Copper Radionuclides: Production and Medical Applications

Phil Blower
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People…

Kent or formerly Kent

- Jason Dearling
- Greg Mullen
- Mike Went
- Gareth Smith
- Tom Castle
- The late Kath Martin

Kings College

- Rowena Paul
- Paul Marsden
- Phil Halsted
- Mike O'Doherty
- Kazumi Chia
- Rick Southworth
- Max Handley

University College/Mount Vernon

- Michele Saunders

St Louis

- Jason Lewis
- Paul McQuade
- Mike Welch

Oxford

- Jon Dilworth
- Greg Mullen

Royal Marsden (formerly)

- Jamal Zweit

Essex

- Chris Reynolds
- Richard Maurer

COPPER RADIONUCLIDES
Why bother?

- selection of isotopes for PET
  - Cu-60, Cu-61, Cu-62, Cu-64
  - short and long half life (small and large molecules)
  - selection of isotopes for therapy
  - Cu-64, Cu-67
- feasible production
  - numerous cyclotrons for PET support
  - generator
- Versatile, well-understood chelate chemistry
- controllable redox activity
- precedent for bioreductive intracellular trapping
  - CuPTSM (Green 1991, 1992)
  - CuATSM (Fujibayashi et al 1997)

COPPER RADIONUCLIDES

Isotope	Half Life	Radiation	Source
^{60}Cu	20 min	β^+ (93%), EC (7%)	cyclotron
^{61}Cu	3.3 hours	β^+ (62%), EC (38%)	cyclotron
^{62}Cu	9.74 mins	β^+ (98%), EC (2%)	generator/cyclotron
^{64}Cu	12.7 hours	β^+ (18%), EC (41%), β^- (37%)	reactor/cyclotron
^{66}Cu	5.1 mins	β^- (100%)	reactor/cyclotron
^{67}Cu	62 hours	β^- (100%) γ (52%)	reactor/cyclotron

Production from Ni-64 (1.1% abundance)

Cu-64 (β^+, β^-, EC, 12.7 h)

- ^{64}Ni(*p,n*)^{64}Cu
- enriched Ni on gold
- 15.5 or 11.4 MeV proton beam
- EOB 0.6 Ci/run
- easy extraction
- nickel-64 expensive but recyclable

Washington Univ, St Louis: Cyclotron Corporation CS15 cyclotron now at St Thomas' and Addenbrookes

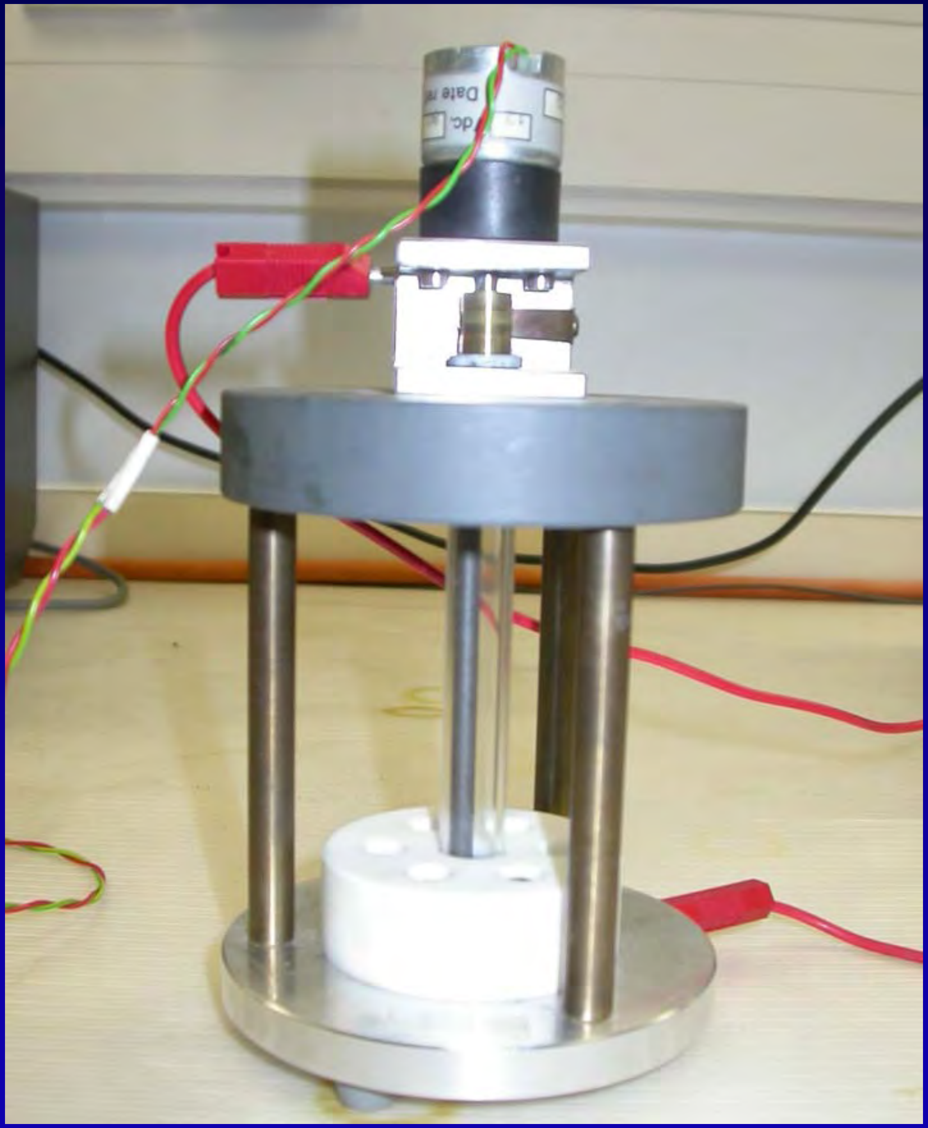
Cu-61 production from Ni-61 (1.7% abundance)

Cu-61 (β^+, 3.3 h)

- $^{60}Ni(d,n)^{61}Cu$
- enriched Ni on gold
- 14.7 or 11 MeV deuteron beam
- 8 mCi/mAh
- EOB 0.1 Ci
- easy extraction
- recyclable nickel
- Also Ni-60 38.5%

Production of Cu-64 : 3 steps

- Electroplating of Ni-64
- Irradiation of target
- Purification of Cu-64
- Synthesis of radiopharmaceutical



Plating Rig:

