UKHealthTech CONFERENCE 2016

14:30 – 15:30 Parallel session

Diagnostics: New diagnostics, precision medicine and advanced therapies

A revolution in healthcare treatments is just around the corner. What does the future of healthcare look like and what are the barriers to delivering new therapies from research into clinic and practice?

UKHealthTech CONFERENCE 2016

Daryl Fernandes
Ludger
Chief Executive

Precision Medicine at Ludger: Glycomics, patient stratification and fat bellies

Paul Seaman
Midatech Pharma
Head of Sustained Delivery

Right Time, Right Place; Exploiting Micro and Nano Particulates for Drug Delivery

Fred Jacobs
Astrimmune
CEO

Targeting cancer at every stage

UKHealthTech CONFERENCE 2016

14:30 – 15:30 Parallel session

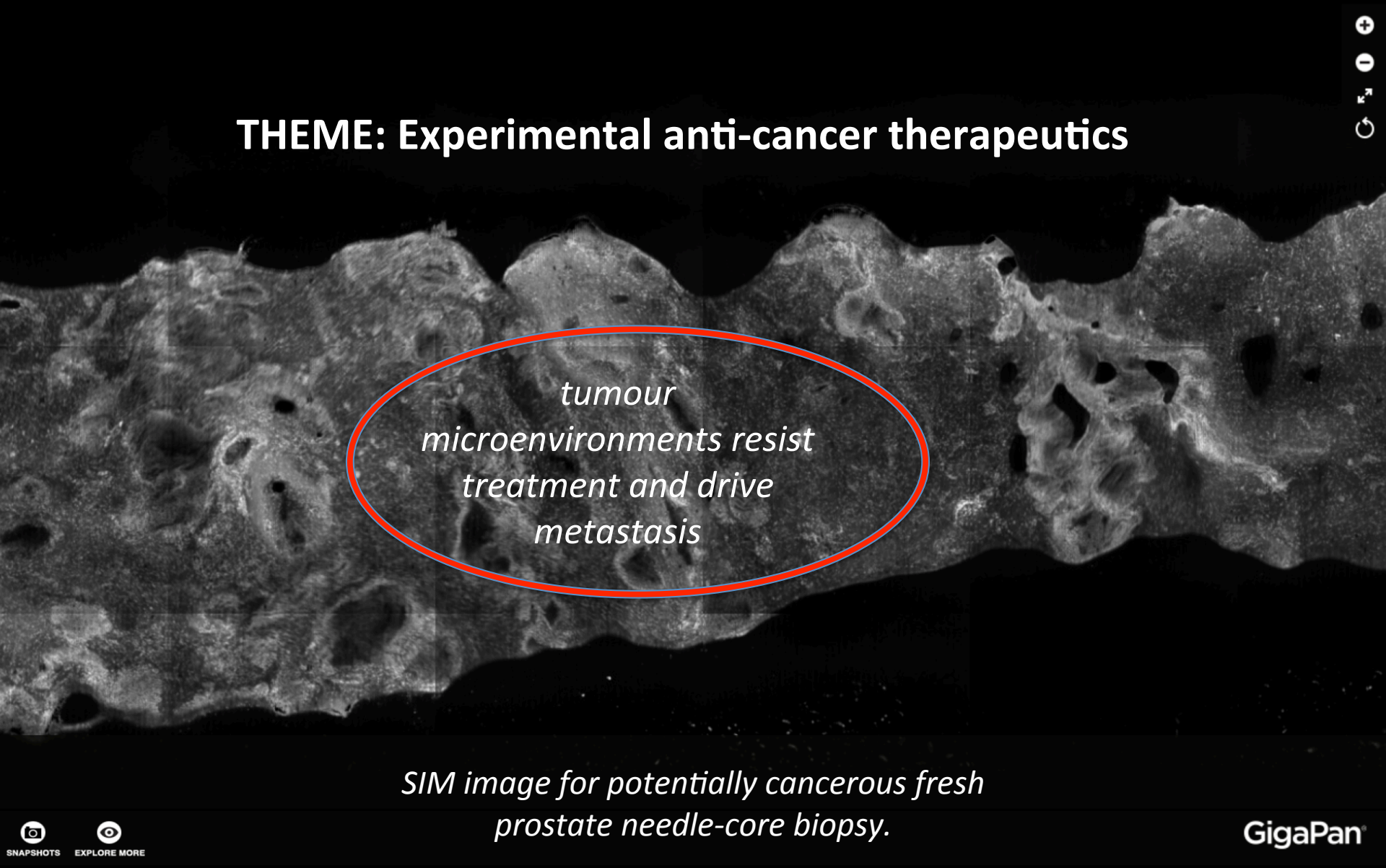
Introduction: Chair Paul J Smith[1,2,3]

Precision Medicine in the Microenvironment

[1]Cardiff Univ, Cardiff, UK,
[2]Biostatus Ltd, UK,
[3]Oncotherics Ltd, UK,


Jaeger-LeCoultre

THEME: Experimental anti-cancer therapeutics



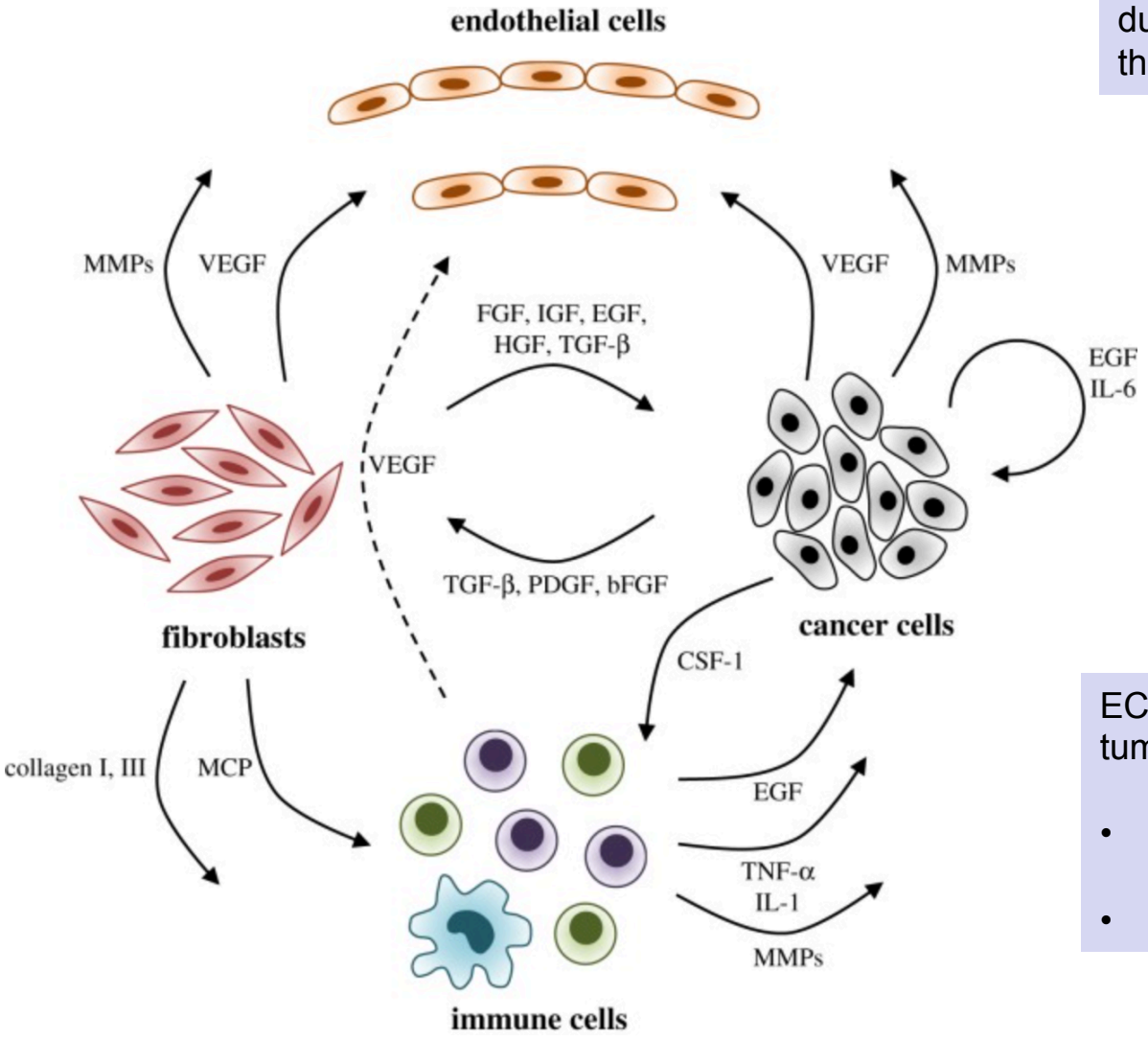
SIM image for potentially cancerous fresh prostate needle-core biopsy.

SNAPSHOTS EXPLORE MORE

GigaPan

David Tulman
Size 0.08 Gigapixels Views stitched 191

The stromal-tumour microenvironment: A new target horizon



Competitive environment rarely duplicated even in current state-of-the art 3-D models

tumours can contain tissue-specific cell types

- pancreatic stellate cells in pancreatic cancers
- adipocytes in ovarian and breast cancers

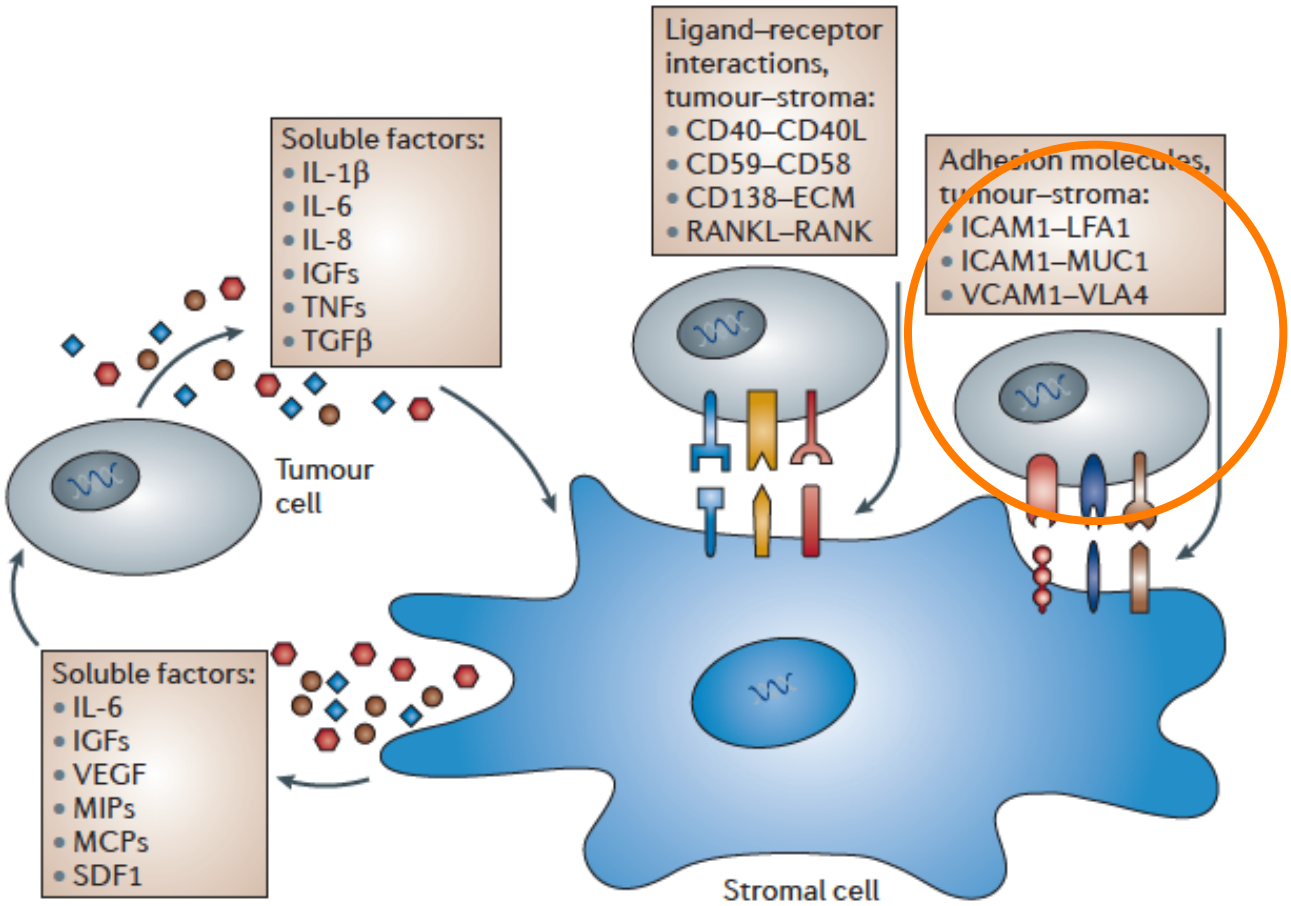
ECM can be uniquely altered in tumours

- *tumour associated collagen signatures* (TACS)
- collagen remodelling in PDAC

Andersen et al. Philosophical Transactions of the Royal Society B: Biological Sciences 2014;369:20130098. .

