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Direct "on-resin" radiofluorination, radiotitanation and radiozirconation using automated radiosynthesis module BioSyntheSizer 2.1

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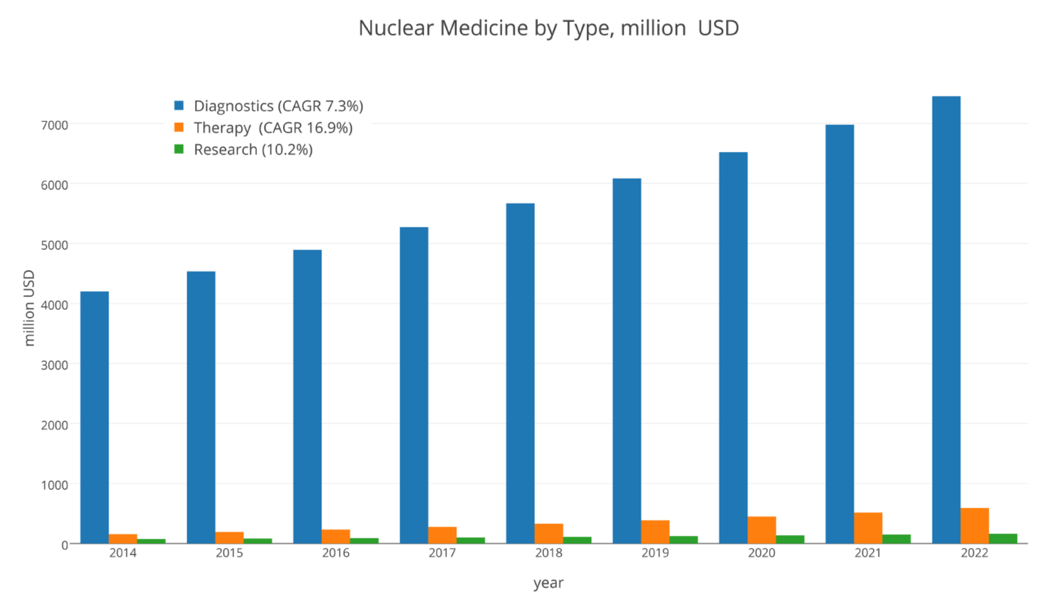
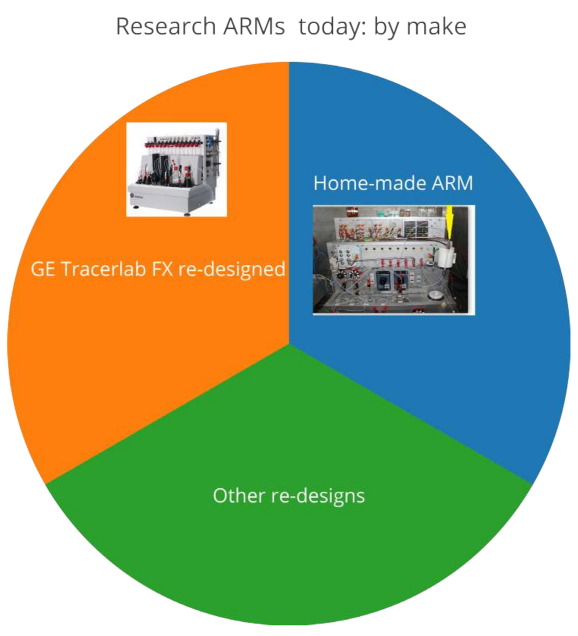
Introduction

Although Nuclear Medicine market is dominated by Diagnostics, Research segment grows by an impressive *10.2%* CAGR. ►





There is an unmet need for automated radiosynthesis modules (ARMs), catering specifically to R&D segment of the market.

◄ According to our survey, home-made or re-designed ARMs are currently the most popular solutions for R&D labs.

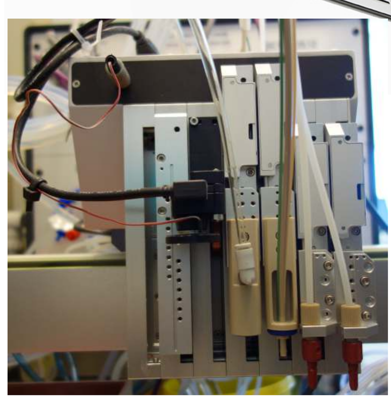
Objectives

Our research program is directed towards new approaches to automated radiofluorination and radiometallation using radiolabeling at the point of radionuclide capture [1-2]. Herein we report automated trapping, trap-and-release, and "on-resin" radiolabeling with ^{18}F, ^{45}Ti, and ^{89}Zr using radiosynthesis module BioSyntheSizer 2.1 (GeSiM mbH, Germany).

