Ga68: First Member of the Theragnostics trio

J.Bonnet MD MBA

7th ISMR, Liège, May 9th 2019

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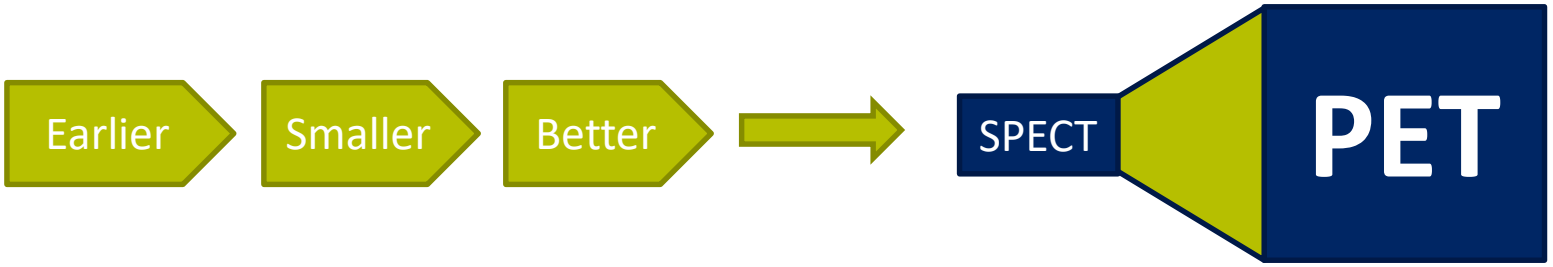
PET Imaging agent:

... and the winner is.....!!!!!

Some contextual elements…

High demand to cover new diagnostics needs



From functional to cellular and molecular imaging

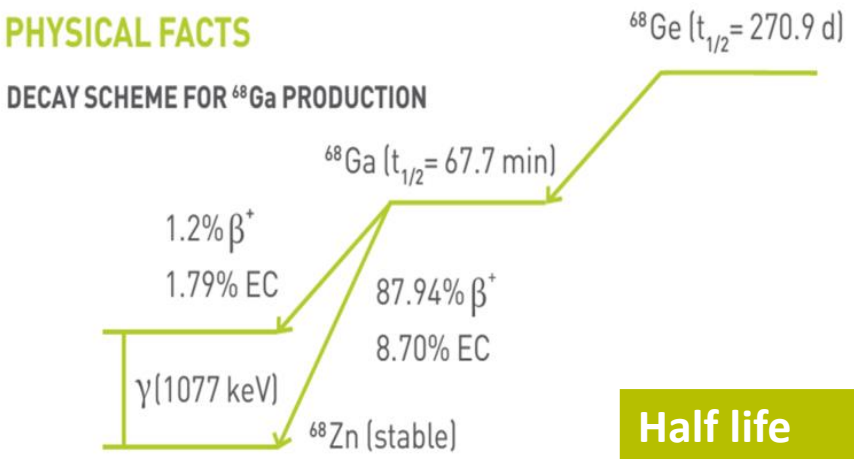
Higher sensitivity and speed, accurate quantitation, dynamic reconstruction

New equipments dedicated to PET imaging:

- Development of new technics and cameras
- New acquisition or renewal in favor of PET

New tracers almost exclusively developped for PET

Ga68: The isotope of choice



Half life	67,7 minutes
Main Decay Scheme	β^+ 88% ; high energy (1,9MeV) EC: ~ 11% γ: 1,08MeV

- Well known labeling chemistry process
- Wide choice and possibility of products available for labelling

Ga68: The isotope of choice

- Favorable profile compared to other imaging agents

Half life vs examination time
Predominant emission of positron
Lower level of Effective dose
Possibility to be produced in generators

Effective doses for some PET and SPECT imaging agents.

