Queen's University Belfast
School of Pharmacy

Novel Approaches to Targeting Tumour Growth

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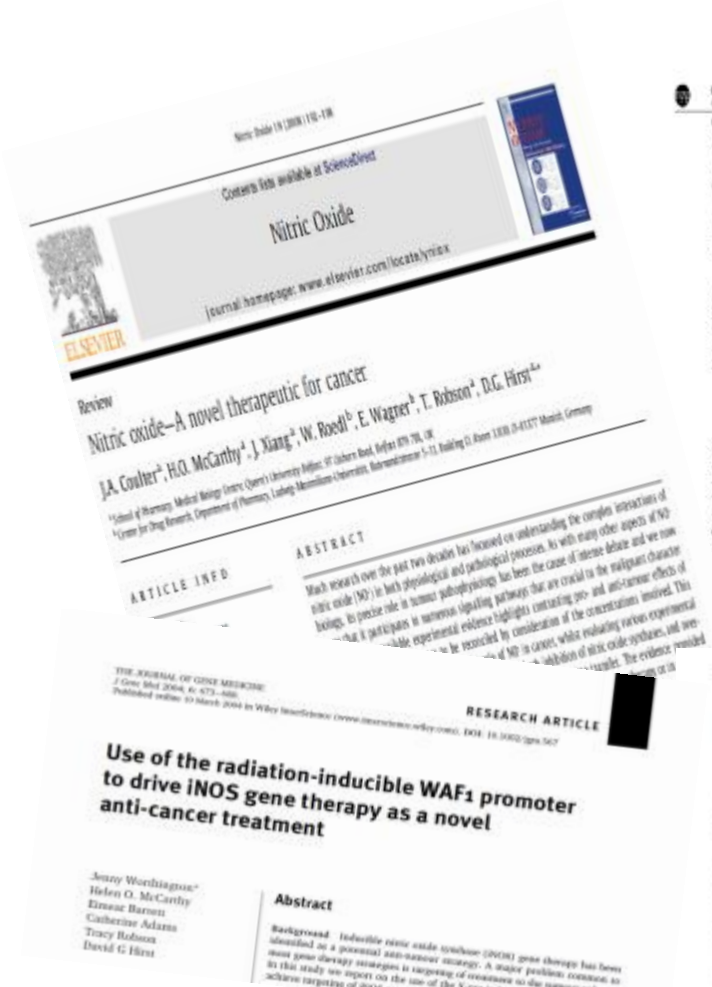
'Designer Biomimetic Vectors for the Delivery of Nucleic Acids

Principle Investigator: Dr Helen McCarthy
Co-investigator: Tracy Robson

iNOS Gene Therapy



Review

Nitric oxide–A novel therapeutic for cancer

J.A. Coulter[a], H.O. McCarthy[a], J. Xiang[a], W. Roedl[b], E. Wagner[b], T. Robson[a], D.G. Hirst[a,*]

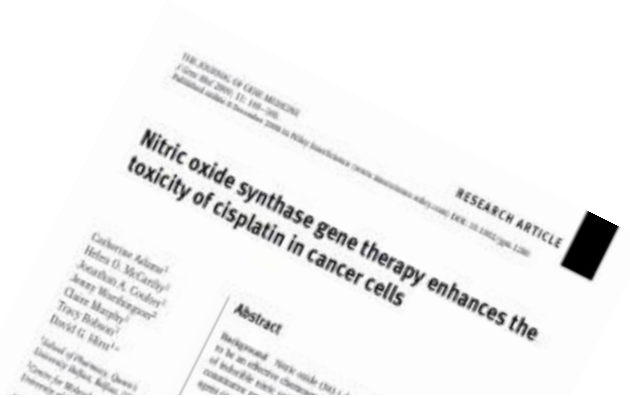
ARTICLE INFO

ABSTRACT

ORIGINAL ARTICLE

p21(WAF1)-mediated transcriptional targeting of inducible nitric oxide synthase gene therapy sensitizes tumours to fractionated radiotherapy

HO McCarthy[1,4], J Worthington[2,4], E Barnett[2], E Cosimo[2], M Boyd[2], RJ Mairs[3], C Ward[2], SR McKeown[2], DG Hirst[1] and T Robson[1]



Nitric oxide synthase gene therapy enhances the toxicity of cisplatin in cancer cells

RESEARCH ARTICLE

Abstract

RESEARCH ARTICLE

Use of the radiation-inducible WAF1 promoter to drive iNOS gene therapy as a novel anti-cancer treatment

Jenny Worthington*, Helen O. McCarthy, Eimear Barnett, Catherine Adams, Tracy Robson, David G Hirst

Abstract

ORIGINAL ARTICLE

The radiation-inducible pE9 promoter driving inducible nitric oxide synthase radiosensitizes hypoxic tumour cells to radiation

JA Coulter[1,4], HO McCarthy[1,4], J Worthington[2], T Robson[1], S Scott[3] and DG Hirst[1]

RESEARCH ARTICLE

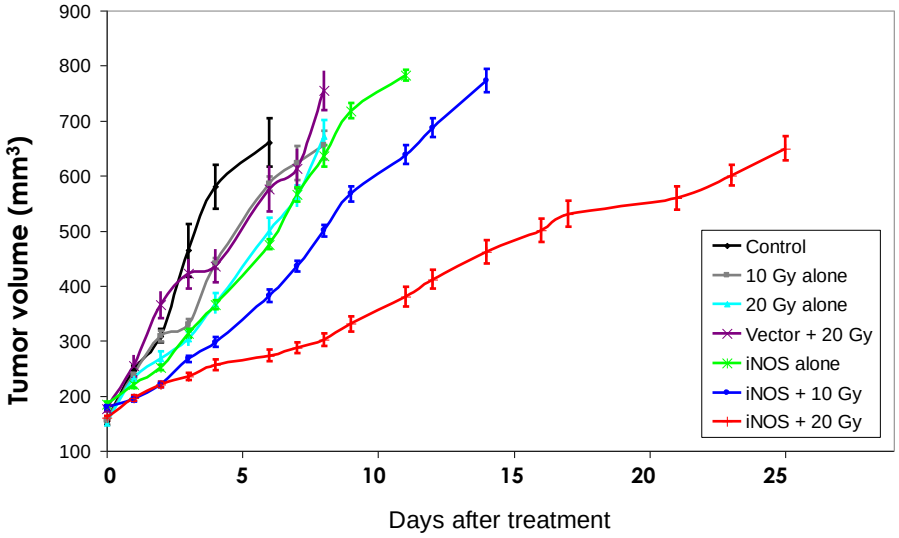
Human osteocalcin: a strong promoter for nitric oxide synthase gene therapy, with specificity for hormone refractory prostate cancer

