TECHNISCHE UNIVERSITÄT DRESDEN

HZDR
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

Development of radiotracers for molecular imaging and detection of tumour-associated matrix-modifying enzymes

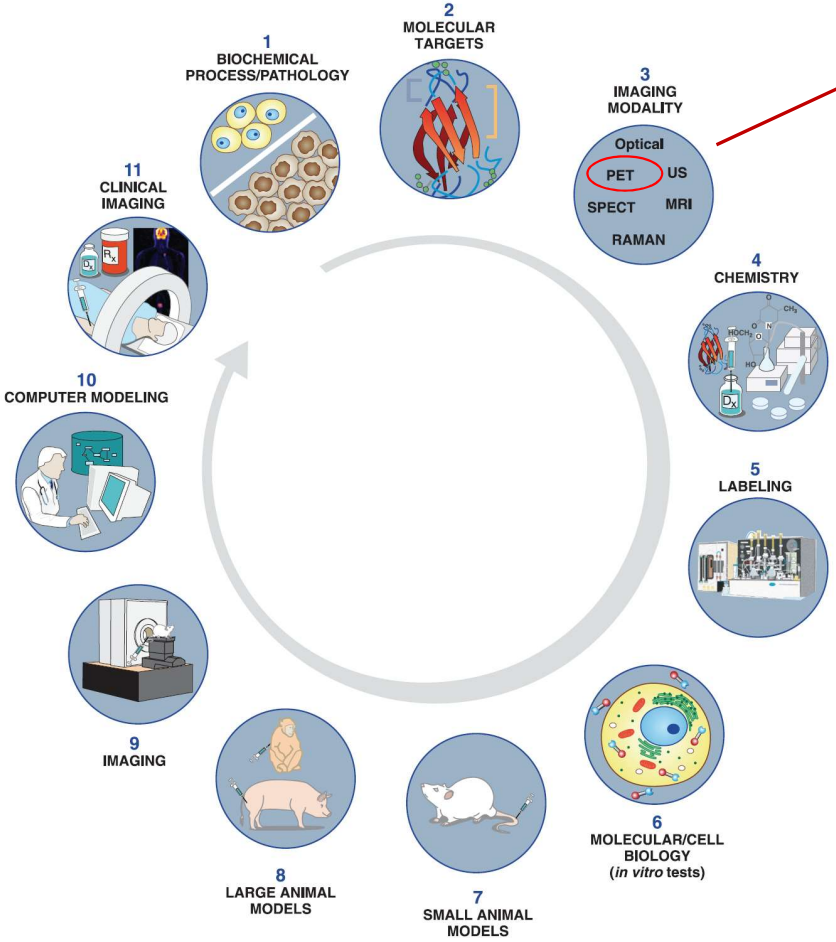
The 9th International Electronic Conference on Medicinal Chemistry (ECMC 2023)

01-30 November 2023

Dr. Reik Löser · Institue of Radiopharmaceutical Cancer Research · www.hzdr.de

DRESDEN concept

Molecular Imaging – a multidisciplinary field



Taken from: James & Gambhir *Physiol. Rev.* **2012**, *92*, 897-965

Positron emission tomography (PET)

Preclinical development of PET tracers

Selection of targets

Medicinal Chemistry

- Identification of lead compoounds
- Structural modifications to facilitate radiolabelling
- Determination of target affinity (kinetic or binding assays)
- Structure-activity relationships

Radiochemistry

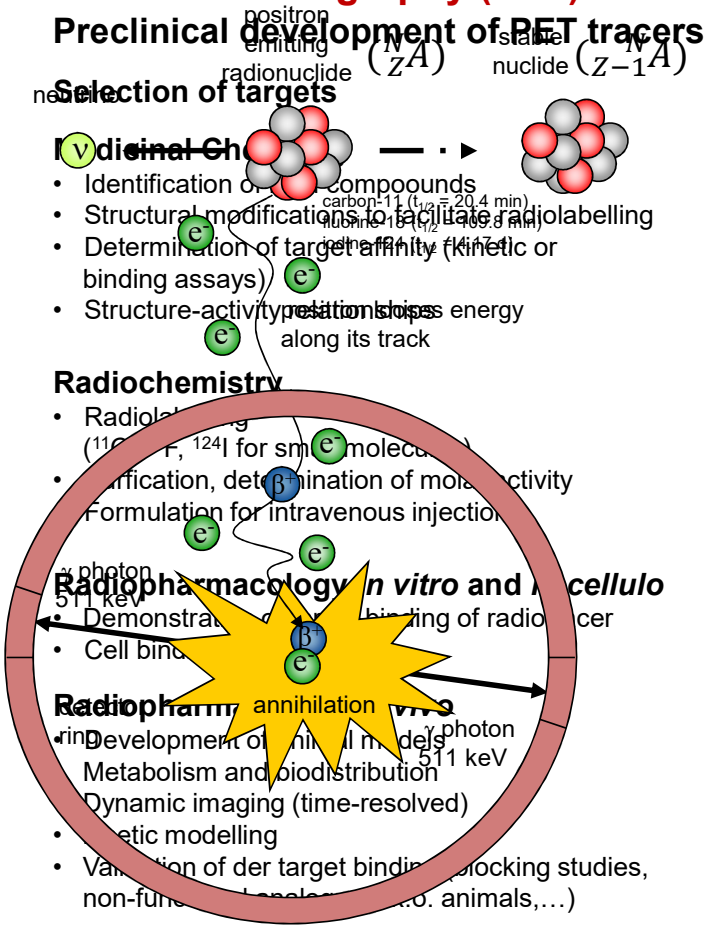
- Radiolabelling (^{11}C, ^{18}F, ^{124}I for small molecules)
- Purification, determination of molar activity
- Formulation for intravenous injection

Radiopharmacology *in vitro* and *ex cellulo*

- Demonstration of binding of radiotracer
- Cell binding

Radiopharmacology *in vivo*

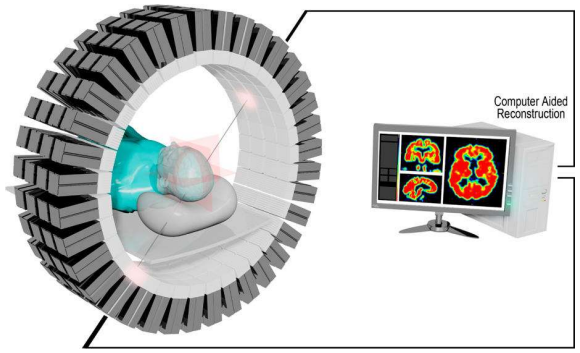
- Development of animal models
- Metabolism and biodistribution
- Dynamic imaging (time-resolved)
- Kinetic modelling
- Validation of der target binding, blocking studies, non-fun... e.g. animals,…)



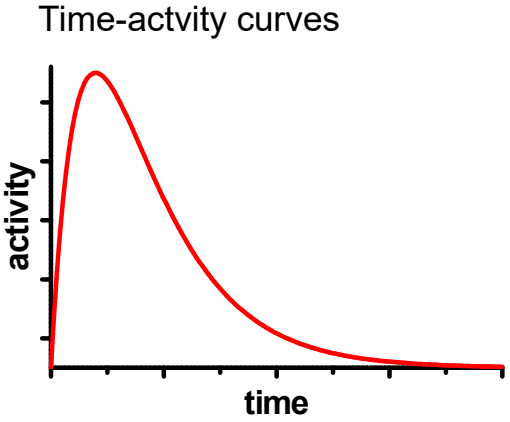
Selection of important PET nuclides

radionuclide	$T_{1/2}$	β^+ fraction	β^+ energy (E_{mean} in keV)	production (nuclear reaction)	labelling chemistry
^{11}C	20.4 min	99.8	386	cyclotron ($^{14}N(p,\alpha)$)	covalent, mainly electrophilic
^{18}F	109.8 min	97	249	cyclotron (predominantly $^{18}O(p,n)$)	covalent, mainly nucleophilic
^{124}I	4.18 d	22.7	820	cyclotron ($^{124}Te(p,n)$, $^{125}Te(p,2n)$)	covalent, mainly electrophilic
^{68}Ga	67.7 min	88,9	829	nuclide generator ($^{68}Ge(EC)^{68}Ga$)	coordinative
^{64}Cu	12.7 h	18	278	cyclotron ($^{64}Ni(p,n)$)	coordinative
^{89}Zr	3.26 d	22.7	396	cyclotron ($^{89}Y(p,n)$	coordinativ

Molecular imaging with PET

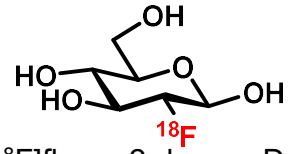


3D-Bild

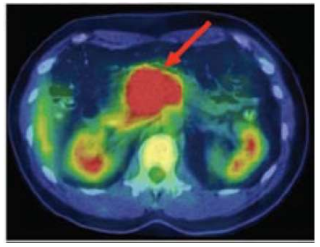


Importance of PET in medical diagnostics

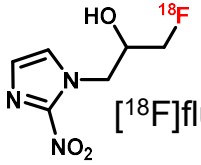
Primay diagnostics
e.g. tumours



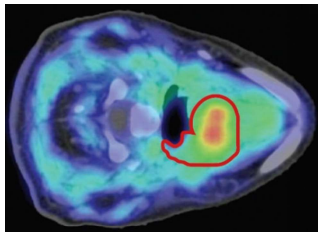
2-[^{18}F]fluoro-2-desoxy-D-glucose ([^{18}F]FDG)



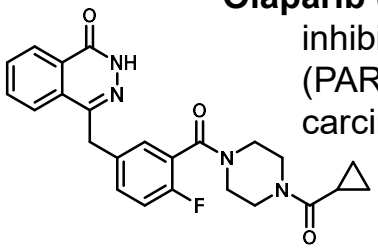
Functional diagnostics
e.g. tumour hypoxia



[^{18}F]fluoromisonidazol ([^{18}F]FMISO)

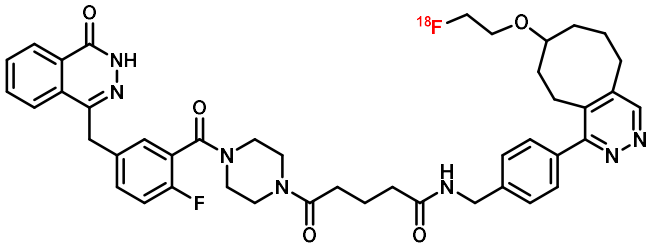


Importance of positron emission tomography in pharmacological research and drug development: Dose optimisation and measurement of target occupancy for verification of therapeutic efficiency through companion diagnostics

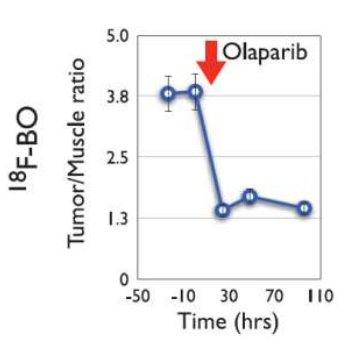


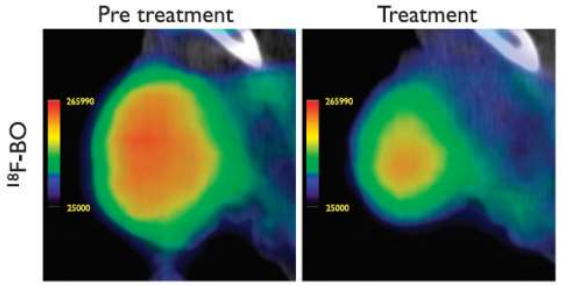
Olaparib (Lynparza):

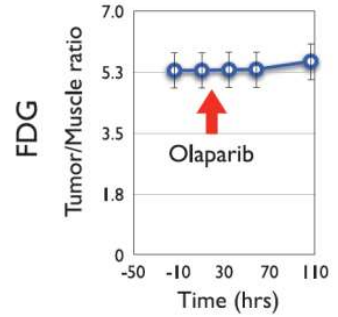
inhibitor of poly-ADP-ribose polymerase (PARP) for treatment of BRCA-mutated carcinomas

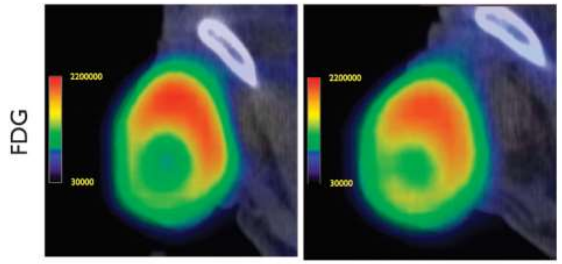


^{18}F-labelled Olaparib derivative (^{18}F-BO)



