Synthesis and evaluation of a radiotracer for PDGFRβ imaging

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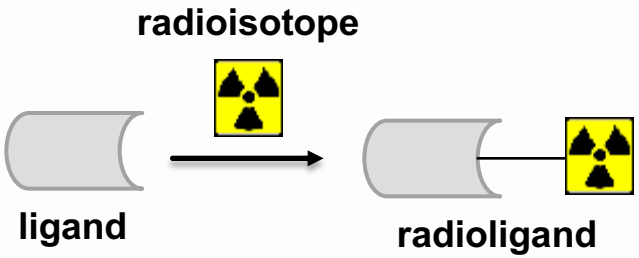
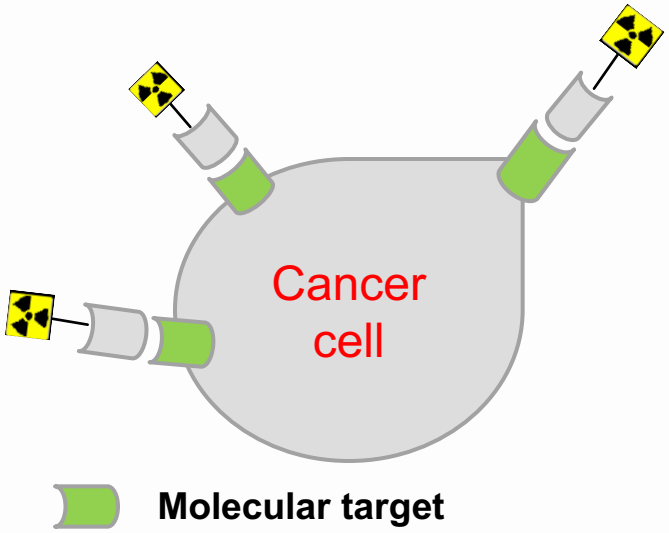
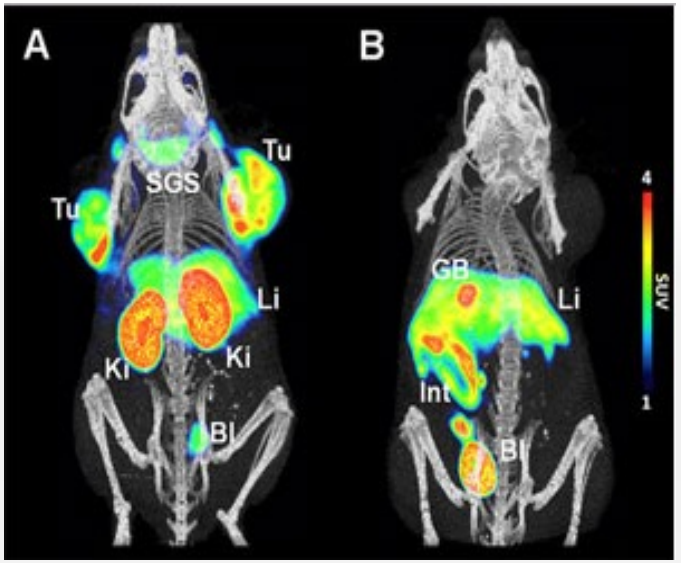
Concept of nuclear medicine imaging



Radioisotopes : ^{123}I, ^{99m}Tc, ^{18}F, ^{68}Ga , ^{11}C , ^{111}In



PET (positron emission tomography) and SPECT (single photon emission computed tomography) are nuclear medicine modalities, can be used to assess level of receptor expression in tumors.



*Molecules. 2013; *18*(5): 5005-31

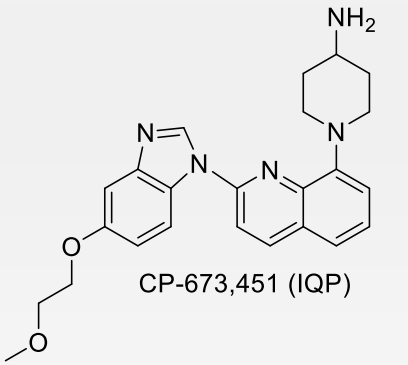
Introduction

1. PDGFRβ (platelet-derived growth factor receptor beta) is one of tyrosine kinase receptors (TKR) overexpressed in various malignant tumors.

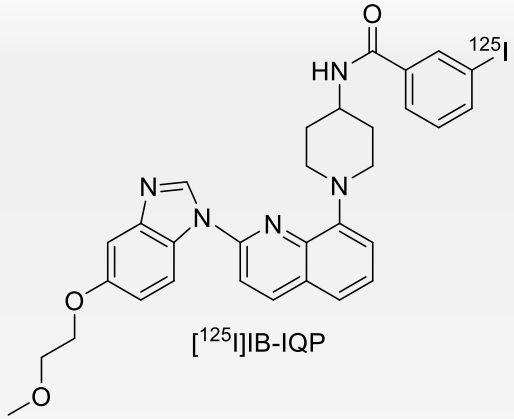
2. Visualization of PDGFRβ expression through radiolabeled PDGFRβ inhibitors might provide important additional diagnostic information and can be used to monitor respond therapy of anticancer drug.