Ni^{2+} solution, aqueous

pH~9

$[NH_4]_2[SO_4]$ electrolyte

Cathode →Au Bullet

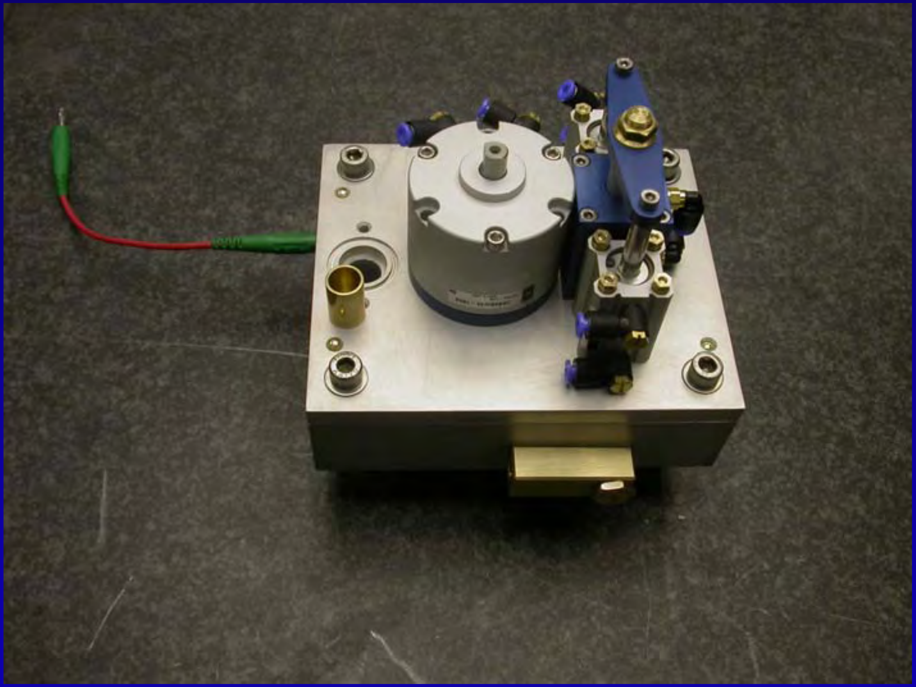
Anode →Pt Wire

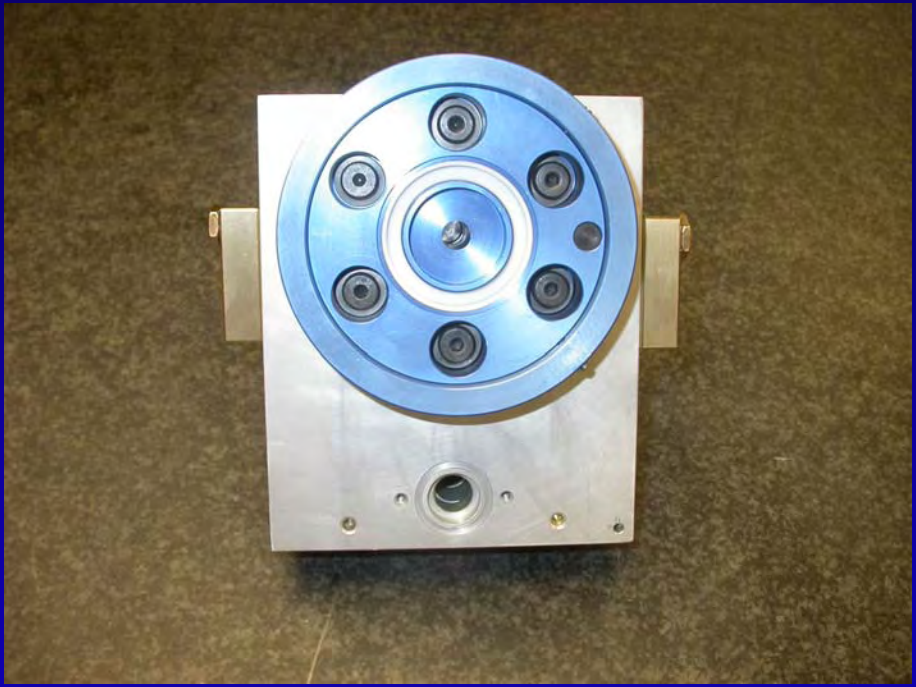
E = ~3 V

24 h

exhaustive

A *Novel* target system for ^{64}Cu

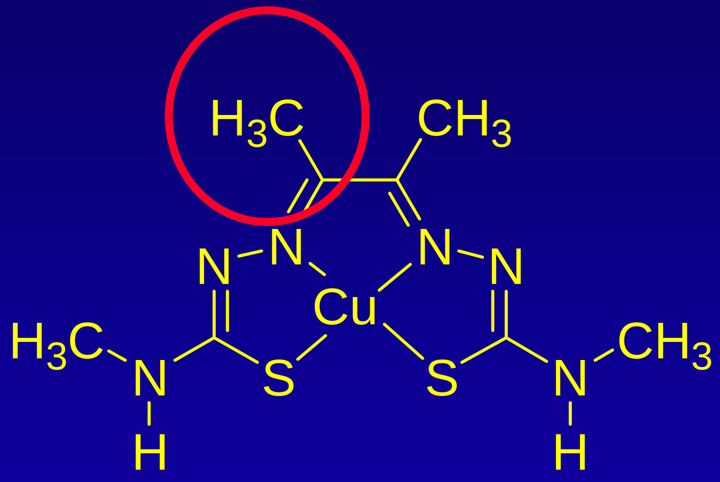




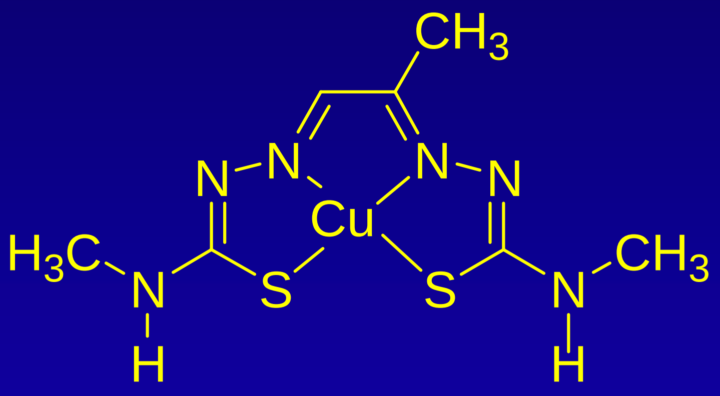
Value of hypoxia imaging in cancer

- tumour hypoxia contributes to failure to respond to radiotherapy
- predict response to radiotherapy
- identify hypoxic regions within tumours requiring higher radiation doses
- locate tumours
- new modality for targeted radionuclide therapy
- Non-cancer: neurosciences, cardiovascular

CuATSM

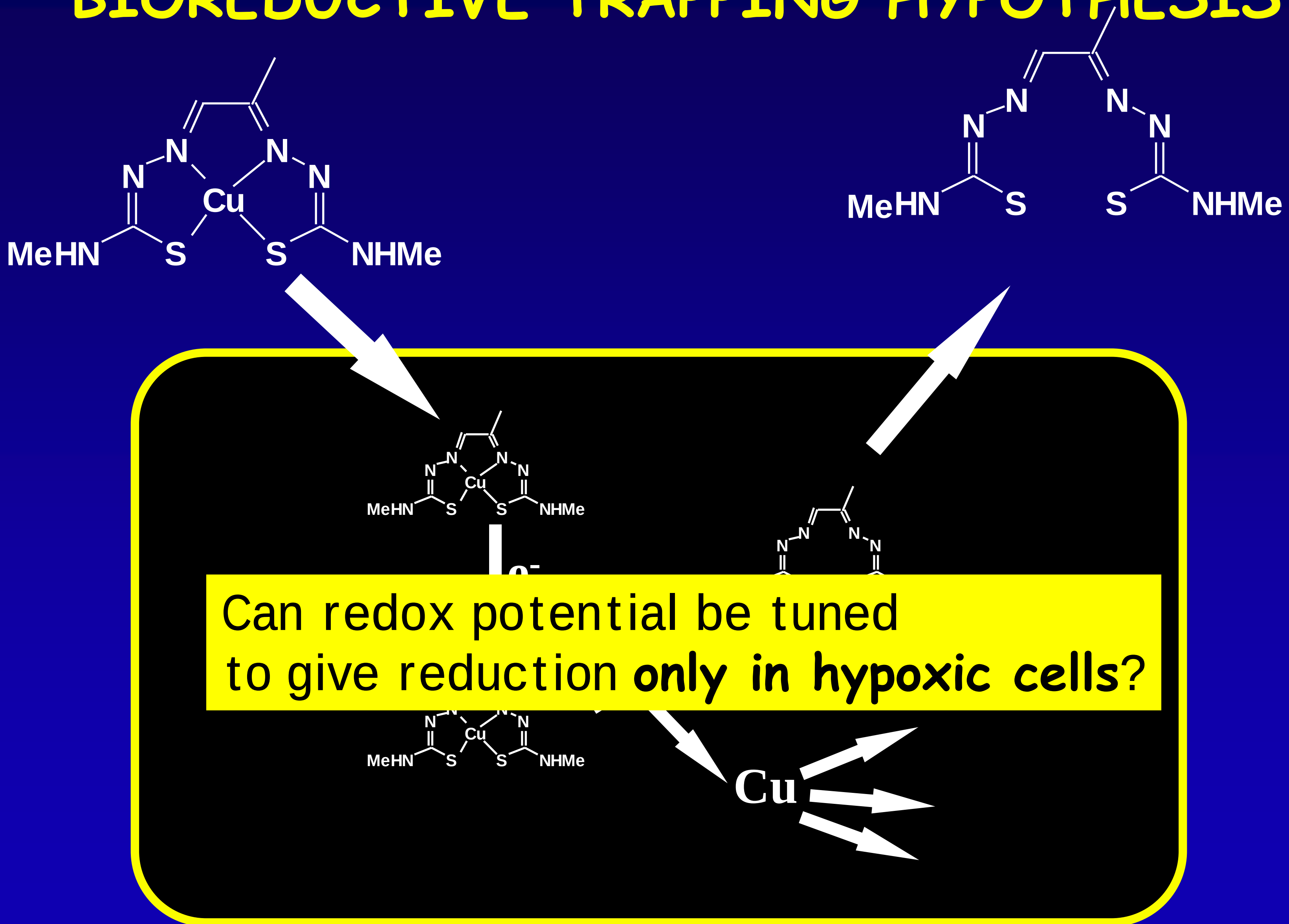


CuATSM
(hypoxia)



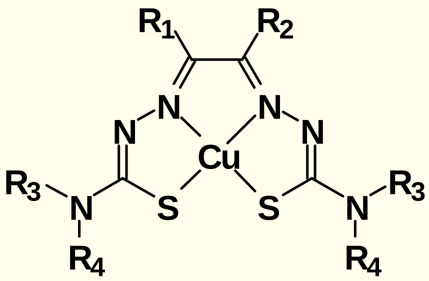
CuPTSM
(flow)

CuPTSM:
BIOREDUCTIVE TRAPPING HYPOTHESIS



Can redox potential be tuned
to give reduction **only in hypoxic cells**?

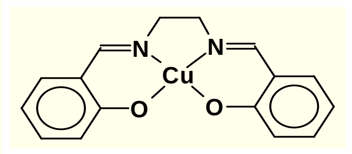
Bis(thiosemi-carbazones)



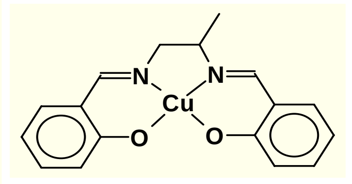
	R1	R2	R3	R4
GTS	H	H	H	H
GTSM	H	H	CH_3	H
PTS	CH_3	H	H	H
PTSM	CH_3	H	CH_3	H
$PTSM_2$	CH_3	H	CH_3	CH_3
PTSE	CH_3	H	C_2H_5	H
PTSP	CH_3	H	C_6H_5	H
ATS	CH_3	CH_3	H	H
ATSM	CH_3	CH_3	CH_3	H
CTS	C_2H_5	CH_3	H	H
CTSM	C_2H_5	CH_3	CH_3	H
DTS	C_2H_5	C_2H_5	H	H
DTSM	C_2H_5	C_2H_5	CH_3	H

Bis(salicyl-aldimines)

