**11C-SAM: a new potential agent for prostate cancer diagnosis**

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**BACKGROUND**

Prostate cancer (PCa) is one of the most common solid cancers in men. In patients with localized PCa, operative therapy is effective but a substantial number of patients experience recurrent disease. 11C-choline (11C-COL) has proved to be useful for restaging PCa in patients that suffer from biochemical failure with an absolute PSA value of > 1 ng/mL. This tracer cannot be recommended as a first-line screening procedure for primary PCa due to its limited sensitivity, its dependence on tumour configuration and its limited specificity in differentiation between PCa and benign pathologies.

Sarcosine (N-methyl glycine) has been identified as a differential metabolite that is highly increased during PCa progression to metastasis. This increase is associated to high levels of glycine-N-methyltransferase (GNMT) in aggressive PCa. GNMT catalyzes the methylation of glycine using S-adenosylmethionine (SAM) as co-enzyme to form sarcosine.

The aim of this study is to identify GNMT ligands as potential radiotracers for aggressive PCa diagnosis. For this purpose SAM was labelled with 11C and biological evaluation was performed. 11C-Choline was selected as the reference radiopharmaceutical.

**METHODOLOGY**

- **Synthetic strategies for 11C-SAM**

The synthetic process begins with the production of 13CO2 in cyclotron (GE PETTrace 16.5 MeV) via the 14N(p, γ)15C nuclear reaction. 11C-CO2 is delivered from the target to the automated synthetic platform (GE TRACERlab® FX CPRO) where it is trapped for purification and further reduction to 11C-H2. Then, it is iodinated to yield 11C-I, having the possibility to be later converted into 11C-IOT. Finally, the labelling reactions are based on 11C-methylations (figure 1).

![Figure 1: Left: GE TRACERlab FX CPRO. Right: production of methylating agent.](image1)

In order to obtain 11C-SAM, different labelling conditions of precursor (S-adenosyl homocysteine, SAM) have been performed, (figure 2). In these assays 11C-I, 11C-Ch3 and 11C-MeOT and 11C-MeDTPA have been tested as methylation agents. TFA/H3PO4, formic acid/DMAF and formic acid as solvents. The tested reaction temperatures were: 40, 60, 80, 100 and 120 ºC. Reaction times were: 1, 5, 10 and 30 min and the amount of precursor were 1, 3, and 5 mg.

![Figure 2: Synthetic strategies for 11C-SAM.](image2)

Crude product from the reactor was separated from impurities using semipreparative HPLC (Phenomenex Luna C18 5µ 250 x 10 mm; buffer sodium acetate 0.1M (pH 4.5); MeCN (98:2); 5.0 mL/min). Fraction containing 11C-SAM was collected over water and purified through Strata X-C SPE (Phenomenex), eluted with NaHPO4 0.1M (pH 5.6); EtOH (9:1) and formulated in saline. The final product was filtered through a 0.2µm sterile membrane.

11C-SAM quality control was performed evaluating according to the following parameters: solution appearance, pH, residual solvents (GC), chemical and radiochemical purity (HPLC), radionuclidic purity and identity, and specific activity.

- **Preliminary Biological Studies of 11C-SAM**

A xenographic human prostate cancer model was produced in two male nude mice. PC-3 cells (3 millions) were subcutaneously injected at the right upper leg of each animal. Appropriate tumour sizes (4.5-7.8 mm diameter) were achieved at four weeks post inoculation. Dynamic PET/CT scans were performed during 60 min in a preclinical Triumph Tri-modality Scanner (Triiloi, Inc.) after iv injection of 11C-SAM (219-231 MBq) or 11C-Choline (18.3-20.1 MBq) through the tail vein. Volumes of interest (VOIs) were drawn over tumour, contralateral muscle and liver to generate time-activity curves. The radioactivity concentration within each VOI was expressed as the Hot Spot Average (5) (kBq/cc). Biodistribution studies were carried out at 60 min post injection of 11C-SAM (10-12.4 TBq). Results were expressed as percentage of activity per gram (% Act/g).

![Figure 3: PET/CT images of PC-3 tumour bearing nude mice injected with 11C-SAM (A) and 11C-COL (B) at 60 minutes of acquisition (1×5 min, 1×15 min, 2×20 min). Time-activity curves of PC-3 tumour with 11C-SAM (C) and 11C-MeOT (D).](image3)

CONCLUSION

It was possible to optimize the 11C-SAM radiosynthesis, obtaining a tracer that is within the quality control specifications. The preliminary biological studies showed higher T/N ratio for 11C-SAM compared to 11C-COL, indicating GNMT ligands seem to be very promising compounds for prostate cancer diagnosis. Further studies must be performed in order to obtain a deeper and complete biological characterization of this compound.

**REFERENCES:**


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