3. CP-673,451 (IQP) is a benzimidazole derivative and potent inhibitor of PDGFR kinase with IC_{50} = 1 nM for PDGFRβ, 10 nM for PDGFRα and >200 fold selective versus a variety of other kinases*.

4. IB-IQP was synthesized by conjugation between IQP and SIB.



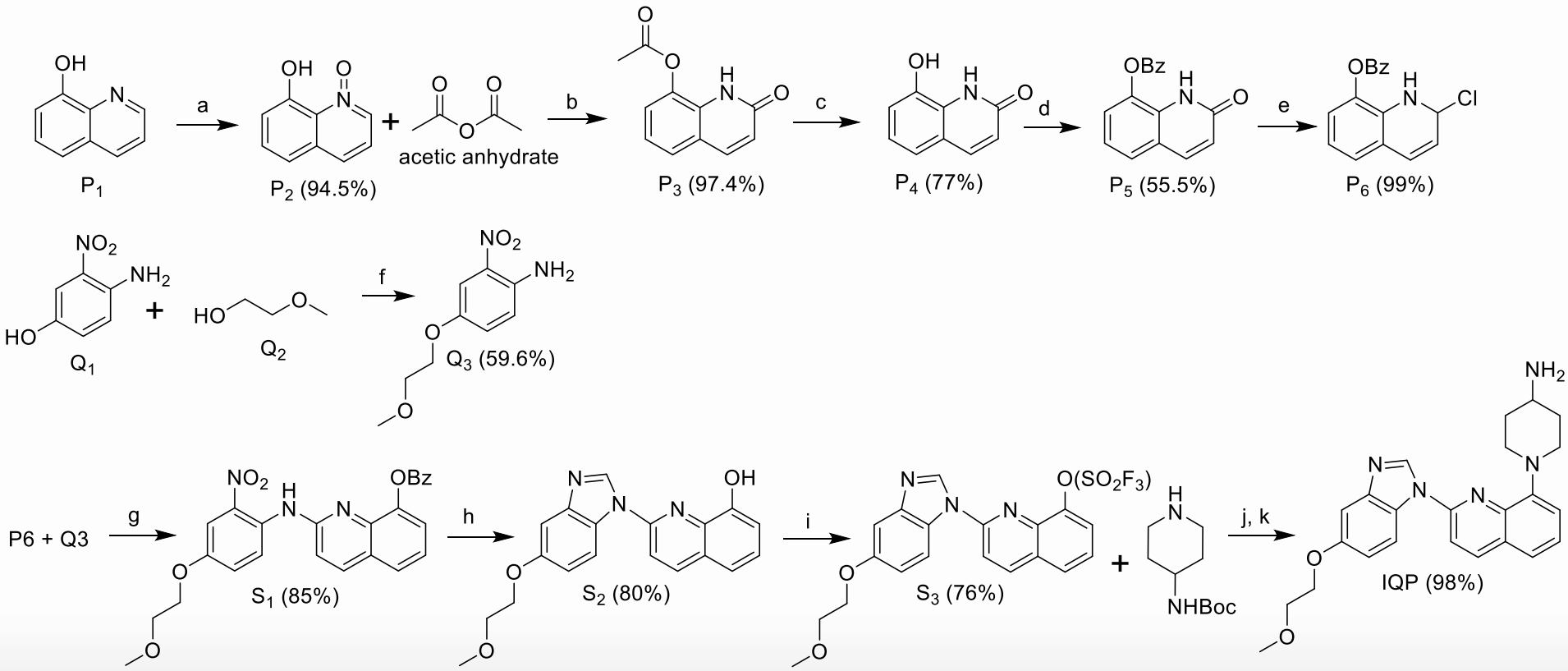
CP-673,451 (IQP)



[125I]IB-IQP

Cancer Res. 2005; *65*(3): 957-66

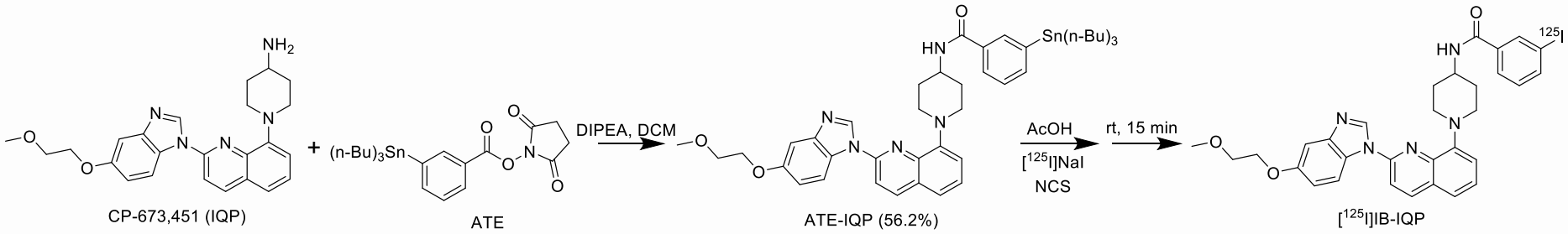
Synthesis of CP-673,451, a small molecule of selective PDGFRβ inhibitor[1, 2]



