Recently Approved and Potential Future Drugs and Their Isotopes

Eldon E. Leutzinger, Ph.D.

Office of New Drug Products, OPQ
CDER / FDA

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Outline of Presentation

1. PET Drugs – new developments
   A. The mounting interest in ^{68}Ga
   B. Trending toward radiotheranostics
   C. Molecular biomarkers with PET - ^{89}Zr-based immuno-PET molecular imaging in cancer patients
2. Recent approvals
   A. PET – ^{11}C, ^{18}F
   B. First alpha-emitting drug – Xofigo ($^{223}RaCl_2$)
3. ^{99m}Tc – what is new for an old isotope
   A. New addition – Lymphoseek – imaging of lymph nodes
   B. Establishing a domestic supply of ^{99}Mo

PET Drugs – New Developments

The mounting Interest in ^{68}Ga

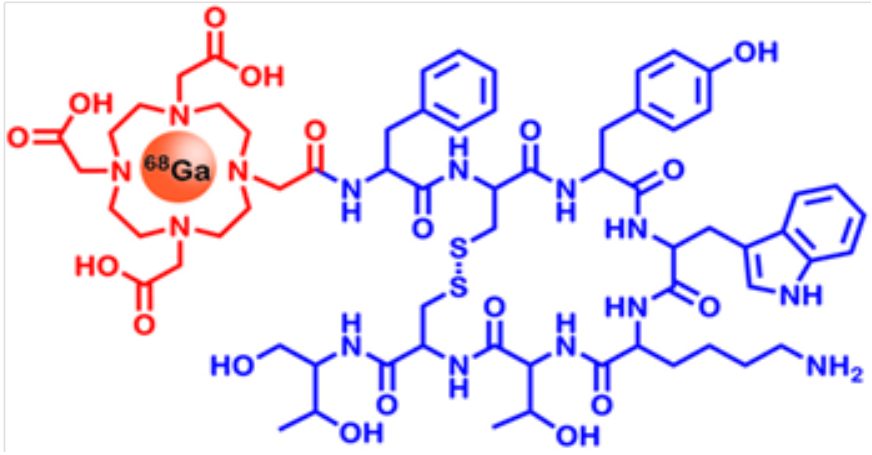
- Rapidly increasing number of publications with ^{68}Ga since 2008 – overall 660 publications since 1966
- Increasing number of incoming IND's with ^{68}Ga over last 5 years

The mounting interest in ^{68}Ga

- High positron emission fraction – 89%, E_{max} at 1899 KeV, E_{mean} at 890 KeV), providing sufficient radioactivity levels for high-quality images
- With $t_{1/2}$ of 68 min, radiation dose to patients is minimized

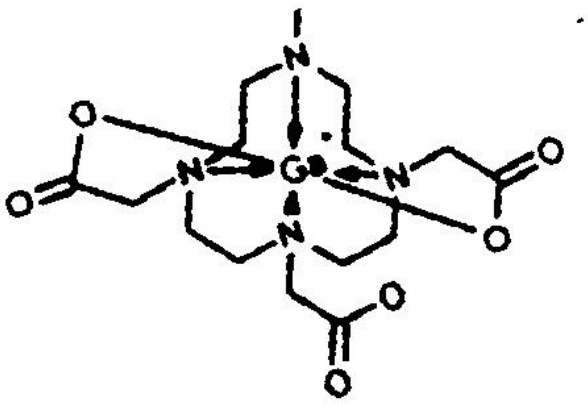
- Robust radiolabeling chemistry
- Use of “kit + generator” concept to make ^{68}Ga-drugs available
- Availability of commercial generators
- Potential use of ^{68}Ga in radiotheranostics

➢ Robust radiolabeling chemistry



^{68}Ga-DOTATOC / ^{68}Ga-DOTATATE

Detection of neuroendocrine tumors



- Advantage of using DOTA chelate
- Mild reaction conditions with $^{68}Ga^{3+}$
  - Stability of disulfide bond
- Rigid cage offers stability against $^{68}Ga^{3+}$-dissociation

- Use of “kit + generator concept” to make ^{68}Ga-drugs available – **regulatory pathway**

Kit concept – after well-established ^{99m}Tc kits (from 1970 with first of the radiopharmaceutical kits – ^{99m}Tc-DTPA). **Kits approved under NDA**.

