Dear Participant,

It is our pleasure to welcome you to the symposium entitled: “New Frontiers in Cancer Immunotherapy” in Fondation Mérieux’s Conference Center “Les Pensières.” We hope you will enjoy this meeting, which brings together some of the world’s foremost experts on Cancer.

The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any questions you may have and to make your stay and conference as comfortable and valuable as possible.

Yours sincerely,

Benoît Miribel
Directeur Général
Fondation Mérieux

P.S.: Your feedback is valuable and allows us to organize conferences of a better quality so please complete the Conference Evaluation form that will be in your package and return it to the front desk before your departure.
New Frontiers in Cancer Immunotherapy
Annecy, Les Penseières, July 9-11, 2007

SCIENTIFIC PROGRAM

Monday, July 9

17.30 - 18.30: Registration

18.30 - 18.45: Welcome address
Christophe Longuet

18.45 - 19.15: Keynote lecture
- Dissecting and manipulating the host immune response to cancer - Hyam Levitsky

19.45: Welcome dinner

Tuesday, July 10

8.30 - 10.50: How to drive tumor-specific immune response?
Chair: H. Levitsky

- 8.30 - 9.05: Optimizing dendritic cells vaccines for cancer - Jacques Banchereau
- 9.40 - 10.00: Targeted antibody approaches - Dimitris Skokos

10.20: Break

10.50 - 19.00: How to enhance function of primed T cells?
Chair: N. Berinstein, E. Shevach

- 10.50 - 11.25: Enhancing cancer vaccines with immunomodulators, clinical overview - Neil Berinstein
- 11.25 - 12.00: Augmenting peptide vaccines with TLR 9 agonist - Pedro Romero
- 12.00 - 12.35: TLR 8 - Rongfu Wang

12.45: Lunch Break
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SCIENTIFIC PROGRAM

14.00 - 14.35: Augmenting cancer vaccination through CD40 pathway - Robert Vonderheide
14.35 - 15.10: Anti CTLA4 and cancer vaccination - Antoni Ribas
15.10: Break
15.40 - 16.15: Manipulating PD1 pathway for cancer vaccination - Mary Keir
16.15 - 16.40: 4-1 B Bigand pathway and cancer vaccines - Byoung S. Kwon
16.40 - 17.15: Redirecting the specificity of T Cells for adoptive cancer therapy - Zelig Eshhar
17.15 - 18.00: IDO Pathway for Treg generation and IMT inhibitor - David H. Munn
19.00: Dinner

Wednesday, July 11
8.00 - 11.35: How to enhance function of primed T cells?
Chair: Z. Eshhar, P. Walden
8.00 - 8.20: Anti IL2 and IL2 - Jonathan Sprent
8.20 - 9.00: Combining interferon with cancer vaccines - Filippo Belardelli
9.10 - 9.50: The potential merits of IL15 and IL-15 Ralpha combination for clinical applications - Yutaka Tagaya
9.50 - 10.35: Combining IL12 with cancer vaccines - Thomas Gajewski
10.35: Break
11.00 - 11.35: Integrating colorectal cancer vaccines with cytotoxic therapy - Richard Harrop
11.35 - 16.40: What kind of appropriate decision can we make today?
Chair: S. Van der Burg, W. Zou

- 11.35 - 12.10: Problems to be solved in the therapeutic vaccination of HPV positive patients - Sjoerd Van der Burg

12.10: Lunch Break

- 14.30 - 15.10: Tregs, Th17 and their regulation in the tumor environment - Weiping Zou
- 15.10 - 15.30: HIV experiences - Giuseppe Pantaleo
- 15.30 - 16.10: Melanoma experience - Pedro Romero

Closing remarks
Ethan Shevach
SESSION
HOW TO DRIVE TUMOR-SPECIFIC IMMUNE RESPONSE?
TUESDAY, JULY 10
DC-based Immunotherapy - which subtype(s) should we use?

Jacques Banchereau, Hideki Ueno, Eynav Klechevsky**, Joseph W. Fay* and A. Karolina Palucka. Baylor Institute for Immunology Research and Sammons Cancer Center*, Dallas, TX, USA; Technion, Haifa, Israel**

Jacques Banchereau
Baylor Institute for Immunology Research
Dallas - USA

Cancer largely remains an unmet medical need. More than 50 years ago it was shown in mice that tumors were immunogenic. Innumerable experiments have shown that protective antitumor immunity can be established in mice. The use of cancer vaccines in humans has yielded however major disappointments. The recent impetus in dendritic cell (DC) biology has revived this area. Ex vivo-generated and antigen-loaded DCs have now been used as vaccines to improve immunity in patients with cancer and chronic HIV infection. In our own series, between March 1999 and February 2005 seventy patients with metastatic melanoma were treated with DCs vaccines in the course of four phase I/IIa clinical trials. Three patients had no evidence of disease upon completion of DC vaccinations. Four patients had experienced objective clinical responses by RECIST criteria (2 CRs and 2 PRs). These included two patients that had failed previous cytotoxic and cytokine therapy. Sixty (60)% of 66 evaluable patients were alive at year one and twenty (20)% of patients are alive as of May 2007. Five of 12 long term survivors had no additional therapy other than DC vaccinations including a patient with CR of liver lesions lasting >80 months. Factors associated with prolonged overall survival include 1) objective clinical responses or stable disease at any time point, normal LDH at entry, M1a substage. The survival benefit associated with DC vaccines needs to be confirmed in randomized trials.

Yet, the clinical efficacy of DC vaccines needs to be improved. Our studies on DC biology demonstrate the complexity of the DC system, which needs to be understood to establish a rational therapeutic manipulation of DCs and improve patient outcomes. The demonstration of in vitro and in vivo priming tumor antigen specific CTLs was carried out in majority of published studies with “classical” monocyte-derived DCs generated with GM-CSF and IL-4. However, we found that myeloid DCs generated in the presence of type I interferon (IFN-DCs), TNF (TNF-DCs) or IL-15 (IL15-DCs) are superior to IL4-DCs in priming specific CD8+ T cell immunity.
DC-based Immunotherapy - which subtype(s) should we use?

