



Cross-Isotopic Bioorthogonal Tools as Molecular Twins for Radiotheranostic Applications

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Radiotheranostics are designed by labeling targeting (bio)molecules with radionuclides for diagnostic or therapeutic application. Because the pharmacokinetics of therapeutic compounds play a pivotal role, chemically closely related imaging agents are used to evaluate the overall feasibility of the therapeutic approach. “Theranostic relatives” that utilize different elements are frequently used in clinical practice. However, variations in pharmacokinetics, biodistribution, and target affinity due to different chemical properties of the radioisotopes remain as hurdles to the design of optimized clinical tools. Herein, the design and synthesis of structurally identical compounds, either for diagnostic (¹⁸F and a stable metal isotope) or therapeutic application (radiometal and stable ¹⁹F), are reported. Such “molecular twins” have been prepared by applying a modular strategy based on click chemistry that enables efficient radiolabeling of compounds containing a metal complex and a tetrazine moiety. This additional bioorthogonal functionality can be used for subsequent radiolabeling of (bio)molecules or pretargeting approaches, which is demonstrated *in vitro*.

Since the discovery of radium-226 by Marie and Pierre Curie in 1898,^[1] the field of nuclear medicine has progressed significantly, and nuclear imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT), have become clinical routine. Furthermore, β^- - or α -emitting isotopes that deliver cytotoxic radiation coupled to targeting vectors, such as antibodies,^[2,3] nanoparticles,^[2,4] peptides,^[5,6] nanobodies,^[7–9] and others,^[10] are

used in ongoing (pre)clinical research toward the treatment of various diseases.

However, to develop effective personalized treatments, the pharmacokinetics of therapeutic radiopharmaceuticals need to be carefully investigated and assessed.^[11,12] Hence, a chemically closely related (or ideally identical) imaging agent is administered to evaluate the overall feasibility of the therapeutic approach and patient-specific dosimetry.^[13] This theranostic principle was introduced decades ago with radioisotopes of iodine, wherein gamma- or positron-emitting ¹²³I, ¹²⁴I, or ¹²⁵I were used as imaging probes prior to the administration of therapeutic ¹³¹I.^[14–20] However, ¹³¹I-radiopharmaceuticals suffer from disadvantages such as poor availability, insufficient *in vivo* stability, and challenging radiochemistry; thus limiting broad application.^[21–24] Yttrium (⁸⁶Y for diagnostics, ⁹⁰Y for therapy) or scandium (⁴³Sc/⁴⁴Sc and ⁴⁷Sc) isotopes can be used to design chemically identical theranostics. However, these approaches are still limited due to the poor availability and/or challenging production of radioisotopes such as ⁸⁶Y and ⁴⁷Sc.^[25–27] To circumvent problems related to the availability of chemically matching radioisotopes with required specific properties, “theranostic relatives” that utilize different elements are frequently used in clinical practice. The targeting carrier is either labeled with established “diagnostic” radiometals (e.g., ⁶⁸Ga, ¹¹¹In) or with therapeutic radionuclides (e.g., ⁹⁰Y, ¹⁷⁷Lu) by using chelators, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).^[28] Due to different radioisotopes, these theranostic relatives are chemically different. Consequently, variations in pharmacokinetics,^[29] biodistribution,^[30] and target affinity^[31,32] are likely; thus adding a degree of uncertainty to therapy planning. For instance, somatostatin receptor ligands (TOC, [Tyr³]-octreotide; TATE, [Tyr³,Thr⁸]-octreotide; and NOC, [Nal³]-octreotide) used for diagnosis and therapy of neuroendocrine tumors have been reported to show highly variable binding properties if labeled with ⁶⁸Ga (PET imaging), compared with other radiometals (e.g., therapeutic ¹⁷⁷Lu).^[32–34] Moreover, the radiometal can even affect the properties of radiolabeled antibodies.^[35] Furthermore, in (pre)clinical research, several limitations exist, if different therapeutic radiometals are compared and evaluated. In addition to limited availability and high costs, a licensed facility and adequate handling and waste-processing procedures are required for each individual radionuclide. For this reason, studies are often limited to one specific emitter.

