

Selective toxicity of Cu-64-ATSM in hypoxic cells



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Cellular DNA

Environmental/
clinical exposure

DNA repair

Damaged DNA

Replication of
damaged template

Cell cycle
arrest

Apoptosis

Mutation

Cancer

Hypoxia

Reduced levels of oxygen in tissues

Present in a number of disorders, especially cardiovascular disease and cancer

Presents a therapeutic problem in cancer; hypoxic tumours less sensitive to conventional radiotherapy due to reduced “oxygen enhancement effect”

Good candidate for nuclear medicine to develop complexes for imaging (to replace invasive oxygen electrode) and, possibly, therapy

Cellular DNA

Clinical exposure to radiation

Reactive oxygen species

DNA repair

Damaged DNA

Replication of damaged template

Cell cycle arrest

Apoptosis

Mutation

Cancer

Copper-64

Short half-life (12.7 hours)

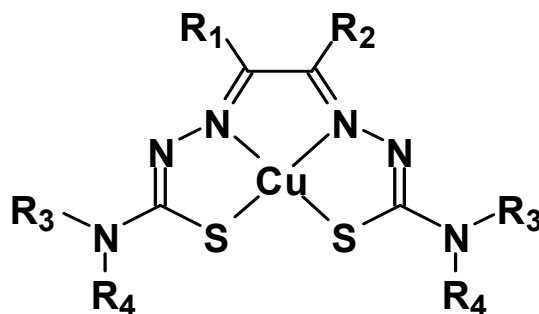
Emits γ -radiation and positrons for imaging (gamma or PET)

Emits β^- and Auger electrons

- Possible applications in targeted therapy

Offers versatile and useful coordination chemistry

Copper-64-bis(thiosemicarbazone) complexes



	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
PTSM₂	CH ₃	H	CH ₃	CH ₃
PTSE	CH ₃	H	C ₂ H ₅	H
PTSP	CH ₃	H	C ₆ H ₅	H
ATS	CH ₃	CH ₃	H	H
ATSM	CH ₃	CH ₃	CH ₃	H
CTS	C ₂ H ₅	CH ₃	H	H
CTSM	C ₂ H ₅	CH ₃	CH ₃	H
DTS	C ₂ H ₅	C ₂ H ₅	H	H
DTSM	C ₂ H ₅	C ₂ H ₅	CH ₃	H

Dearling et al (2002)

