^{68}Ga-PSMA and ^{177}Lu-PSMA of high specific activity for targeted diagnosis and therapy of prostate cancer in patients

N. Bentancor, V. Trindade, E. Vasilskis, I. Sanz, H. Balter, H. Engler

Uruguayan Centre of Molecular Imaging (CUDIM) – Montevideo – Uruguay

Abstract

Prostate-specific membrane antigen (PSMA) is a membrane enzyme expressed in nearly all prostate cancers with increased expression in poorly differentiated, metastatic and hormone-refractory carcinomas.

The urea-based inhibitors of PSMA exhibiting Glu-NH-CO-NH-Lys are excellent pharmacophores to bind this enzyme. Its conjugation to HBED-CC or DOTA and its labelling with ^{68}Ga or ^{177}Lu allow to obtain radiopharmaceuticals for PET/CT diagnosis or β^- emitter therapy.

Objectives

Development of a pair of radiopharmaceuticals with high specific activity (SA) and radiochemical purity (RP), preserving high recognition by its target (PSMA) suitable for diagnotherapy. This includes:

- Optimize the radiolabelling of Glu-NH-CO-NH-Lys-(Ahx)-HBED-CC with ^{68}Ga (^{68}Ga-PSMA) and PSMA-617 (2-[3-(1-Carboxy-5-{3-naphthalen-2-yl-2-[(4-{[2-(4,7,10-tris-carboxy methyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-methyl}-cyclohexanecarbonyl)-amino]-propionylamino}-pentyl)-ureido]-pentanedioic acid)-DOTA with ^{177}Lu (^{177}Lu-PSMA)
- Study their stability
- Evaluate of the radiochemical purity (RP) identifying the main potential impurities
- Study the binding properties of ^{177}Lu-PSMA to prostate cancer cells that express PSMA receptor (LNCaP cells).
- Develop the GMP production of this radiopharmaceuticals, with maximum specific activity to be used in patients.

Methods

^{68}Ga-PSMA-11 Optimization

1000 µL **$^{68}GaCl_3$** (360 MBq in HCl 0.05 N)
+
250 µL NaOAc 0.25 M (to pH = 4.0)
+
0.04 – 1.25 µg of **PSMA-11** precursor (0.04 – 1.32 nmoles)

↓ 1-5 min / 100ºC

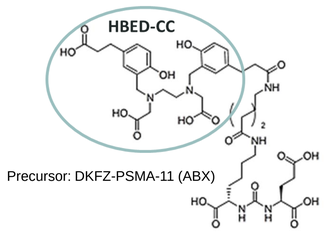
^{68}Ga-PSMA-11

↓ Only for GMP production

Sep-Pak C18 light

↓

Quality Control: RCP, RNP, Residual solvents, pH…



Precursor: DKFZ-PSMA-11 (ABX)

RP of ^{68}Ga-PSMA was controlled by ITLC-SG and RP-HPLC.
The scaling up production of ^{68}Ga-PSMA for patients was done with a microfluidics system (ITG) inside a shielded laminar flow hood Class A.

^{177}Lu-PSMA-617 Optimization

$^{177}LuCl_3$ nca (345 MBq in HCl 0.04 N)
+
180 µL NaOAc 0,8 M / gentisic acid 0,24 M buffer (to pH = 5.0)
+
0.56 – 4.46 nmol of **PSMA-617**

↓ 5-15 min / 90-100ºC

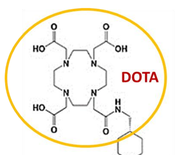
^{177}Lu-PSMA-617

↓

Quality Control: RCP, RNP, pH…

↓

Stability up to 8 days (*in vitro* at R.T.)



Precursor: DKFZ-PSMA-617 (ABX)

RP and stability of ^{177}Lu-PSMA was evaluated by RP-HPLC and ITLC-SG up to 8 days.
The in vitro cell assay was performed with LNCaP cells, which were incubated with ^{177}Lu-PSMA for 1 hour at 37ºC. Competitive blocking was done with the unlabelled precursor. The bound to membrane fraction was obtained by glycine acid buffer washing. The internalized fraction was obtained by cell lysis with NaOH 10M.

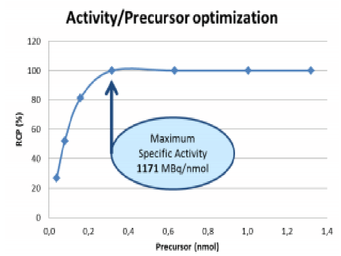
Results

^{68}Ga-PSMA-11

Validation batches

Activity of $^{68}GaCl_3$:	1131± 29 MBq
Global yield (ndc):	90 ± 1 %
Radiochemical Purity:	97 ±1 %
Specific Activity:	418 ±15 MBq/nmol

At CUDIM Since August 2015 → 95 productions of ^{68}Ga-PSMA
RCP = (98 ± 2) %
Specific Activity = (234 ± 76) MBq/nmol

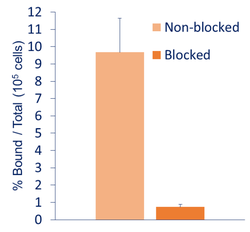


^{177}Lu-PSMA-617

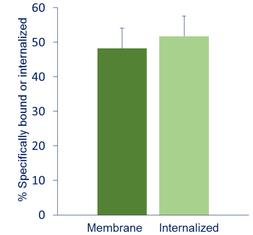
Validation batches

Activity of $^{177}LuCl_3$:	372 ±18 MBq
Global yield (ndc):	88 ±3 %
Radiochemical Purity:	> 99,9 %
Specific Activity:	128 ± 6 MBq/nmol

It was possible to obtain a radiopharmaceutical stable for 8 days (RP>95%).



Data are expressed as mean ± SD (n = 3)



Plot nº1 - The pronounced difference between blocked and non blocked cells shows the specificity of the radiopharmaceutical for its target.

Plot nº2 - After 1 hour of incubation, nearly half of the activity was internalized by the receptor and the other half remained bound to the membrane.

Conclusion

The high specific activities required for the clinical application of these radiopharmaceuticals for prostate cancer diagnosis and therapy, require careful control of the ratio activity/precursor, incubation temperature and time. ^{68}Ga-PSMA of high RP and SA is being used in patients at CUDIM with excellent results. ^{177}Lu-PSMA is ready to start a pilot study with patients.

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