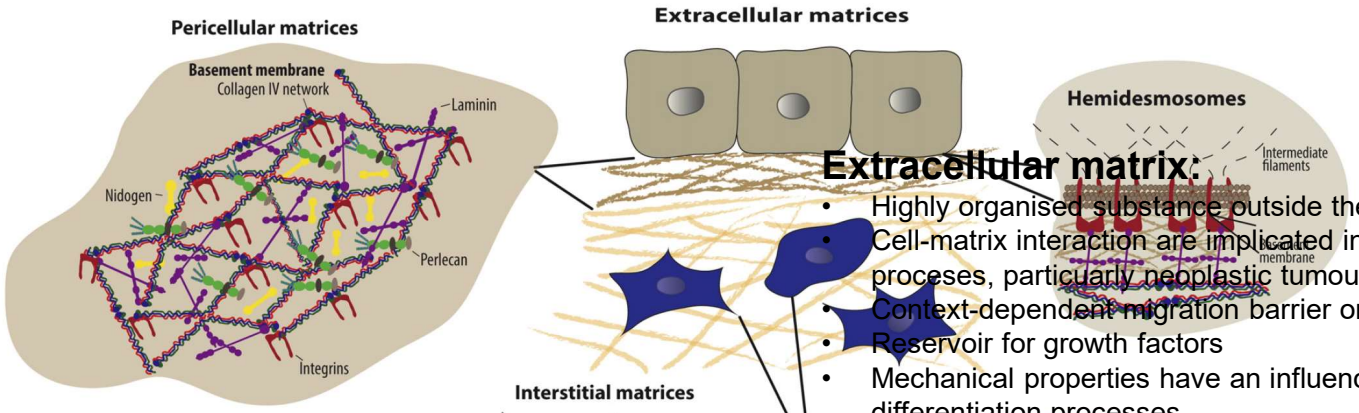






Reiner *et al. Neoplasia* **2012**, *14*, 169–77

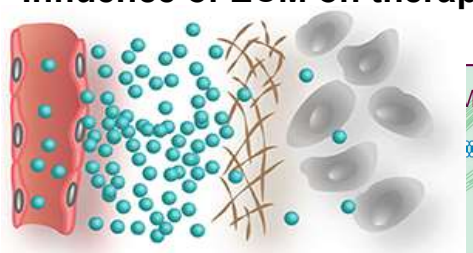
Individualisation of tumour therapy through target-directed molecular imaging



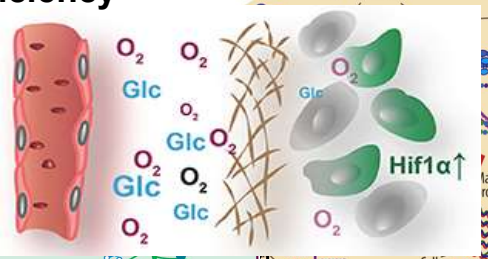
Extracellular matrix:

- Highly organised substance outside the cells
- Cell-matrix interaction are implicated in almost all pathogenetic processes, particularly neoplastic tumour diseases
- Context-dependent migration barrier or migration path for cells
- Reservoir for growth factors
- Mechanical properties have an influence on cell growth and differentiation processes

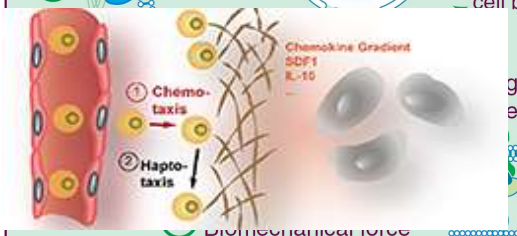
Influence of ECM on therapy efficiency



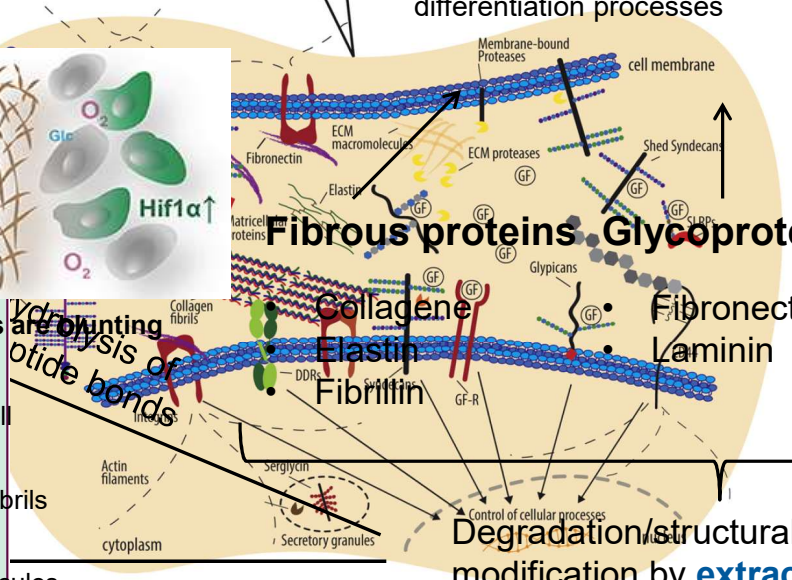
Diffusion barrier for drug molecules



Hypoxic conditions are counting radiation therapy



Immuntoherapy: haptotactic deflection of immune cells



Fibrous proteins **Glycoproteine**

Glycosamino-glycans and proteoglycans

- Collagene
- Elastin
- Fibrillin
- Fibronectin
- Laminin

ydrolysis of otide bonds

iation of acid side chains

Degradation/structural modification by **extracellular enzymes**

from: Theocharis *et al. Adv. Drg Delivery Rev.* **2016**, *97*, 4–27

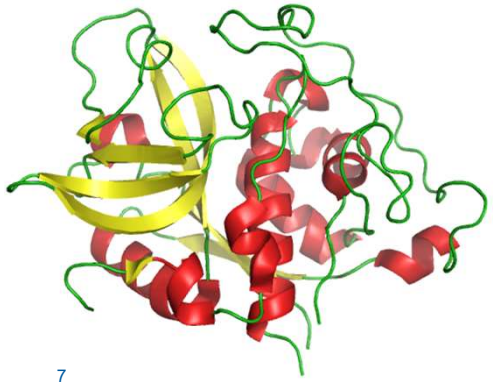
Adapted from: Henke *et al. Front Mol. Biosci.* **2019**, *6*, 160

taken from Lu et al. *Cold Spring Harb Perspect Biol.* **2011**;3. a005058

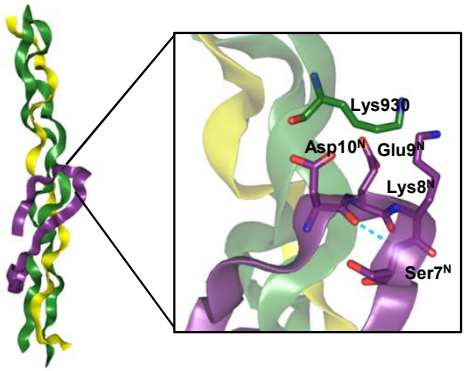
Development of radiotracers for novel imaging targets for functional characterisation of tumours using PET

Matrix-modifying enzymes

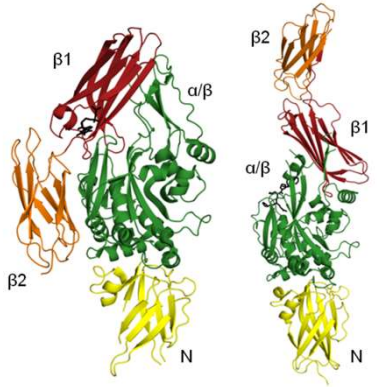
Cysteine cathepsins



Lysyl oxidases

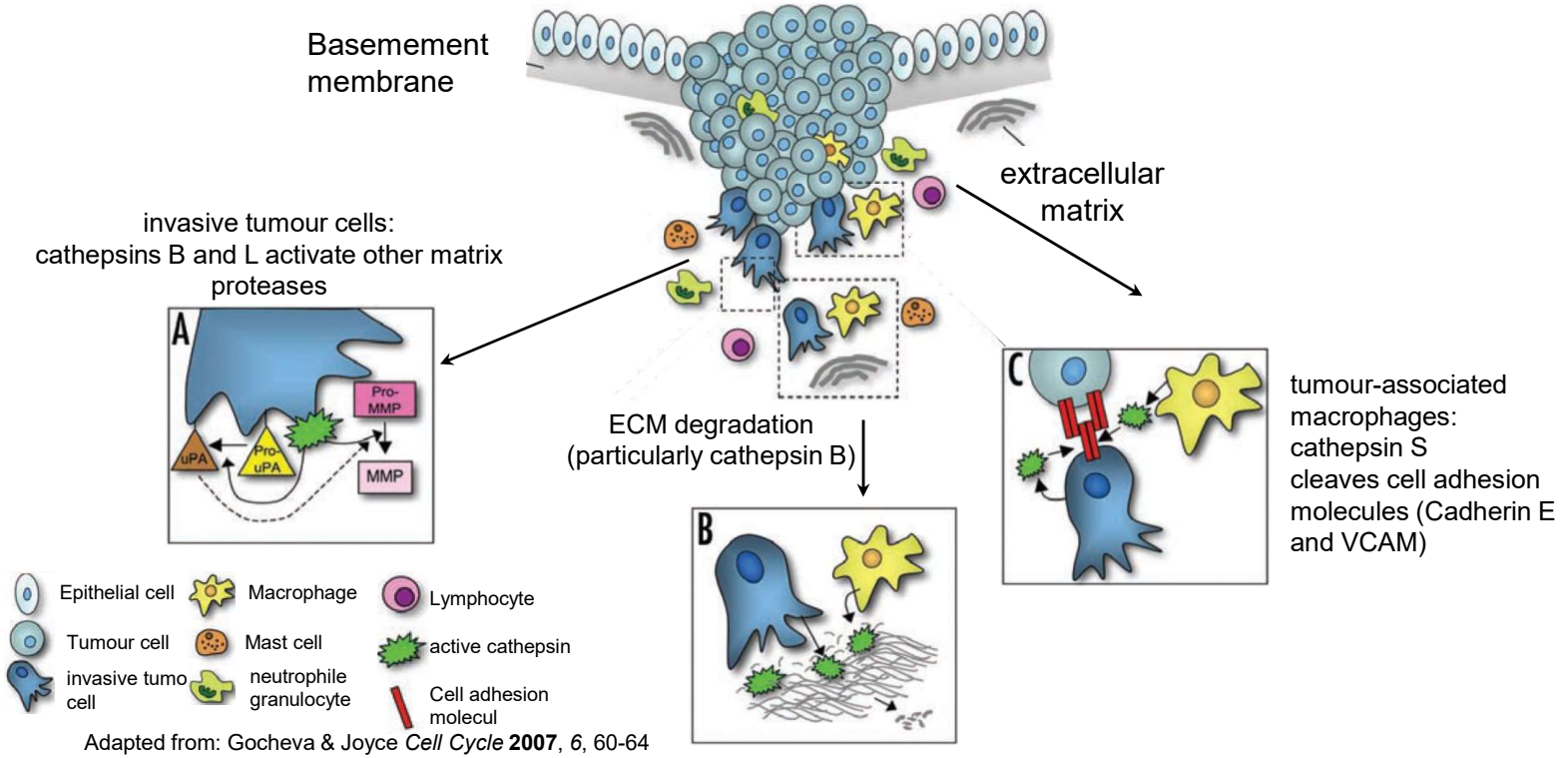


Transglutaminase 2



Cysteine cathepsine and tumour progression

- 11 different cathepsins with cysteine residues in the active site identified in humans:
  L, V, S, K, B, C, H, O, F, W, X



Adapted from: Gocheva & Joyce *Cell Cycle* **2007**, *6*, 60-64

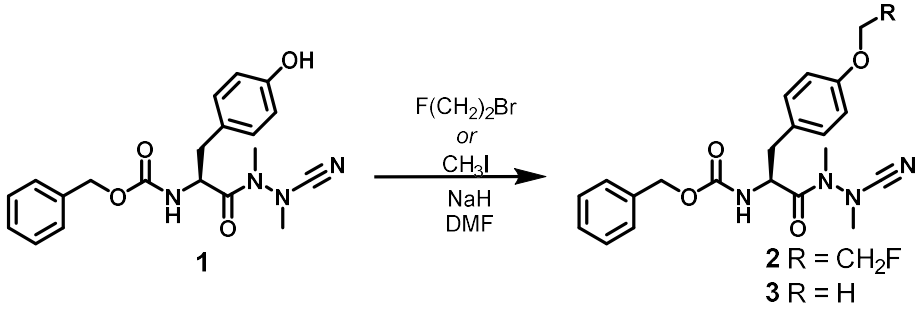
- Increased activity in tumours is associated with reduced sensitivity to radiotherapy and chemotherapy

Löser & Pietzsch *Front. Chem.* **2015**, *3*, 37

Radiotracer development

Inhibitor-based tracer design

Azadipeptide nitriles: highly potent inhibitors, stable against proteolytic degradation

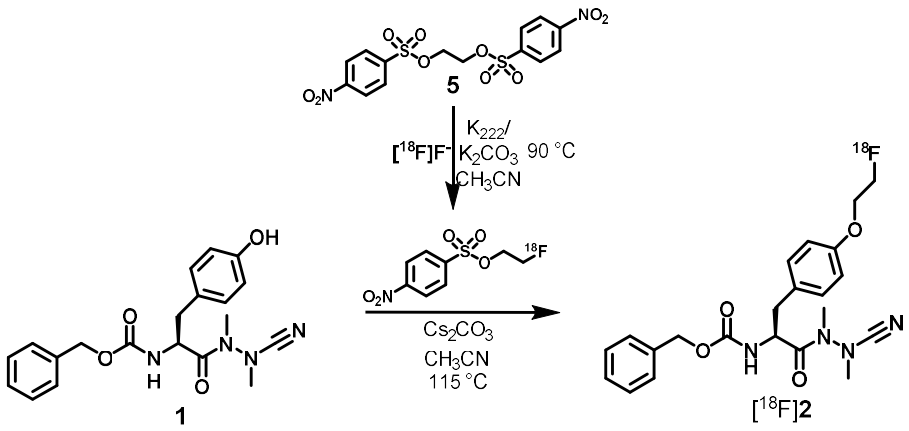


cpd.	K_i (nM)			
	cathepsin L	cathepsin S	cathepsin B	cathepsin K
1	0.36 ± 0.03	0.86 ± 0.02	0.38 ± 0.03	0.16 ± 0.01
2	0.73 ± 0.06	0.79 ± 0.06	2.4 ± 0.1	0.17 ± 0.01
3	0.68 ± 0.06	0.46 ± 0.05	2.2 ± 0.4	0.085 ± 0.01

