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TARGETING THE IMMUNE SYSTEM TO TREAT SMALL CELL LUNG CANCER

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Overview of Small Cell Lung Cancer

In the United States, 219,440 new cases of lung cancer were diagnosed in 2009(1). Small Cell Lung Cancer (SCLC) accounts for approximately 13-15% of those diagnosed, the remaining are classified as Non-Small Cell Lung Cancer (NSCLC). Because of its aggressive nature, SCLC follows a simplified staging system where patients are either classified as having limited (localized) or extensive (distant) disease and about 70-80% of patients present with extensive stage disease (ES-SCLC) at the time of diagnosis. Despite the fact that SCLC typically grows rapidly, it responds well to chemotherapy which has been the cornerstone of the treatment of SCLC for decades (first line chemotherapy typically consists of an etoposide-platinum combination) and is responsible for the considerable survival improvements achieved during this time (2) ES-SCLC patients achieve overall response rates (ORR) of greater than 70% and complete response rates of 20-30%, however, they rarely survive beyond 2 years (10-20%), and median survival times range only from 7-10 months (2). Clearly, new therapies are urgently needed and evidence suggests that immunotherapy may have a potential role in SCLC treatment, particularly if used in association with chemotherapy(3, 4).

Understanding the Role of Immunotherapy

Immunotherapy is a form of biologic therapy that harnesses the immune system to fight diseases, including cancer. Immunotherapy works by either directly stimulating the body's own natural



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defense system, making it work harder and/or by circumventing mechanisms that can depress immune system components. Immunotherapy has been used alone to treat cancer, but often immunotherapy is combined with other treatment strategies to boost the effects.

Over the last few decades, researchers have made great progress in this field and immunotherapy is proving that it can play an important role in both protecting the body against the development of cancer (prevention) and in combating a cancer that has already developed (therapy).

Evidence suggests that a patient's immune system can play a key role in slowing down the recurrence and metastasis or spread of cancer. Thus, immunotherapy is about harnessing the body's natural ability to develop an immune response and then using that to target cancers. Immunotherapy offers great promise and clinical research will be instrumental to continue to move this field forward.

Understanding p53 as a Target for Cancer Immunotherapy

The p53 tumor suppressor gene plays a central role in the control of cell growth and differentiation, which is the process by which cells become progressively more specialized and mature. Normally, p53 is a short-lived protein that is localized in the cell nucleus. Approximately 50% of all human cancers and more than 90% of SCLC have an altered p53 gene with the consequent protein dysfunction. This leads to accumulation of mutant or wild-type p53 protein outside the cell nucleus (whereas normal tissues have low to undetectable levels) and expression of p53-derived epitopes on the surface of tumor cells. Epitopes are the part of an antigen that is recognized by the immune system (7). Furthermore, since mutant forms of p53 can result in oncogenic function, giving rise to tumors or causing tumor formation, it is unlikely that they can escape anti-p53 cytotoxic T lymphocytes, which are lymphocytes that kill tumor and other diseased cells, by restoring wild type p53 status. Thus, p53 has many characteristics of an "ideal" tumor-associated antigen, making it a very attractive target for anti-p53-based cancer immunotherapy.

Anti-p53 Dendritic Cell-Based Immunotherapy

Dendritic cells are the most potent antigen presenting cells and the most effective in inducing a primary



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cytotoxic T lymphocytes response or immune induced antitumor effect. Furthermore, there are numerous methods of loading dendritic cells with a variety of different tumor associated antigens to induce the desired, specific cytotoxic immune response. Because cells carrying a mutant p53 gene usually overexpress the p53 protein and because there is a large body of evidence in melanoma targeting overexpressed but not mutant proteins, a practical approach to immunotherapy would be to develop a strategy that targets the non-mutant portions of the p53 overexpressed in tumors utilizing a reliable and effective method to deliver the tumor associated antigen.

Therefore, Moffitt investigators have focused on utilizing dendritic cells transfected, which is the process of deliberately introducing nucleic acids into cells, with the full-length p53 gene. The Dendritic cells are grown by harvesting peripheral blood mononuclear cells (PBMC) from the patient and are infected with an adenoviral construct containing wild type p53 to generate Ad.p53-DC (vaccine). This Ad.p53-DC vaccine is being tested in clinical trials.

A clinical trial testing the safety and efficacy of the Ad.p53-DC vaccine in ES-SCLC patients demonstrated that the vaccine was safe and resulted in a substantial immunological response, as well as some tumor responses. Of greater significance was the high frequency of objective tumor regressions observed in patients treated with chemotherapy given immediately after Ad.p53-DC vaccination, suggesting a vaccine-chemotherapy synergy. This observation was quite unexpected since the existing paradigm suggests that chemotherapy is detrimental to the maintenance of an immune response. The paramount implications and significance of these results deserve further testing and they have prompted our continued research of these issues.

Specifically, we are currently conducting a clinical trial where patients with ES-SCLC, after receiving initial chemotherapy, are randomized to 1) observation (standard of care), 2) Ad.p53-DC, or 3) Ad.p53-DC plus all trans retinoic acid (ATRA). Upon progression, all patients are treated with single-agent paclitaxel (salvage chemotherapy). Our hypotheses are: 1) salvage chemotherapy in combination with Ad.p53-DC results in a substantial improvement in clinical outcomes, and 2) ATRA, by reversing the influence of immunosuppressive cells, substantially improves the p53-specific immune response to Ad.p53-DC and hence, clinical outcomes.



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Conclusion

Very little progress has been made in SCLC using conventional treatment modalities, and applying novel modalities such as immunotherapy represents both a rational and promising approach. Immunotherapy research is breathing new hope for those suffering from lung cancer. Progress is being made and we are moving closer to our overall goal of improving clinical outcomes for those affected by this devastating disease.

Alberto A. Chiappori, MD currently serves as Associate Professor of Oncology and Medicine for the Thoracic Oncology Program at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida.

Dr Chiappori received his MD from the Universidad Peruana Cayetano Heredia in Lima, Peru. After graduation, he completed his residency at Southern Illinois University School of Medicine in Springfield, Illinois. He then went on to finish his fellowship and senior fellowship in medical oncology-hematology at Vanderbilt University School of Medicine in Nashville, Tennessee. Dr. Chiappori has been a member of the Moffitt Cancer Center since September 2001.

Dr Chiappori has coauthored numerous articles in journals including *Journal of Clinical Oncology*, *Clinical Cancer Research*, *Cancer* and *Journal of Thoracic Oncology*. He is also an active member of the American Society of Clinical Oncology, the International Association for the Study of Lung Cancer, the American Association for Cancer Research and the American Society of Hematology.



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