Jacques Banchereau, Hideki Ueno, Eynav Klechevsky**, Joseph W. Fay* and A. Karolina Palucka. Baylor Institute for Immunology Research and Sammons Cancer Center*, Dallas, TX, USA; Technion, Haifa, Israel**

Jacques Banchereau
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A possible explanation is the type of DCs that are generated in these cultures. Indeed, culture of blood monocytes with GM-CSF and IL-4 yield a uniform population of immature DC resembling interstitial DCs (intDCs). This contrast with hematopoietic stem cells that, when cultured with GM-CSF and TNF, yield preparations that include intDCs as well as Langerhans cells (LCs). Likewise, monocytes cultured with GM-CSF and TNF, IL-15 or IFN alpha yield cells with phenotype of LCs. Our pre-clinical studies actually demonstrate that LCs are superior in their capacity to prime high affinity melanoma-specific CD8+ T cells able to kill authentic tumor targets. Furthermore, LCs prime Th1/Th2 responses while intDCs prime B cells and T follicular helper (Tfh) cells. Thus, the ultimate ex vivo-generated DC vaccine will be heterogeneous and composed of several subsets, each of which will target a specific immune effector. These ex vivo strategies should help to identify the parameters for DC targeting in vivo, which represents the next step in DC-based vaccination strategies.
RHAMM/CD168-R3 peptide vaccination of patients with hematological malignancies elicits both immunological and clinical responses.

Michael Schmitt
University of Ulm
Ulm - Germany

Patients with myeloid and lymphocytic leukemias (AML, MDS, CML, CLL) and multiple myeloma (MM) express the receptor for hyaluronic acid mediated motility (RHAMM/CD168). RHAMM/CD168 elicits as a leukemia-associated antigen (LAA) both humoral and cellular immune responses in patients before and after allogeneic stem cell transplantation. On the basis of these preclinical data, we initiated a phase I/II R3 peptide vaccination to induce immunological and hematological responses for patients with AML, MDS, MM, CLL overexpressing RHAMM/CD168. Patients were included with positive RHAMM/CD168 expression but with a limited tumor load. At a biweekly interval, RHAMM R3 peptide (300 mcg for the first 12 patients and 1000 mcg for patients 13-24) emulsified with the incomplete Freund’s adjuvant (day 3) and GM-CSF (100 mcg, days 1-5) was administrated four times subcutaneously.

Since December 2004, 19 patients have been enrolled in the study. The first ten patients (2 AML, 4 MDS, 4 MM) have completed the course of four vaccinations and have been completely evaluated. Therapy related adverse events observed under R3-peptide vaccination were erythema and induration of the skin at the site of injection (CTC I°). In 8/10 patients, we detected in the peripheral blood a significant increase of specific CD8+ T cells recognizing the R3 peptide in enzyme linked immunospot (ELISpot) assays and seven-color flow cytometry including tetramer staining. After vaccination with the HLA class I peptide R3 no significant increase of IgG titers against the antigen RHAMM could be detected. Clinically, patients showed a reduction of the tumor-specific expressed antigen RHAMM/CD168 in real-time RT-PCR analysis after vaccination. 3/6 patients with myeloid disorders (1 AML, 2 MDS/RAEB1) showed a reduction of CD33+ cells in FACS analysis of the bone-marrow after four vaccinations from 10 and 7 % to 1-2 and <1%, respectively. One patient with MDS did not need further erythrocyte substitution. Two patients with MM showed a reduction of free light chains in the serum. One patient with AML and one patient with MM showed a progressive disease.

In summary, RHAMM/CD168 induced both immunological and clinical results and therefore constitutes a promising target antigen for immunotherapies in patients with hematological malignancies. RHAMM-R3 peptide vaccination should also be evaluated after allo-PBSCT for the enhancement of a GVL effect and eradication of a minimal residual disease.
Visualizing dendritic - T cell dynamic interactions

Dimitris Skokos1, Guy Shakhar2, Rajat Varma2, Janelle C. Waite2, Thomas O. Cameron2, Randall L. Lindquist1, Tanja Schwickert1, Michel C. Nussenzweig1, 3 and Michael L. Dustin2.

Dimitri Skokos
The Rockefeller University
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T cells survey antigen presenting dendritic cells (DCs) by migrating through DC networks. Upon encountering high potency peptide-MHC complexes (pMHC) in vivo, T cells arrest and maintain contact with DCs for several hours; how lower potency pMHC that are relevant in autoimmunity control T cell migration is unknown. Furthermore, the molecular mechanism that controls T cell stop signals in vivo is unidentified. Here we establish an in vivo model for T cell response to high, medium and low potency pMHC. All potencies of pMHC induce CD69 up-regulation, T cell anergy and retention in lymph nodes. However, only high potency pMHC induce Ca²⁺-dependent T cell deceleration on DCs while inducing calcineurin-dependent anergy. In contrast, lower potency pMHC induce anergy via a bio-chemically distinct process without perturbing T cell dynamics.

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SESSION
HOW TO ENHANCE FUNCTION
OF PRIMED T CELLS?
TUESDAY, JULY 10
Harnessing the immune system to specifically control cancer has been a dream of cancer immunotherapists for many years. Although specific immune responses to tumour associated antigenic targets can be induced in some patients, these immune responses are not sufficiently functional to reproducibly and consistently mediate useful anti-tumour clinical activity. Many checks and balances have been incorporated into the immune response by nature to prevent or reduce the likelihood of autoimmunity or exaggerated protective inflammatory responses. Tolerance to self antigens expressed on tumours is a major limitation in generating functional anti-tumour responses. Many of the pathways and molecular controls of these pathways that mediate this tolerance have recently been identified. Moreover, reagents that can be used in the clinic to manipulate these pathways and augment the functional immune response to cancer have been evaluated in combination with various cancer vaccine approaches. These include: a) pathways to activate professional antigen presenting cells such as through Toll-like receptors, growth factors such as GM-CSF and the CD40 pathway, b) use of cytokines such as IL2, IL12 and Interferon to enhance immune activation and c) pathways that inhibit T cell inhibitory signals or Tregs. Although there are some limitations with the interpretation of many published results, promising combination vaccine/immunomodulator combination treatments based upon published clinical trial results will be discussed.
LECTURE

Augmenting the immunogenicity of peptide vaccines with TLR9 agonists

Pedro Romero
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Lausanne - Switzerland