These limitations motivated us to develop a modular and versatile strategy based on click chemistry to enable the preparation of structurally identical compounds that can either be labeled with 1) the low-cost, readily available PET isotope fluo-

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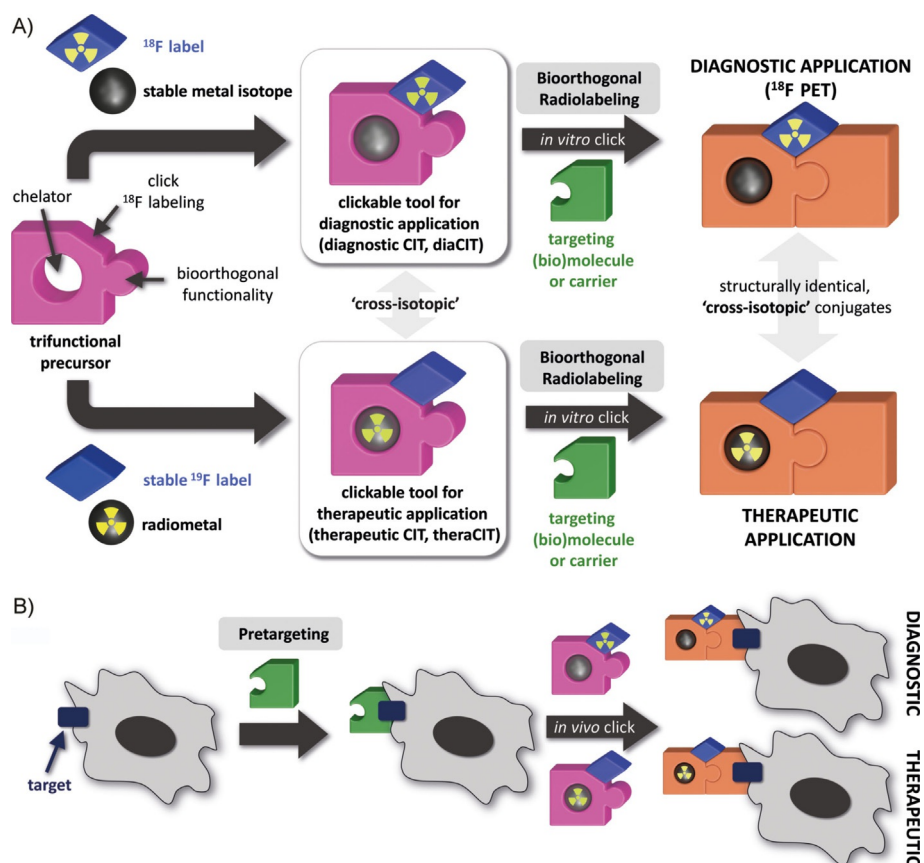
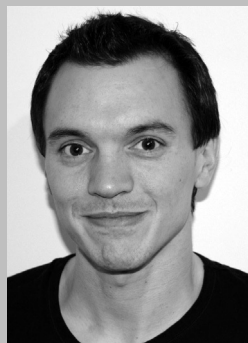


Figure 1. Concept of "cross-isotopic" theranostic tools (CITs). A trifunctional precursor can be used to introduce a stable metal isotope and subsequently be radiofluorinated through copper-catalyzed click chemistry. An additional bioorthogonal moiety can be applied for A) radiolabeling of (bio)molecules or B) pre-targeting approaches through in vivo click chemistry.

rine-18 in combination with any non-radioactive metal, or 2) a radiometal in combination with stable fluorine-19 (Figure 1 A). The resulting clickable theranostic tools can be considered perfect "molecular twins" (differing in isotopic characteristics only), for which we define the term cross-isotopic theranostic tools (CITs).

