Les Complexes Métalliques en Médecine

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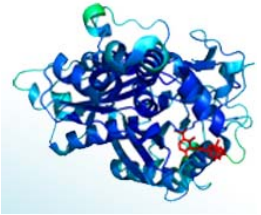
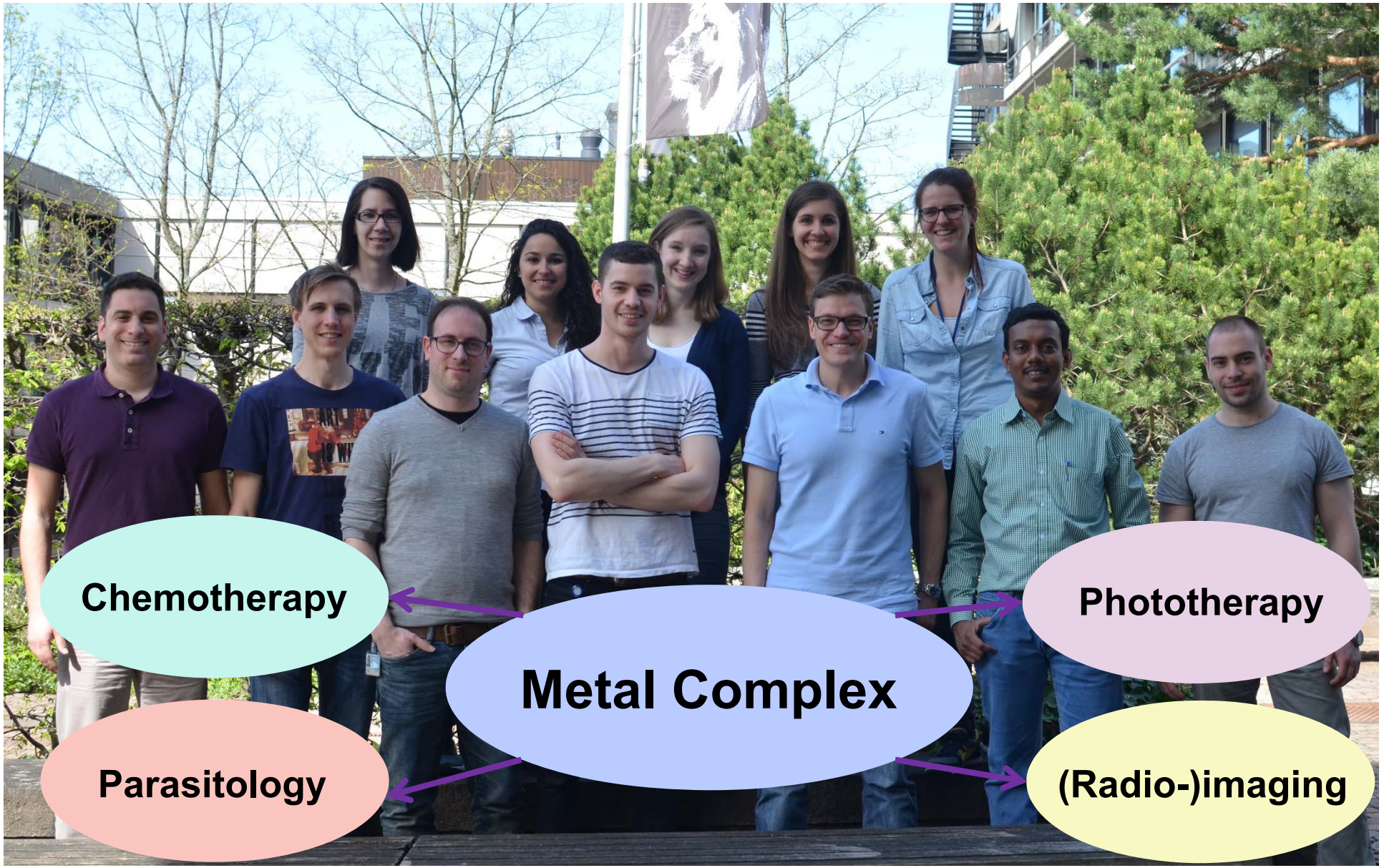
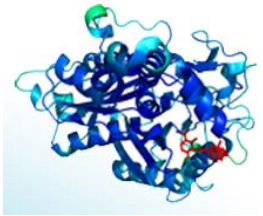


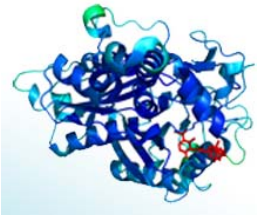




Cancer

1) Cancer has caused over 8.8 million casualties or 1 out of 6 of all deaths worldwide in 2015.
2) Approximately 70% of deaths from cancer occur in low- and middle-income countries.
3) Breast cancer affects about 1 in 8 women.
4) 78% of the patients with breast cancer survive 10 or more years in the UK.
5) 99% of the patients with testicular cancer survive 10 or more years in the UK.
6) Several types of cancer have very poor prognoses (e.g. pancreatic or brain cancer).

www.who.int/mediacentre/factsheets/fs297/en
www.cancerresearchuk.org

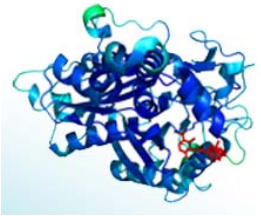


Cancer Treatment

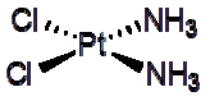
Surgery Chemotherapy Radiotherapy

- Side effects.
- Some cancers resistant to treatment.

➡ **Novel Drugs/Strategies are required.**

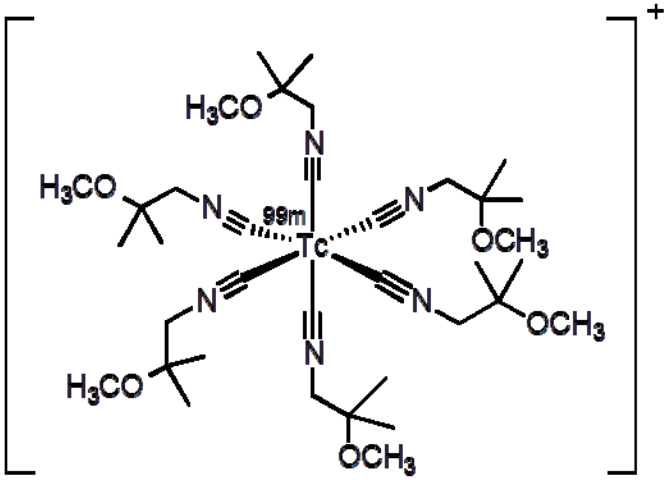


Metal-Based Drugs on the Market



Cisplatin

Anticancer Agent



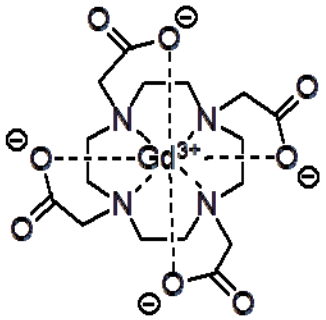
Cardiolite®

Nuclear Imaging Agent

As_2O_3

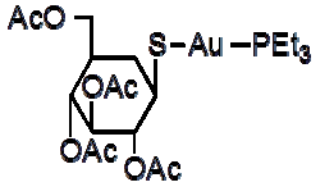
Trisenox®

Anticancer Agent



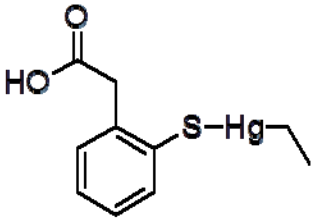
DOTAREM®

MRI Agent



Auranofin®

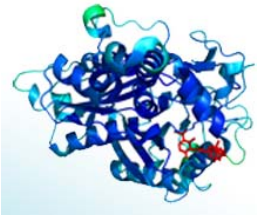
Antiarthritic Agent



Thimerosal®

Preservative for Vaccines

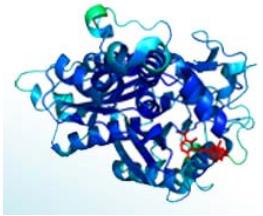
Alessio, E., *Bioinorganic Medicinal Chemistry,* Wiley-VCH Verlag: Weinheim, 2011.



Advantages of Metal-Based Drugs

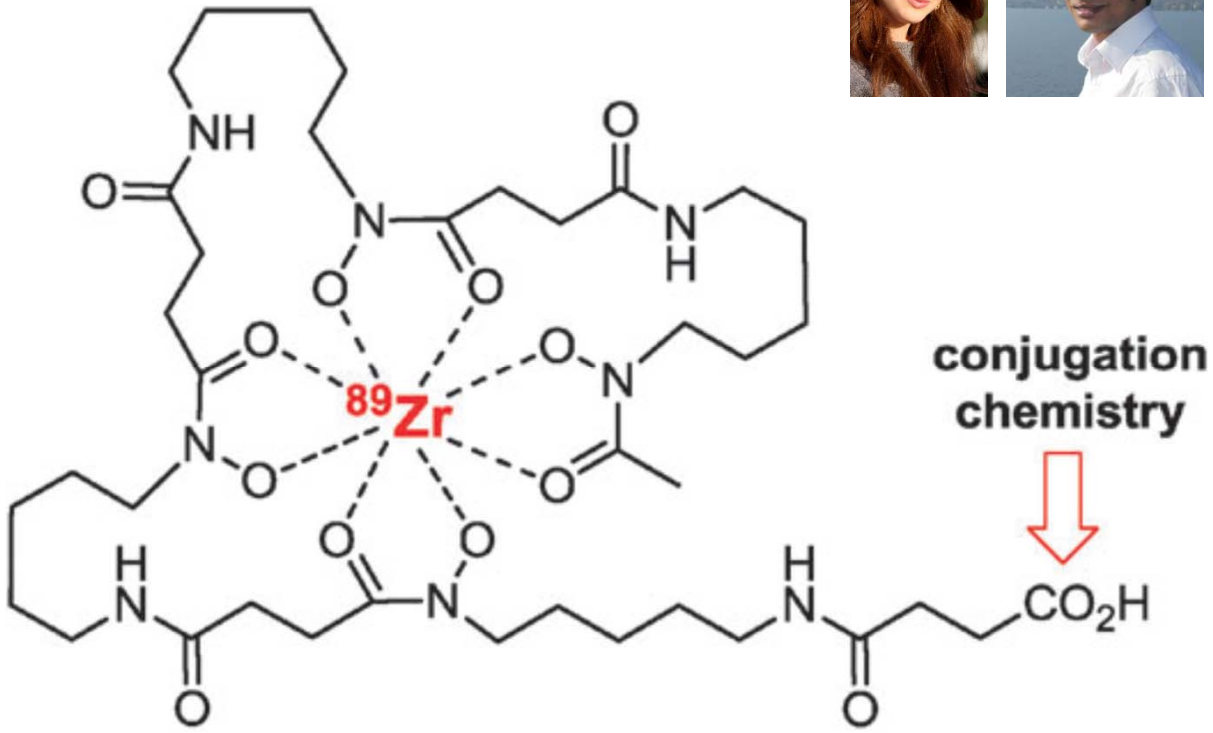
1) Ligand Exchange
2) Redox Activity
3) Higher Structural Diversity
4) Catalytic Properties
5) Radioisotopes

G. Gasser *et al.*, *Curr. Op. Chem. Biol.*, **2012**, *16,* 84-91.

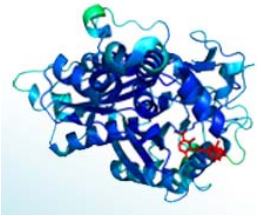


1. Improved Chelators for ^{89}Zr for Applications in Immuno-PET



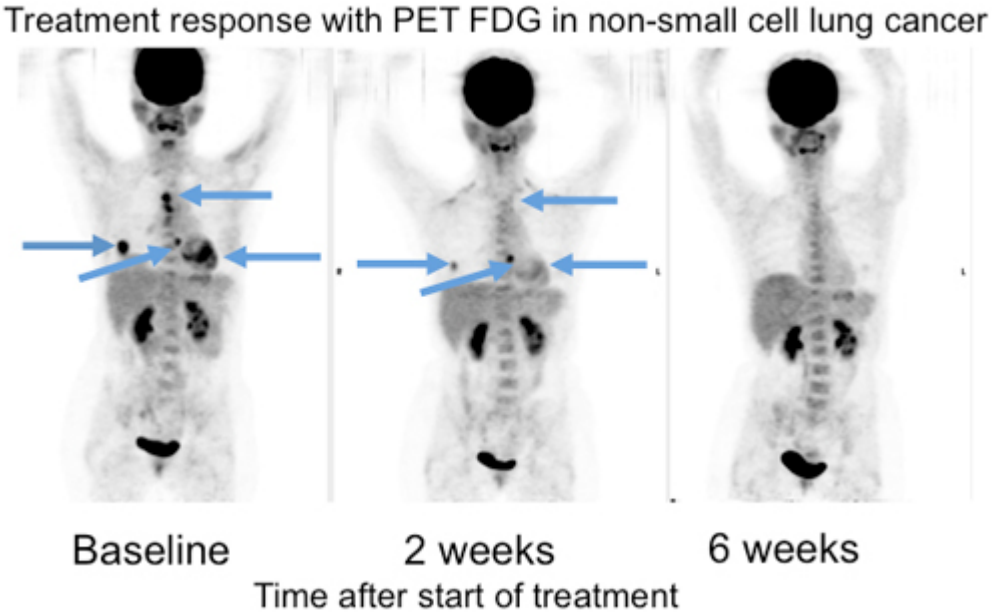


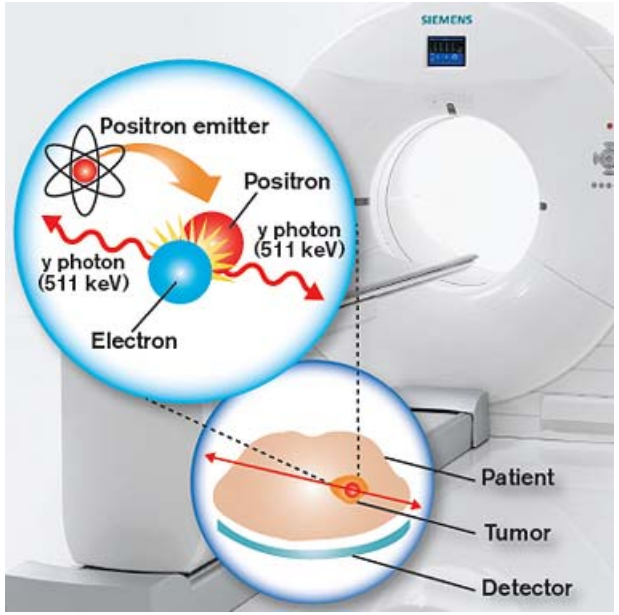
M. Patra, *al*., *Chem. Commun.*, **2014**, *50*, 11523-11525.
D. Vugts, *et al*., *Eur. J. Nucl. Med. Mol. Imag.*, **2017**, *44*, 286-295.
G. Gasser *et al*., EP14160792.9.



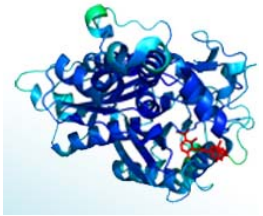
Immuno-PET Imaging

- Produce a 3D image of functional processes in the body.
- System detects pairs of gamma rays emitted indirectly by a positron-emitting tracer.
- β^+-emitter --> annihilation: $e^- + e^+$ --> 2 γ (511 keV)
- ^{68}Ga (68 min), ^{18}F (1.1 h), ^{64}Cu (12.4 h), ^{89}Zr (78.4 h)





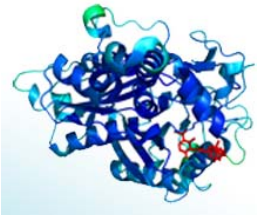
https://upload.wikimedia.org/wikipedia/commons/thumb/4/42/Scintigraphie_osseuse.jpg/330px-Scintigraphie_osseuse.jpg (14.07.2015)
http://www.lifeextension.com/magazine/mag2012/images/jul2012_Value-Of-PET_03.jpg (14.07.2015)
http://www.kavlifoundation.org/sites/default/files/image/resources/Spotlight-Nano-Cancer_PET-Treatment.jpg (14.07.2015)



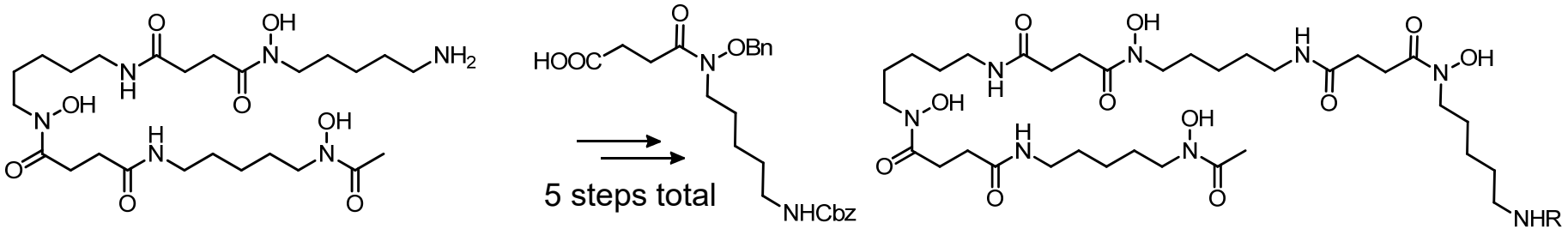
^{89}Zr for Immuno-PET

- ^{89}Zr (22.7% β^+) is an emerging, metallic, non-standard PET radionuclide.
- Physical half-life ($t_{½}$ = 3.3 d) matches the biological half-life of antibodies (Ab).
- Several clinical studies with ^{89}Zr-labeled Ab have demonstrated their potential for immuno-PET.
- Today radiolabeling of Ab is exclusively done with the chelator Desferrioxamine (DFO).
- Incomplete coordination of $^{89}Zr^{4+}$ by DFO leads to *in vivo* instable radioconjugates and **accumulation of the radiometal in sensitive bones** (up to 10-15% i.d./g reported).

