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-bearing associated macrophages with nanobody-functionalized nanogels through SPAAC ligation.

In STRIT, administration of the therapeutic 177Lu-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 MMR Nb, re-educated against MMR, efficiently accumulated in tumoral MMR-bearing associated macrophages and specifically penetrated beyond solid mouse tumors. These findings paved the way for the employment of an anti-MMR Nb for targeted TAM therapy and describe the evolution: the Stromal Targeting RadioligandioTherapy (STRIT) and the re-education of anti-inflammatory MMR-bearing TAMs towards a pro-inflammatory phenotype by stimulation of TLR7/8 signaling.

In STRIT, administration of the therapeutic 177Lu-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 MMR Nb, re-educated against MMR, efficiently accumulated in tumoral MMR-bearing associated macrophages and specifically penetrated beyond solid mouse tumors. These findings paved the way for the employment of an anti-MMR Nb for targeted TAM therapy and describe the evolution: the Stromal Targeting RadioligandioTherapy (STRIT) and the re-education of anti-inflammatory MMR-bearing TAMs towards a pro-inflammatory phenotype by stimulation of TLR7/8 signaling.

In conclusion, considering the implication of TAMs in stimulating primary tumor growth, 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-bearing associated macrophages with nanobody-functionalized nanogels through SPAAC ligation.

In STRIT, administration of the therapeutic 177Lu-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 MMR Nb, re-educated against MMR, efficiently accumulated in tumoral MMR-bearing associated macrophages and specifically penetrated beyond solid mouse tumors. These findings paved the way for the employment of an anti-MMR Nb for targeted TAM therapy and describe the evolution: the Stromal Targeting RadioligandioTherapy (STRIT) and the re-education of anti-inflammatory MMR-bearing TAMs towards a pro-inflammatory phenotype by stimulation of TLR7/8 signaling.

In STRIT, administration of the therapeutic 177Lu-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 MMR Nb, re-educated against MMR, efficiently accumulated in tumoral MMR-bearing associated macrophages and specifically penetrated beyond solid mouse tumors. These findings paved the way for the employment of an anti-MMR Nb for targeted TAM therapy and describe the evolution: the Stromal Targeting RadioligandioTherapy (STRIT) and the re-education of anti-inflammatory MMR-bearing TAMs towards a pro-inflammatory phenotype by stimulation of TLR7/8 signaling.