Research Proposal

T1EDK-01404 NEOBIOPRO

IDENTIFICATION OF NEW PROGNOSTICS BIOMARKERS FOR PROSTATE CANCER

The enterprise Cellular and Molecular Immunological Applications (CeMIA SA) in cooperation with the National Hellenic Research Foundation, the Urology Clinic/Department of Immunology of "Agios Savvas" Hospital and ANTISEL SA has joined the Single RTDI State Aid Action "RESEARCH - CREATE - INNOVATE" funded by the Operational Program Competitiveness, Entrepreneurship and Innovation 2014-2020 (EPAnEK).

The measure aims to support research and innovation, technological development and demonstration at operating enterprises for the development of new or improved products, the development of synergies among enterprises, research and development centers and higher education sector as well as to support the patentability of research results and industrial property.

In that context, the main objectives of the measure are:
- Economic development based on knowledge and sustainable specialization;
- Integration of new knowledge and innovation to existing and new products, services, production systems and value chains;
- Connection of academic research with market needs and economy.

The Action is co-financed by Greece and the European Union - European Regional Development Fund.

BACKGROUND/AIM

Prostate cancer is the second highest cancer incidence and sixth cause of male population death [1]. Finding biomarkers predictive of the clinical course of the disease, and biomarkers predictive of response to a therapeutic approach constitutes a very important research field for timely and better treatment of the disease.

In previous studies vaccinating patients with prostate cancer with a hybrid peptide (AE37) of the oncoprotein HER-2 / neu [2-4], demonstrated that a significant percentage of patients who responded to AE37 with increased immunological and clinical responses (i.e. with increased survival) expressed (i) HLA-DR11 and/or HLA-A24 alleles, (ii) low levels of serum TGFβ prior to vaccinations and (iii) elevated IFNγ production upon stimulation with AE37 vaccine. A significant percentage of patients (41% compared with 27% of the Greek population) were HLA-A24 +, while this percentage was even higher (53%) among patients who had survived for more than four years after the initial diagnosis and had disease stabilization for more than three years after the completion of six monthly vaccination and a booster dose [3-6]. Furthermore, HLA-A24+ patients had elevated frequencies of circulating CD8 + T-cells specific for the PSA p152-160 peptide (CD8+/PSA152-160+), which existed before the vaccination and either kept at the same level or even increased 3 years after a booster dose of vaccine AE37 . In contrast, the overall survival and the immune responses were significantly reduced in patients expressing the HLA-A2 allele and had elevated levels of TGFβ. These findings in a relatively small sample of patients (32 in total) constitute an initial indication that these indicators may constitute prognostic biomarkers (Pro-b) on the disease process and predictive ones (Pre-b) for response to treatments. Moreover, tumor-suppressive miRNAs in patients' serum have been shown to have an essential role in prostate cancer progression [7].

This proposal relates first, to the validation of these biomarkers, and second, to the identification of new, all of which will form an immune signature with strong prognostic and predictive value for prostate cancer. Validated as Pro-b will be the alleles HLA-A24, HLA-DR11 and HLA-A2.1 whereas as Pre-b we will validate the levels of serum TGFβ and those of IFNγ upon activation with tumor antigens HER-2/neu and PSA for which there is evidence that prostate cancer patients have preexisting immunity [5,6] . The miR-34a,-145, -224, -452, -200b, -382, -372, -133, and -146a will be also validated as Pro-b.

Moreover, the frequency of CD8+/PSA152-160+ cells will be validated as Pro-b and Pre-b in HLA-A24+ patients. Because there will oligoclonal expansion of these cells in the periphery, we shall study the structure of their T-cell receptor (TCR) and in particular the expression of genes encoding the variable regions (TCR- Vβ). We will then correlate the increased frequencies of TCR- Vβ in peripheral blood in conjunction with the frequencies of CD8+/PSA152-160+ cells by estimating the frequencies of the PSA-specific cells (ie, CD8+/PSA152-160+ cells) co-expressing the particular Vβ genes. These TCR-Vβ genes will form an additional favorable Pre-b for HLA-A24+ patients.

Upon confirmation of these data in a large sample of patients with pre-established, homogeneous clinical characteristics during the control period, the examination of the above markers will result in statistically significant results that will establish their role as important prognostic and/or predictive biomarkers for prostate cancer. We believe that these biomarkers will constitute for the physician an important tool in order to better define the group of patients who will have the greatest clinical response to treatment, knowing that these patients have a favorable prognosis (i.e., slow progression of their disease).

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