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123I-ADAM10 inhibitor as a new theranostic agent for cervical cancer

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The aim of this study is to evaluate the suitability of ADAM10 as a target for imaging cervical cancer using a 123I-radiolabelled ADAM10 inhibitor. A Disintegrin and Metalloproteinases (ADAMs) exhibit proteolytic activity like matrix metalloproteinases and ADAM10 sheds a range of membrane-bound proteins that play a role in cancer progression, radioresistance and the tumor micro-environment. First, the therapeutic and radiosensitizing effects of the non-radiolabelled ADAM10 inhibitor (GI254023X, GI) were evaluated in cervical cancer cells (Hela, C33A). This includes effects on proliferation, clonogenicity, migration, invasion, apoptosis, DNA damage and adhesion. Preliminary results show an inhibition of migration but no effect on cell cycle progression, apoptosis, nor radiosensitizing effects. Secondly, GI was radiolabelled with Iodine-123 (98% radiochemical purity, ± 44 MBq/mL). 123I-GI is enantiomerically pure with a thermal stability up to 125℃. Whole blood and protein binding studies confirmed a 34% binding to read blood cells with 66% activity located in serum (0-1-2-24 hrs). Within the serum, 33% was protein bound. The partition coefficient indicated a lipophilicity of 0.555. Preliminary in vitro studies demonstrated that 123I-GI was taken up in cervical cancer cells. Blocking studies with an overdose of cold GI did not affect the uptake of 123I-GI in Hela/C33A cells. The effect of 123I-GI on clonogenicity of Hela/C33A cells is ongoing (auger effect). The potential of 123I-GI as a cancer diagnostic agent will further be investigated using a xenograft cervical cancer model. The biodistribution, pharmacokinetics and targeting will be determined in vivo (μSPECT-CT and autoradiography). All these in vitro, ex vivo and in vivo validations of GI and 123I-GI will give more insights into the cell surface protein's activity, function and its role in tumorigenesis. This will set the scene for evaluating GI linked to the alpha therapeutic nuclide 211At or the beta emitting 131I. This study will be the first step in establishing a pipeline for theranostics research at iThemba LABS.

Attendance Type

Remote

Primary authors: BOLCAEN, Julie (Radiobiology, Radiation Biophysics, iThemba LABS, Cape Town); Dr NAIR, Shankari (iThemba LABS); Dr DRIVER, Cathryn HS (Radiochemistry, South African Nuclear Energy Corporation (NECSA), Pelindaba, Brits 0240, South Africa); MULLER, Xanthene (iThemba LABS); Dr VANDEVOORDE, Charlot (Biophysics Department, GSI Helmholtzzentrum für Schwerionenforschung, 64291 Darmstadt, Germany); FISHER, Randall (Division of Radiation Biophysics, NRF iThemba LABS); Prof. EBENHAN, Thomas (Department of Nuclear Medicine, University of Pretoria Steve Biko Academic Hospital, Pretoria 0001, South Africa); Dr ZEEVAERT, Jan Rijn (Department of Radiochemistry, South African Nuclear Energy Corporation, Pretoria 001, South Africa.)

Presenter: BOLCAEN, Julie (Radiobiology, Radiation Biophysics, iThemba LABS, Cape Town)

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