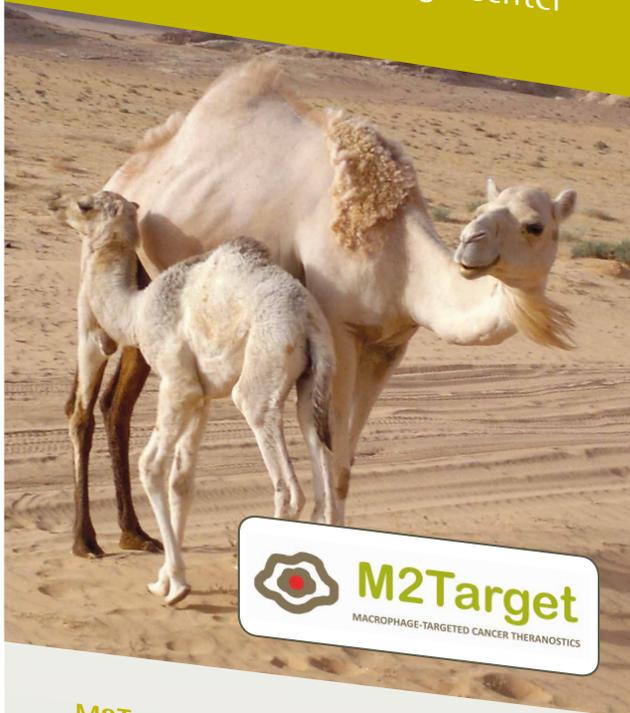


IOF Knowledge Center



M2Target

Medical Imaging (MIMA)

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Cellular and Molecular Immunology (CMIM)

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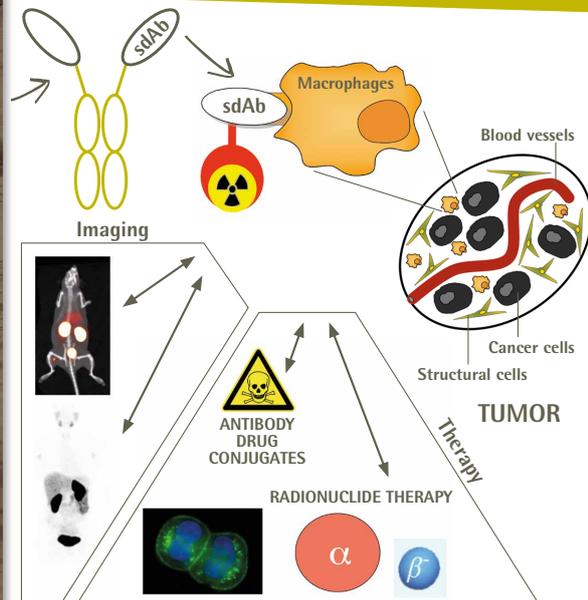
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M2Target



whereby systemically injected cytotoxic radiation is rapidly and specifically delivered to cancer cells, with minimal exposure to healthy tissue. This allows taking applications of sdAbs as in vivo targeting vehicles a step beyond molecular imaging to theranostics, whereby related compounds are employed both for diagnosis and therapy.

Macrophages as targets for sdAbs-based cancer theranostics

Since 2003, the VIB-VUB spin-off Ablynx develops sdAbs - named **Nanobodies®** - into protein therapeutics for cancer, inflammation and immune diseases. In 2014, MIMA and CMIM scientists co-founded the VUB spin-off Camel-IDS, leveraging sdAbs as vehicles for **targeted radionuclide therapy of cancer**, with initial focus on targets expressed on malignant cancer cells. Based on our identification of distinct subpopulations of tumor associated macrophages (TAMs) within the stromal compartment of non-transformed cells found in tumors, the current M2Target program uses sdAbs for **targeting tumor-supporting and therapy resistance-promoting subtypes of TAMs as a cutting-edge innovative cancer theranostics approach**.

The multidisciplinary M2Target platform

Jo Van Ginderachter's group within the Cellular and Molecular Immunology unit is affiliated to the Faculty of Sciences and Bio-engineering Sciences at the Vrije Universiteit Brussel, as

Expertise & Techniques

The **Cellular and Molecular Immunology unit (CMIM)**, headed by Prof. Jo Van Ginderachter, combines scientific expertise and know-how on cellular immunology, tumor immunobiology, immunoparasitology and antibody engineering. Central research topics include elucidation of the *in vivo* developmental and functional heterogeneity of myeloid cells such as macrophages as well as the use of camelidae-derived single-domain antibody fragments (sdAbs) for *in vivo* therapeutic targeting in cancer and infectious diseases and, in collaboration with the ICMI unit, for *in vivo* imaging of cancer and immune cells. The available CMIM facilities include an animal unit and separate laboratory rooms for mammalian cell culture, molecular biology, protein purification and phage display, including equipment for flow cytometry, cell sorting and Surface Plasmon Resonance.