Extracellular tumour-microenvironment interactions: New horizon for diagnostics - challenge of complexity

- **soluble**
- **membrane-bound** mediators
- **mediators can be shared** by both the tumour and stroma



modulation of migration & spread by glycosylation

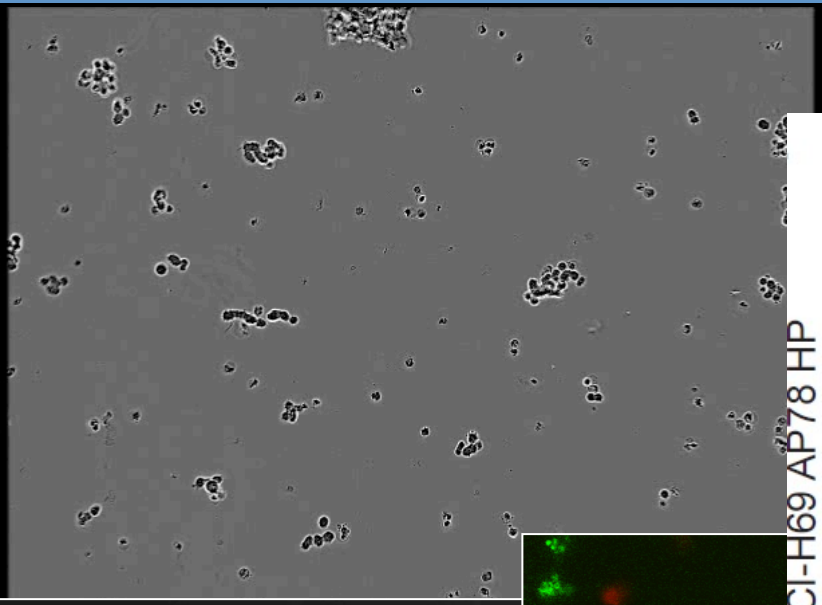
eg polysialylation NCAM in small cell lung cancer

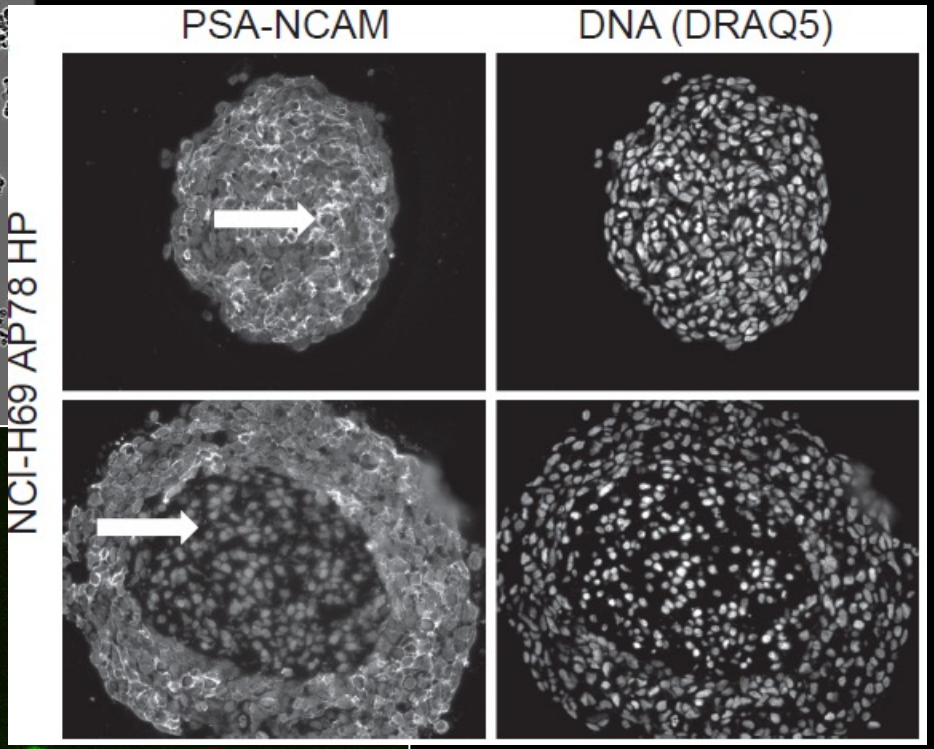
Cell surface glycome affects:

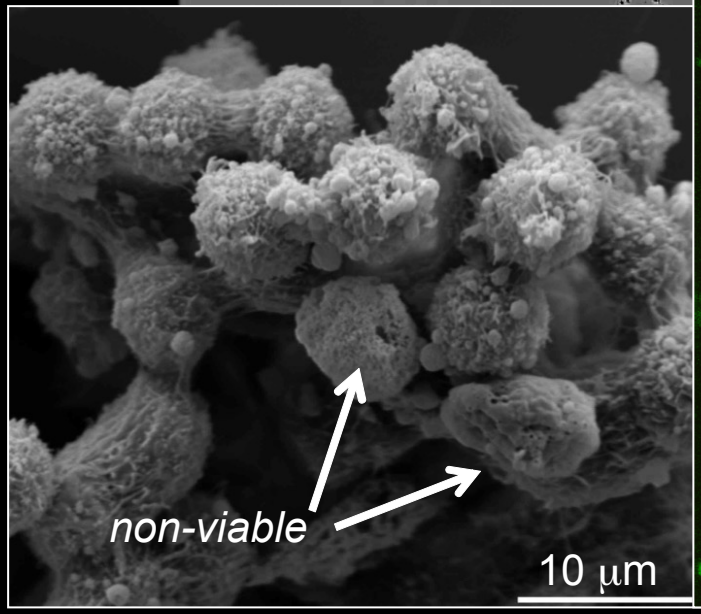
- substrate adherence
- cell-cell contacts
- matrix interactions
- migration
- immune recognition
- membrane apposition
- lectin binding etc
- cell surface protein & receptor function

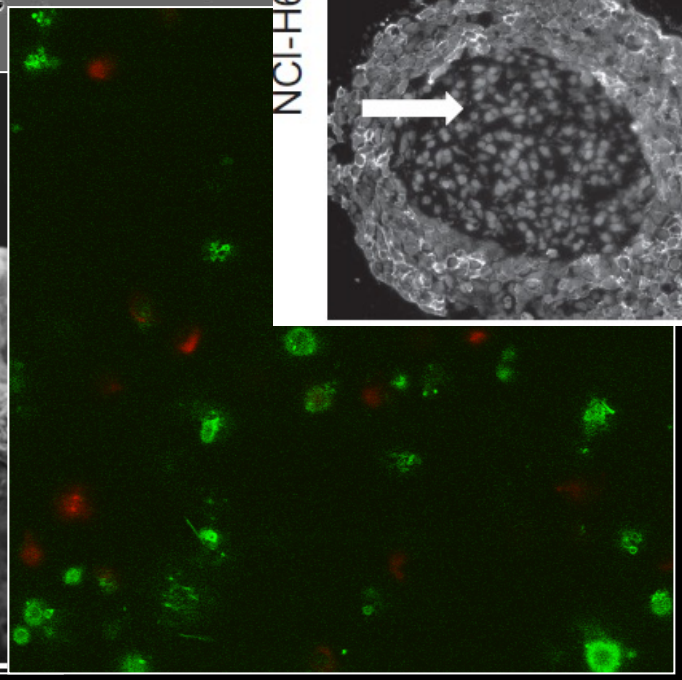
McMillin DW, **Negri** JM, **Mitsiades** CS. Nat Rev Drug Discov. 2013 Mar;12(3):217-28.

3D culture models increasingly used in drug discovery: Problem of re-capitulating the tumour microenvironment?







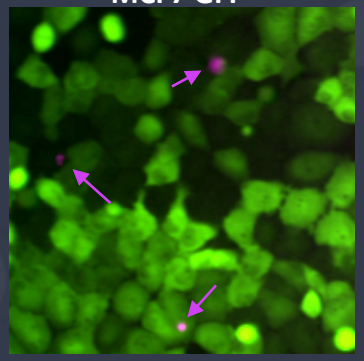


***Smith** et al Cytometry A. 2013*

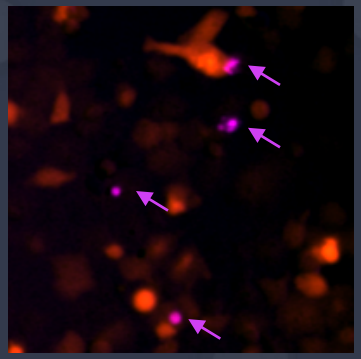
Real Time Screens Capture Dynamic Events in Drug Discovery Screens:
Viability screens with DRAQ7 technology

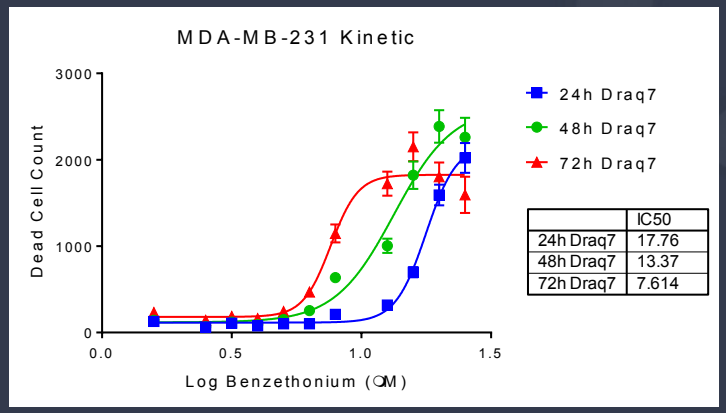
DRAQ7 Dead dye can help monitor kinetic viability of GFP or RFP transfected cell lines

MCF7 GFP



MDA-MB-231 RFP

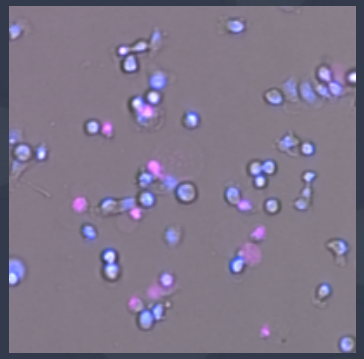




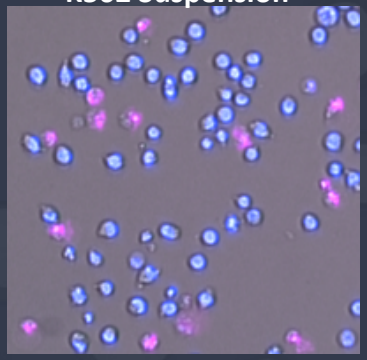
	IC50
24h Draq7	17.76
48h Draq7	13.37
72h Draq7	7.614

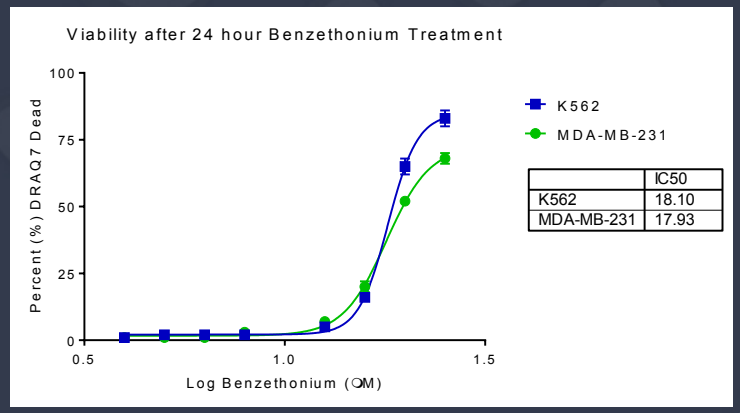
DRAQ7 dye can be used with Hoechst as an end point assay for measuring percentage of dead cells

MDA-MB-231 Adherent



K562 Suspension





	IC50
K562	18.10
MDA-MB-231	17.93

DRAQ7™ product of BioStatus Ltd

Nexcelom Bioscience

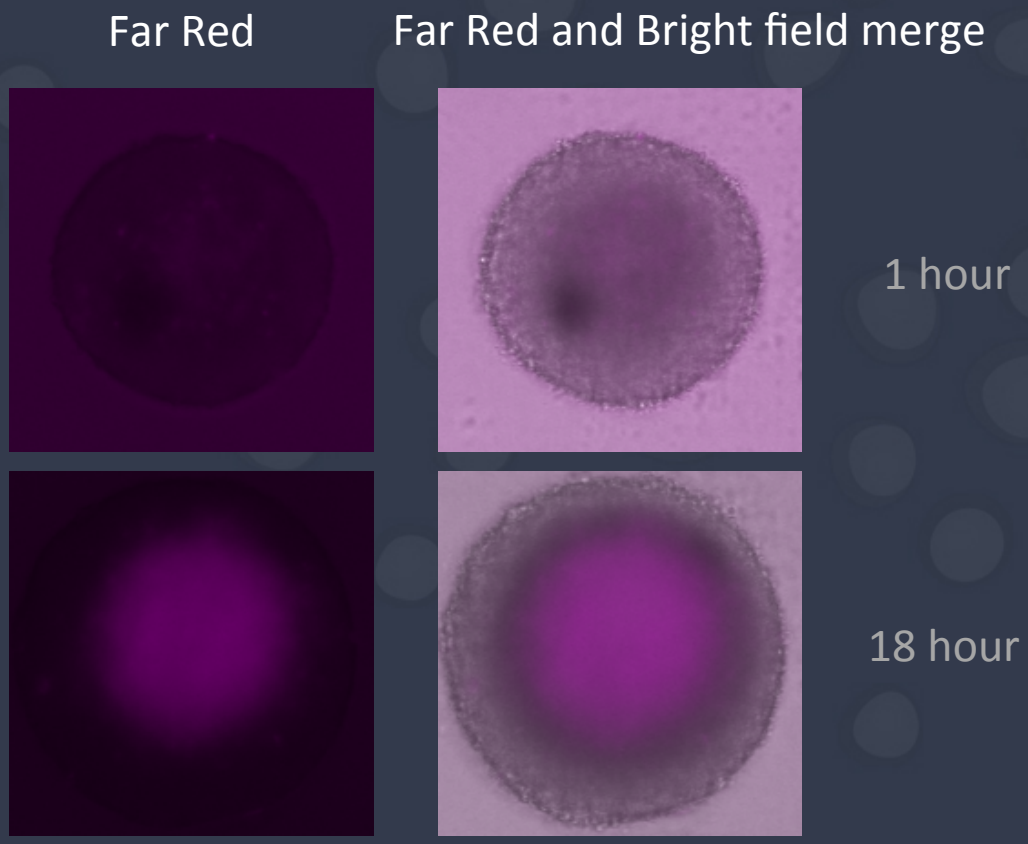
Innovation and Expertise in the Science of Cell Counting