Hannes Mikula obtained his PhD from TU Wien in 2014, under the supervision of Prof. Johannes Fröhlich. Inspired by the emerging field of bioorthogonal chemistry, he then joined the lab of Prof. Ralph Weissleder at Massachusetts General Hospital and Harvard Medical School as a postdoctoral fellow funded by the Austrian Science Fund (FWF). In 2016, he returned to Vienna and currently leads the Molecular Chemistry and Chemical Biology group at the Institute of Applied Synthetic Chemistry (TU Wien). His team focuses on the development of bioorthogonal tools and reactions for in vivo chemistry, medical imaging, and theranostic applications.



Click chemistry has been used for highly efficient assembly of radiotracers and rapid radiolabeling of biomolecules.^[36] In particular, the copper-catalyzed alkyne-azide cycloaddition (CuAAC) represents a highly efficient tool for ^{18}F -labeling.^[37-39] Furthermore, the reaction between 1,2,4,5-tetrazines (Tzs) and *trans*-cyclooctenes (TCOs), the fastest bioorthogonal ligation reported so far,^[40] has successfully been applied to achieve diagnostic and therapeutic pretargeting in vivo.^[41] Those studies revealed enhanced image contrast and elevated tumor dose with minimal effect on healthy tissues.^[42]

We aimed to implement an efficient click approach to facilitate ^{18}F -labeling by means of CuAAC with ^{18}F -labeled alkyl azides as prosthetic groups. The implementation of a Tz moiety as an additional bioorthogonal functionality maximizes the versatility of the approach (e.g., targeted vs. pretargeted) and simplifies postlabeling ligation to TCO-tagged targeting carriers (Figure 1 B).

Tz 1 (previously shown to be sufficiently stable during CuAAC modification)^[43] was modified with a short azido-PEG-amine (PEG: poly(ethylene glycol)) linker to afford compound 2, which was then attached to the propargylated L-tyrosine derivative 3^[44] to obtain intermediate 4 (Figure 2A). Several chelators are available for complexation of pharmaceutically relevant (radio)metals, such as DOTA, 1,4,7-triazacyclononane-*N,N',N''*-triacetic acid (NOTA), and diethylenetriaminepentaace-