BioSyntheSizer platform

GESIM ►

BioSyntheSizer 2.1 (BSys) is an advanced robotic platform for complex laboratory automation. A toolhead movable in 3D controls fluidics via luer-lock manifolds connected to syringe pumps for easy aspiration/dispensing operations. The reagent rack can host a variety of vials (1-50 mL), and solid-phase extraction (SPE) cartridges. ►
A unique feature is handling of syringe needles and Eppendorf pipette tips.

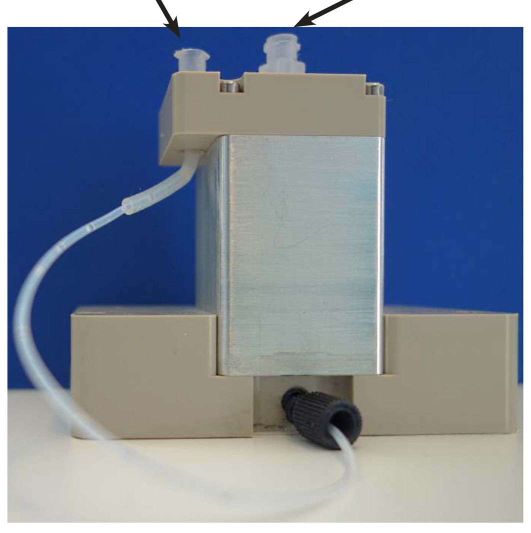


◄ A 3D movable toolhead combines the versatility of manual operator with reproducibility of a machine.

Solid Phase Flow Reaction Module

Our developer's version of BSys is equipped with a solid phase flow reaction module. The module is electronically integrated and software-controlled in the BSys allowing for trapping, trap-and-release, and "on-resin" radiolabeling. ►
The module features:
1. Fine temperature control
2. Accomodates different sizes of glass columns for radiofluorination and radiometallation

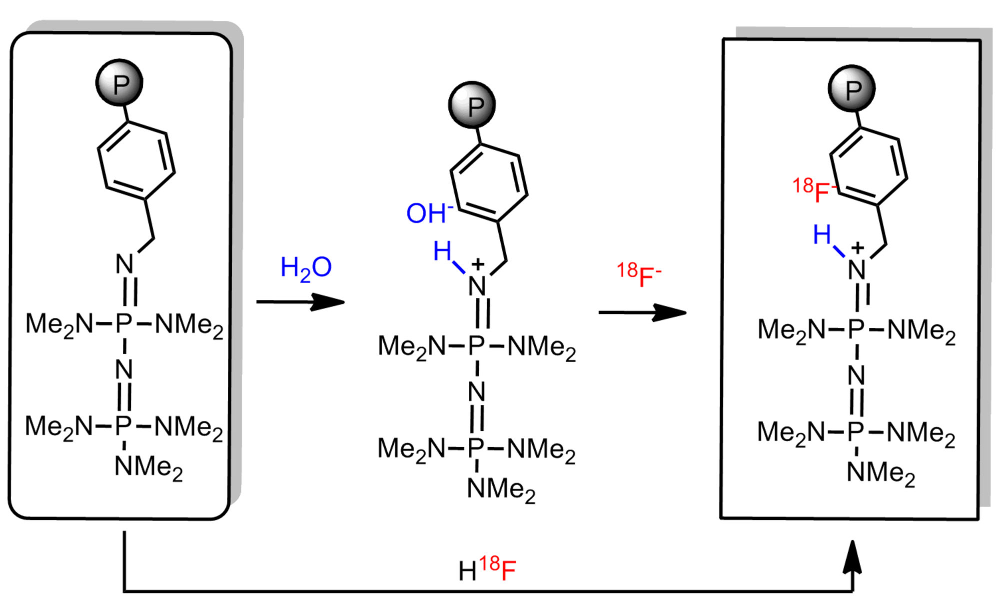
Luer2 (L2) Luer1 (L1)