G. Fischer, *al*., *Molecules,* **2013**, *18*, 6469-6490.
M.A. Deri, *et al*., *Nucl. Med. Biol.,* **2013**, *40*, 3-14.

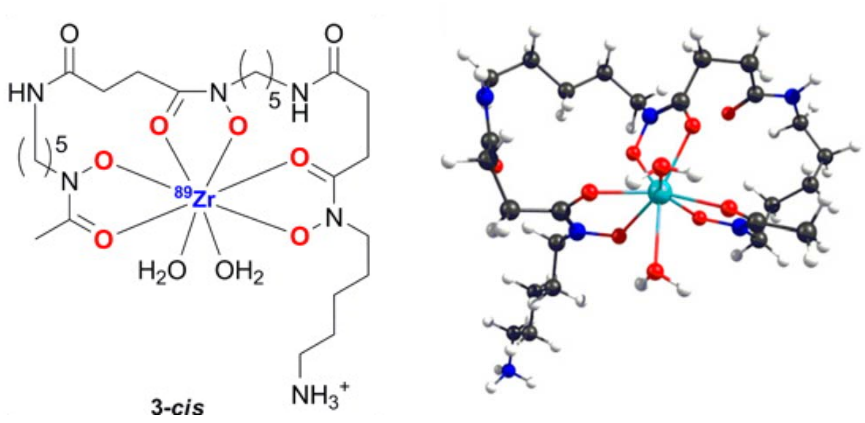


DFO* - A New Octadentate Chelator for $^{89}Zr^{4+}$

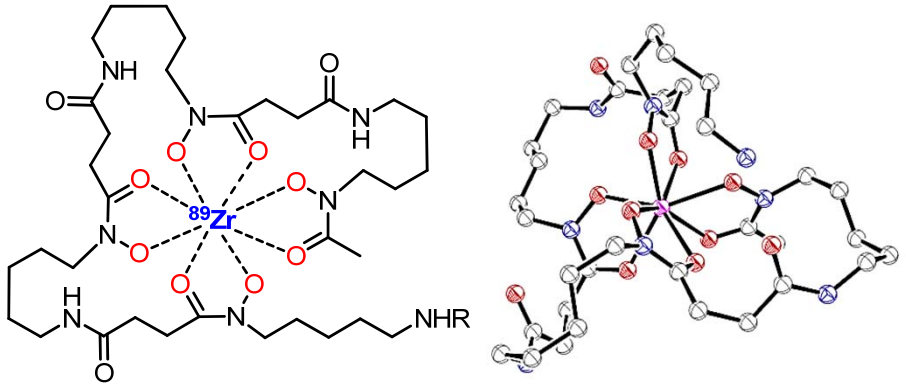


DFO – a **hexa**dentate chelator

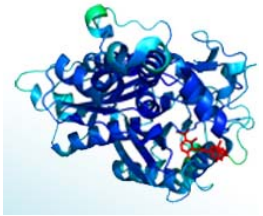
DFO* – an **octa**dentate chelator
(R = $CO(CH_2)_2CO_2H$)



J. P. Holland *et al.*, *J. Nucl. Med.*, **2010**



Gasser, Mindt *et al., Chem Commun.*, **2014**

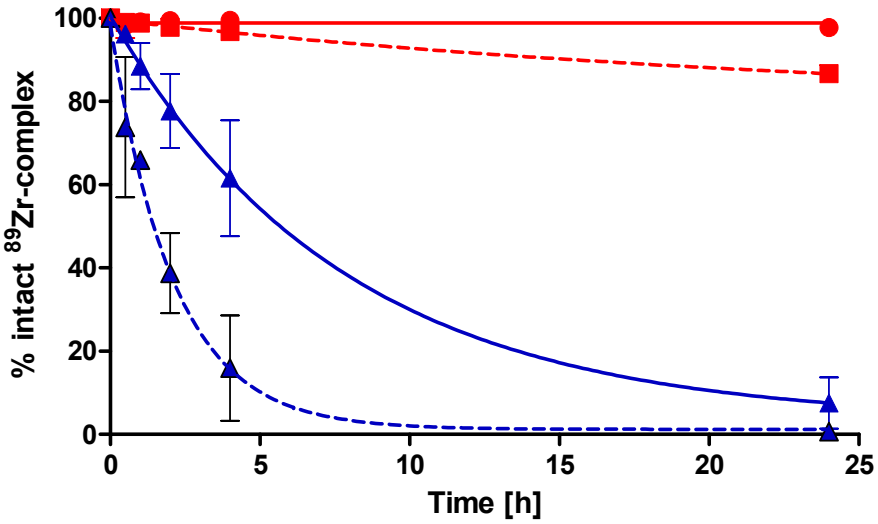


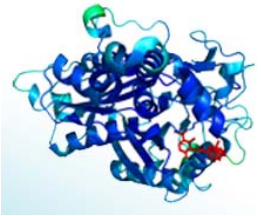
Comparison of the ^{89}Zr Chelators

- DFO* and DFO were coupled to the binding sequence of bombesin BBS(7-14) as tumour-targeting model compound.
- Quantitative radiolabeling with [^{89}Zr]Zr-oxalate was achieved at pH 7 and room temperature with clinically useful specific molar activities of 5-6 GBq/µmol within 60-90 min.

Transchelation experiments

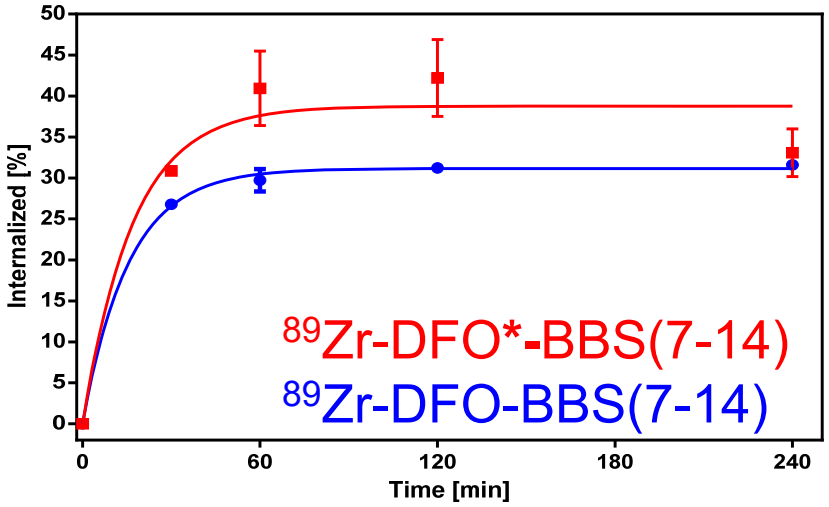
- Transmetallation experiments with 300/3000-fold molar excess of DFO revealed a **remarkable improved stability** of the DFO* complex *in vitro.*



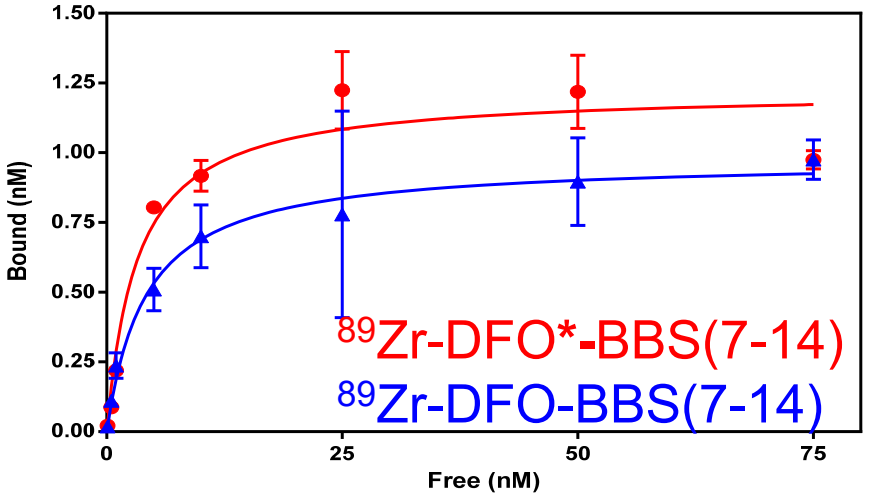


Comparison of the ^{89}Zr Chelators

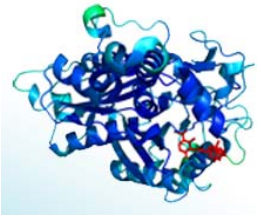
Internalization into PC3 cells



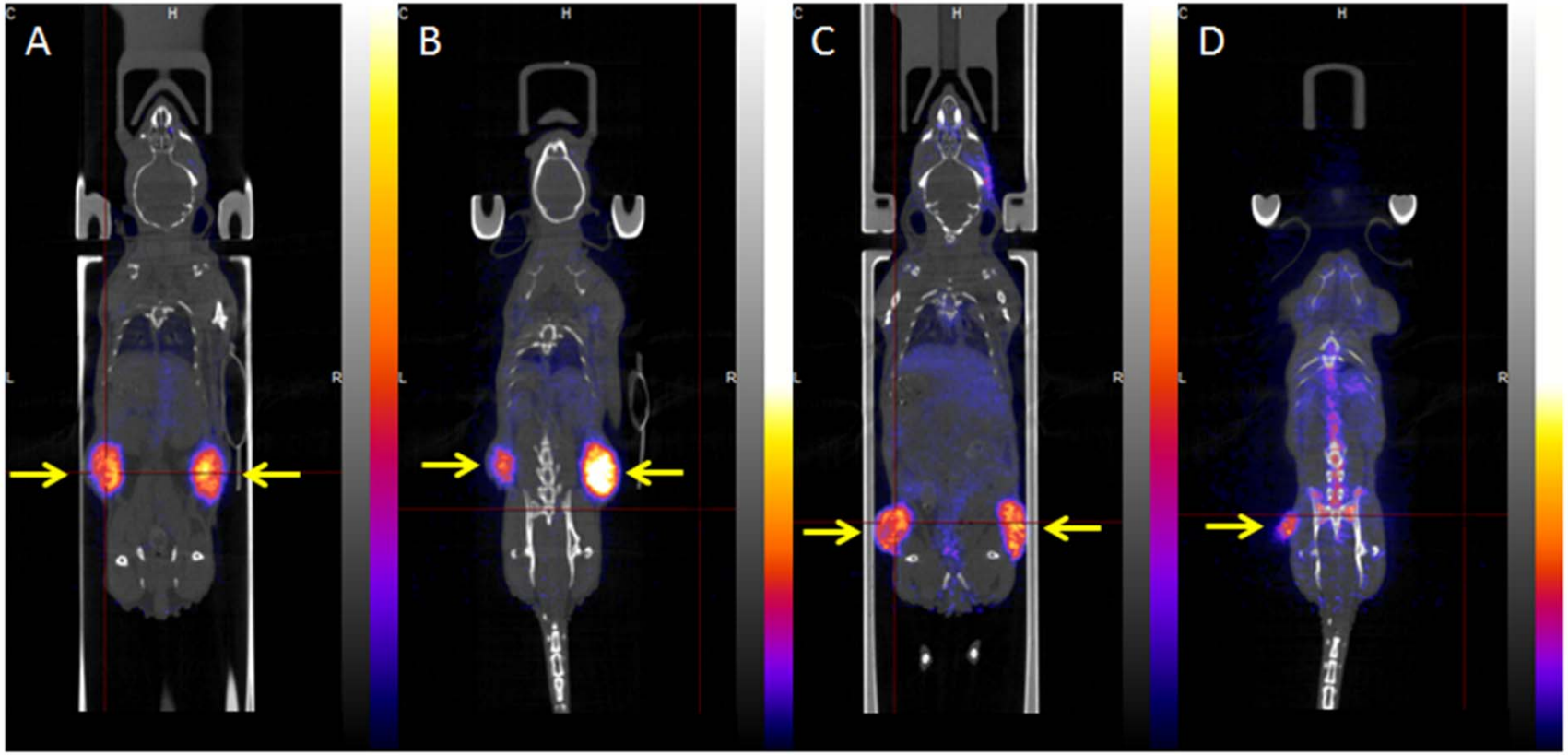
Receptor saturation experiments



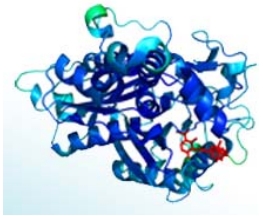
No significant differences between the compounds in terms of cell internalization, GRP receptor binding affinities (3-4 nM), and logP (-1.5).



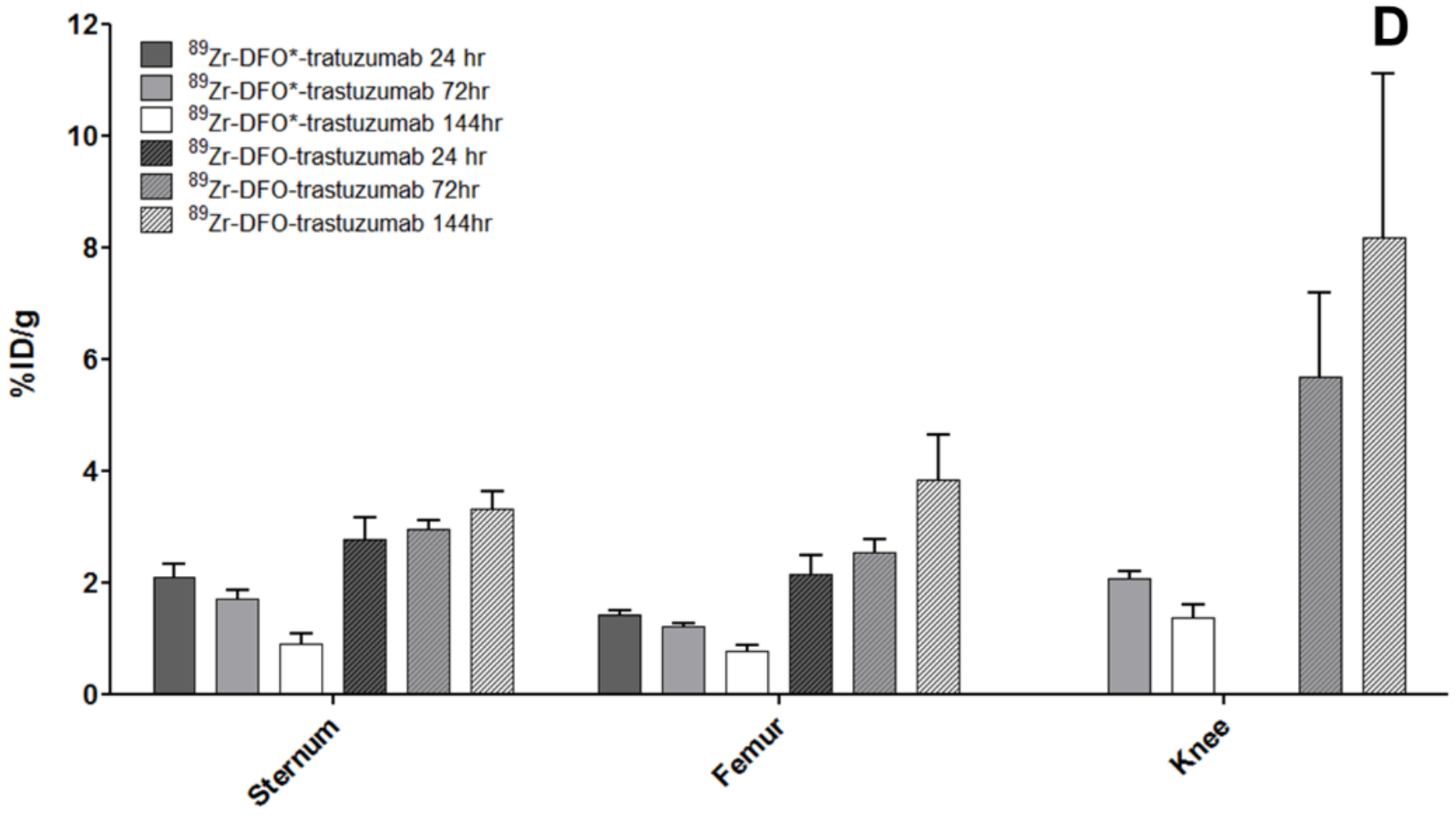
In vivo Studies



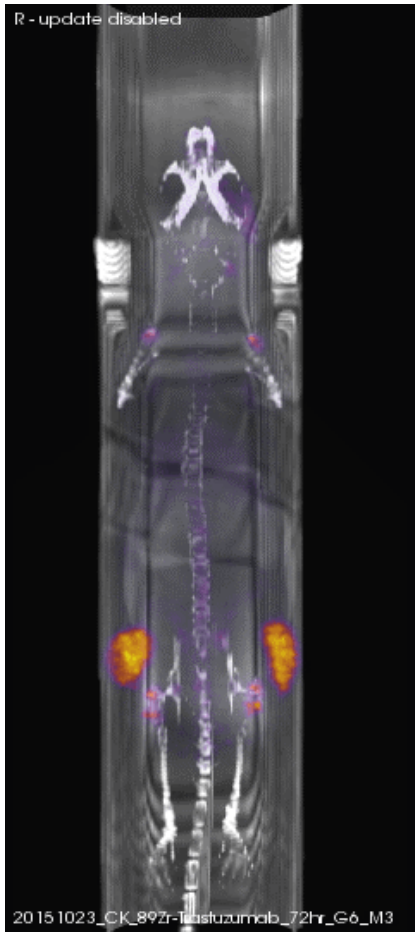
Coronal PET images of N87 tumor bearing nude mice acquired 72 h after injection of either 100 µg, 2 MBq ^{89}Zr-DFO*-trastuzumab (A-B) or ^{89}Zr-DFO-trastuzumab (C-D). A, C: plane at level of tumor; B, D: plane at level of vertebra. Tumors are indicated with a yellow arrow.

