^{211}At Production for Translational Science in Radiotherapy

"Tahereh Taghvaee"
Makvandi Lab, Kitchen Chemistry

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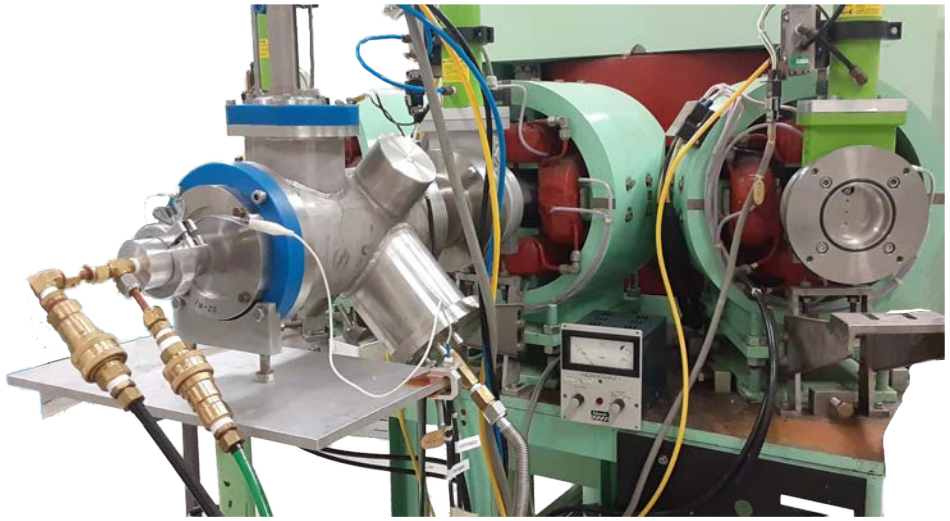
DOE-IP Users Group Meeting
10-AUG-2021

Facility

cGMP chemistry suite

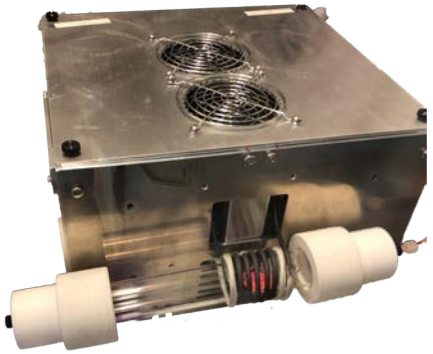
Targetry

Alpha Beam electrical currents ~20 µA



Y station port At-211 production,
X and Z stations available for R&D

Isolation



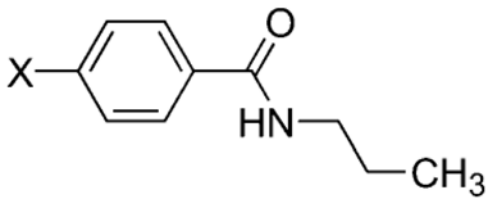
Induction heater

”Rapid recovery of At-211 by extraction chromatography”. Separation and Purification Technology 256 (2021) 117794.

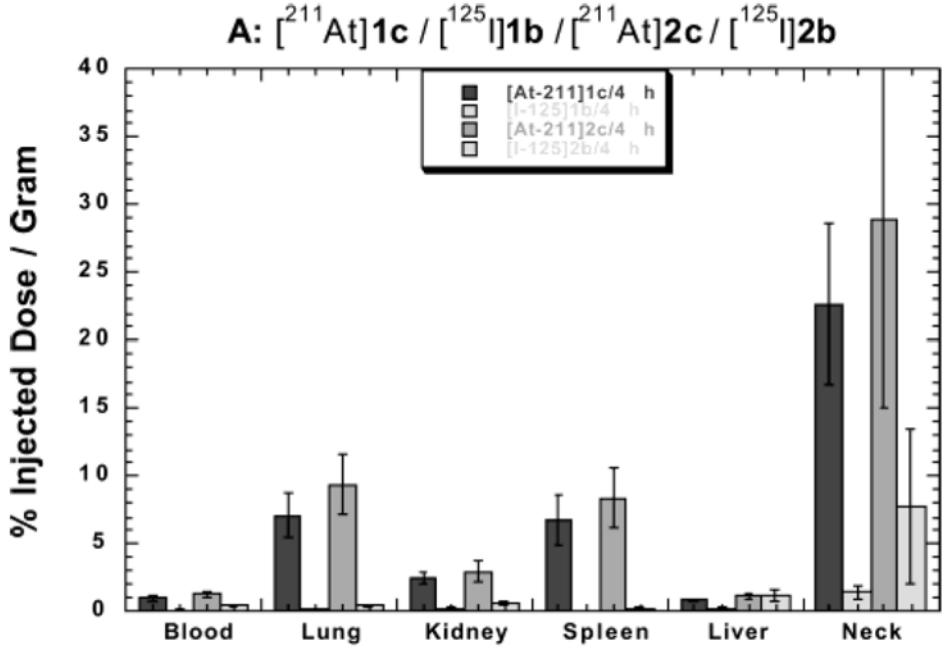
What are the chemical properties of astatine that determine biostability?