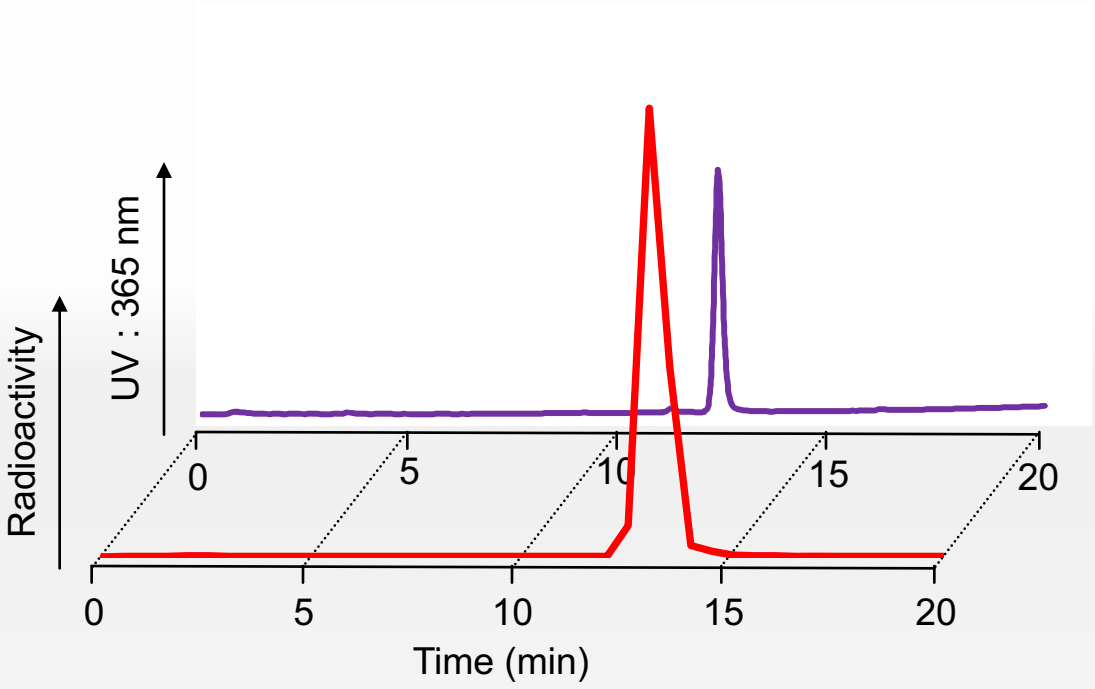
(a) sodium tungstate dihydrate, hydrogen peroxide, 75°C, 5 h (b) 100°C, 7.5 h (c) hydrogen chloride, 95°C, 2h (d) potassium carbonate, benzyl bromide, refluxed, 6 h (e) phosphoryl chloride, refluxed, 16 h (f) methanesulfonyl chloride, cesium carbonate, 60°C, 3 d (g) palladium(II) acetate, cesium carbonate, 1,2-*bis*(diphenylphosphino)ethane, toluene, refluxed, 3 d (h) palladium(II) chloride, triethylamine, formic acid, formamidine acetate, refluxed, 15 h (i) *n*-phenyl-bis(trifluoromethanesulfonimide), dimethylformamide, trifluoroacetic acid, room temperature, 2 d (j) cesium carbonate, tris(dibenzylideneacetone)dipalladium(0), (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, toluene, refluxed, 3 d (k) trifluoroacetic acid, room temperature, 15 min

[1]*European patent specification.* 2006; EP 1 235825 B1
[2]*Chem Med Chem.* 2014; *9*(10): 2360-70

Synthesis of [^{125}I]IB-IQP



ATE : *n*-succinimidyl 3-(tri-nbutylstannyl)benzoate, DIPEA : *n, n*-diisopropylethylamine, DCM : dichloromethane, AcOH : acetic acid, NaI : sodium iodid, NCS : *n*-chlorosuccinimide



