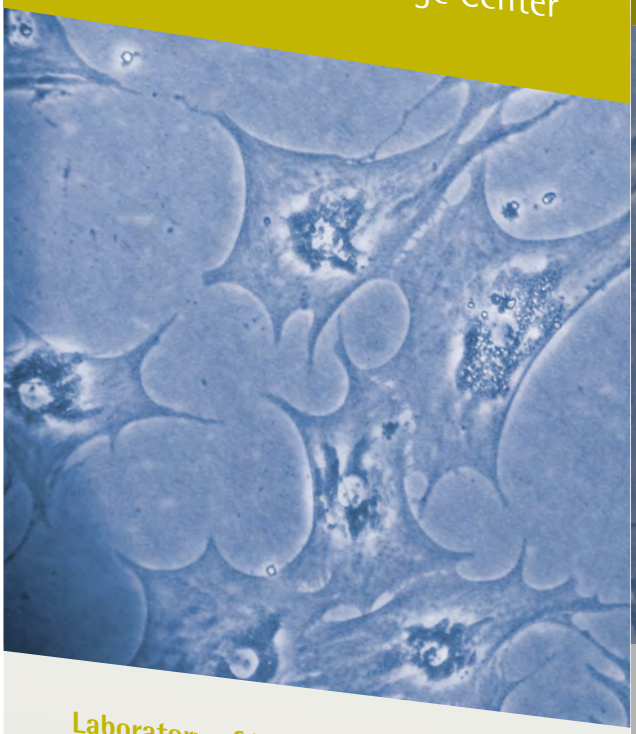
IOF Knowledge Center



Laboratory of Molecular and Cellular Therapy

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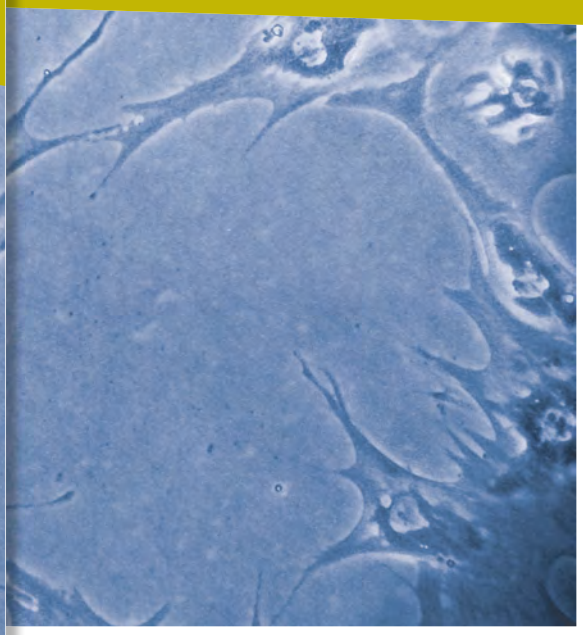

Dendritic cells

tious diseases. The LMCT developed different **strategies to genetically modify dendritic cells.** A first extensively studied platform uses **messenger ribonucleic acids (mRNA)** to reprogram dendritic cells. This approach has successfully been evaluated for *ex vivo* as well as *in vivo* modification of dendritic cells. The **TriMix technology** platform has been developed specifically for this approach and allows to optimize the stimulatory capacity of dendritic cells. The use of the TriMix technology represents a turning point in the quest for an effective dendritic cell-based immunotherapy.

A second platform uses **lentiviral vectors:** these are HIV-1 derived vectors that are targeted to specific cell types, based on the presence of nanobodies® that specifically bind to that cell type. A proof-of-concept on the **"nanobody display technology"** was generated in collaboration with the Cellular Immunology research team of Prof. Patrick De Baetselier (CMIM).

Oncology

Since tumor cells and their environment exploit a plethora of mechanisms to inhibit anti-tumor immune responses, LMCT's research has therefore furthermore been focused on understanding these mechanisms and designing strategies to counteract them. Dendritic cells can present tumor antigens to T cells and as such activate the latter to search for and destroy tumor cells. Today it is recognized that activation of T cells by

Expertise

The Laboratory of Molecular and Cellular Therapy (LMCT) is a **keyplayer in the field of immunotherapy and in cancer & infectious disease research.** Immunotherapeutic and immunomodulatory strategies are being tested in preclinical models and when succesful, translated towards clinical applications in phase I/II trials.