Helen O. McCarthy, Jonathan A. Coulter, Jenny Worthington, Tracy Robson, David G. Hirst

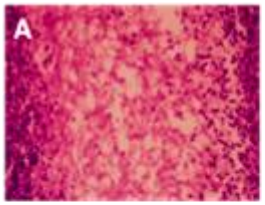
Abstract

iNOS radiogenic therapy

Cytotoxicity and radiosensitisation of RIF-1 tumours *in vivo*.

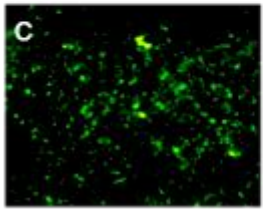


Necrosis and apoptosis (*in vivo*)

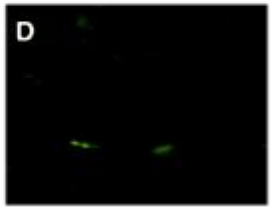


H & E tumour 24 h after CMV/iNOS

H & E of control tumour.

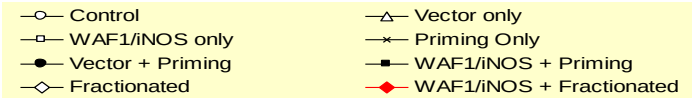


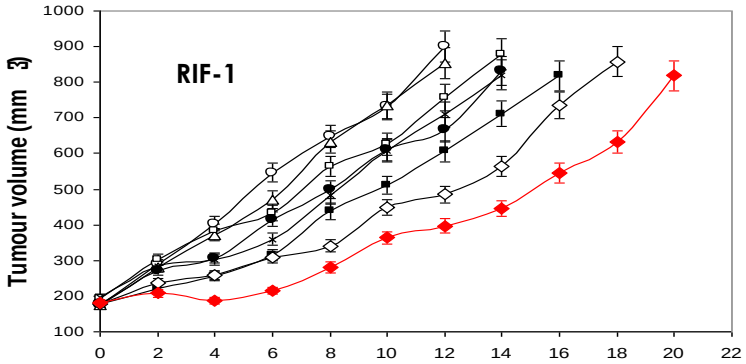
Tunel (CMViNOS)

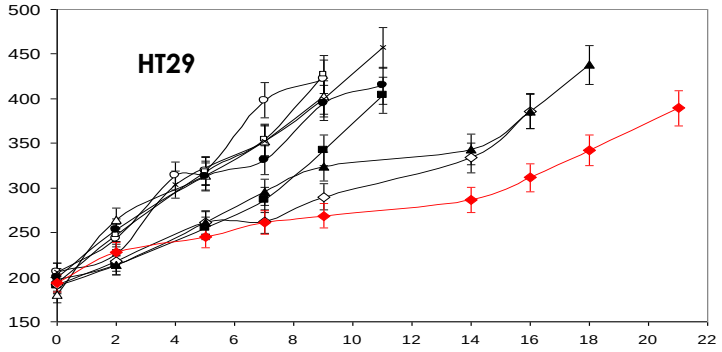


Tunel (control)

Also effective in fractionated protocols



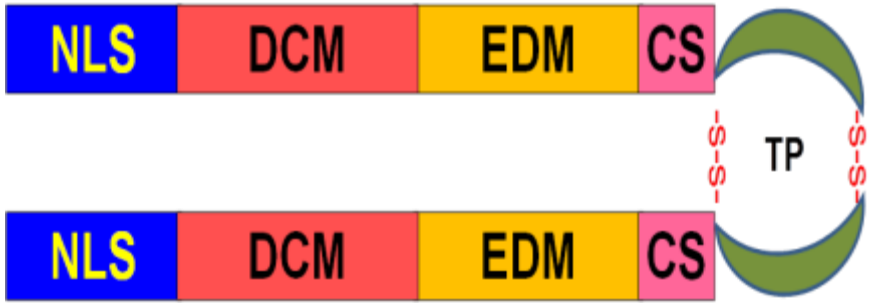




Conclusion: NO· production by activation of the transfected iNOS gene kills tumour cells and sensitises them to radiation *in vivo*.