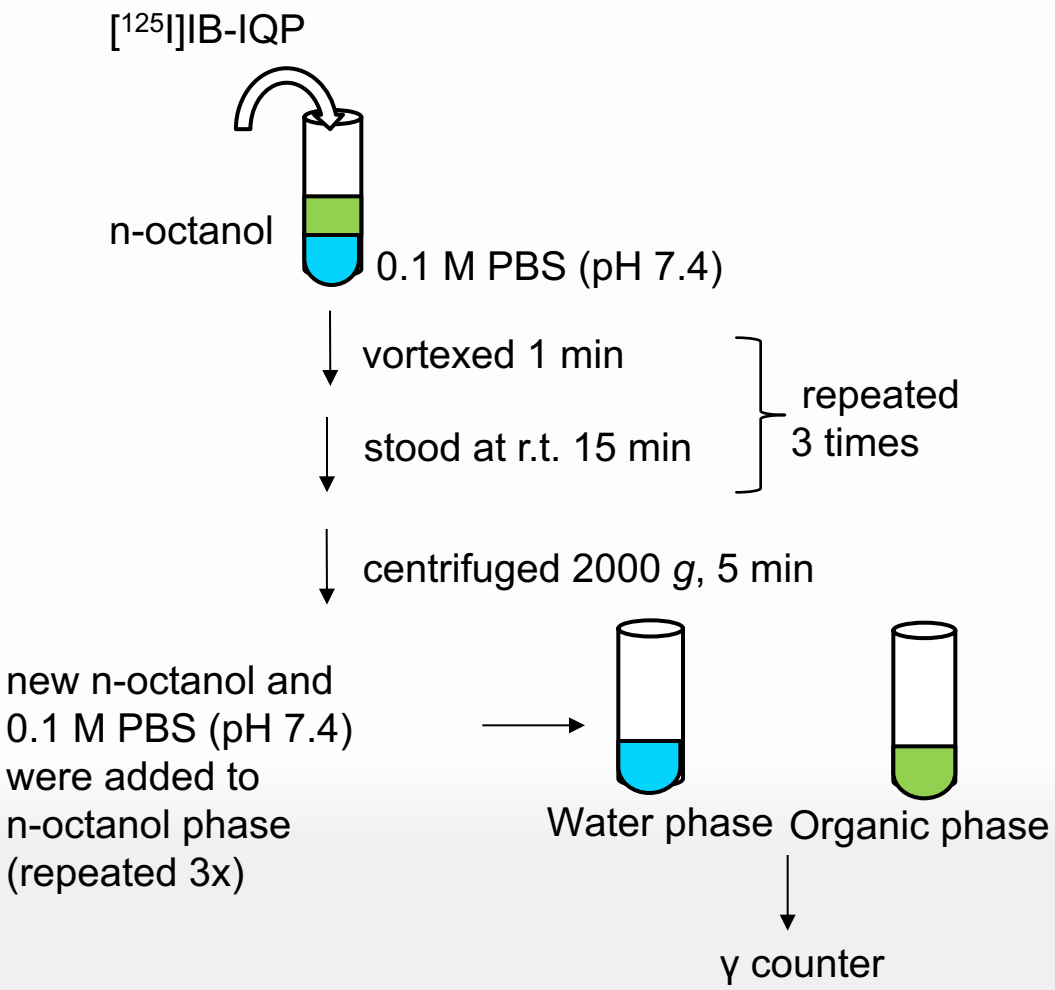
Radiochemical yield **: 85%**
Radiochemical purity **: 98%**

mobile phase:
A : methanol with 0.05% triethylamine
B : water with 0.05% triethylamine
A : 70 – 90%, 0 – 20 min

flow rate : 1 mL/min
column : 5C_{18}MS-II (4.6 x 150 mm)
temperature : 40^{o}C

Partition coefficient

Method

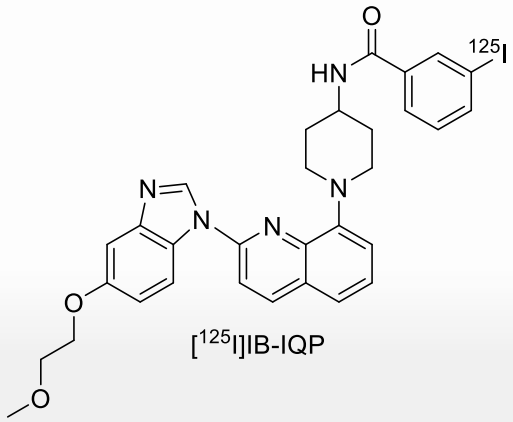


Result

Partition coefficient

$$= \log \frac{\text{radioactivity of organic layer}}{\text{radioactivity of water layer}}$$