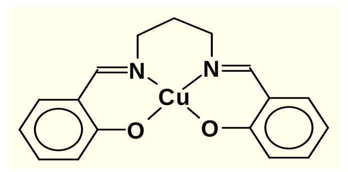
EDS



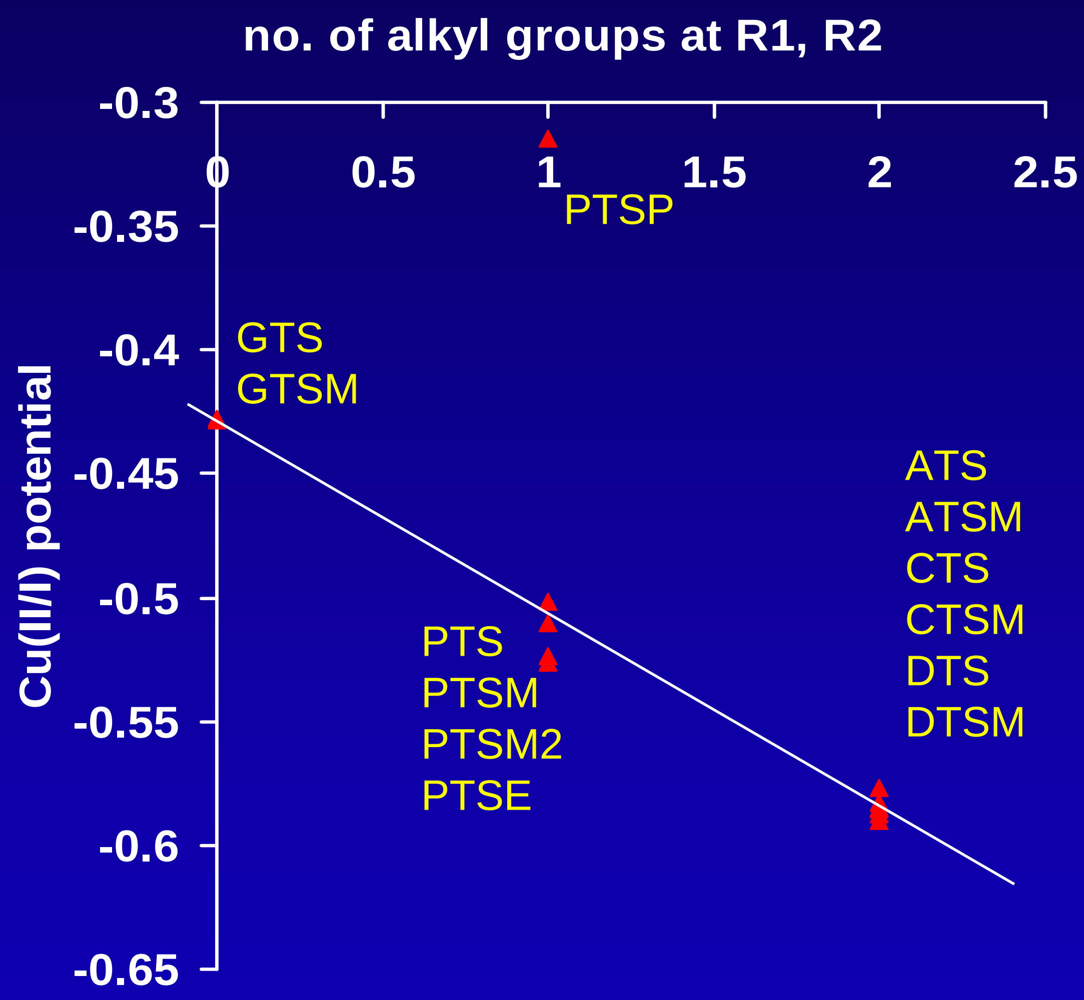
EDSM

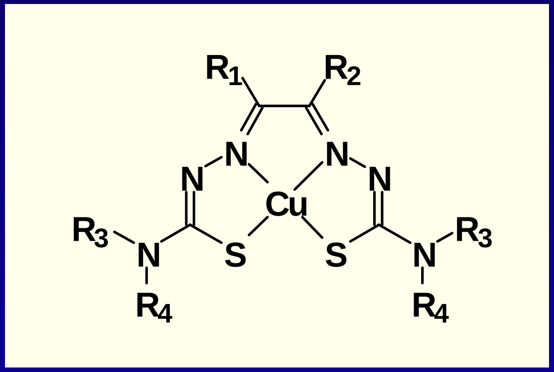


PDS



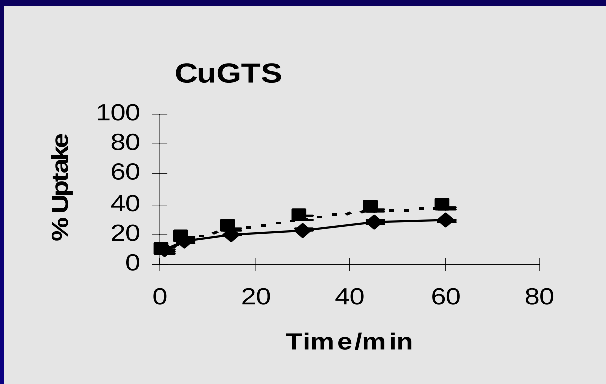
Bis(thiosemicarbazone) complexes: Alkylation/redox potential relation