Peptide based cancer vaccines provide several advantages compared to other types of vaccines. These include their relatively low cost and the possibility to stringently purify and formulate them as pharmacologically defined products. However, from the immunological stand point, peptides are weak immunogens. Indeed, while they efficiently provide signal 1 to specific T cells, they need to be accompanied by other costimulatory signals in order to prime an immune response. It is increasingly accepted that TLR agonists are good candidates for molecularly defined adjuvants. They are thought to efficiently trigger the activation and maturation of dendritic cells which in turn should initiate vaccine specific T cell responses. With these concepts in mind, we have conducted phase I clinical trials of vaccination combining antigenic peptide and a synthetic TLR9 agonist in the same incomplete Freund’s adjuvant emulsion. The vaccine is administered montly via the subcutaneous route to stage III-IV melanoma patients. Monitoring of the vaccine specific CD8 T cell response using fluorescent multimers and differentiation associated cell surface markers by flow cytometry, we have gathered evidence that this is indeed a very potent vaccine formulation. It confers strong immunogenicity to even a melanoma peptide that binds weakly to HLA-A2. In my presentation I will discuss our recent results as well as their implications for vaccine optimization.
Regulatory T (Treg) cells play an important role in the prevention of autoimmune diseases by suppressing immune responses, but may have a detrimental effect on immune responses against cancer and infectious diseases. Consistent with this notion, increased proportions of CD4+ CD25+ Treg cells in total CD4+ T cell populations have been observed in patients with different types of cancers. In addition to previously known CD4+ Treg cells, we recently identified a dominant population of gamma-delta TCR T cells from prostate and breast cancers. These unconventional T cells function as Treg cells because they have potent ability to inhibit naive and effector T cell proliferation and to block DC maturation and function. Therefore, the key to successful immunotherapy of cancer is to control the suppressive function of conventional (alpha-beta TCR) CD4+ Treg cells as well as unconventional gamma-delta TCR Treg cells. Although we recently describe a novel mechanism linking Toll-like receptor (TLR) 8 signaling to the control of CD4+ Treg cell function, it is not clear whether the TLR8 signaling is required for the functional regulation of gamma-delta TCR Treg cells. We now show that TLR8 signaling pathway is shared by different subsets of Treg cells for the control of their suppressive function. We further identify the downstream key molecules or pathways required for linking between TLR8 activation and Treg cell function. Adoptive transfer of TLR8 ligand-stimulated Treg cells into tumor-bearing animal models enhanced antitumor immunity. These results provide new insights into functional regulation of different subsets of Treg cells, raising the possibility that manipulation of Treg cells by TLR signaling may improve therapeutic potential of cancer vaccines.

References:

The cell-surface molecule CD40, a member of the tumor necrosis factor receptor superfamily, broadly regulates immune activation and mediates tumor apoptosis. CD40 is expressed by dendritic cells, B lymphocytes, monocytes, and other normal cells. Considerable data demonstrate that signaling via CD40 activates APC including dendritic cells and B cells. The natural ligand for CD40 is CD154, which is expressed primarily on the surface of activated T lymphocytes and provides a major component of T-cell «help» for immune responses. Agonistic CD40 antibodies substitute for the function of CD4+ lymphocytes in murine models of T cell-mediated immunity. In tumor-bearing hosts, CD40 agonists trigger effective immune responses against tumor-associated antigens. CD40 is also expressed on many tumor cells and mediates a direct cytotoxic effect. Engagement of CD40 on tumor cells results in apoptosis in vitro and impaired tumor growth in vivo.

We recently completed a first-in-human clinical trial of the agonistic, fully human CD40 mAb CP-870,893 (Pfizer). CP-870,893 activates human APC in vitro and inhibits growth of human tumors in both immune-deficient and immune-reconstituted mice. Twenty-nine patients with refractory solid tumors were treated with a single intravenous dose of CP-870,893, and the maximum tolerated dose was estimated as 0.2 mg/kg based on dose-limiting toxicities observed at higher doses (venous thromboembolism in one patient and grade 3 headache in a second patient). The most common adverse event was cytokine release syndrome (grade 1 or 2), which typically manifest as chills, rigors, and fevers on the day of infusion and associated with acute elevations of serum TNF-alpha and IL-6. Transient laboratory abnormalities affecting lymphocytes, platelets, D-dimer and liver function tests were observed 24-48 hrs after infusion. Four patients with melanoma (14% of all patients and 27% of melanoma patients) had objective partial responses by RECIST, sustained in one patient at 18+ months. CP-870,893 infusion resulted in a marked, rapid, and dose-dependent decrease in the percentage of CD19+ B cells in peripheral blood and a marked, rapid upregulation of CD86. Overall, the CD40 agonist mAb CP-870,893 was well-tolerated, biologically active, and was associated with anti-tumor activity. Further studies of repeated doses of CP-870,893 alone and in combination with antineoplastic agents, including vaccines and other immunotherapies, are warranted.
The human immune system has developed multiple ways to avoid reacting against endogenous tissues to prevent the development of autoimmunity. Cancer cells exploit these processes and can grow largely ignored by the immune system. Improved understanding of these negative immune regulatory mechanisms has allowed the testing of new immunotherapy drugs for cancer.

The majority of immune regulatory molecules that shape immune responses to cancer are co-stimulatory and co-inhibitory surface receptors and ligands, which are accessible to monoclonal antibodies. The cytotoxic T lymphocyte antigen 4 (CTLA4) is a main negative regulator of the immune system, which inhibits the costimulatory signaling for T cells provided by CD80 (B7.1) and CD86 (B7.2). Preclinical studies pioneered by James P. Allison and colleagues demonstrated that blocking antibodies against CTLA4 could induce regression of some murine tumors.

Based on the data from preclinical models, two CTLA4 blocking monoclonal antibodies entered clinical development approximately 6 years ago, and are currently in pivotal clinical trial testing. Ipilimumab (formerly MDX010) was developed by Medarex Inc. and is currently in joint clinical development with Bristol-Myers-Squib. This is an IgG1 fully human monoclonal antibody made in HuMab mice. CP-675,206 from Pfizer Inc. was transiently called ticilimumab, a name that had to be discontinued due to similarity with another monoclonal antibody. It is an IgG2 fully human monoclonal antibody generated at Abgenix using XenoMice.
Early clinical data demonstrated that both antibodies lead to objective durable tumor regressions in a subset of patients with metastatic melanoma. Across several clinical trials, including dose escalation, single dose, multi-dose, and in combination with a variety of other immune stimulants like peptide vaccines or interleukin-2, objective tumor responses in the range of 10 to 20% were obtained in patients with in-transit and metastatic melanoma.