J Biol Inorg Chem, **7**: 249-259

Measuring cellular responses to radiopharmaceuticals



Treat cells
with Cu-64-
ATSM



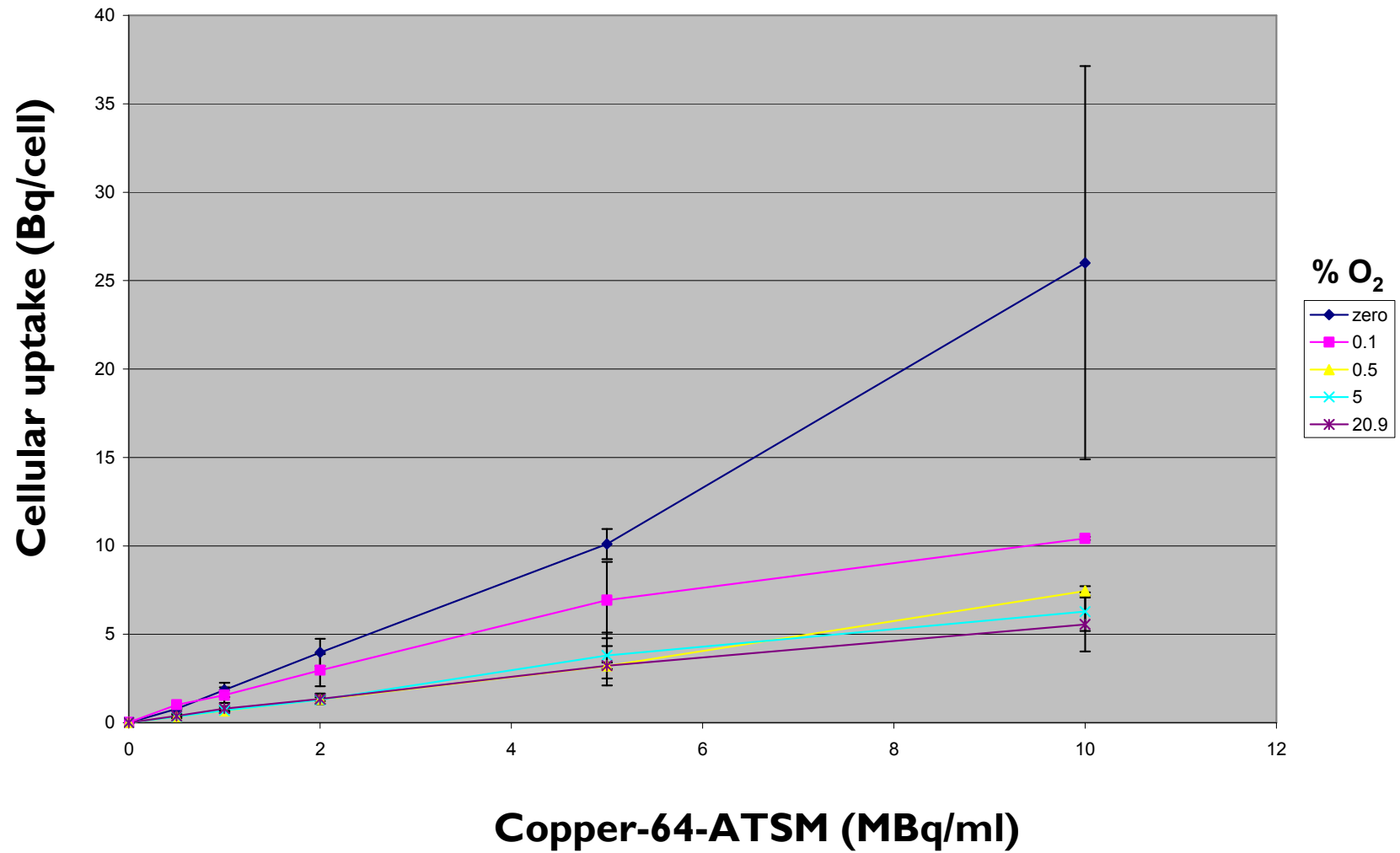
Clonogenic survival
assay

Measure
cellular
uptake using
phosphor-
imager

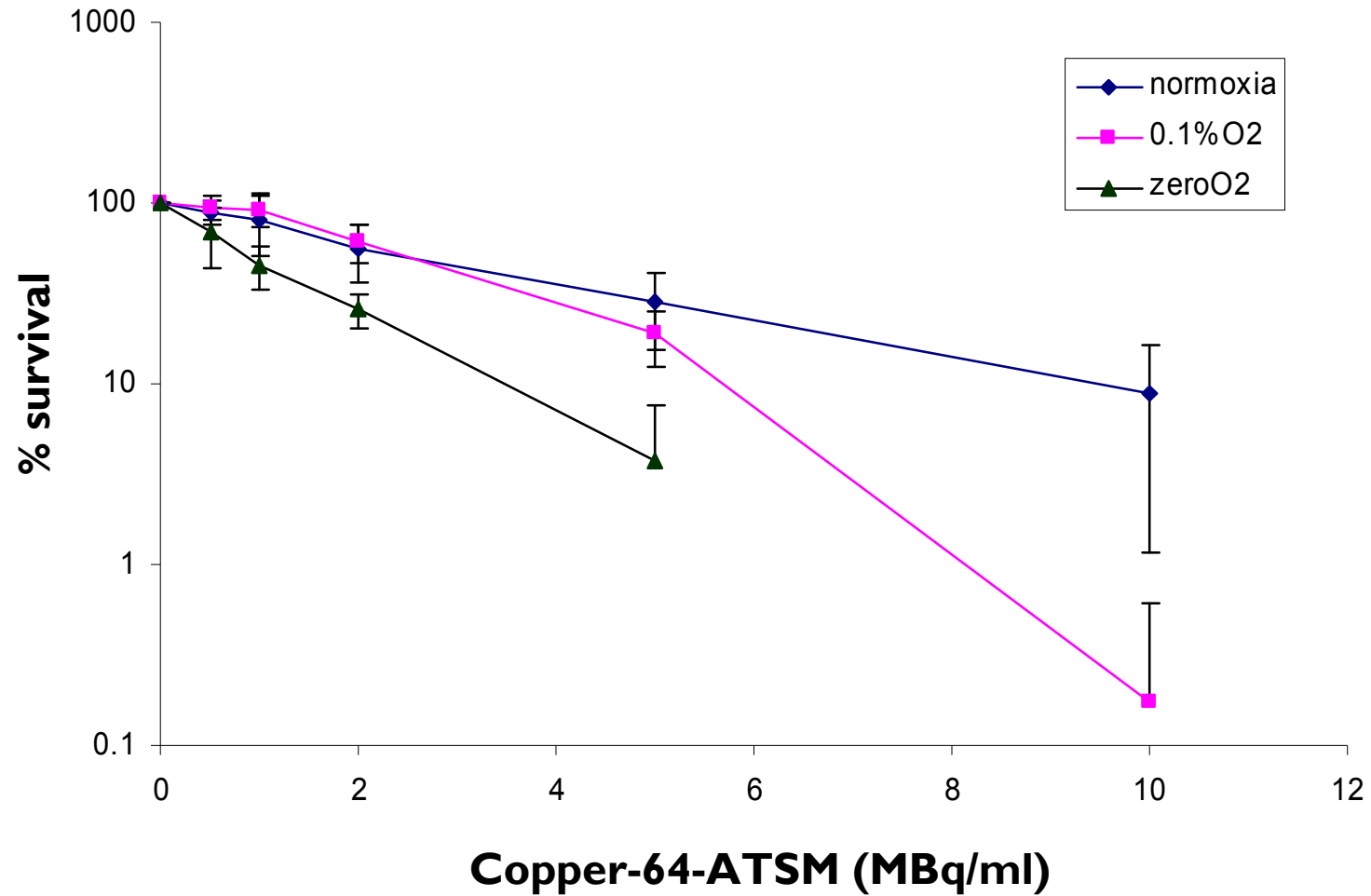


Single cell gel
electrophoresis
(Comet) assay

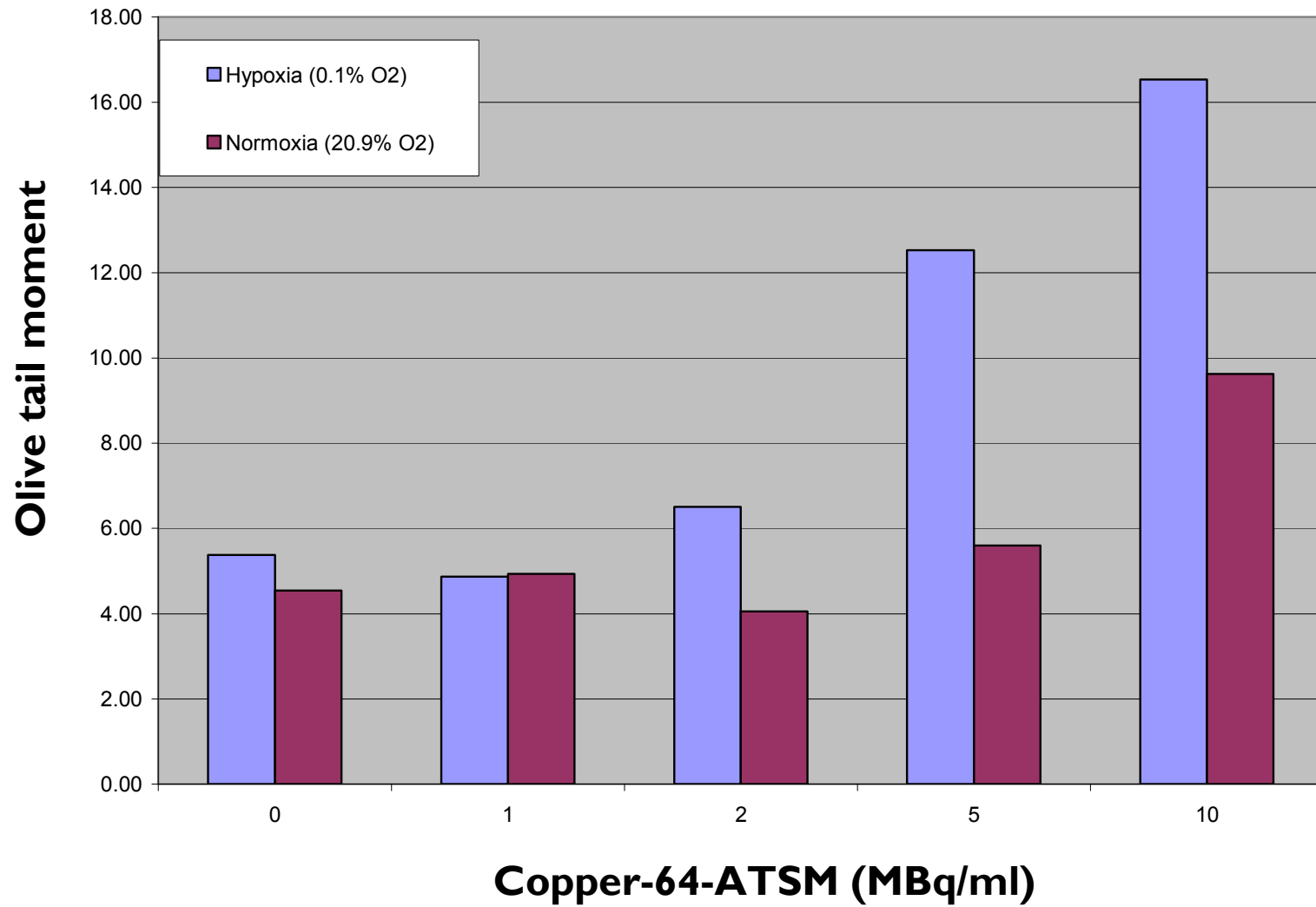
Hypoxia-selective uptake of Cu-64-ATSM in MCF7 cells



Hypoxia-selective toxicity of Cu-64-ATSM in MCF7 cells