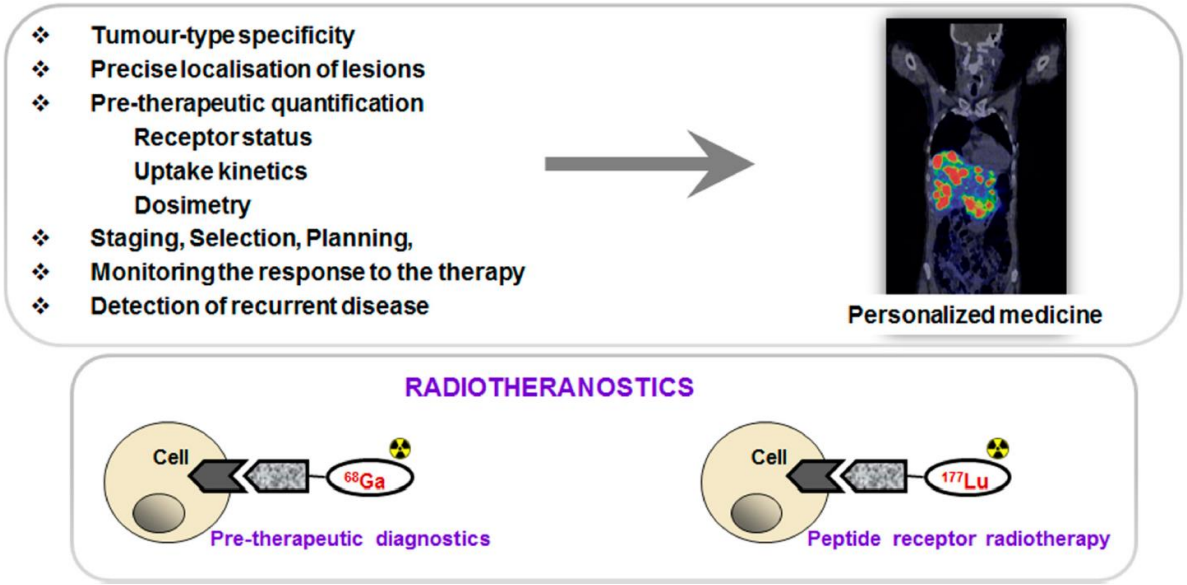
Agent	Examination time	Effective dose, [mSv]
[^{111}In]In-DTPA-octreotide/SPECT	24-48 h	10.8
[^{68}Ga]Ga-DOTA-TOC/PET	30-60 min	2.3
[^{18}F]FDG/PET	60-120 min	5.6
[^{99m}Tc]-BPAMD/SPECT	2-6 h	6
[^{99m}Tc]-MDP/SPECT	2-6 h	3-4
[^{68}Ga]Ga-BPAMD/PET	30-60 min	3-4

Radionuclide	Half-life	E_{max} (keV)	Radiation	Production
Positron emitters				
^{11}C	20.3 min	961	β^+ (100%)	Cyclotron
^{18}F	110 min	634	β^+ (97%)	Cyclotron
^{64}Cu	12.8 h	656	β^+ (19%)	Cyclotron
^{66}Ga	9.5 h	4153	β^+ (56%)	Cyclotron
^{68}Ga	67.6 min	1899, 770	β^+ (89%)	Generator
^{89}Zr	78.4 h	900	β^+ (23%)	Cyclotron
^{124}I	4.17 d	2100	β^+ (23%)	Cyclotron

Theranostics 2014, Vol. 4, Issue 1

Ga68: Ideal Partner & Team Player

- ^{68}Ga labeled products can be small molecules, peptides or antibody fragments with short biological half-life: fast pharmacokinetics
- Robust labeling chemistry diversity
- Potential for personalized medicine

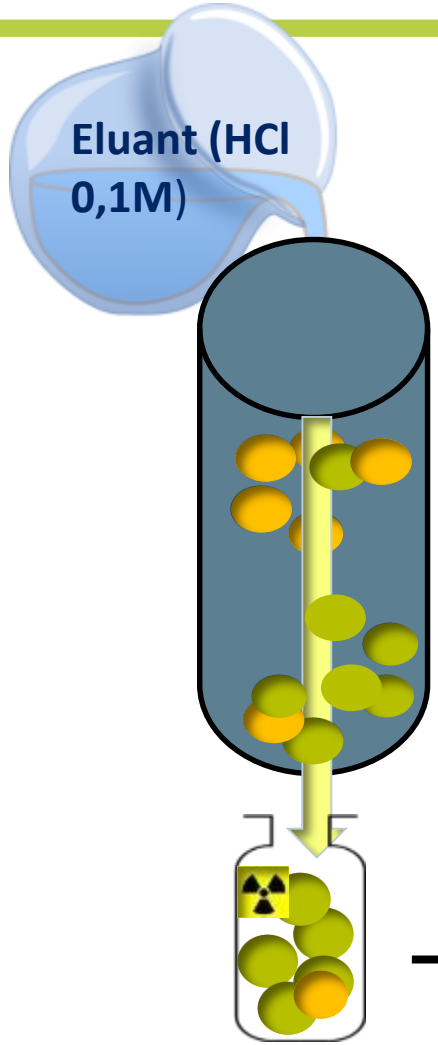


Molecules 2015, 20, 12913-12943

Ga68 Generator

Not Why, not What.... But How

Ga68 Generator: Feeling of « déjà-vu »