The early clinical testing also demonstrated that these CTLA4 blocking antibodies can lead to significant toxicities, most with an inflammatory or immune mediated mechanism of action. These include colitis and skin rash as the most common toxicities, and a variety of autoimmune processes against multiple organs including the hypophysis, eyes, thyroid, liver, pancreas and joints. Some of these toxicities require immune suppressive therapy and may lead to permanent damage in occasional patients.

Both programs have proceeded to pivotal trials in patients with metastatic melanoma. A large phase II clinical trial of single agent ipilimumab in second line therapy concluded enrollment in January of 2007, while a similar clinical trial with CP-675,206 concluded enrollment in October 2006. Both clinical trials had response rate as primary endpoint, with the major difference in patient eligibility being the exclusion of patients with high LDH in the study with CP-675,206.

A large phase III clinical trial comparing DTIC with the combination of DTIC plus ipilimumab is currently enrolling patients. This clinical trial has as primary endpoint progression free survival at 6 months. The phase III testing of CP-675,206 has the primary endpoint of overall survival, and compares single agent CP-675,206 with DTIC or temozolomide.

In conclusion, two monoclonal antibodies blocking CTLA4 are in the late stages of clinical development for the treatment of metastatic melanoma. Both antibodies have demonstrated ability to break tolerance to self-tissues and result in objective cancer regressions, most lasting years.
Immune surveillance functions as a primary line of defense against cancer. The ability of the immune system to recognize and eliminate cancerous cells is advantageous; non-specific forms of cancer elimination, like chemotherapy, target all rapidly dividing cells, which can cause serious side effects in patients. Despite the potential of the immune system to eliminate cancerous cells, studies have shown that the majority of tumor-specific immune cells in the peripheral circulation of cancer patients have been inactivated, and are consequently unable to effectively target and attack malignant tumor cells. The tumor microenvironment itself can also promote immune cell activation. Therefore, much interest has been focused on identifying and exploiting mechanisms of tumor immune evasion. Among these pathways, significant gains have been made in understanding the role of costimulatory molecules of immune cell co-receptors, in tumor immunology. Encouraging clinical data has shown therapeutic promise for targeting CTLA-4, a member of the CD28/B7 superfamily, in the generation of effective anti-tumor immunity.

PD-1, another member of the CD28/B7 family, participates in the induction and maintenance of peripheral tolerance. PD-1 is upregulated on CD4+ and CD8+ T cells after activation, and functions to downregulate antigen receptor responses. PD-1 has two ligands, PD-L1 and PD-L2, with distinct expression patterns. PD-L1 is expressed broadly on hematopoietic and parenchymal cells, while PD-L2 expression is limited to antigen presenting cells such as macrophages and dendritic cells. In viral systems, PD-1 has been identified as a key molecule that is upregulated on exhausted, or anergic, cells and antibody blockade of PD-1 or its ligand PD-L1 has been shown to reactivate antigen-specific T cell responses. In the absence of PD-1 or PD-L1, T cells undergo sustained proliferation and make an increased amount of inflammatory cytokines, such as IFN-γ and TNF-α. The robust responses to antigen in the absence of PD-1 or PD-L1 are reflected in the increased incidence and severity of autoimmunity in several mouse models. Therefore, PD-1 and PD-L1 can function to inhibit antigen-specific T cell responses, but loss of these inhibitory molecules may result in autoimmunity.
PD-1 ligands are expressed on several tumor cell lines from various tissues, including breast cancer and lymphomas, which may increase the ability of these transformed cells to evade immune detection. PD-L1 expression on carcinomas is correlated with poor clinical prognosis of renal and gastric carcinomas, breast cancer carcinomas, and esophageal cancers. Expression of PD-L2 has been found on a unique subtype of B cell lymphomas. In vitro blockade of PD-L1 enhances tumor-specific T cell responses and PD-1−/− mice have an increased resistance to tumor engraftment and growth that correlates with increased effector cytokine production and the preservation of tumor-specific T cell responses in tumor-bearing mice. These findings suggest a promising role for PD-1 and PD-L1 in tumor immunity and immunotherapy, and therapeutics are currently being developed to exploit this pathway in the clinic. However, the shared expression of PD-L on tumors and on tissues that are the target of autoimmune attack (e.g. the pancreas) may complicate therapeutic blockade strategies for tumor immunotherapy. Long-term treatment of patients with PD-1 or PD-L1 neutralizing antibodies may induce autoimmune responses as an unintended consequence of therapy, a possibility that will require further study.
Mechanisms involved in synergistic anti-cancer effect of combination between chemotherapeutics and anti-4-1BB

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Cross-linking of 4-1BB on CD8+ T and NK cells by anti-4-1BB produced a strong anti-tumor effect, resulting in complete remission of established tumors in immunogenic tumor models. 4-1BB-mediated tumor therapy, however, have not caused a complete eradication of poorly immunogenic or non-immunogenic tumors. Because 4-1BB is induced by some of the chemotherapeutics on T cell surface and cross-linking of the 4-1BB by anti-4-1BB protected the T cells from apoptosis, we tested whether the combination of anti-4-1BB and chemotherapeutics produced a synergistic therapeutic effects. Combination of anti-4-1BB with cyclophosphamide or cisplatin showed a synergistic anti-cancer effect in the poorly immunogenic tumors. Anti-4-1BB protected naive T cells as well as effector/memory and memory T cells from chemotherapeutics-mediated killing. Anti-4-1BB induced a rapid repopulation of T and B cells after the chemotherapy. It appears that anti-4-1BB preferentially expands the tumor-specific lymphocytes when the lymphocytes were repopulated after the chemo-mediated lymphopenic condition because the combination treatment group produced 2.4-fold more tumor-specific lymphocytes than anti-4-1BB alone did. The tumor-free mice from the combination therapy showed the formation of a long-lasting anti-tumor memory. Treatment with anti-4-1BB and cisplatin resulted in the prevention of cisplatin-mediated nephrotoxicity. We found that 4-1BB was induced on the kidney tubular epithelium upon receiving cisplatin. It appears that cross-linking of the 4-1BB protected renal tubular epithelium from chemo-mediated apoptosis. We present data that the combination of genotoxic agents such as chemotherapeutics, or γ-radiation with anti-4-1BB will synergize the tumor killing and reduce global or organ-specific toxicity.
Redirection of T cells with antitumor specificity: towards clinical trials