^{68}Ga generator – without “stand-alone” indication – **DMF** (Type II)

- Availability of $^{68}Ge/^{68}Ga$ generators

Eckert & Ziegler (Ziegler Radiopharma, Inc, Germany – TiO_2 – 0.1N HCl

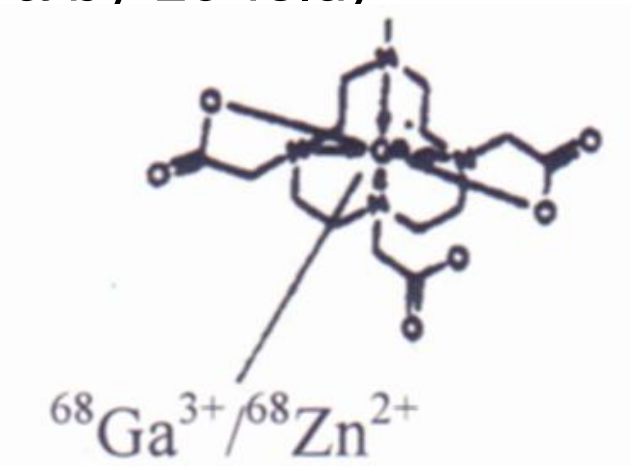
ITG (Isotope Technologies Garching, Germany) – organic matrix – 0.05N HCl eluent

iThemba (iThemba Labs, South Africa) – SnO_2 – 0.6N HCl

$^{68}Ge/^{68}Ga$ Generator

- Short glass column packed with metal oxide solid matrix
- $^{68}Ge^{4+}$ (some chemical form) absorbed onto matrix
- ^{68}Ge (275 d) → ^{68}Ga (68.3 min) → stable ^{68}Zn
  (at Secular equilibrium, ^{68}Zn > ^{68}Ga by 10-fold)

- Labeling interference – $^{68}Zn^{2+}$
  also labels DOTA-peptides



- First elution discarded – $^{68}Ga/^{68}Zn$ = 1.2 at 136 min
- Use more ligand; remove $^{68}Zn^{2+}$ prior to radiolabeling
- Interference by other cations (Cu^{2+}, Fe^{3+}/Fe^{2+}, …)

$^{68}Ge/^{68}Ga$ Generator

SOURCE of ^{68}Ge

- Cyclotron-produced, ^{nat}Ga (p,xn)^{68}Ge; but, only one commercial source for ^{68}Ge for use in production of generators

- Looms as potential problem in the face of mounting interest in ^{68}Ga, with the specter of potential future availability issues

- Assurance of ^{68}Ge quality at some risk, due to loss of good handle on its production, target quality, bombardment characteristics, etc. (similar to issues for ^{99}Mo, ^{82}Sr, ….)

Trending toward radiotheranostics

Turning an imaging drug into a therapeutic counterpart in a diagnostic / therapy pair

- $^{68}Ga/^{177}Lu$ – choice of chelate is essential – in vivo performance / targeting properties must be similar as possible between imaging and radiotherapeutic molecules

- To establish pre-therapeutic quantification of receptor sites, uptake kinetics, dosimetry

- Allow for therapy selection / planning in personalized medicine

^{89}Zr-Based Immuno-PET (molecular imaging in cancer patients)

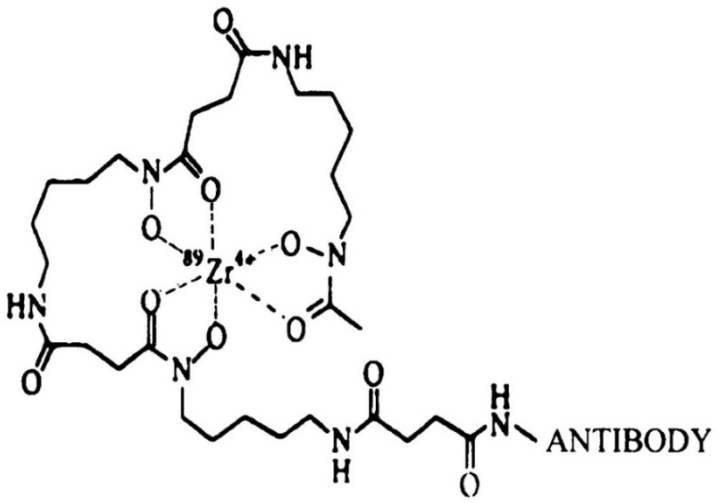
Conjugation strategy with N-succinimidyl DFO

Low energy positrons (395 KeV, ave) – high resolution PET images; $t_{1/2}$=78.4 hr

DFO a good chelator, releasing only 0.2% of free $^{89}Zr^{4+}$

Issues: interference of chelator with antigen-binding domain

Visualize / characterize tumor images

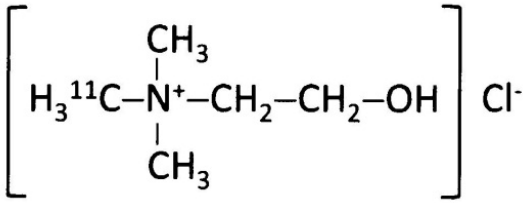


n-Succinimidyl-DFO

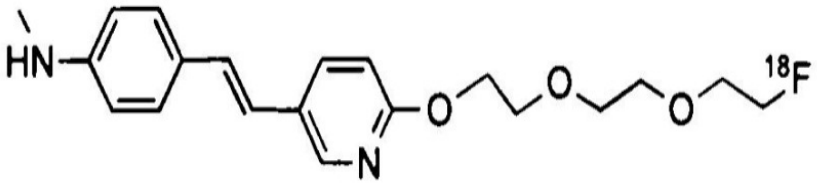
Recent Approvals

PET Drugs –

- ^{11}Choline – 2012 – in suspected prostate cancer recurrence



- ^{18}F-Florbetapir (Amyvid) – 2012 – in patients with suspected Alzheimer's Disease – estimate β-amyloid plaque density