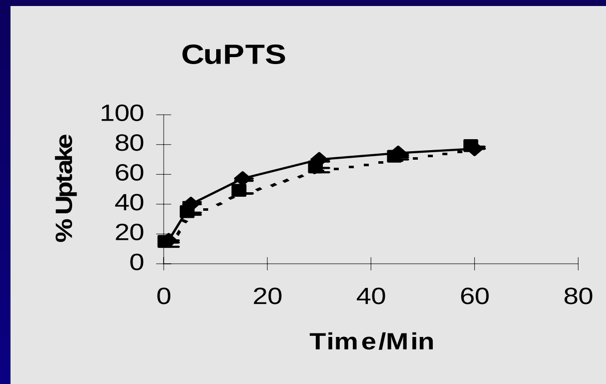


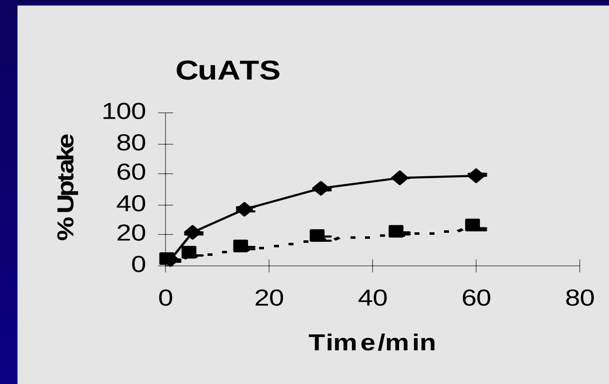


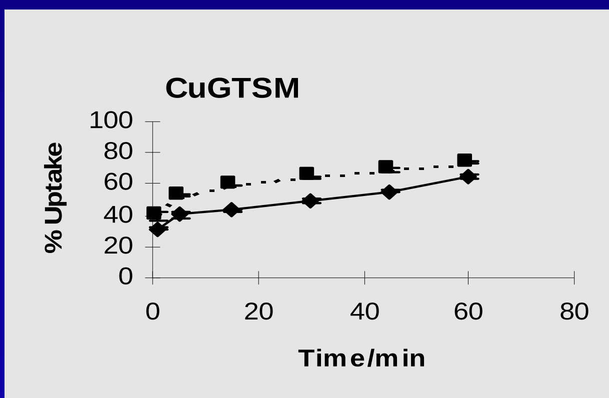
Representative cell uptake profiles

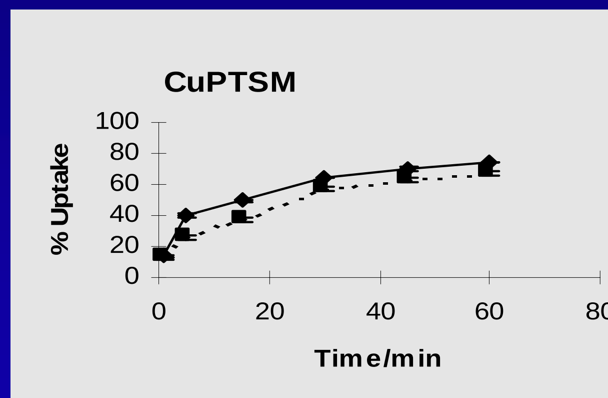
n = 0 1 2

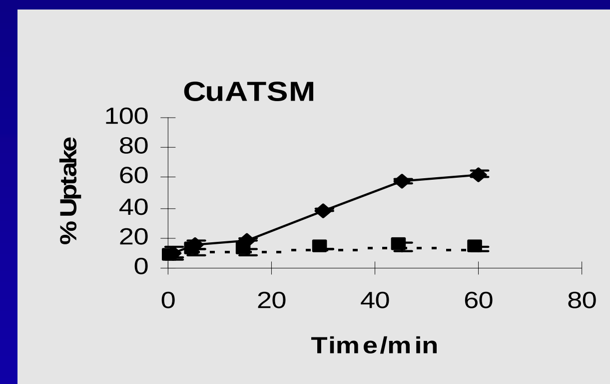


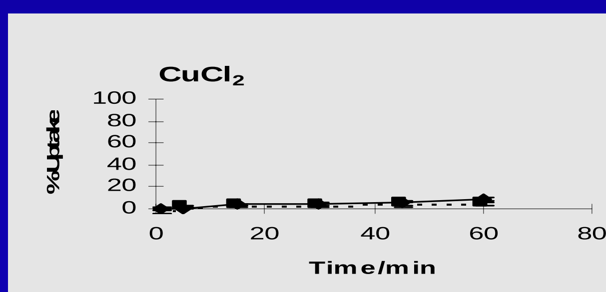


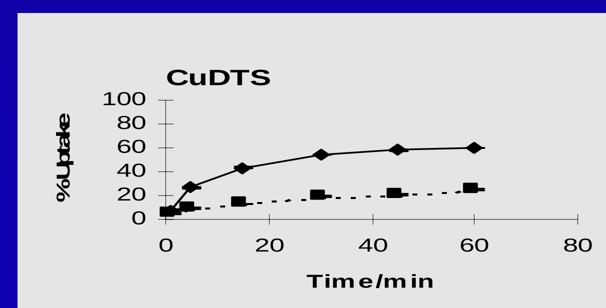




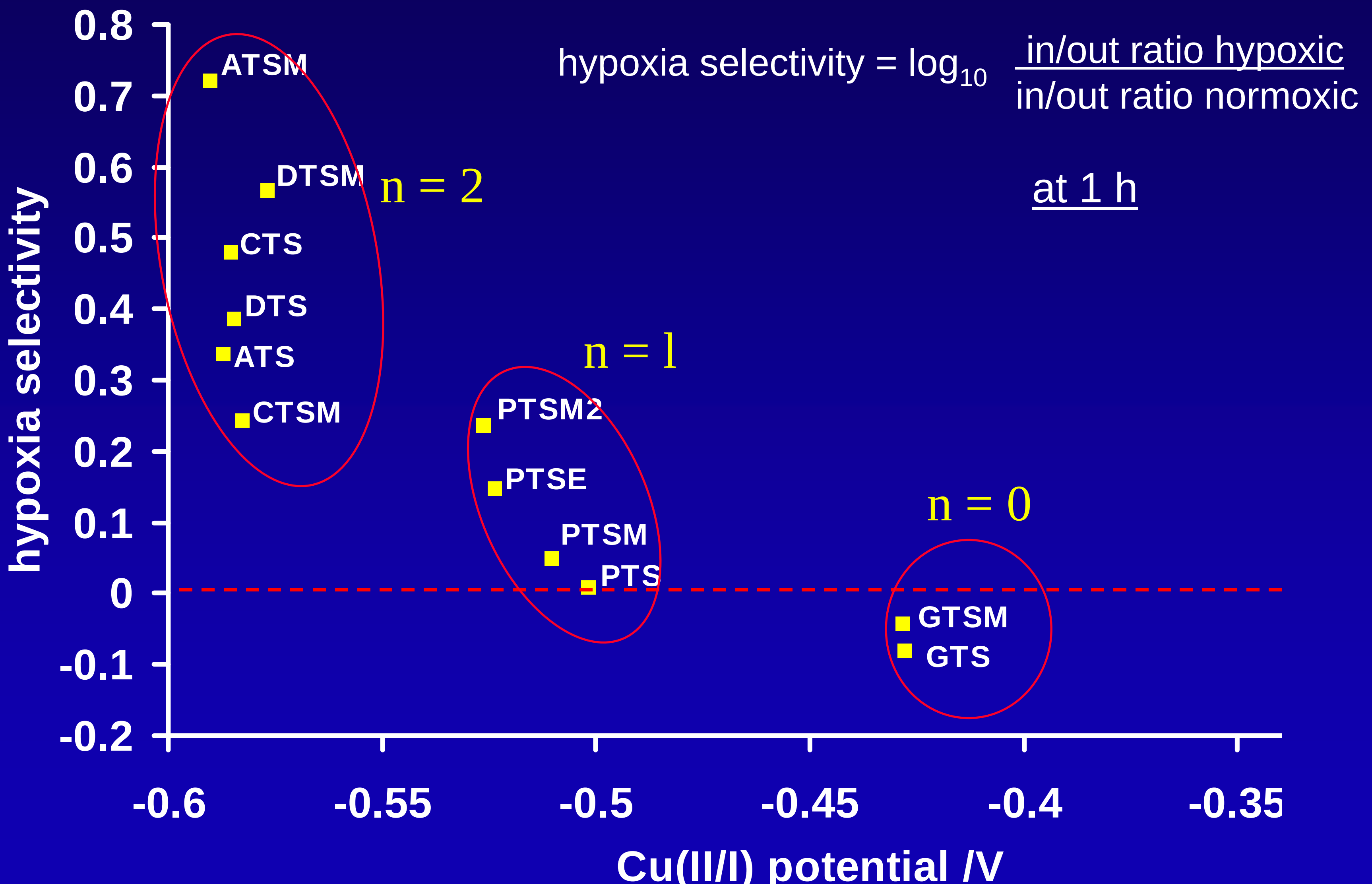






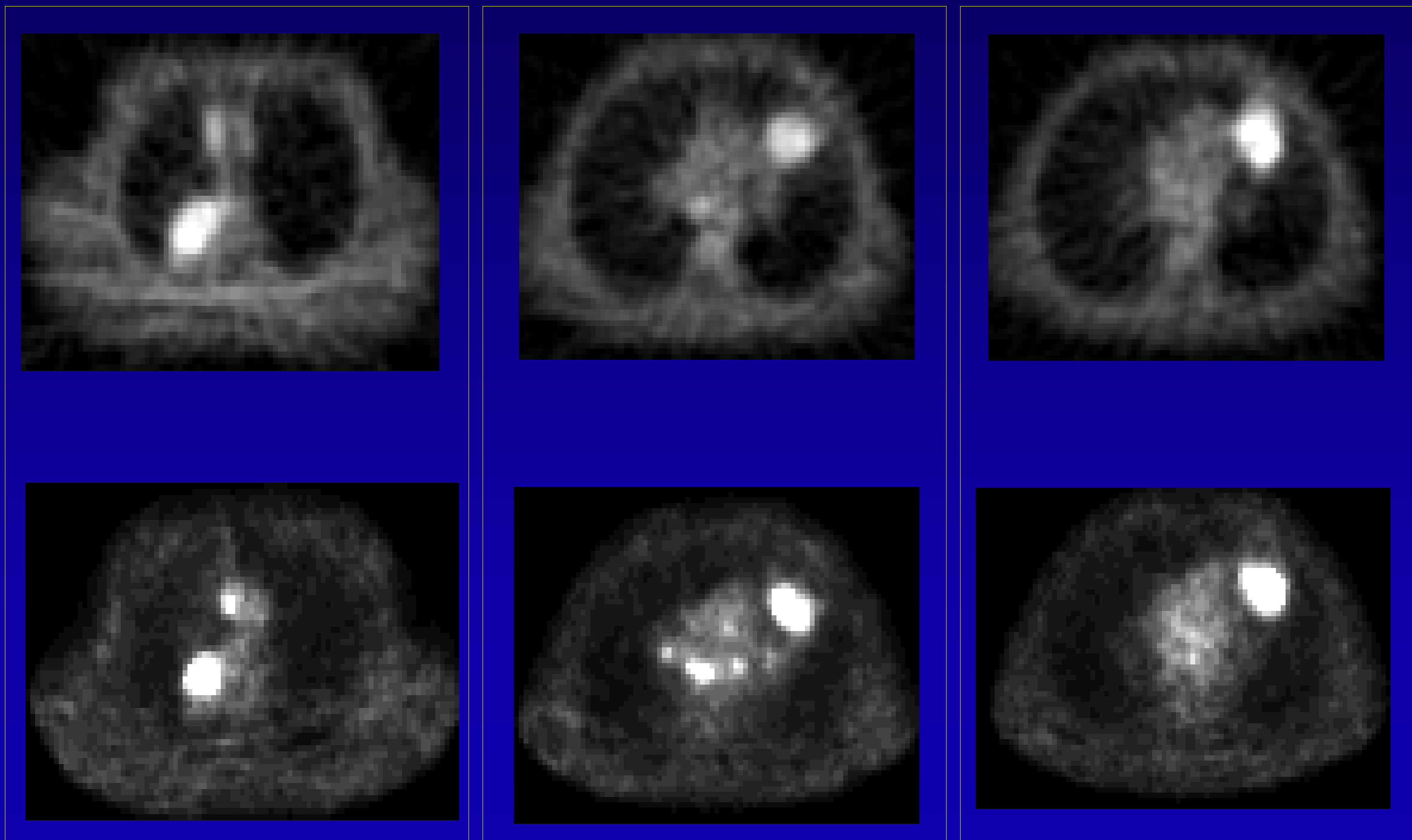


Redox potential/selectivity relationship



Patient Studies: ^{60}CuATSM in Lung Tumour: Comparison with ^{18}F-FDG PET (St Louis)

^{60}Cu(ATSM)-PET

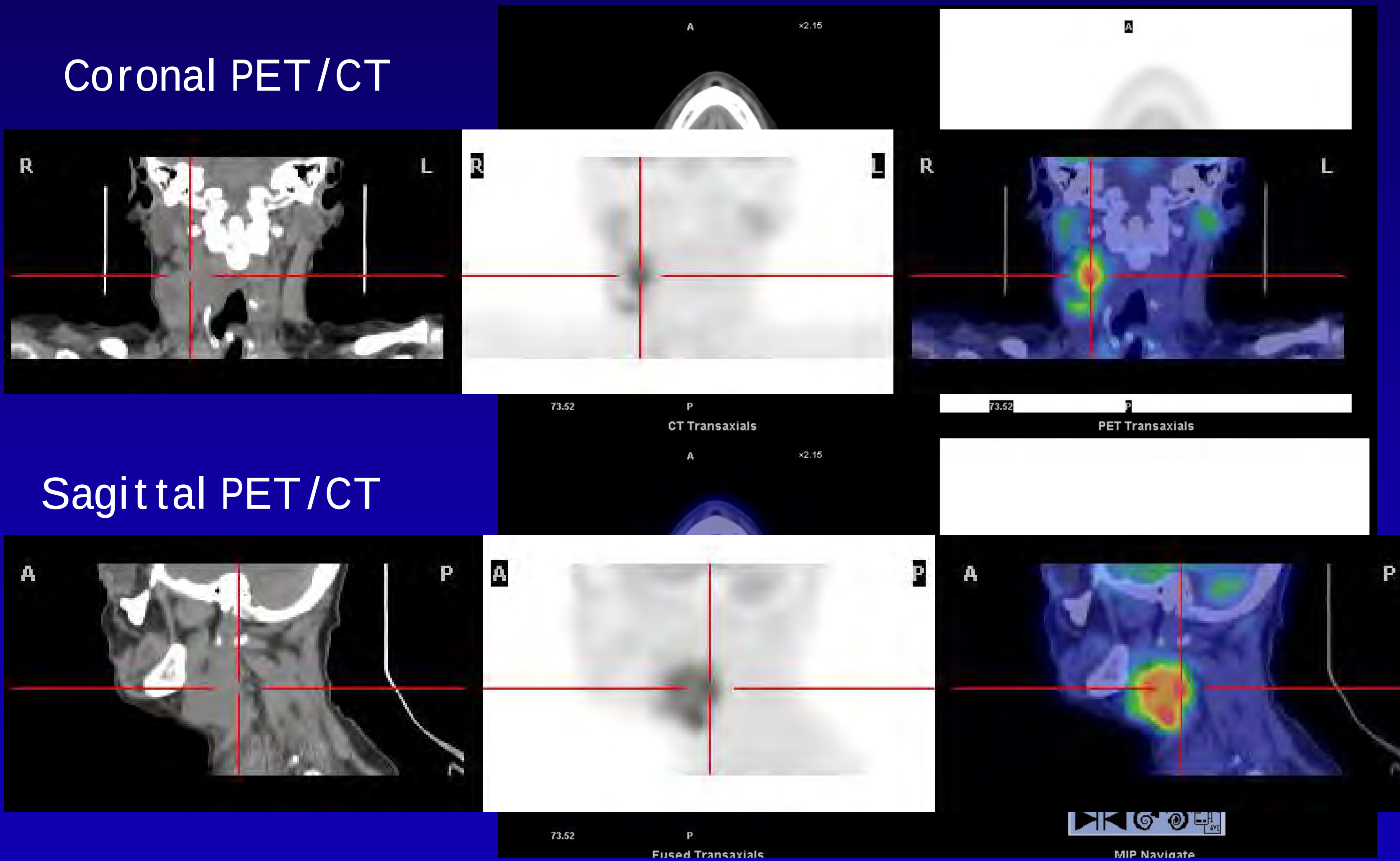


FDG-PET

Patient studies: head and neck cancer (KCL/Mount Vernon)