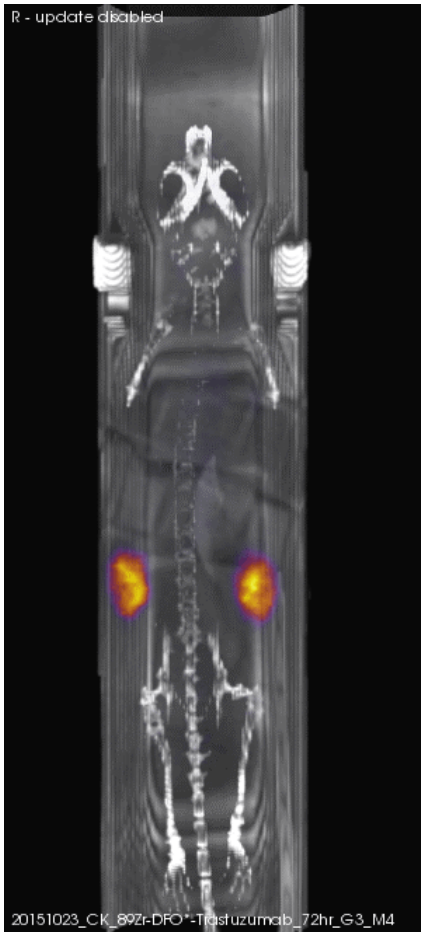


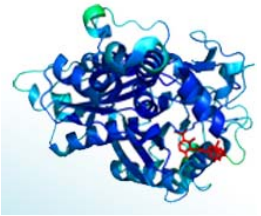
In vivo Studies



In vivo Studies





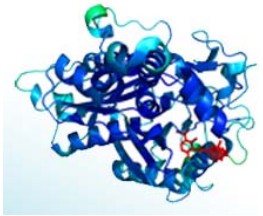


Summary/Perspectives

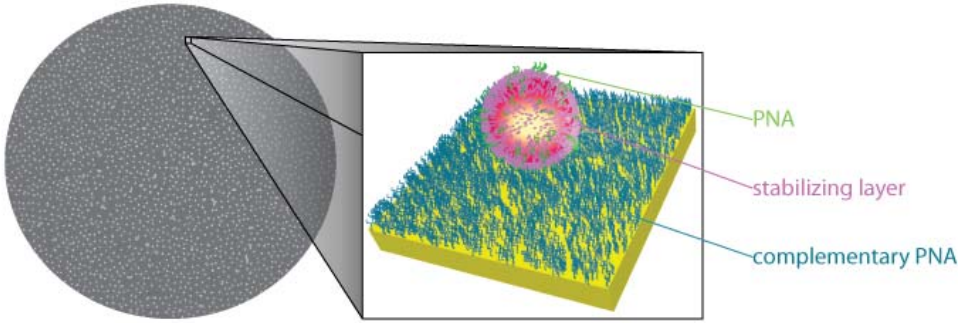
- *In vivo* evaluation of Zr-89 complexes of DFO* attached to an antibody have confirmed our initial assumptions ➔ Less bone accumulation.
- Design and synthesis of a series of bifunctional versions of DFO* for bioconjugation chemistry (maleimde, azide, activated ester, isothiocyanate etc.).
- Design and synthesis of DFO* derivatives with improved water solubility.

➔ ^{89}Zr and DFO* have an enormous potential!

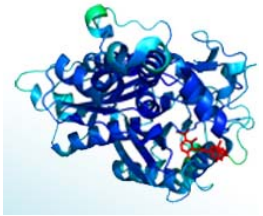
M. Patra, *al*., *Chem. Commun.,* **2014**, *50*, 11523-11525.
D. Vugts, *et al*., *Eur. J. Nucl. Med. Mol. Imag.,* **2017**, *44*, 286-295.
G. Gasser *et al*., EP14160792.9



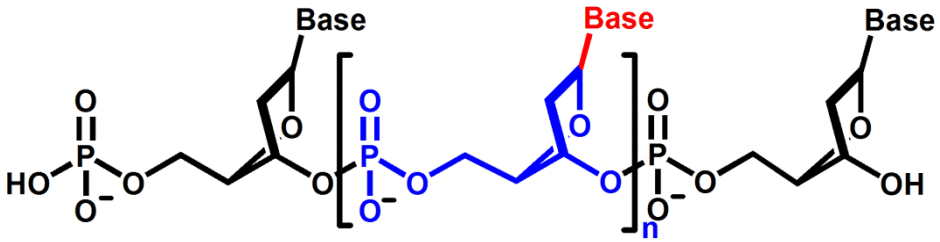
2. Novel Applications for PNAs



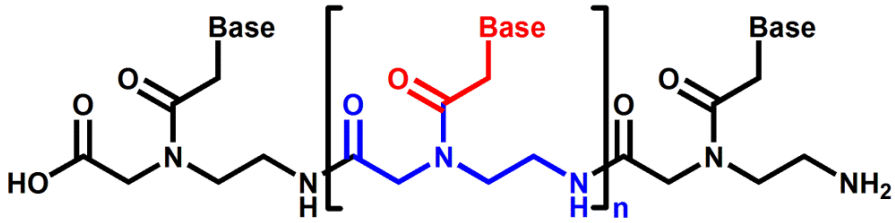
M. Patra, et al., *Chem. Soc. Rev.*, **2016**, *45*, 6415 - 6431
P. Anstaett, *et al., Angew. Chem. Int. Ed.*, **2013**, *52,* 4217-4220.
A. Leonidova, *et al.*, *Chem. Sci.,* **2015**, *6*, 5601-5616.
A. Schmitz, *et al.*, *ChemBioChem*, **2015**, *16*, 1302-1306.
G. Gasser, *et al., J. Inorg. Biochem.*, **2010**, *104*, 1133-1140.
P. Anstaett, *et al.*, *Chimia*, **2014**, *68*, 264-268.



Peptide Nucleic Acids (PNAs)



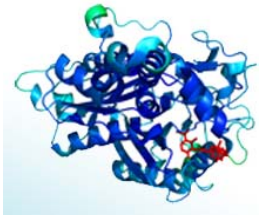
DNA



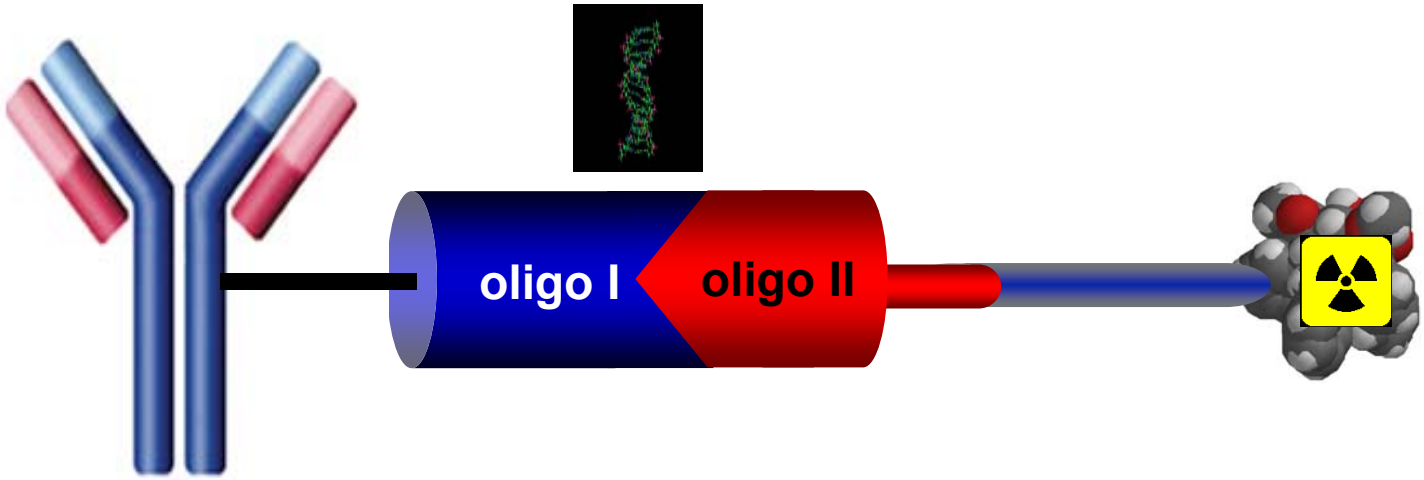
PNA

- PNA-DNA duplex more stable than DNA-DNA duplex
- Higher sensitivity to single base mismatch
- Faster hybridisation
- Stable to nucleases
- Automated synthesis
- Antisense/Antigene therapy

P.E. Nielsen *et al.*, *Science* **1991**, *254*, 1497-1500.



Principle of the Pretargeting Approach



non-radioactive mAb

large, slow distribution, clearance and binding

complementary oligonucleotides I, II

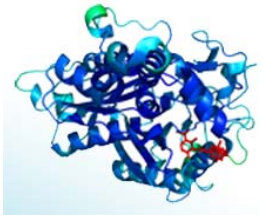
radionuclide/ chelator

small, fast blood and body clearance

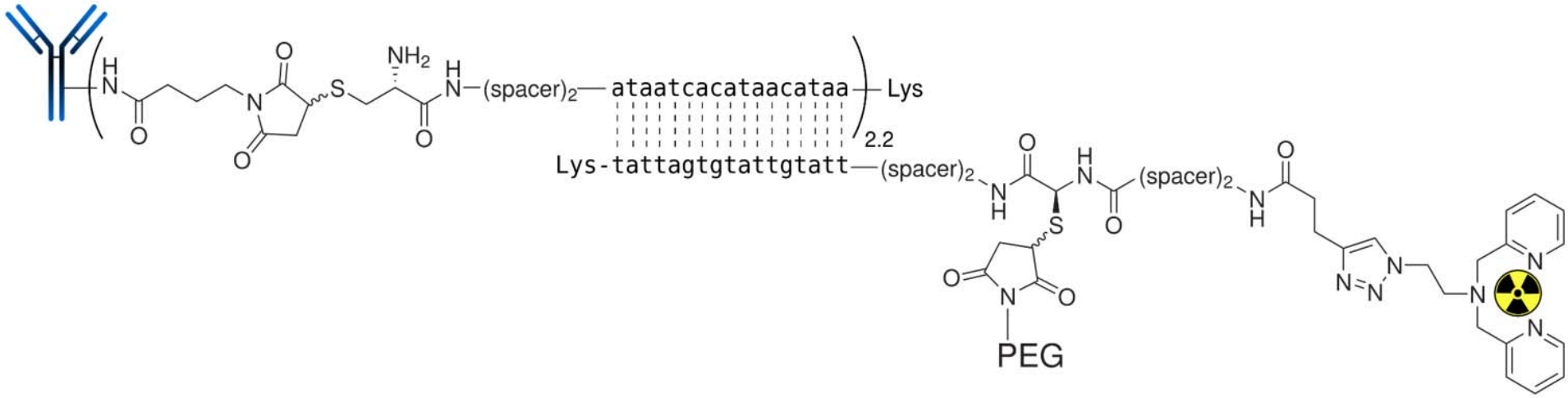
1. Step → **1–3 days** → **2. Step**

IMAGING/DESTRUCTION OF CELLS BY RADIATION

Y. Wang, *et al*. *Bioconjug. Chem.* **2001**, *12*, 807-816



Design - Synthesis



Does it work?

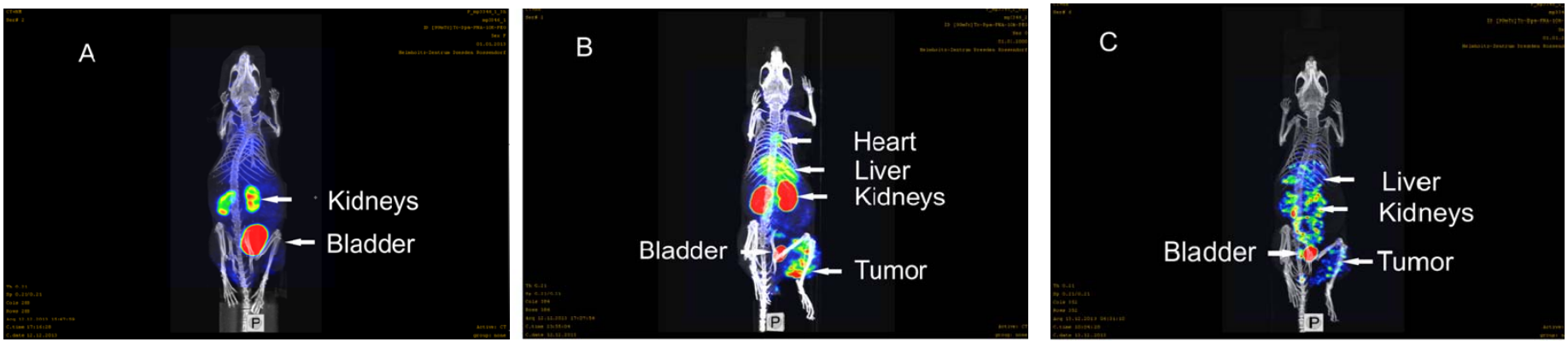
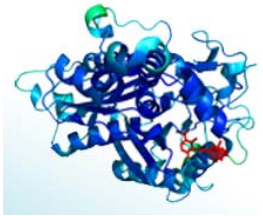
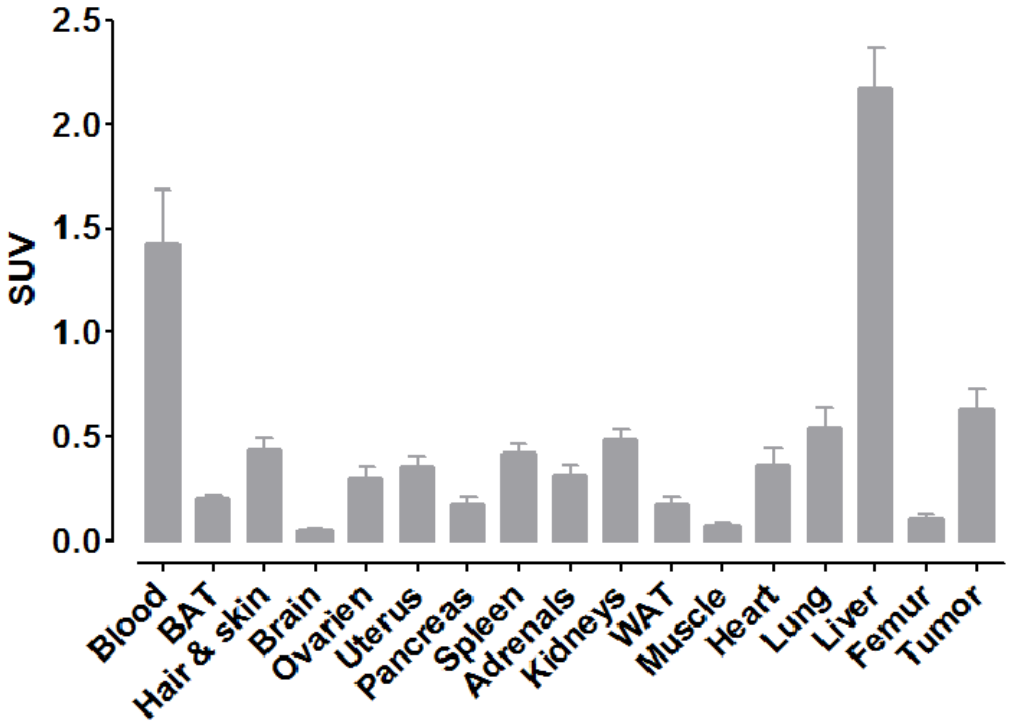


Figure 4: SPECT/CT maximum intensity projection images of **[^{99m}Tc](Tc-Dpa)-(Cys-PEG$_{10kDa}$)-PNA** in murine A431 tumor xenograft (NMRI nu/nu mice; tumor located at right thigh). (A) 1 h post injection of **[^{99m}Tc](Tc-Dpa)-(Cys-PEG$_{10kDa}$)-PNA** without preinjection of **(NOTA)$_3$-C225-Cys-c-PNA**. (B) 1 h post injection of radiotracer; **(NOTA)$_3$-C225-Cys-c-PNA** was administered 24 h before injection of radiotracer. (C) 20 h post injection of radiotracer; **(NOTA)$_3$-C225-Cys-c-PNA** was administered 24 h before injection of radiotracer.

