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Procedures for the GMP-Compliant Production and Quality Control of [^{18}F]PSMA-1007: A Next Generation Radiofluorinated Tracer for the Detection of Prostate Cancer

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Research for a Life without Cancer
ABX advanced biochemical compounds

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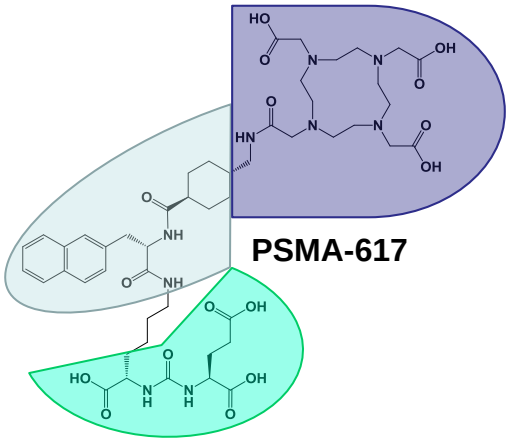
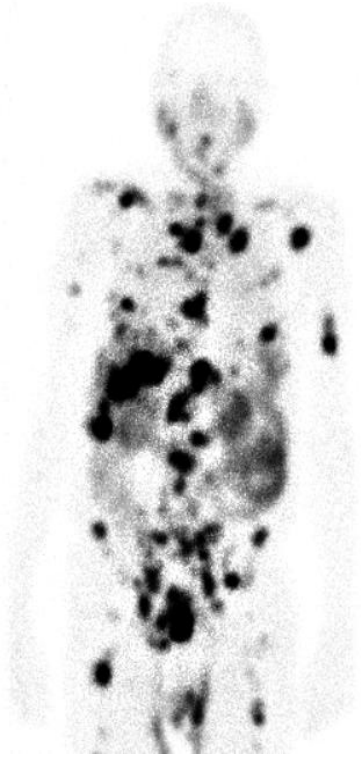
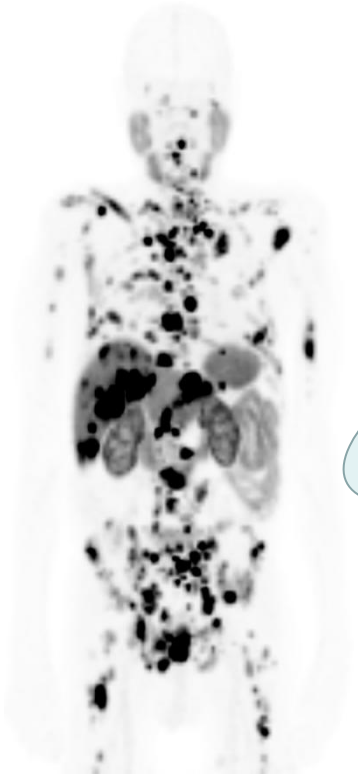
Abstract:
Radiolabeled tracers targeting the prostate-specific membrane antigen (PSMA) have become important radiopharmaceuticals for the PET-imaging of prostate cancer. In this connection, we recently developed the fluorine-18-labelled PSMA-ligand [^{18}F]PSMA-1007 as the next generation radiofluorinated Glu-ureido PSMA inhibitor after [^{18}F]DCFPyL and [18F]DCFBC. Since radiosynthesis so far has been suffering from rather poor yields, novel procedures for the automated radiosyntheses of [^{18}F]PSMA-1007 have been developed. We herein report on both the two-step and the novel one-step procedures, which have been performed on different commonly-used radiosynthesisers. Using the novel one-step procedure, the [^{18}F]PSMA-1007 was produced in good radiochemical yields ranging from 25 to 80% and synthesis times of less than 55 min. Furthermore, upscaling to product activities up to 50 GBq per batch was successfully conducted. All batches passed quality control according to European Pharmacopoeia standards. Therefore, we were able to disclose a new, simple and, at the same time, high yielding production pathway for the next generation PSMA radioligand [^{18}F]PSMA-1007. Actually, it turned out that the radiosynthesis is as easily realised as the well-known [^{18}F]FDG synthesis and, thus, transferable to all currently-available radiosynthesisers. Using the new procedures, the clinical daily routine can be sustainably supported in-house even in larger hospitals by a single production batch.
Keywords: PSMA; fluorine-18; PET; GMP; automation

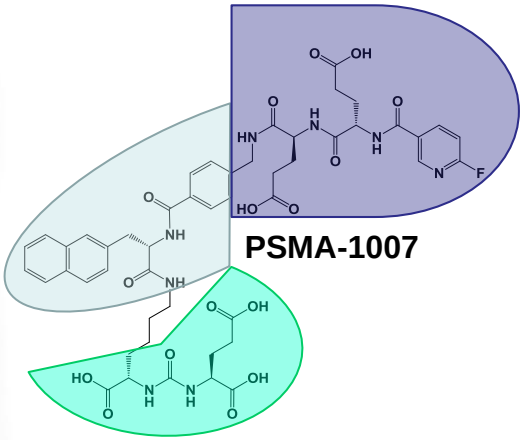
Transformation of PSMA-617 into PSMA-1007