Zelig Eshhar
The Weizmann Institute of Science
Rehovot - Israël

We have pioneered and developed the ‘T-body’ approach in which the patient’s own T and NK cells are redirected with antibody specificity to fight his/her cancer. T-bodies are effector lymphocytes genetically modified to express chimaeric receptors composed of antibody recognition unit in the form of scFv linked to intracellular co-stimulatory and stimulatory domains of T-cells’ receptor chains. Following to the expression of cancer-specific tripartite chimeric receptor, T-bodies are geared to undergo full activation in non-MHC dependent or restricted manner and eliminate the cancer target. As such T-bodies have a non-individual specificity, can be applied to a broad spectrum of patients and can eliminate cancer cells that have evaded the immune system by not expressing either HLA and/or co-stimulatory ligands such as B7. For our studies we have chosen to redirect the T-bodies to HER2/neu that is over-expressed in several types of tumors, is associated with more aggressive phenotype of both tumors and metastases. Using several prostate and breast xenografts in the SCID mouse model, we have demonstrated the ability of human PBL endowed with HER2/neu specificity to recognize and eliminate established PC growing either orthotopically in the murine prostate or mammary gland or bone lesions. Intratumoral administration of T-bodies into localized tumors were effective in the rejection of relatively large volume of tumors. To obtain a therapeutic effect following to a systemic administration of T-bodies, the mouse ‘patients’ have to be pretreated by mild lymphoablative regimens of irradiation and/or cyclophosphamide. Interestingly these treatments induced an increased levels of the chemokine SDF-1, the receptor of which CXCR4 is being down regulated on the surface of the T-bodies during their ex-vivo transduction process. IL-2, as well as other homeostatic interleukines (e.g. IL-7, IL-15) help to improve the persistence and anti-tumor effect of the T-bodies in-vivo. This was also manifested by their better ability to home in to the PC xenografts in remote sites, including bone metastases, undergo activation at the tumor site and specifically arrest the growth and reject the cancer xenografts. Our, and similar studies of others in different types of cancer have provided a proof of concept in animal models for phase I clinical trials in various types of cancer patients that are either carried out already or are in an advanced stage of preparation in several centers world wide.
Redirection of T cells with antitumor specificity: towards clinical trials

Zelig Eshhar
The Weizmann Institute of Science
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To study the function of naïve T-cells redirected with antibody-type specificity, we have generated various transgenic (Tg) mouse strains in which the tripartite chimeric receptor (TPCR) genes were expressed under the CD2 enhancer/promoter that directs their expression in T and NK cells. Naïve T cells of different sub-populations from these mice, specific to either tumor antigen (HER2/neu or to TNP manifested their full function in vitro following to their activation in the absence of MHC or co-stimulatory ligands. Tg mice expressing HER2/neu-specific TPCRs rejected completely HER2/neu-expressing syngeneic tumors, either in their solid state or in experimental lung metastatic models. No preconditioning of the mice with lymphoablative (e.g. sublethal irradiation or cyclophosphamide) treatments or vaccination. Moreover, Tg T-cells adoptively transferred to tumor-bearing wild-type mice prevented metastases formation in the lungs and prolonged the survival of the treated mice. Importantly, lymphoablation and IL-2 were needed to obtain substantiated effect.

Comparison between the transgenic to ex-vivo T-bodies transduced provides us with clues of how to improve the later for anticancer treatment.
Tumor-draining lymph nodes (TDLNs) undergo profound alteration due to the presence of the upstream malignancy. Presentation of tumor-derived antigens in the milieu of the TDLN not only fails to elicit a protective immune response, but may actively create systemic tolerance toward these antigens. The tolerogenic mechanisms active in tumors and TDLNs constitute an important barrier to effective immunotherapy.

In mice, a subset of plasmacytoid dendritic cells (pDCs) in TDLNs expressed high levels of the immuno-suppressive enzyme indoleamine 2,3-dioxygenase (IDO). IDO+ pDCs from TDLNs suppressed the proliferation of effector CD4+ and CD8+ T cells, both in vitro and in vivo, and rendered the suppressed T cells durably anergic. In addition, IDO+ TDLN pDCs caused marked activation of CD4+CD25+Foxp3+ Tregs. Resting Tregs exposed to IDO+ pDCs became rapidly activated for potent suppressor activity, without the need for mitogen or exogenous anti-CD3 crosslinking. IDO-induced Treg activation was MHC-restricted, required an intact GCN2-kinase signaling pathway in the Tregs, and was abrogated by blocking antibodies against CTLA4. Tregs activated by IDO caused suppression of target T cells via a novel mechanism. IDO-activated Tregs caused marked upregulation of PD L1 and PD L2 expression on target DCs, and the ability of IDO-activated Tregs to suppress target T cell proliferation was abrogated by blocking antibodies against the PD 1/PD ligand pathway. In contrast, Tregs activated by αCD3 crosslinking did not cause upregulation of PD-ligands on DCs, and suppression by CD3-activated Tregs was unaffected by blocking the PD 1/PD ligand pathway. In vivo, Tregs isolated directly from tumor-draining LNs showed potent PD 1/PD ligand-mediated suppression, which was selectively lost when tumors were grown in IDO-knockout hosts. We hypothesize that IDO+ pDCs and IDO-activated Tregs act synergistically to create a profoundly suppressive microenvironment within the TDLN.
IDO, Treg activation and 1MT inhibitor in cancer

David H. Munn
Medical College of Georgia
Augusta - USA

In human subjects, IDO-expressing host cells with plasmacytoid morphology are found in draining LNs of patients with melanoma, breast cancer and other tumors. In patients with melanoma, the presence of IDO+ host cells in draining (sentinel) LNs was associated with a significantly worse long-term survival. In breast cancer, upregulation of IDO in TDLNs could be found at all stages of tumor progression, including very early lesions such as ductal carcinoma in situ (DCIS). IDO can also be expressed by tumor cells themselves, including expression in ovarian cancer, colon cancer, AML and other malignancies, and expression of IDO may correlate with worse prognosis.