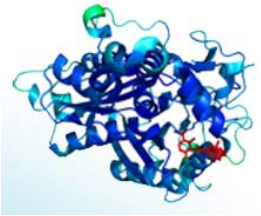


Does it work?

Blood	1.42 ± 0.75
Kidneys	0.48 ± 0.16
Adrenals	0.32 ± 0.14
Liver	2.18 ± 0.11
Spleen	0.42 ± 0.12
Pancreas	0.18 ± 0.10
Muscles	0.08 ± 0.03
Lung	0.55 ± 0.26
Heart	0.36 ± 0.24
Femur	0.11 ± 0.05
Brain	0.05 ± 0.03
Tumor	0.63 ± 0.27
Tumor/Muscle	**8.29 ± 1.28**
Tumor/Blood	**0.48 ± 0.09**



A. Leonidova, *et al*., *Chem. Sci*., **2015**, *6*, 5601-5616.

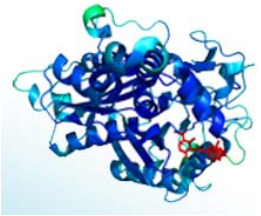


Summary

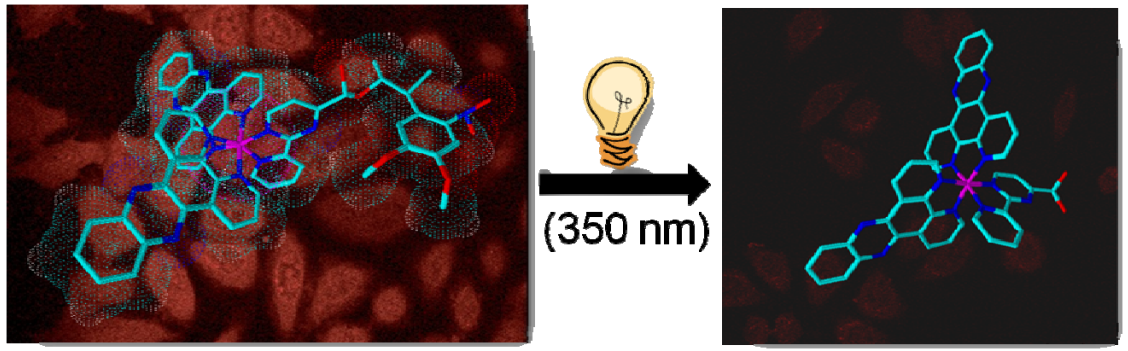
- Use of PNA bioconjugates in a pretargeting approach to image tumours is very promising.
- Much more work is required since a lot of parameters play a role.
- Funding is required...

➔ PNAs have an enormous potential!

P. Anstaett, *et al., Angew. Chem. Int. Ed.*, **2013**, *52,* 4217-4220.
A. Leonidova, *et al.*, *Chem. Sci.,* **2015**, *6*, 5601-5616.
A. Schmitz, *et al.*, *ChemBioChem*, **2015**, *16*, 1302-1306.
G. Gasser, *et al., J. Inorg. Biochem.*, **2010**, *104*, 1133-1140.
P. Anstaett, *et al.*, *Chimia*, **2014**, *68*, 264-268.

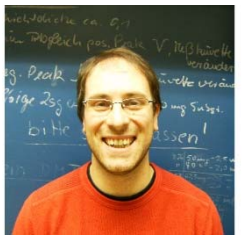


3. Photoactivation of Metal Complexes

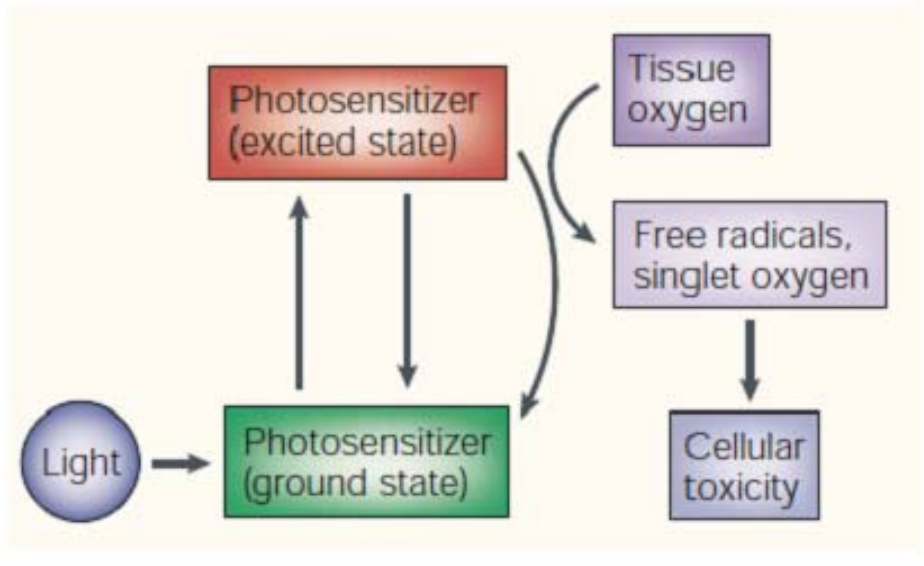


IC_{50} scale

H. Huang *et al*., **2015**, *Angew. Chem. Int. Ed*., **2015**, *54*, 14049-14052 (VIP Article).
T. Joshi, V. Pierroz *et al*., *Angew. Chem. Int. Ed*., **2014**, *53*, 2960-2963.
A. Naik, R. Rubbiani *et al*., *Angew. Chem. Int. Ed*., **2014**, *53*, 6938-6941.
C. Mari, V. Pierroz, *et al., Chem. Sci.,* **2015**, *69*, 2660-2686.
A. Leonidova, V. Pierroz, R. Rubbiani *et al., Chem. Sci.,* **2014**, *5*, 4044-4056.
C. Mari, V. Pierroz, *et al., Chem. Eur. J*., **2014**, *44*, 14421-14436.
I. Kitanovic , A. Leonidova *et al*., *Chem. Eur. J*., **2014**, *20*, 2496-2507.
A. Frei, R. Rubbiani *et al*., *J. Med. Chem*., **2014**, *57*, 7280-7292.
A. Leonidova, P. Anstaett *et al., Inorg. Chem*., **2015**, *54*, 9740-9748.
A. Leonidova, C. Mari, *et al*., *Organometallics,* **2016**, *5*, 851-854.
A. Leonidova, V. Pierroz *et al., Dalton Trans.,* **2014**, *43*, 4287-4294.
P. Anstaett, V. Pierroz *et al., Photochem. Photobiol. Sci*., **2015**, *14*, 1821-1825.
T. Joshi, V. Pierroz *et al*., *ChemMedChem,* **2014**, *9*, 1419-1427.
P. Anstaett, A. Leonidova *et al*., *ChemPhysChem,* **2015**, *16*, 1857-1860.
P. Anstaett, A. Leonidova *et al*., *ChemPhysChem,* **2015**, *16*, 1863-1866.
T. Joshi *et al*., *Synlett*, **2015**, *26*, 275-284.
W.I. O'Malley, R. Rubbiani, *et al., Molecules,* **2016**, *21*, 194.



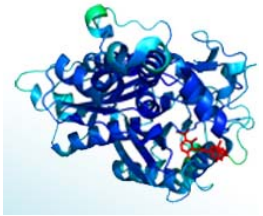
Photodynamic Therapy (PDT)



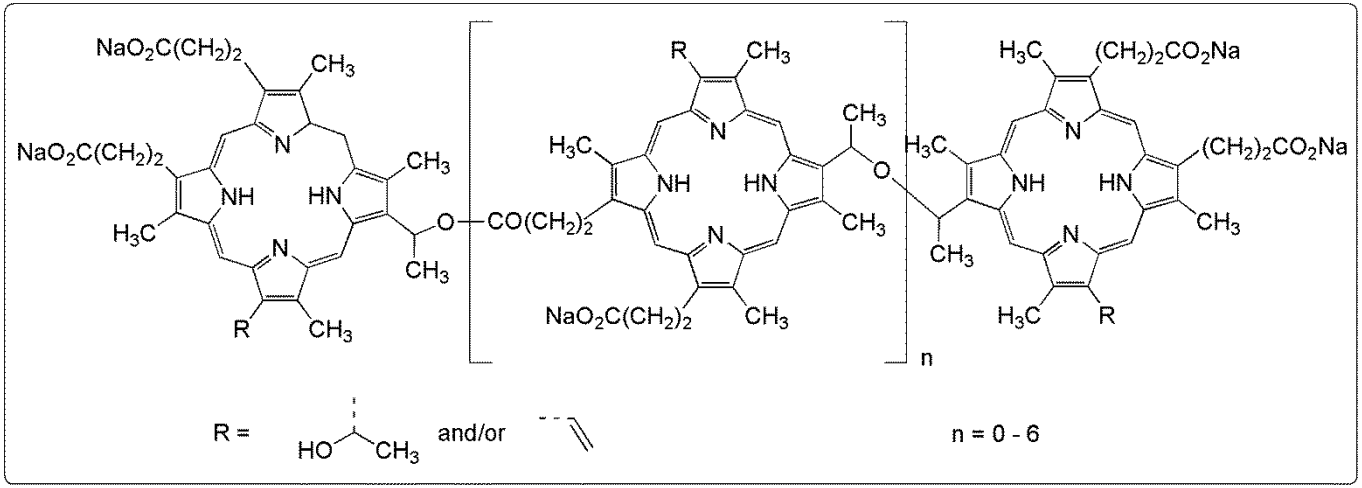
Used to treat skin, prostate, brain, head & neck and gastro-intestinal cancers

Enormous potential to treat infections (e.g. sinusitis)

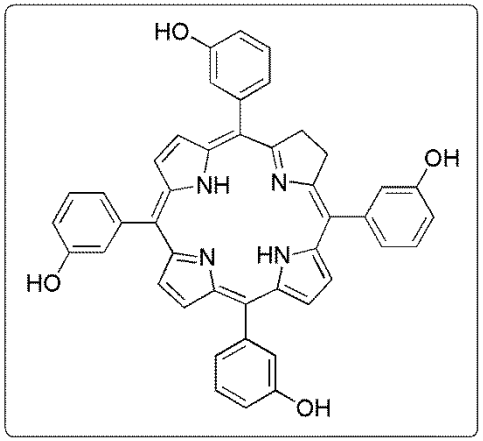
D.E.J.G.J. Dolmans, D. Fukumura and R.K. Jain, *Nat. Rev. Cancer,* **2003**, *3,* 380-387.



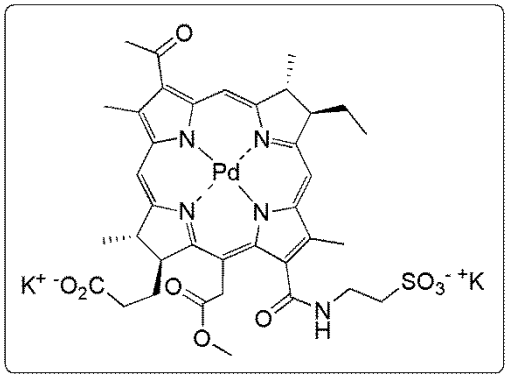
PDT Photosensitizers



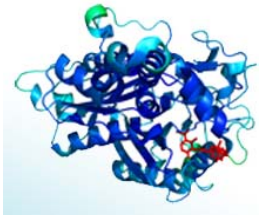
Photofrin



Foscan



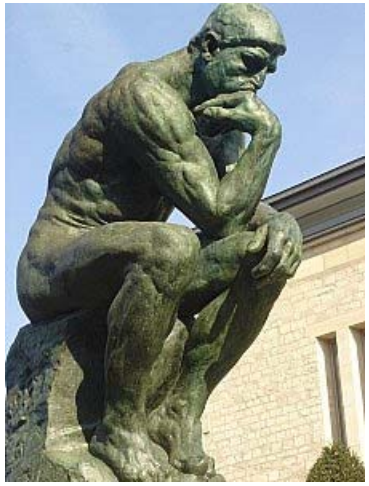
Tookad



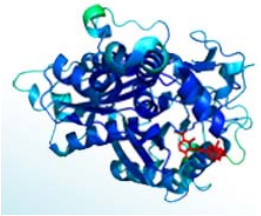
Drawbacks of the current PDT Photosensitizers

1) Poor water solubility.
2) Tedious synthesis.
3) Low excretion metabolism leading to photosensitivity.
4) Low cancer cell selectivity.

Is it possible to prepare novel PDT photosensitizers without relying on porphyrin-based agents?

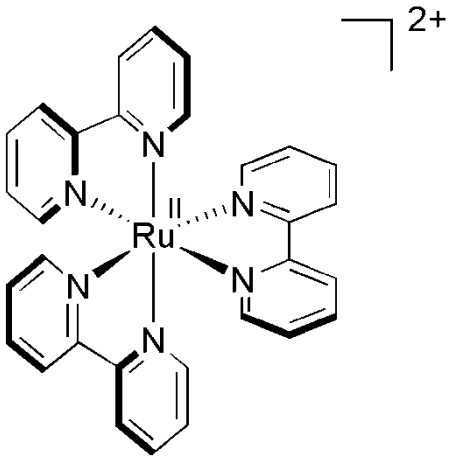


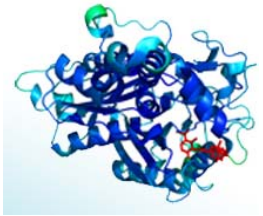
Ru(II) Polypyridyl Complexes



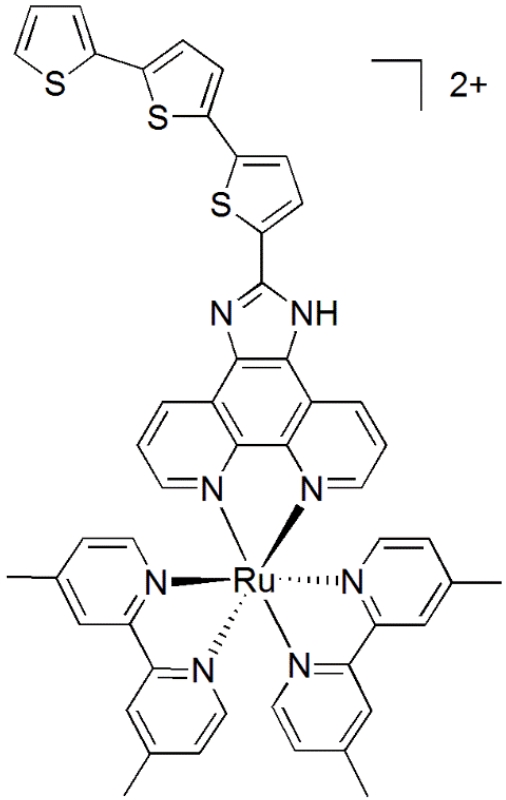
Why Ruthenium Polypyridyl Complexes?

1) Can produce $^1O_2$.
2) No photobleaching.
3) Easy synthesis.
4) High water solubility.
5) Inert compounds.
6) No toxicity.
7) Relatively cheap.





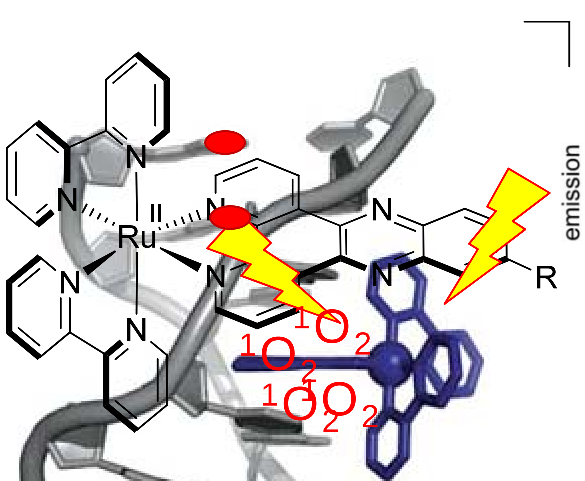
Importantly!