Cellometer® | Celigo S

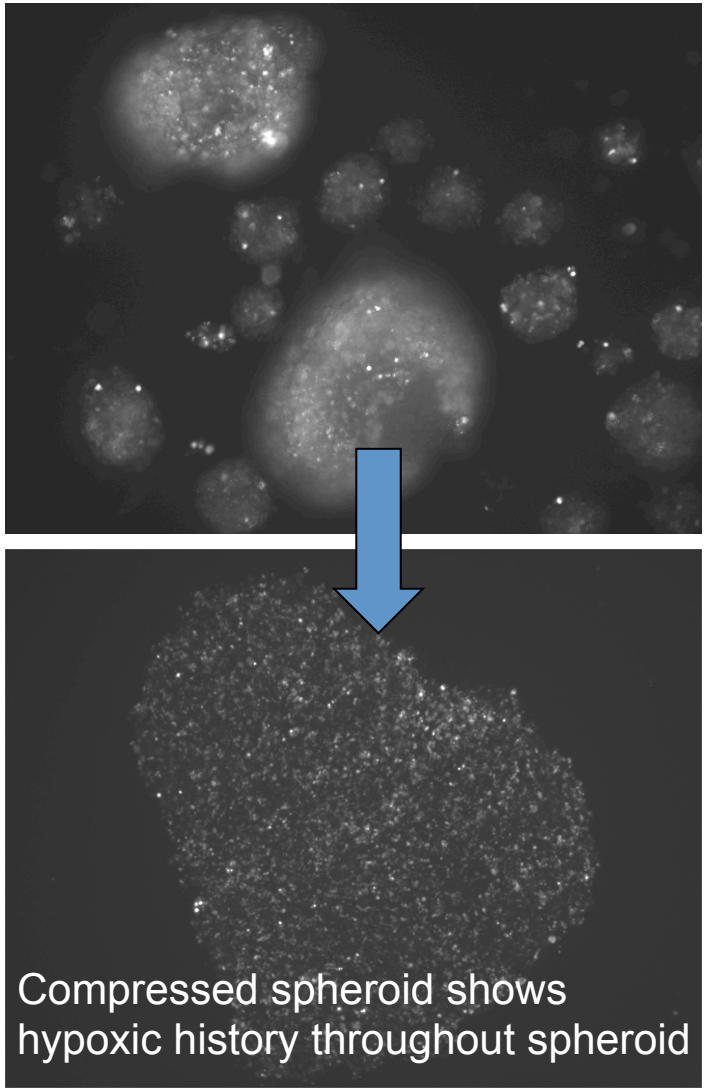
Assays moving to 3D MCTS: Real-time monitor necrotic core formation using DRAQ7

U87MG spheroids : 500 cells 4 day formation of MCTS and stained with D7 1.5uM

DRAQ7 dye can be used to detect the development of the necrotic core



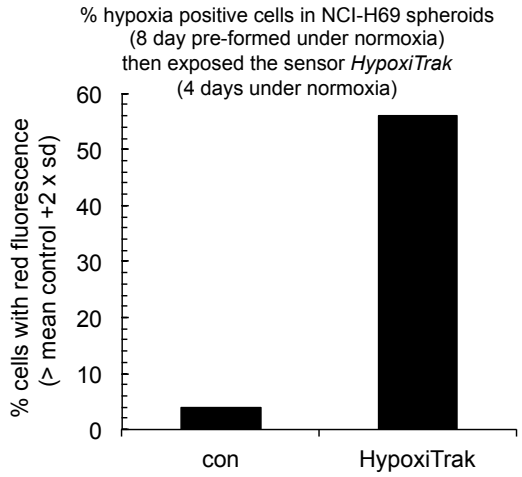
SCLC spheroids: sensing the microenvironment in 3D systems



far-red camera image: AP78 microspheroid images

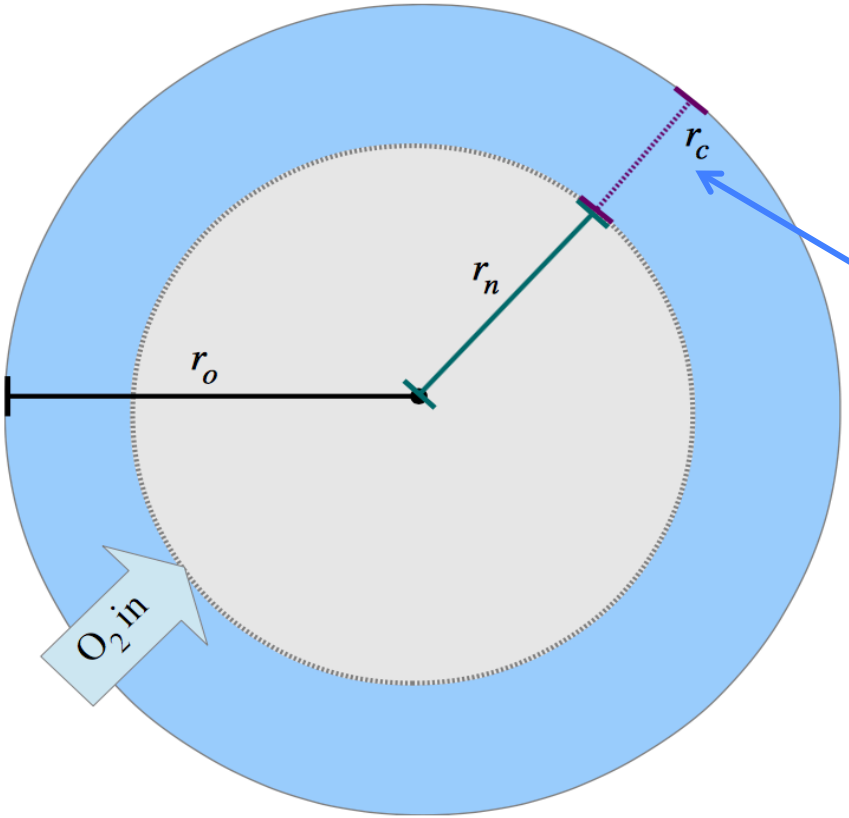
7 days plus 5 day treatment with HypoxiTrak

Hypoxic fraction by *HypoxiTrak* flow cytometry



monitoring cell health in 3D systems

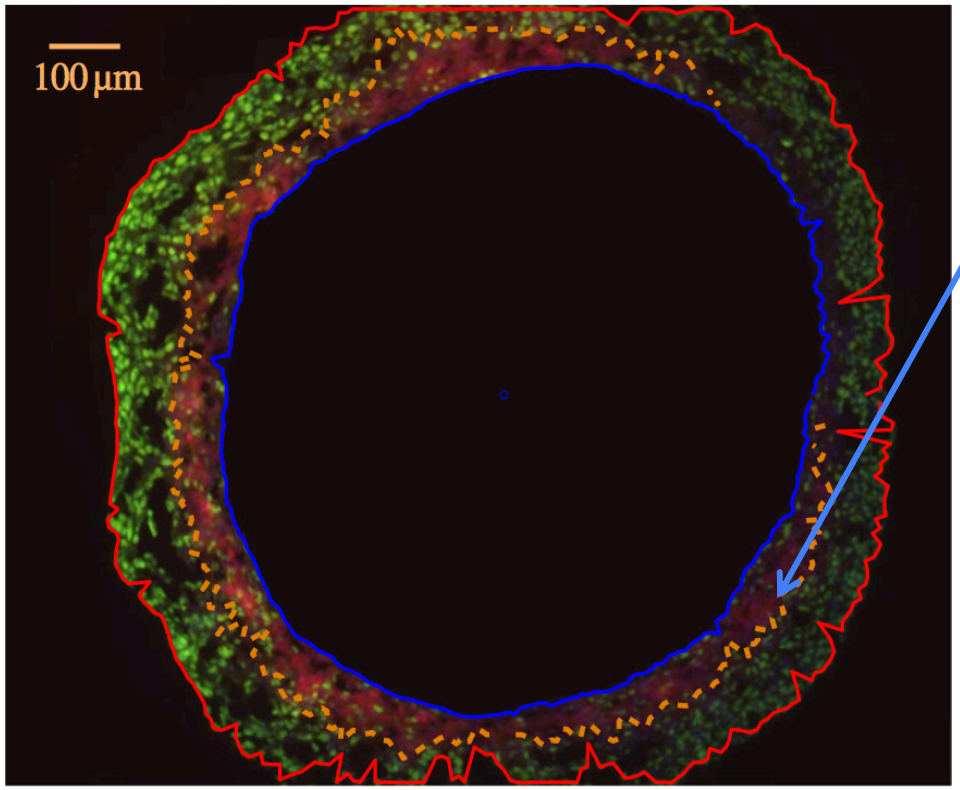
Oxygen consumption rate in multicellular tumour spheroids



- Cross section of a tumour spheroid of radius ro.
- Oxygen partial pressure is non-zero in the region rc.
- region rc comprises all viable cells both hypoxic and oxic.
- Oxygen cannot penetrate into region rn, which is anoxic.

Grimes et al J R Soc Interface. 2014 Jan 15;11(92):20131124.

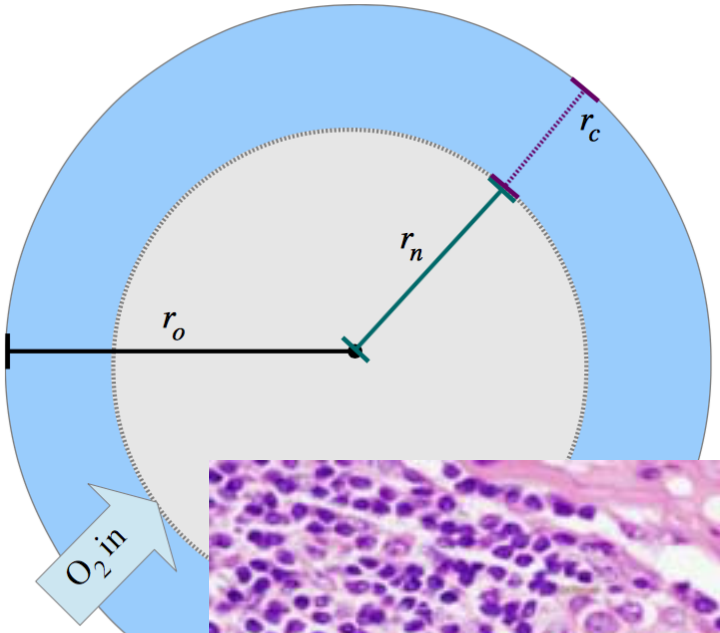
Oxygen consumption rate in multicellular tumour spheroids



- semi-automatic detection on the boundary between proliferating and hypoxic regions on a **day 17 spheroid**

Grimes et al J R Soc Interface. 2014 Jan 15;11(92):20131124.

Oxygen consumption rate in multicellular tumour spheroids



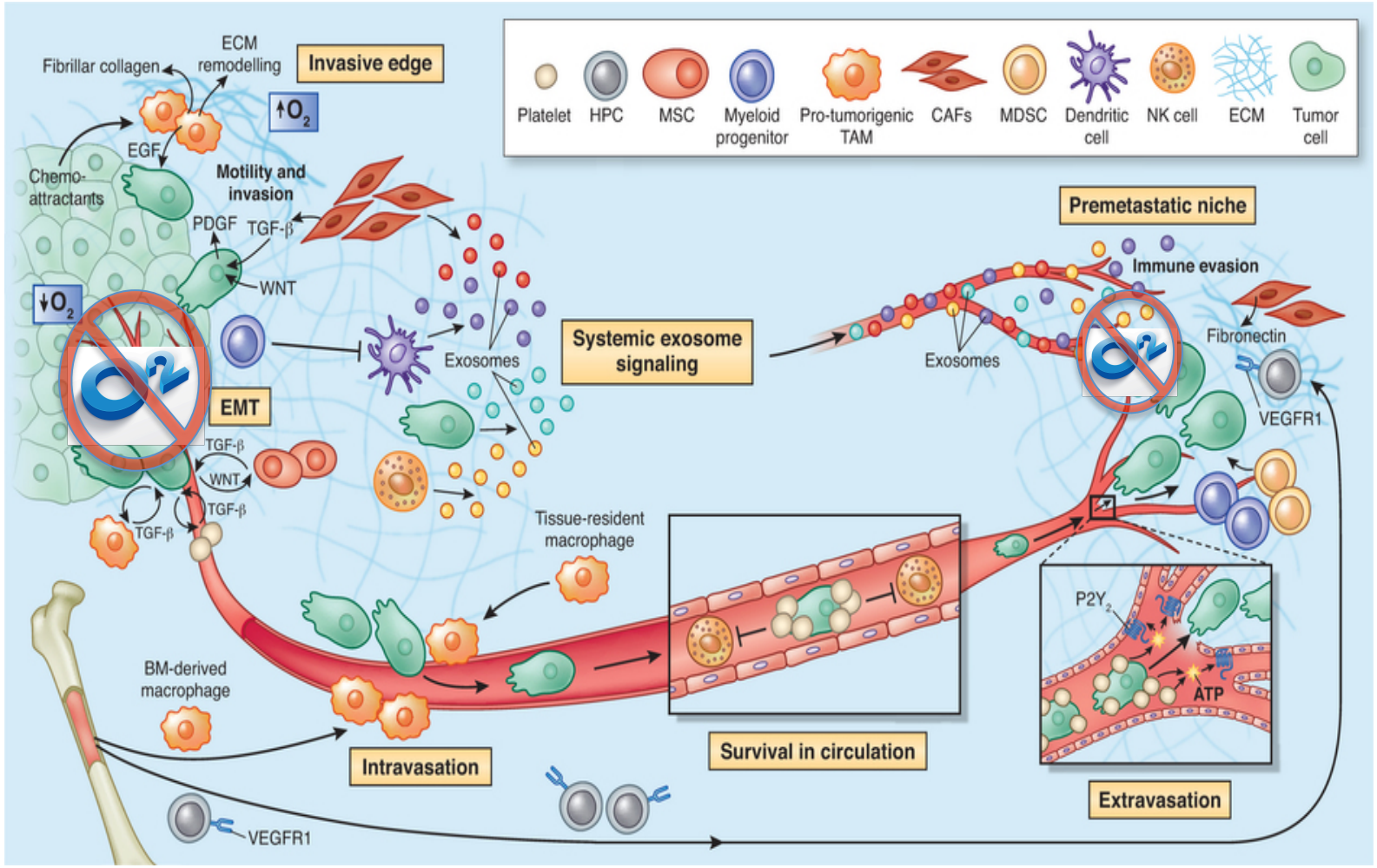
- O2 consumption rate of 7.29 ± 1.4 × 10(-7) m(3) kg(-1) s(-1)
- constant experimentally derived **diffusion limit of 0.232 ± 0.022 mm**

Micrometastases are defined as > **0.2 mm** - **<2 mm**

Grimes et al J R Soc Interface. 2014 Jan 15;11(92):20131124.