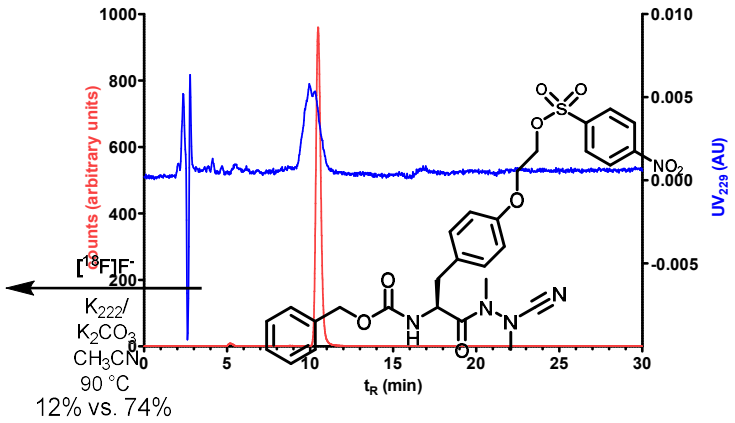
Löser *et al*. *Angew. Chem. Int. Ed.* **2008**, *47*, 4331-4

Radiolabelling: Fluorine-18

Radiosynthesis via [^{18}F]fluoroethyl nosylate, optimised procedure

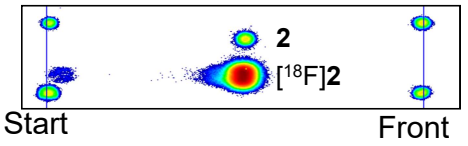


Radio-HPLC



- Two-step, one-pot radiosynthesis
- Radiochemical yield (RCY, d.c.) 23.6±2.2 % (*n*=17)
- Mean synthesis time 143±4 min (*n*=17)
- Radiochemical purity 98-99 % (HPLC, DC)
- Molare activity 11.8±3.6 GBq/µmol (*n*=9)

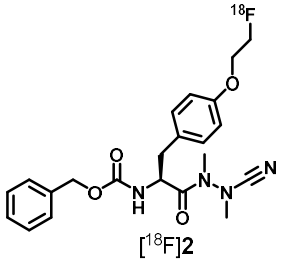
Radio-TLC

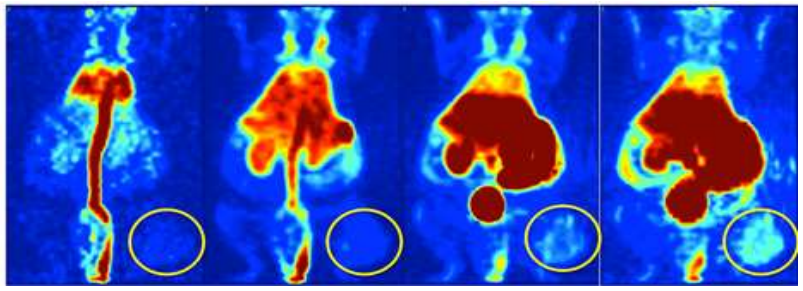


Löser *et al*. *ChemMedChem* **2013**, *8*, 1330-44

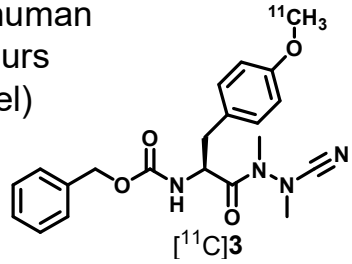
Radiopharmacology

Dynamic PET imaging





NMRI mice with subcutaneous human NCI-H292 tumours (xenograft model)



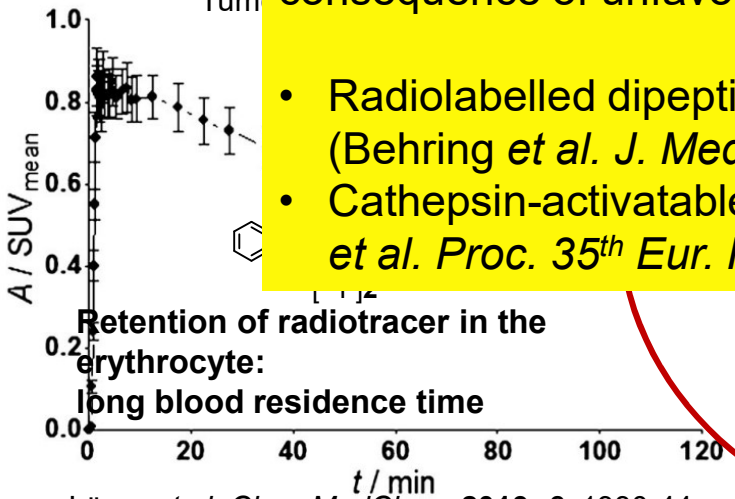
Time-activ
Tum

gous ^{11}C-labelled
ound:
psin-mediated tumour
e confirmed by PET imaging
blockade with inhibitor

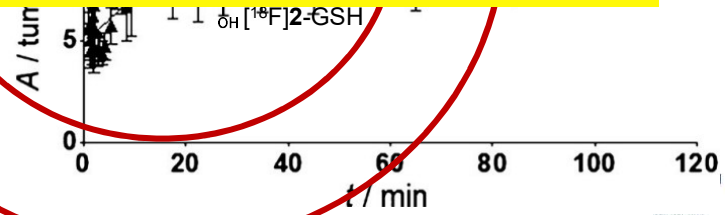
l.,
ompd. Radiopharm. **2019**, *62*, 448-59

Currently pursued approaches for cathepsin imaging in consequence of unfavourable warhead-thiol reactivity:

- Radiolabelled dipeptide alkynes as irreversible inhibitors (Behring *et al. J. Med. Chem*. **2023**, *66*, 3818.51)
- Cathepsin-activatable cell-penetrating peptides (Kuhne *et al. Proc. 35th Eur. Peptide Symp.* **2018**, 52-55)

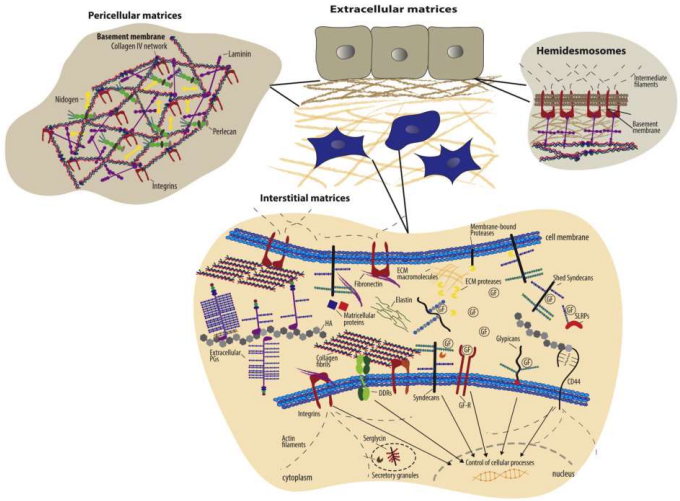


Retention of radiotracer in the erythrocyte:
long blood residence time



[^{18}F]**2**-GSH

Löser *et al*. *ChemMedChem* **2013**, *8*, 1330-44



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Fibrous proteins

- Collagene
- Elastin
- Fibrillin

Glycoproteine

- Fibronectin
- Laminin

Glycosamino-glycans and proteoglycans

Degradation/structural modification by **extracellular enzymes**

Hydrolysis of peptide bonds

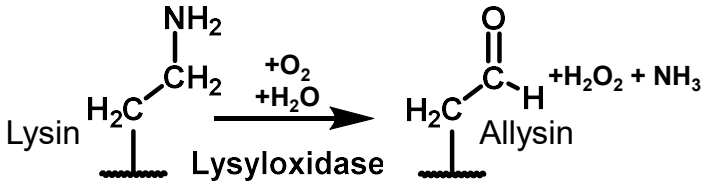
Proteases
e.g. **cysteine cathepsins**

Modification of amino acid side chains

Lysyl oxidases
Transglutaminases
and other Enzymes

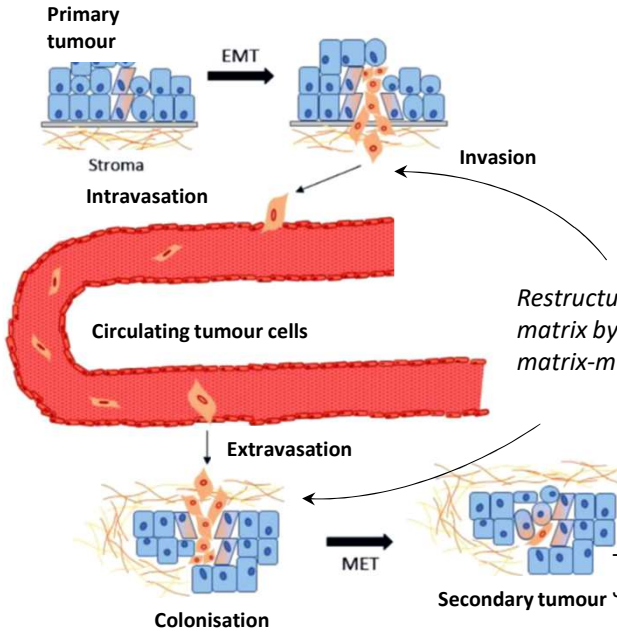
Lysyl oxidases

Cu-dependent amine oxidases



Physiological function:
Cross-linking of structural proteins (**collagen**, elastin) in connective tissues

5 Homologues: lysyl oxidases (LOX) and lysyl oxidase-like 1-4 (LOXL1-4)



Restructuring of the der extracellular matrix by lysyl oxidases (and other matrix-modifying enzymes)

Taken and adapted from:
Jones *et al. Adv. Therap.* **2020**, *3*, 1900119

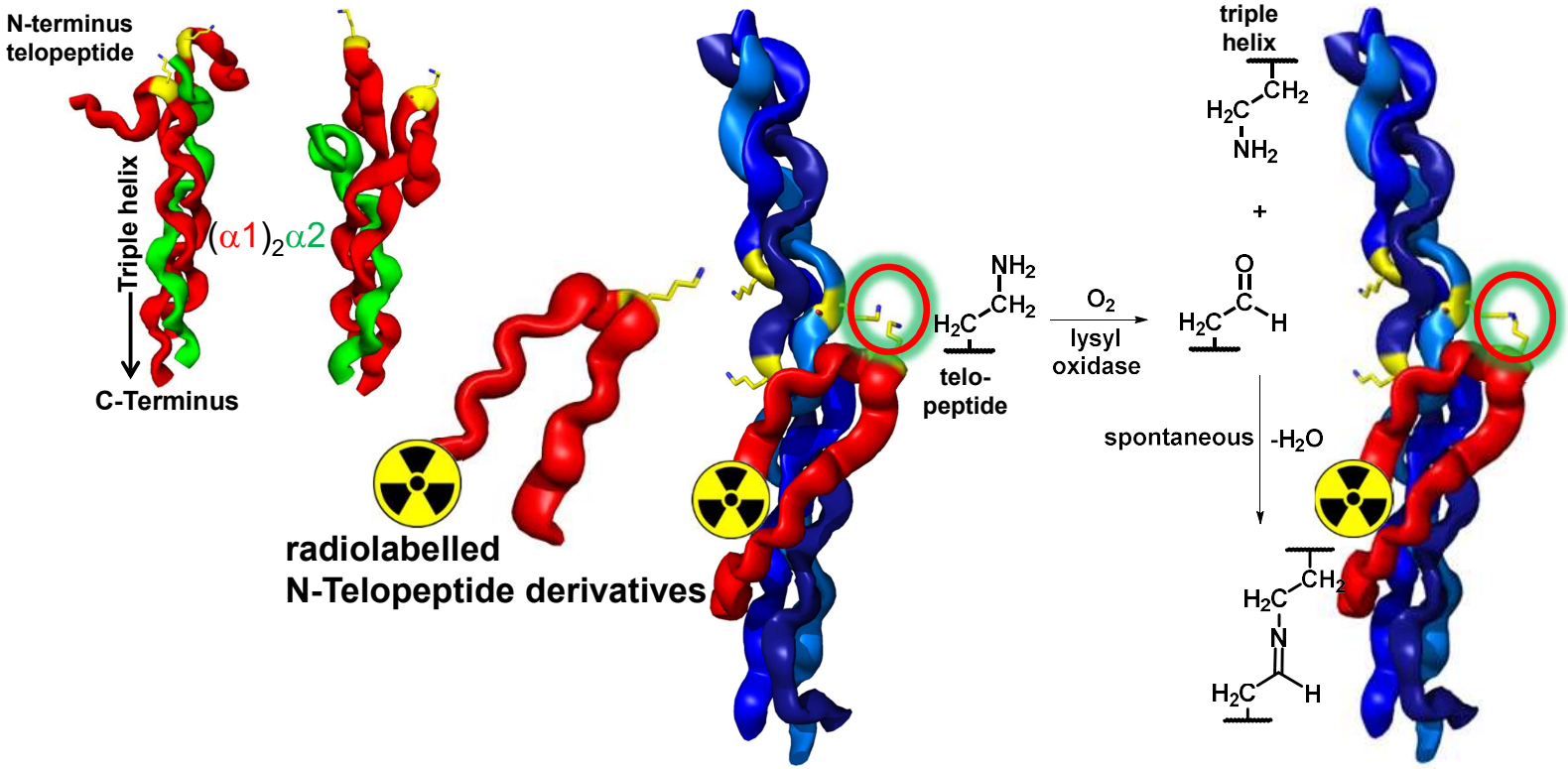
Lysyl oxidases:
- **Restructuring of the tumour-associated extracellular matrix**
- **Increased expression under hypoxic conditions**
  ⇒ Key enzymes of hypoxia-induced tumour metastasis