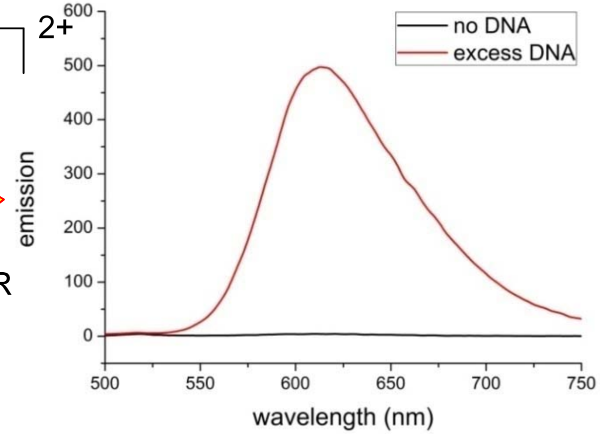
TLD-1433

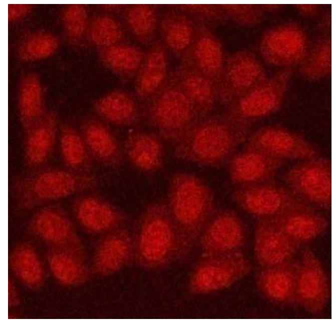
https://clinicaltrials.gov/ct2/show/study/NCT03053635?term=tld-1433&rank=1.

Ru-dppz Complexes as PS

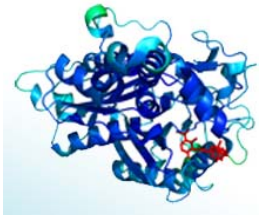


R = NH_2 **1**
OMe **2**
OAc **3**
OH **4**
CH_2OH **5**
CH_2Cl **6**





C. Mari, V. Pierroz, et al., Chem. Eur. J. 2014, 14421-14436.
J. Barton et al., J. Am. Chem. Soc. 1990, 112, 4960-4962.



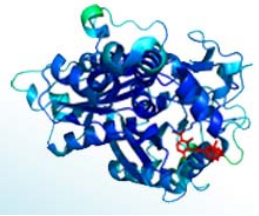
Cyto- and Phototoxicity Evaluation

IC_{50} μM		1	2	3	4	5	6	cisplatin
MRC-5[a]		>100	>100	>100	>100	>100	>100	16.8 ±1.8
HeLa	Dark[a]	>100	>100	>100	>100	>100	>100	8.9 ±2.6

[a)] 48 h incubation. [b)] 4 h incubation, light dose 2.58 J·cm^{-2}. [c)] 4 h incubation, light dose 9.27 J·cm^{-2}.

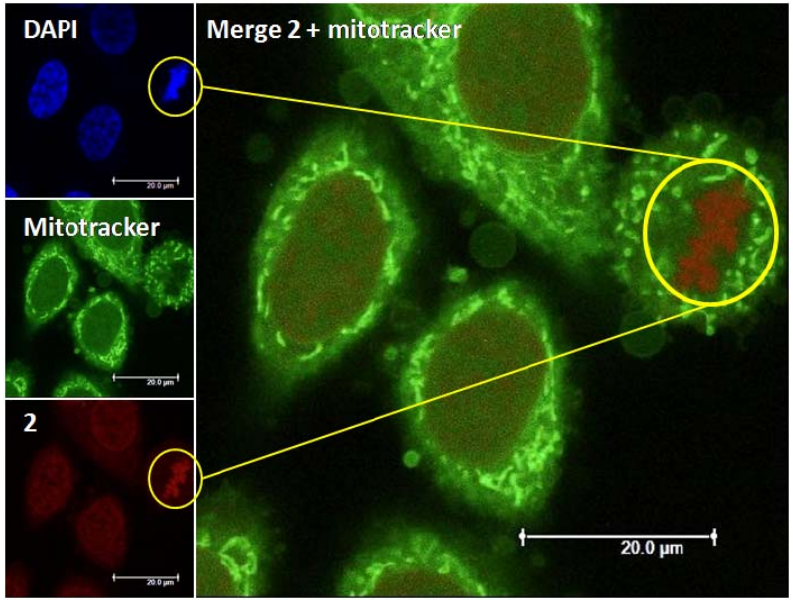
Photofrin® IC_{50}light = 4.3 μM, PI >10, @400-650nm, 5 J/cm^2.

E. Delaey *et al., J. Photochem. Photobiol. B*, **2000**, *55*, 27-36.



Cellular Localization and Uptake

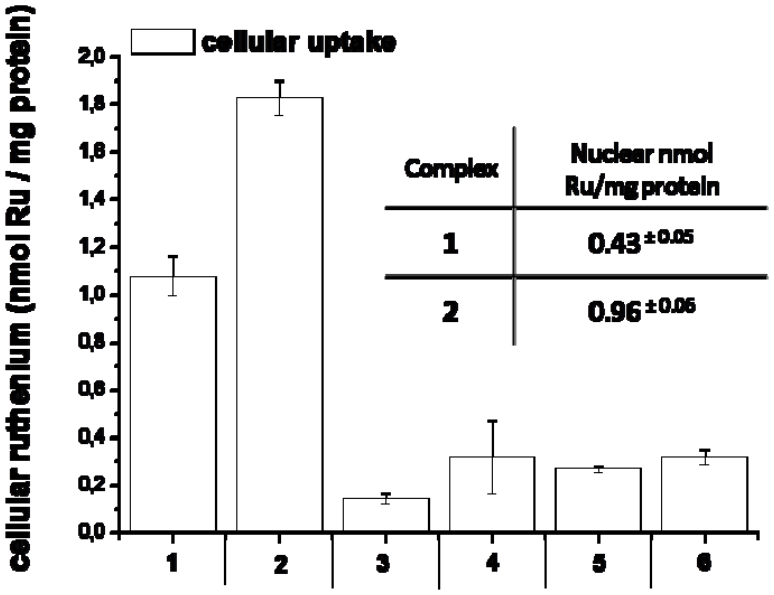
Cellular localization of complex **2** from luminescence microscopy on HeLa cells.



HeLa cells treated with **2** (100 µM), 2 h incubation.

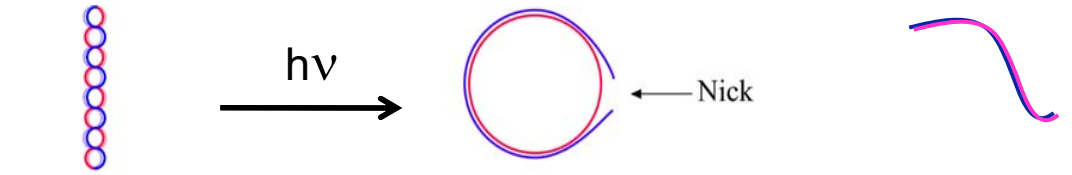
Weak luminescence for **1**.

Cellular uptake from HR-CS AAS analysis on HeLa cells treated with the ruthenium complexes. In the inset: nuclear uptake for complexes **1** and **2**.

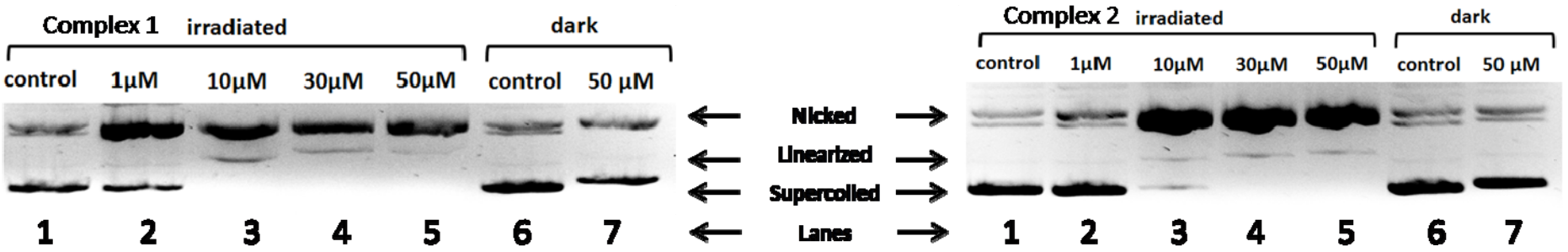


HeLa cells treated with the complexes (20 µM), 4 h incubation.

DNA Photocleavage at 420 nm



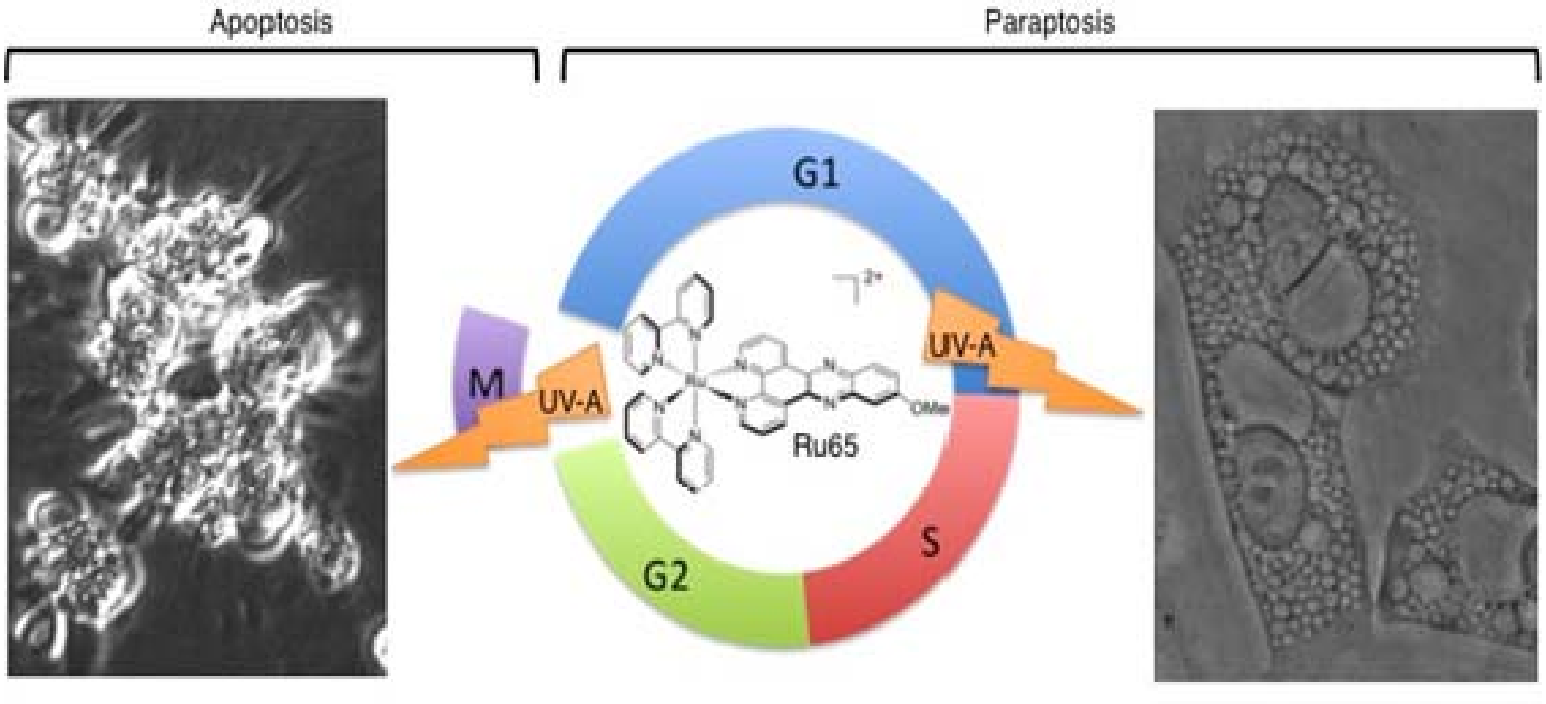
Supercoiled Open circular Linearized



pcDNA3 plasmid untreated and irradiated for 20 minutes at 420 nm (lanes 1); plasmid treated with **1** (left) and **2** (right) at different concentrations and irradiated (lanes 2-5); plasmid untreated in the dark (lanes 6); plasmid treated with **1** (left) and **2** (right) at 50 μM in the dark (lanes 7).

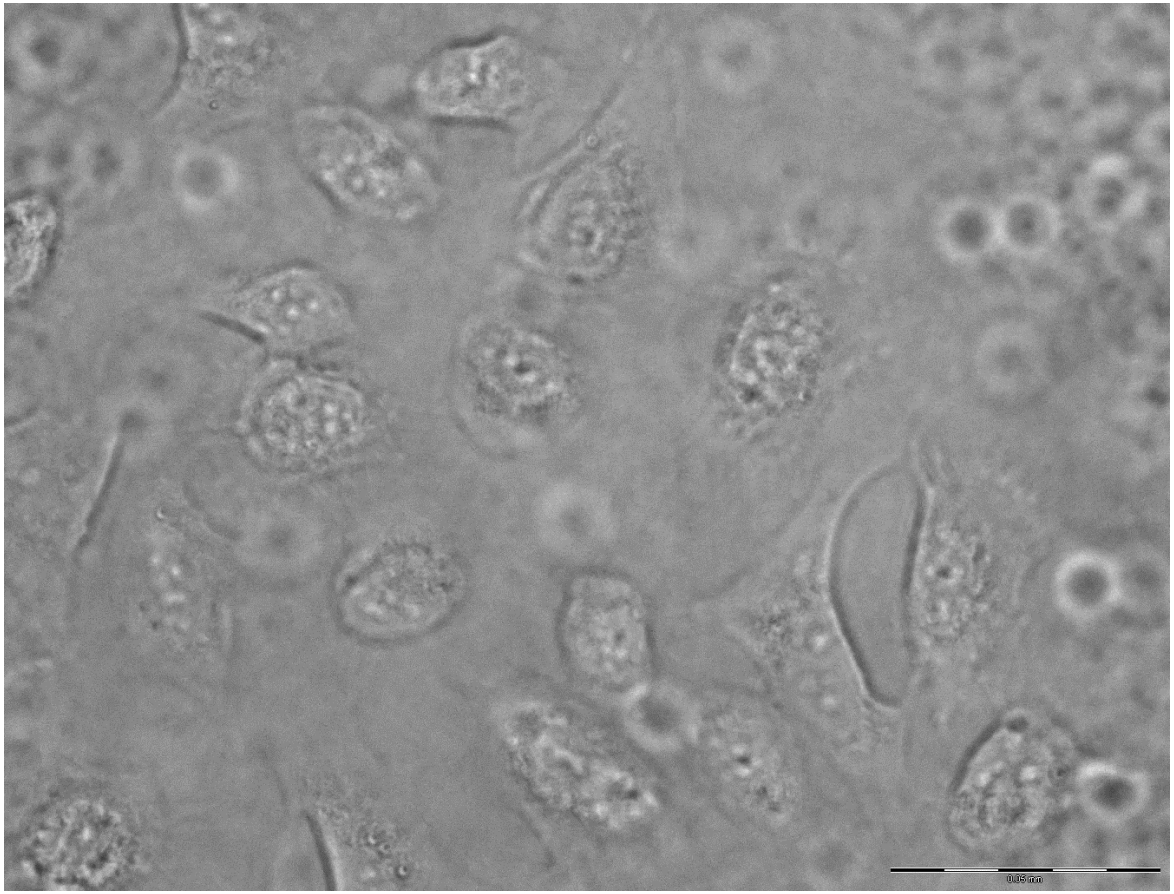
C. Mari, V. Pierroz, *et al., Chem. Eur. J.*, **2014**, *44*, 14421–14436.

In-Depth Biology

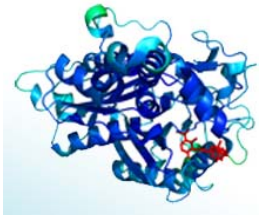


V. Pierroz, *et al., Chem. Sci.*, **2016**, *7*, 6115-6124.

In-Depth Biology



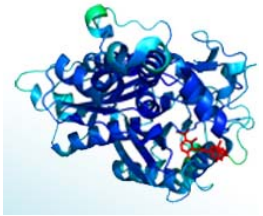
V. Pierroz, *et al., Chem. Sci.*, **2016**, *7*, 6115-6124.



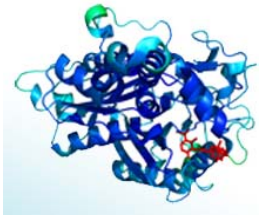
Main Conclusion

UV-A irradiation of Ru65 in cells synchronized by G2/M block-release with a selective CDK1 inhibitor led to blocking mitotic entry and rapid cell death through classic apoptotic pathways. Importantly, targeting mitotic cells with Ru65 allowed increasing its photo-toxicity by a factor of 3.6. Overall, our findings show that the use of a combination of a cell cycle inhibitor and a PS targeting the nucleus could open new avenues in PDT.