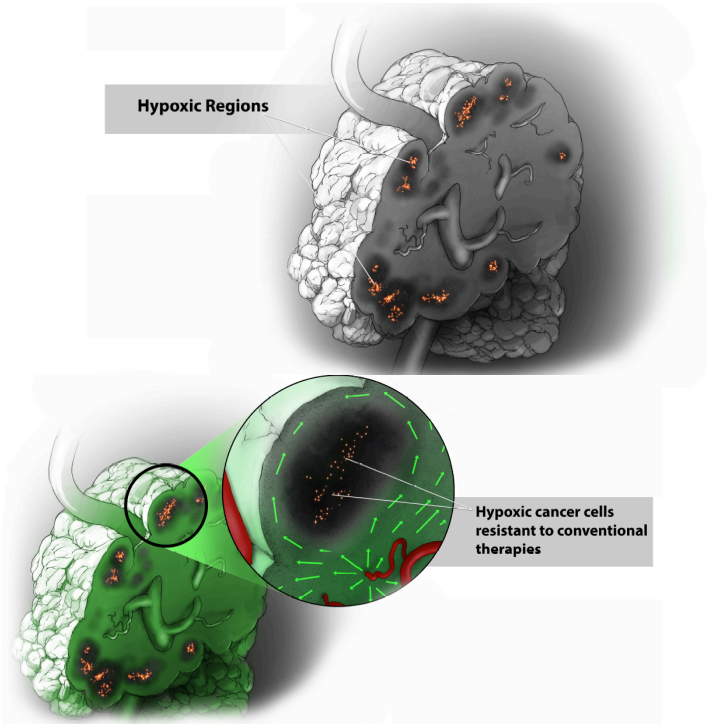

HYPOXIA - context of cancer therapeutics

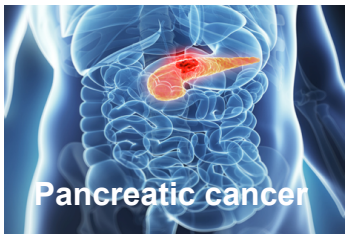
Cellular niches - low oxygen micro-environments



Quail, D. F. and J. A. Joyce (2013). Nat Med **19**(11): 1423-37

CLINICAL PROBLEM vs OPPORTUNITY: hypoxia





pO2 tumour/norm (mmHg)
2.7/51 2.4/30

ORIGINS?

- **Modified metabolism**
- **Loss of vascularity**
- **Therapy-induced**
- **High proliferation rates**

IMPACT?

- **immunosuppressive**
- **POOR drug penetration**
- **Modified drug metabolism**
- **Radiation/chemoresistance**
- **Reservoir for origins of relapse**
- **Modified biological responses**

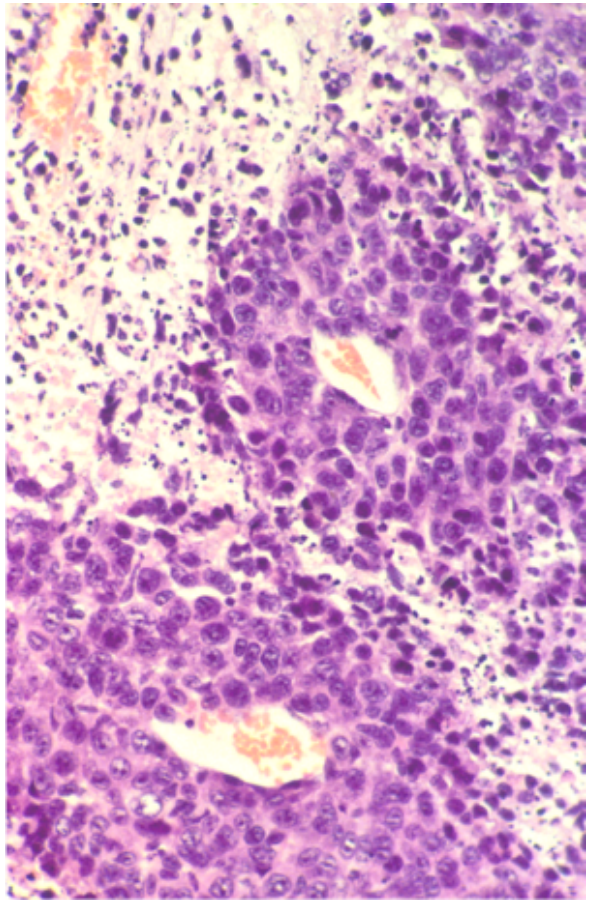
TARGETING?

- **Overcoming SOC resistance**
- **Combination or neoadjuvant settings?**
- **Reducing metastasis drivers**
- **Cancer stem cell niche targeting**
- **Delaying early relapse**
- **Extending the window for surgery**
- **Novel targeting**
- **PRECISION MEDICINE**

HYPOXIC CANCERS: PRIORITY INDICATIONS

OncoTherics

tumor type	Median tumor pO_2(mmHg) (number of patients)	Median normal pO_2* (number of patients)	Fold reduction average pO_2
Glioblastoma	4.9 (10) 5.6 (14)	ND (not determined) ND	-
Head and neck carcinoma	12.2 (30) 14.7 (23) 14.6 (65)	40.0 (14) 43.8 (30) 51.2 (65)	3.3 3.0 3.5
Lung cancer	7.5 (17)	38.5 (17)	5.1
Breast cancer	10.0 (15)	ND	-
Cervical cancer	5.0 (8) 5.0 (74) 3 (86)	51 (8) ND ND	10.2
Pancreatic cancer	2.7 (7)	51.6 (7)	19.1
Prostate cancer	2.4 (59)	30.0 (59)	12.5
Soft-tissue sarcoma	6.2 (34) 18 (22)	ND ND	-