PSMA-617







PSMA-1007

Radiolabel-bearing Moiety

Functional Spacer

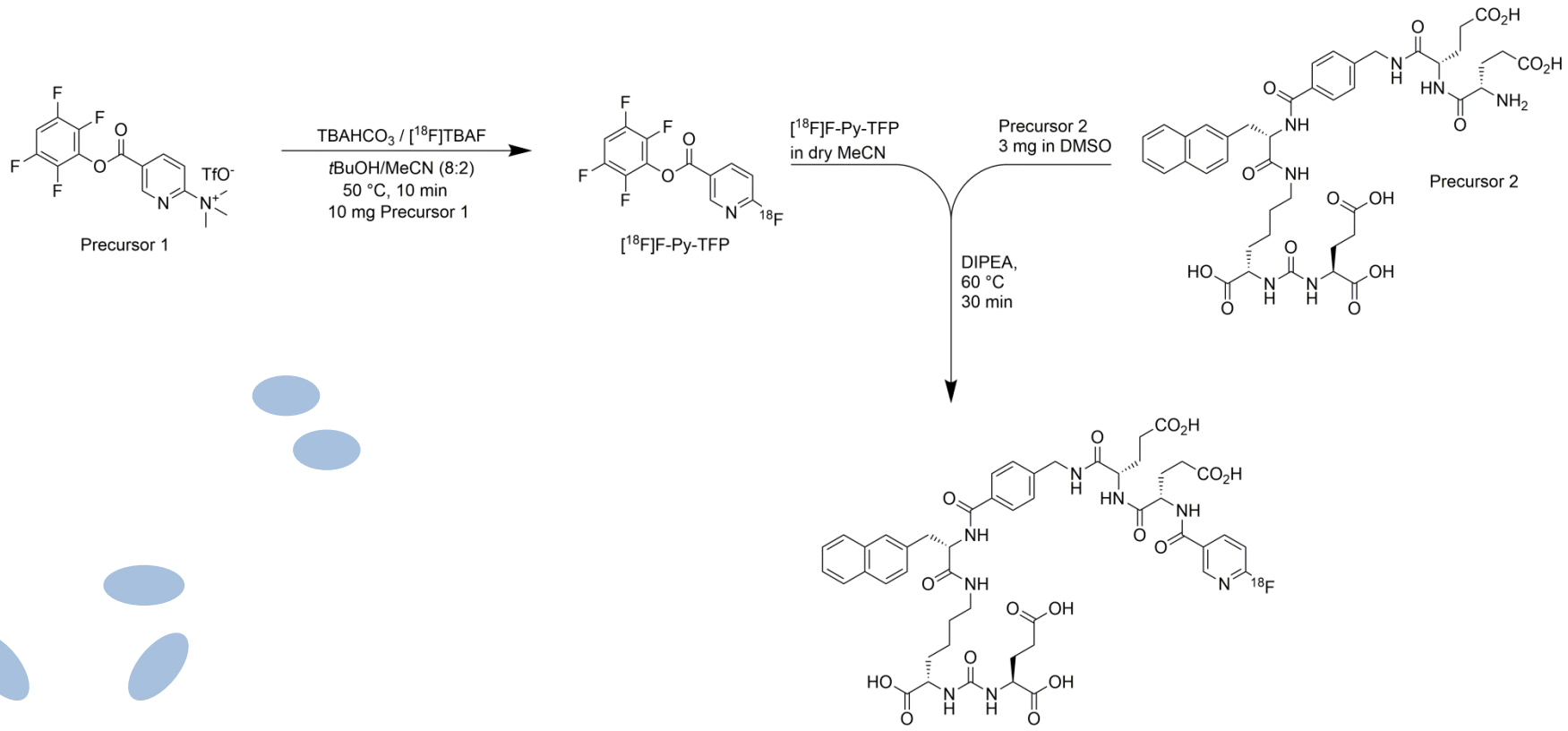
Pharmacophore

[^{177}Lu]PSMA-617
GM 24 h p.i.

[^{18}F]PSMA-1007
MIP 1 h p.i.

Giesel *et al.*, Eur J Nucl Med Mol Imaging 2016, 43 (10), 1929-1930.