The IDO-inhibitor drug 1 methyl tryptophan (1MT) is in development for Phase I clinical trials. This drug exists in two stereoisomers (D and L). L-1MT was the more potent inhibitor of IDO activity using the purified enzyme or HeLa cells; whereas D-1MT was more effective in reversing the suppression of T cells created by IDO+ DCs, using both human monocyte-derived DCs and murine TDLN pDCs. In murine in vivo studies, 1MT showed synergy with a number of conventional chemotherapy agents, and the D isomer was more efficacious than the L isomer for chemo immunotherapy. Synergy between 1MT and chemotherapeutic agents has been demonstrated using cyclophosphamide, paclitaxel, gemcitabine, doxorubicin and cisplatin.

We hypothesize that the combination of 1MT + chemotherapy acts to disrupt the state of established immunologic tolerance toward tumors. Breaking tolerance with 1MT + chemotherapy may thus open a window of opportunity for enhanced efficacy of vaccines or other immunomodulatory agents.
SESSION
HOW TO ENHANCE FUNCTION
OF PRIMED T CELLS?
WEDNESDAY, JULY 11
LECTURE

Modulating cytokine function with antibodies

Onur Boyman, Marc Rubinstein, Charles D Surh, Jonathan Sprent

Jonathan Sprent
Garvan Institute of Medical Research
Sydney - Australia

The biological activity of IL-2 and other γc cytokines on mouse T cells in vivo can be enhanced by association with certain anti-cytokine mAbs. For IL-2, binding to S4B6 and related anti-IL-2 mAbs greatly augments the activity of both exogenous and endogenous IL-2 for cells expressing the low-affinity βγIL-2R, namely CD8 cells and NK cells. For IL-2 and IL-7, association with specific mAbs can be used to augment the expansion of naïve CD8 cells, as well as memory CD8 and NK cells. How mAb binding boosts the activity of cytokines is unknown but the phenomenon applies only in vivo and not in vitro and requires intact mAb. For other cytokines, the activity of IL-15 can be increased by association with soluble IL-15Rα. Like IL-2, IL-15 binds to the low-affinity βγIL-2R. Some T cells, notably T regulatory cells (Tregs) express the high-affinity αβIL-2R. Significantly, association of IL-2 with one particular IL-2 mAb, JES6-1, can be used to cause selective expansion of Tregs in vivo. The potential applications of these findings will be discussed.
Half a century has passed since the discovery of interferons (IFNs) as antiviral factors released by virus-infected cells. In the early 1980s, when recombinant IFNs became available, it begun to be recognized that this family of cytokines, comprising the type I or "viral" IFNs (mainly IFN-α, IFN-β) and the type II or "immune" IFN (IFN-γ), could also exert multiple biological activities on cell growth, differentiation and immune response. IFNs-α are the cytokines with a longest record of clinical use and are still extensively used in patients with some malignancies and viral diseases, while IFN-γ is currently used in patients with multiple sclerosis. An ensemble of recent studies have underscored new effects of IFNs (especially type I IFN) on cells of the immune system (including T cells and dendritic cells), which are important in linking innate and adaptive immunity. Thus, in mouse models, type I IFN can act as a powerful vaccine adjuvant by acting on dendritic cells (DCs). Likewise, DCs rapidly generated from human monocytes after exposure to IFN-γ (IFN-DCs) act as powerful cellular adjuvants for the generation of MHC class I restricted CD8+ T cell responses against viral (HIV and EBV) and tumor (melanoma) antigens and efficiently cross-present complex antigens in the context of MHC class I antigens, resulting in a potent in vivo cross-priming of CD8+ T cells. On the whole, the preclinical data suggest that these IFN-DCs exhibit some unique characteristics particularly suitable for the generation of effective DC-based vaccines. Of note, the results of a pilot clinical trial aimed at assessing the effectiveness of IFN-γ administered as a vaccine adjuvant in melanoma patients injected with a peptide-based vaccine showed a remarkable increase of the expansion of blood-derived tumor specific CD8+ T cells. Thus, new therapeutic strategies can now be based on a novel rationale for using IFN-γ including the direct in vivo use of these cytokines as vaccine adjuvants and their in vitro use to generate highly active patient’s monocyte-derived DCs to be utilized in therapeutic vaccination protocols. The immune suppression features frequently observed in cancer patients could be effectively restored by IFN-induced immune interventions targeted to DCs and by additional combination treatments. Clinical studies are expected to provide evidence on the importance of IFN-DC interactions in patients and on the perspectives of this novel use of IFN-γ in immunotherapy protocols.
Interleukin-15 (IL-15) plays a crucial role in the development of natural killer (NK) and CD8 T cells. IL-15 also augments the cytotoxicity of these cells. Thus IL-15 facilitates the eradication of tumor cells and virally infected cells through the activation of cytotoxic immune cells. This feature of IL-15 renders it a promising candidate for clinical interventions including vaccine therapies. To this end, attempts are being made at the National Institutes of Health (USA) to prepare a large amount of GMP-grade recombinant human IL-15.

Previous data from our group demonstrated a strong adjuvant effect of IL-15 on the establishment of CD8-mediated immunity in mice using a vaccinia construct carrying an HIV-epitope and IL-15 (Ou, Berzofsky, Waldmann and Liyanage PNAS 2003). Notably this effect was very persistent. Because of its stable interaction with the IL-15Ralpha on cell surfaces (Dubois, Waldmann and Tagaya, Immunity 2002), IL-15 effects in vivo sustain much longer than those by other cytokines (Sato, Waldmann and Tagaya PNAS 2007). For example, a similar vaccinia construct carrying IL-2, instead of IL-15, triggered better response in mice than IL-15 at first, but its effect quickly decayed with time. The effect of recombinant IL-15 injected into an IL-15Ralpha transgenic mouse was remarkably augmented and sustained. Thus one of the unique features of IL-15 effects in vivo is its persistency, which is mediated by the presence of the IL-15Ralpha molecule.