Erler et al. *Nature* **2006**, *440*, 1222-1226
Levental et al. *Cell* **2009**, *139*, 891-906
Granchi et al. *ChemMedChem* **2009**, *4*, 1590-1594

Review: Baker et al. *Nat. Rev. Cancer* **2012**, *12*, 540-552
Current review including inhibitor development and imaging: Löser *et al. ChemMedChem* **2023**, *18*, e202300331

Lysyl oxidases – development of radiotracers

Starting from collagen α1(I) N-telopeptide derivatives



Development of radiotracers

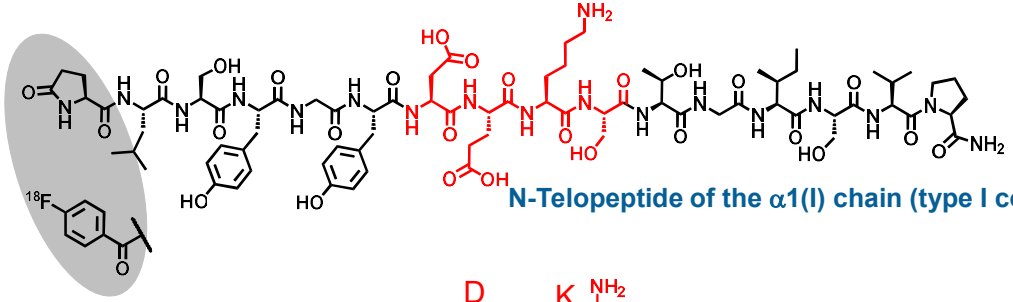
Substrates of lysyl oxidase – N-telopeptide derivatives of type I collagen α1 chain

Trapping of radiolabelled peptides in the ECM and imaging by PET

replacement Pyroglutamate

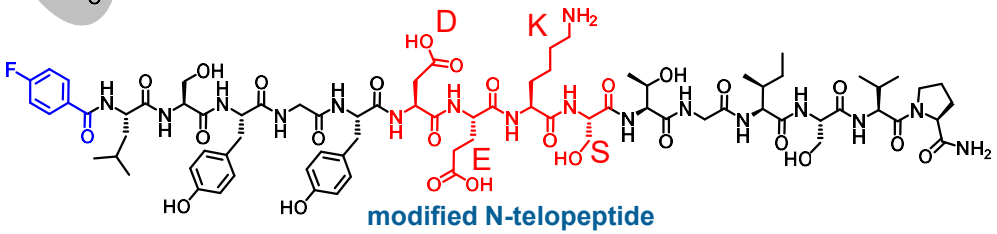
⇕

[^{18}F]Fluorobenzoyl



N-Telopeptide of the α1(I) chain (type I collagen)

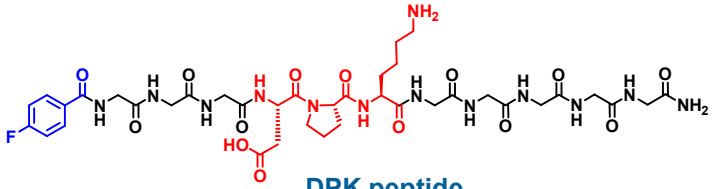
1.



modified N-telopeptide

(N-terminally acetylated derivative k_{cat}/K_m=2 $M^{-1}s^{-1}$*)

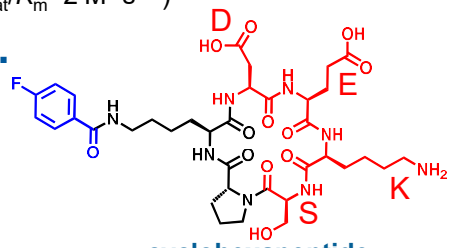
2.



DPK peptide

(N-terminally acetylated derivative k_{cat}/K_m=110 $M^{-1}s^{-1}$*)

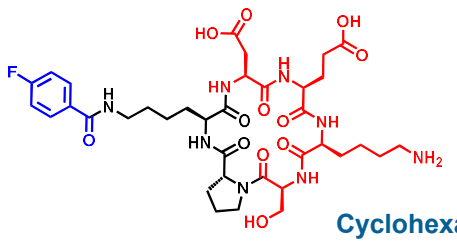
3.



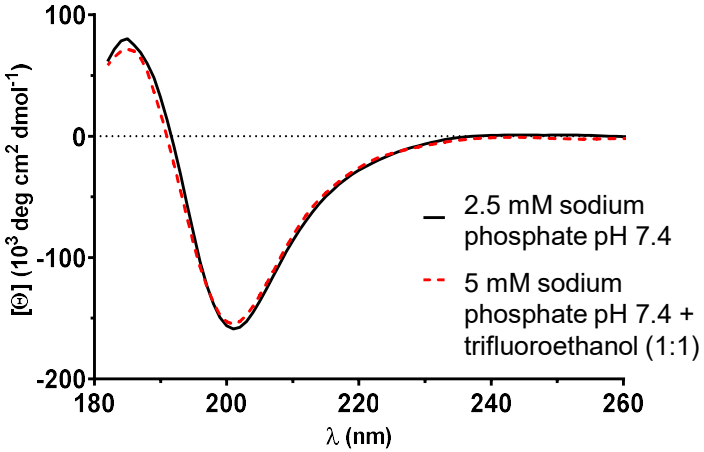
cyclohexapeptide

*Nagan & Kagan, *J. Biol. Chem.* **1994**, *35*, 22366-71

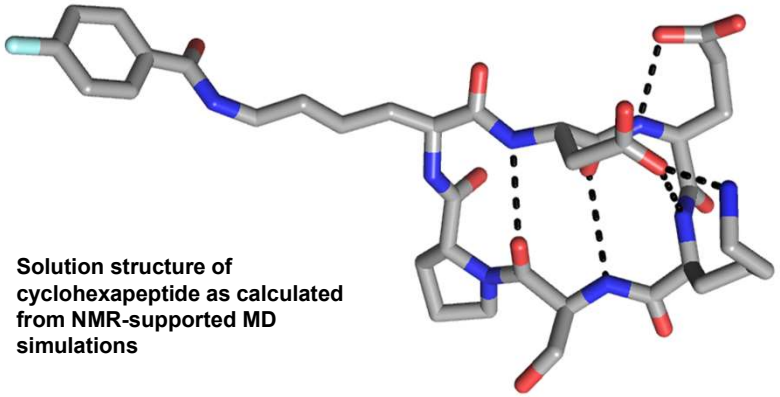
Cyclic peptide as potential LOX substrate - Derivation of 3D structure by CD and NMR spectroscopy and MD simulations



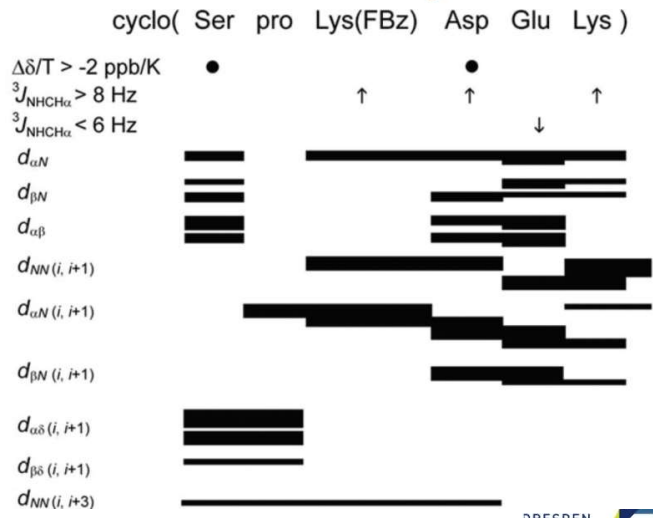
Cyclohexapeptide



CD spectrum of cyclohexapeptide



Solution structure of cyclohexapeptide as calculated from NMR-supported MD simulations



Wodtke *et al. Org. Biomol. Chem.* **2015**, 1878-96

Development of radiotracers

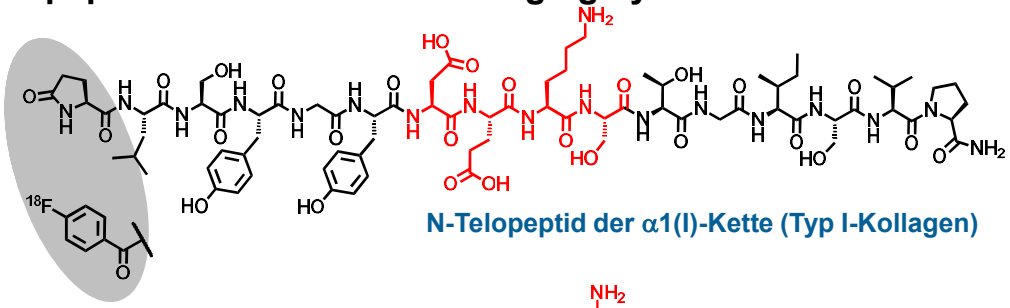
Substrates of lysyl oxidase – N-telopeptide derivatives of type I collagen α1 chain

Trapping of radiolabelled peptides in the ECM and imaging by PET

replacement Pyroglutamate

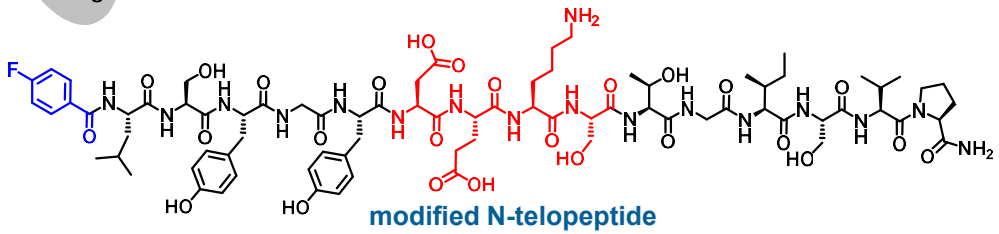
⇕

[^{18}F]Fluorobenzoyl



N-Telopeptid der α1(I)-Kette (Typ I-Kollagen)

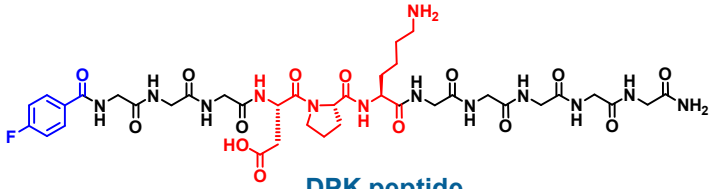
1.



modified N-telopeptide

(N-terminally acetylated derivative k_{cat}/K_m=2 $M^{-1}s^{-1}$*)

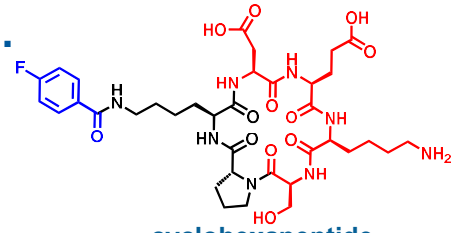
2.



DPK peptide

(N-terminally acetylated derivative k_{cat}/K_m=110 $M^{-1}s^{-1}$*)

3.



cyclohexapeptide

*Nagan & Kagan, *J. Biol. Chem.* **1994**, *35*, 22366-71

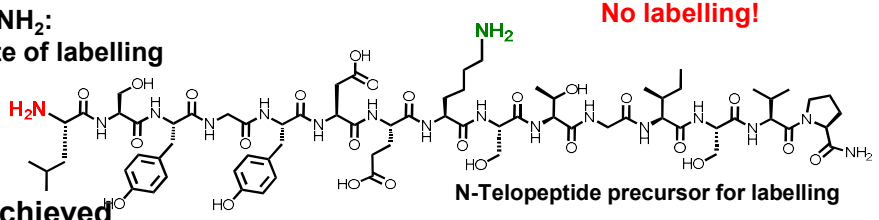
Regioselective labelling of peptides with fluorine-18

- **Labelling with fluorine-18**
- **^{18}F-Fluorobenzoylation with [^{18}F]SFB**
- **Problem: selective labelling at N-terminus should be achieved**
- **Method for regioselective labelling 18F-fluorbenzoylation was developed**

α-NH_2: Site of labelling

ε-NH_2: enzymatic conversion by lysyl oxidase

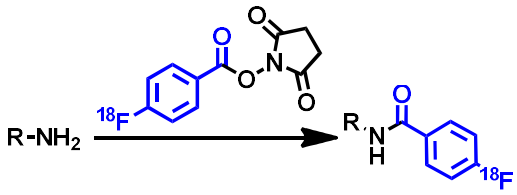
No labelling!