Biological environment? or Enzymatic?

Wilbur et al. 2004 – "Although some biomolecules labeled with astatinated deactivated aryl groups have been found to be stable to in vivo deastatination, other biomolecules… undergo extensive deastatination in vivo"

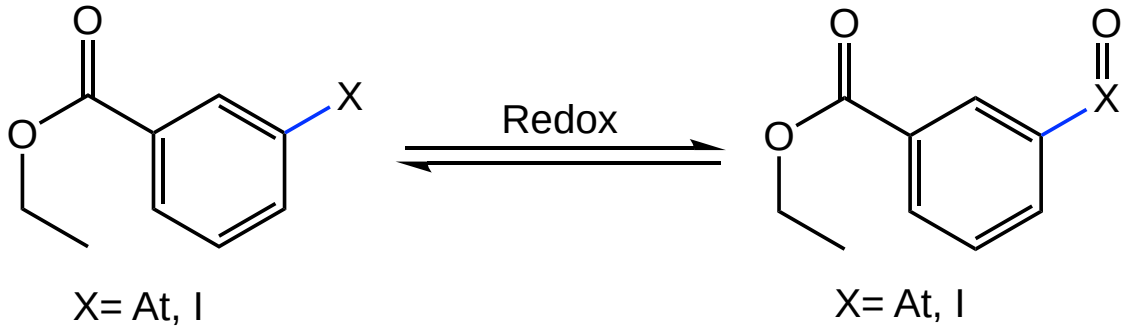


1a: X = $SnBu_3$
1b: X = I, I-125
1c: X = At-211



Bioconjug Chem. 2004 Jan-Feb;15(1):203-23. doi: 10.1021/bc034175k.PMID: 14733601