Major research interests and topics include:

- Dendritic cell *ex vivo* based immunotherapy in myeloma and melanoma patients
- Dendritic cell *in vivo* based immunotherapy in hepatocellular carcinoma patients and patients suffering from papilloma virus induced precancerous cervix lesions
- Role of immunomodulatory drugs in enhancing the efficacy of an anti-melanoma vaccination strategy
- Characterization of spontaneous and vaccine-induced immune responses and analysis of their influence on the clinical course of the disease
- Inhibitory mechanisms exerted by tumor cells and their environment
- Comprehensive biomarker profiling of the tumor microenvironment and the immune response during immunotherapy
- Study of the tumor microenvironment to develop predictive *in silico* models of personalized immunotherapy
- Multitargeted therapy: development of novel therapeutic combination for augmenting the potency of cancer vaccines
- Manipulation of the immune system using targeted lentiviral vectors
- Development of therapeutic anti-HIV and anti-HPV vaccines

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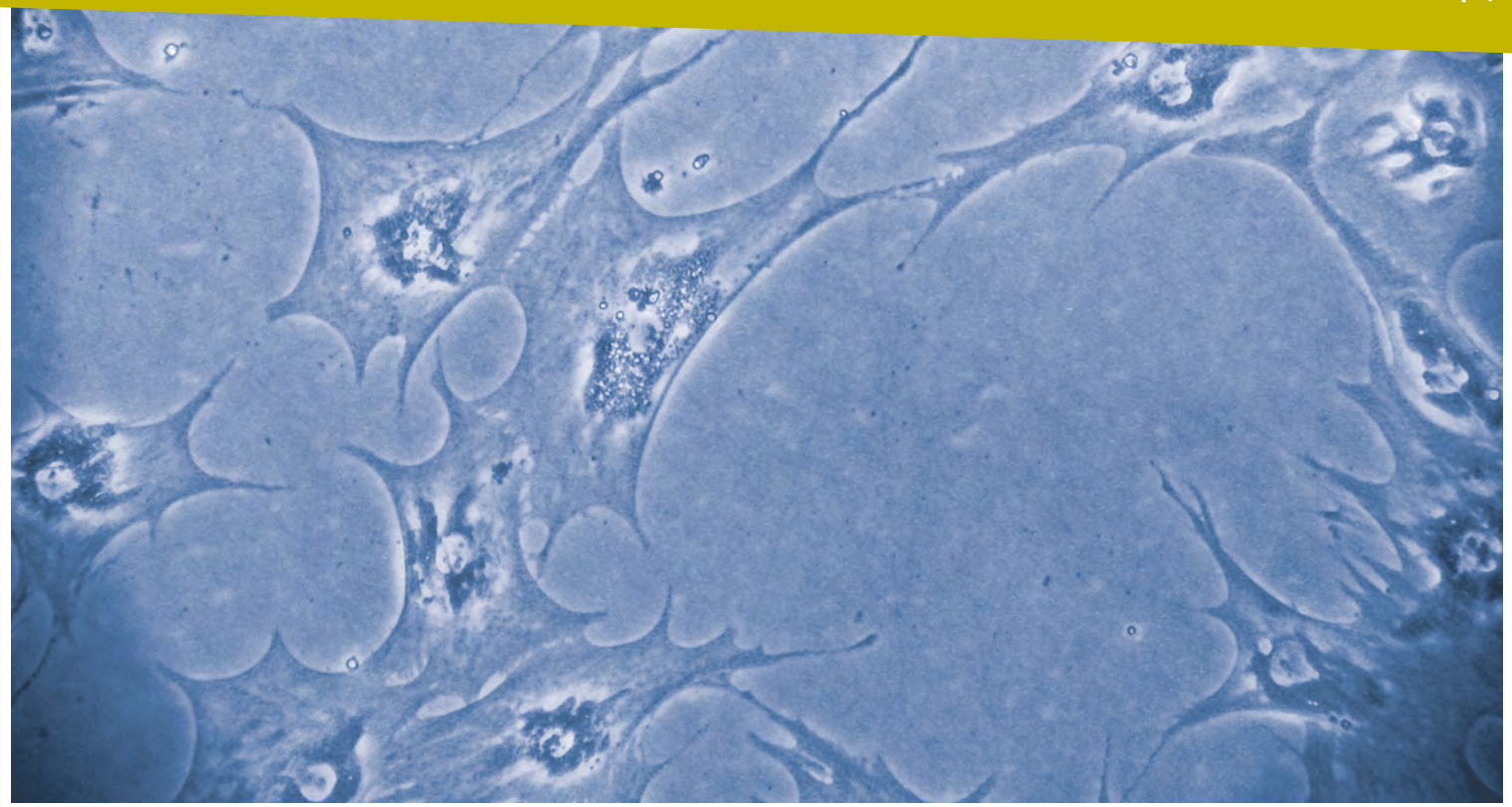