log *P* = 3.15 ± 0.19



In vitro stability

Method

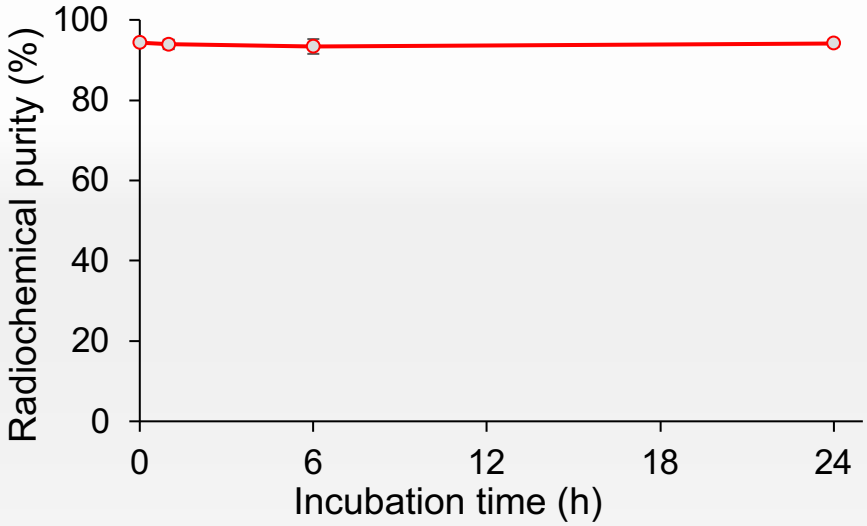
[^{125}I]IB-IQP

1, 6, 24 h

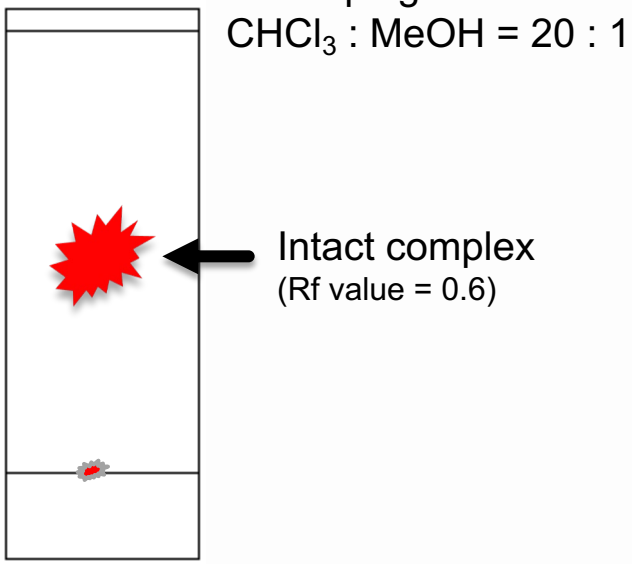
37°C

TLC analysis

0.1 M PBS pH 7.4

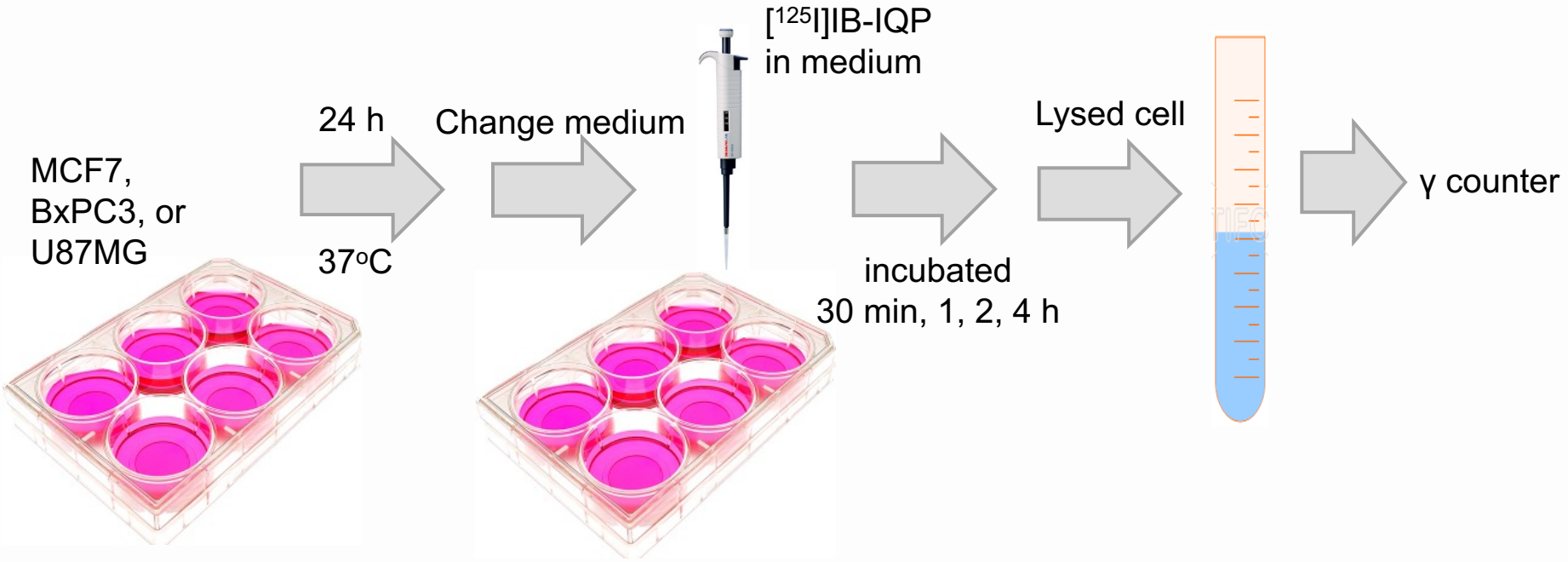


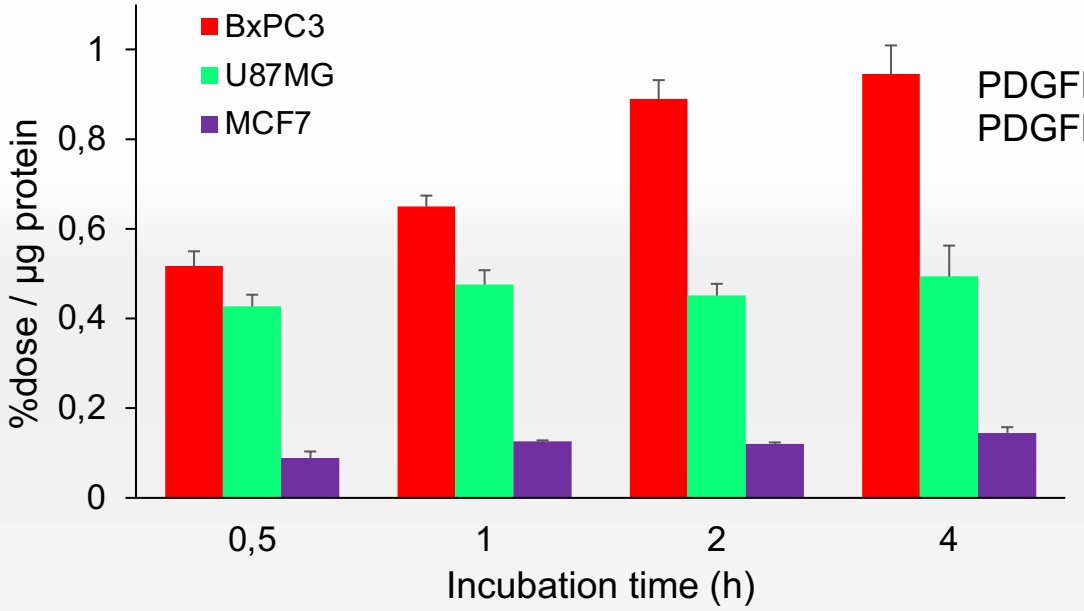
Result



[^{125}I]IB-IQP was **stable** in 0.1 M PBS pH 7.4 with radiochemical purity more than 90% during 24 h incubation.