[^{18}F]PSMA-1007: From two-step to single-step synthesis



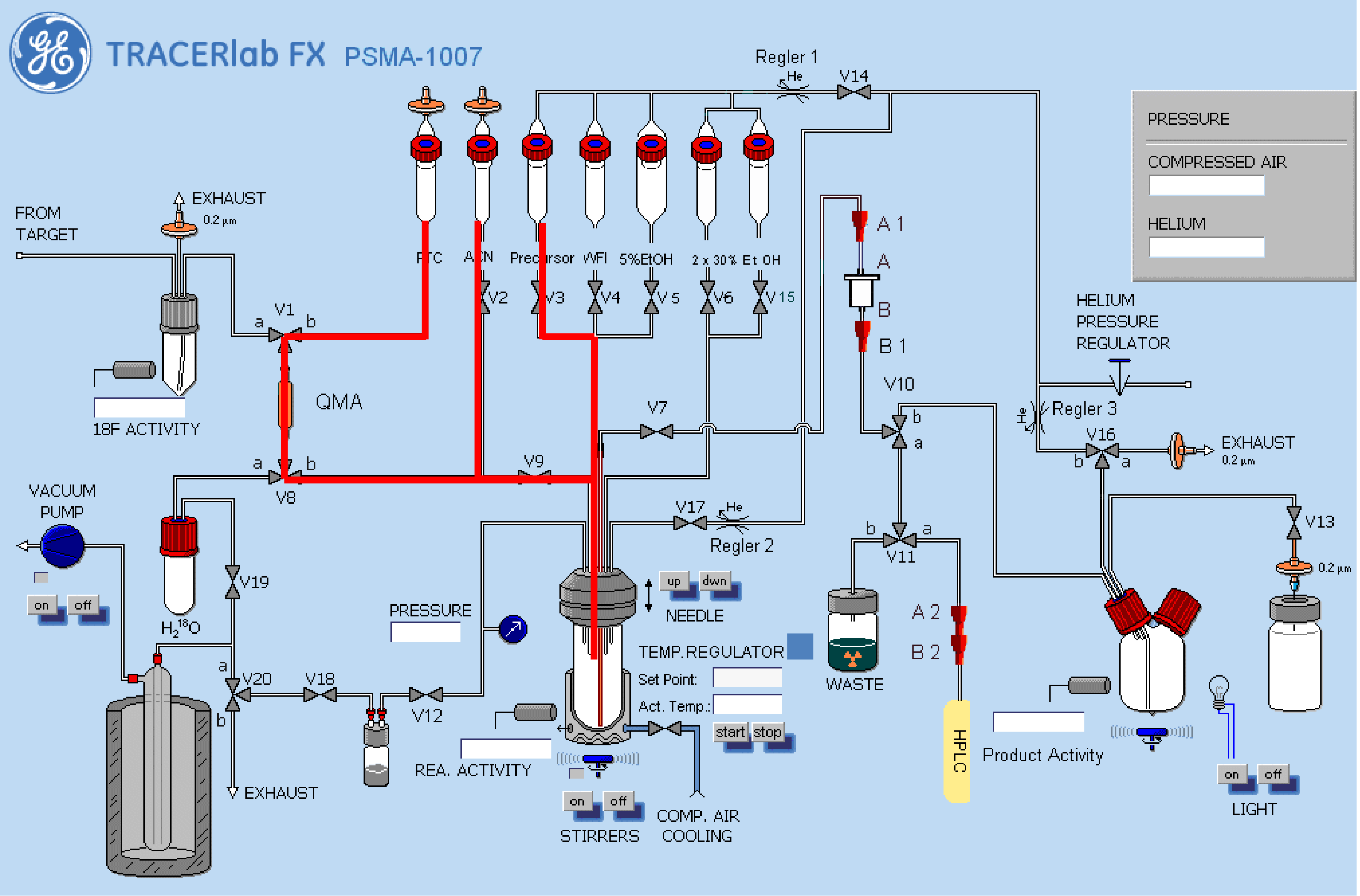
Olberg *et al.*, J Med Chem 2010, 53 (4), 1732–1740.

Cardinale *et al.*, J Nucl Med 2017, 58 (3),425-432.

Cardinale *et al.*, Pharmaceuticals (Basel) 2017, 10 (4), pii: E77.

Automation on a NI FDG / GE Tracerlab FX FN module

Addition of 750 µg PSMA-1007 precursor solution into reactor in 2 mL DMSO and subsequent heating at 85°C for 10 minutes