Coronal PET/CT

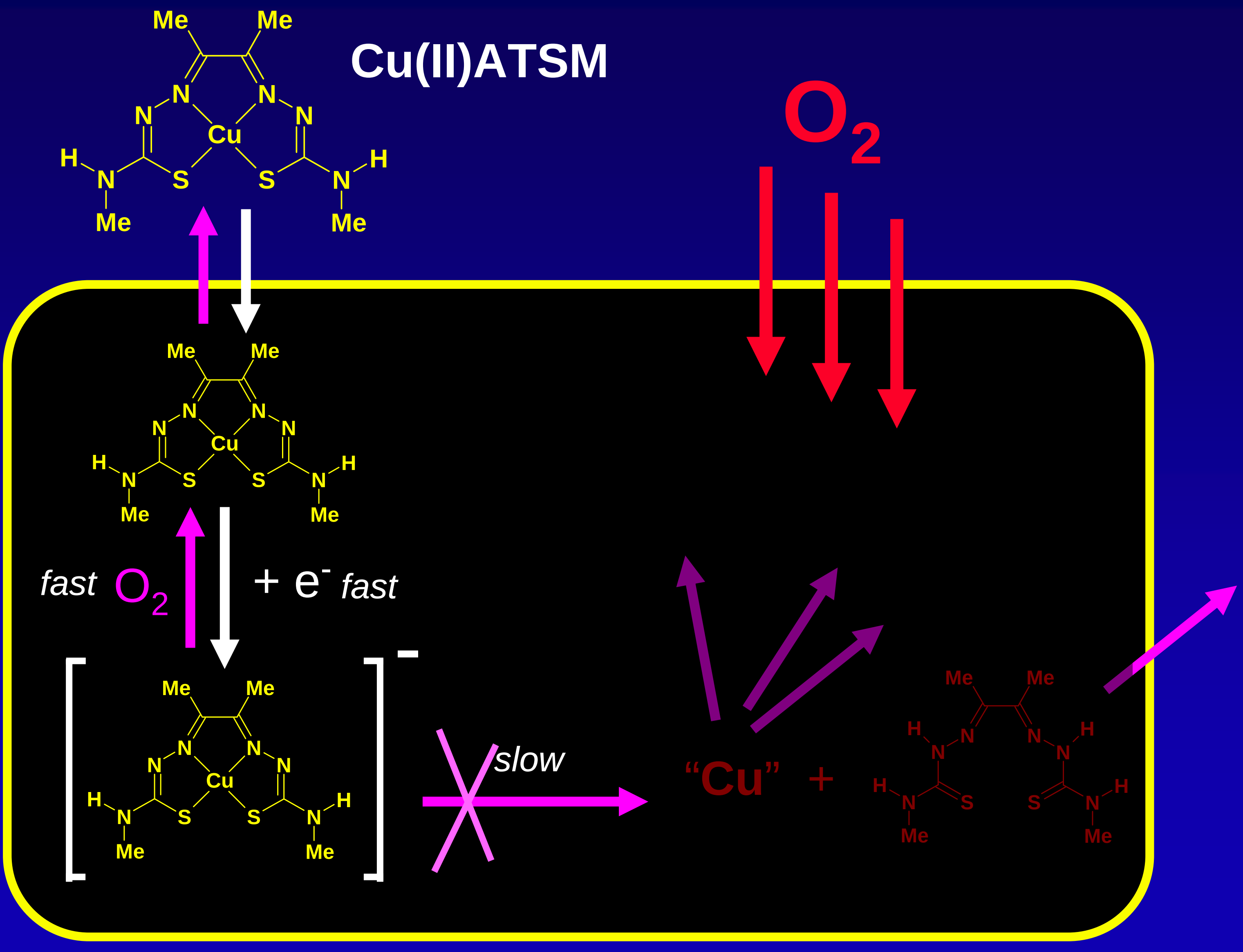
Sagittal PET/CT



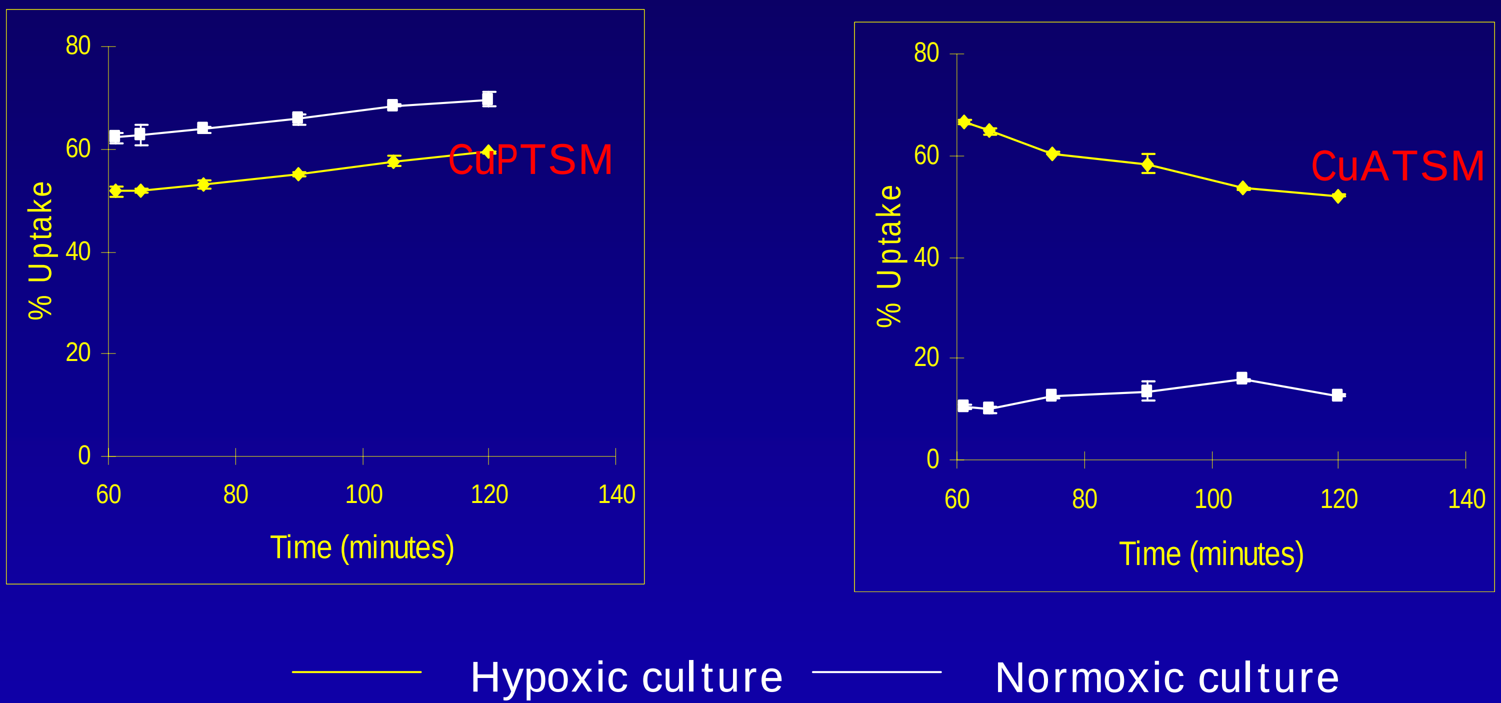
Properties of CuATSM

- Correlates with O_2 electrode *in vivo*
- high predictive value of tumour:muscle (T/M) uptake ratios for response to radiotherapy in non-small cell lung, cervical, colorectal cancer
  - T/M > 3.0 predicts poor response (Dehdashti et al. 2003, 2008)
- Higher and faster cellular uptake than FMISO *in vitro* (Lewis et al 1999)
- Optimal imaging time ca. 0.5 - 1 h (c.f. several hours for FMISO)