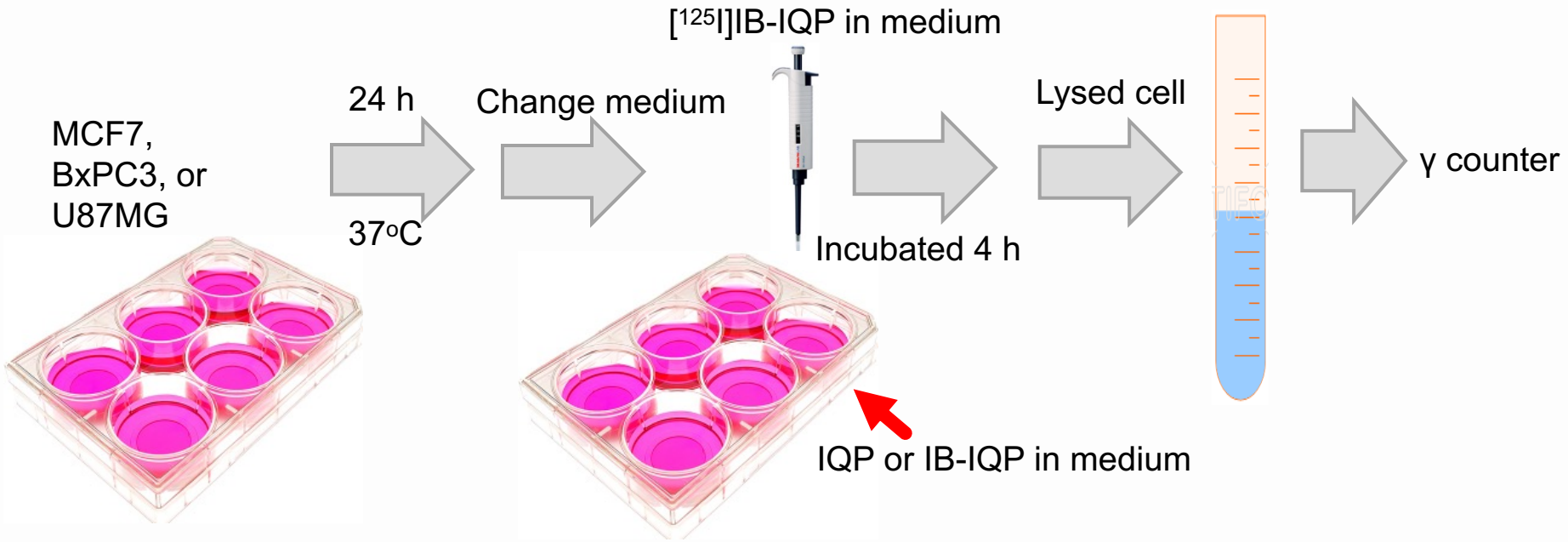
Cell uptake studies

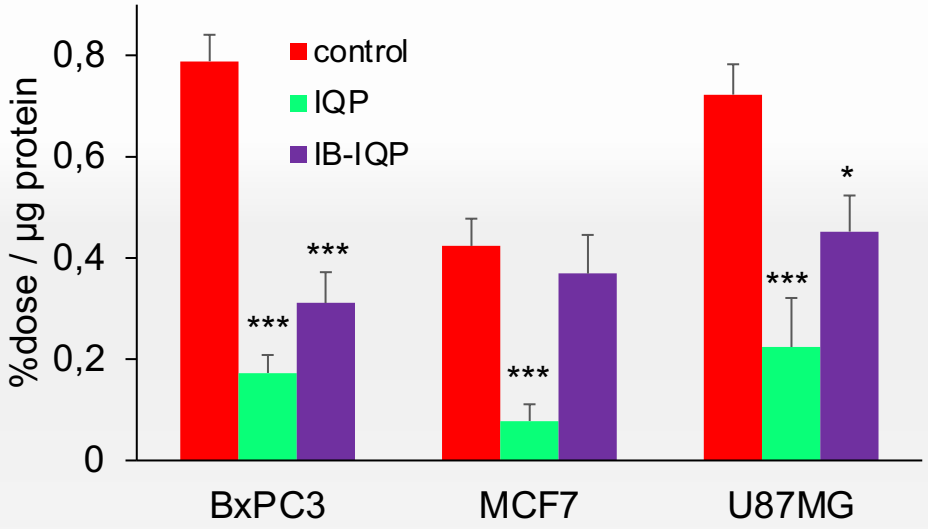




PDGFRβ high expression : BxPC3 & U87MG
PDGFRβ low expression : MCF7

in vitro blocking studies





PDGFRβ high expression : BxPC3 & U87MG
PDGFRβ low expression : MCF7

control : [125I]IB-IQP
inhibitors : IQP or IB-IQP

* $P < 0.05$, ** $P < 0.01$, * $P < 0.001$ vs control group

Biodistribution of [^{125}I]IB-IQP in normal mice

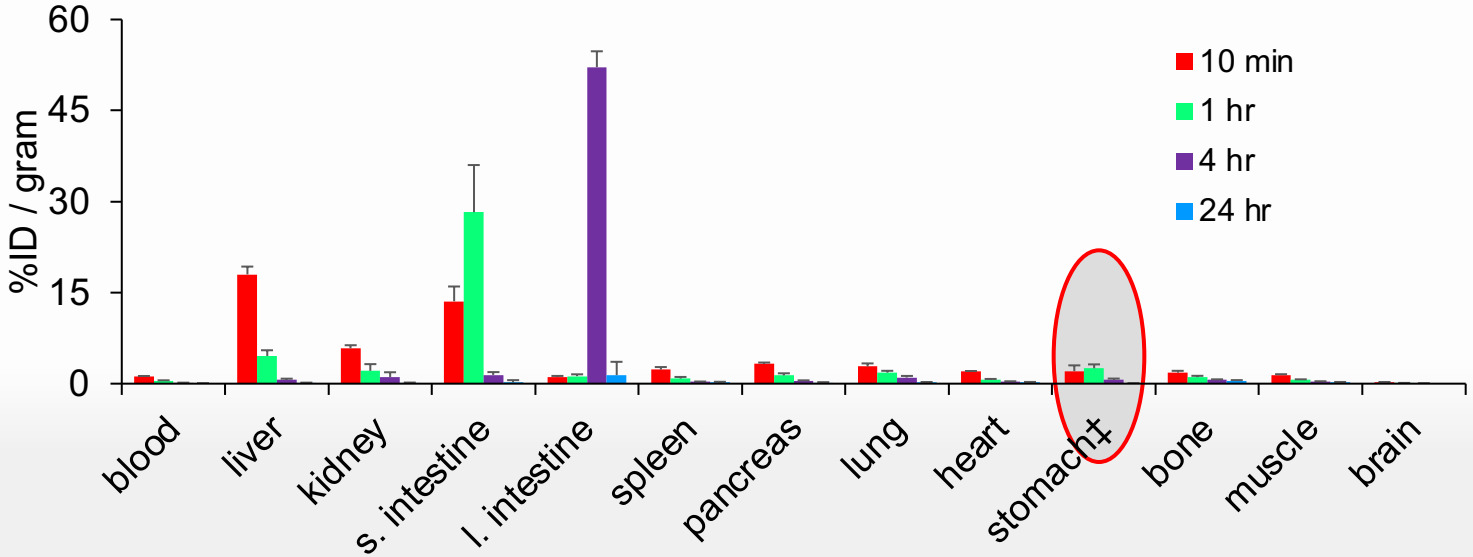
[^{125}I]IB-IQP intravenously

ddY mice, male, 6 weeks

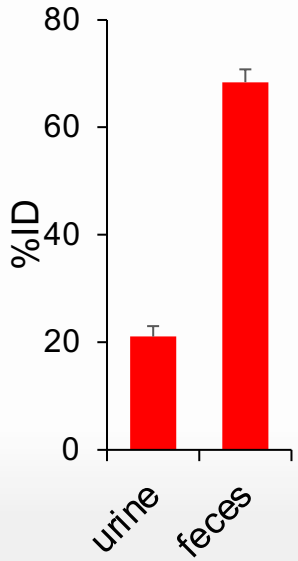
10 min, 1, 4, 24 h

mice were sacrificed