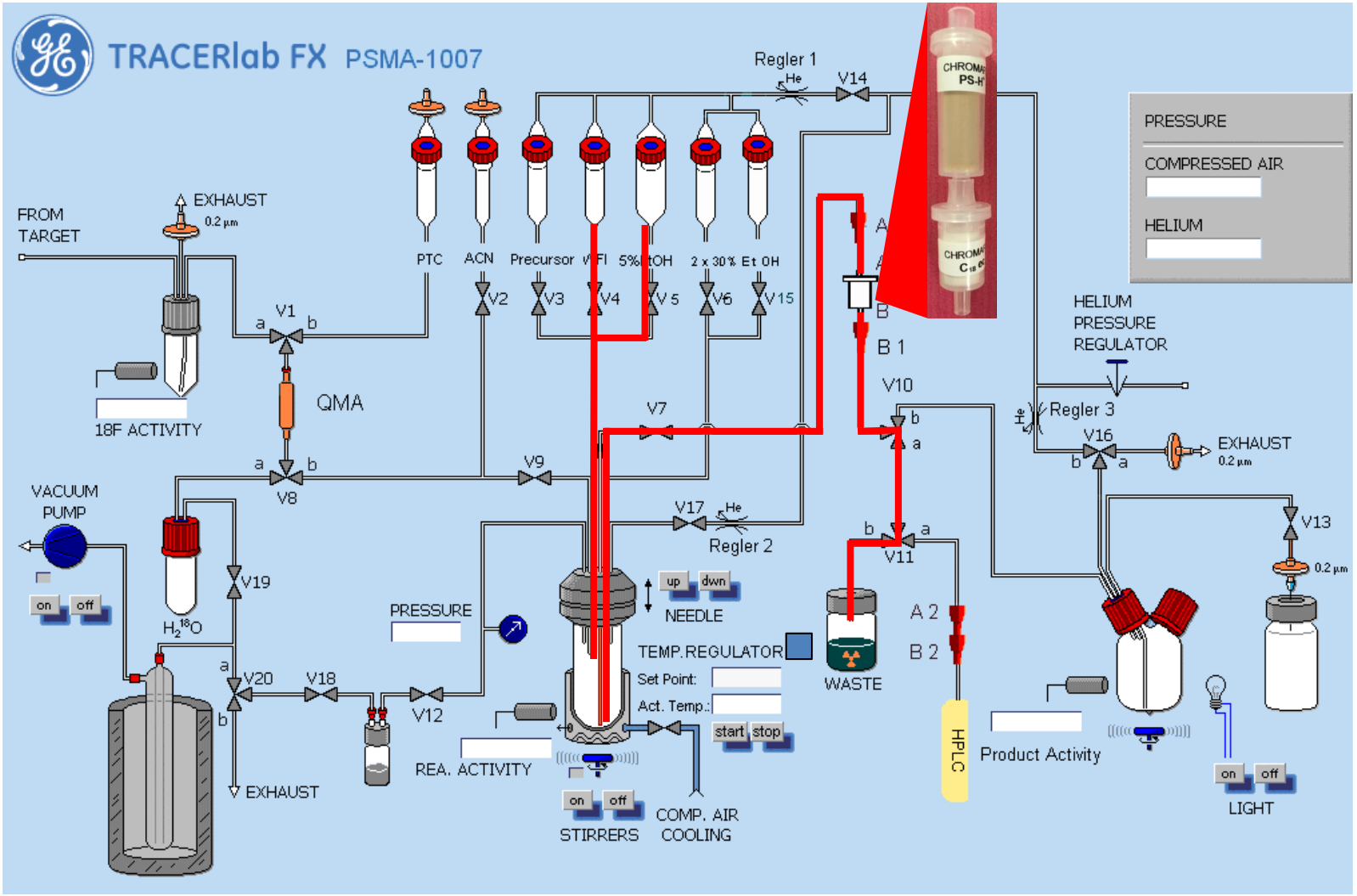
TRACERlab FX PSMA-1007
Regler 1
He
V14
PRESSURE
COMPRESSED AIR
HELIUM
FROM TARGET
EXHAUST
0.2 µm
PTC
ACN
Precursor
WFI
5%EtOH
2 x 30% Et OH
V1
V2
V3
V4
V 5
V6
V 15
A 1
A
B
B 1
HELIUM PRESSURE REGULATOR
QMA
18F ACTIVITY
V7
V10
Regler 3
V16
EXHAUST
0.2 µm
V8
V9
VACUUM PUMP
V17
Regler 2
V11
V13
0.2 µm
V19
$H_2^{18}O$
on off
up dwn
NEEDLE
PRESSURE
TEMP.REGULATOR
Set Point:
Act. Temp.:
WASTE
A 2
B 2
V20
V18
V12
start stop
HPLC
Product Activity
REA. ACTIVITY
EXHAUST
on off
STIRRERS
COMP. AIR COOLING
LIGHT