Ge-68 → Ga-68

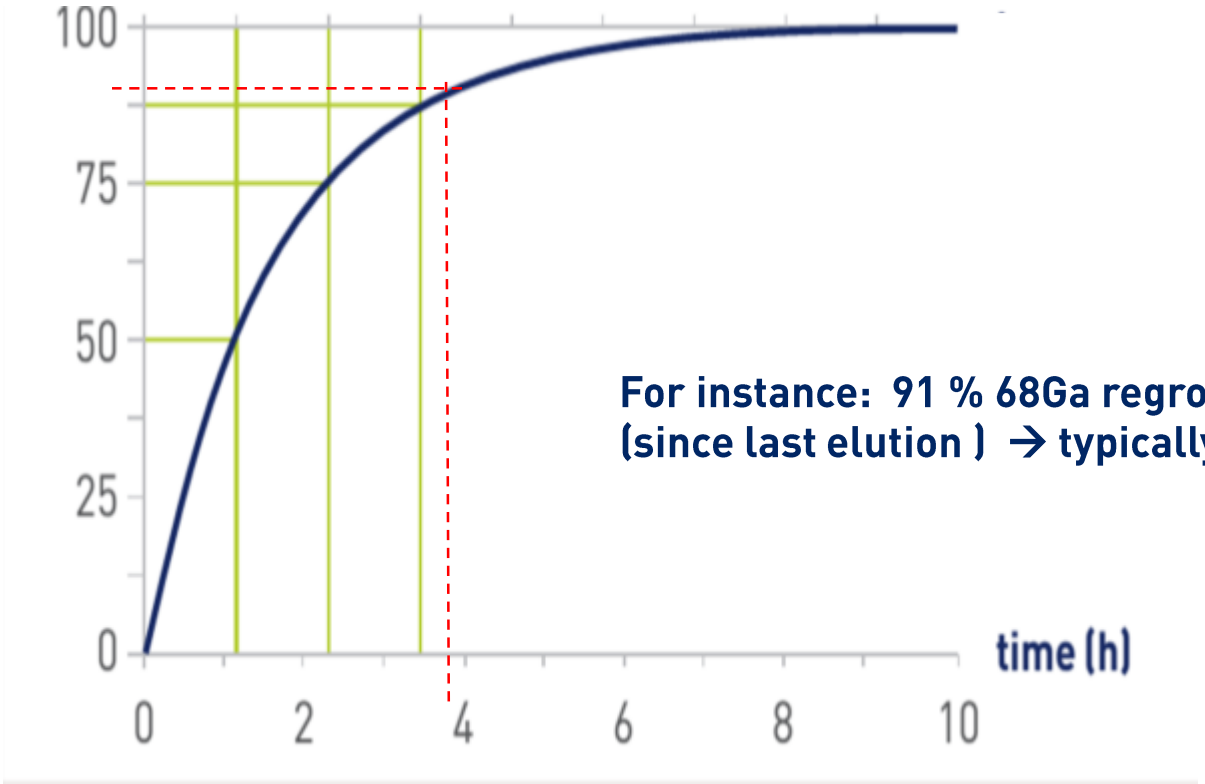
Liquide phase (mobile phase) = eluate

Elution :
Preferential driving of the Ga-68 by means of a liquid mobile phase passed through the column of the generator.