DNA damage induced by Cu-64-ATSM in MCF7 cells increases with hypoxia



Summary

Successful application of experimental framework for measuring uptake, DNA-damage and toxicity of Cu-64

Selective uptake of Cu-64-ATSM into hypoxic MCF-7 cells

Increased toxicity in radioresistant, hypoxic MCF-7 cells

Increased DNA damage in radioresistant, hypoxic MCF7 cells

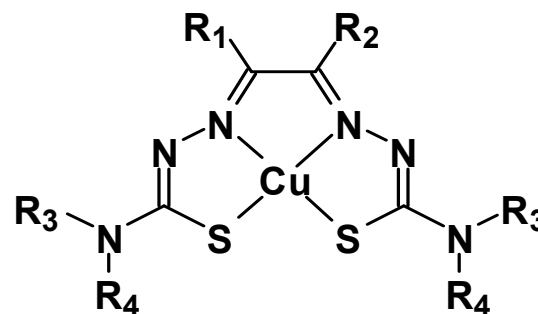
DNA damage correlates well with toxicity and is an early marker of increased cellular sensitivity

Future directions

Subcellular distribution of copper-64

Bystander toxicity

Screening of other
bis(thiosemicarbazone)
complexes



	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
PTSM₂	CH ₃	H	CH ₃	CH ₃
PTSE	CH ₃	H	C ₂ H ₅	H
PTSP	CH ₃	H	C ₆ H ₅	H
ATS	CH ₃	CH ₃	H	H
ATSM	CH ₃	CH ₃	CH ₃	H
CTS	C ₂ H ₅	CH ₃	H	H
CTSM	C ₂ H ₅	CH ₃	CH ₃	H
DTS	C ₂ H ₅	C ₂ H ₅	H	H
DTSM	C ₂ H ₅	C ₂ H ₅	CH ₃	H

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