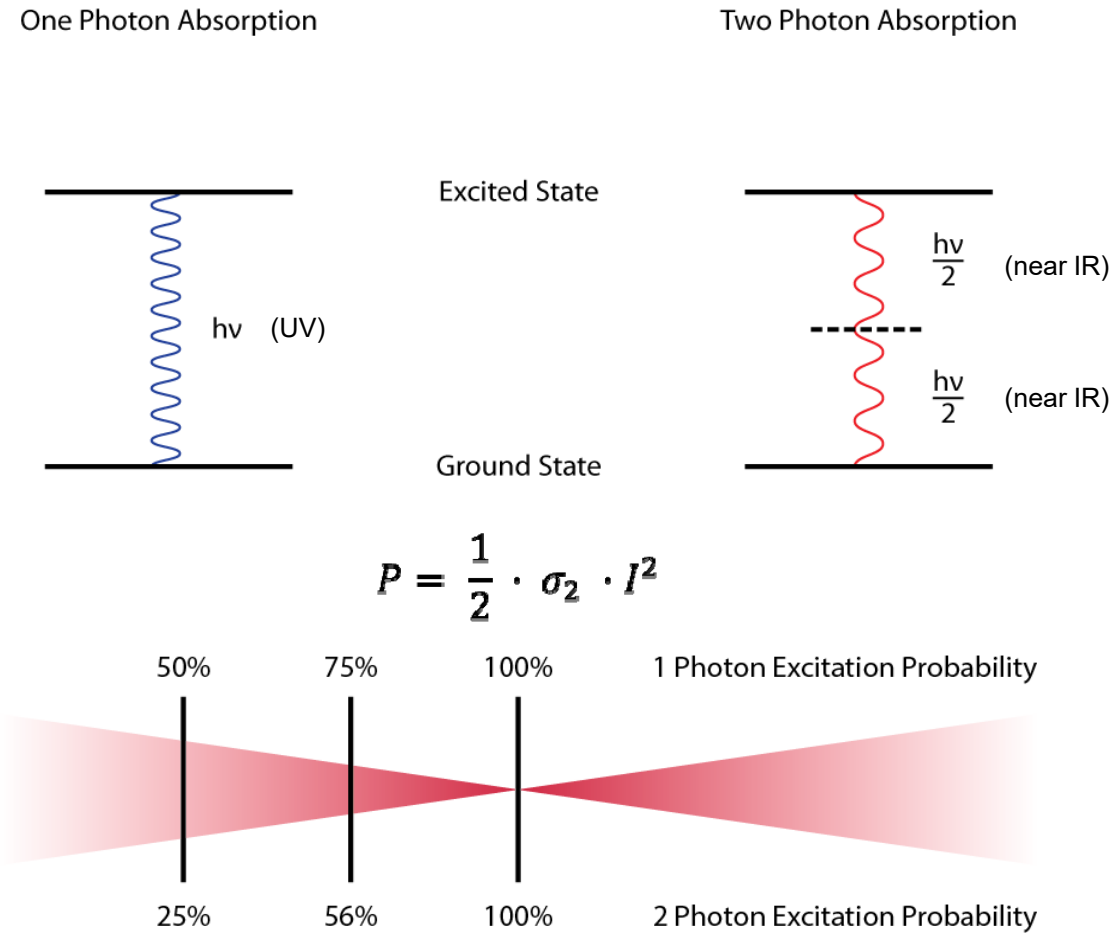
V. Pierroz, *et al., Chem. Sci*., **2016**, *7*, 6115-6124.

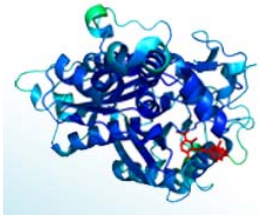


Can we do better?

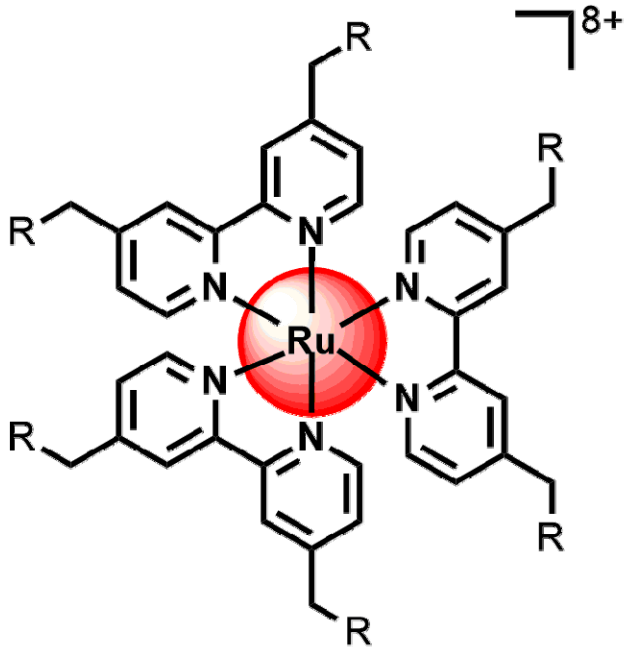


Two-Photon PDT





Two-Photon Photosensitizers

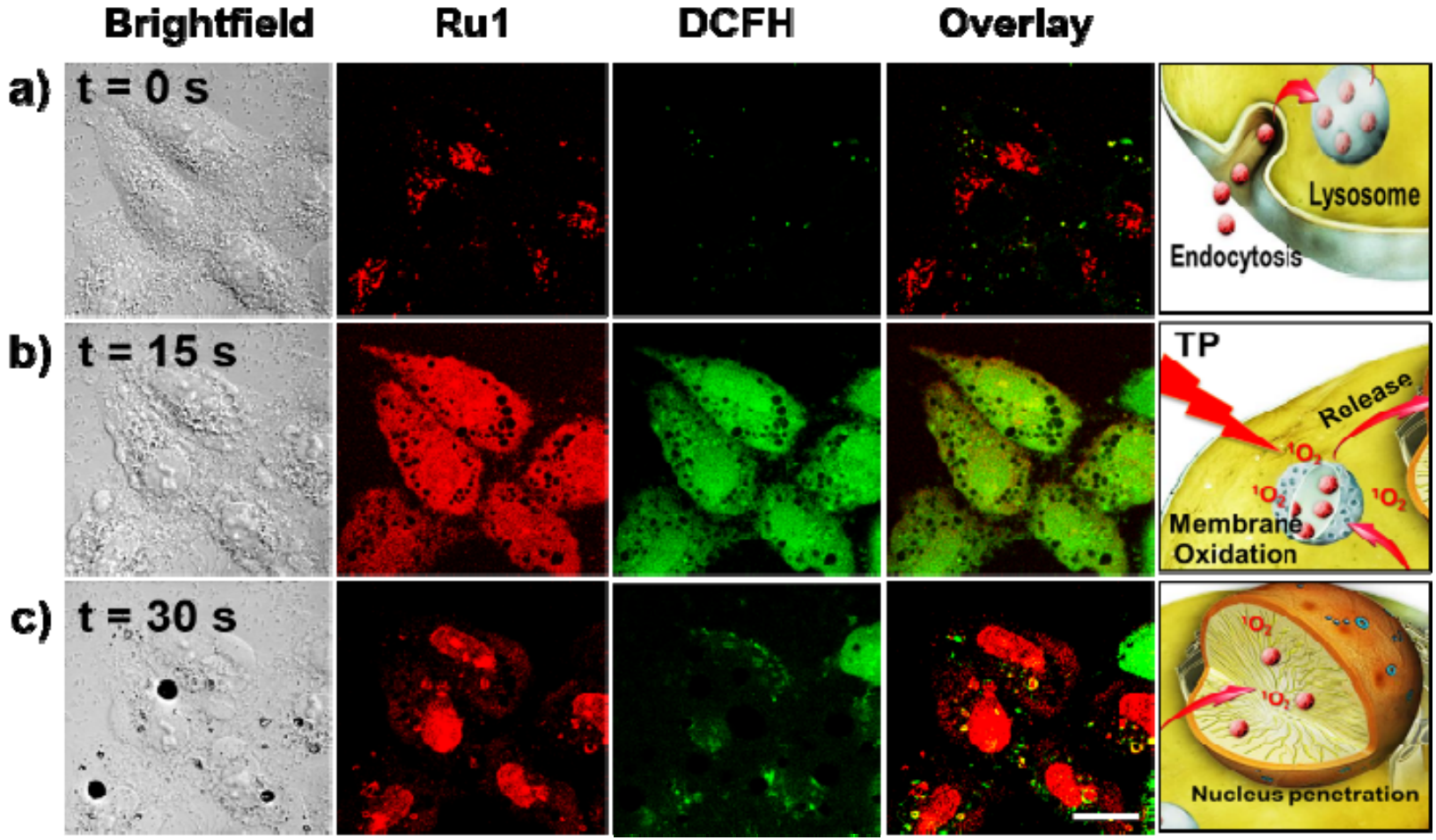


$R_1 = N(CH_3)_3$

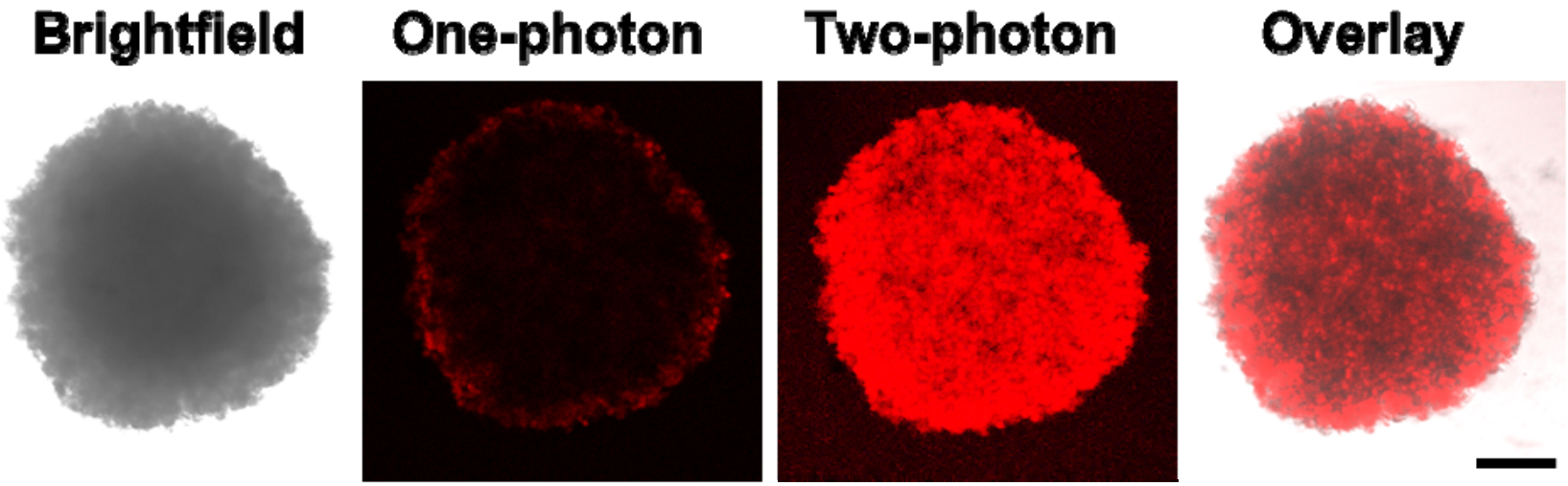
$R_2 = N(CH_2CH_3)_3$

$R_3 = N(CH_2CH_2CH_2CH_3)_3$

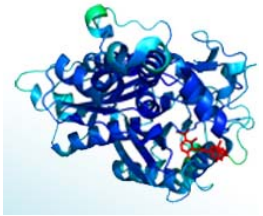
Cellular Relocalization



Biology on Spheroids



H. Huaiyi *et al*., *Angew. Chem. Int. Ed*., **2015**, *54*, 14049-14052 (VIP Article).



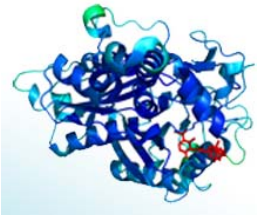
Conclusions & Perspectives

- Killing of cancer cells and bacteria could be achieved using low irradiation doses.
- High PI.
- Two-photon irradiation can be envisaged as an irradiation technique.

➔ Metal complexes have an enormous potential in PDT

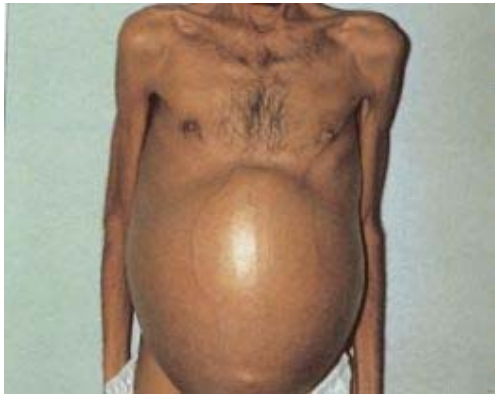
4. Towards Novel Organometallic Antischistosomal Drug Candidates

M. Patra, K. Ingram *et al*., *J. Med. Chem.* **2012**, *55*, 8790.
M. Patra, K. Ingram *et al*., *Chem. Eur. J.* **2013**, *19*, 2232.
M. Patra, K. Ingram *et al*., *J. Med. Chem.* **2013**, *56*, 9192.
J. Keiser *et al*., *Parasites & Vectors*, **2014**, *7*, 424.
J. Hess *et al.*, *Future Med. Chem*., **2015**, *7*, 821.
S. Clède *et al., ChemBioChem,* **2016**, *17*, 1004-1007.
J. Hess *et al*., **2017**, *submitted*.

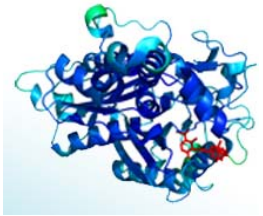


Schistosomiasis

- Parasitic disease caused by trematodes of the genus *Schistosoma*.
- Major health problem worldwide, particularly in tropical regions where up to 280,000 deaths are reported annually.
- More than 207 million people, mostly in Africa, are infected and nearly 800 million are at risk of being infected.

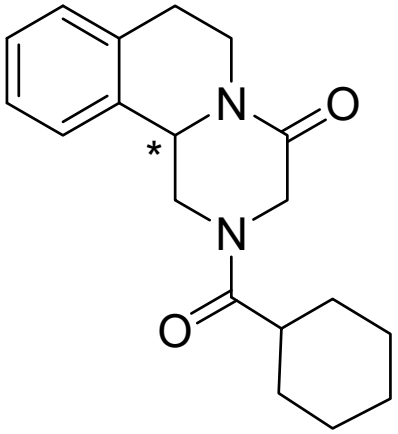


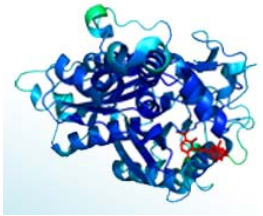
D.L. Williams *et al*., *Nat. Med.,* **2008,** 14, 407.
M.-S. Jiang, *Parasites & Vectors,* **2011,** 4, 201.



Praziquantel I

- THE anthelmintic!
- Widely used, as a racemic mixture, to control this infection in human as well as in animals.
- Treats infections caused by worms belonging to all species of Schistosoma (e.g. *S. mekongi*, *S. japonicum*, *S. mansoni*, and *S. hematobium*).



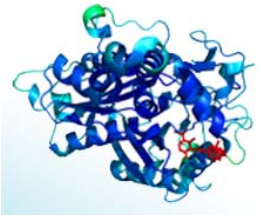


Praziquantel II

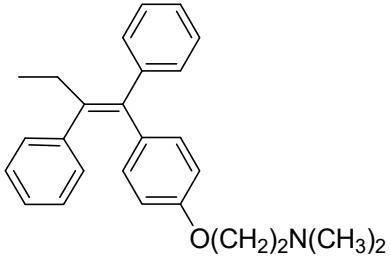
BUT

- Not active against the juvenile stage of the parasite.
- Low metabolic stability.
- Over-consumption of PZQ could lead to an emergence of PZQ resistant parasites in the near future.

