploring the value of miRNA as therapeutic targets [11] and predictive biomarkers of melanoma patient outcome [12]. Below is a description of some of our ongoing projects:

Study of miRNA in melanomagenesis. We are using a novel ‘pooled’ library of microRNA ‘decoys’ to screen in vitro and in vivo for tumor suppressor miRNA whose inhibition is sufficient for melanocyte transformation. MicroRNA identified by this screen may play a critical role early in melanomagenesis. Candidate miRNA will be confirmed individually and their expression examined in human melanoma patient datasets. Then we will study the mechanism(s) and targets by which they exert their roles and investigate the cause for their inactivation in human melanoma.

Identification of early miRNA alterations that predict and modulate melanoma metastasis. Melanoma is curable for most patients whose primary tumors are adequately removed; however, many patients recur and progress to advanced disease and death. Clinical staging is insufficient to account for heterogeneity within stage of disease outcome, and reliable prognostic molecular biomarkers have not yet been identified or clinically implemented. We have found a microRNA (miRNA) signature derived from profiling of two cohorts of primary melanoma tumors that robustly classifies patients into high or low risk of recurrence at the time of diagnosis. Further, from these data, in a high-throughput in vitro invasion assay, we identified a set of miRNA, whose expression is lower in more aggressive primary tumors, that suppressed invasion in vitro and metastasis in vivo. Our data document that aberrant expression of specific miRNAs is predictive of and functionally impacts progression of primary melanoma. We are currently investigating the critical targets that mediate...
these miRNA effects. This project will involve 1) identify direct miRNA targets by expression arrays and luciferase reporter assays, 2) determine if target suppression recapitulates the anti-metastatic effects of a miRNA overexpression in vivo, 3) determine if target overexpression counteracts the anti-metastatic effect of a miRNA in vivo.

**miRNA as mediators of tissue-specific metastasis.** Brain metastasis occurs in a large proportion of melanoma metastatic melanoma patients and is associated with a dismal prognosis. However, the molecular mechanisms that govern melanoma tropism to the brain remain poorly understood [13]. A miRNA microarray analysis of metastatic melanoma tissues revealed a robust signature of miRNAs differentially expressed in brain metastases relative to other sites. Deep investigation of their potential role in melanoma oncogenesis revealed a miRNA cluster, miR-30b/30d, that promotes metastasis by concurrently enhancing the invasive capability of melanoma cells and suppressing immune surveillance mechanisms, allowing the tumor cells to reach and colonize foreign tissue. Both these effects of miR-30b/30d are mediated by direct suppression of GalNAc transferases that resulted in significantly altered glycosylation patterns of melanoma cells [8]. In order to investigate the role of this cluster, as well as of other miRNAs altered in our signature, in the modulation of melanoma brain metastasis specifically, we have developed and characterized an *in vivo* model of melanoma brain metastasis. Using this model together with surrogate *in vitro* assays for angiogenesis, adhesion, and proliferation in the brain microenvironment, we are attempting to elucidate the functional roles of selected miRNAs in melanoma dissemination to the brain.

**Relevant literature**


**Relevant publications from our laboratory**


David Zagzag, M.D., Ph.D.

THE ROLE OF HYPOXIA, ANGIOGENESIS, AND INVASION IN GLIOMA PROGRESSION

Despite the great advances in improving the survival and quality of life of cancer patients, there remains little hope for those suffering from glioblastoma (GBM). Glioblastomas (GBMs) are the most common and aggressive primary brain tumors in adults, with a median survival of only 14 months despite the best available treatments. GBMs are characterized by their resistance to radiotherapy and chemotherapy, as well as their abundant and aberrant vasculature and marked invasion. GBM remains difficult to treat as it is not only resistant to the traditional therapies of chemotherapy and radiation, but also thrives within a hypoxic environment, a salient feature of this infiltrative disease. Previous studies by our group and others have also demonstrated that hypoxia stimulates glioma cell migration in vitro and invasion in experimental glioma models and human gliomas in vivo. We have previously shown that the knock down of HIF-1α reduces migration ability of glioma cells in vitro and leads to overall less invasive tumors in vivo. Given the well-established role of hypoxia in GBM angiogenesis and invasion, we believe that targeting a hypoxia-induced mechanism is a critical step in developing a successful treatment for GBM.

There have been extensive publications describing the process of vascular co-option, angiogenesis and vasculogenesis in gliomas. Recently, however, it has become clear that these three processes are not the only mechanisms by which neovascularization occurs in gliomas. Further, it seems that these processes interact extensively, to the point that there is potential overlap between them. At least five mechanisms by which gliomas achieve neovascularization have been described including vascular co-option (Figure 1) and angiogenesis (Figure 2).

During a concentration, a student would examine the effect of hypoxia on the glioma associated angiogenesis and invasion. This would be done using human tissue samples as well as samples from mouse models. In addition, in vitro investigations using glioma cell lines would also be performed. For these purposes, techniques such as immunohistochemistry, Western Blot, Q-PCR, and transfections will be utilized.

Relevant literature


**Figure 1. Vascular Co-option.** Temporally, vascular co-option is the first process by which gliomas attain a vascular supply. The process involves organization of tumor cells into cuffs around normal microvessels (inset). Vascular co-option has been shown to precede angiogenesis in tumor models by up to four weeks.

**Figure 2. Angiogenesis.** Angiogenesis follows vascular co-option during tumor vasculature development and is defined as the development of new vessels from pre-existing ones. Hypoxic pseudopalisading glioma cells around necrosis (inset) release pro-angiogenic factors. This results in the shift of the angiogenic balance towards a pro-angiogenic phenotype, inducing sprouting from pre-existing vessels. Hypoxia-independent mechanisms driving angiogenesis have also been described.