From Worthington et al. 2002, *Gene therapy; McCarthy et al. 2007 Gene Therapy*

Designer Biomimetic Vector



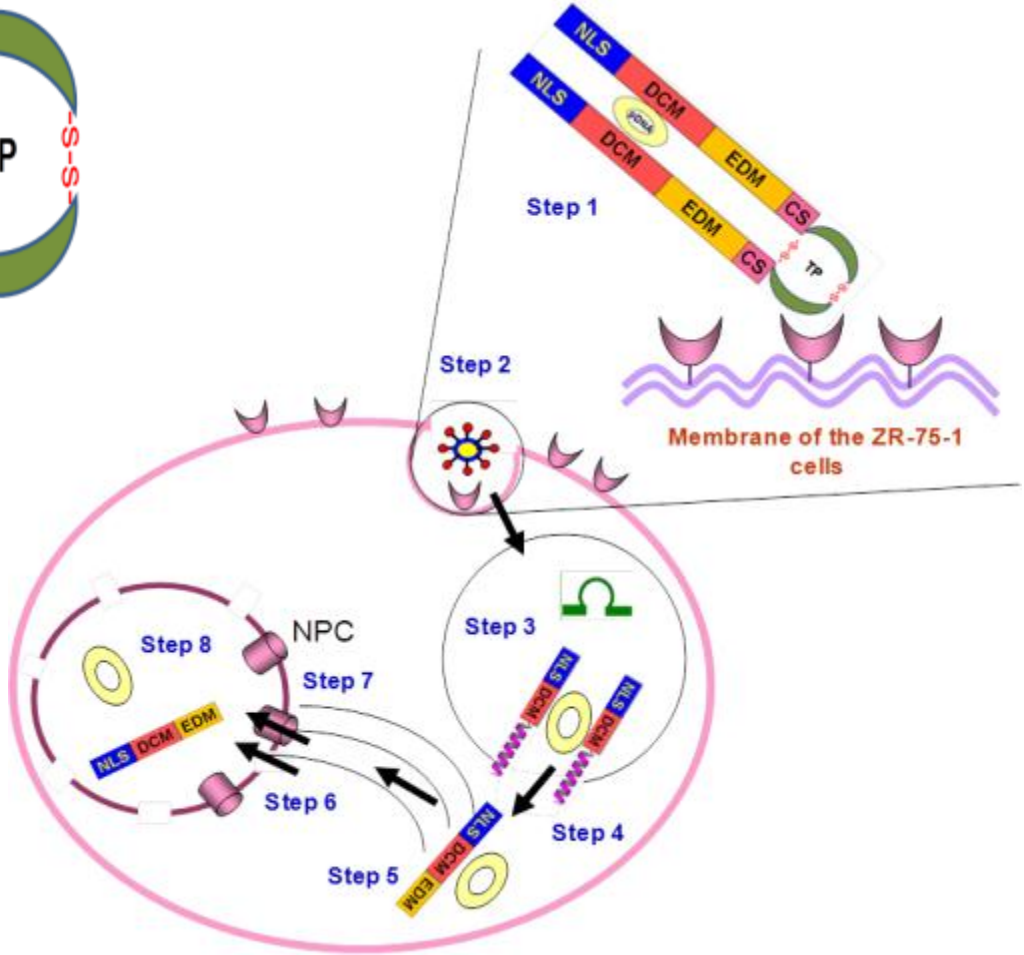
NLS – Nuclear Localisation Signal

DCM – DNA Condensing Motif

EDM- Endosomal Disruption Motif

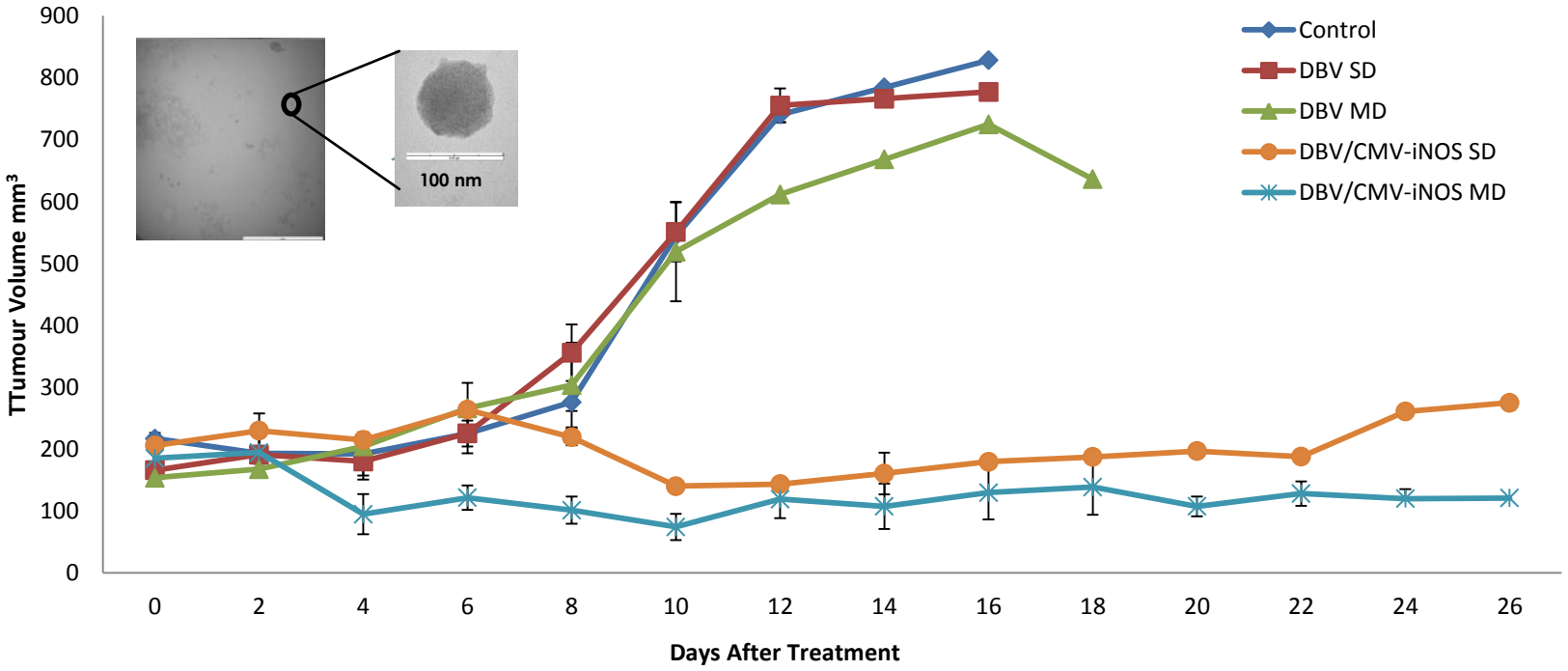
TP- Targeting Peptide

CS – Cathepsin Substrate



McCarthy et al., Int J Pharm., 2011; McCarthy et al., Expert Opin Drug Deliv., 2010