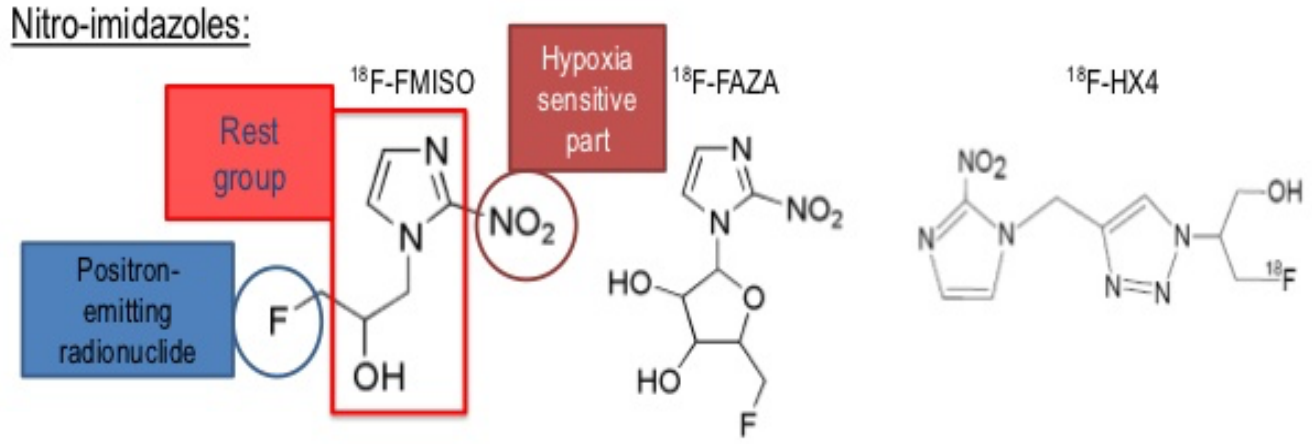


pO_2 7.5 mmHg approx. 1 % oxygen
In vitro studies @ 1% & 3% O_2

Development of Hypoxia Sensors - a long search for the clinical probes

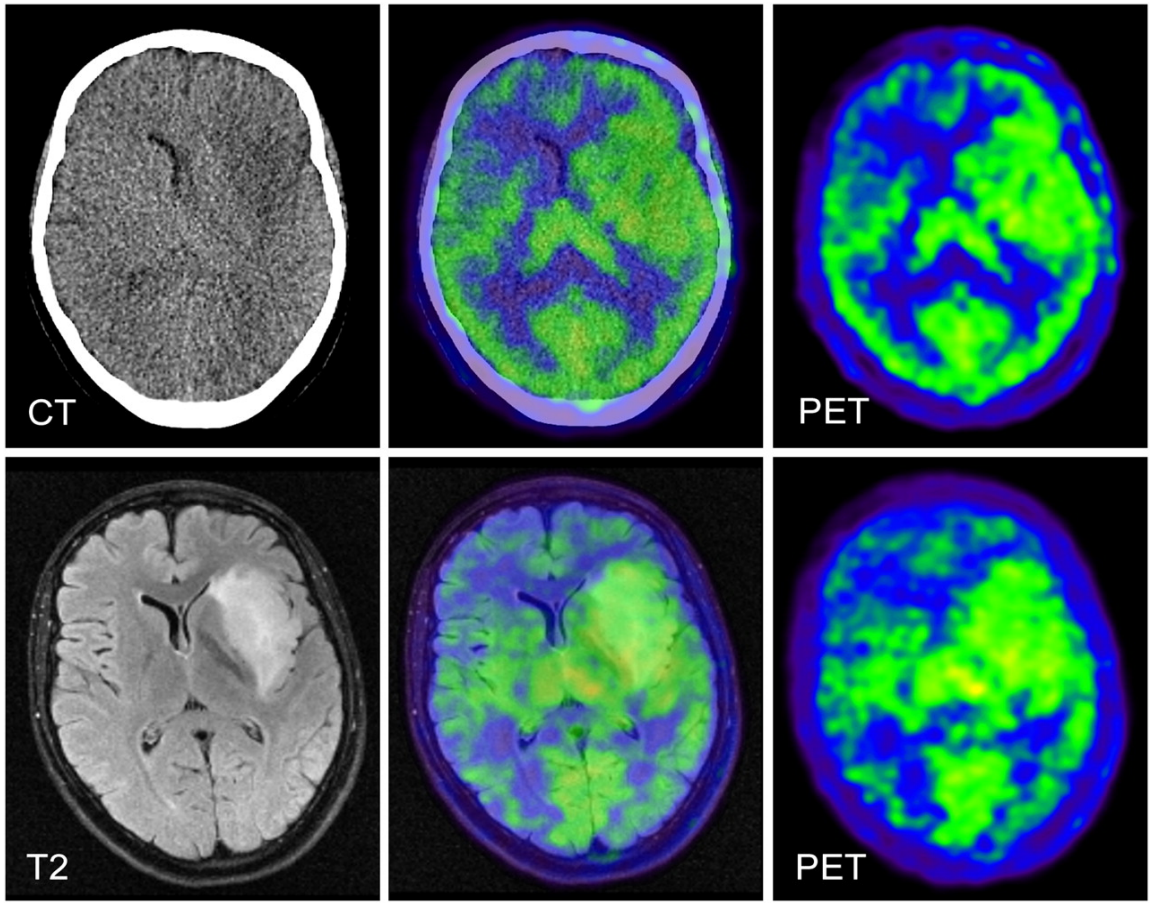
OncoTherics

Hypoxia PET tracers



- clinical practice is changing

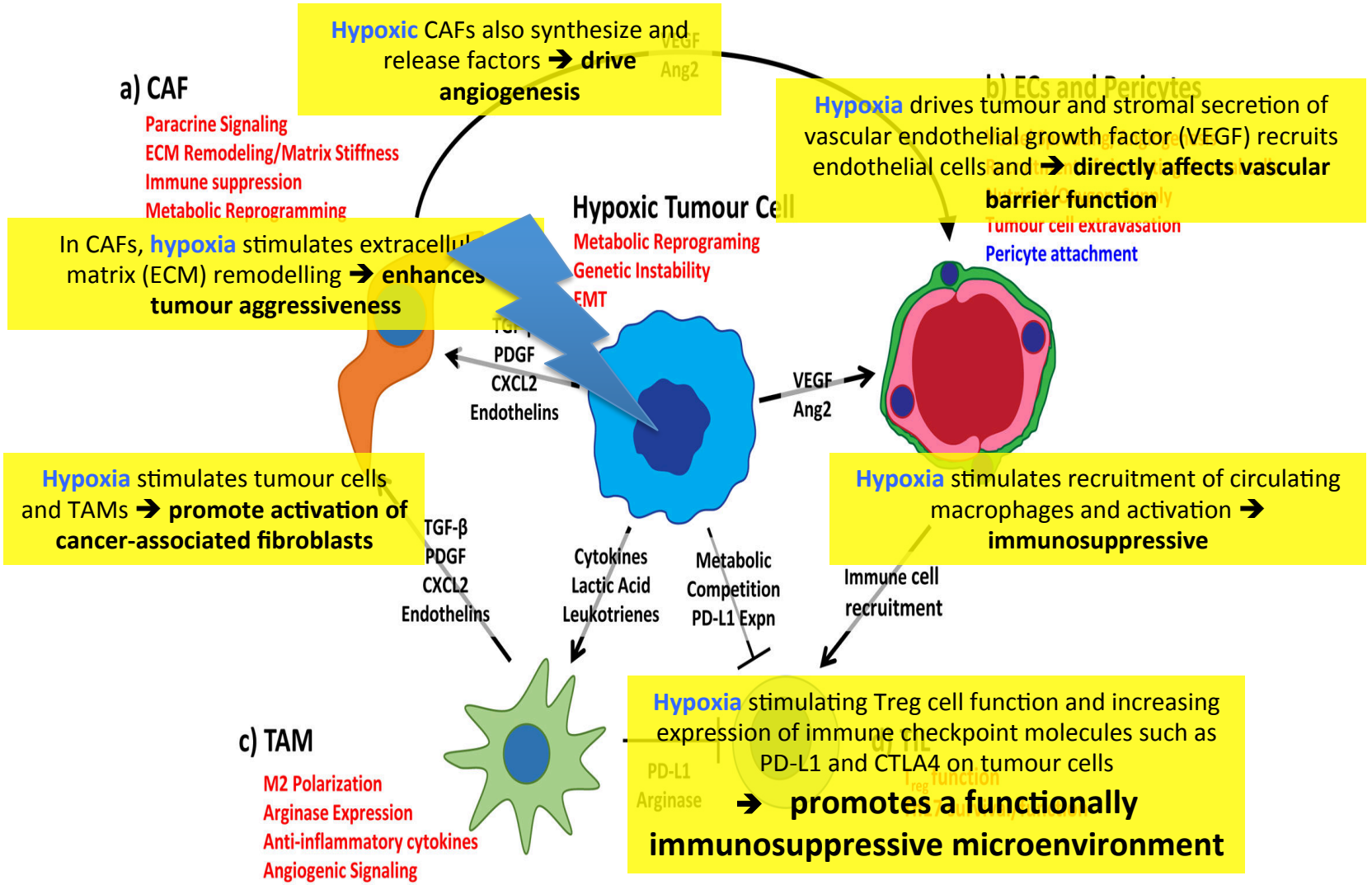
JNM The Journal of NUCLEAR MEDICINE



Hybrid PET/MRI of Intracranial Masses

PET/MR and PET/CT images of 30-y-old patient with low-grade glioma (patient 6) extending on left side from insular cortex to temporal lobe and frontal operculum. Andreas Boss et al. J Nucl Med 2010;51:1198-1205

Meeting the needs of new generation therapeutics: Tumour hypoxia co-opts the stroma to potentiate tumourigenesis



LaGory EL, Giaccia AJ. Nat Cell Biol. 2016

OncoTherics

novel **u**nidirectional **H**ypoxia-**A**ctivated **P**rodrugs (uHAPs) for the treatment of Cancer

contact us: enquiry@oncotherics.com

OncoTherics TEAM: A blend of expertise in science, clinical delivery, commercial drug development, & regulatory approval

LEADERSHIP AND MANAGEMENT

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Dr. Thomas Morris
CMO

Prof. Paul Smith
CSO

Mike Leyland
Finance

Prof. Stephanie McKeown
Director

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Director

Dr. Roy Eady
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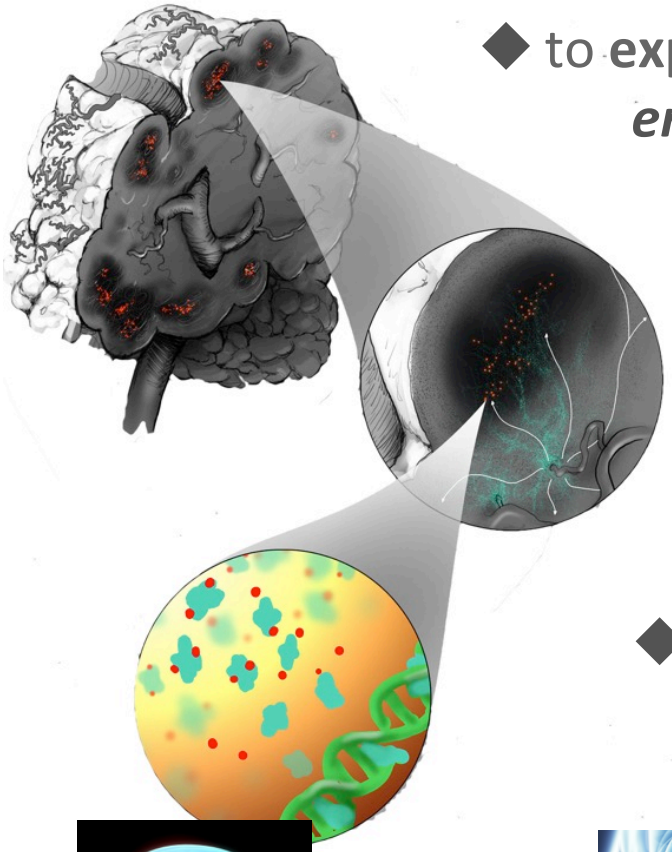
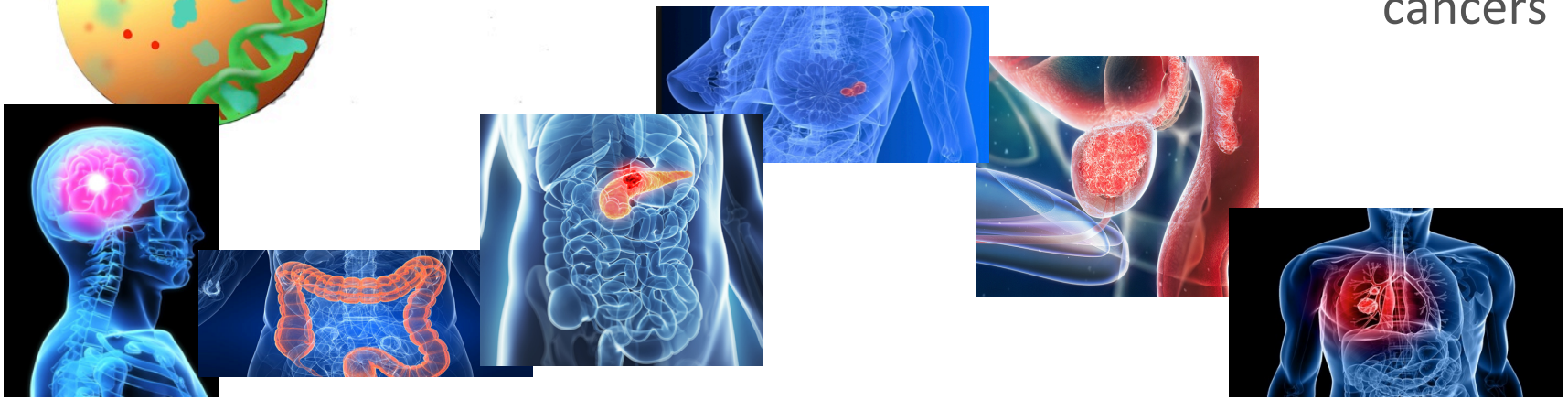
University of Cambridge
University of Bradford

University of Ulster
Cardiff University
University of Manchester

OncoTherics MISSION

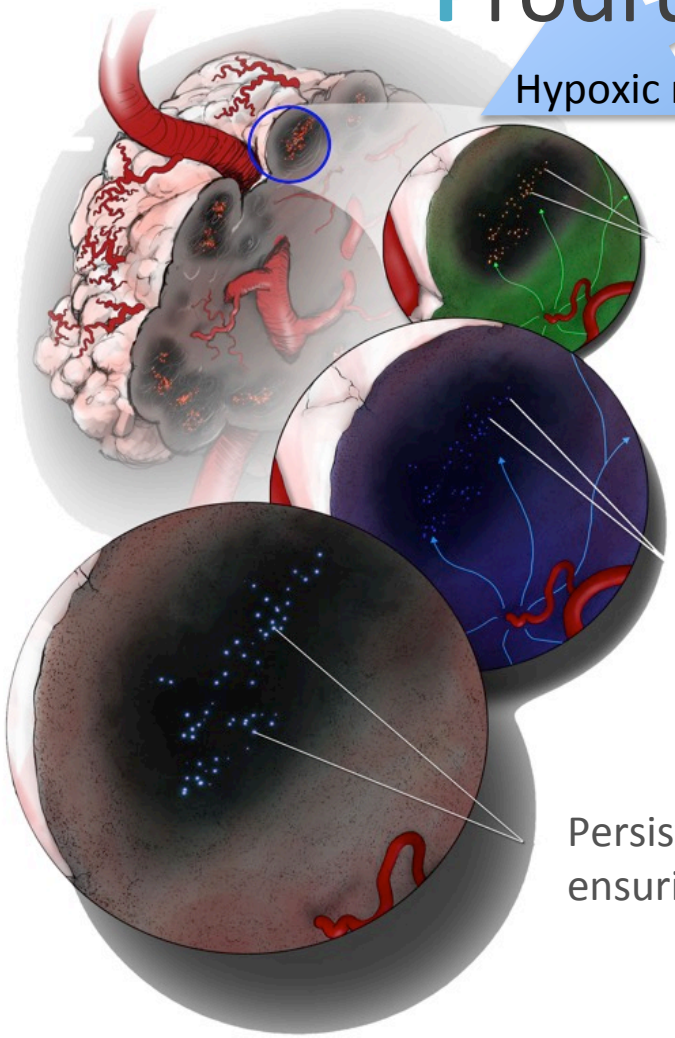


- to **exploit** new insights into ***tumour HYPOXIC micro-environments*** and its widespread role in tumour progression and treatment resistance
- to **collaborate** with world-leading centres
- to **identify** novel drug targeting opportunities that can be easily combined with current & new targeted therapies
- to **deliver** better drugs for a WIDE RANGE OF cancers

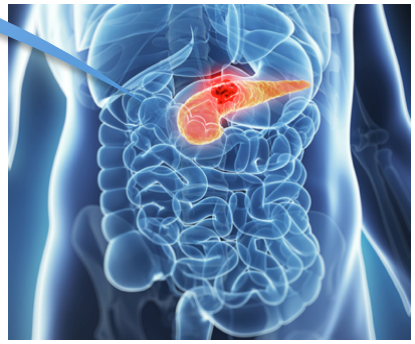


OUR SOLUTION: novel uHAP's

novel **u**nidirectional **H**ypoxia-**A**ctivated **P**rodrugs (uHAP's)



Hypoxic regions of tumours are **treatment resistant**



uHAP given alongside conventional chemotherapy

Non-Toxic – fewer side effects than conventional drugs

uHAP penetrates the whole tumour and is irreversibly activated to a highly effective Topoisomerase II inhibitor in Hypoxic tumour cells

Persistent activated drug targets cells in the hypoxic regions - ensuring effective treatment of the whole tumour

Development of Hypoxia-Activated Prodrugs - a long search for the right drug

1. nitro(hetero)cyclic compounds
   extensive exploration in the clinic (PR-104A a dinitrobenzamide mustard withdrawn) and TH-302 (evofosfamide) fails at Phase III
2. aromatic N-oxides
   early entry N-oxide tirapazamine (TPZ; SR4233) ends in failure highlighting the need for patient selection
3. quinones
   EO9 (Apaziquone) failed to show activity in phase II clinical trials

4. aliphatic N-oxides
   OCT1004 & OCT1002

5. metal complexes
   have the potential to be used as hypoxia-selective agents, but to date, none have been developed for clinical use.

PET

INNOVATIVE drug design of our lead investment opportunity

OCT1002
a novel uHAP
with modified bioreduction properties
but retaining high tissue penetration
and potentially offering a modified PK profile

DNA affinic cytotoxic DNA topoisomerase inhibitor

Inactivation

Non-toxic prodrug platform

Modify key bioreduction sites

OCT1002

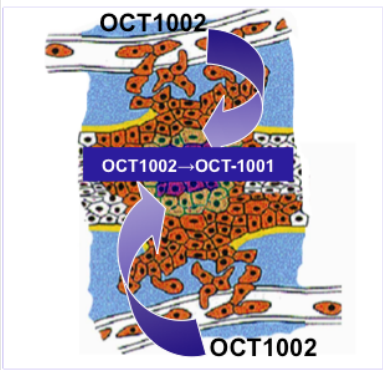
The non-toxic uHAP COMPETITIVE ADVANTAGE?