The **Medical Imaging unit (MIMA)** and the **UZ Brussel Nuclear Medicine Department**, headed by Prof. Tony Lahoutte, feature centralized multiple small animal imaging modalities including CT, SPECT, PET, MRI, optical and near-infrared fluorescent imaging as well as clinical PET/CT, together with a radiochemistry unit and a vivarium for housing animals. The main research topic is the development, preclinical validation and clinical translation (including clinical trials) of sdAbs as targeting vehicles for molecular imaging and radioimmunotherapy, with applications in oncology, cardiovascular medicine and diabetes.

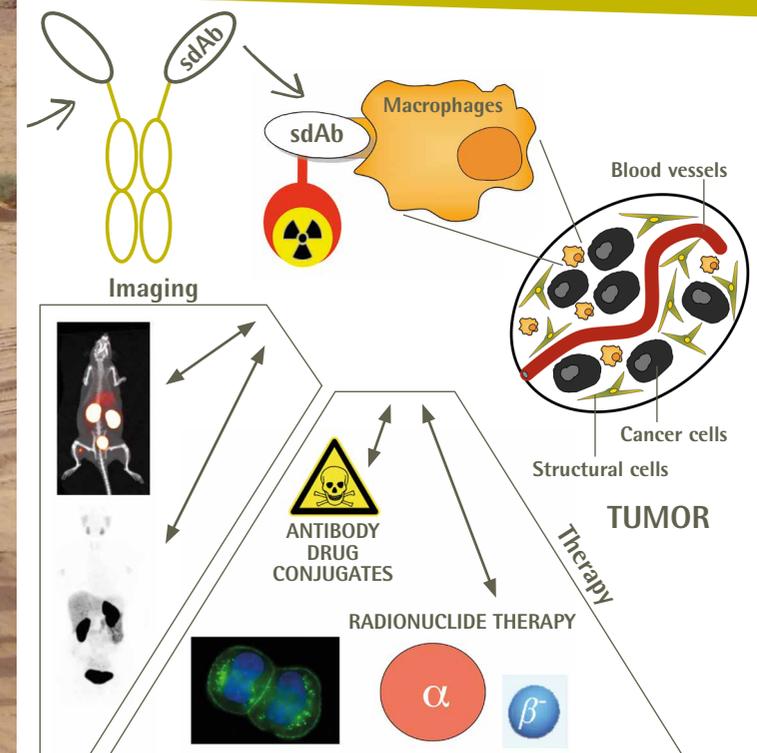


Camelidae-derived single-domain antibody fragments as *in vivo* targeting vehicles

In 1992, the team of Emeritus Prof. Raymond Hamers made the seminal discovery that the serum of Camelidae contains bona fide antibodies devoid of light chains. The **antigen-binding units of such heavy-chain-only antibodies consist of a single domain** and thus offer many biotechnological advantages, including easy recombinant production and much smaller size as compared to conventional antibodies. Within the CMIM unit, Serge Muyldermans, Patrick De Baetselier, Stefan Magez and Jo Van Ginderachter have pioneered various biomedical applications of such camelidae-derived single-domain antibody fragments (sdAbs).

In collaboration with Tony Lahoutte's group, radiolabeled sdAbs were shown to be **excellent probes for molecular *in vivo* imaging** in animal models of cancer, atherosclerosis and autoimmune diseases such as arthritis. Due to their small size, sdAbs have an excellent tissue and organ penetration potential, combined with a rapid clearance of unbound sdAbs from the blood circulation. As a consequence, **whole body images with a high target-to-background ratio** can be obtained within a few hours after probe inoculation. A first-in-human phase I clinical trial has also confirmed the game-changing potential of sdAbs for **same-day molecular imaging in humans**.

As a more recent development, sdAbs were also shown to be **effective vehicles for targeted radionuclide therapy**,



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The multidisciplinary M2Target platform

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well as to the Inflammation Research Center within VIB, a Flanders-based life science research center of excellence. Tony Lahoutte's Molecular Imaging unit combines an affiliation to the Faculty of Medicine and Pharmacy at the Vrije Universiteit Brussel, with a clinical link to UZ Brussel. Both groups have a history of valorization-oriented Strategic Basic Research projects, contract research for biotech and pharma companies and fruitful joint research projects in the context of sdAbs-based molecular imaging and therapy.