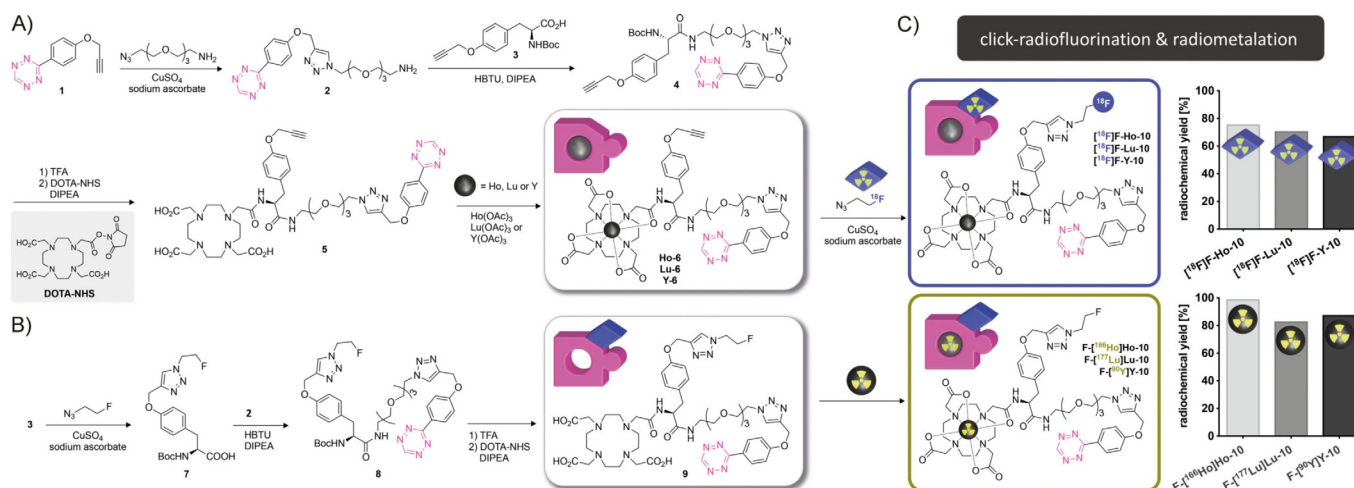


Figure 2. A) Chemical synthesis of tetrazine-modified metal complexes by using stable metal isotopes of holmium, lutetium, and yttrium. B) Preparation of precursor compounds (containing stable fluorine-19) for subsequent labeling with therapeutic radiometals. C) Click-radiofluorination (top) and radiometalation (bottom) to afford diagnostic (diaCITs) and therapeutic CITs (theraCITs), respectively, in good to excellent radiochemical yields. Boc: *tert*-butyloxycarbonyl, HBTU: 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, DIPEA: *N,N*-diisopropylethylamine, TFA: trifluoroacetic acid.

tic acid (DTPA).^[45] In this study, we used DOTA as a chelator due to its high affinity to most (radio)metals and good stability of the resulting chelates. To introduce this chelator, compound **4** was deprotected (removal of the Boc group) and subsequently reacted with DOTA-NHS to afford compound **5** (Figure 2A).

The choice of therapeutic radiometal commonly depends on the availability and decay characteristics of the isotope.^[46–48] In this study, we used the established β^- emitters yttrium-90 ($t_{1/2}=64.1$ h, 2.3 MeV), holmium-166 ($t_{1/2}=26.8$ h, 1.9 MeV), and lutetium-177 ($t_{1/2}=6.7$ d, 0.5 MeV). These radiometals cover a broad range of half-lives and decay energies, and are either commercially available (^{90}Y , ^{177}Lu) or can easily be produced through neutron activation (^{166}Ho , ^{177}Lu). For the introduction of stable isotopes of these metals, DOTA-Tz **5** was reacted with holmium triacetate, lutetium triacetate, and yttrium triacetate in acetate buffer at pH 6 to yield compounds Ho-**6**, Lu-**6**, and Y-**6**, respectively (Figure 2A). Heating to mildly elevated temperatures (45 °C) for 60–120 min was required to achieve quantitative yields. The compounds were isolated by using C_{18} solid-phase extraction (SPE) cartridges and were sufficiently pure to be used for further modification. The remaining propargyl moiety on the tyrosine linker allows straightforward chemical modification by CuAAC, including efficient radiolabeling with ^{18}F -azides.

For the synthesis of chemically identical therapeutic agents, stable fluorine-19 was attached by CuAAC reaction of **3** with 1-azido-2-fluoroethane to obtain compound **7**, which was further modified by conjugation to Tz-amine **2**. The resulting intermediate, **8**, was deprotected and reacted with DOTA-NHS to obtain precursor **9** (Figure 2B). For analytical characterization and as references for identification of radiolabeled compounds by HPLC, the stable compounds F-Ho-**10**, F-Lu-**10**, and F-Y-**10** were obtained by treating **9** with the respective metal acetates, as described above (not shown in Figure 2; see the Supporting Information).

$[^{18}F]$ Fluoroethyl azide was prepared from cyclotron-produced $[^{18}F]$ fluoride by using known procedures and purified by codistillation with acetonitrile.^[49] This ^{18}F -synthon was reacted with precursors Ho-**6**, Lu-**6**, and Y-**6** to afford the diaCITs $[^{18}F]F$ -Ho-**10**, $[^{18}F]F$ -Lu-**10**, and $[^{18}F]F$ -Y-**10** in radiochemical yields of 67–76% (Figure 2C). The theraCITs were prepared by reaction of **9** with the respective radiometals in acetate buffer (pH 6) at elevated temperatures for 30–45 min. The radiolabeled compounds were isolated from the reaction mixture by using C_{18} SPE cartridges, to obtain F- $[^{166}Ho]$ Ho-**10**, F- $[^{177}Lu]$ Lu-**10**, and F- $[^{90}Y]$ Y-**10** in radiochemical yields of 83–99% (Figure 2C). HPLC retention times of the radiolabeled products (diaCITs and theraCITs) matched those of reference compounds F-Ho-**10**, F-Lu-**10**, and F-Y-**10** (as shown for Ho compounds in Figure 3A), and all isolated compounds rapidly reacted with TCO (as investigated by HPLC); thus confirming sufficient stability of the Tz moiety.