- FAR FEWER SIDE EFFECTS than conventional HAP's
- HIGHER DOSES possible due to unidirectional conversion
- EXCELLENT PENETRATION across all tissues
- HIGHLY SPECIFIC TARGETING for tumour site conversion
- EXPLOITS NEW EVIDENCE on impact of hypoxia on cancer treatments

$4e + 4H^+ \rightarrow 2H_2O$

....unique mechanism of activation in hypoxic cells

....tumour targeting with unique mechanism of action



targets tumour growth & metastasis and overcoming drug resistance

OCT1001

Active drug OCT1001 with enhanced intracellular persistence properties

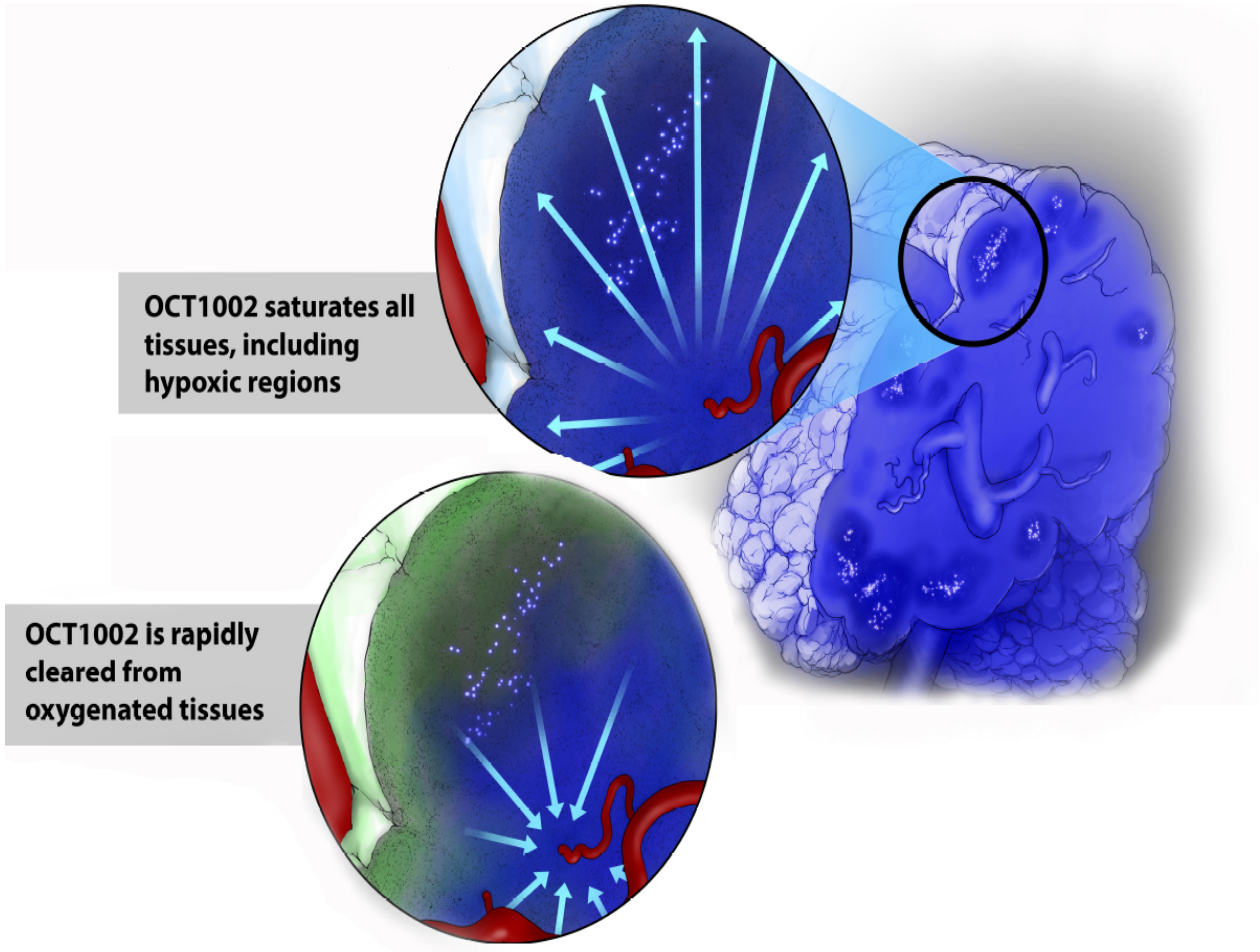
....unique mechanism of action

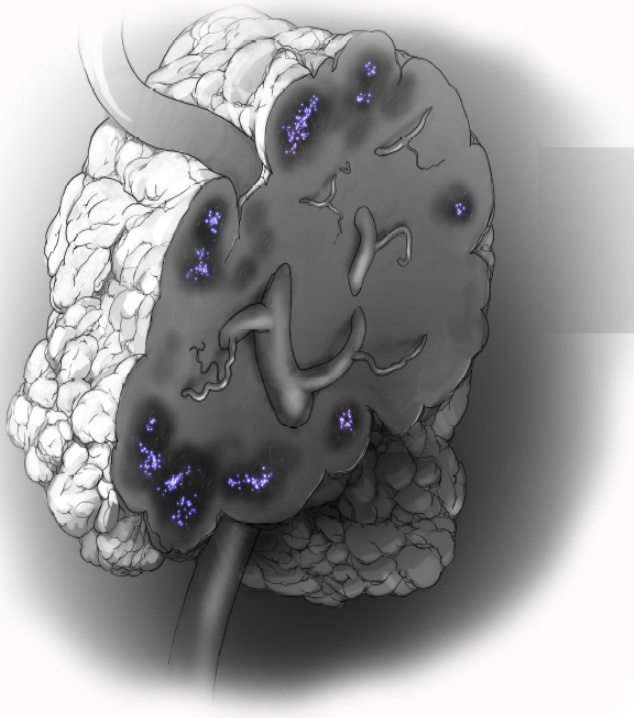
OCT1002

a novel uHAP

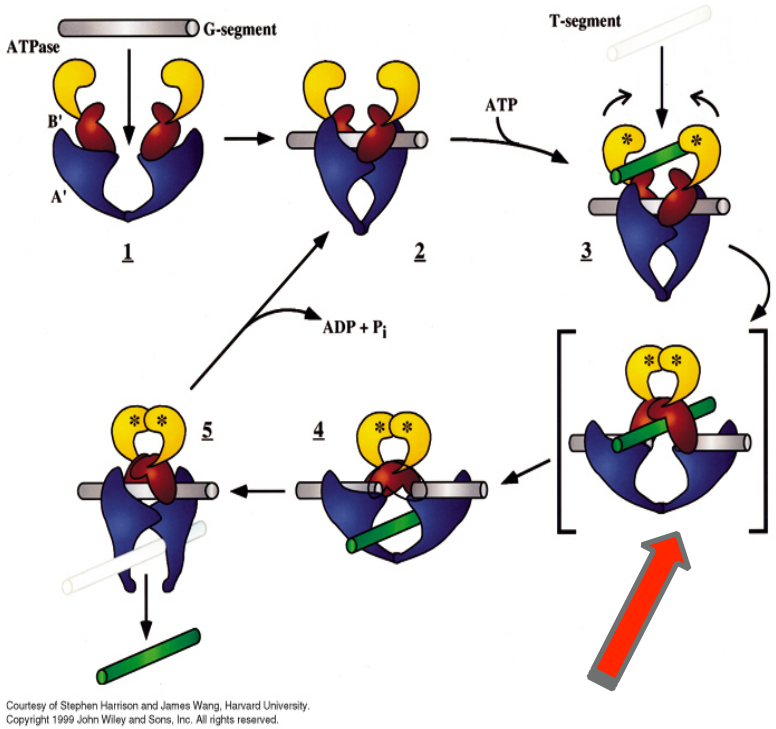
unidirectional Hypoxia Activated Pro-drug

OncoTherics



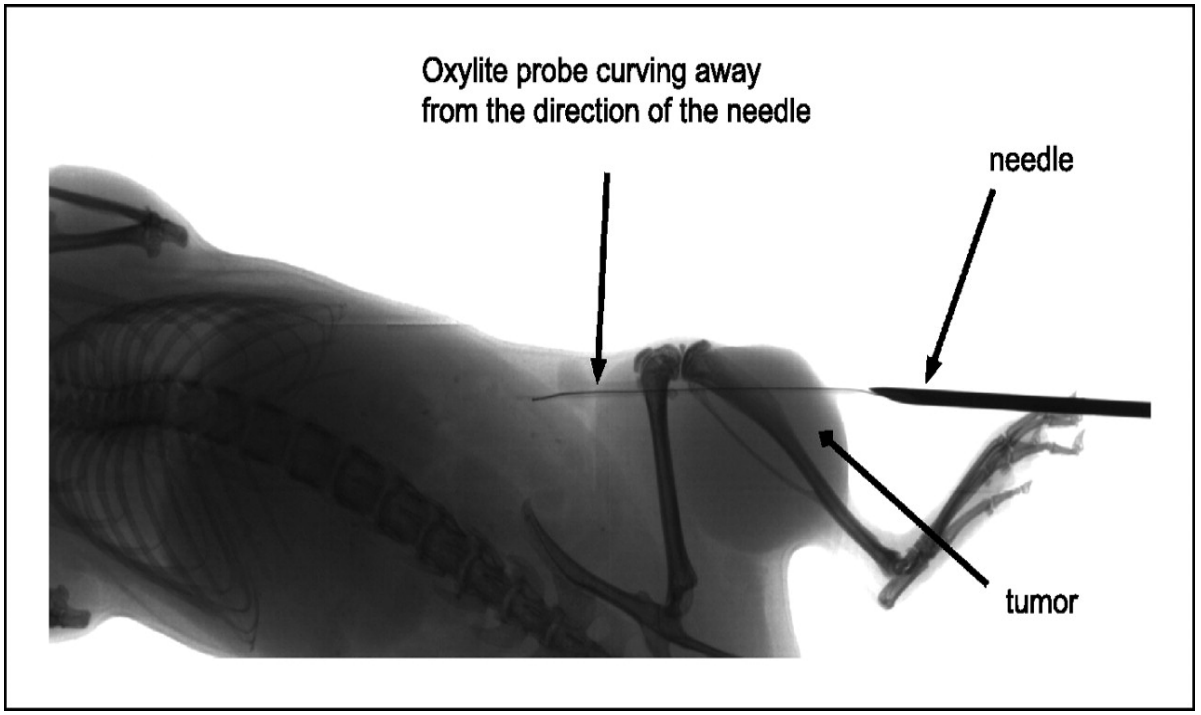


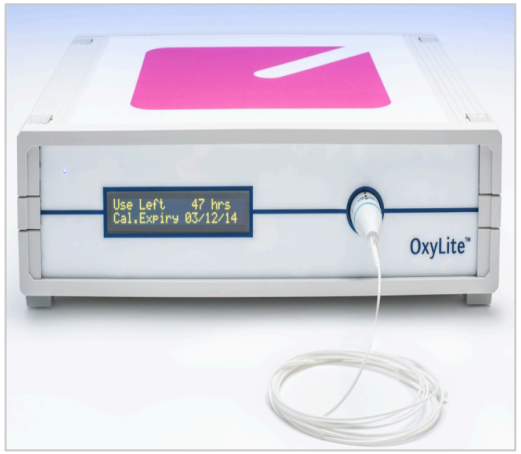
OCT1002 converts to highly toxic OCT1001 in hypoxic cells and kills the cells when they become active



- OCT-1001 acts as a potent DNA topoisomerase II inhibitor

Accessible in vivo systems:
X-ray image of C3H mouse with Oxylite probe in a tumour



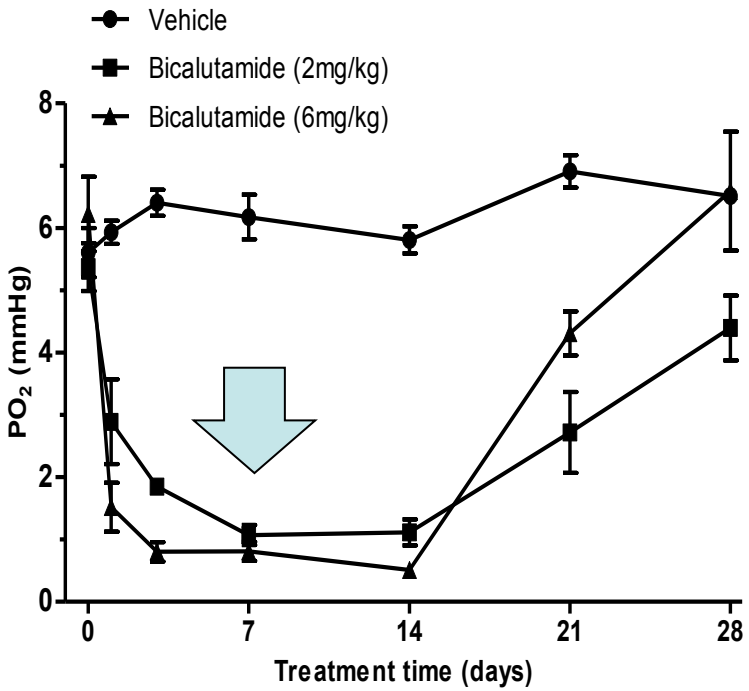


- The needle guides the Oxylite to the tumor The Oxylite protrudes from the needle and is seen curving away from the direction of the needle.
- The actual optic fiber is seen as a faint shadow accompanying a thin, well-resolved filament (the thermocouple for temperature correction for the Oxylite)