Based on our data, we propose to consider IL-15/IL-15Ralpha as a membrane-associated dimer cytokine. The enhancement of IL-15 activity in vivo and the therapeutic efficacy of recombinant IL-15 in humans depend on the simultaneous expression of IL-15Ralpha, either by an intrinsic constitutive mechanism or by external manipulations. The potential benefit of, together with some practical precautions for, the combined use of IL-15 and IL-15Ralpha in vivo will be discussed.
IL-12-based immunization in melanoma: mechanisms of response versus resistance.

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The complexities of an anti-tumor immune response, and the mechanisms of tumor escape from the immune system, are just beginning to be unravelled. The molecular identification of tumor antigens has enabled the development both of monitoring tools for analyzing details of the immune response in patients, and also the creation of tumor antigen-specific vaccine approaches. We have explored immunization approaches using melanoma tumor antigen peptides co-administered with the cytokine IL-12, which promotes generation of effector CD8+ T cells. Vaccination of patients with advanced melanoma induces detectable increases in antigen-specific CD8+ T cells, and has resulted in clinical responses in around 10% of cases. The fact that tumors can progress despite the presence of specific T cells in the blood has prompted studies of the melanoma microenvironment. Using gene expression profiling and confirmatory assays, we have identified two potential categories of resistance to T cell-based tumor regression. First, some tumors express a chemokine profile that can mediate recruitment of CD8+ effector cells and some do not. Thus, failed T cell migration is likely one important barrier. Second, tumors that contain CD8+ T cells have the highest presence of negative regulatory factors that can suppress T cell function. These include IDO, PD-L1, and FoxP3+ regulatory T cells. Tumors also contain minimal levels of B7 costimulatory ligands, arguing for an anergy-promoting environment as well. Preclinical experiments have supported a mechanistic role for each of these inhibitory processes in regulating anti-tumor immunity. Our results suggest that promoting T cell migration, and interfering with negative regulatory factors, in the tumor microenvironment may be necessary to achieve optimal efficacy of melanoma vaccines.
MVA-5T4 (TroVax) Induces Potent Immune Responses When Administered to Colorectal Cancer Patients in Combination With Chemotherapy

Miles W Carroll
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The cancer vaccine TroVax is based on the oncofetal tumour associated antigen 5T4, delivered by the highly attenuated poxvirus MVA. The glycosylated 5T4 protein is expressed on the surface of a broad spectrum of common carcinomas including colorectal, breast, prostate and renal.

The safety and immunogenicity TroVax has previously been assessed in colorectal cancer (CRC) patients, at least 10 weeks, after completion of first or second line chemotherapy. The study illustrated that TroVax can induce 5T4 antibody and CD4 proliferation responses in the majority of patients. However in this early study there was a paucity of detectable CD8 responses.

In two recently completed Phase II clinical studies TroVax was administered before, during and after completion of standard of care CRC chemotherapy that consisted of 5FU plus Oxaliplatin or 5FU plus Irinotecan. Both antibody and CD8 ELISPOT analysis was performed at a variety of time points. Encouragingly, significant 5T4 CD8 ELISPOT frequencies were detected using pools of 5T4 peptides. Additionally, there was an increase in the intensity of the 5T4 antibody responses in patients that received TroVax in combination with chemotherapy compared to TroVax vaccination in the absence of chemotherapy. Furthermore, there was a statistically significant relationship between 5T4 immune response and clinical outcome in this study.

In summary, TroVax is safe and well tolerated when administered in combination with chemotherapy. TroVax appears to induce a more efficacious immune response in the chemotherapy setting, which may be due to the effects of lytic tumour cell antigen release and or the effect of chemotherapy on regulatory T cells.
SESSION
WHAT KIND OF APPROPRIATE DECISION CAN WE MAKE TODAY?
WEDNESDAY, JULY 11
Problems to be solved in the therapeutic vaccination of HPV positive patients

Sjoerd Van Der Burg
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Leiden - The Netherlands

Cervical carcinomas arises as result of an uncontrolled persistent infection with a high-risk type of human papillomavirus, in particular types 16 (HPV16) and 18 (HPV18) that account for approximately two-third of these cancers. The HPV E6 and E7 proteins play a pivotal role in carcinogenesis and are expressed in both pre-malignant and advanced cervical lesions. Because HPV proteins are foreign to the body, one would expect the immune system to mount a response against these antigens when expressed in the cervical epithelium. Indeed, circulating HPV16 E6, E7 and E2-specific Th1- and Th2-type CD4+ T-cells, able to migrate into the skin upon antigenic challenge, were frequently detected in healthy individuals, showing that successful defense against HPV16 infection is commonly associated with the installment of a systemic effector T-cell response against these viral antigens. In contrast, the development of high-risk HPV-positive cervical cancer is associated with a HPV-specific T-cell response that fails at least at three different levels. In about half of the patients, PBMC lack the capacity to mount a detectable proliferative response against HPV16 E6, E7 and E2, whereas the other half displayed antigen-specific proliferative responses exhibiting a non-inflammatory cytokine profile. Analysis of the local immune response revealed that in many cases HPV-specific effector T-cells failed to home to the tumors or to infiltrate the cancer cell nests. Moreover, we recently demonstrated that HPV E6- and E7-specific CD4+ regulatory T-cells can be isolated from lymph node biopsies of cervical cancer patients and, moreover, that such T-cells can infiltrate tumors, suggesting that anti-tumor immunity in cervical cancer patients is suppressed at both the induction and effector level. Notably, the viral antigens concerned are the prime components of all therapeutic vaccines against cervical cancer that are currently under development. Although such vaccines are designed to enhance CD4+ and CD8+ T-cell effector immunity against the E6 and E7 oncoproteins of HPV16 and/or 18, the presence of pre-existing E6 and E7-specific CD4+ regulatory T-cells in lymph nodes and tumors from cervical cancer patients brings forward the possibility that vaccination might also – or instead – result in activation and expansion of this regulatory T-cell subset. Our data argue that this scenario must be taken into account when vaccinating cervical cancer patients with E6/E7-specific vaccines, and indicate that strategies to eliminate or disarm regulatory T-cells prior to vaccination, which are now widely considered in the context of modalities that aim at inducing effective immune responses against tumor-associated auto-antigens, should also be considered for immunotherapeutic strategies against cancers with viral etiology.
IL-17+ T cells and their regulation in the tumor microenvironment

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IL-17+CD4+ T cells (Th17) play an active role in inflammation and autoimmune diseases. However, the nature and regulation of Th17 in the context of tumor immunity remain unknown. We have studied the distribution and regulation of IL-17+ T cells.