To exclude undesired metal exchange of Y, Ho, and Lu by Cu (which is known to be chelated by DOTA) during click radiolabeling by CuAAC, we investigated the purified decayed diaCITs $[^{18}F]F$ -Ho-**10** and $[^{18}F]F$ -Lu-**10** by means of neutron activation analysis. Samples were irradiated in a neutron flux of $2 \times 10^{12} \text{ cm}^{-2} \text{ s}^{-1}$ for 60 min and analyzed by means of gamma spectroscopy. In contrast to significant amounts of the activation products of holmium and lutetium, copper was not detected (Figure 3B); thus confirming sufficient stability of metal-DOTA complexes **6** during modification/radiolabeling by the CuAAC reaction.

The applicability of CITs as bioorthogonal agents for radiolabeling, targeting, and pretargeting was investigated by using prostate specific membrane antigen (PSMA)-positive LNCaP cells (androgen-sensitive human prostate adenocarcinoma) as a model system. PSMA is overexpressed in many prostate cancers and is a frequently used target for the development of diagnostic and therapeutic approaches.^[50] The PSMA ligand S,S-2-[3-(5-amino-1-carboxypentyl)ureido]pentanedioic acid

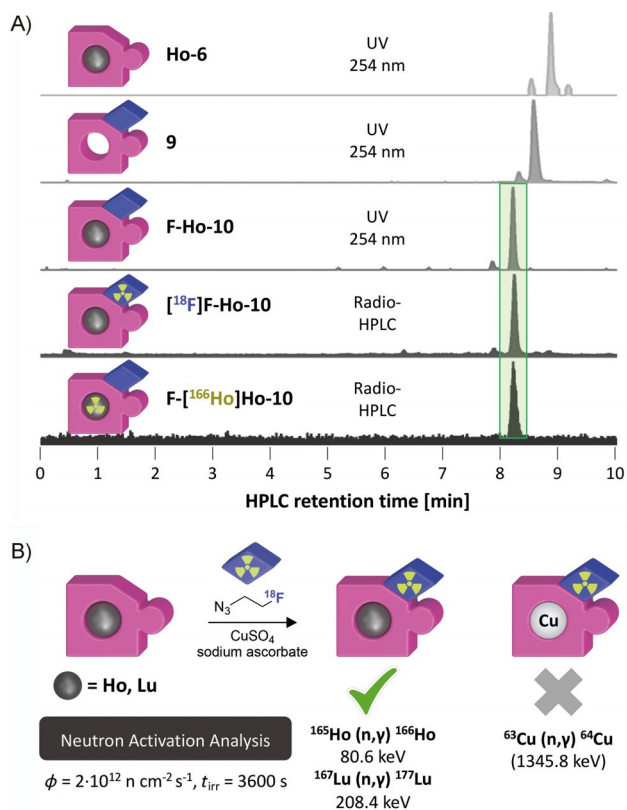


Figure 3. A) Verification of click radiofluorination and radiometalation by HPLC for holmium CITs. B) Neutron activation analysis of radiofluorinated di-aCITs, showing sufficient stability of the metal–DOTA complexes during radiolabeling through copper-catalyzed click chemistry.