Mechanism of Hypoxia Selectivity



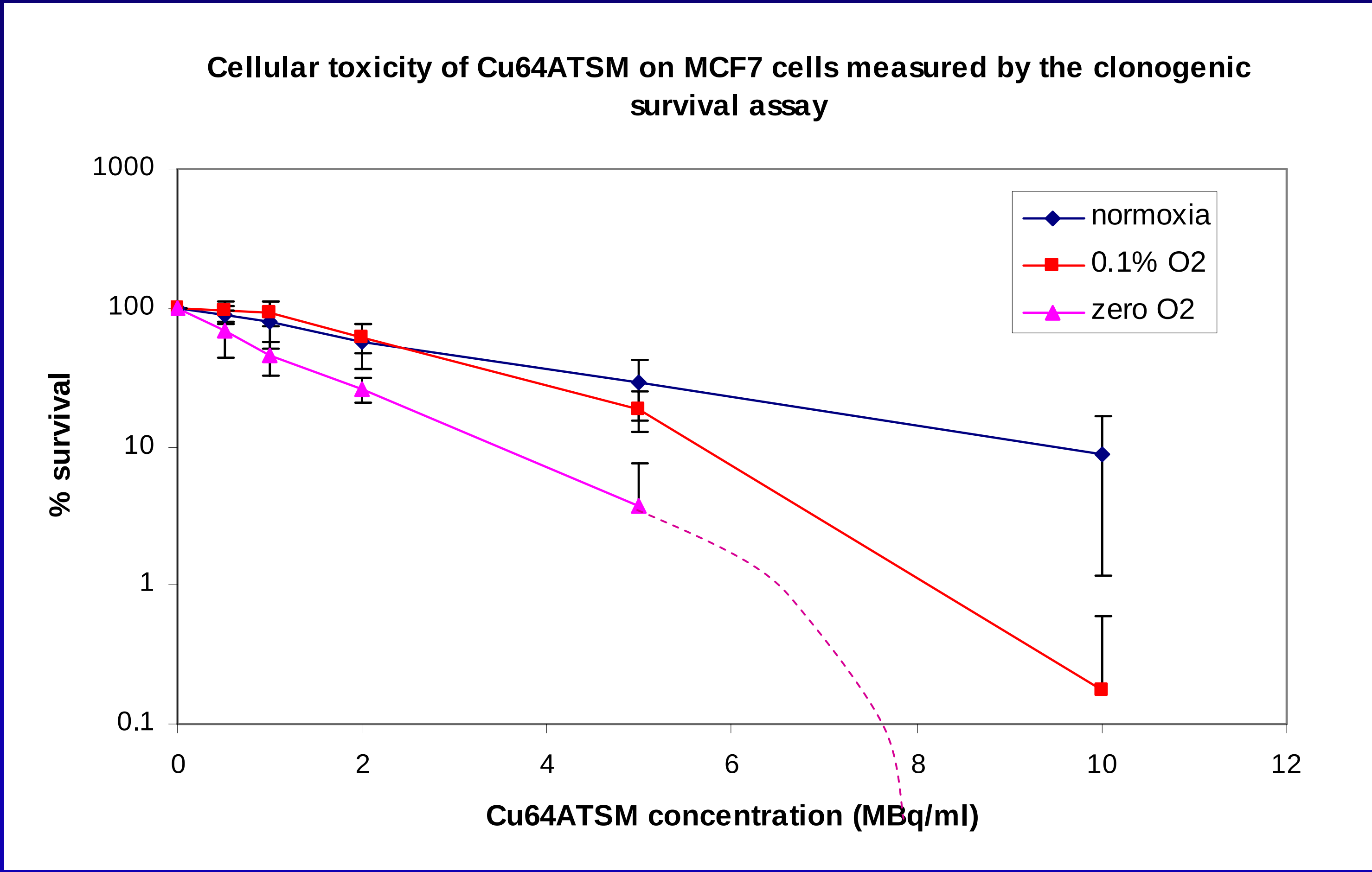
In vitro reoxygenation experiments



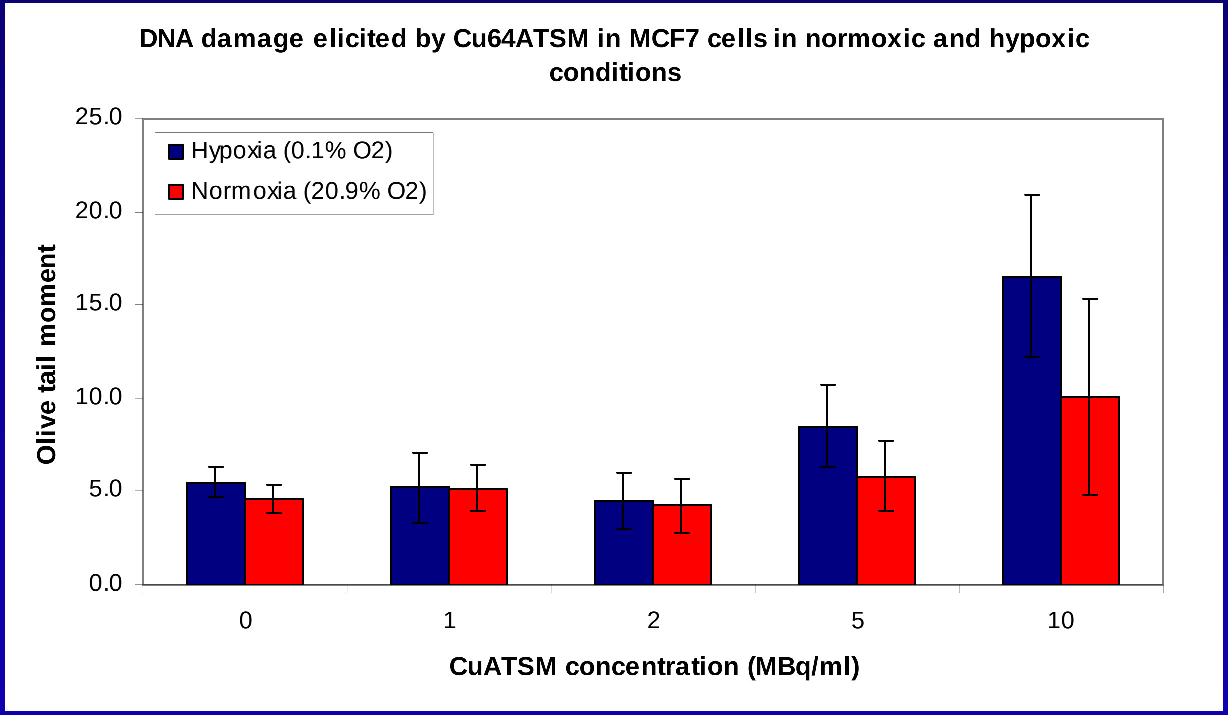
Non-selective complexes: trapping is immediate and irreversible

Hypoxia-selective complexes: trapping is immediate but initially reversible

Therapeutic potential of CuATSM: Toxicity in MCF-7 cells increases with hypoxia

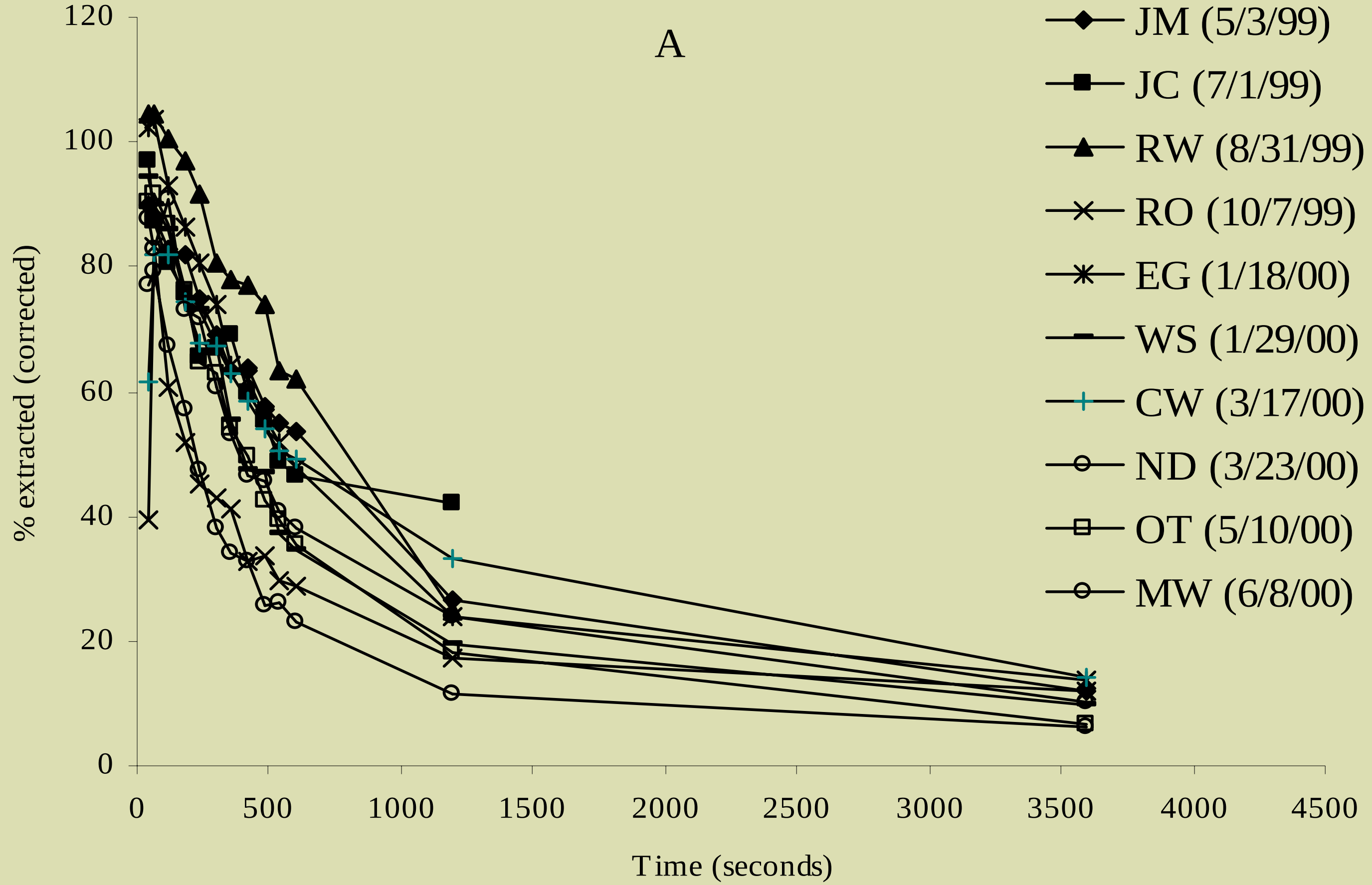


DNA damage elicited by Cu64ATSM in MCF7 cells increases in hypoxia



Problems with CuATSM

In vivo stability – octanol extraction from blood (humans)

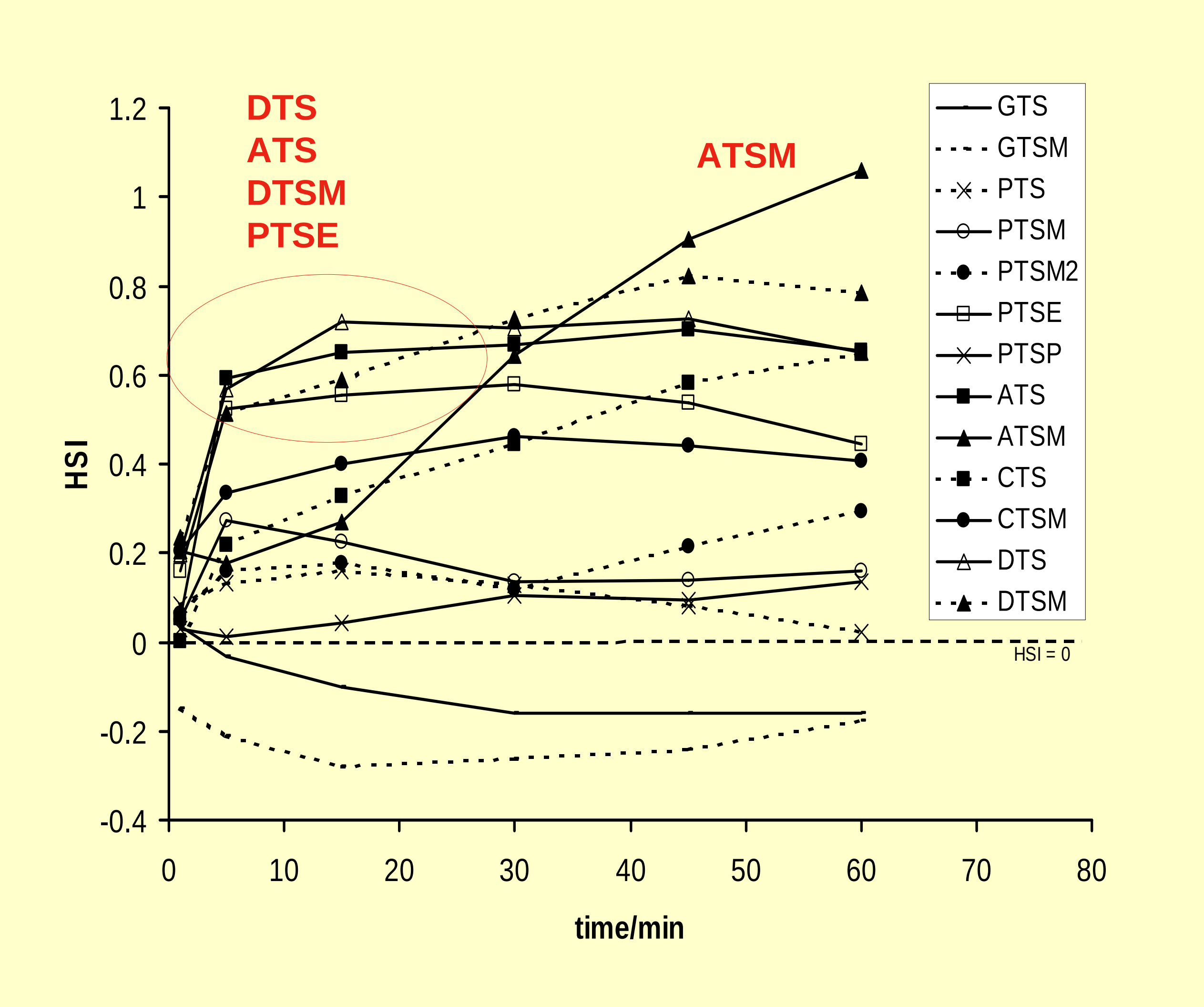


(data from St Louis lab)