N-Telopeptide precursor for labelling

Agent for ^{18}F labelling:

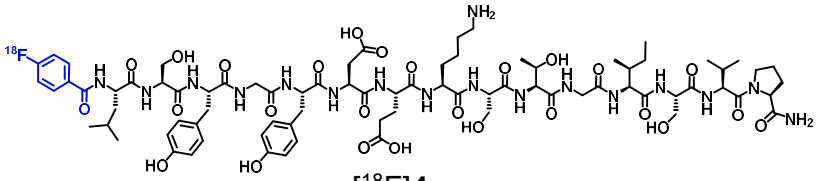
***N*-Succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB)**



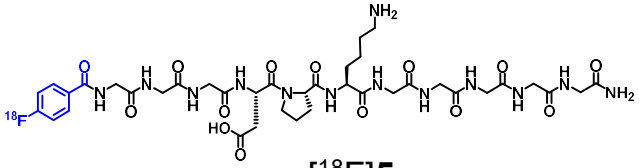
Kuchar *et al. Amino Acids* **2012**, *43*, 1431-43
Kuchar *et al. Front. Chem.* **2018**, *6*, 121
Löser *et al. Amino Acids* **2019**, *51*, 219-44

Evaluation of the ^{18}F-labelled telopeptide-derived lysyl oxidase substrate in A375 tumours (murine xenograft model)

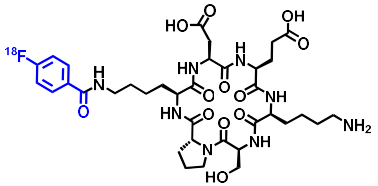
Time-activity curves



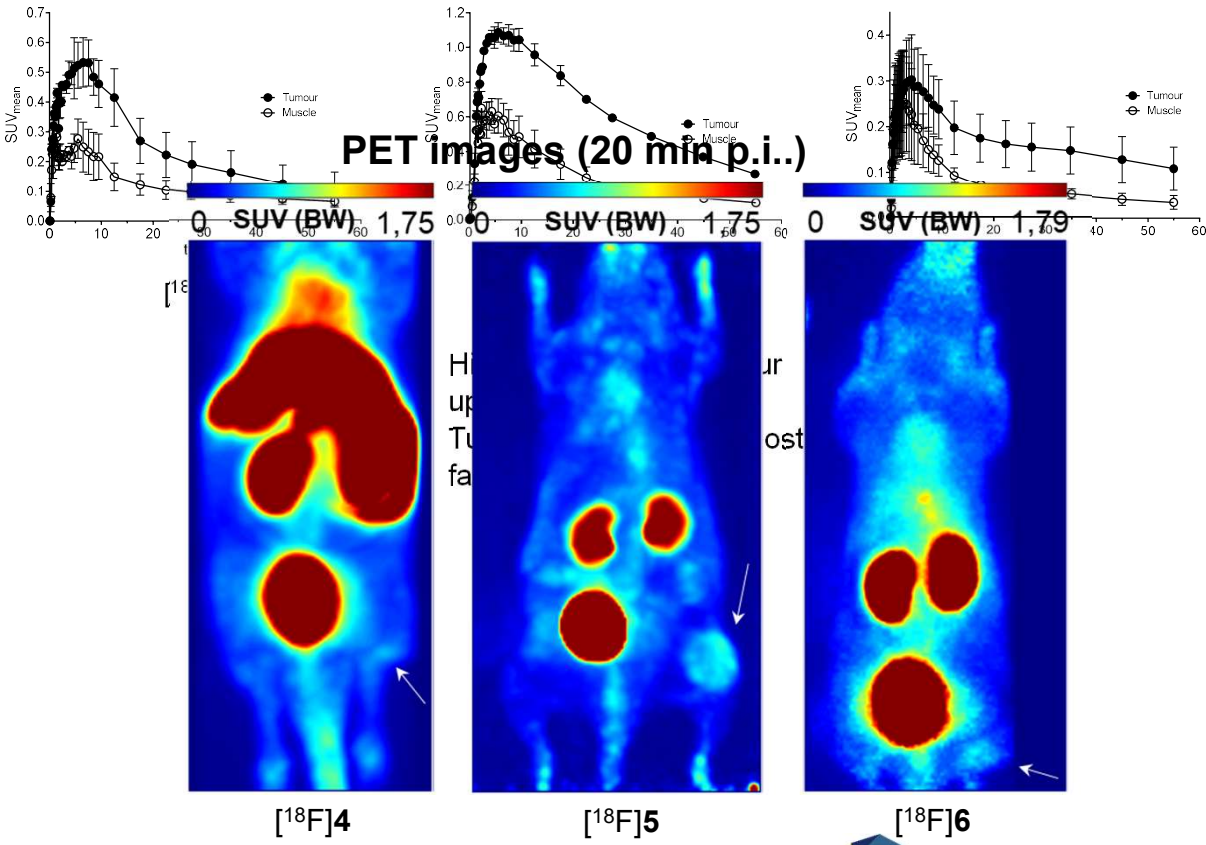
[^{18}F]**4**



[^{18}F]**5**



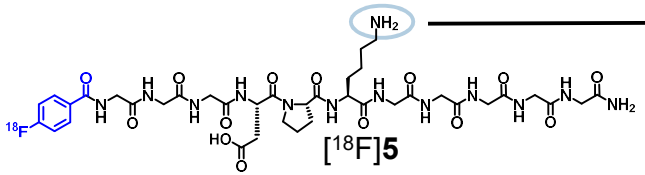
[^{18}F]**6**



Kuchar *et al. Front. Chem.* **2018**, *6*, 121

Evaluation of the ^{18}F-labelled telopeptide-derived Lysyl oxidase substrate in A375 tumours (murine xenograft model)

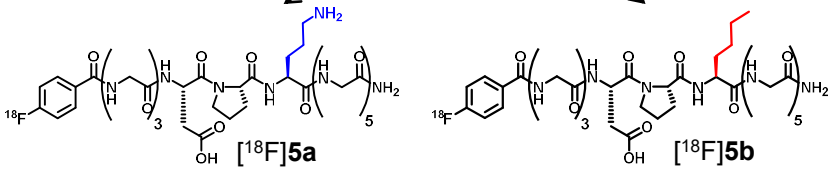
Pharmacological blocking and non-functional analogues confirm lysyl oxidase-mediated tumour uptake



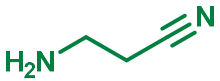
Non-functional analogues

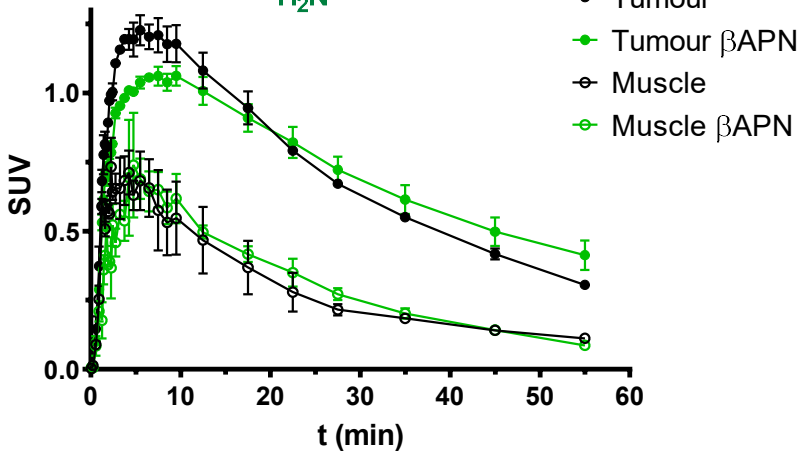
Lys → Orn
attenutated enzymatic conversion

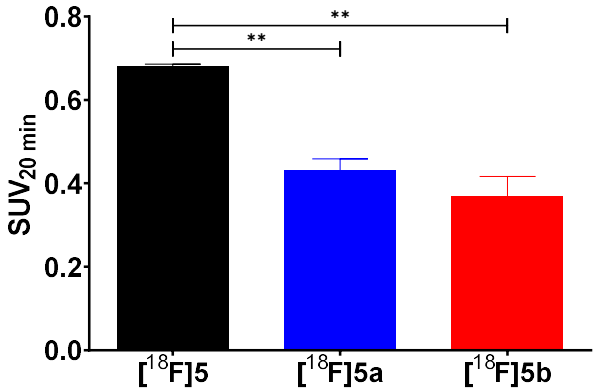
Lys → Nle
no enzymatic conversion



Pretreatment with lysyl oxidase inhibitor: β-aminopropionitrile (βAPN; 100 mg/kg)





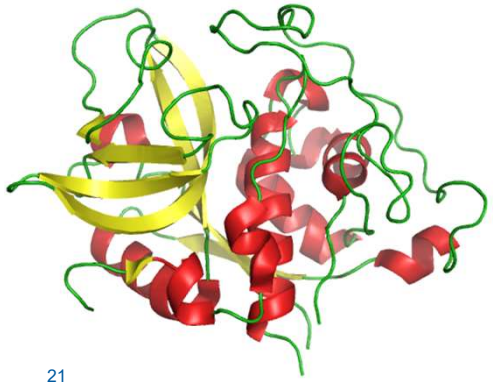


Kuchar *et al. Front. Chem.* **2018**, *6*, 121

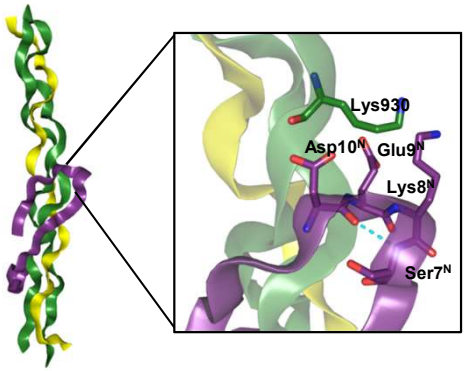
Development of radiotracers for novel imaging targets for functional characterisation of tumours using PET

Matrix-modifying enzymes

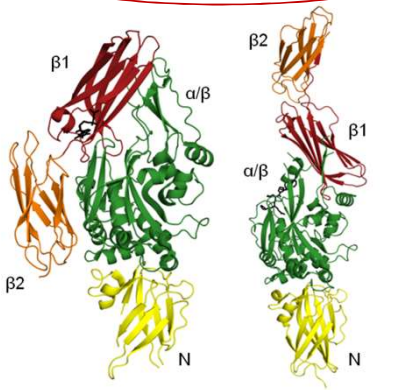
Cysteine cathepsins



Lysyl oxidases

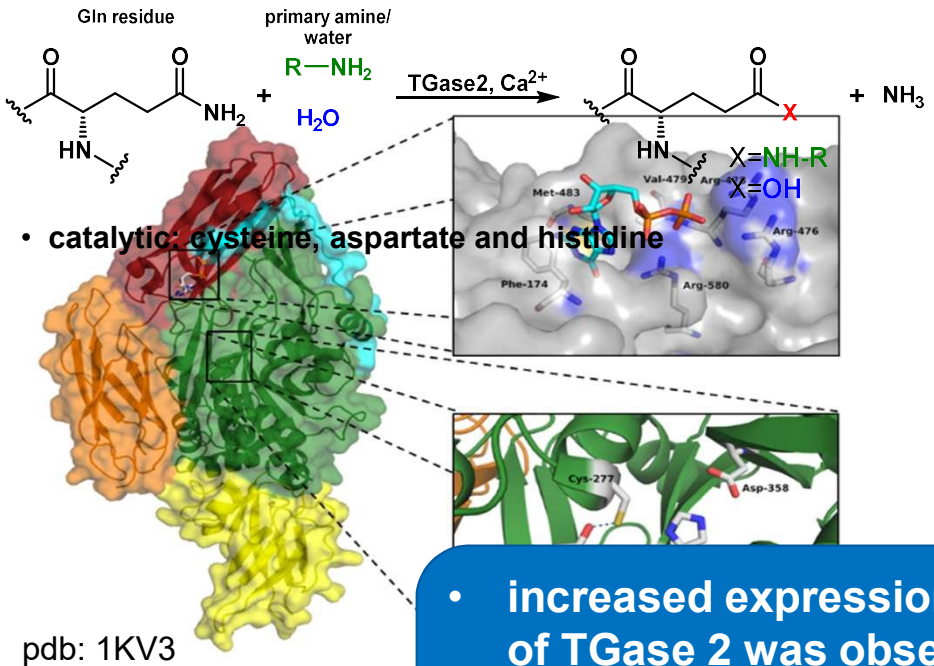


Transglutaminase 2



Transglutaminase (TGase) 2

- **TGases catalyse the formation of isopeptide bonds**



- **catalytic: cysteine, aspartate and histidine**

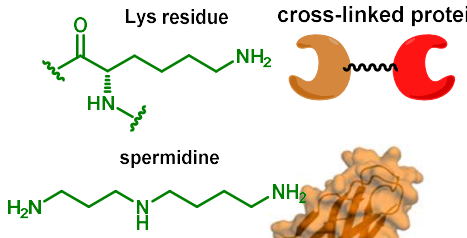
pdb: 1KV3

„closed confor

[Ca²⁺] low
[GTP]/[GDP] hig

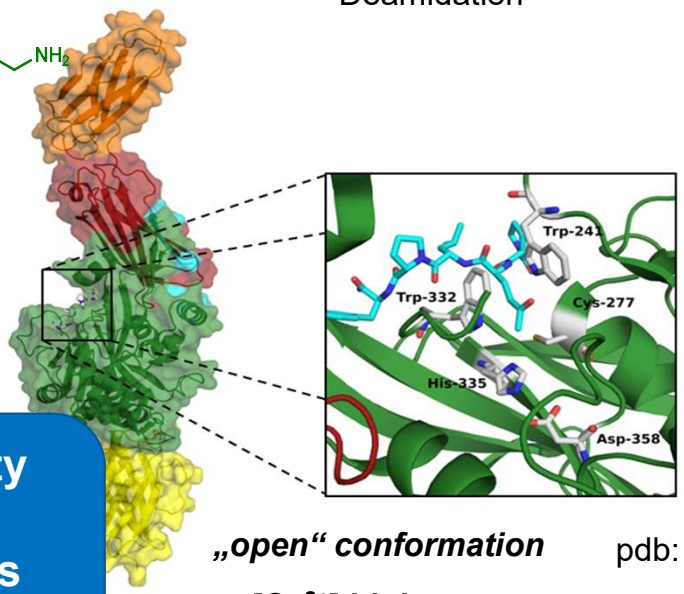
- Function as G-protein und GTPase
- Funktion als adapter protein