Systemic Delivery of DBV/CMV-iNOS *In Vivo*



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Ms Zahra Karjoo-Diarkhan
Dr Arash Hatefi

breast cancer CAMPAIGN researching the cure

Royal Pharmaceutical Society of Great Britain

THE PROSTATE CANCER CHARITY

EXCELLENCE IN SCIENCE

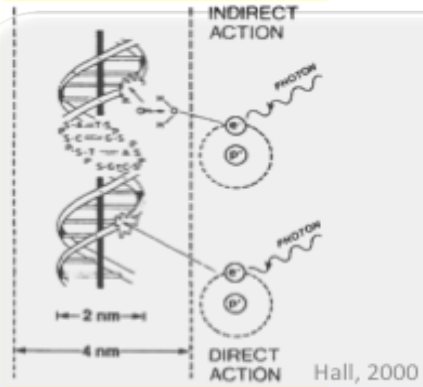
CANCER RESEARCH UK

Functionalised GNPs as Radiosensitisers

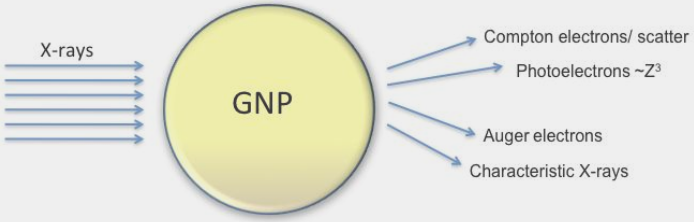
Principle Investigator: Dr Jonathan Coulter

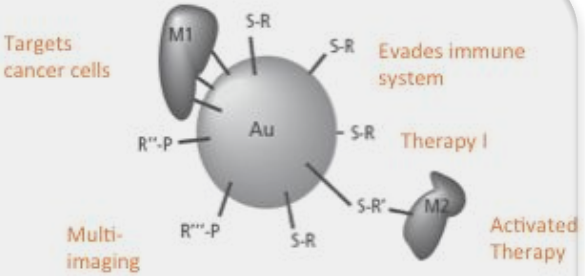
Co-investigators: Fred Currell, Kevin Prise, Joe O'Sullivan, Alan Hounsell, Helen McCarthy, Marie Migaud

