User project report

Theranostic terbium-labeled immunoconjugates targeting prostate cancer (TheraTerb)

Coordinator: Michel Meyer (michel.meyer@u-bourgogne.fr)

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1. Authors

Partner	Name	First name	Position	Role & responsibilities in the project
Partner 1 ICMUB	MEYER	Michel	CNRS Researcher	Solution coordination chemistry
	BRANDES	Stéphane	CNRS Research Engineer	Organic/inorganic synthesis
	CARON	David	PhD student	Organic synthesis
	VACHEY	Lucas	Contractual Engineer	Solution coordination chemistry
Partner 2 IC-UNISTRA	CHAMBRON	Jean-Claude	CNRS Research Director	Organic/inorganic synthesis
	ZUJEW	Laurie	PhD student	Organic/inorganic synthesis, radiochemistry
	DEPRET	Léa	M2 student	Organic synthesis
Partner 3 Syndivia	KOLODYCH	Sergii	Chief Scientific Officer	Bioconjugation
	SCHLIMPEN	Fabian	Research Scientist	Bioconjugation
Partner 3 IJCLab	SLADKOV	Vladimir	CNRS Researcher	Solution coordination chemistry
	LAM	Sabine	PhD student	Solution coordination chemistry

PRISMAP partner: Dr David VIERTL, CHUV Lausanne

2. Context of the project

The aim was to evaluate *in vitro* and *in vivo* yet unavailable ^{161}Tb-labeled immunoconjugates for the treatment by targeted radionuclide therapy of metastasized castration-resistant prostate cancer (mCRPC). The design of our theranostic agents intends to circumvent all major clinical drawbacks of ^{177}Lu(DOTA) conjugates. Their originality stems from (a) the replacement of DOTA by open-chain chelators of tetrapodal or linear topologies, forming rapidly (< 10 min) stable and inert complexes at room temperature; (b) the vectorization through an IgG1 monoclonal antibody (mAb) that specifically binds to an antigen expressed on prostate cancer cells; (c) site-specific conjugation with a strictly controlled drug-to-antibody ratio (DAR) using the innovative GeminiMab™ Technology.

3. Results and discussion

Two bifunctional chelators, synthesized at ICMUB and IC-UNISTRA, were bioconjugated site-specifically in the hinge region of the IgG1 mAb by Syndivia with a controlled DAR of 1 (bismaleimide linker) or 2 (monomaleimide linker) by applying the GeminiMab™ Zn^{2+}-based protection strategy. Four constructs were successfully labeled with ^{161}Tb (radiolabeling yield > 99%) at room temperature in less than 2 min at CHUV (Lausanne). The resulting theranostics stayed intact over 14 d, while immunobinding assays revealed good uptake (>50%) by various prostate cancer cell lines. Biodistribution and µ-SPECT-CT scans at 4 to 11 days post-injection of mice bearing a RM1-PGLS xenograft showed good tumor accumulation and inhibition of the tracer uptake when the animals were co-injected with a large excess of native IgG1 mAb.

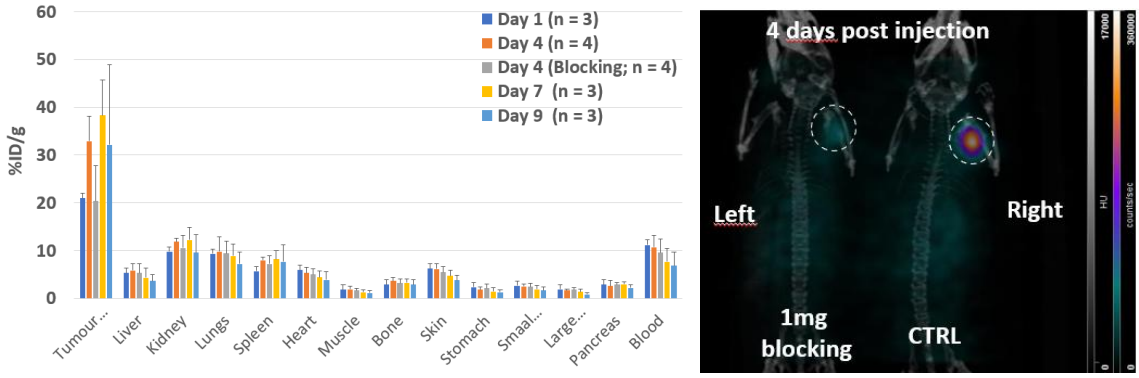

Figure 1. Biodistribution (right) and volume rendered SPECT/CT images (left) of RM1-PGLS xenograft bearing mice (right shoulder) acquired 4-days post injection of 12 MBq ^{161}Tb-chelator-IgG1 (50 µg total protein dose; CTRL). SPECT/CT imaging of the inhibition of target-specific tracer accumulation was performed by co injecting 1 mg of unlabeled IgG1 mAb (1 mg blocking).

4. Conclusions

Within 9 months and 2 deliveries of ^{161}Tb, the TheraTerb project has demonstrated our ability to radiolabel at room temperature DAR 1 or 2 immunoconjugates bearing in the hinge region linear or tetrapodal high-affinity chelators in place of DOTA, with a yield > 99% in less than 2 min. The latter were specifically designed to bind the antigen expressed on prostate cancer cells and take advantage of the additional emission of low-energy Auger/conversion electrons by ^{161}Tb in contrast to the clinically used β^- emitter ^{177}Lu. With no Tb release in human plasma over 14 d and good tumor uptake even 11 d post-injection, as proven by µ-SPECT-CT and biodistribution studies, our constructs pave the way towards innovative immunotheranostic agents for treating prostate cancer.

5. Involvement of the PRISMAP services

Thanks to the support of PRISMAP, the French partners could pursue a most fruitful collaboration with Dr David Viertl (Centre Hospitalier Universitaire Vaudois, Lausanne) initiated in 2024 through the PRISMAP-funded TerbCheNuM project. Our Swiss partner has offered us twice a 5-d long access to his accredited biomedical facilities (PRISMAP biomedical hub) in 2025, where 5 of us, including a Master (L.D.) and PhD student (D.C.) could assist him in the experimental work.

Moreover, the team could benefit from 2 × 500 GBq of ^{161}Tb, delivered by the Paul Scherer Institute (PSI) in May and September 2025.

Three of us (M.M., J.-C.C., V.S.) took also part in the *PRISMAP Radiolanthanides Workshop* organized by PSI the 3–5 September 2024 in Villigen (CH).

6. Feedback to PRISMAP

We are grateful to PRISMAP and to all our interlocutors for their kindness and dedication. Without this support, our project would have never reached so rapidly the current level of maturity of our project.

7. Publications and other dissemination activities (conferences etc.)

TheraTerb can be viewed as a follow-up project of the TerbCheNuM one, also supported by PRISMAP in 2024. As the coordinator of both of them, M. Meyer was invited to give an on-line oral communication at the Public event session hold during the *8th PRISMAP Consortium Meeting* on April 3, 2025 entitled "*Terbium Chelation*

for Nuclear Medicine (TerbCheNuM)". Else, no scientific details about the bioconjugates have been disclosed, as we might most likely file in a patent application.