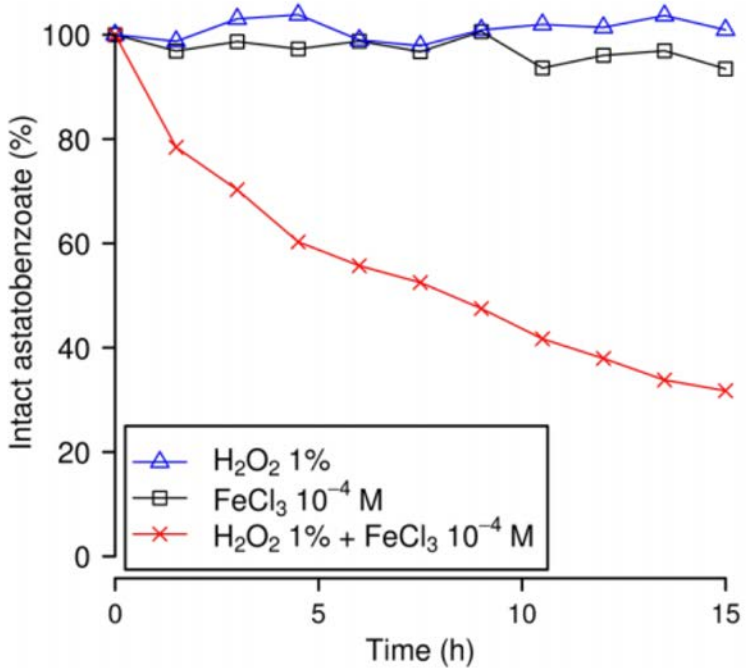
Halo benzoate



X= At, I

X= At, I

X=I, BDE= **37.8** kcal/mol
X= At, BDE= **28.2** kcal/mol



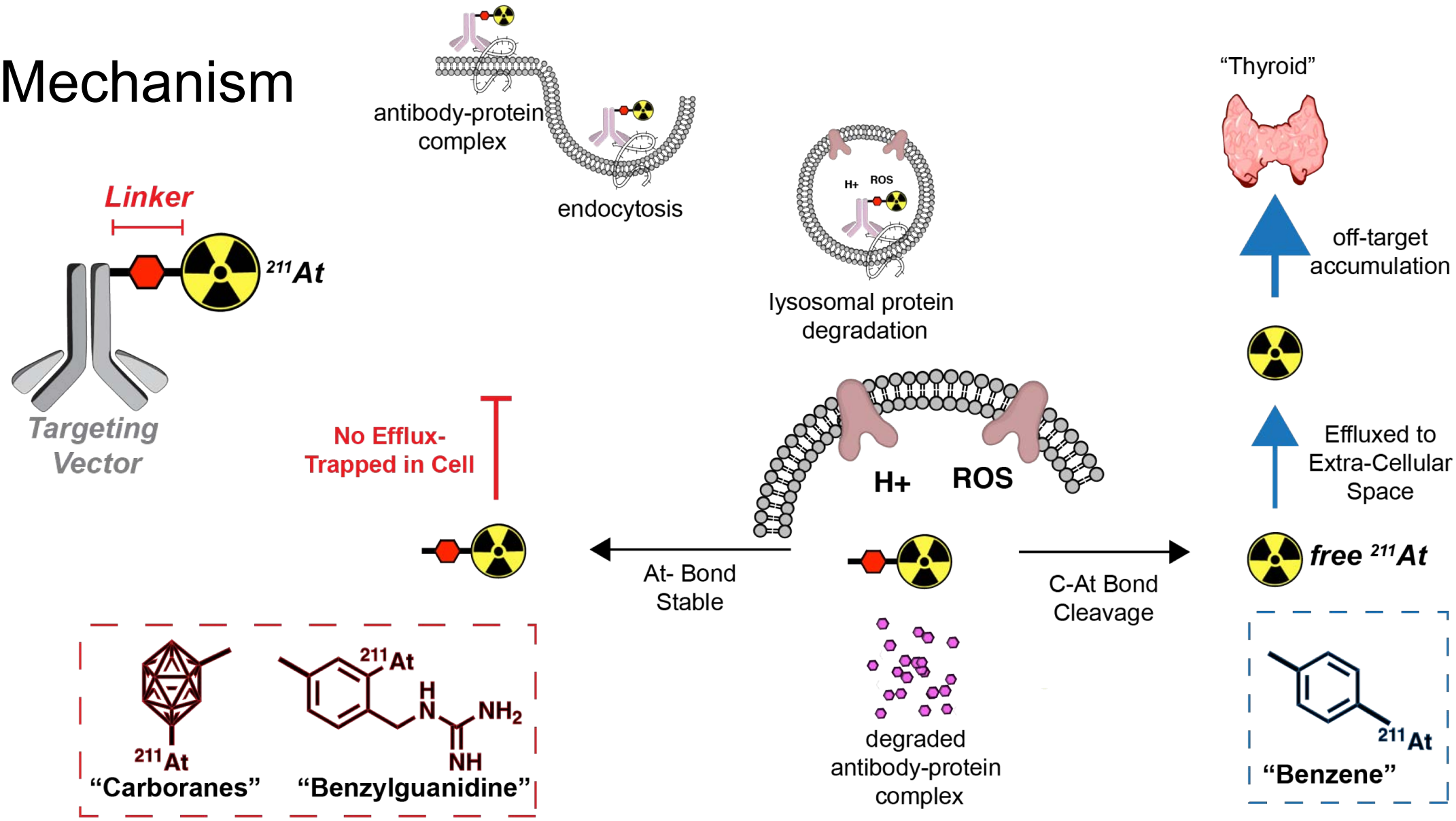
BDE: C-At < C-I (C-At bond is weaker)

Oxidative dehalogenation: C-At > C-I

Can computational methods predict bond stability?

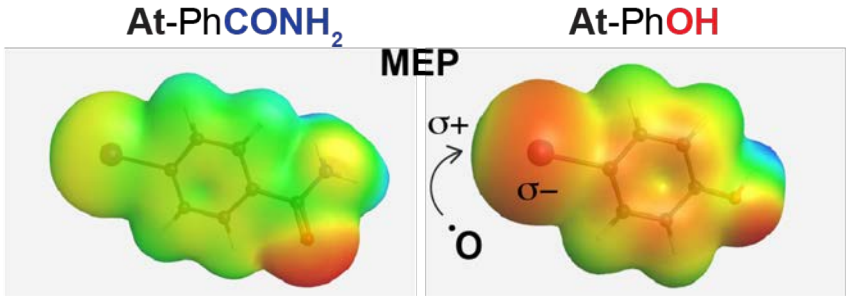
Montavon et al., Sci Rep. 2017;7(1):2579.