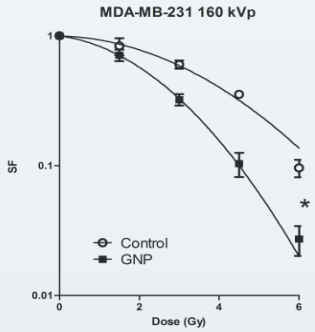
Functionalised GNPs as Radiosensitisers

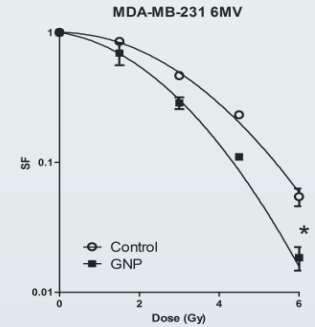


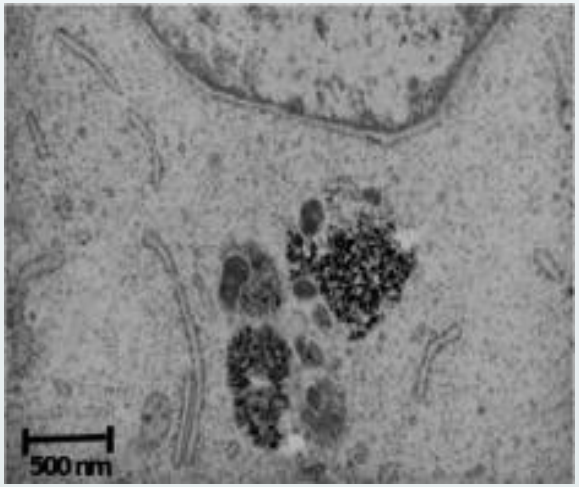
Hall, 2000

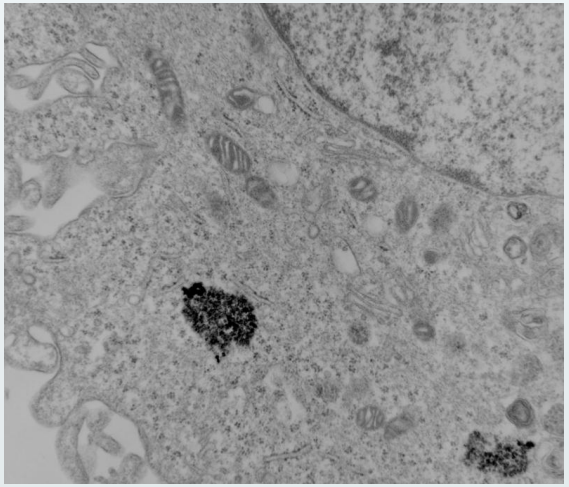










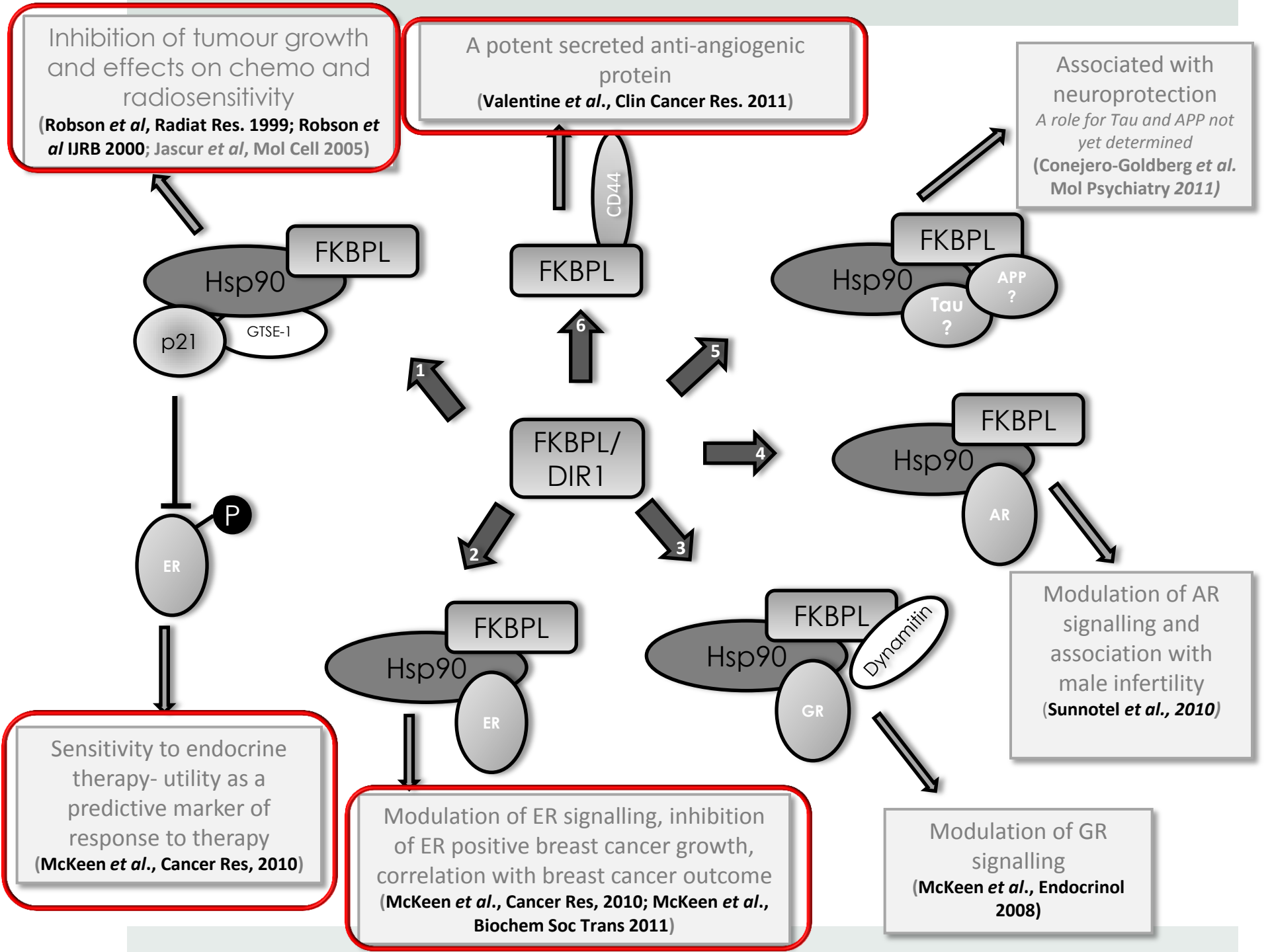


Typical accumulation of 1.9 nm GNPs

Jain et al., 2011 *Int J Radiat Oncol Biol Phys.*, 2011; Coulter et al., *Int J Nanomed.*, 2012

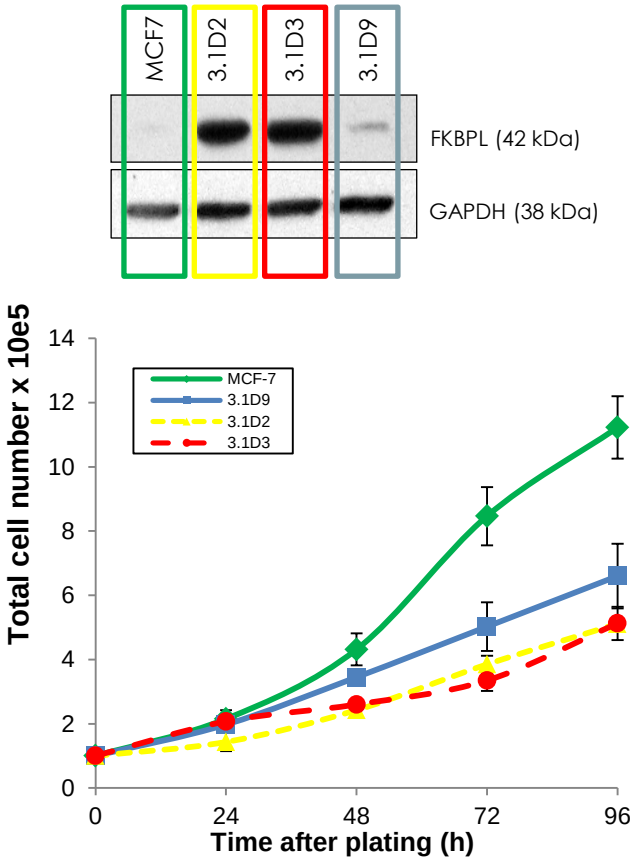
The therapeutic and diagnostic potential of FKBPL; a novel anti-cancer protein