Automation on a NI FDG / GE Tracerlab FX FN module

Transfer of crude with 23 mL 5% EtOH

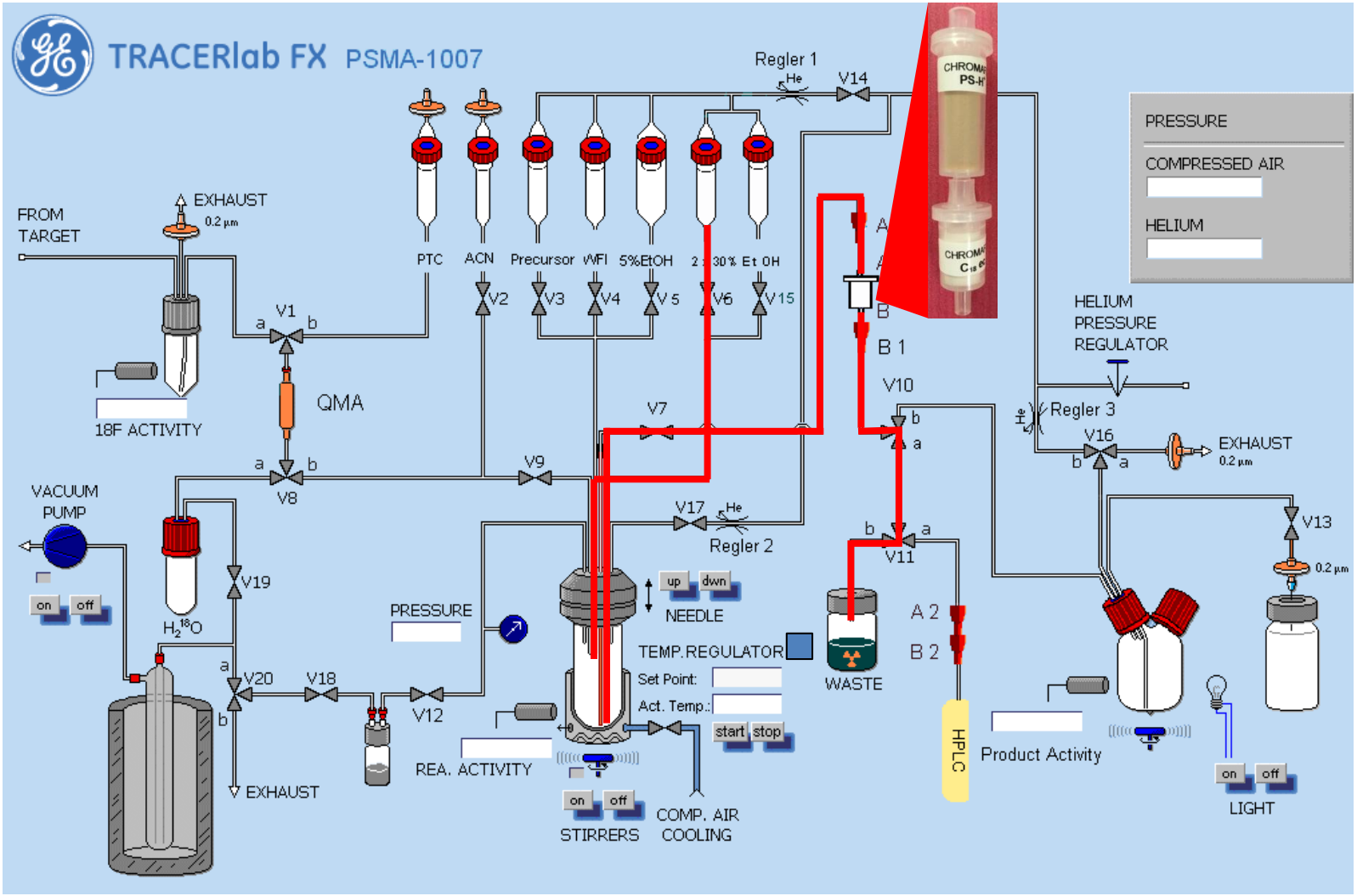
Rinsing of reactor with 10 mL 5% EtOH

cartridge combination with 10 mL 5% EtOH



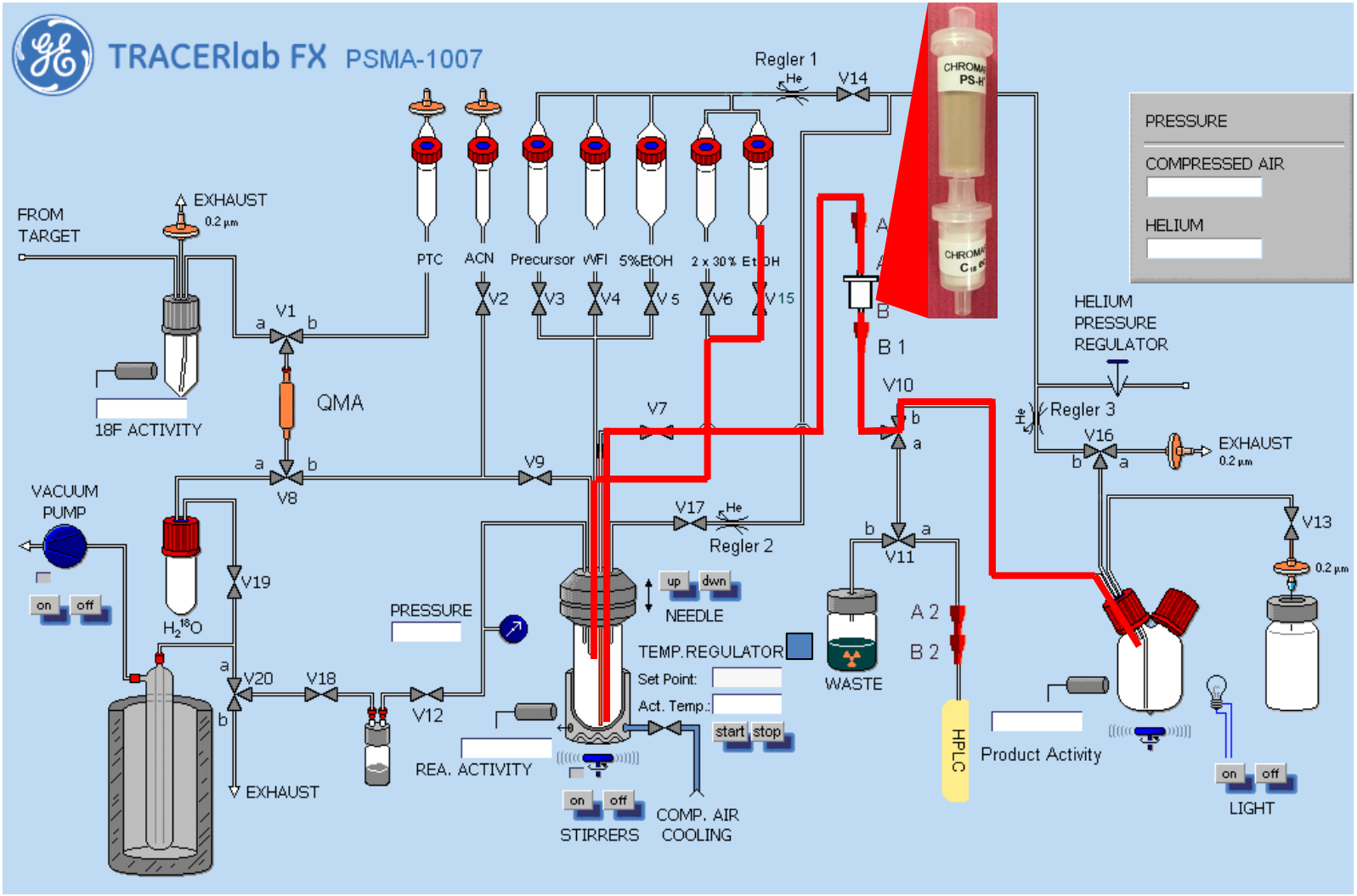
Automation on a NI FDG / GE Tracerlab FX FN module