Recent Approvals

Radium (^{223}Ra) -

Xofigo – $^{223}RaCl_2$ – 2013 - first alpha-emitting drug for treatment of castration-resistant prostate cancer

- Predominantly alpha emitter – energetic – short range (<0.1 mm)
- Induces greater lethal tumoricidal effects
- Less surrounding tissue exposure / less hematologic toxicity and myelosuppression

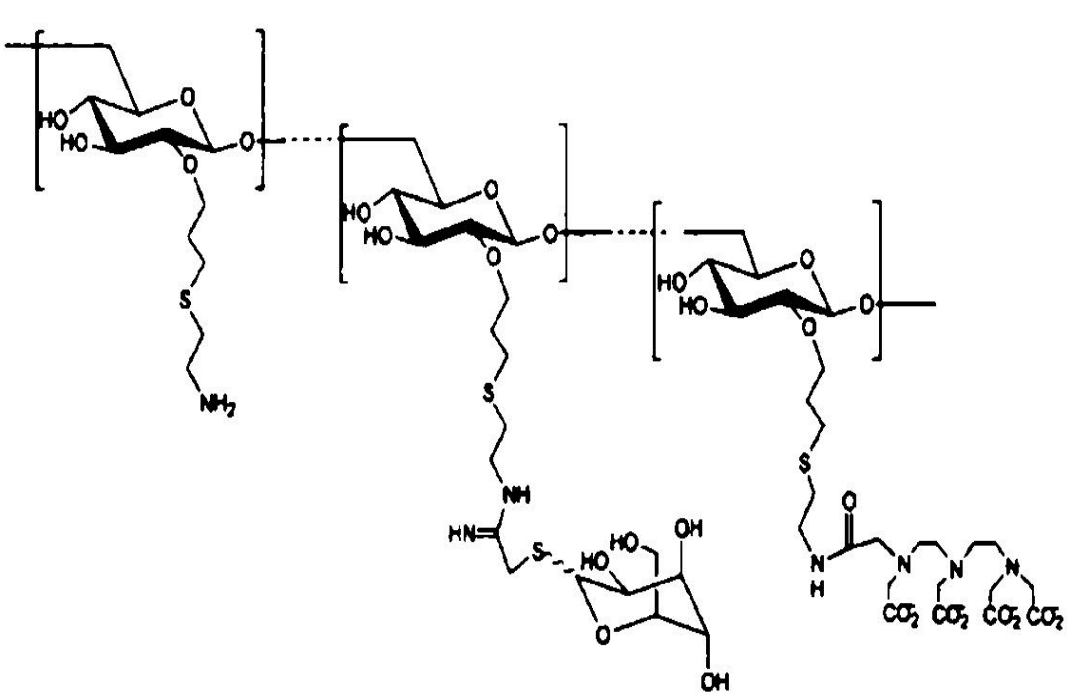
^{99m}Tc – What is New for an Old Isotope

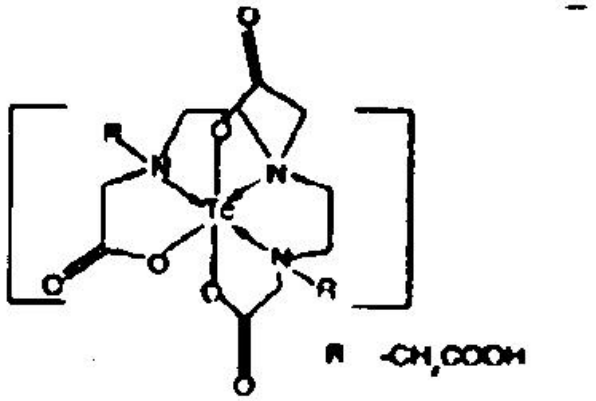
- An isotope with rich experience history, with 20+ ^{99m}Tc drugs approved from early 1970's – "nuclear medicine workhorse," accounting for 80% of procedures performed in U.S.

- Adds another - Lymphoseek (technetium Tc 99m tilmanocept) – 2013 – imaging of lymph nodes

Lymphoseek –

- Lymphatic mapping with handheld gamma counter
- Locate lymph nodes draining a primary tumor
- Guiding sentinel lymph node biopsy-breast cancer, melanoma, oral cancer





^{99m}Tc- its prominent place in nuclear medicine continues

- Activities toward establishing a reliable domestic supply of ^{99}Mo for production of ^{99m}Tc generators
- General Atomics recently received award of $9.7 million from NNSA to develop unique technical methods to produce ^{99}Mo
- Collaborative project combining capabilities of MURR and Nordion with General Atomics gas extraction technology to produce LEU
- Northstar – use low specific activity ^{99}Mo in technetium generators

Thank You