- **increased expression and activity of TGase 2 was observed in a variety of tumours and correlates with metastasis and resistance to radiation and chemotherapy**



Posttranslational modifications of glutamine residues:

- Cross-linking
- (Poly)amination
- Deamidation

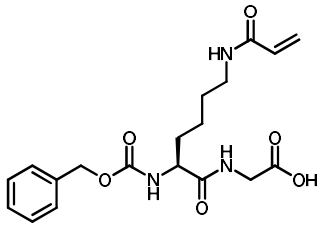


„open" conformation pdb: 2Q3Z

[Ca²⁺] high
[GTP]/[GDP] low

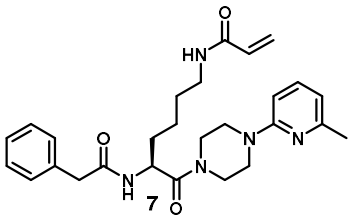
- **Acyltransferase activity**
- Protein-disulfide isomerase and kinase activity

N^{ε}-Acryloyllysine-derived inhibitors as starting point for TGase 2-directed radiotracers



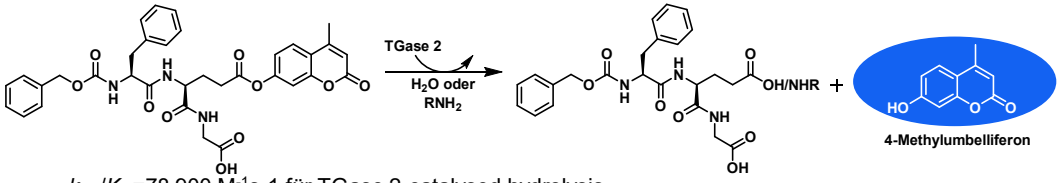
TGase 2
IC_{50} = 3.1 µM

Marrano et al. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 1923



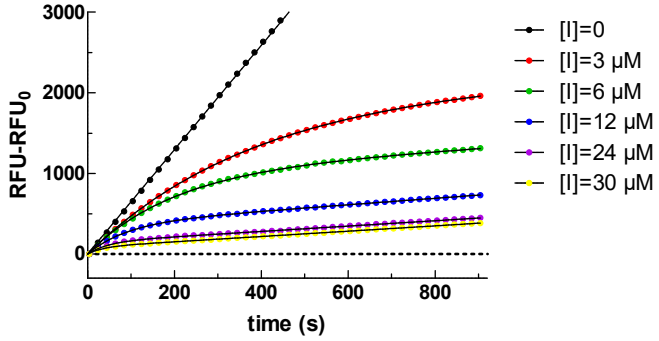
TGase 2
IC_{50} = 0.014 µM

Wityak et al. *ACS Med. Chem. Lett.* **2012**, *3*, 1024

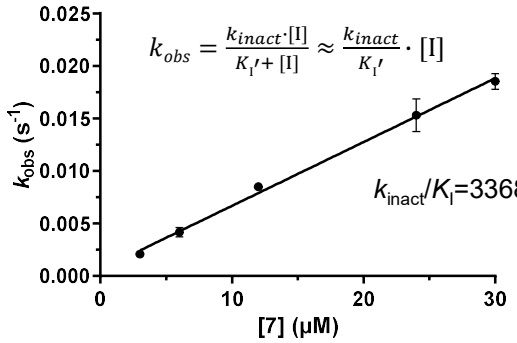


k_{cat}/K_m=78 900 $M^{-1}s^{-1}$ für TGase 2-catalysed hydrolysis

$$E + I \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} EI \xrightarrow{k_{inact}} E\text{-}I \qquad K_I = \frac{k_{-1} + k_{inact}}{k_{+1}}$$



$$RFU - RFU_0 = v_S \cdot t + \frac{(v_i - v_S) \cdot (1 - e^{-k_{obs} \cdot t})}{k_{obs}}$$



$$k_{obs} = \frac{k_{inact} \cdot [I]}{K_I' + [I]} \approx \frac{k_{inact}}{K_I'} \cdot [I]$$

$$K_I' = K_I(1 + \frac{[S]}{K_m})$$

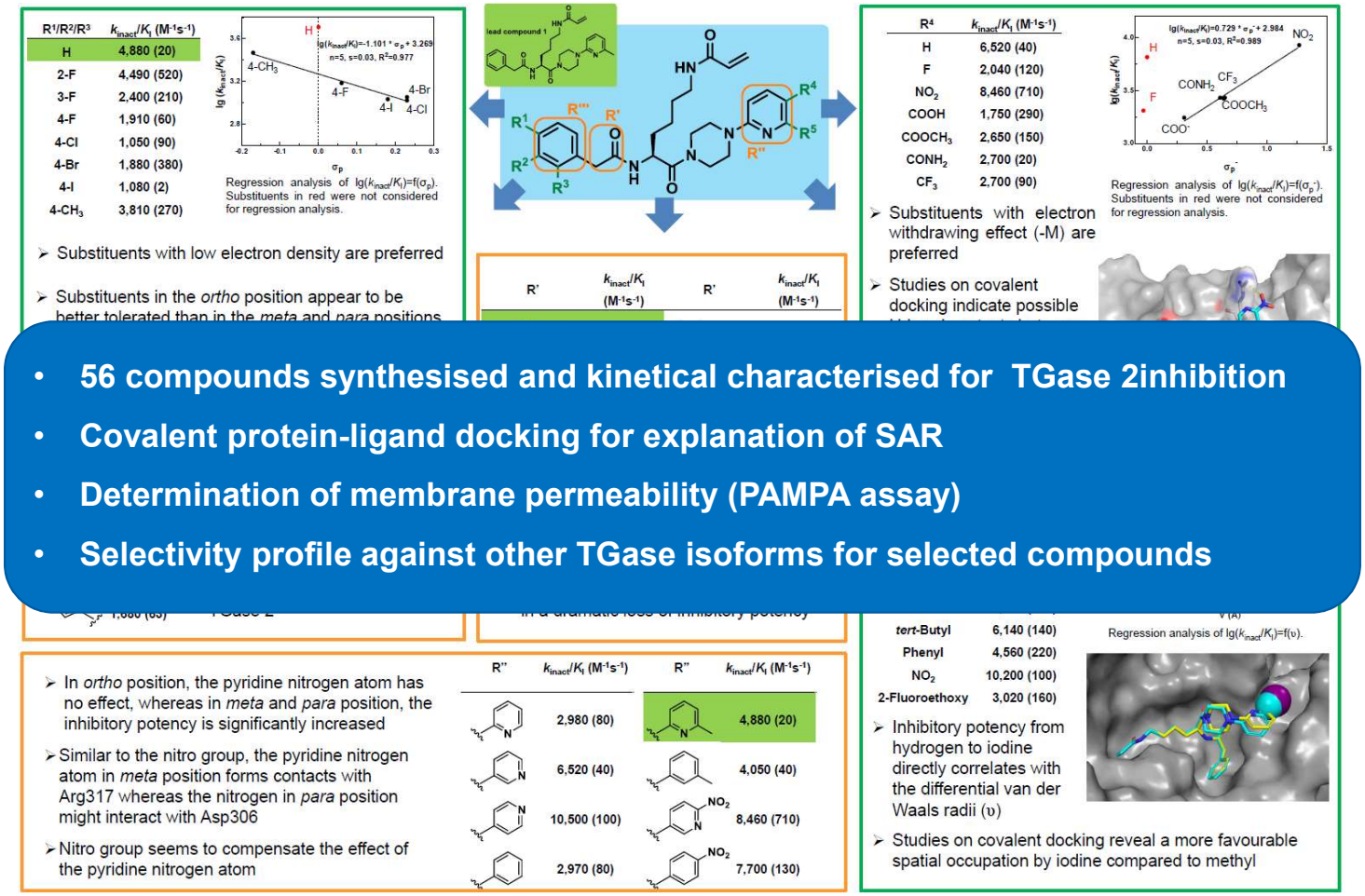
K_m=8,6 µM

[S]=30 µM

k_{inact}/K_I=3368 $M^{-1}s^{-1}$

Wodtke *et al. ChemBioChem* **2016**, *17*, 1263-81
Wodtke *et al. Anal. Biochem.* **2020**, *595*, 113612

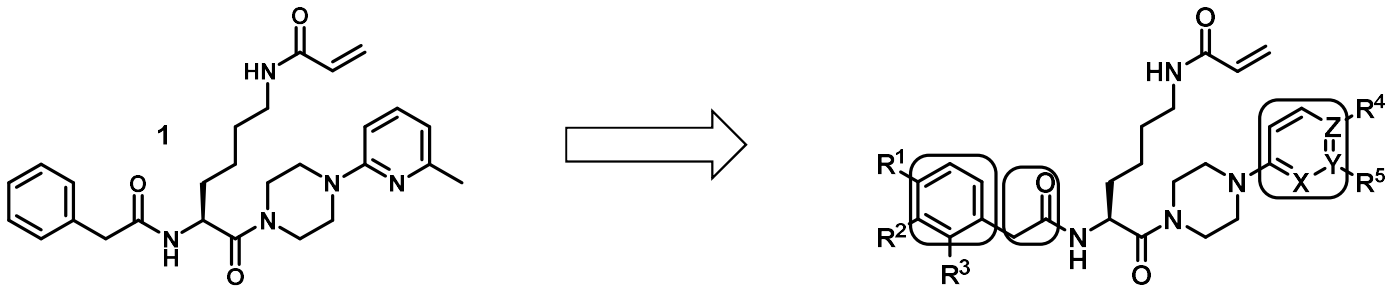
Structure-activity relationships

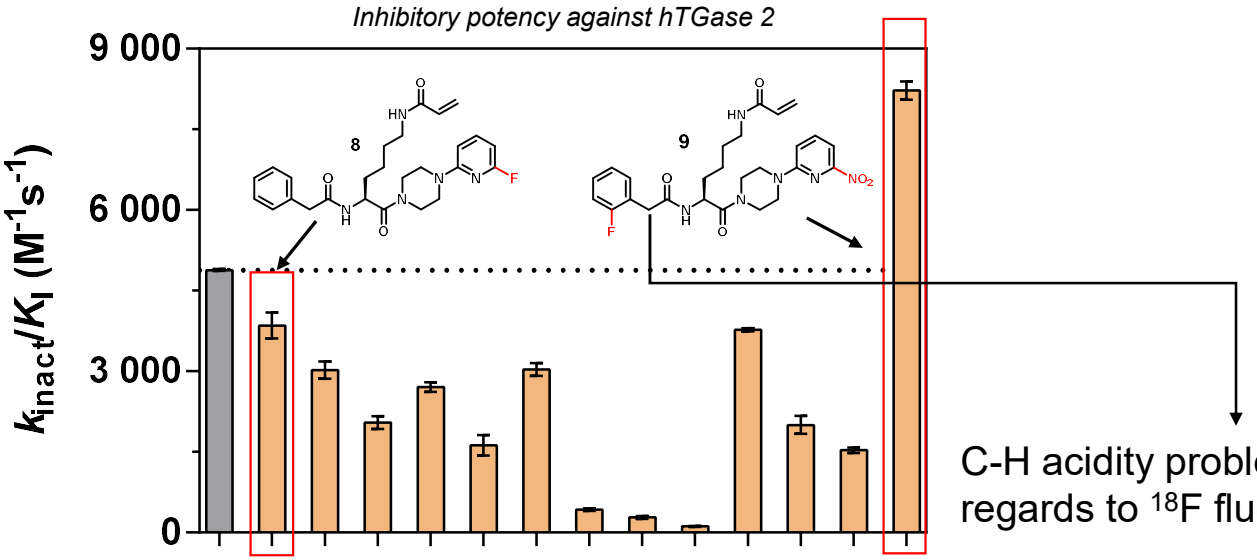


- **56 compounds synthesised and kinetical characterised for TGase 2inhibition**
- **Covalent protein-ligand docking for explanation of SAR**
- **Determination of membrane permeability (PAMPA assay)**
- **Selectivity profile against other TGase isoforms for selected compounds**

Wodtke *et al.* Löser *J. Med. Chem.* **2018**, *61*, 4528-60

Inhibition of hTGase 2 by fluorinated *N*ε-acryloyllysines



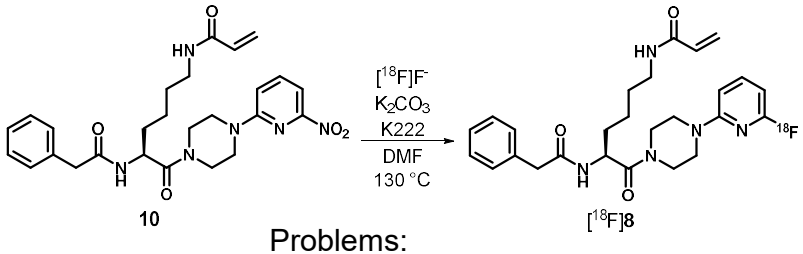


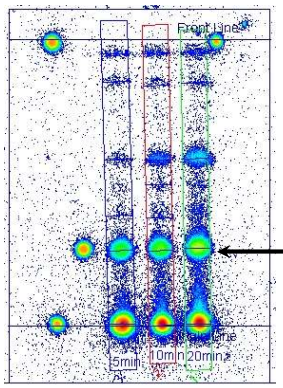
C-H acidity problematic with regards to ^{18}F fluorination