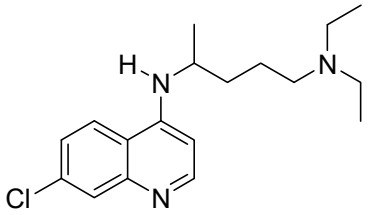
➔ **Discovery of novel drug candidates desired.**



Organometallic Derivatization

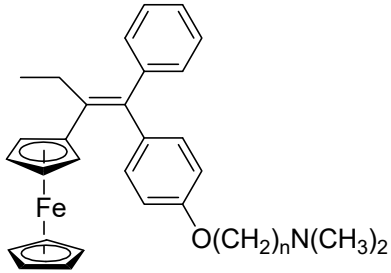


Tamoxifen

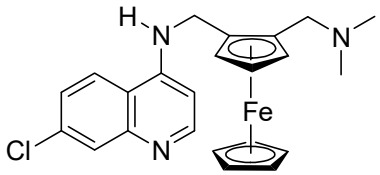


Chloroquine

Organometallic Derivatization

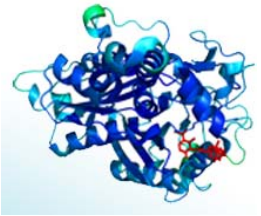


Ferrocifens (n=2,3,4,5,8)

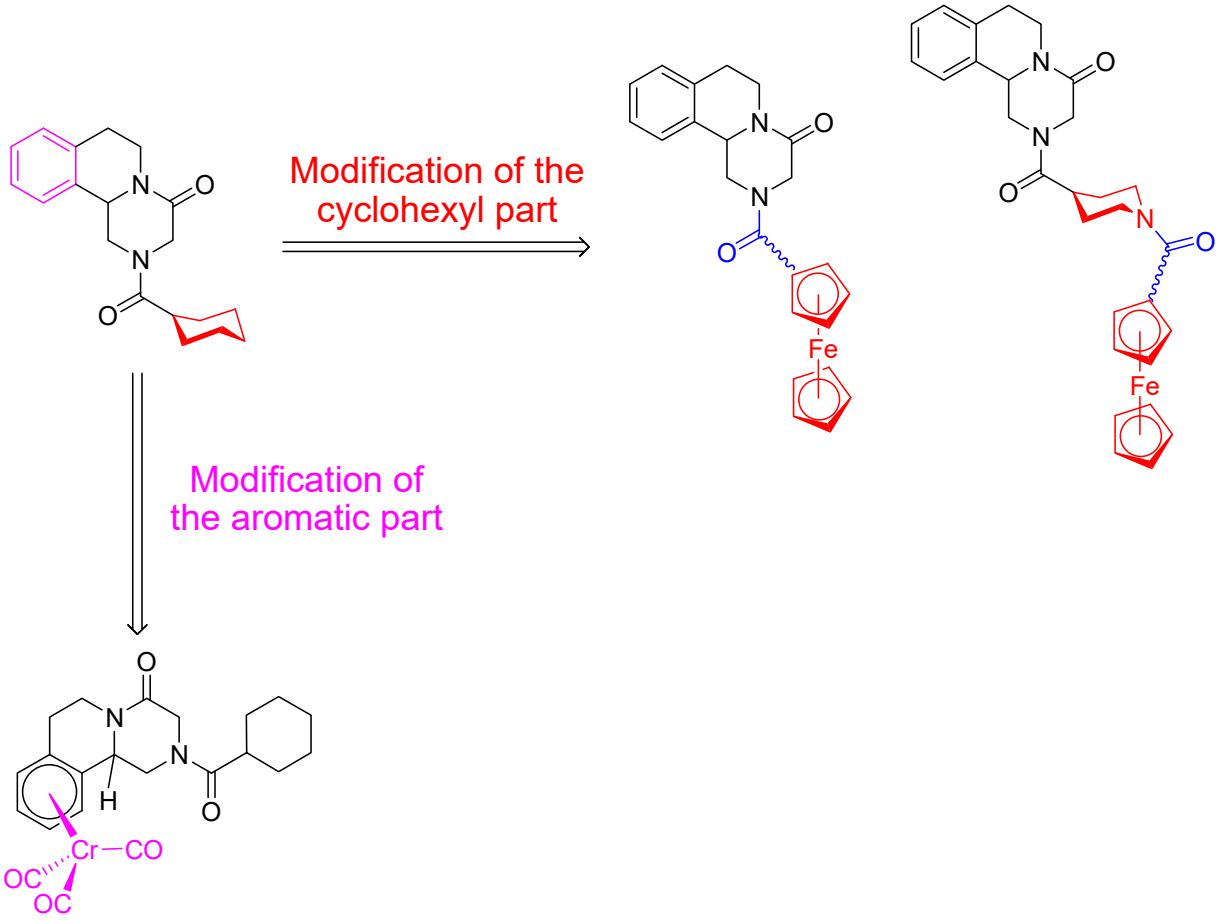


Ferroquine

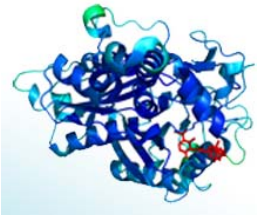
J. Brocard *et al.*, *J. Med. Chem.,* **1997**, *40*, 3715.
G. Jaouen *et al.*, *Curr. Med. Chem.*, **2004**, *11*, 2505.



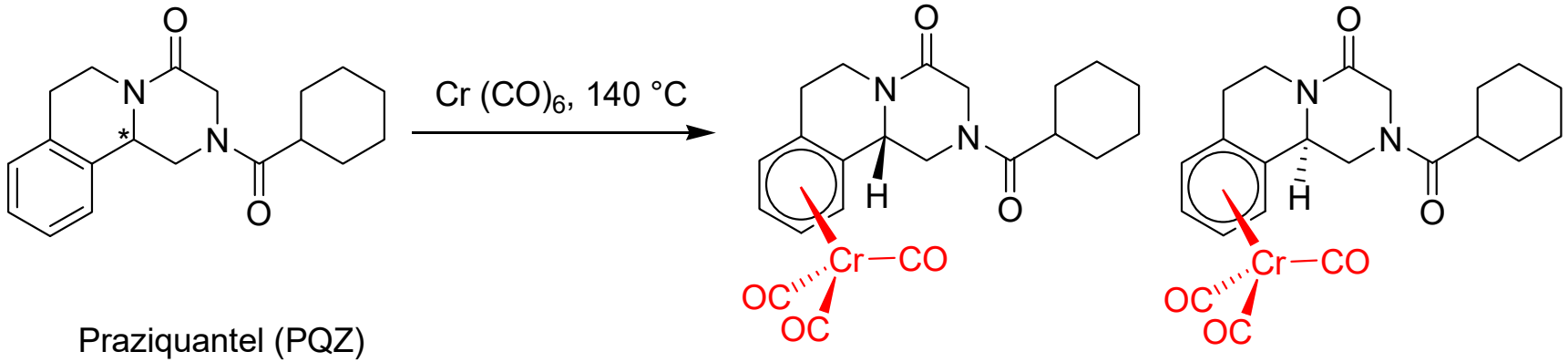
Let‘s go Chromium



G. Jaouen *et al*., *J. Am. Chem. Soc*., **1985**, *107*, 4778.
N. Metzler-Nolte *et al*., *ChemMedChem,* **2009**, *4*, 1930.
H.-G. Schmalz *et al*., *ChemMedChem,* **2010**, *5*, 2065.



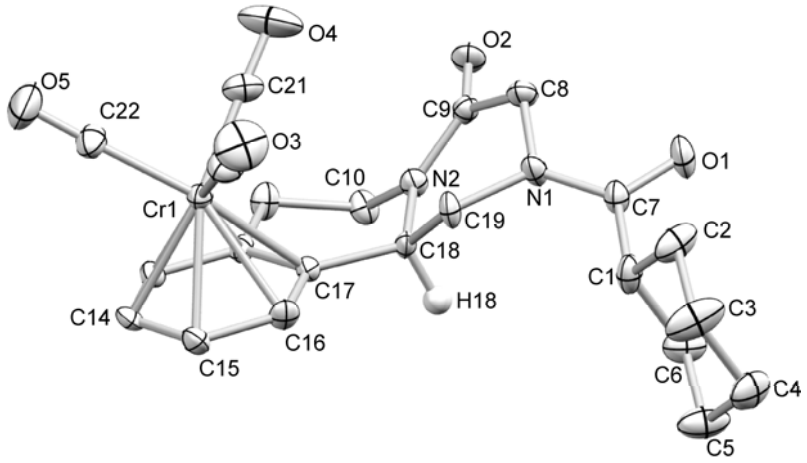
Synthesis

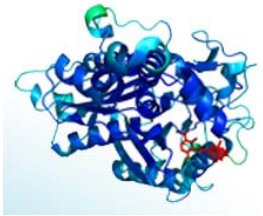


Praziquantel (PQZ)

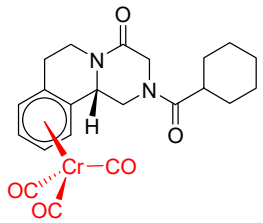
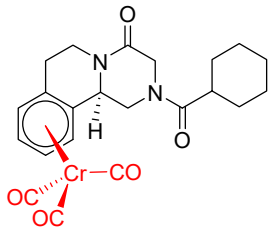
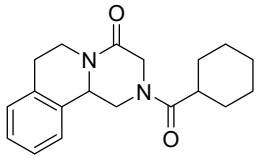
1
65%

2
35%

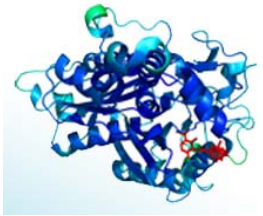




In vitro Anthelmintic Activity on *S. mansoni*

Compounds	IC_{50} adult *S.mansoni* [µM]	IC_{50} HeLa	IC_{50} MRC-5
	0.25	68.5 ± 3.0	>100
	0.27	81.4 ± 1.5	>100
	0.1	>100	ND

M. Patra, K. Ingram *et al.*, *Chem. Eur. J.*, **2013**, *19*, 2232.

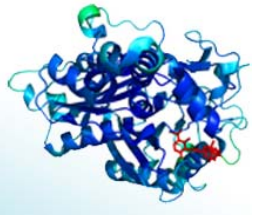


In vivo Results

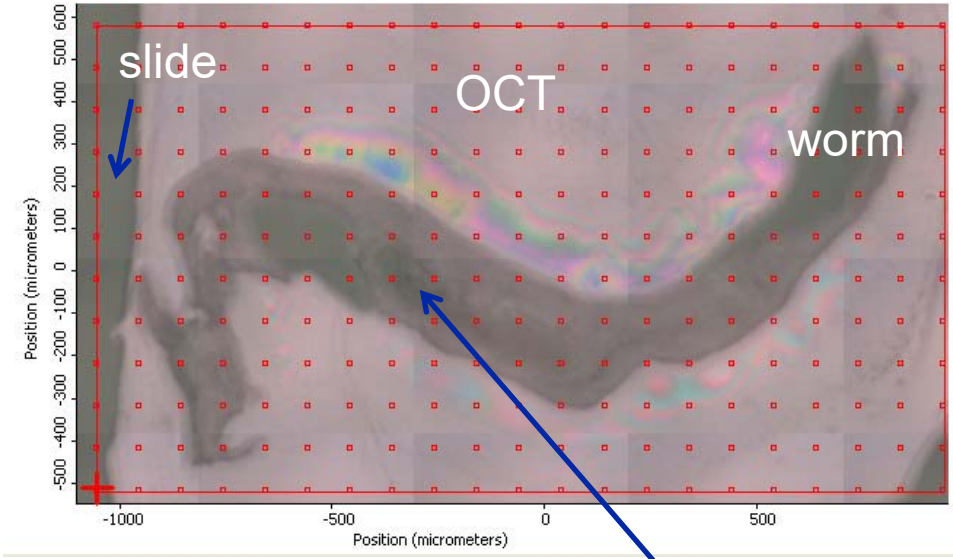
Table. *In vivo* activity of two Cr-PQZ derivatives administered at single oral doses of 400 mg/kg to mice harboring adult *S. mansoni.*

Group	No. of mice investigated	No. of mice cured	Mean number of worms (SD)	TWR [%]	p-value
Control	9	-	36.7 (8.2)	-	-
1	5	0	28 (5.9)	24	**>0.05**
2	5	0	26.3 (19.9)	29	**>0.05**
PZQ	**N/A**	**N/A**	**N/A**	**96**	**N/A**

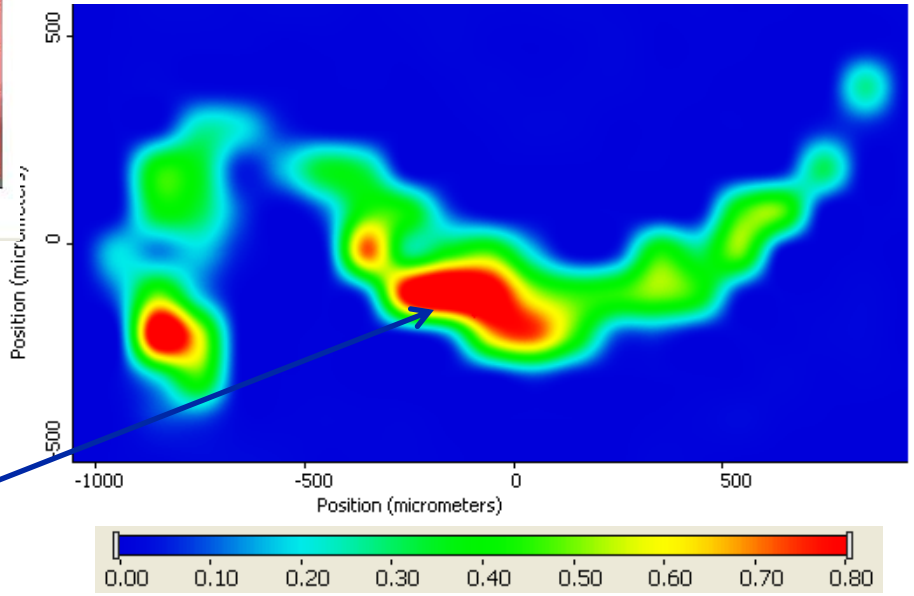
M. Patra, K. Ingram *et al.*, *J. Med. Chem.,* **2013**, *56*, 9192.



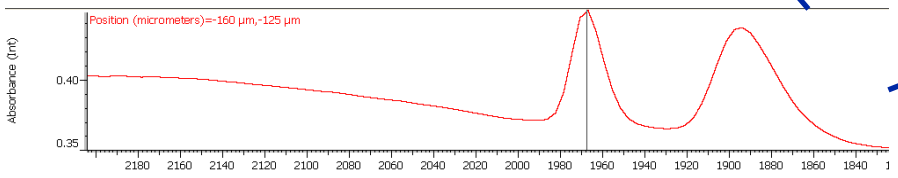
Towards the Mechanism of Action of PZQ?



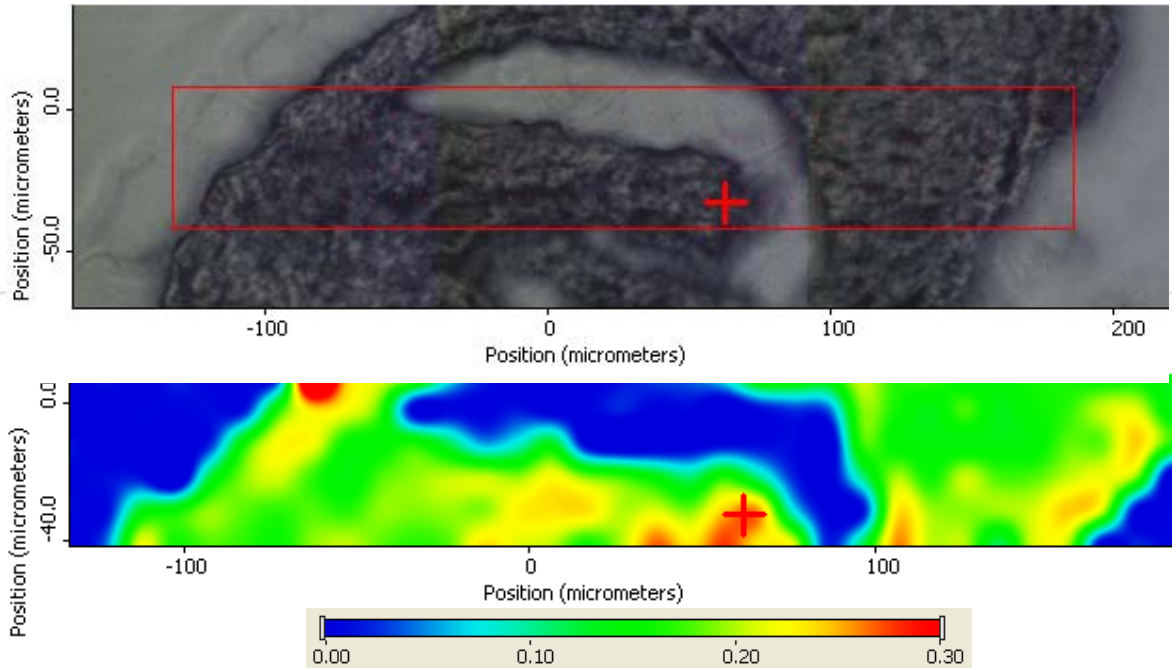
Mapping of a CO band
1980-1945 cm^{-1}

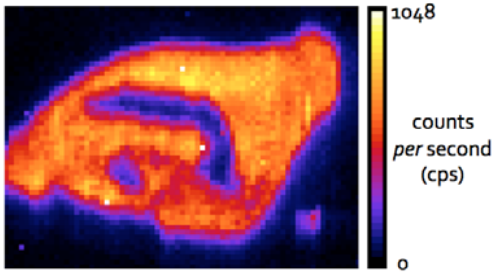


2 CO bands detected
at 1967 and 1895 cm^{-1}



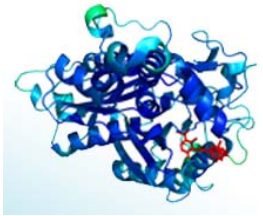
Towards the Mechanism of Action of PZQ?