Martyna Elas et al. Clin Cancer Res 2006;12:4209-4217

Clinical Cancer Research
AACR American Association for Cancer Research

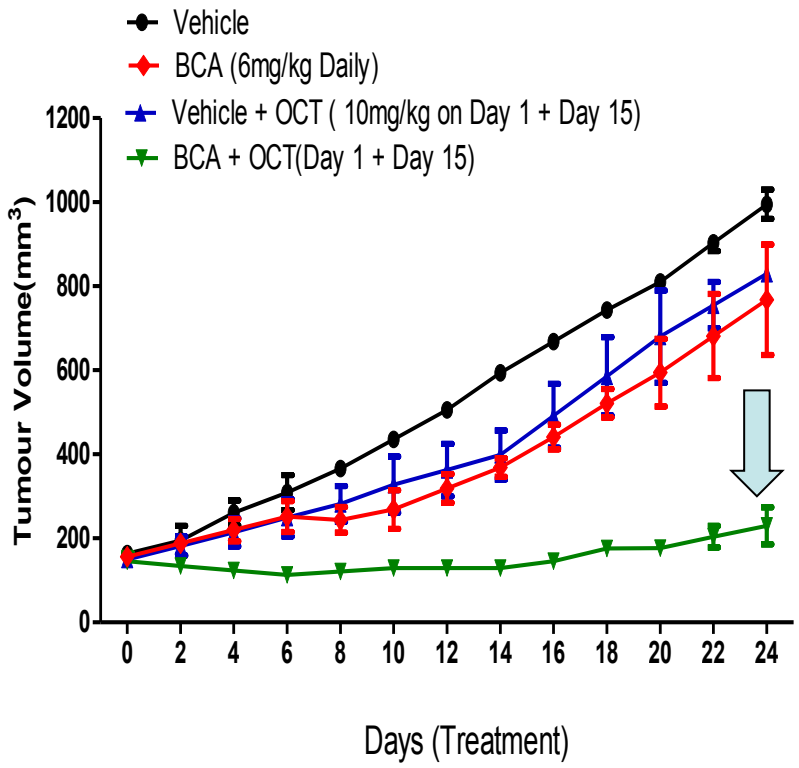
pO2 readings of prostate LNCaP tumours during Bicalutamide (anti androgen; BCA) treatment



LNCaP xenografts were grown to ~100-150mm^3. Results are mean ± S.E.M (n=5)

Clin Cancer Res. 2016
Nesbitt, Byrne, Williams, Ming, Worthington, Errington, Patterson, Smith, McKeown & McKenna

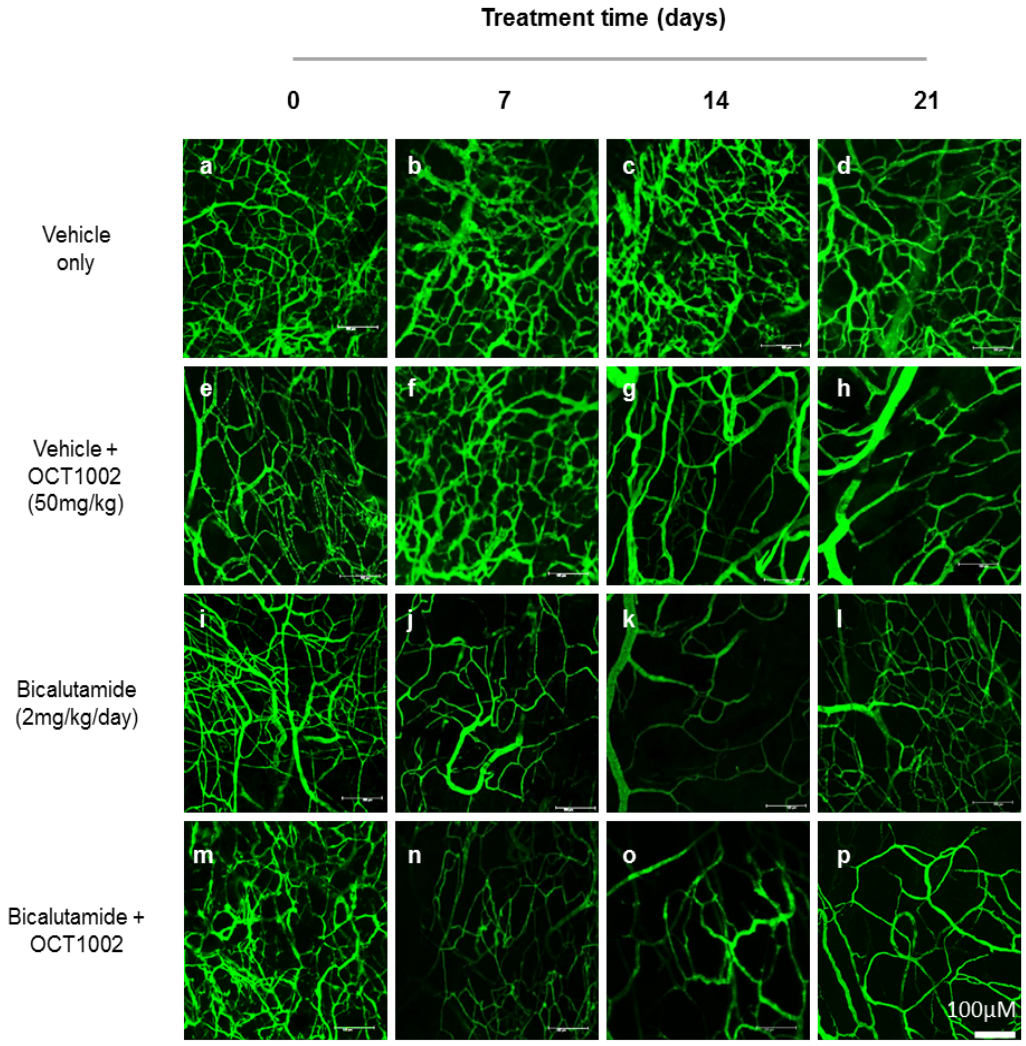
Very low but double dosing with OCT-1002 (10mg/kg) in combination + BCA



Double dosing with OCT1002 in combination with BCA controls LNCaP tumour

SCID mice were implanted with $4x10^6$ LNCaP-Luc cells. When tumours reached $150mm^3$ mice were treated with a range of combinations: vehicle (1% DMSO), BCA (6mg/kg Daily), vehicle + OCT1002 (10mg/kg Day 1 & 15), BCA + OCT-1002 (Day 1 &15).

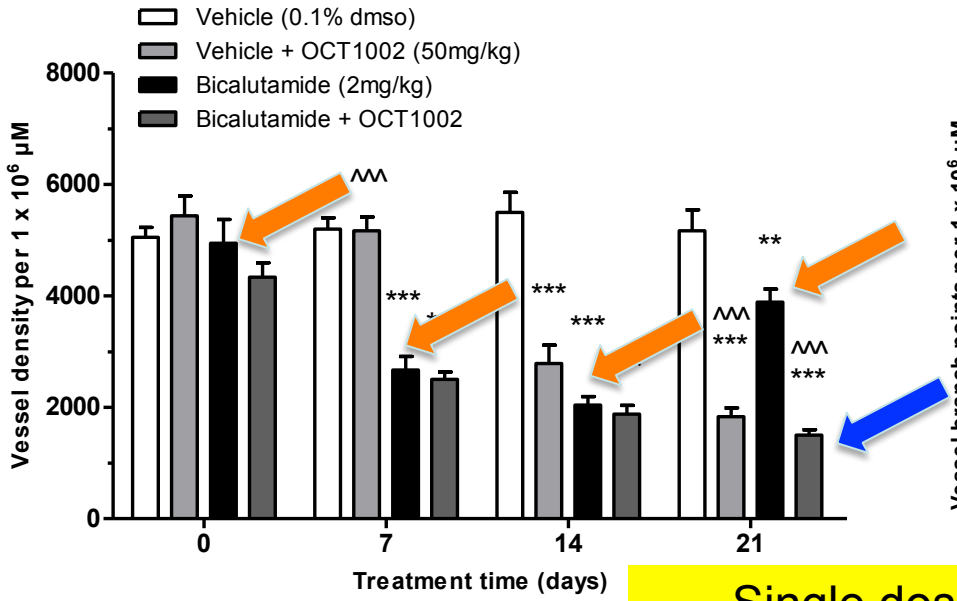
Vascular changes induced by BCA in combination with the OCT1002 on LNCaP-Luc tumours xenografts

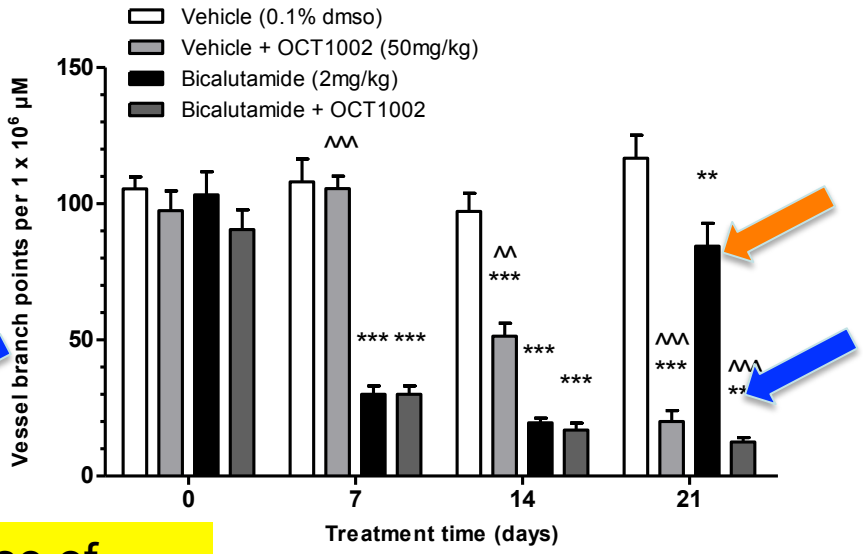


- Vehicle (1% DMSO in corn oil p.o.)
- OCT1002 (50mg/kg in PBS i.p. day 7)
- BCA (2mg/kg in vehicle p.o.).

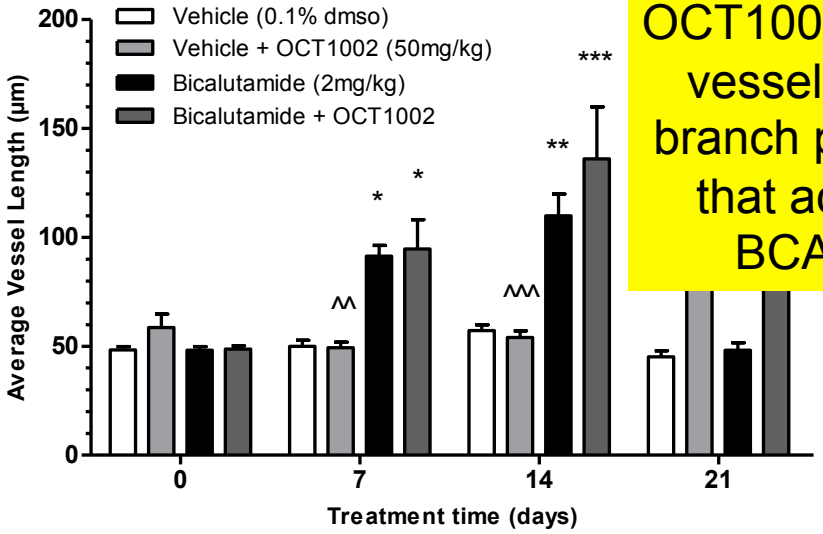
Nesbitt et al., Clin Cancer Res. 2016

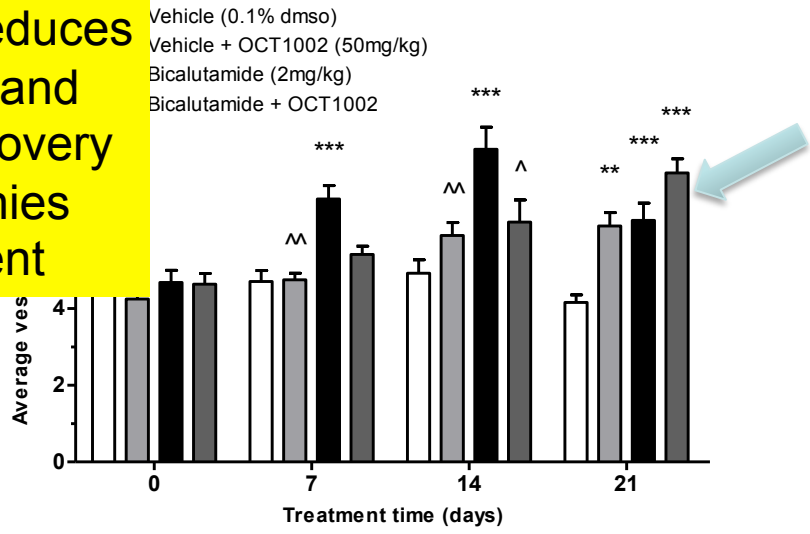
Stereological assessment of the effect of bicalutamide ± OCT1002 on vascular parameters in LNCaP tumours