Wodtke *et al.* Löser *J. Med. Chem.* **2018**, *61*, 4528-60

Fluorine-18 labelling of TGase 2 inhibitors

One-step radiolabelling



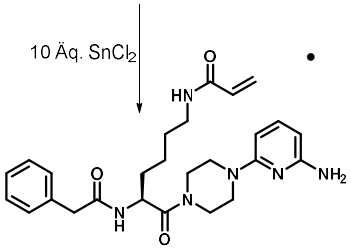


Radio-TLC

[^{18}F]**8**; 15 % after 20 min

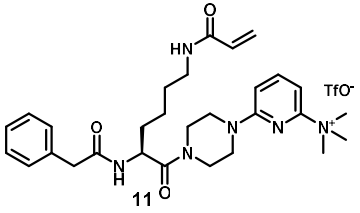
Problems:

- Separation of **10** and [^{18}F]**8** difficult → Reduction after ^{18}F-labelling
- base-induced side reactions at the benzylic CH_2 group: oxidation and cyclisation

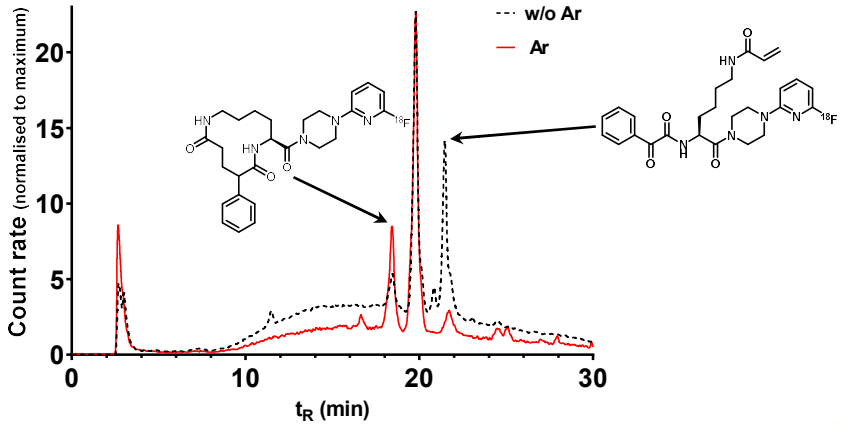


Conclusion:

- Alternative precursor required



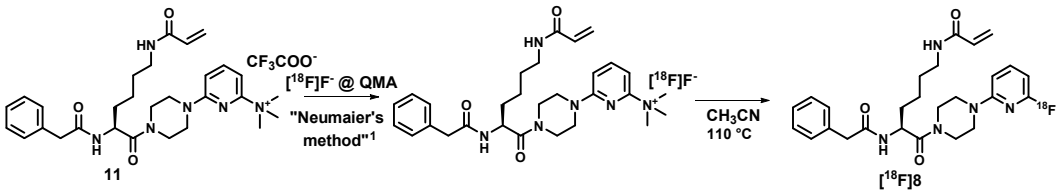
Radio-HPLC



Wodtke *et al. J. Med. Chem.* **2021**, *64*, 3462-78

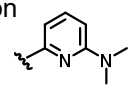
Fluor-18-labelling of TGase 2 inhibitors

One-step radiolabelling

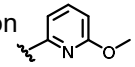


Side reactions:

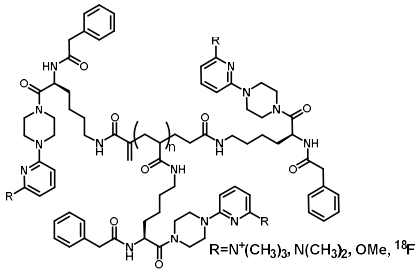
Demethylation



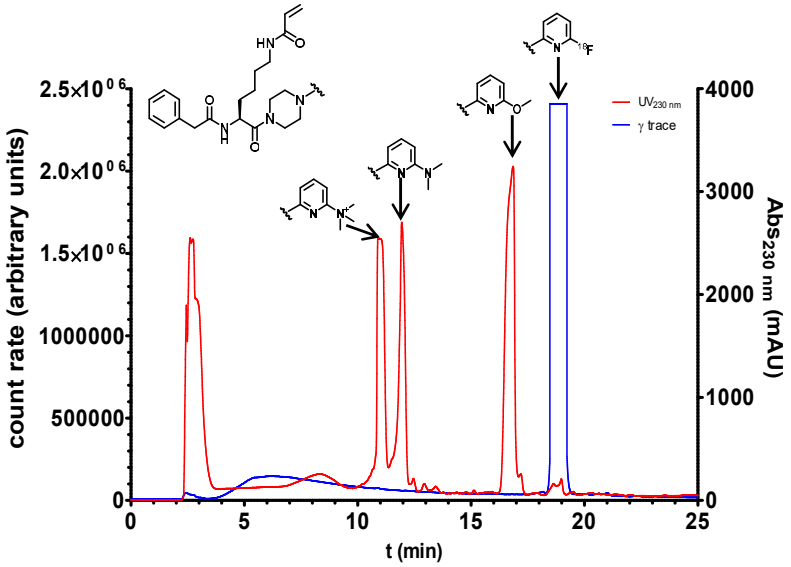
Methoxylation



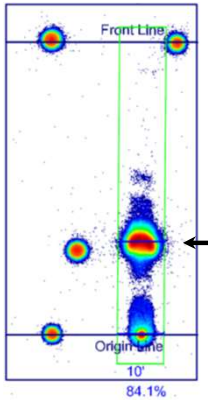
Anionic polymerisation



Chromatogramme (semiprep. HPLC)



Radio-TLC



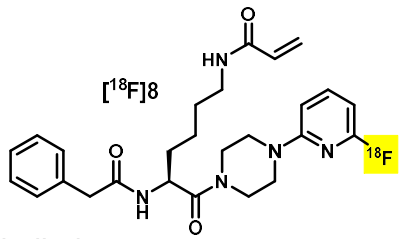
[18F]**8**; 84 % after 10 min

Radiosynthesis data (mean ± SEM)	
Labelling yield	74 ± 13 %
Radiochemical yield (d.c.)	33 ± 14 %
Radiochemical purity	97 ± 0.5 % (radio-TLC)
	97 ± 0.6 % (radio-HPLC)
Synthesis time	136 ± 24 min
Molar activity	16.8-158.0 GBq/µmol
Absolute activity	140-707 MBq
n	22

Wodtke, *et al.* Löser *J. Med. Chem.* **2021**, *64*, 3462 [1]Richarz *et al.Org. Biomol. Chem.* **2014**, *12*,8094-8099

Interaction of [^{18}F]8 with TGase 2 *in vitro*

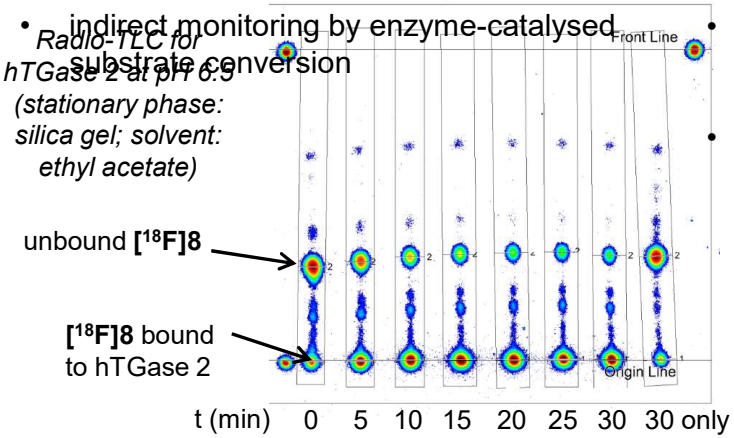
$$E + I \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} EI \xrightarrow{k_{inact}} E\text{-}I$$



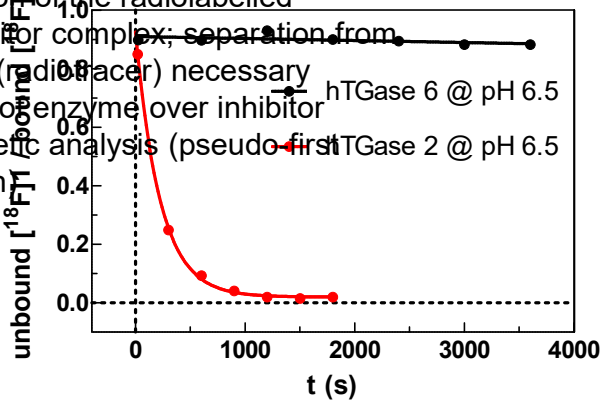
Classical enzyme inhibition experiment [E]<<[I] ⟷ **Radiotracer experiment** [E]>>[I]

- indirect monitoring by enzyme-catalysed substrate conversion

Radio-TLC for hTGase 2 at pH 6.5 (stationary phase: silica gel; solvent: ethyl acetate)



- direct detection of the radiolabelled enzyme-inhibitor complex; separation from free inhibitor (radiotracer) necessary
- large excess of enzyme over inhibitor simplifies kinetic analysis (pseudo-first order reaction)



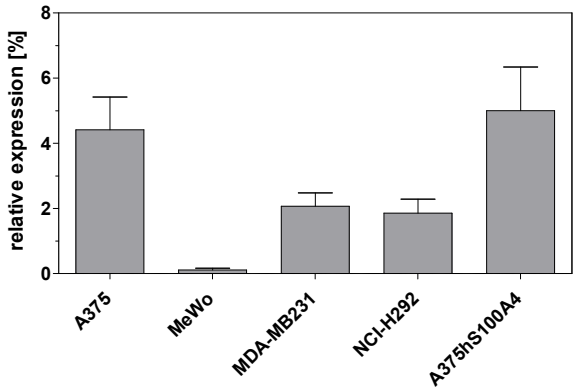
	pH	k_{inact}/K_I ($M^{-1}s^{-1}$) radiometric	k_{inact}/K_I ($M^{-1}s^{-1}$) fluorimetric#
hTGase 2	6.5	4 070 ± 590	3 850 ± 240
	7.4	9 760	-
	8.0	9 660	-
hTGase 6	6.5	7	14

*Conditions: 3 mM $CaCl_2$, 500 µM TCEP, 1 µM TGase and < 0.2 µM **[^{18}F]8**

- Confirmation of inhibitory potency of **[^{18}F]8** by radiometric assay method
- Inhibitory potency is dependent on the pH value (indicates involvement of an ionisable amino acid residue in binding of **8**)

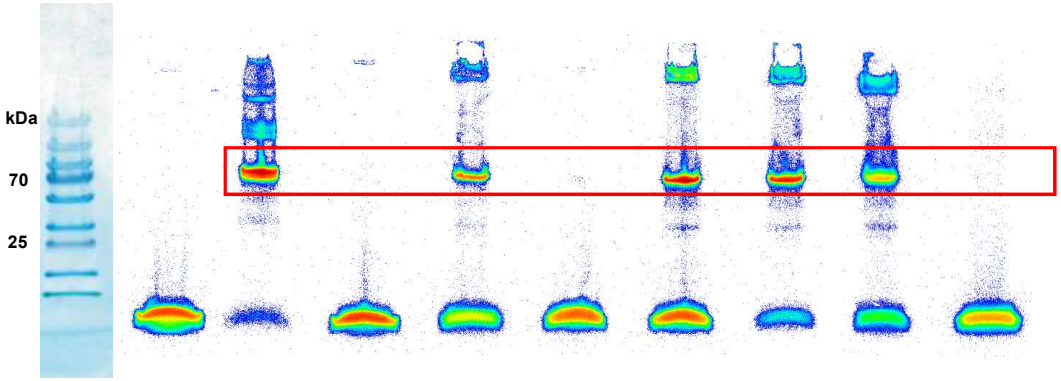
Reactivity of [^{18}F]8 in cell lysates

Densitometric Western blot analysis of cell lysates



A375…malignant melanoma cell line
MeWo…malignant melanoma cell line
MDA-MB-231…breast cancer cell line
NCI-H292…lung, mucoepidermoid carcinoma cell line
A375hS100A4…A375 cells overexpressing human S100A4 protein

*Radio-SDS-PAGE after incubation of cell lysates with **[^{18}F]8** (25 min, 3 mM $CaCl_2$)*



[^{18}F]8	hTG2 (78 kDa)	hTG6 (78 kDa)	A375	MeWo	MDA-MB231	NCI-H292	A375 hS100A4	A375 hS100A4 + **Z006***

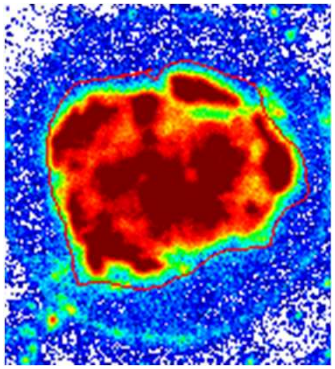
- **[^{18}F]8** shows selective (and specific) binding to hTGase 2 in cell lysates