Dendritic cells

Innovative strategies for cancer & infectious disease treatment

The main goal of the research activities at the LMCT is **to develop an integrated partnership between innovative immunotherapeutic and immunomodulatory strategies.** The strategies under development include optimization of dendritic cell based immunization strategies and modes to engineer the tumor environment. These are extensively tested in preclinical mouse tumor models as well as *in vitro* models using human cells. When successful, these strategies are translated towards clinical applications in phase I/II trials.
Lessons learned from the cancer-immunotherapy approaches are being translated towards other domains such as HIV.

Dendritic Cells

Although our immune system is capable of discriminating healthy cells from tumor cells and infectious agents, it has failed in destroying tumor cells in cancer patients. Therefore, medical science has focused on the development of several strategies that aid the immune system in the surveillance and elimination of tumor cells and infectious agents. **Dendritic cells are 'the professional' antigen-presenting cells of our immune system and are recognized as key players in the instigation of immune responses.** Much effort has been put in their exploitation in immunotherapy for cancer and infectious diseases. The LMCT developed different **strategies to genetically modify dendritic cells.** A first extensively studied platform uses **messenger ribonucleic acids (mRNA)** to reprogram dendritic cells. This approach has successfully been evaluated for *ex vivo* as well as *in vivo* modification of dendritic cells. The **TriMix technology** platform has been developed specifically for this approach and allows to optimize the stimulatory capacity of dendritic cells. The use of the TriMix technology represents a turning point in the quest for an effective dendritic cell-based immunotherapy.

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dendritic cells was a major step forward in the treatment of cancer. However, tumor cells create an environment in which they can thrive and in which they collaborate with suppressive immune cells to counteract anti-tumor immune responses. Therefore, it is generally accepted that **an effective immunotherapy has to be multifaceted, aiming at stimulation of T cell responses, whilst reprogramming the immunosuppressive tumor environment.**

Both the use of lentiviral vectors as well as mRNA are under investigation at the LMCT for this purpose. Lentiviral vectors have already been used to directly manipulate tumor cells, evaluating strategies to induce tumor cell death or knock out molecules critical for the progression of tumor cells. Several strategies are in development to deliver mRNA to other cell types in order to enhance the prospective of mRNA for engineering of the tumor environment.

Infectious Diseases

The development of antiretroviral therapy has led to a significant improvement in life expectancy and quality of HIV-infected individuals. Nevertheless, several problems are associated with the long-term use of this therapy. Different alternatives are being explored of which **therapeutic vaccination** seems to be one with a promising potential. At the VUB LMCT, **HIV-derived antigens or fragments thereof are administered to the patient in an immunogenic context in order to stimulate CD4+ and CD8+ T cells.**

During the last years, the VUB LMCT has developed an extensive experience in HIV-1 immunotherapy and the administration of *ex vivo* generated, *in vitro* modified dendritic cells. The VUB LMCT is currently setting up a clinical trial where HIV patients are vaccinated intranodally with mRNA encoding on the one hand HIV antigens (covering the whole genome, based on a rational selection of protective regions) and on the other hand various activation signals (caTLR4, CD40L and CD70).

