Contribution ID: **38** Type: **Oral**

Development of 213Bi-labelled somatostatin analogues: Finding the optimal match between radiometal and chelator

Tuesday, 30 April 2019 15:40 (20 minutes)

Objectives: Targeted α-radionuclide therapy is a promising cancer therapy that allows targeted irradiation of primary tumour and its metastases. 213Bi-DOTATATE targeting the somatostatin receptor has been reported to delay growth in small and large volume endocrine tumours in mice (1,2). However, DOTA chelator has poor labelling kinetics and radiochemical purity with Bismuth-213. It appears that 3-p-*C*-NETA and 3-p-*C*-DEPA are the best current alternatives to DOTA for fast radiolabeling kinetics and excellent *in vivo* stability with Bismuth-213. As they are not commercially available, here we present the synthesis of 3-p-*C*-NETA-NO2 and 3-p-*C*-DEPA-NO2 to allow efficient one-step radiolabelling of 213Bi-somatostatin analogues for therapeutic applications (1–4).

Approach: This synthetic route was adapted from Song *et al.* and was inspired by the high efficiency and regiospecificity of the ring opening reaction of aziridinium **9** (3) Treatment of **1** with mild reducing agent BH3-THF afforded **2** (89%) followed by bromination with PBr3 to afford **3** (82%). The bromine was substituted by diethyl acetamidomalonate to provide **4** (60%) followed by hydrolysis to provide the amino acid **5** (52%). This product was esterified to enhance easy reduction to amino alcohol **7** (79%). Iodination of **8** using imidazole and PPh3 followed by intramolecular rearrangement to provide the aziridinium salt **9** (81%) and subsequent regiospecific ring opening of **9** with di-*tert*-butyl-2,2'-(1,4,7-triazonane-1,4-diyl)diacetate and tri-*tert*-butyl-2,2',2"-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl) triacetate will provide 3-p-*C*-NETA-NO2 and 3-p-*C*-DEPA-NO2 respectively.

Conclusion: An already established synthetic scheme has been modified using mild reaction conditions to reach better reaction yields. These bifunctional chelators will be used to obtain a second generation of 213Bi-somatostatin analogues.

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Session Classification: Ovarian cancer (PART I)

Track Classification: Preclinical research and development of new radiopharmaceuticals