Moving on: ATSM analogues

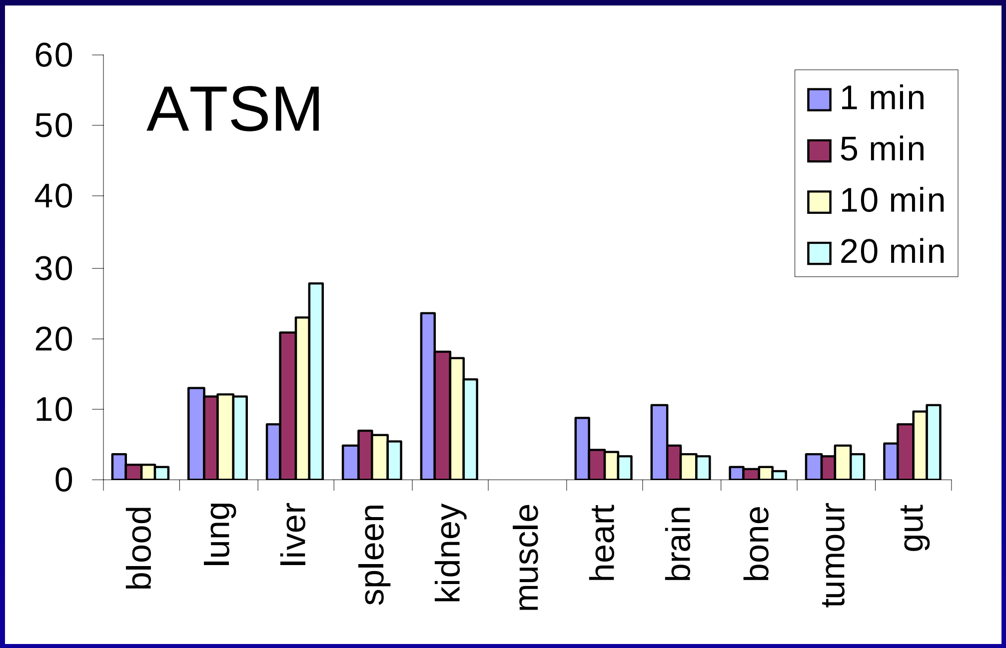
- ATSM is just a prototype
- Approx. 20 analogues studied *in vitro* so far
- Several show hypoxia selectivity
- Many more can be synthesised easily
- Can optimal properties be selected?

Rate of attainment of selectivity *in vitro*

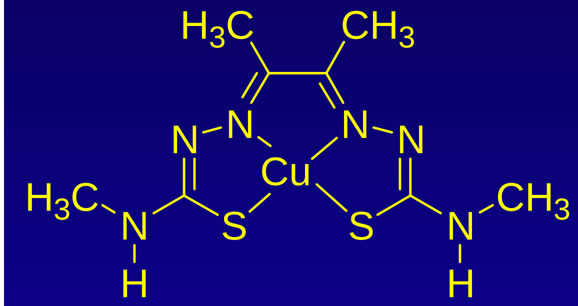


Some analogues achieve selectivity more quickly than ATSM

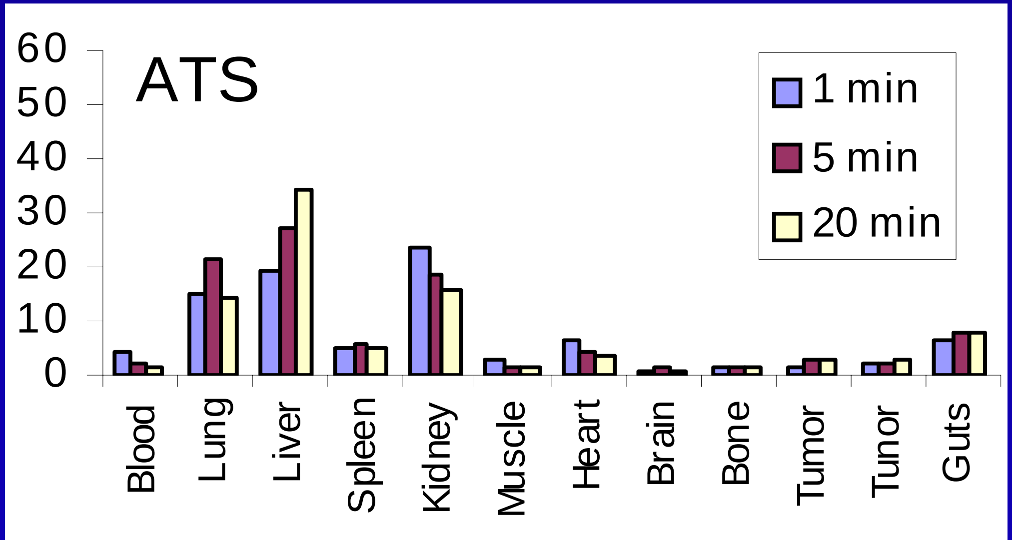
ATSM and ATS: comparative biodistribution