PI: Professor Tracy Robson
Co-Inv: Dr Helen McCarthy

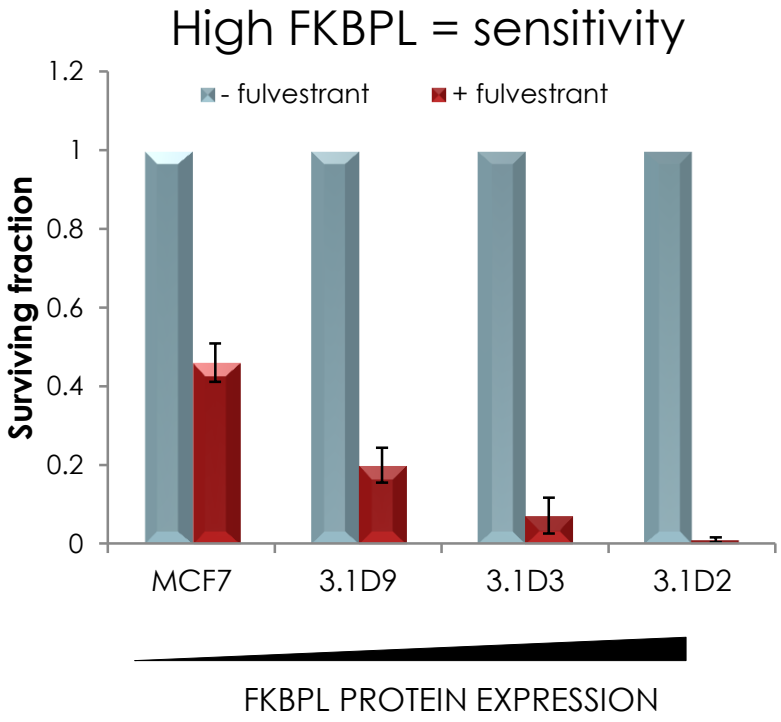

Inhibition of tumour growth and effects on chemo and radiosensitivity
(Robson et al, Radiat Res. 1999; Robson et al IJRB 2000; Jascur et al, Mol Cell 2005)
A potent secreted anti-angiogenic protein
(Valentine et al., Clin Cancer Res. 2011)
Associated with neuroprotection
A role for Tau and APP not yet determined
(Conejero-Goldberg et al. Mol Psychiatry 2011)
FKBPL
Hsp90
p21
GTSE-1
CD44
FKBPL
FKBPL
Hsp90
APP ?
Tau ?
6
1
5
FKBPL/ DIR1
4
FKBPL
Hsp90
AR
P
ER
2
3
FKBPL
Hsp90
ER
FKBPL
Hsp90
Dynamitin
GR
Modulation of AR signalling and association with male infertility
(Sunnotel et al., 2010)
Sensitivity to endocrine therapy- utility as a predictive marker of response to therapy
(McKeen et al., Cancer Res, 2010)
Modulation of ER signalling, inhibition of ER positive breast cancer growth, correlation with breast cancer outcome
(McKeen et al., Cancer Res, 2010; McKeen et al., Biochem Soc Trans 2011)
Modulation of GR signalling
(McKeen et al., Endocrinol 2008)

