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111In-labelled bifunctional agents for dual targeting of breast cancer cells

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Background/Objective
Breast cancer (BC) is the most common invasive cancer diagnosed in women worldwide. The estrogen receptor (ER) is a well-established biomarker for prognosis and guiding treatment of patients and is a good target for molecular imaging and radionuclide therapy. The objective of this study was to improve the theranostic value of previously studied 111In-labelled ER-targeting moieties (e.g. estradiol derivatives/LXXLL-based peptides) by enhancing the delivery of the radionuclide into BC cells'nucleus in close proximity to DNA. To achieve that goal, we have explored an approach that combines into a single 111In-hybrid compound two different biological targeting moieties for dual targeting of BC cells. Hybrid compounds containing an ER ligand conjugated to a DOTA derivative functionalized with a nuclear-targeting moiety (DNA-intercalating agent, AO, or a peptidic nuclear localizing sequence, NLS) were synthesized. The bifunctional compounds were radiolabelled with the Auger electron emitter Indium-111 that has simultaneous emission of gamma radiation aiming the selective delivery into ER+ breast cancer cells.
Methodology
Synthesis of a DOTA- based prochelator that can allow double vectorization with two different molecular entities was achieved by following an orthogonal strategy. The versatility of this chelator to prepare radiolabelled hybrid compounds was demonstrated by the synthesis of three different conjugates containing an ER-binding molecule and a nuclear-targeting agent. Radiolabelling with 111In was performed at 95ºC, pH=5 acetate buffer. Radiochemical purity and in vitro stability of the radiolabelled compound was evaluated by HPLC. Cellular uptake of 111In-conjugates was assessed in MCF-7 (ER+) and MDA-MB-231 (ER-) human BC cells. The subcellular localization, in particular the internalization into the cell nucleus was also evaluated. The ability of 111In-compounds to induce DNA damage in vitro was tested by incubation with double-stranded plasmid DNA for 140 hours. Biodistribution was assessed in female mice with MCF-7 xenografts.
Results
The synthesis of dual-conjugates comprising an ER-targeting and a nuclear-targeting moieties was successfully achieved by following an orthogonal strategy. The In-/111In- complexes of the hybrid conjugates were successfully prepared and the radiolabelled conjugates demonstrated high stability. The prepared dual-targeting radiolabelled probes [111In]ER3AO, [111In]E2NLS and [111In]E2AO demonstrated high nuclear internalization (higher than 50%) in MCF-7 cells, proving the efficacy of the applied nuclear-targeting approaches. Moreover, [111In]ER3AO demonstrated ability to cause direct damage in DNA. Preliminary biodistribution studies of [111In]ER3AO in tumor-bearing mice were also encouraging since high in vivo stability, fast blood clearance from blood and uptake in the ER-rich organs and in the tumor as well as high target tissue/ non-target tissue radioactivity ratios were obtained.
Conclusion
A straightforward and versatile synthetic approach was used for the synthesis of bifunctional radioconjugates bearing two different molecular entities. The favourable biological results of the 111In-conjugates in cellular and animal models represent promising properties for the development of radiopharmaceuticals for Auger therapy.
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Primary authors: Dr VULTOS, Filipe (Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa); Dr GANO, Lurdes (Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa,)

Co-authors: Dr FERNANDES, Célia (Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa,); Dr MENDES, Filipa (Centro de Ciências e Tecnologias Nucleares, Instituto Superior

Técnico, Universidade de Lisboa); Dr D. G. CORREIA, João (Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa)

Presenter: Dr GANO, Lurdes (Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico, Universidade de Lisboa,)