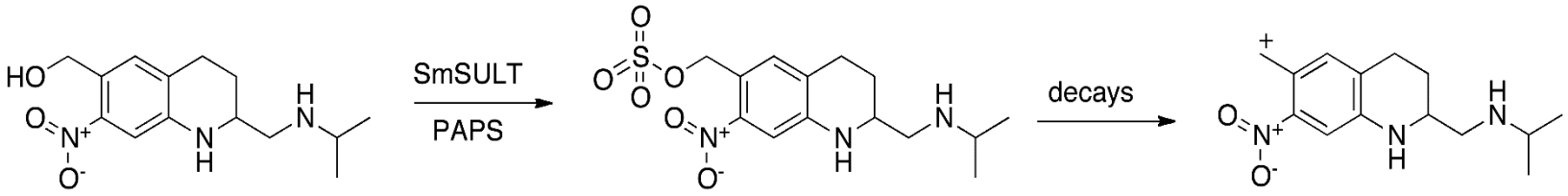
CO band
1980-1945 cm^{-1}

S. Clède *et al.*, *ChemBioChem,* **2016**, *17*, 1004-1007.



Oxamniquine

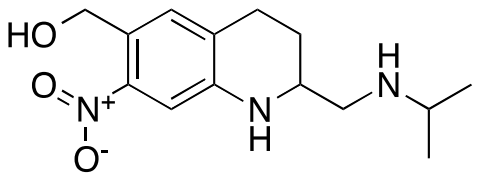
- Has activity against *S. mansoni*, but not against other *Schistosoma* spp.
- Was the drug of choice in Brazil until the 1990s.
- Resistance was then observed.



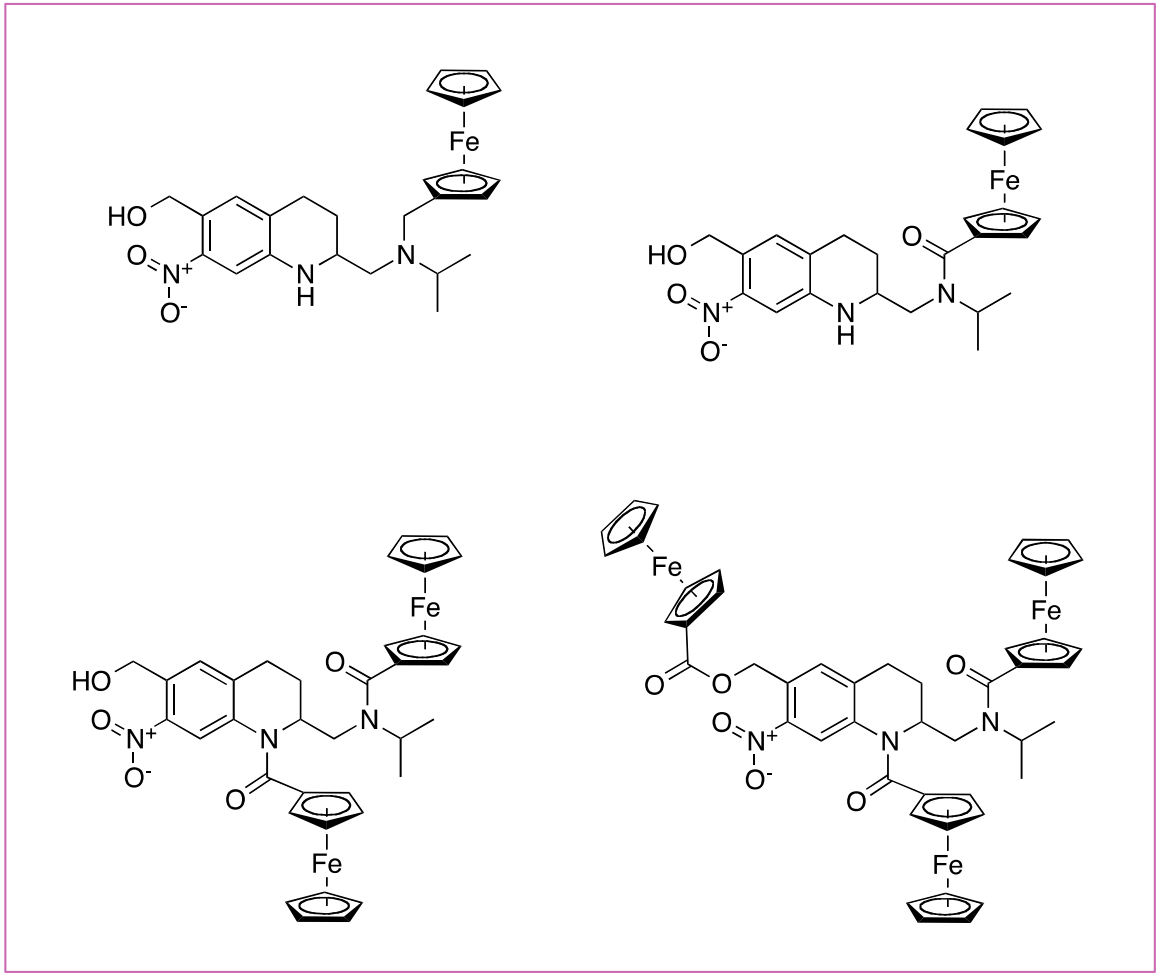
OXA **sulfonated- OXA** **electrophilic- OXA**

Cioli, D. *et al*. *Life Science* **1985**, *37*, 161.
Valentim, C. L. L. *et al. Science* **2013**, *342*, 1385.

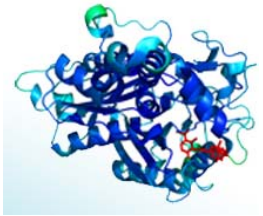
Organometallic Derivatives of Oxamniquine



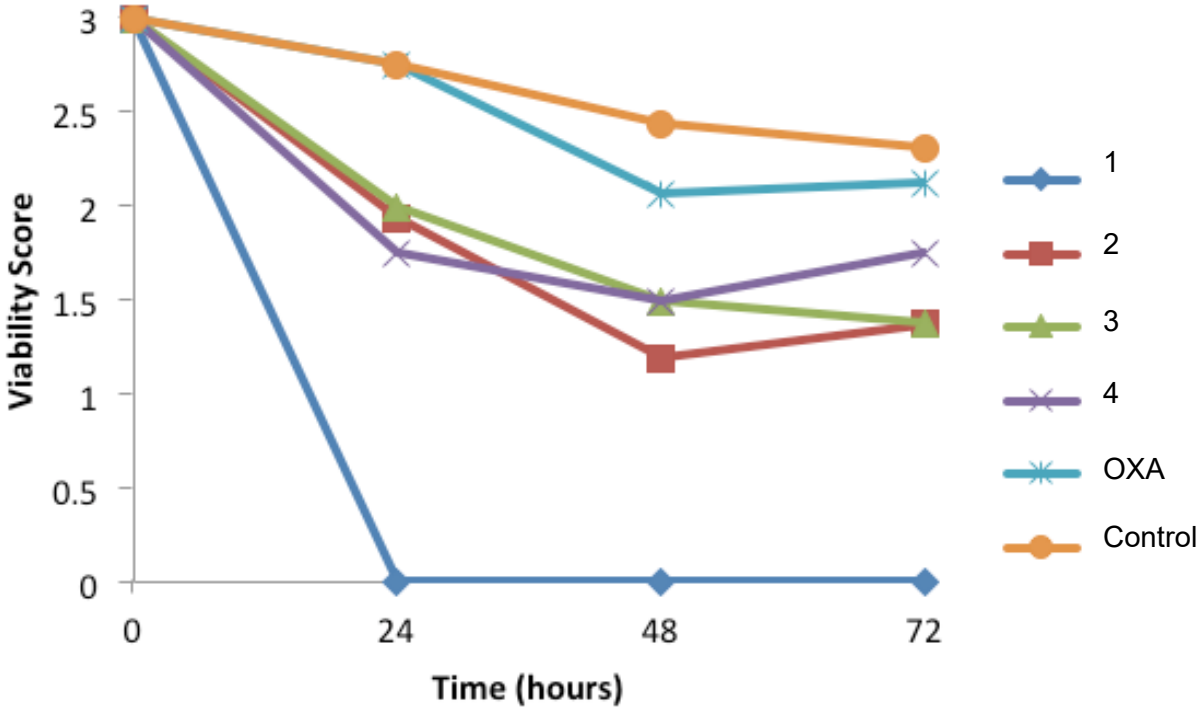
Oxamniquine

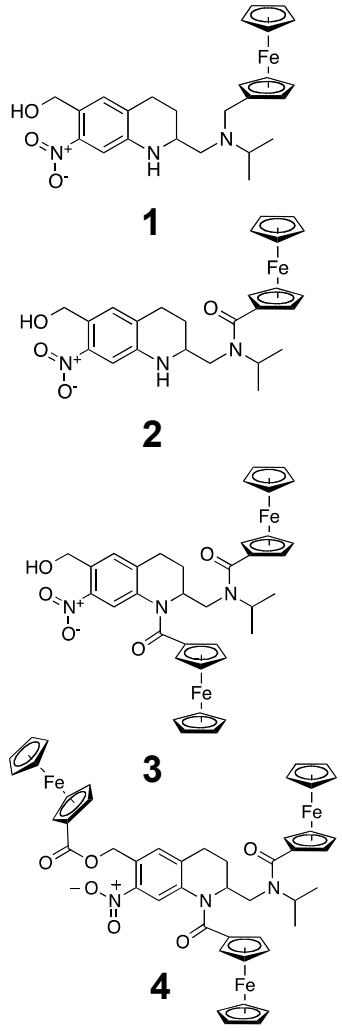


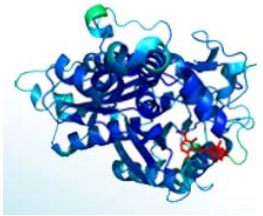
J. Hess *et al.*, **2017**, *submitted*.



In vitro Antischistosomal Activity





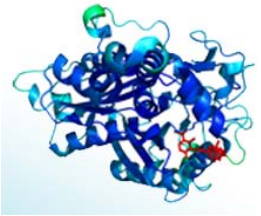


In vivo Antischistosomal Activity

Compound	Dose (mg/kg)	No. of mice	Worm Burden		Worm Burden Reduction (%)	
			Female	Total	Female	Total
Control Batch 1	Untreated	8	13.4	23.0	-	-
Control Batch 2*	Untreated	8			-	-
Oxamniquine	200	4	0.0	0.0	100	100
1*	200	4	0.0	0.0	100	100
2	200	3	14.7	22.0	-9.7	4.3
3	200	4	11.0	17.3	17.8	25.0
4*	200	2	13.5	20.0	25.9	31.6

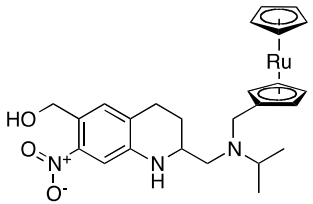
*WBR for this treatment arm calculated based on worm burden of Control Batch 1.

J. Hess *et al.*, **2016**, *submitted*.



At 100 mg/kg with two Controls...

Compound	No. of mice	Worm Burden		Worm Burden Reduction (%)	
		Female	Total	Female	Total
Control Batch 1	8	14.2	30.2	-	-
Control Batch 2	8	11.13	19.9	-	-
OXA[a]	4	0.3	0.3	98.2[c]	99.2[c]
1[a]	4	4.5	5.8	68.4	81.0[c]
5[b]	4	1.00	1.3	91.0[c]	93.7[c]
6[b]	4	3.50	4.8	68.5	76.1[c]



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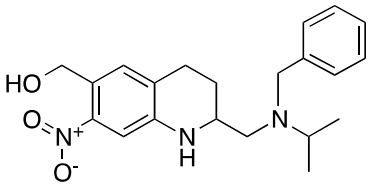
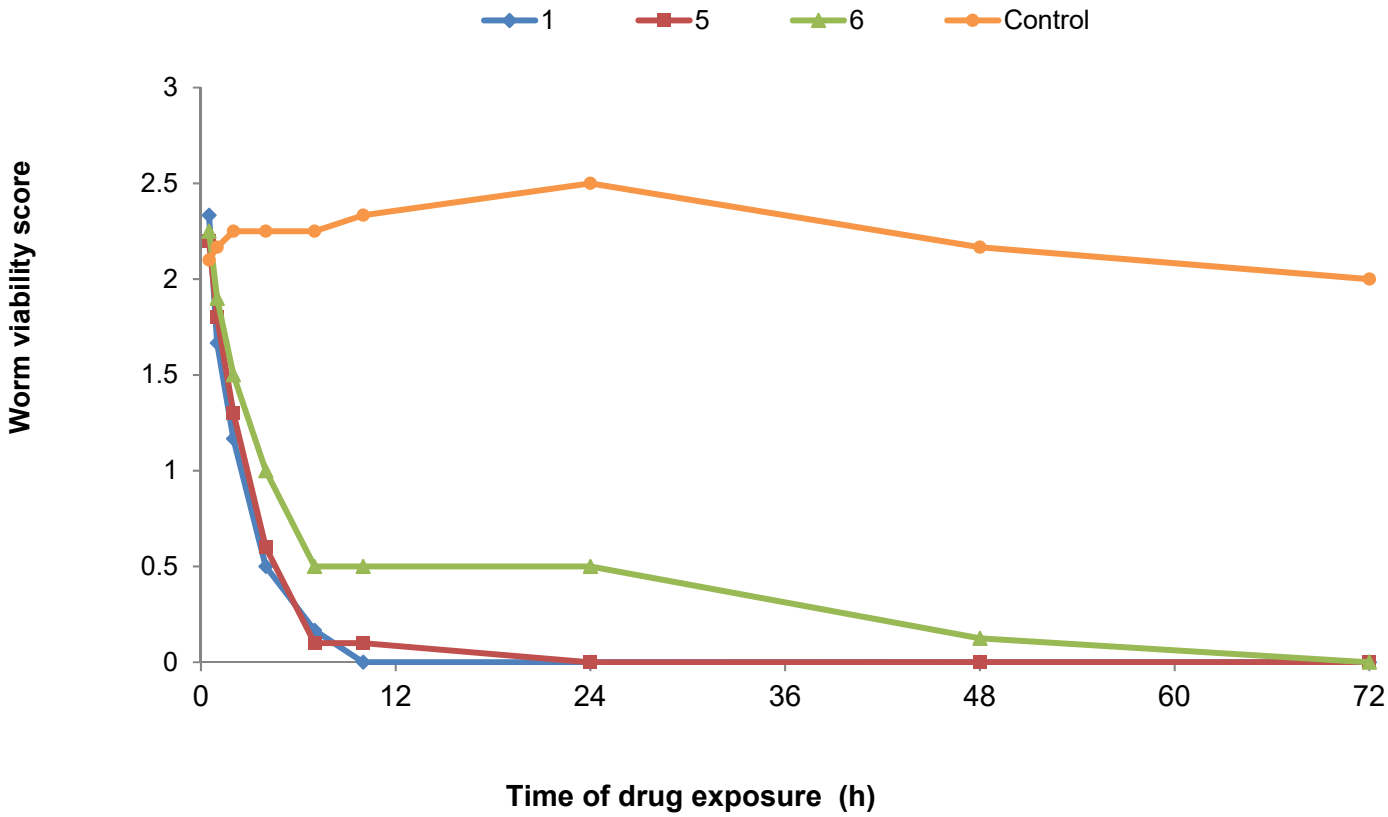
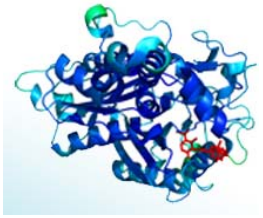


6

Activity against *S. haematobium*!!!





Summary

Medicinal Organometallic Chemistry has a bright future!

M. Patra, K. Ingram *et al*., *J. Med. Chem.* **2012**, *55*, 8790.
M. Patra, K. Ingram *et al*., *Chem. Eur. J.* **2013**, *19*, 2232.
M. Patra, K. Ingram *et al*., *J. Med. Chem.* **2013**, *56*, 9192.
J. Keiser *et al*., *Parasites & Vectors*, **2014**, *7*, 424.
J. Hess *et al.*, *Future Med. Chem*., **2015**, *7*, 821.
S. Clède *et al., ChemBioChem,* **2016**, *17*, 1004-1007.
J. Hess *et al*., **2017**, *submitted*.

Dream Team in Paris

Post-Doc




Msc Students



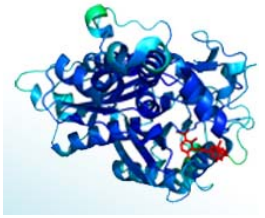

PhD Students









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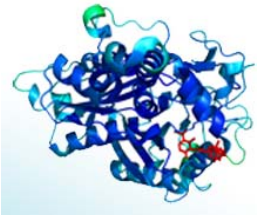

Acknowledgments

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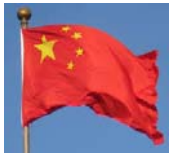
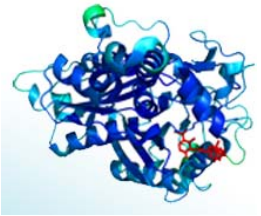
Michèle Clerc





Acknowledgments

Collaborations

PD Dr. Stefano Ferrari
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Prof. Stefan Wölfl
Dr. Andres Käch
Prof. Roland Sigel
Prof. Jennifer Keiser
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Prof. Christian Bochet
Prof. Guus van Dongen
Dr. Danielle Vugts
Dr. Ilaria Ciofini
Prof. Carlo Adamo
Prof. Frank Würthner

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