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Design and synthesis of steroid-based agents targeting estrogen and progesterone receptors for breast cancer radiotheranostics

Due to the high variation in surface receptor expression, breast cancer (BCa) is a highly heterogeneous disease presenting significant challenges for early detection and treatment. Four molecular subtypes have been identified including estrogen receptor (ER)- and progesterone receptor (PR)-positive BCa. ER and PR are overexpressed in ≈ 80% of all BCa which promotes cell proliferation. The expression of PR in target tissues is highly dependent on the presence of ER conducting in less than 1% of ER-negative/PR-positive BCa. Estradiol, an estrogen steroid and the major female sex hormone, possesses a high affinity for ER. Katzenellenbogen and coworkers have developed the clinically approved radiotracer 16α-[18F]fluoro-17β-estradiol ([18F]FES) for BCa diagnostic by positron emission tomography (PET). However, due to its high lipophilicity, [18F]FES is rapidly metabolised in the liver resulting in a high hepatic uptake and background signal preventing its use in targeted radionuclide therapy (TRT). This group has proposed derivates of estradiol and progesterone radiolabelled with fluorine-18, technetium-99m and rhenium-188 for theranostics but their high lipophilicity has prevented further studies. This project aims to develop steroid-based ligands suitable for radiotheranostics applications in ER/PR-expressing BCa. For this purpose, versatile DOTA chelator was selected for complexation of various diagnostic and therapeutic radionuclides. DOTA-lysine-estradiol has been synthesised on solid phase with a yield of 15% and purity of >95%. Coupling of estradiol was achieved by Copper(I)-catalysed Azide-Alkyne Cycloaddition (CuAAC) between ethynylestradiol and lysine-resin. DOTA was then coupled using classic amidation method. The synthesis of other DOTA-estradiol and DOTA-progesterone derivatives are currently ongoing. These derivatives will be radiolabelled using [177Lu]LuCl3 (~5 MBq, 0.4 M NaOAc pH 5, 95℃, 30 min). Internalisation assays of 177Lu-conjugates will be performed on ER/PR-positive and -negative cell lines with the aim to validate radioligands targeting ER and PR to improve the early detection and stratification of BCa patients followed by TRT.

Research type

Basic research

Primary authors: WAGNER, Laurène (Deutsches Krebsforschungszentrum); TAS, Harun (Deutsches Krebsforschungszentrum); KOVACS DOS SANTOS, Luciana (Deutsches Krebsforschungszentrum); BAUDER-WÜST, Ulrike (Deutsches Krebsforschungszentrum); SCHÄFER, Martin (Deutsches Krebsforschungszentrum); BENESOVA-SCHÄFER, Martina (Deutsches Krebsforschungszentrum)

Presenter: WAGNER, Laurène (Deutsches Krebsforschungszentrum)

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