The M2Target platform is supported via VUB-IOF funding as Group of Expertise in Applied Research in order to consolidate our cutting-edge combined expertise on macrophage-targeted cancer theranostics into concrete industrial offerings. Our pre-clinical research is aimed at assessing therapeutic approaches (targeted radionuclide therapy, antibody-drug conjugates), **optimizing/automating coupling and optimizing pharmacokinetics** (selective targeting). Our clinical translation is aimed at **validating macrophages as theranostic targets and sdAbs as theranostic probes in a clinical setting**, ultimately striving for patient stratification, monitoring and personalized medicine. Our valorization efforts mainly focus on licensing, contracting and strategic partnerships.

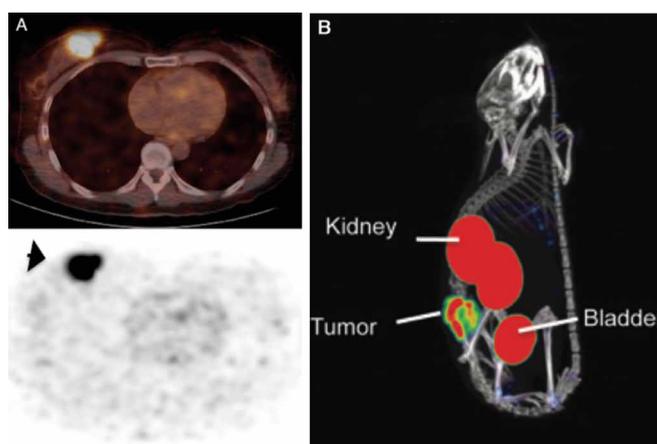
Overall, we offer a **multidisciplinary M2Target team mastering among others in vivo animal models, sdAbs generation technology, cellular and molecular biology, radiochemistry, molecular imaging and radioimmunotherapy in a bench-to-bedside manner.**

Key Patents

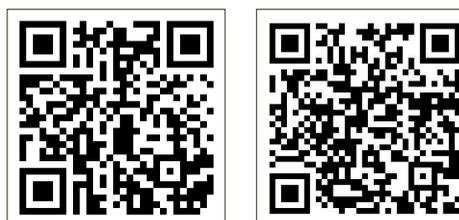
- "Selective targeting of intratumoral cells", US2011262348
- "Anti-macrophage mannose receptor single variable domains for targeting and in vivo imaging of tumor-associated macrophages", US2015093336
- "Radio-labeled antibody fragments for use in the prognosis, diagnosis of cancer as well as for the prediction of cancer therapy response", PCT/EP2015/067424
- "Radio-labeled antibody fragments for use in the prevention and/or treatment of cancer", PCT/EP2015/066430

Key Publications

- Keyaerts et al., Phase I Study of 68Ga-HER2-Nanobody for PET/CT Assessment of HER2 Expression in Breast Carcinoma. *J Nucl Med.* 2016; 57(1):27-33.
- Blykers et al., PET Imaging of Macrophage Mannose Receptor-Expressing Macrophages in Tumor Stroma Using 18F-Radiolabeled Camelid Single-Domain Antibody Fragments. *J Nucl Med.* 2015; 56(8):1265-71.
- Laoui et al., Tumor hypoxia does not drive differentiation of tumor-associated macrophages but rather fine-tunes the M2-like macrophage population. *Cancer Res.* 2014; 74(1):24-30.
- D'Huyvetter et al., Targeted radionuclide therapy with A 177Lu-labeled anti-HER2 nanobody; *Theranostics.* 2014; 4(7):708-20.
- Movahedi et al., Nanobody-based targeting of the macrophage mannose receptor for effective in vivo imaging of tumor-associated macrophages. *Cancer Res.* 2012; 72(16):4165-77.



A: Transverse slice of fused PET/CT (top row) and PET (bottom row) images in a breast cancer patient with the lesion indicated by the black arrow. HER2-positive tumor cells are visualized by radioactively labeled sdAbs at 1 hour post-injection (adapted from *J.Nucl.Med.*, 2016; 57:27). **B:** Fused pinhole SPECT/micro-CT images of a tumor-bearing mouse. The macrophage mannose receptor in the tumor lesion is specifically visualized by radioactively labeled sdAbs 3 hours post-injection. Targeting to macrophages in non-cancer tissues has been blocked by co-injection of an excess of unlabeled sdAbs. Unbound sdAbs are cleared via kidneys and bladder (adapted from *Cancer Res.*, 2012; 72: 4165).



Scan QR codes for 3D rotating images



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