The diagnostic potential of FKBPL

Increased FKBPL slows breast cancer cell proliferation

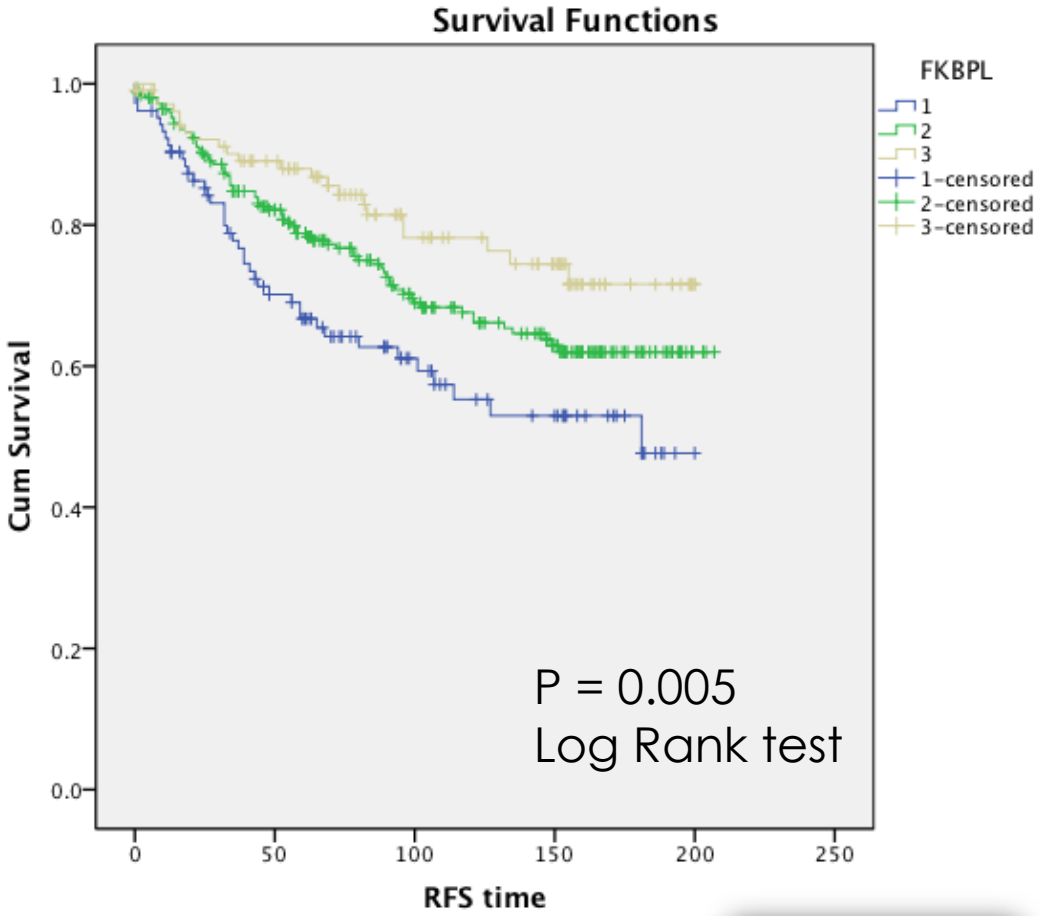


FKBPL modulates the response to endocrine therapy

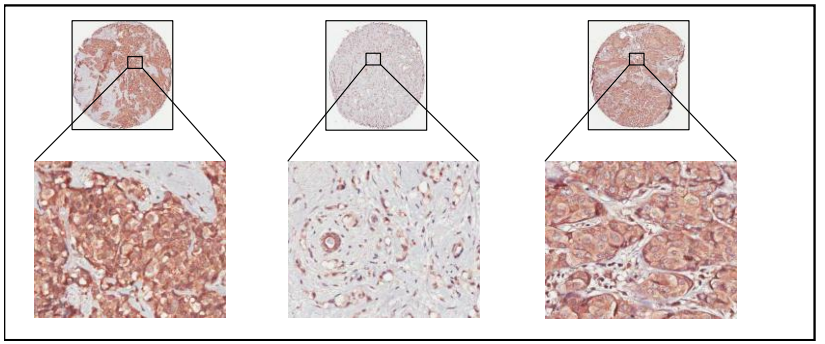


McKeen *et al., Cancer Res.* 2010

FKBPL increases recurrence free survival



Screening breast cancer TMA for FKBPL



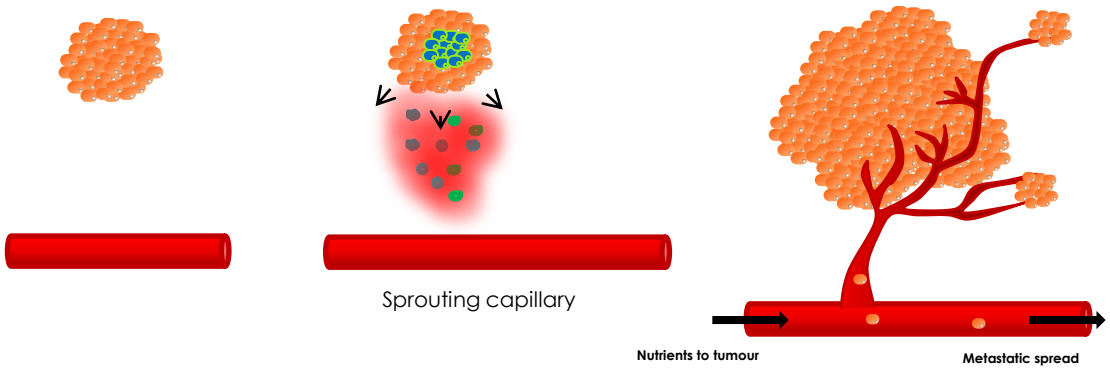
FKBPL	Total N	N of Events	Censored	
			N	Percent
1	104	41	63	60.6%
2	256	76	180	70.3%
3	105	22	83	79.0%
Overall	465	139	326	70.1%

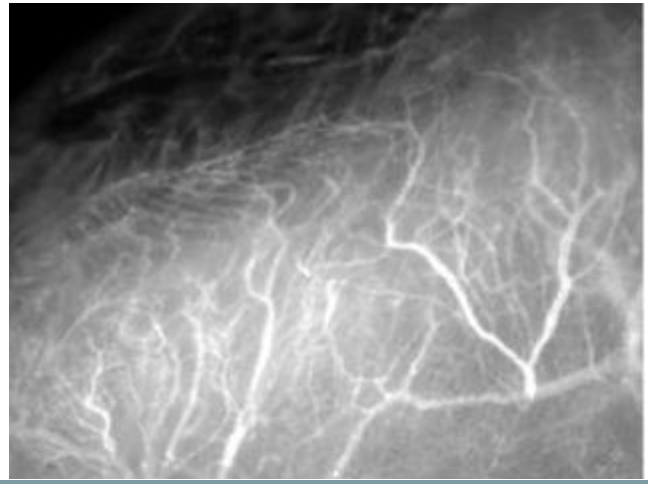
High FKBPL also correlated with:
- **Small tumour size (P= 0.023)**
- **Low grade (P=0.001)**