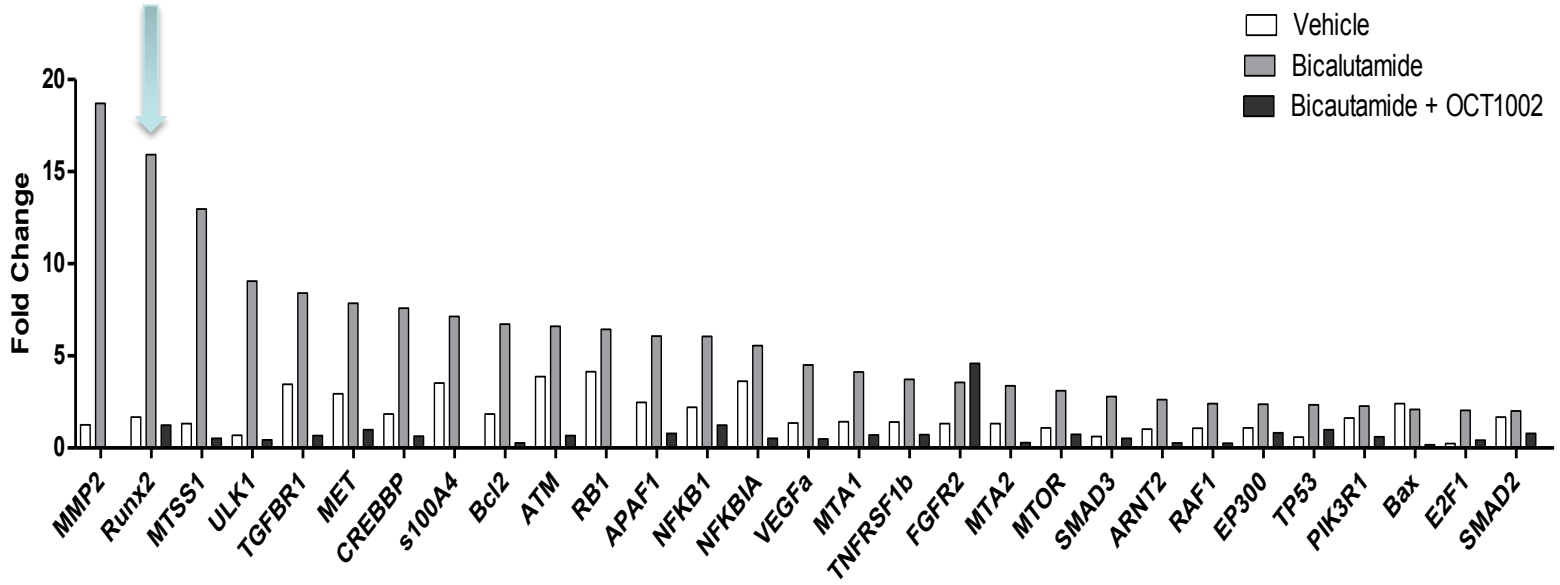


Single dose of OCT1002 also reduces vessel density and branch point recovery that accompanies BCA treatment



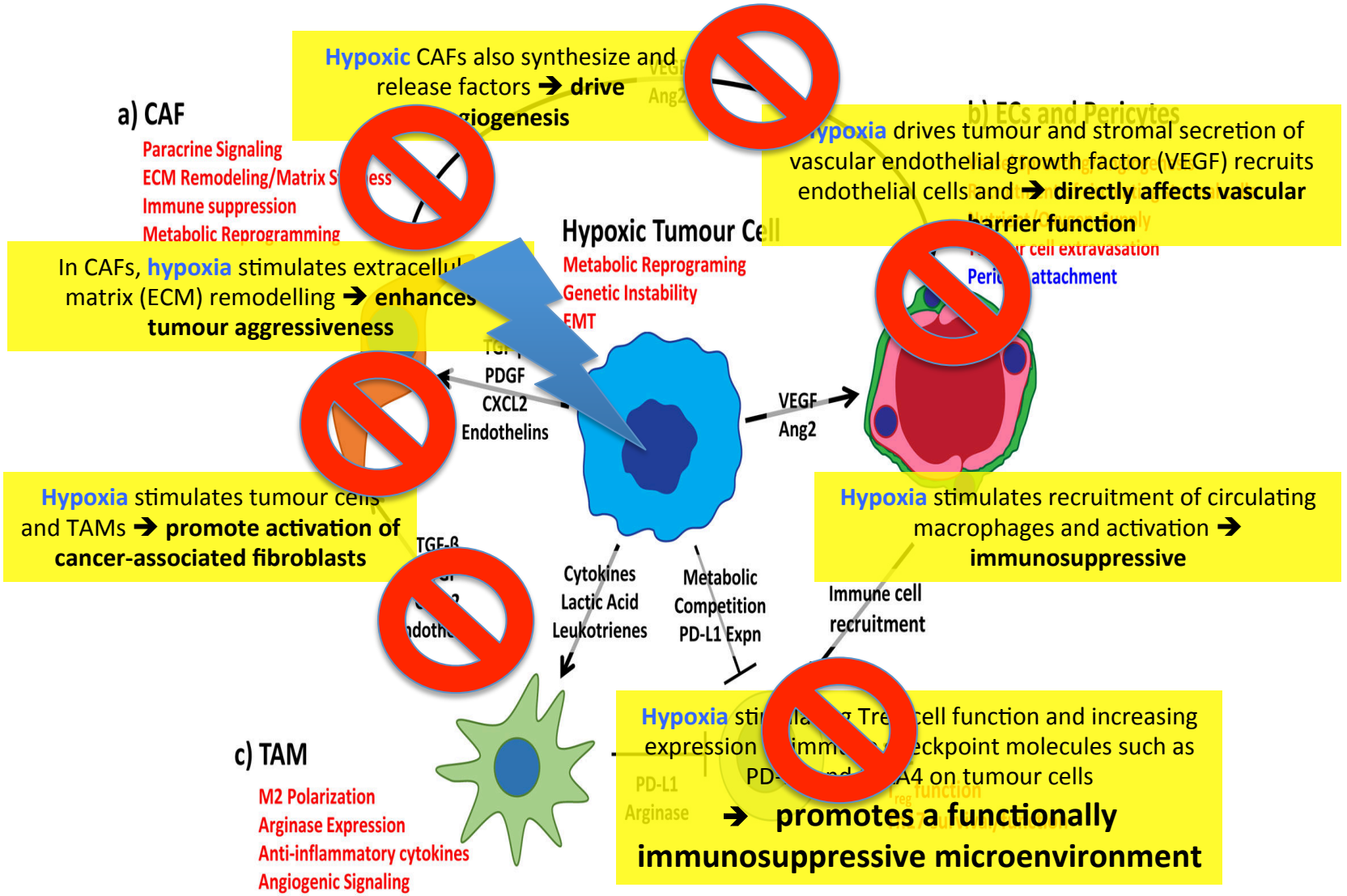


Up-regulation of pro-survival genes induced by bicalutamide is blocked by OCT1002



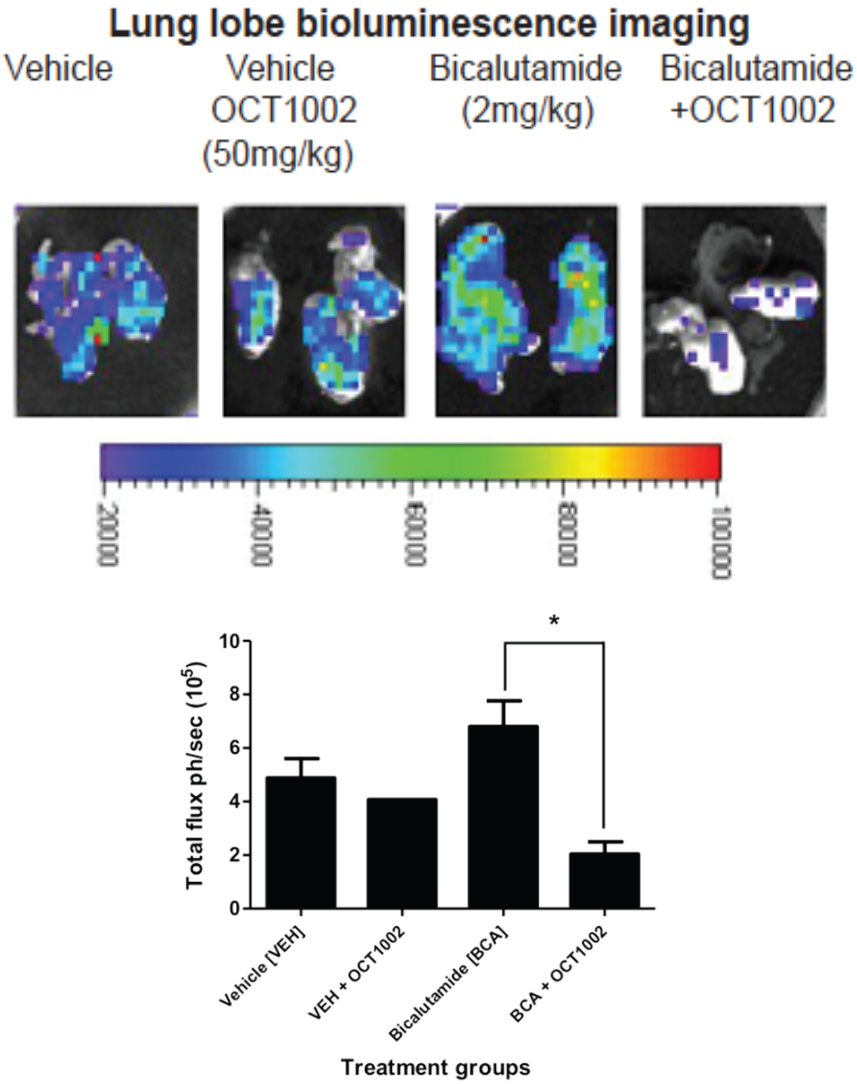
- link between hypoxic stress and *RUNX2*
- *RUNX2* expression is up-regulated in prostate, breast and colon cancer
- thought to contribute to a more aggressive, metastatic phenotype by altering expression of many genes involved in migration, invasion, metastasis, apoptosis and angiogenesis

Tumour hypoxia co-opts the stroma to potentiate tumourigenesis



LaGory EL, Giaccia AJ. Nat Cell Biol. 2016

Single dose OCT1002 inhibits lung metastasis & tumour growth in hypoxic prostate tumours



- LNCaP-Luc xenografts in SCID mice (≥8 week old) bearing 100-200mm3 tumours
- oral vehicle or bicalutamide every day x 28 days with 2mg/kg) ± OCT1002 (50mg/kg i.p. day 7).
- At day 28, mice injected with luciferin. At 15 min lungs excised and luminescence quantified

- OCT1002 inhibition of metastasis *p = ≤ 0.05 (two-tailed t-test)

From Bed to Bench: clinical insight to prompt research - two previous large-scale randomised trials of prostate radiotherapy

+Radiotherapy
+Anti-hormonal

- Scandinavian SPCG-7 trial & MRC PR07 trial
- locally advanced prostate cancer at high risk of occult metastatic disease
- ADT or ADT plus prostate RTx.
- radiotherapy dramatically improved 10-year outcomes: **mortality halved.**
- benefit **started to emerge as early as 3 years** from randomisation

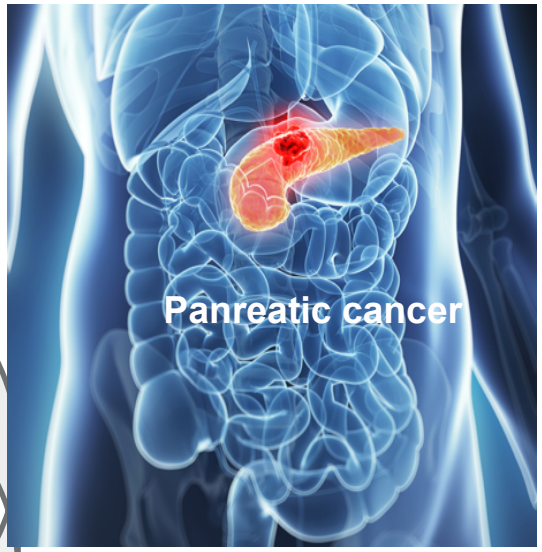
- seems **improbably early** if the benefit of local treatment is mediated via the prevention of subsequent disease dissemination.

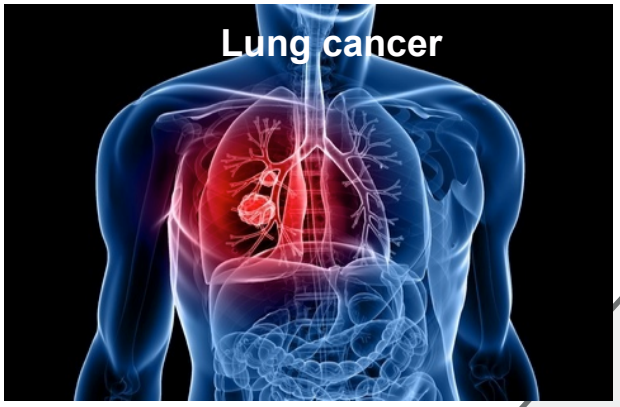
- *…..more consistent with local treatment impacts rate of progression* ***of existing micrometastatic disease****.*

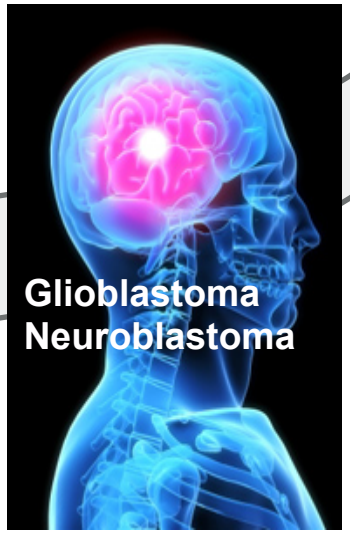
- *That very concept challenges how micro-communities distant from a primary treatment site respond and how cytometry could evaluate the dynamics and nature of that response - and what in vivo model systems are needed*

Microenvironment targeting complements multiple modalities in multiple indications

+Radiotherapy
+Anti-hormonal
+Anti-proliferative
+Immunotherapy
+Cytotoxic & prodrug







UKHealthTech CONFERENCE 2016

Daryl Fernandes
Ludger
Chief Executive

Precision Medicine at Ludger: Glycomics, patient stratification and fat bellies

Ludger is a bioscience company specialising in analytical technology for medical applications of glycobiology

Paul Seaman
Midatech Pharma
Head of Sustained Delivery

Right Time, Right Place; Exploiting Micro and Nano Particulates for Drug Delivery

An international specialty pharmaceutical company focused on developing and commercialising products in oncology and other therapeutic areas.

Fred Jacobs
Astrimmune
CEO

Targeting cancer at every stage

Astrimmune was incorporated in 2011 to house newly created intellectual property related to the treatment of gastrointestinal cancers in general