Immunomonitoring

To understand how the immune system of a patient responds to the dendritic cell vaccine, an **immunomonitoring platform** was developed. Specific assays allow immunomonitoring using a small number of patients T cells and independent on prior knowledge of the patients HLA type or tumor antigen expression.

Clinical Trials

LMCT's expertise on cancer immunology and the investment in technology has allowed the rational design of a dendritic cell-based active immunotherapy, delivering encouraging results in recent clinical trials:

1. "A Study on the Safety and Immunogenicity of Combined Intradermal and Intravenous Administration of an Autologous mRNA Electroporated Dendritic Cell Vaccine in Patients With Previously Treated Unresectable Stage III or IV Melanoma" EUDRACT Study Number: 2009-015748-40
2. "Autologous TriMix-DC Therapeutic Vaccine in Combination With Ipilimumab in Patients With Previously Treated Unresectable Stage III or IV Melanoma (TriMix-Ipi)" EUDRACT Study Number: 2010- 023058-35
3. "Randomized Controlled Phase II Clinical Trial on mRNA Electroporated Autologous Dendritic Cells for Stage III/IV Melanoma Patients who are Disease-free Following the Local Treatment of Macrometastases" EUDRACT Study Number: 2011-001410-33
4. "A phase I study on the feasibility and safety of mRNA immunotherapy in combination with RFA in patients with hepatocellular carcinoma" EUDRACT Study Number: 2012-005572-34
5. "A phase I/II study on the safety and immunogenicity of perilesional and intralesional administration of mRNA vaccine in patients with hr-HPV positive cervical intraepithelial neoplasia (CIN grade 2-3)" EUDRACT Study Number: requested
6. "A phase I/II study on the safety and immunogenicity of the intranodal administration of an mRNA vaccine in patients with HIV. FP7 project iHIVARNA, in preparation

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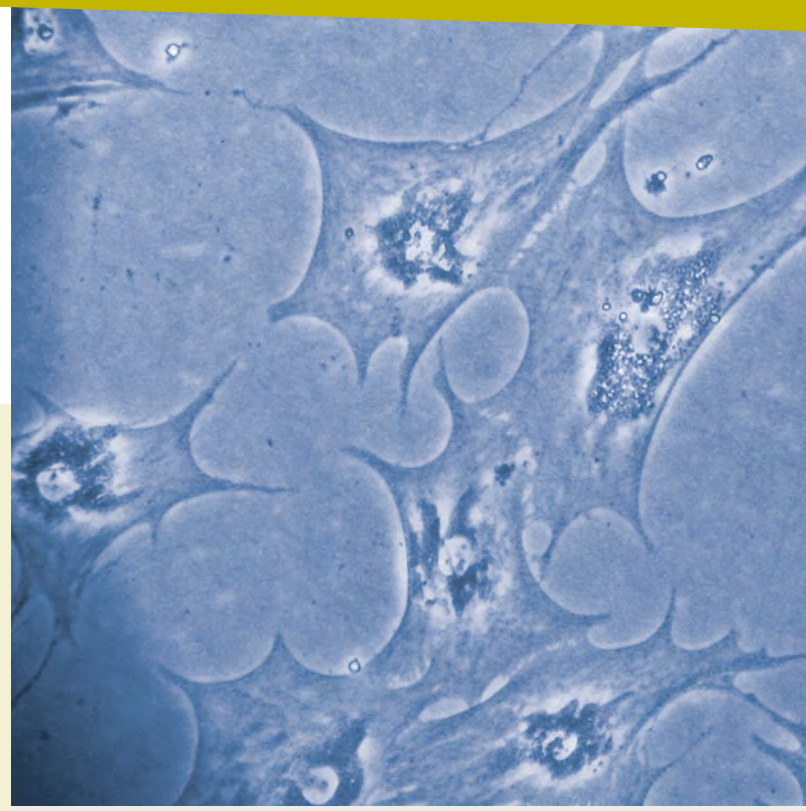

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