

A BRIEF REPORT ON TUMOR IMMUNOLOGY RESEARCH IN THE RADBOUD UNIVERSITY MEDICAL CENTER, NETHERLANDS

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Studying Medicine is challenging, and I believe that every medical student should seek to base their graduation on three pillars: education, research and patient care, in order to graduate as the most complete professional as six years may possibly allow. And aiming to improve my research skills and experiences, I decided to apply to the Science Without Borders Program, sponsored by the Brazilian government, looking for an opportunity to have new medical experiences in a foreign country, with an excellently structured healthcare system and great research centers, such as the Netherlands. So I decided to apply for a six months research internship at the Tumor Immunology Department at the Radboud Institute for Molecular Life Sciences in the Radboud University Medical Center, Nijmegen.

The Tumor Immunology Department research focuses in understanding the body's immune system in order to develop curative therapies for cancer patients. Most of the research are in dendritic cells, that are known to be master regulators of the immune response, and the department studies from fundamental knowledge about Dendritic Cell immunobiology to the application of this knowledge to exploit these Dendritic Cells as cancer vaccines¹.

The importance of this work was evidenced by 2011 Nobel Prize for professor Ralph Steinman for discovering dendritic cells in 1973. He speculated

that it could be important in the immune system and decided to test whether dendritic cells could activate T cells, a cell type that has a key role in adaptive immunity and develops an immunologic memory against many different substances. In cell culture experiments, he showed that the presence of dendritic cells resulted in vivid responses of T cells to such substances. These findings were initially met with skepticism but subsequent work by Steinman demonstrated that dendritic cells have a unique capacity to activate T cells^{2,3}. The discoveries that were awarded the 2011 Nobel Prize have provided novel insights into the activation and regulation of our immune system. They have opened new doors for the development of new methods for preventing and treating disease, giving subsidy to researches for improved vaccines against infections and in attempts to stimulate the immune system to attack tumors. These discoveries also provided new clues for novel treatment of inflammatory diseases⁴. Cancer immunotherapy was also elected as the breakthrough of the year 2013 in Science journal, and scientists are racing to identify biomarkers that might offer answers of its effectiveness and experimenting ways to make therapies more effective⁵. One thing is certain: immunotherapy has taken center stage in the treatment of cancer.

On my internship, I joined the nanomedicine group, in which the main projects focus on studying

immunological and cell biological research questions with advanced microscopy methods in order to understand fundamental molecular mechanisms regulating dendritic cell function. Thus a better understanding of the functions of immune cells is necessary to gain more insight into the immune system and at the same time provide novel strategies to improve therapies being used to fight cancer, inflammatory diseases and autoimmune diseases.

My research project specifically involved studying the invadopodia formation which is believed to be related with tumor cell metastasis. Metastasis is known to be a complex multistep process that represents the most deadly aspect of cancer and involves cells escaping from a primary tumor, migrating through the stroma, and entering into the vasculature and disseminating to distant sites. Invadopodia are finger-like, actin-rich protrusions that are formed by metastatic tumor cells to degrade the extracellular matrix (ECM). Invadopodia presumably facilitate each step of the metastatic cascade; breaching the basement membrane that surrounds a tumor in situ, promoting invasive cancer cell migration through the dense stromal ECM and degrading the endothelial basement membrane for entry into the blood⁶.

Extensive efforts to characterize invadopodia have revealed that they are mainly composed of actin and actin-associated proteins⁷. These active persistent structures can be recognized at the light microscopy level by the co-localization of a number of markers (at least 2 or more, e.g. actin, cortactin, dynamin 2, and phosphotyrosine residues) with evident areas of degradation⁸. For my project, I have investigated the role prostaglandin E2 receptors in invadopodia formation in human breast cancer cells by designing two approaches, a three dimensional model to study cancer cell invasion and an immunofluorescence assay to study invadopodia formation.

The experience of working in this department was by far one of the most enriching experiences I have ever had during my graduation. It was really important for me to understand how science and knowledge are developed, from bench to bedside. Also, this experience allowed me to develop and improve my presentation skills in English, since I had to present my work several times to an audience composed of experts in the field. I also had the opportunity to learn how to prepare myself to answer about

complicated matters to a professional audience. I have also had the chance to watch several different presentations and lectures on different subjects from PhD candidates and Post-Docs students from all over the world, learning new concepts and ideas on scientific fields that are in the spotlight in worldwide science.

The experience of studying in a research oriented university was very enriching and different from most of Brazilian universities. Even in clinical disciplines lectures, the students are induced to make research questions, to elaborate research propositions and to be critical students. I believe this experience was unique for my future medical practice because I believe that we, as future doctors, need to think outside of the box. Regardless of whether a student plans to become a clinician, a surgeon or follow the path of a clinical scientist, they will be engaged in learning projects to address patient care issues and improve quality and effectiveness of care. We need to be more than medical technicians; we need to be scientists.

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