*Preincubation for 5 min @10 µM

Wodtke *et al. J. Med. Chem.* **2021**, *64*, 3462

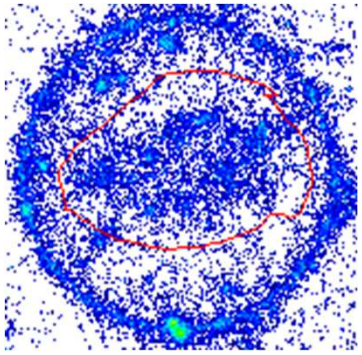
Radiopharmacological investigations: Radioluminography of tumour tissue sections

A375: TGase 2(+) Control



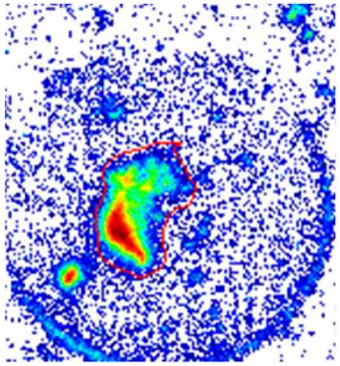
A375 ([Ca^{2+}]=3 mM)

A375: TGase 2(+) Blockade



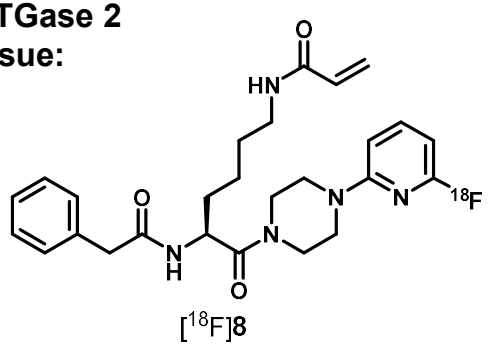
A375 ([Ca^{2+}]=3 mM) in the presence of **8** (10 µM)

MeWO: TGase 2(-)



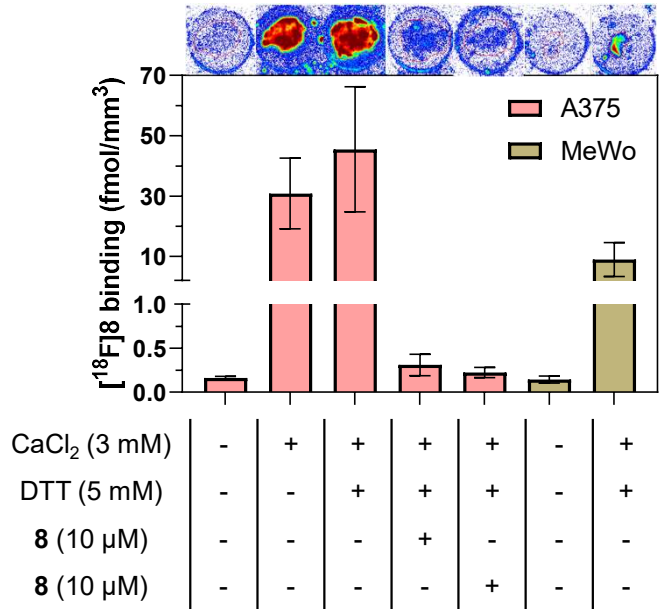
MeWo ([Ca^{2+}]=3 mM)

Expression level of TGase 2 in A375 xenograft tissue: 45.5 fmol/mm^3



[^{18}F]**8**

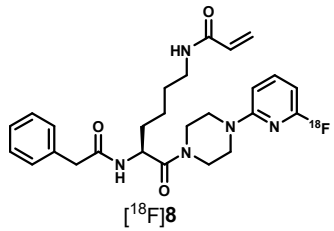
Low but detectable tracer binding in MeWo: Invasion of TGase 2 (+) benigne host cells

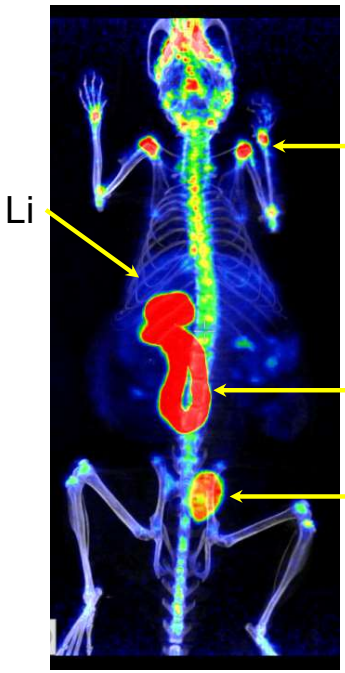


Wodtke, *et al. J. Med. Chem.* **2021**, *64*, 3462-78

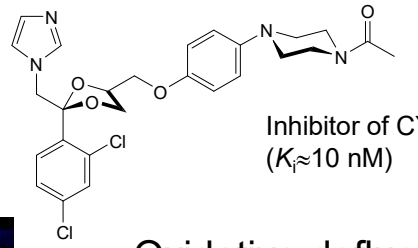
Radiopharmacological investigations: biodistribution by PET

Control (baseline)





Blockade with ketoconazol (50 mg/kg i.p.)



Inhibitor of CYP3A4
(K_i≈10 nM)

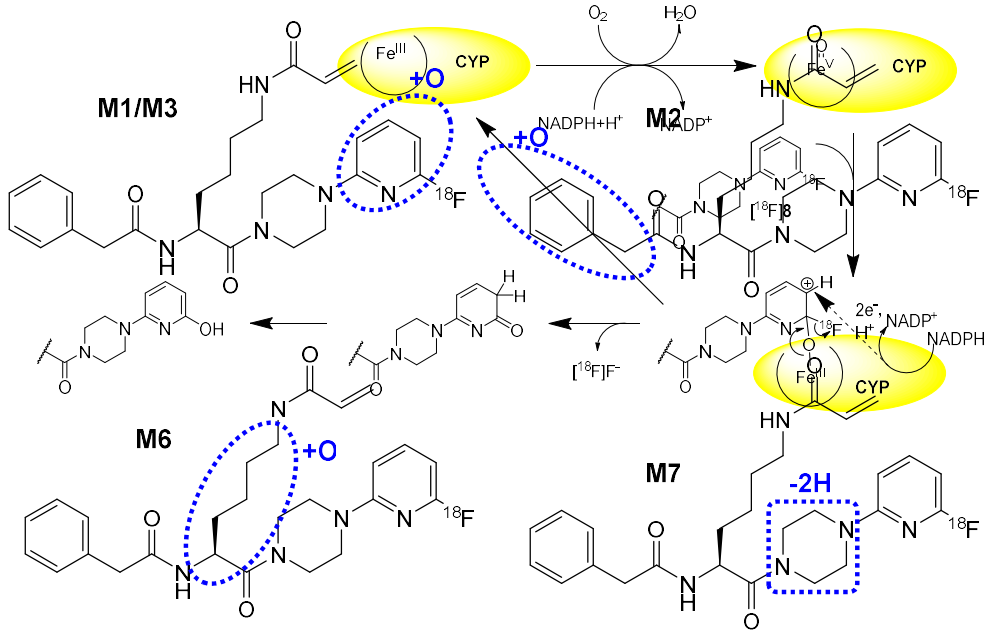
Bl urinary bladder
Epi Epiphysis ossis
Ki kidney
Li liver
Si small intestine

PET-CT (rescaled images) 60 min p.i.

Wodtke *et al.*, submitted

Oxidative defluorination:

Further CYP-mediated oxidative biotransformations:

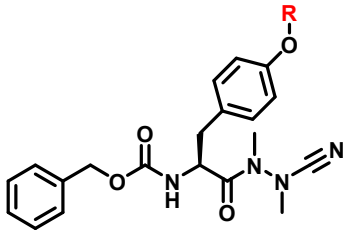


Summary

Development of matrix-modifying enzymes covering the follwoing aspects

- Synthesis of lead compounds, substrates, inhibitors and labelling precursors
- Biochemical characterisation of substrates and inhibitors
- Establishing and optmising radiolabelling with fluorine-18 and carbon-11
- Radiopharmacological investigations *in vitro*, *in cellulo* and *in vivo* (xenograft models in mice)

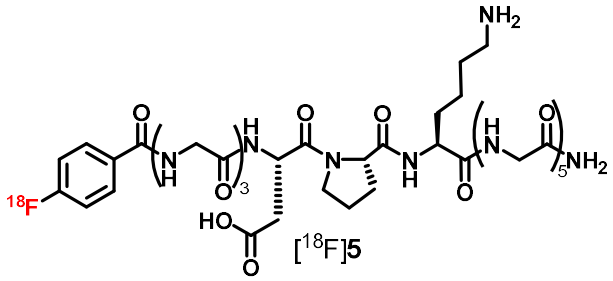
Cysteine cathepsins



[^{18}F]**2** (R=(CH$_2$)$_2$^{18}F)
[^{11}C]**3** (R=^{11}CH$_3$)

- Inhibitor-basied radiotracer design
- Target-mediated tumour uptake evidenced (kinetics and blocking studies)
- Spontaneous thiol reaktivity as reason for complex pharmacokinetics identified

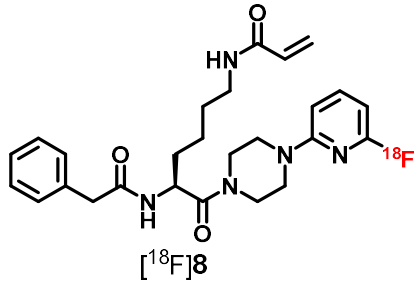
Lysyl oxidases



[^{18}F]**5**

- Substrate-based radiotracer design
- Target-mediated tumour uptake demonstrated by blocking studies and non-functional analogues

Transglutaminase 2



[^{18}F]**8**

- Inhibitor-based radiotracer design
- Target binding *in vitro* and *in cellulo* demonstrated by multiple experiments
- ^{18}F-Defluorination in vivo

Thanks!

HZDR

Prof. Dr. Jörg Steinbach
Prof. Dr. Jens Pietzsch
Prof. Dr. Klaus Kopka
Prof. Dr. Michael Bachmann
Prof. Dr. Jörg van den Hoff
Dr. Torsten Knieß
Dr. Constantin Mamat
Dr. Markus Laube
Dr. Ralf Bergmann
Dr. Birgit Belter
Dr. Christin Neuber
Dr. Sandra Hauser
Dr. Cathleen Haase-Kohn
Dr. Martin Ullrich
Dr. Steffen Fischer
Dr. F. Alexander Ludwig
Dr. Achim Hiller
Dr. Holger Stephan
Dr. Georg Schramm
Dr. Hans-Jürgen Pietzsch
Dr. Martin Kreller
Johanna Wodtke
Peggy Wecke
Andrea Suhr
Regina Herrlich
Aline Morgenegg
Catharina Knöfel
Mareike Barth
Karin Landrock
Julia Aldinger
Kai Fischer
Juliane Meyer

Dr. Manuela Kuchar
Dr. Robert Wodtke
Dr. Lydia Behring
Konstantin Kuhne
David Bauer
Henrike Beck
Michaela Brunzel
Lilli Dombrowski
Elisabeth Jäckel
Jan Kiebist
Miriam Liebe
Martin Lohse
Riccardo Pitzschler
Alan Wong

TU Dresden, BIOTEC
Prof. Dr. M. Teresa Pisabarro
Dr. Gloria Ruiz Gómez

University Cologne, Centre for Pharmacology & University of Applied Science Cologne
Prof. Dr. Markus Pietsch
Dr. Christoph Hauser
Paul Sommerfeld
Sophia Eimermacher

University of Bonn, Pharmaceutical Institute
Prof. Dr. Michael Gütschow
Dr. Maxim Frizler

University of Chemistry and Technology, Prague
Prof. Dr. Marie Urbanová
Dr. Pavlina Novotná

University of Rostock
Prof. Dr. Martin Köckerling

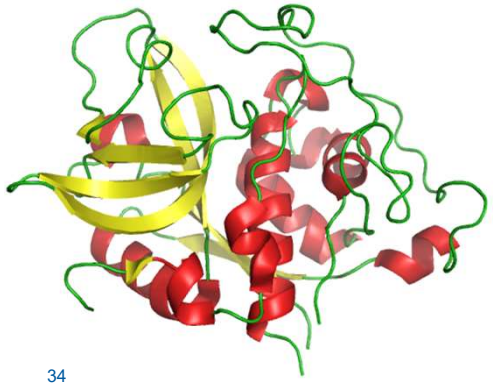
Biochemistry

Organic Chemistry

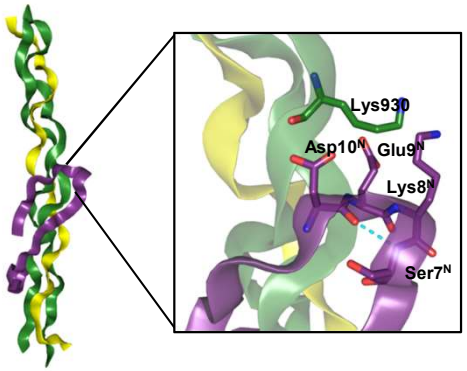
Radiochemistry

Radiotracers for matrix-modifying enzymes

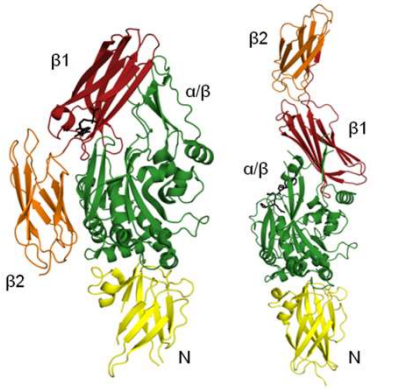
Cysteine cathepsins



Lysyl oxidases



Transglutaminase 2



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DRESDEN concept

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