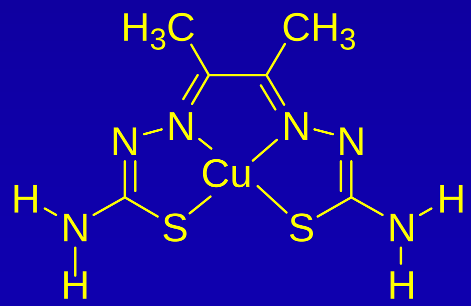


BALB/c mice, EMT6 tumour



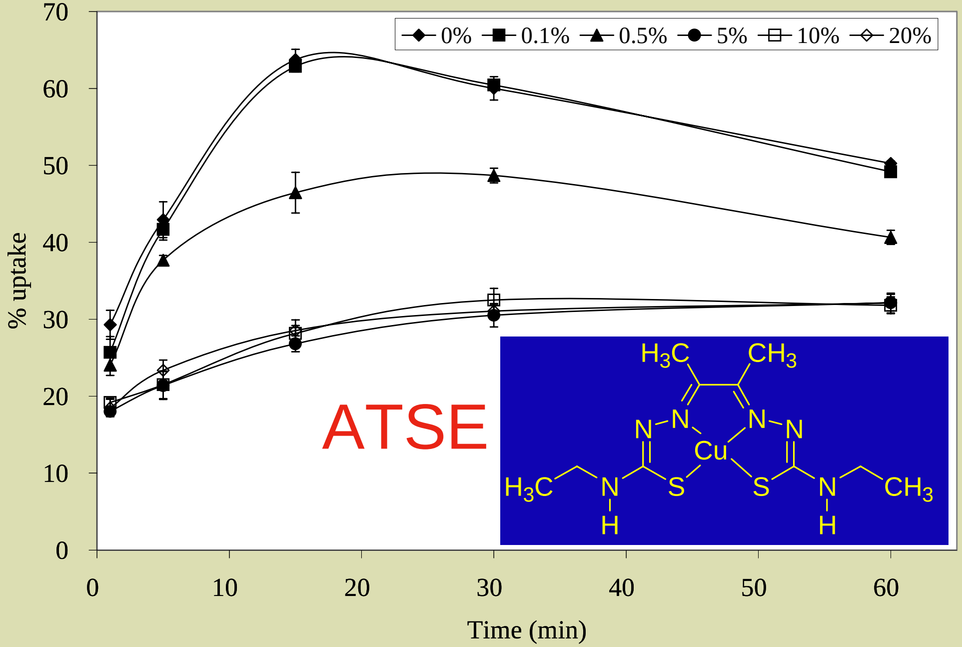
ATSM: brain uptake and rapid clearance

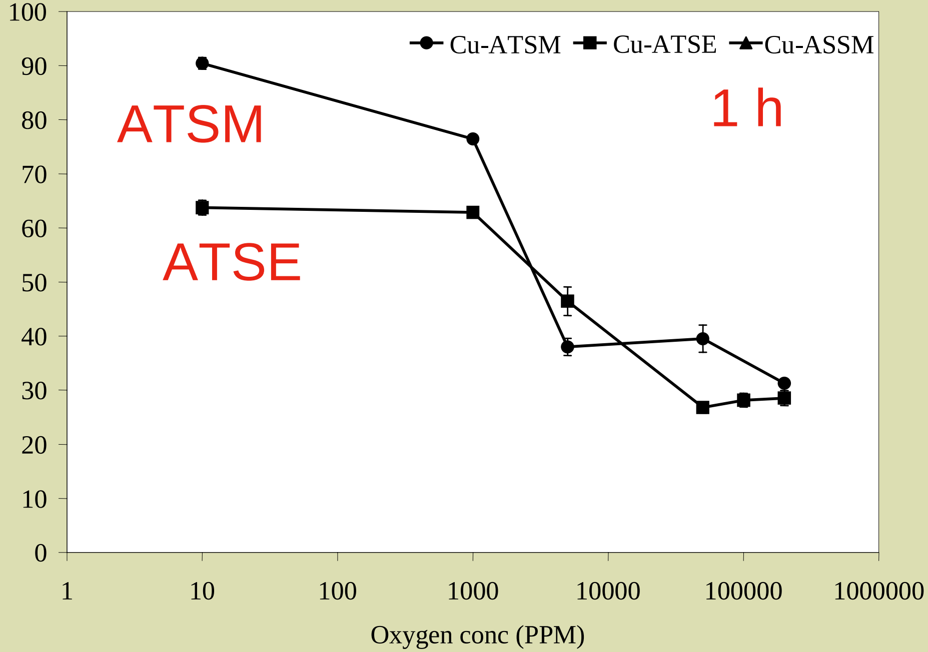




ATS: no brain uptake

ATSE: uptake at different oxygen levels *in vitro*

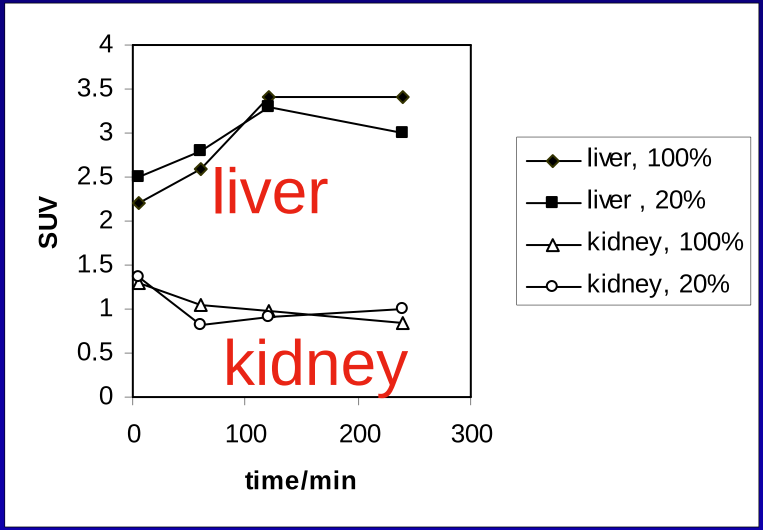


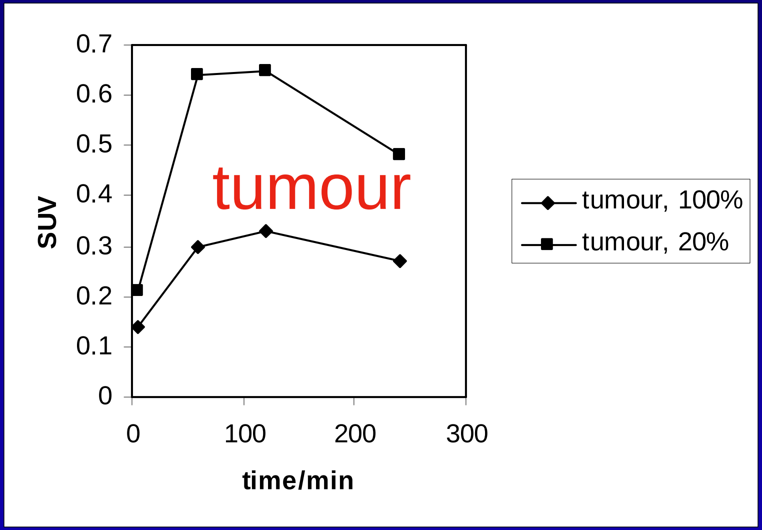


ATSE uptake switches on at higher O_2 levels (10x less hypoxic) than ATSM: more relevant to radiobiological hypoxia

ATSE *in vivo*: Effect of O_2 level

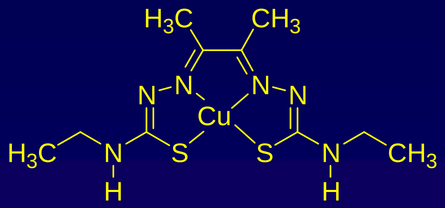
BALB/c mice,
EMT6 tumour,
breathing air or 100% O_2



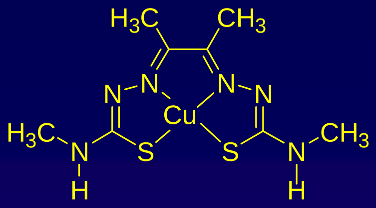


O_2 affects SUV in tumour (hypoxic)
but not other tissues

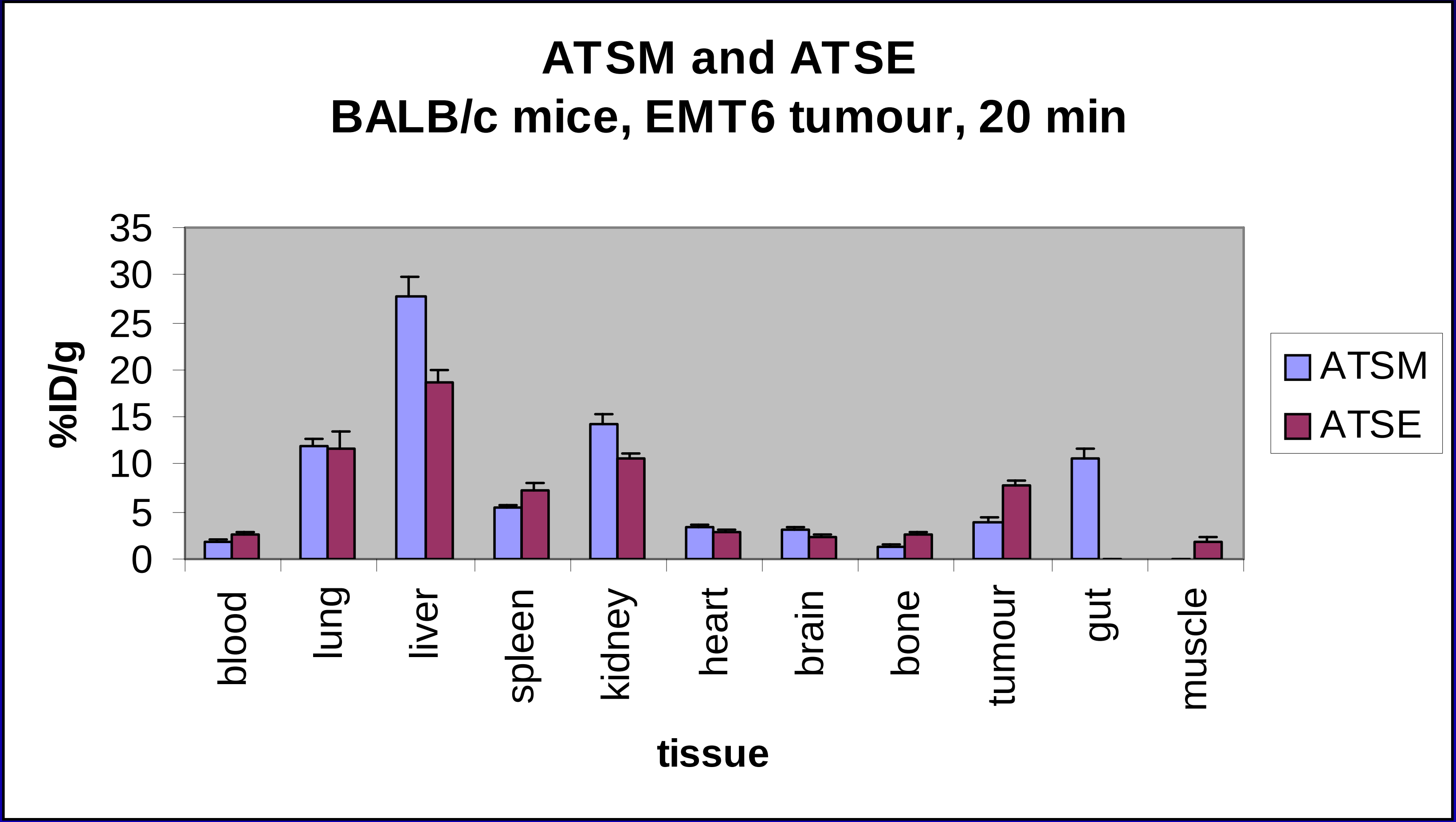
ATSE vs. ATSM: biodistribution



ATSE

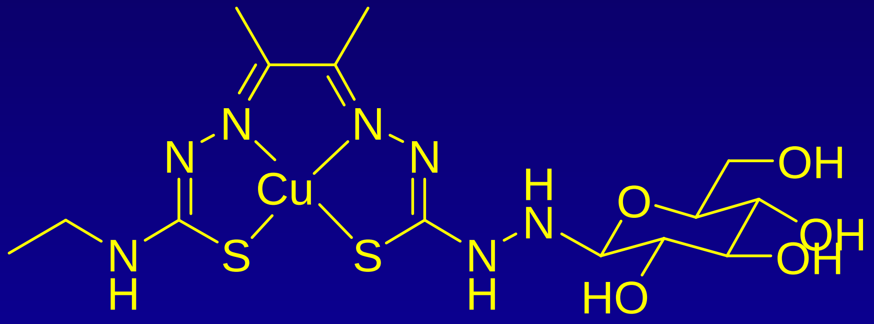


ATSM



ATSE uptake higher in tumour, lower in liver and kidney

Another step



(Dilworth, Christlieb et al. 2008)
More hydrophilic
Less liver uptake
Less brain uptake
Partial renal excretion
Retains hypoxia selectivity in vitro

Quo vadis: son of ATSM (siblings of ATSE?)

- There is a possibility to tune properties for optimal **biodistribution**, **uptake/clearance time**, and **switching O_2 concentration**
  - CuATSM and CuATS are both hypoxia selective, CuATSM crosses BBB, CuATS does not
  - Several complexes reach plateau faster than CuATSM
  - Clinically/radiobiologically relevant hypoxia level depends on context; in oncology < 20 mm Hg is significant
  - CuATSM is selective at < 1 mm Hg O_2, CuATSE is selective at < 38 mm Hg O_2
  - CuATSE shows higher tumour uptake, lower liver & kidney
- Blood flow agents possible (non-selective e.g. CuPTSM)
- Radionuclide therapy of hypoxic tumours (Cu-64/67)
- Understand pharmacology of complexes?

Current work

- Screen new bis(thiosemicarbazone) structures (including unsymmetrical ones)
- Correlate uptake with radiosensitivity
- Cardiovascular applications
  - Myocardial hypoxia
  - Atherosclerotic plaque hypoxia

Thank you…

- EPSRC (Kent and KCL 2004-2007)
- CRUK (UCH/Mount Vernon/KCL, Gray Lab 2005-2010)
- MRC (Kent 1995-1998)
- CRUK (KCL clinical training fellowship 2008-2011)
- EPSRC (KCL 2008-2011)