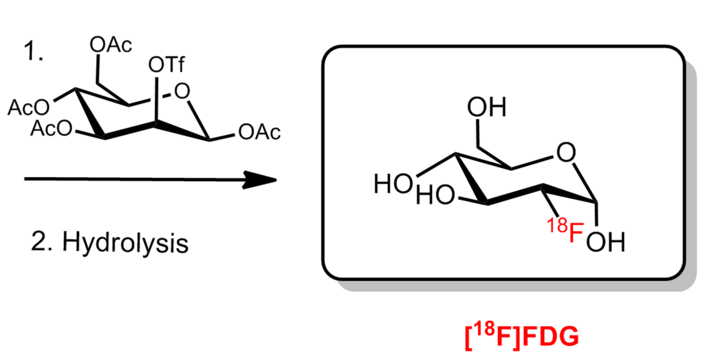
Radiofluorination column ▼

Radiometallation column ►

Radiofluorination



Radiochemistry



1. Column is loaded with polymer-supported phosphazene
2. Target water is passed through, (L1→L2) 98-99% of fluoride is trapped
3. A quick wash with acetonitrile (ACN) removes residual water from the column (does not have to be very dry!)
4. A substrate in a suitable solvent (toluene, ACN) is passed through the column while the column is heated at 80 - 100 °C (L1→L2)
5. The product is collected in L2. RCY = 40–60%.
6. With many substrates the resin can be reused at least 4 times

Radiometalation: ^{45}Ti, ^{89}Zr

^{45}Ti is great for peptide & affibody PET

- 3.08 h half life
- 85% positron branch
- E_0 = 1.04 MeV
- E_{ave} = 439 keV
- $^{nat}Sc(p,n)^{45}Ti$

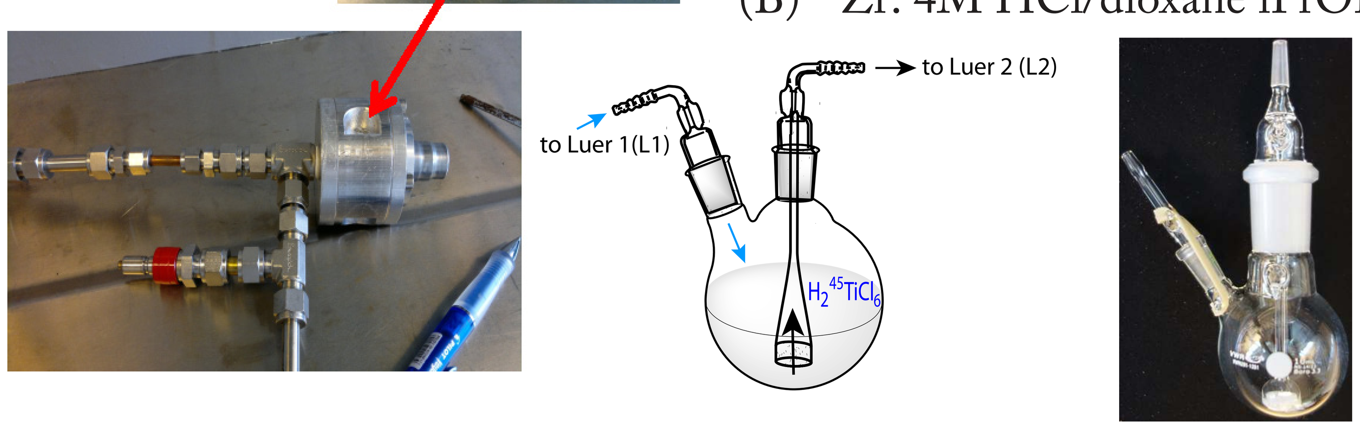
^{89}Zr is great for immuno PET

- 78.4 h half life
- 23% positron branch
- E_0 = 0.90 MeV
- E_{ave} = 396 keV
- $^{nat}Y(p,n)^{89}Zr$