Mechanism

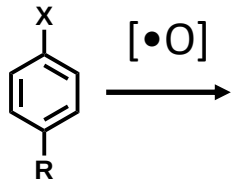


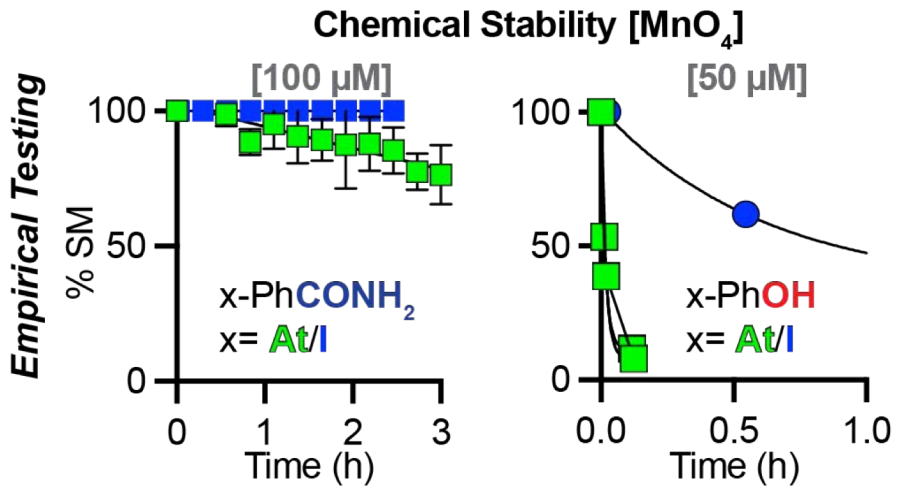
Hypothesis: B-At and C-At bonds can be stable

Null: C-At bonds are unstable

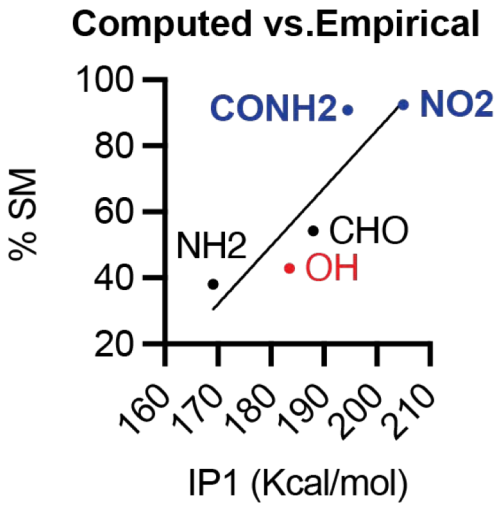


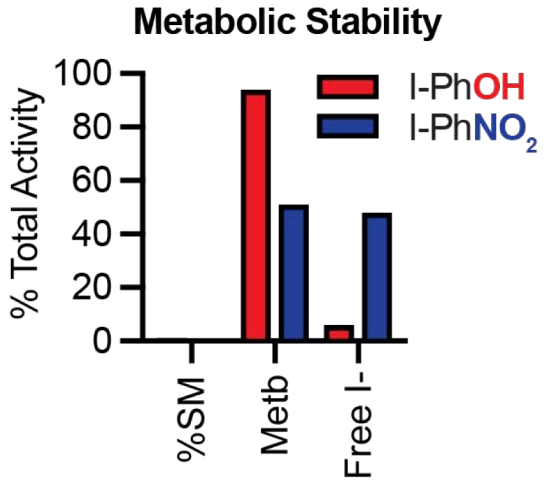
Fenton
$NaMnO_4$





C-At < C-I; astato-benzamide > iodo-phenol





Substituent effects stability towards oxidation

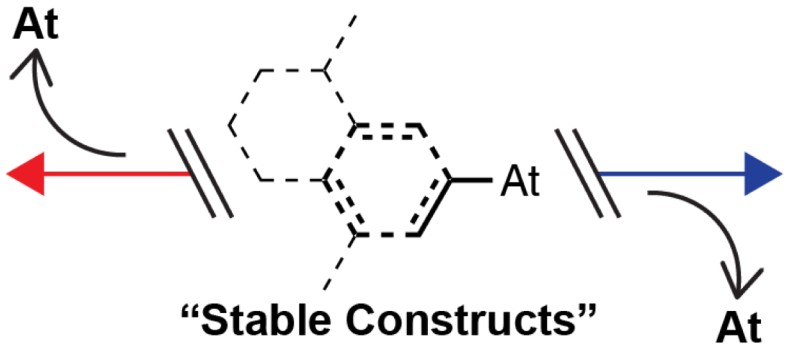
- activating = decreased stability
- deactivating = increased stability