(ACUPA)^[51] was modified by reaction with TCO-NHS (equatorial, “major” isomer) to obtain ACUPA-TCO (11), which was conjugated to [¹⁸F]F-Y-10 (Figure 4) through rapid Tz/TCO ligation to afford radiolabeled [¹⁸F]F-Y-ACUPA within minutes. The solution was diluted to concentrations of 500 and 1000 nM based on 11 and directly applied to PSMA-positive LNCaP cells (without removal of excess 11). After incubation for 90 min the cells were washed and cell uptake was assessed by activity measurements by using a gamma counter (Figure 5A). In an *in vitro* pretargeting experiment, LNCaP cells were first treated with 11 (500 or 1000 nM), followed by washing and subsequent treatment with [¹⁸F]F-Y-10. After 90 min cells were washed and cell uptake was again measured by using a gamma counter (Figure 5B). In control experiments, LNCaP cells were first treated with the PSMA inhibitor 2-PMPA^[52] prior to targeting and pre-targeting (blocking experiments; Figure 5C). Further control experiments were performed either with no cells or without primary agent 11 in the pretargeting approach ([¹⁸F]F-Y-10 only). In addition, [¹⁸F]F-Y-10 was incubated in complete cell growth media to show sufficient stability of this diaCIT (see the Supporting Information). The results of the targeting approach with preclicked conjugate [¹⁸F]F-Y-ACUPA clearly indicate competition between the radiolabeled probe and remaining excess 11. Both the absolute uptake of activity and the relative uptake in comparison with the blocking experiment (ratio unblock/block) decreased with increasing concentration

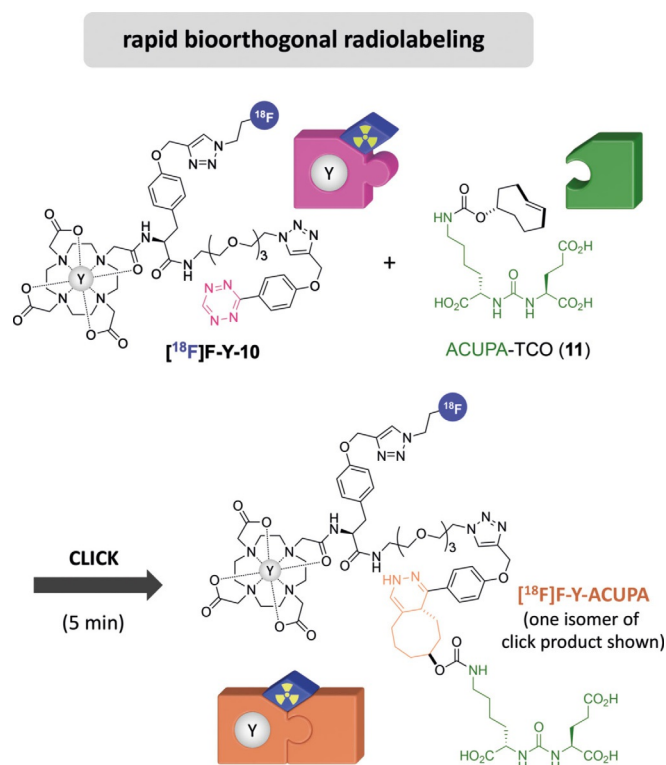


Figure 4. A) Synthesis of an ¹⁸F-labeled and yttrium-DOTA modified ACUPA conjugate.

