SCIENCES & BIOENGINEERING SCIENCES

The Research Group

## Cellular and Molecular Immunology

has the honor to invite you to the public defense of the PhD thesis of

## Evangelia BOLLI

to obtain the degree of Doctor of Bio-Engineering Sciences

Title of the PhD thesis:

**Nanobody-mediated targeting of tumor-associated macrophages for cancer therapy**

**Promotor:**

Prof. dr. ir. Jo Van Ginderachter

The defence will take place on

**Wednesday June 19 2019 at 17:00h**

in Auditorium D.2.01 at the Campus Humanities, Sciences and Engineering of the Vrije Universiteit Brussel, Pleinlaan 2 - 1050 Elsene, and will be followed by a reception.

**Members of the jury:**

Prof. dr. ir. Jan Steyaert (chairperson)
Prof. dr. ir. Eveline Peeters (secretary)
Dr. Kiavash Movahedi (co-promotor)
Prof. dr. Eline Menu
Prof. dr. ir. Martin Guilliams (VIB-UGent)
Prof. dr. Paola Allavena (Humanitas Clinical and Research Center, Milano, Italy)

### Curriculum vitae

**09/2008 – 08/2012: University of Crete | Heraklion, Greece**
**BSc: Biomolecular Sciences and Biotechnology**
**Thesis title: The role of Sall1 and microRNAs in the regulation of differentiation of embryonic stem cells**

**09/2012 – 08/2014: Vrije Universiteit Brussel | Brussels, Belgium**
**MSc in Biomolecular Sciences**
**Thesis Title: The role of CCL8 and CCR8 in myeloid subsets in the tumor microenvironment**

**01/2015 – present: VUB, PhD: Bio-engineering Sciences**

**Main Publications**

**Peer-Reviewed**

Nuhn*, L., **Bolli, E. ***, Massa, S., Vandenberghe, I., Movahedi, K., Devreese, B., et al. ***Equal contribution**. (2018). Targeting protumoral tumor-associated macrophages with nanobody-functionalized nanogels through SPAAC ligation. Bioconjugate Chemistry, 29(7):2394–2405. doi: 10.1021/acs.bioconjchem.8b00319. (IF: 4.818) (5 cit.)

**Bolli, E.**, Movahedi, K., Laoui, D., and Van Ginderachter, J. A. (2017). Novel insights in the regulation and function of macrophages in the tumor microenvironment. Current Opinion in Oncology, 29(1), 55–61. doi: 10.1097/CCO.0000000000000344. Review. (IF: 3.653) (20 cit.)

**Submitted-Under Revision**

**Bolli, E.***, D'Huyvetter, M.*, Lahoutte, T., Gonçalves, A., Vuylsteke, M., Raes, G., Devoogdt, N., Movahedi, K. and Van Ginderachter, J. A. ***Equal contribution.** Stromal-targeting radioimmunotherapy mitigates the progression of therapy-resistant tumors. Journal of Controlled Release

### Abstract of the PhD research


It has become clear that tumors do not consist only of cancer cells but also of non-transformed types of cells such as immune cells, and that a bidirectional interplay exists between transformed cancer cells and immune cells, regulating tumor progression and metastasis. Most importantly, macrophages in the tumor or TAMs are abundant in many cancer types, are often associated with bad prognosis and worse overall survival and play key roles in induction of tumor progression, metastasis and resistance to (immuno)therapies. Thus, therapies that target TAMs by either depleting them or re-educating them towards an anti-tumoral phenotype are considered as promising novel therapeutic modalities.

In this PhD, we examined the use of nanobodies as carriers for targeted delivery of therapeutic payloads to the tumor by targeting specifically the pro-tumoral TAMs. Recent evidence, from our lab and others, identified MMR as a stable molecular target on the pro-tumoral TAMs. We could prove that nanobodies, generated against MMR, efficiently penetrate solid mouse tumors and specifically recognize MMR$^{high}$ TAMs in the hypoxic tumor area, providing a solid basis for nanobody-mediated TAM targeting. Here, we provide the first evidence for the employment of an anti-MMR Nb for targeted TAM therapy and describe two main approaches: the Stromal Targeting RadioImmunoTherapy (STRIT) and the re-education of anti-inflammatory MMR$^{high}$ TAMs towards a pro-inflammatory phenotype by stimulation of TLR7/8 signaling.

In STRIT, administration of the therapeutic $^{177}$Lu-labeled anti-MMR Nb resulted in significant tumor retardation of a mammary murine carcinoma model and outcompeted the effects of anti-PD1 immune checkpoint blockade, anti-VEGFR2 anti-angiogenic therapy and doxorubicin and paclitaxel chemotherapies.

For TAM re-education, we first demonstrated that IMDQ, an agonist of TLR7 and TLR8, either alone or encapsulated in nanogels is a potent driver of TAM re-education. Then, we showed that anti-MMR Nb-functionalized nanogels were highly efficient in targeting MMR$^{high}$ TAMs *in vivo*. Similarly, α-MMR Nb-IMDQ conjugates accumulated in the tumor *in vivo* in a MMR-specific manner. These findings pave the road for targeted modulation of pro-tumoral MMR$^{high}$ TAMs by anti-MMR Nb-mediated TAM reprogramming through stimulation of TLR7/8 signaling.