Elution of sideproducts with 3 mL 30% EtOH



Automation on a NI FDG / GE Tracerlab FX FN module

Elution of [^{18}F]PSMA-1007 with 4 mL 30% EtOH into collection vial holding 11 mL 0.9% saline and 100 mg sodium ascorbate



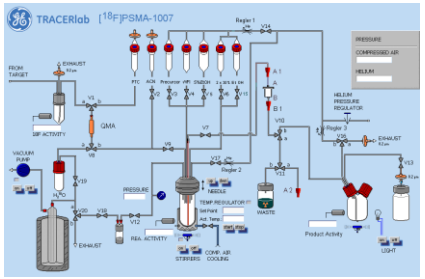
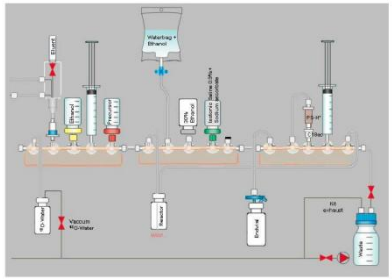
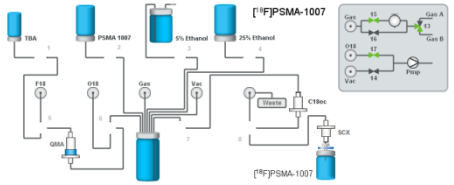
[^{18}F]PSMA-1007: Specification

Active ingredients	**100 – 2000 MBq [^{18}F]PSMA-1007/mL**	
Other ingredients	Sodium ascorbate	
Solution	0,9 % NaCl	≥ 90 Vol%
	Ethanol	≤ 10 Vol%
V_{max}*	10 mL	
	Specification	
Appearance	Clear and colorless	
pH	4.5 – 7.5	
Radiochemical purity	[^{18}F]PSMA-1007:	≥ 95 % (HPLC/TLC)
	[^{18}F]Fluoride and other radiochemical impurities:	≤ 5 % (HPLC/TLC)
Chemical purity	Acetone:	≤ 50 mg/V_{max}
	Acetonitrile:	≤ 4.1 mg/V_{max}
	DMSO:	≤ 50 mg/V_{max}
	TBA:	≤ 2.6 mg/V_{max}
	PSMA-1007:	≤ 0.1 mg/V_{max}
	Any single unspecific impurity (with reference to PSMA-1007 solution):	≤ 0.1 mg/V_{max}
	The sum of PSMA-1007 and all unspecific impurities (with reference to PSMA-1007 solution):	≤ 0.5 mg/V_{max}
	Disregard limit (with reference to PSMA-1007 solution):	≤ 0.3 of 0.1 mg/V_{max}
Radionuclidic purity	Identity ^{18}F corresponding to a peak at 511 keV	≥ 99,9 %
	Approximate half-life	110 ± 5 min
Sterility	Sterile	
Endotoxins	≤ 175 I.E./V_{max}	
Shelf-life	8 hours	