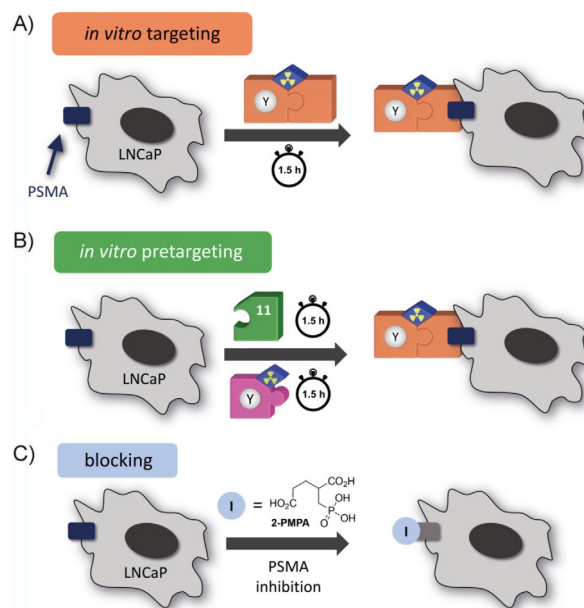


Figure 5. A) The application of [¹⁸F]F-Y-ACUPA to study uptake in PSMA-positive LNCaP cells. B) Treatment of LNCaP cells first with ACUPA-TCO (11), followed by [¹⁸F]F-Y-10, to investigate the application of CITs towards pre-targeting approaches. C) The PSMA inhibitor 2-PMPA was used in control experiments (blocking).

of 11 from 500 to 1000 nM, and thus, higher competition (Figure 6A). In contrast to the targeting experiment, the opposite result was obtained in the pretargeting approach. In this strategy, ACUPA-TCO (11) binds to PSMA on the surface of LNCaP

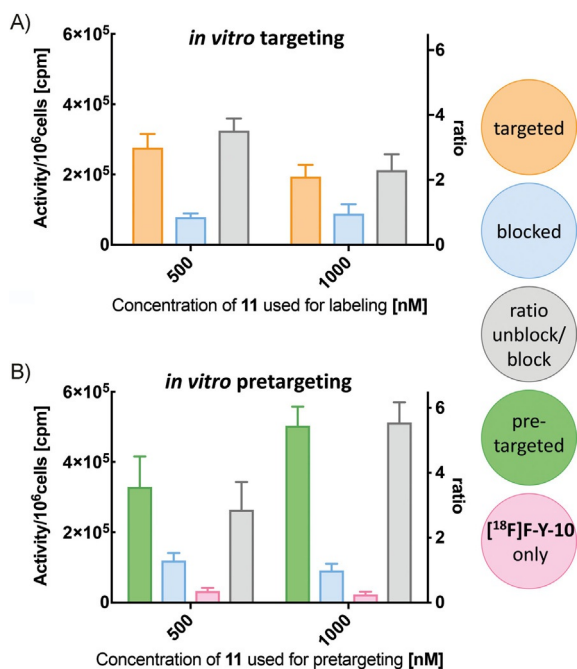


Figure 6. A) Results of in vitro targeting and B) in vitro pretargeting by applying different concentrations of **11** (500, 1000 nM) for labeling and pretargeting ($n = 3$).

cells during the first incubation step and excess **11** is then removed by washing. In the second step, [¹⁸F]F-Y-10 is administered and bioorthogonal ligation with PSMA-bound **11** occurs on target without any competition. Thus, higher (absolute and relative) uptake values were observed upon increasing the concentration of **11** from 500 to 1000 nM (Figure 6B). Although PSMA is known to be an internalizing target, and CITs are likely to be noninternalizing due to the high polarity of DOTA derivatives, the pretargeting approach resulted in higher absolute uptake/binding of activity due to eliminated competition. Overall, the in vitro investigations indicate the applicability of the CIT approach for radiolabeling and pretargeting.

In summary, we were able to develop a modular strategy for the synthesis of chemically identical radiolabeled bioorthogonal probes by combining radiometalation and ¹⁸F-click labeling. The described CITs can either easily be attached to various TCO-tagged carriers or targeting (bio)molecules, or applied as secondary agents in pretargeting experiments through rapid and bioorthogonal tetrazine ligation. Hence, we are convinced that the CIT approach represents a suitable strategy to study the biodistribution of theranostic agents (containing different radiometals) solely by using the PET radionuclide fluorine-18; thus potentially enabling pretherapy assessment, evaluation, and comparison of different therapeutic radiometals by using their stable isotopes in combination with ¹⁸F.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: bioorthogonal chemistry • click chemistry • isotopes • radiochemistry • radiopharmaceuticals

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