CYP450 enzymatic dehalogenation

- nucleophilic and electrophilic

Hypothesis

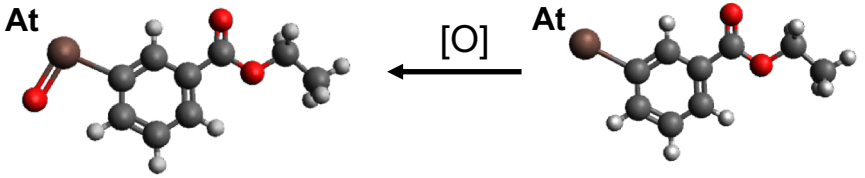
"Lysosomal Oxidative Deastatination"



"Stable Constructs"

"Enzymatic Deastatination"

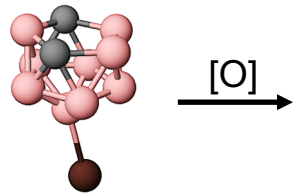
Astatobenzoate **(SAB)**



BDE= **28.2** Kcal/mol

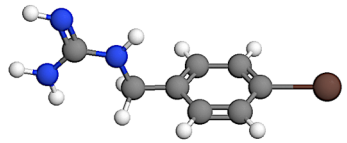
IP1= **185.3** kcal/mol
BDE= **44.9** Kcal/mol

Astatocarboranes



BDE= **>60** Kcal/mol

(*p*-ABG)

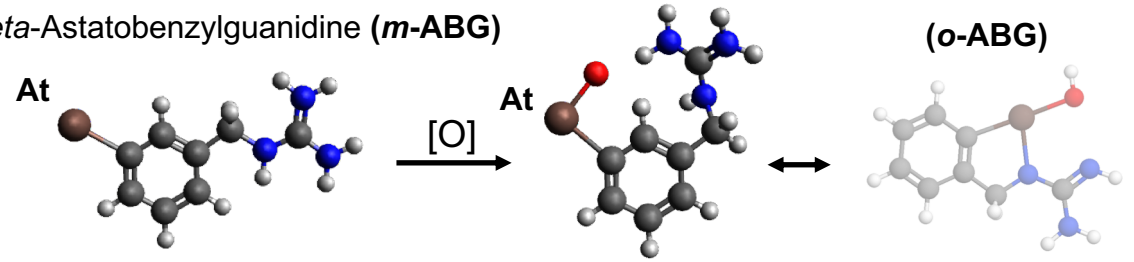


metabolically unstable

ΔE_{tot} *para* > *meta* = *ortho*

(Hartree-Fock)

meta-Astatobenzylguanidine **(*m*-ABG)**



(*o*-ABG)

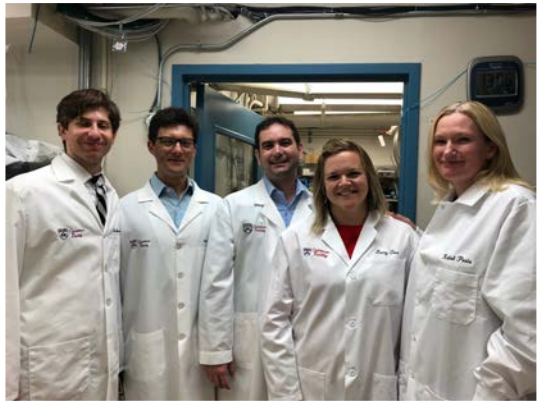
IP1= **249.4** Kcal/mol
BDE= 44.5 Kcal/mol

BDE= **43.5** Kcal/mol

Clinical Trials on the Horizon

- ^{211}At-MABG: Adult neuroendocrine tumors
- ^{211}At-Parthanatine: Adult solid tumors (breast, prostate, ovarian, and neuroendocrine)

IND submissions Fall 2021



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- EHRS

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DOE-IP

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NIH

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- NCI (R01CA219006)

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Children's Hospital of Philadelphia

Basser Center for BRCA, Penn Medicine

Isotope Program, U.S. Department of Energy

NIH National Institute of Biomedical Imaging and Bioengineering

NIH National Cancer Institute

questions?