Targetry

23 mg Sc
8 Gbq EOB

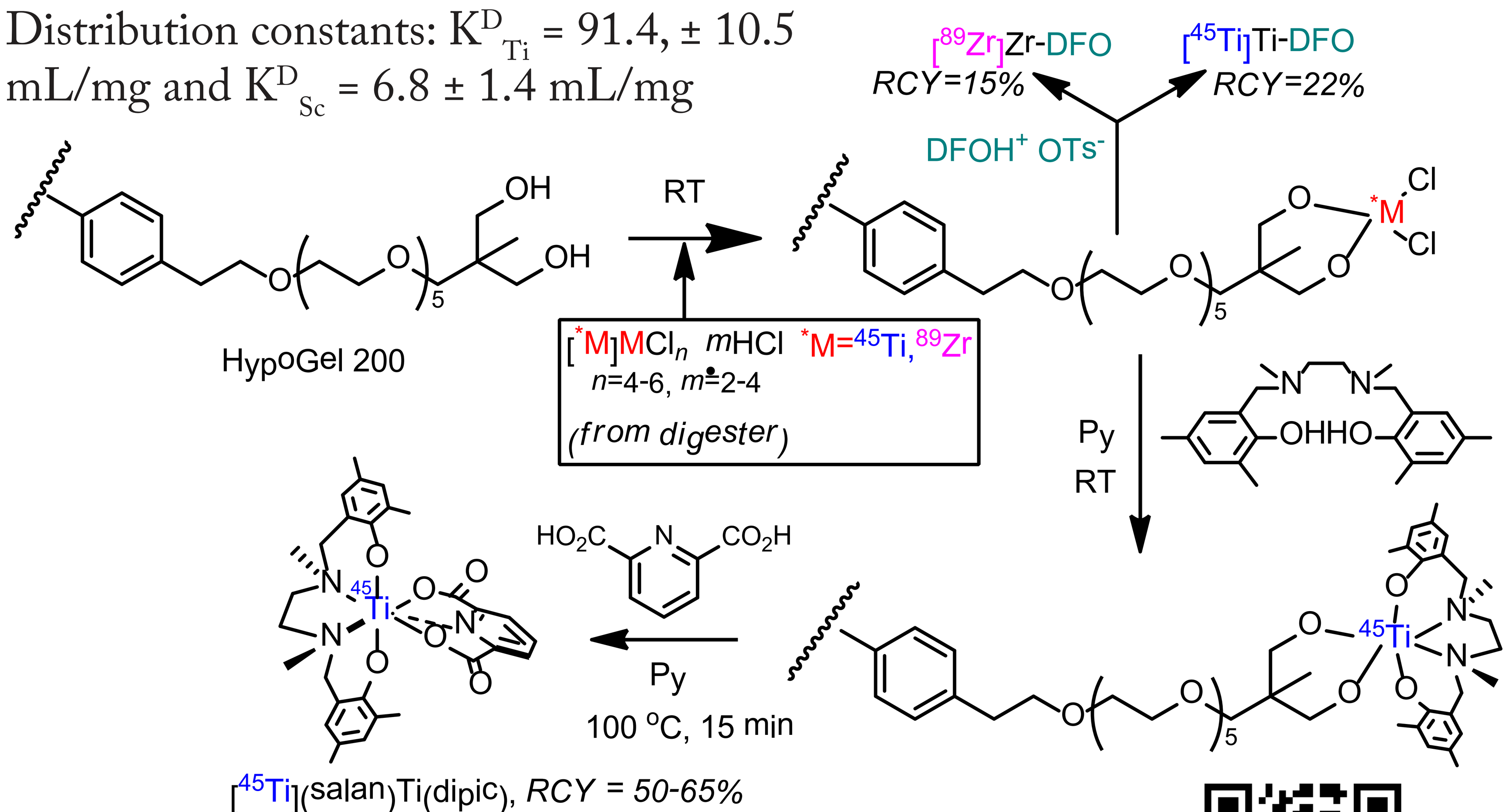
Automated target foil digestion: no manual handling
(A) ^{45}Ti, ^{89}Zr: 37% HCl
(B) ^{89}Zr: 4M HCl/dioxane iPrOH



Automated digestion: ► YouTube

Radiochemistry

Distribution constants: K^D_{Ti} = 91.4, ± 10.5 mL/mg and K^D_{Sc} = 6.8 ± 1.4 mL/mg



Automated radiometalation: ► YouTube

Conclusions

1. Integrated target digester and the solid phase flow reactor enabled automated radiosynthesis of [^{18}F]F-FDG, and showcased radiometalation with ^{45}Ti and ^{89}Zr directly on a radionuclide trapping resin.
2. The fluidics and robotics proved to be tolerant to fuming HCl, and non-aqueous HCl/dioxane.
3. The flexible design of the radiosynthesizer allowing for creation of fluid path on demand via a 3D movable fluidics head required no hardware re-configuration in-between radiometal and fluorine-18 radiolabeling

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References:[1] Mathiessen, B.; Zhuravlev, F.* *Molecules* **2013**, *18* (9), 10531–10547.
[2] Severin, G. W.; Nielsen, C. H.; Jensen, A. I.; Fonslet, J.; Kjær, A.; Zhuravlev, F.* *J. Med. Chem.* **2015**, *58* (18), 7591–7595.