→ Eluate (^{68}Ga)

Ga68 Generator: Regrowth Principle

% of 68Ga regrowth (since last elution)



For instance: 91 % 68Ga regrowth after 4 h (since last elution) → typically 2 or 3 elutions /day

Ga68 Generator: Challenges

- **Breakthrough level** (contamination of the separated daughter by the parent radionuclide): high and/or variable level over time may require a pre-purification step to remove Ge-68 from the eluate.
- **Metallic impurities level :** high level of metallic impurities such as Fe, Zn or Cu that may compete for the ligand and affect performance and yeld during the Ga-68 radiopharmaceutical preparation.
- **Volume of the eluate :** when too high (4 to 6ml), may render buffering or linking process difficult especially for use with kit to form radiopharmaceutical.
- **Sterility** not guaranteed over time.
- **Cumbersome** manipulation and low easiness

Regulatory constraints

Ga68 Generator: Towards a « 2.0*» model?

When we asked users :

“What should be the specifications for an ideal 68Ga generator ?”

Radiopharmacists / chemists most often answered:

- ❑ **High concentration**
- ❑ **High yield**
- ❑ **Low breakthrough**
- ❑ **No metallic impurities**
- ❑ **Low elution volume**
- ❑ **Sterility guaranteed**
- ❑ **Easy to use**

* 2.0 :used to denote a superior or more advanced version of an original concept, product, service, etc.

Ga68 Generator: Our goals and drivers

A real « 2.0 » Ga68 Generator

- ☑ **Should have all these specifications**
- ☑ **Should be Tc-99m like**
  - ☑ ***Instant kit reconstitution***
  - ☑ ***Direct labelling***
  - ☑ ***« Shake and bake »***

Ga68 Generator: New Features

1.Original Stationery phase

» **Dry column**

Whereas wet column means continuous exchanges between column & eluent

» **Inorganic material**

- No radiolysis deterioration compared to organic phase leading to potential high Ge-68 release in generator eluates.
- 0 cleaning elution needed for up to 3 days without use
- Column composed of highly pure material releasing extremely low levels of impurities in eluates far below European Pharmacopea Requirements

2.Low & Reproducible Volume: 1,1ml

- High radioactive Ga-68 concentration of the eluate
- Easy to buffer
- No need for fractionation step during elution
- Ideal for cold kit reconstitution

3.Integrated Eluant

- **Closed system**
  - Control chromatographic parameters
  - Sterility guaranteed over 12 months
  - Stability of specifications over time (specifically for breakthrough and yield)
  - Highest number of elution (450)
  - No additional cost (eluent, consumables…)

- **Only one outlet port connection**
  - Minimized risk of microbiological contamination
  - Minimize risk of misuse

Ga68 Generator: Production Standards

- 100% Registered Pharmaceutical product
- Approved in FDA & EMA
- Heavy QC procedures at:
  - Ingredients & components selection
  - Supply phase
  - Production and Manufacturing phase
  - Release phase
  - Shipping Phase

Ga68 Generator: Production Standards

ELUATE	
Breakthrough	Throughout the generator's life < 0.001 %
Chemical purity Al, Cu, Fe, Ni, Pb, Zn, Ga	≤ 10 µg / GBq
pH	<2
Endotoxin	< 0,5 EU/mL
Microbiological quality	Sterile
Half-life	About 68 min

Radiation Control

GENERATOR	
Chemical Form	$^{68}GaCl_3$
Activity	20-30-40-50 mCi 0.74- 1.11-1.48-1.85 GBq.
Eluent	Sterile 0.1 M HCl
Elution volume	1.1 mL
Elution time	3 min
Elution yield	> 67% at release - > 55% end of life
Shielding	Equivalent to 50 mm lead thickness
Radiation dose	The average surface or contact radiation for the ($^{68}Ge/^{68}Ga$) radionuclide generator is less than 0.054 µSv/h per MBq of ^{68}Ge. For example, a 1.85 GBq generator will reach a maximum average surface dose rate of 100 µSv/h
Shelf life	450 elutions or 1 year
Dimensions (W*D*H)	220 mm * 210mm * 230 mm
Weight	16,5 kg

Using Ga68 Generator

- Parent nuclide easy to get.
- The half-life of 68Ga permits production and application of resultant agents, and the labelling synthesis is amenable to automation and kit type preparation.
- It provides sufficient levels of radioactivity for high quality images, short scanning time (fast patient examination) while minimizing the radiation dose to the patient and personnel, and allows fast dischargement of the patient.
- It gives flexibility in patient flow and patient management
- It also allows repetitive examinations within the same day.
- The majority of the therapeutic radionuclides is also metals and might allow for the theranostic development.

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