weight and radioactivity in each tissue were measured



metabolite analysis

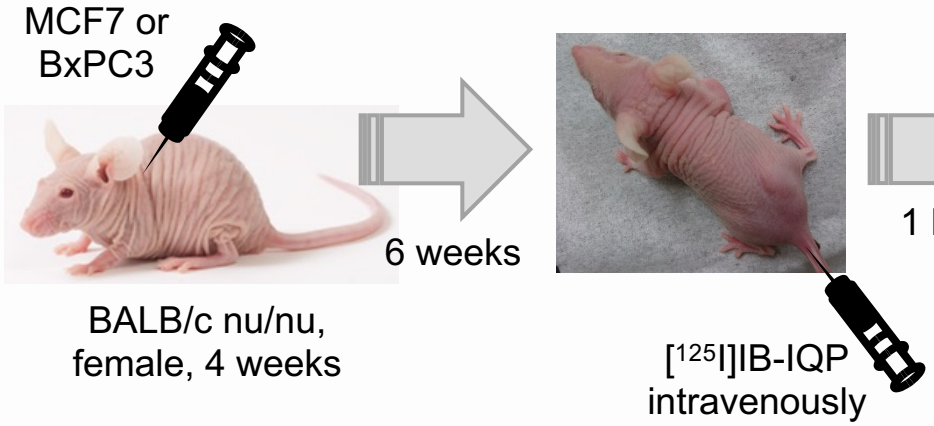


Hepatobiliary excretion as mainly pathway of [^{125}I]IB-IQP

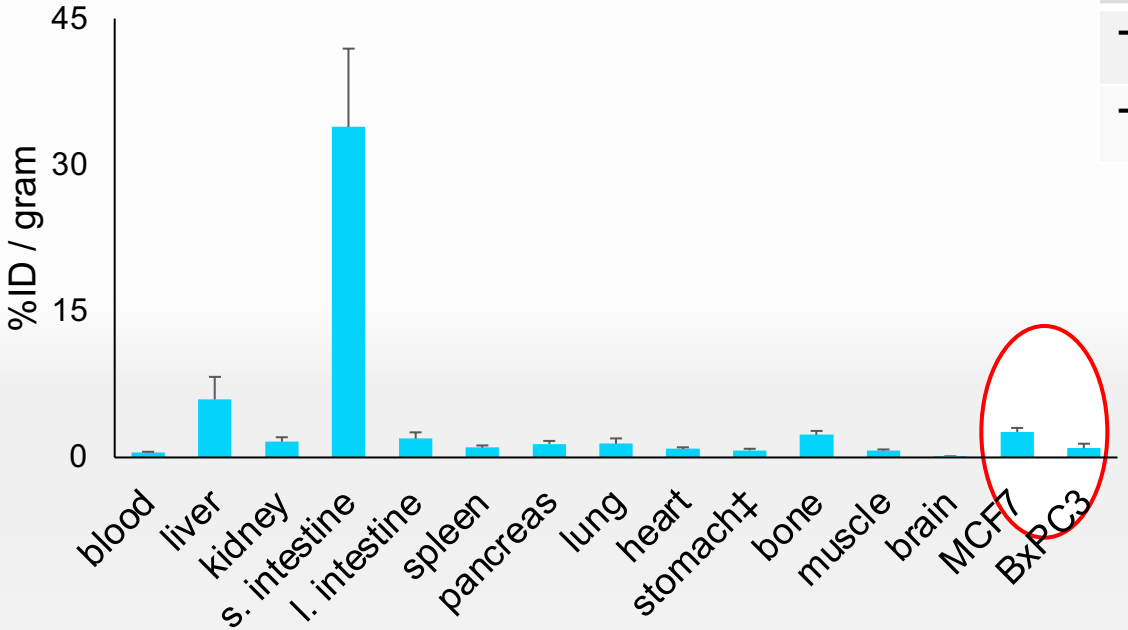
‡Expressed as % injected dose

expressed as % injected dose per gram tissue (%ID / gram). Each value represents mean (SD) for three or four mice

Biodistribution of [^{125}I]IB-IQP in tumor bearing mice[a]



ratio	BxPC3	MCF7
Tumor to muscle	1.39	3.72
Tumor to blood	1.72	4.83



‡Expressed as % injected dose

expressed as % injected dose per gram tissue (%ID / gram). Each value represents mean (SD) for four mice

Summary

1. [^{125}I]IB-IQP was conveniently prepared by an iododestannylation reaction using NCS (*N*-chlorosuccinimide) as an oxidizing agent with radiochemical yield 85% and radiochemical purity 98%.
2. [^{125}I]IB-IQP biodistribution in normal mice demonstrated hepatobiliary as mainly excretion pathway.
3. Tumor to blood and tumor to muscle ratios of [^{125}I]IB-IQP 1 h post-injection were 1.72 and 1.39 for BxPC3 tumor bearing mice and 4.83 and 3.72 for MCF7 tumor bearing mice, respectively.

Structural modification is needed to give higher *in vivo* tumor accumulation.