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Targeted-Alpha-Therapy with Astatine-211-*Meta*-Astatobenzylguanidine (^{211}At-MABG) in the Treatment of Pheochromocytoma

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Background: Pheochromocytoma/paraganglioma (pheo) overexpresses the norepinephrine transporter (NET) that can be molecularly targeted for tumor selective therapeutic drug delivery. By utilizing a known specific NET substrate *meta*-benzylguanidine conjugated to the alpha-emitting radionuclide astatine-211 we provide a mechanism to selectively deliver a cytotoxic dose to tumor cells in pheo. Due to its alpha emission properties ^{211}At offers a cytotoxic potential that has been shown to overcome radio- and chemo-resistance. In this work we report the synthesis of ^{211}At-MABG through the use of UltraTrace resin and in vitro internalization and cytotoxicity in mouse pheo cells (MPC).

Methods: *Production and chemistry*- Astatine-211 was produced at the University of Pennsylvania Cyclotron Facility on an external solid target and processed by dry distillation. Next, through electrophilic aromatic substitution ^{211}At was covalently linked to *meta*-benzylguanidine to afford ^{211}At-MABG.

In vitro MPC internalization experiments- Cells were treated with ^{211}At-MABG or ^{211}At-MABG and desipramine, a NET specific reuptake inhibitor. At time points over 2 hours the treatment was removed and the cells were washed and assayed for radioactivity.
In vitro MPC Cell Viability experiments- Using a modified clonogenic/cell viability assay cells were treated in 96 well format with ^{211}At-MABG at doses of 740kBq/mL, 370 kBq/mL, 195 kBq/mL, and 1:10 serial dilutions. Astatine-211-sodium astatide was used as a non-targeted control at similar doses. Cell viability was assayed using XTT and absorbance was measured on plate reader.

Results: *Internalization experiments/ Cell Viability Experiments*- Astatine-211-MABG was shown to internalize rapidly in MPC's and was effectively blocked by a NET specific reuptake inhibitor desipramine. The cell viability experiments revealed a highly targeted cytotoxic potential at extremely low doses of ^{211}At-MABG.

Conclusion: Through cellular uptake and cytotoxicity experiments we show the effective delivery and selective therapeutic effect of ^{211}At-MABG in malignant mouse pheo cells as a proof of concept for future pre-clinical studies.

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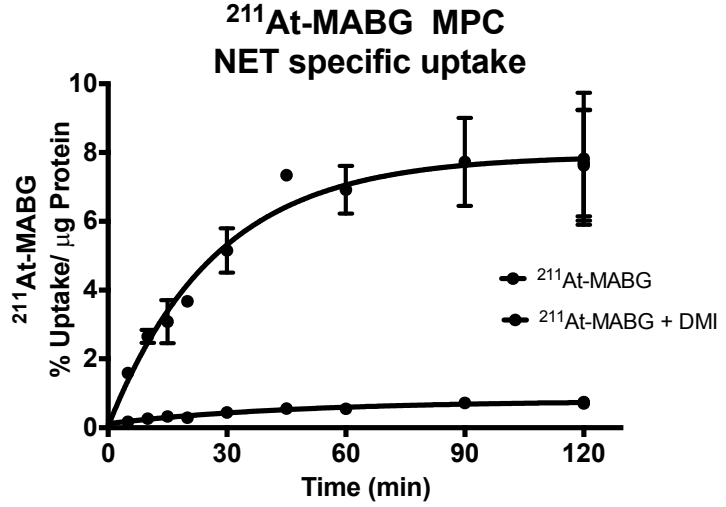
Supplemental figures:

A) MPC NET specific internalization of ^{211}At-*meta*-astatobenzylguanidine.



B) Cell viability of MPC treated with varying doses of ^{211}At-*meta*-astatobenzylguanidine.