V_{max} being the maximum injectable volume per patient

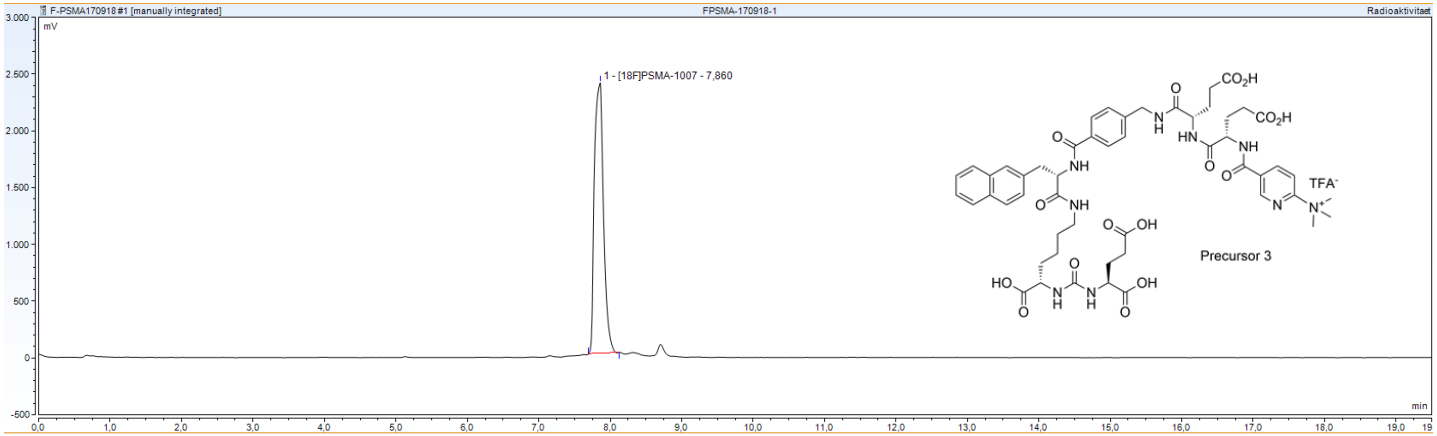
Cardinale *et al.*, Pharmaceuticals (Basel) 2017, 10 (4), pii: E77.

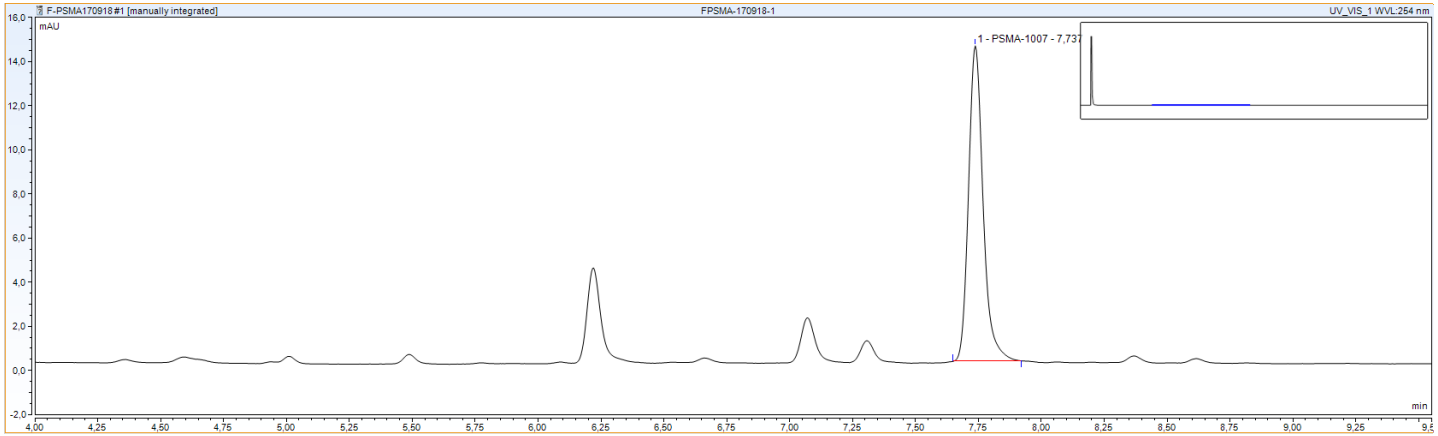
[^{18}F]PSMA-1007: Radiosynthesis results

	NI FDG / GE Tracerlab FX FN	GE Tracerlab MX / ORA Neptis Mosaic-RS	IBA Synthera+
			
N=	16	10	10
Amount of Precursor used	1.6 mg	1.6 mg	1.0 mg
Radiochemical Yields (n.d.c.)	24.3 - 82.4 %	43.3 - 52.8 %	59.5 - 72.8 %
Synthesis Time	55 min	45 min	35 min
Quality Control	All results within specification		

Cardinale *et al.*, Pharmaceuticals (Basel) 2017, 10 (4), pii: E77.