We observed 2 populations of IL-17+ T cells: IL-17+CD4+ T cells and IL-17+CD8+ T cells. Primary IL-17+ T cells are largely found in lung and digestive mucosa compartments in normal mice. The number of CD4+IL-17+ T cells and CD4+FOXP3+ Treg cells was gradually and synchronically increased in the tumor microenvironment during tumor development. However, there were limited IL-17+CD8+ T cells in the early stages of tumor growth with greater numbers of IL-17+CD8+ T cells appearing in later stages of tumor development. Although the trend of increase was similar between Treg cells and IL-17+CD4+ T cells in the tumor, the prevalence of Treg cells was significantly and constantly higher than that of IL-17+ T cells in the tumor. Further, the number of IL-17+ T cells remained limited during tumor development in the tumor draining lymph nodes, including advanced tumor stages. TGFβ and IL-6 are the key cytokines capable of stimulating IL-17+CD4+ cell differentiation. High levels of TGFβ and IL-6 are often observed in the tumor environment. Why, then do we observe limited levels of IL-17+ T cells and high levels of Treg cells? The data suggest that certain factor(s) may suppress IL-17+ T cells and promote Treg cells in the tumor environment factors.

IL-2 is crucial for the production and function of Treg cells. IL-2 is used to boost immunity in patients with cancer. We observed that IL-2 promotes Treg cells and inhibits IL-17+ T cell pool in human and mice with cancers. Consistent with these data, tumor infiltrating T cells are capable of producing high levels of IL-2. This may explain why the levels of Treg are high and the numbers of IL-17+ T cells are limited in the tumor microenvironment. The work reveals a novel role for IL-2 in controlling the balance between IL-17+ and Treg cells.
On the hand, active inflammation is often accompanied with local immune infiltration, activation and IL-2 production in multiple autoimmune diseases. IL-2 strongly suppresses Th17 cell differentiation. Why, then, have we often observed an accumulation of Th17 cells in certain autoimmune diseases? The reason may lie in the fact that IL-17+ T cell pool may be controlled by a complicated local environmental cytokine network, and the suppressive effects of IL-2 on Th17 cells may be subverted by other cytokines. In fact, we observed that IL-1 and IL-2 play opposite roles in controlling IL-17+ T cells. Further, IL-1 stimulates and restores multiple gene transcripts involved in regulating Th17 cell differentiation including RORγt, IL-23 receptor and IL-1 receptor. IL-1 completely subverts the suppressive effects of IL-2 on Th17 cell differentiation. Interestingly, although IL-1 is produced in the tumor environment, high levels of IL-1 antagonist are able to neutralize the effects of IL-1. Therefore, it may further explain why there are limited numbers of IL-17+ T cells in the tumor microenvironment.

In summary, we show that IL-1 and IL-2 play opposite roles in controlling IL-17+ T cells. Local cytokine networks may determine IL-17+ T cell pool in multiple disease models including tumor and autoimmune diseases.
Monitoring adaptive anti-tumor responses: the melanoma experience

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Studies in many laboratories have demonstrated that naturally acquired T cell responses are often detectable in metastatic melanoma patients and even in other cancer types. The first experimental system that allowed to show evidence for this was the so-called autologous mixed lymphocyte tumor cell culture. Through this culture system, cloned T cells from patients displaying specific tumor reactivity provided the tools to clone tumor associated antigens.

Recent progress in monitoring antigen-specific T cells enables direct quantitation and thorough phenotypic and functional characterization. In particular, fluorescent peptide-MHC multimers allow to directly visualize antigen-specific T cells by flow cytometry for their enumeration, characterization and isolation as single T cell clones. We have used exploited the possibilities provide by this approach to study in detail both CD8 and CD4 T cell responses to several melanoma associated antigens such as Melan-A/Mart-1 and NY-ESO-1. In my talk I will present a summary of our main findings and their application to cancer vaccine design and monitoring in the context of phase I clinical trials.
Activation of human dendritic cells by Viscum album preparations: Possible mechanism of immunomodulation in tumor regression

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Cancer is the disease in which the cells in the body undergo uncontrolled growth endangering the individual’s own survival. The secretion of various factors by the growing tumor cells lead to the inactivation of the immune system. Various therapies to treat cancer have been proposed which can involve the tumors, its microenvironment and the immune system. Immunotherapy of cancer can help the individual to fight the growing tumor and also become healthy. However, very few therapies can boast of killing the tumor and stimulating the immune system. The presence of cytotoxic properties against tumor and stimulatory capacity towards the immune system is not common.

Viscum album (VA) preparations are used as a complimentary therapy in cancer. Even though, they have been used in clinical practice for many decades, the exact mechanism of action of these preparations is still unclear. The biologically active components of VA preparations include Mistletoe lectins (ML), viscotoxins, several enzymes, peptides (such as viscumamide), amino acids, thiols, amines, polysaccharides, cyclitoles, lipids, phytosterols, triterpines, flavonoids, phenylpropanes and minerals. In addition to their cytotoxic properties, they have also been shown to have immunomodulatory properties that facilitate tumor regression. In the present study, we hypothesize that the effect of VA preparations on the dendritic cells (DCs) may be one of their immune modulatory mechanisms that help in effective tumor regression. VA M Spez and VA Qu Spez at 10µg/ml show increased expression of antigen presenting HLA-DR molecule and co-stimulatory CD40, CD80 and CD86 molecules on the DCs after 48 hrs of treatment accompanied with increased IL-6, IL-8 and IL-1β secretion. The ability of the DCs treated with VA preparations on the proliferation of allogenic CD4+ T cells substantiates the trend that was observed in the expression of various surface molecules and in the secretion of pro-inflammatory cytokines.

Further studies of the status of DCs in the patients treated with VA preparations can help to understand their immunostimulatory properties.
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Annecy is a splendid town full of art treasures, as well as the perfect city for sports and leisure activities.

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Le Freti (Local Cuisine)
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