ImmunoTools *special* Award 2014

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Development of immunotherapy for penile cancer

Human papillomavirus (HPV) could cause genital cancers such as the cervix, vulva, vagina, penis, oropharynx and anus. As one of them, penile cancer is an uncommon disease with devastating physical and psychological effects on patients. Based on the definitions of TNM, the curability of penile cancer decreases sharply for stage III and stage IV. For the patients with 1-2 involved inguinal nodes containing differentiated cancer, the overall recurrence rate is 80%, and the 5-year survival rate is 10%-15%. Thus, there is a great need for new and improved treatments.

HPV has been found the association with penile carcinoma in 15–80% and penile intraepithelial neoplasia (PIN) in 70–100%, specifically with HPV types 16 and 18. The HPV major capsid protein L1 can spontaneously self-assemble into VLPs that resemble authentic HPV virions. As a prophylactic HPV vaccine, Gardasil contains recombinant VLPs assembled from the L1 proteins of HPV types 6, 11, 16 and 18. The L1 proteins are produced by separate fermentations in recombinant Saccharomyces cerevisiae and self-assembled into VLPs. In December 2010, Gardasil was approved by the FDA for prevention of anal cancer and associated precancerous lesions due to HPV types 6, 11, 16, and 18 in people ages 9 through 26 years. Thus, Gardasil may have potential usage as the antigen of penile cancer in T cell-based tumor immunotherapy.

Cytokeratin is broadly expressed in various advanced cancer including in penile cancer, and seems to be an attractive new cancer-associated antigen for penile cancer immunotherapy. In the present study, we will predict and identify HLA-A2–restricted cytotoxic T lymphocyte (CTL) epitopes from the amino acid sequence of human cytokeratin, then synthesis the predicted peptides.

T cell-based tumor immunotherapy has shown promising results and has appeared as an appealing novel modality of cancer treatment. The Sentinel node is defined as the lymph nodes that first receive lymphatic drainage from a tumor, also being the first nodes to be

exposed to metastatic tumor cells. In colon cancer, we have investigated the feasibility of using sentinel node-acquired lymphocytes for adoptive immunotherapy. The sentinel node-acquired lymphocytes were activated and expanded against autologous tumor extract and returned as a transfusion. We have observed and monitored 16 patients for 4 years. Stage IV patients display a significantly increased survival of 2.6 years compared to control patients 0.8 years, and no toxic side effects or other adverse effects were observed. Thus, freshly isolated sentinel node-acquired lymphocytes can be expanded and safely transfused back to the patient without complications, and these cells are able to elicit significant biological responses.

To develop the immunotherapy for penile cancer, we plan to extract tumor activated T cells from the sentinel nodes, and then stimulate the cells with the tumor antigen for further proliferation of tumor specific $CD8^+$ cells in vitro for the late autotransfusion. The tumor activated T cells will be extracted from the sentinel node of penile cancer patients, and then Tumor extract, Gardasil and the predicted cytokeratin Peptides will be used as tumor antigen to stimulate the extracted T cells *in vitro* to get tumor specific $CD8^+$ cell expansion. The proliferation of $CD8^+$ cells will be evaluated the effect of different stimulators to the tumor specific $CD8^+$ cell expansion. The finding will be valuable for late tumor treatment of patient autotransfusion, and the potential immunotherapy for the other HPV derived genital cancers in the future.

The reagents from ImmunoTools will majorly contribute in investigating the immune response situation for different immune cells of sentinel node, tumor tissue, peripheral blood penile cancer and evaluating the immune respond of expanded $CD8^+$ T cells after different stimulators.

ImmunoTools *special* AWARD for **Jin Hu** includes 25 reagents

FITC - conjugated anti-human CD3, CD8, CD86, HLA-DR, Control-IgG1, Control-IgG2b,

PE - conjugated anti-human CD4, CD25, CD56, CD69, IFN-gamma,

PerCP - conjugated anti-human CD4, CD8,

APC - conjugated anti-human CD8, CD14, CD25, CD69,

Multicolour combinations anti-human:
CD4 FITC / CD8 PE / CD45 PerCP
CD4 FITC / CD8 PE / CD45 PE-Dy647

recombinant human cytokines: rh GM-CSF, rh IFNgamma, rh IL-2, rh IL-7, rh IL-15, rh IL-21

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