Chi-squared test/Pearson's correlation coefficient

MRC Medical Research Council

McKeen et al., Biochem Soc Trans 2011

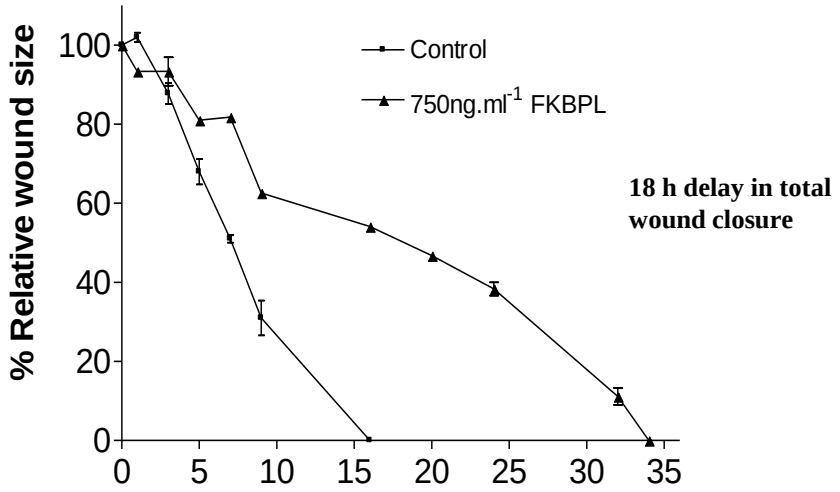




The therapeutic potential of FKBPL; an anti-angiogenic protein

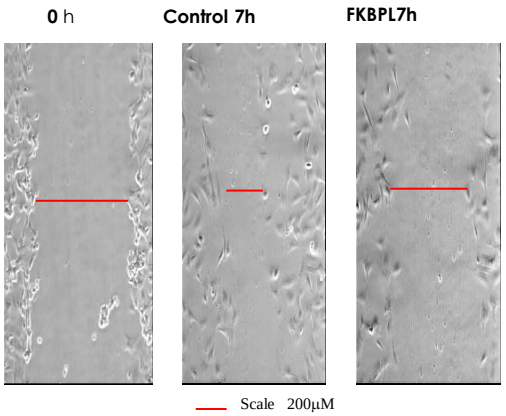
ALMAC DISCOVERY

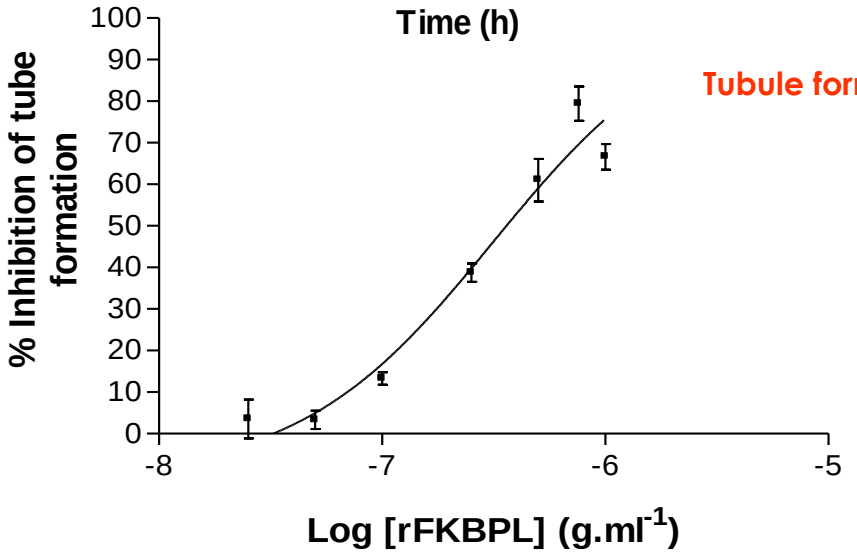
FKBPL is an anti-angiogenic protein;



18 h delay in total wound closure

HMEC-1 migration assay



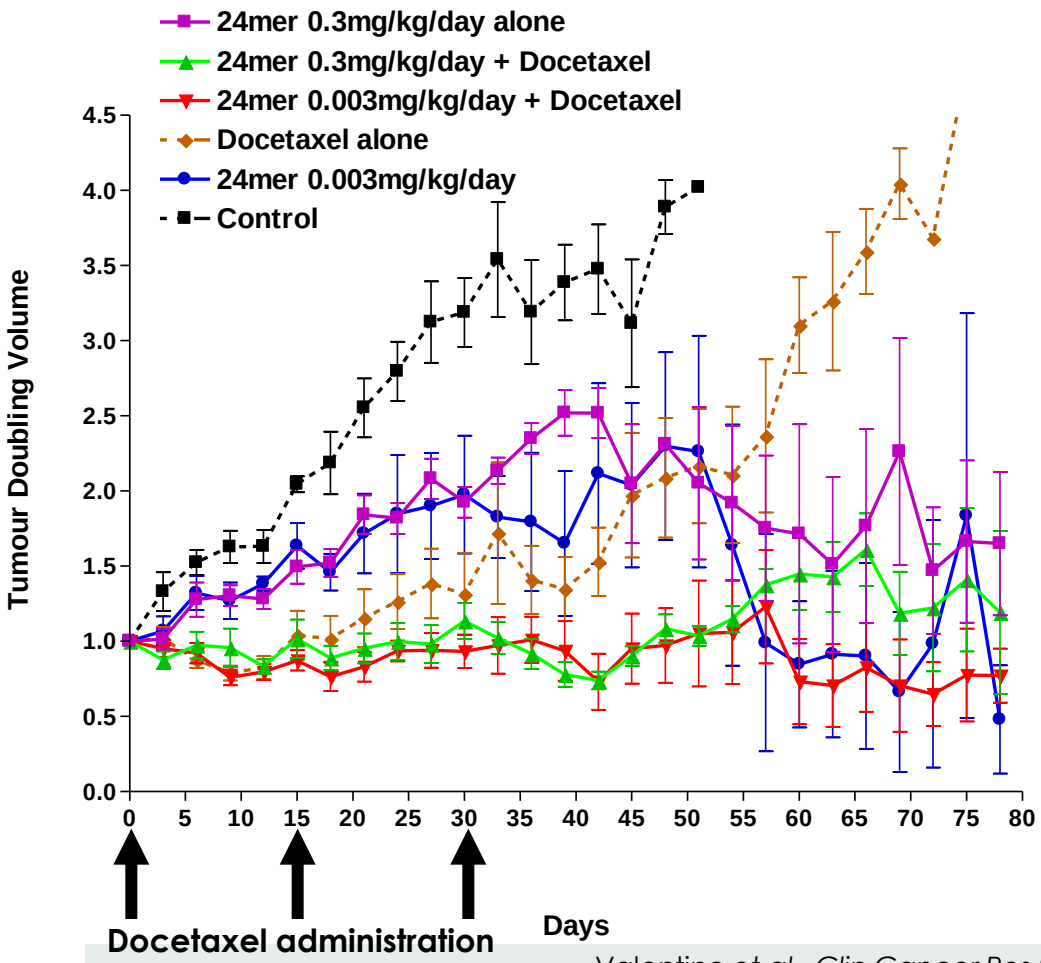


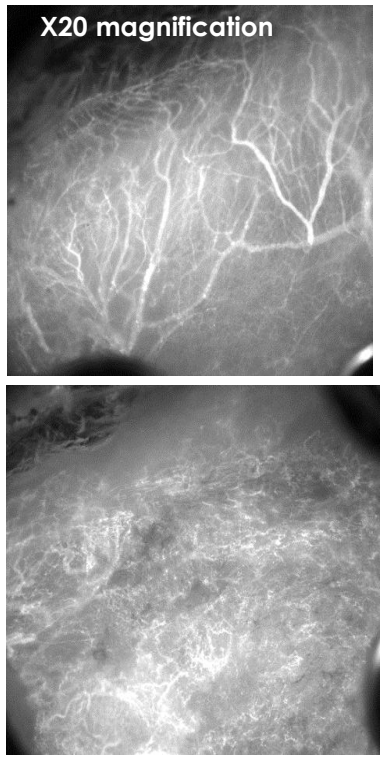
Tubule formation assay

Valentine *et al., Clin Cancer Res* 2011

AD-01, a 24mer FKBPL peptide inhibits tumour xenograft growth and prevents angiogenesis *in vivo*

Tumour model: DU145 human prostate
Treatment: 24mer, docetaxel
Dosage: 24mer I.P. daily; 0.3mg/kg and 0.003mg/kg; Docetaxel 20mg/kg once in 15 days in 3 cycles





Valentine *et al., Clin Cancer Res* 2011; Robson and James, *Drug Discovery Today* 2012

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