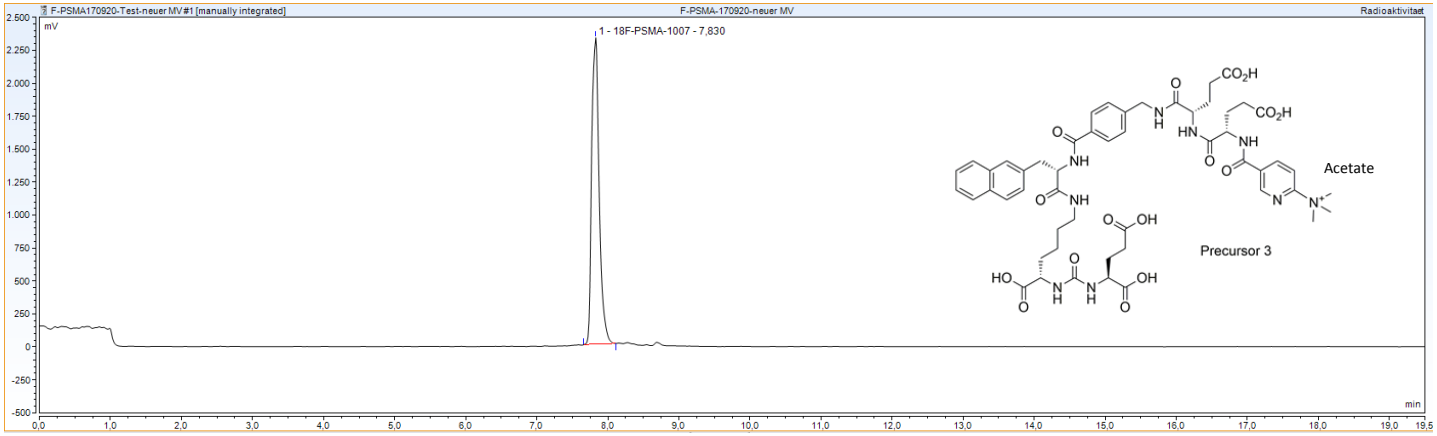
[^{18}F]PSMA-1007: Improvement of Quality

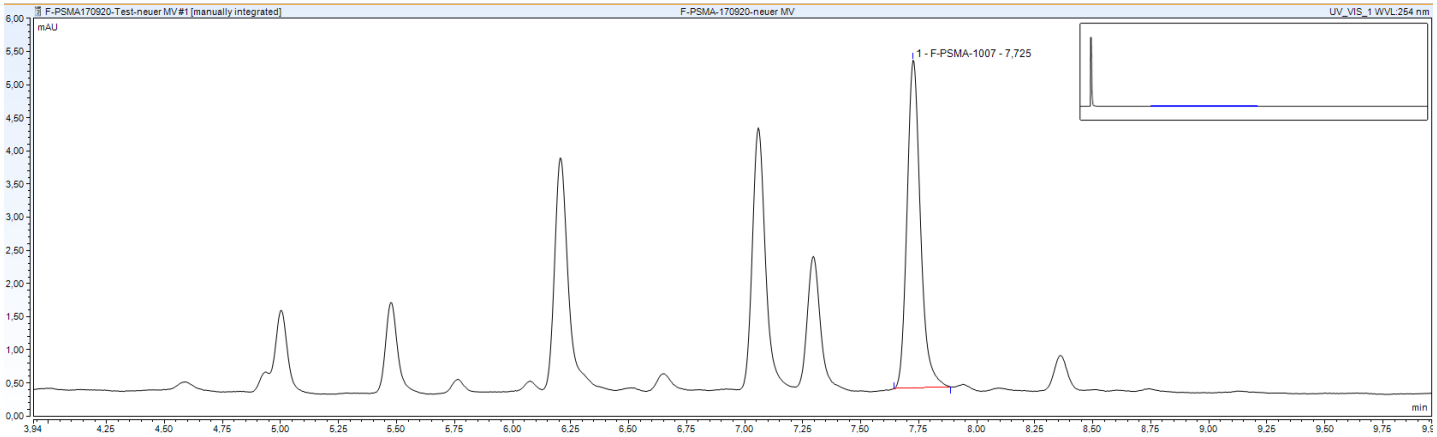




PSMA-1007: 8.2 µg/mL

[^{18}F]PSMA-1007: Improvement of Quality





PSMA-1007: 2.7 µg/mL

Conclusion and outlook

- GMP-compliant radiosynthesis of [^{18}F]PSMA-1007 using SPE purification on a range of commercially available radiosynthesizers in very good radiochemical yields and (improved) quality
- [^{18}F]PSMA-1007 has arrived in the clinic rapidly and can be used in combination with ^{177}Lu/^{225}Ac-PSMA-617 in theragnostic applications
- A global academic initiative will start soon to assess the clinical value of [^{18}F]PSMA-1007 (www.psma-imaging.org)
- Remaining challenges: identify the (radio)chemical impurities and investigate the mechanism of radiofluorination of unprotected precursor

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