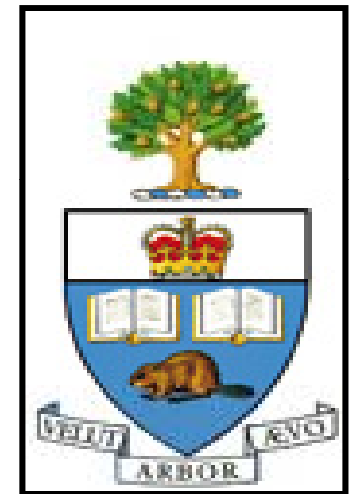


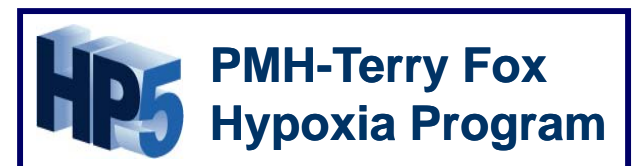
Genetic/Individual Predictors For Prostate Cancer Radiotherapy



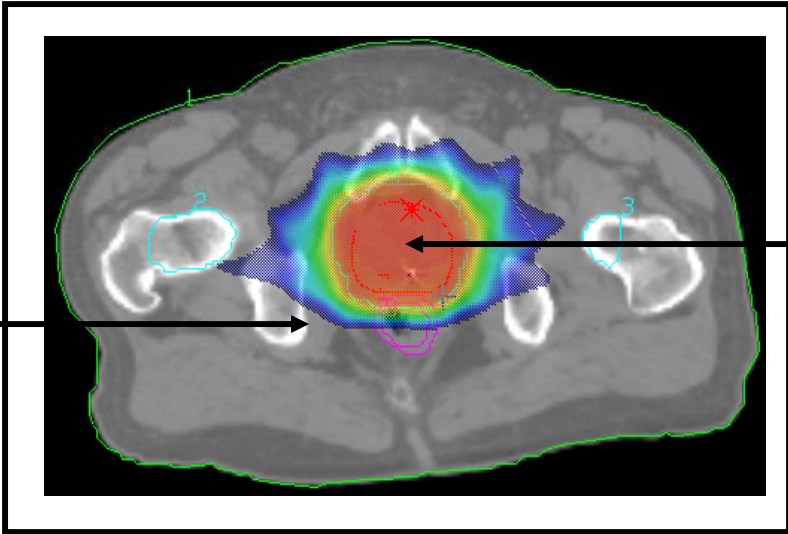
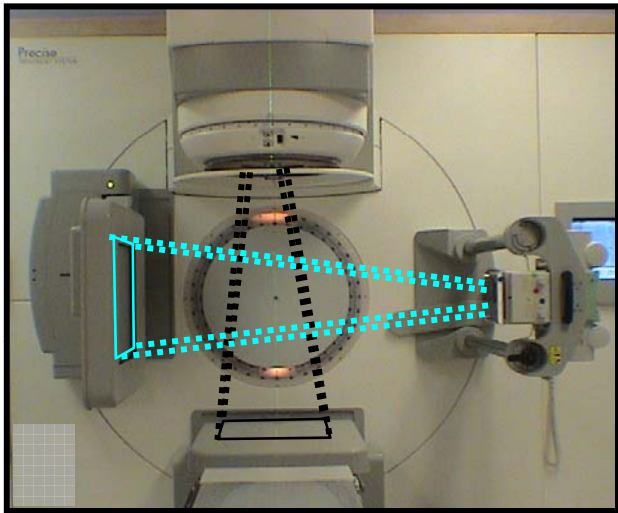
Robert Bristow MD, PhD FRCPC
Clinician-Scientist, Radiation Oncology and Medical
Biophysics, University of Toronto and Princess
Margaret Hospital (University Health Network)



PMH-2008



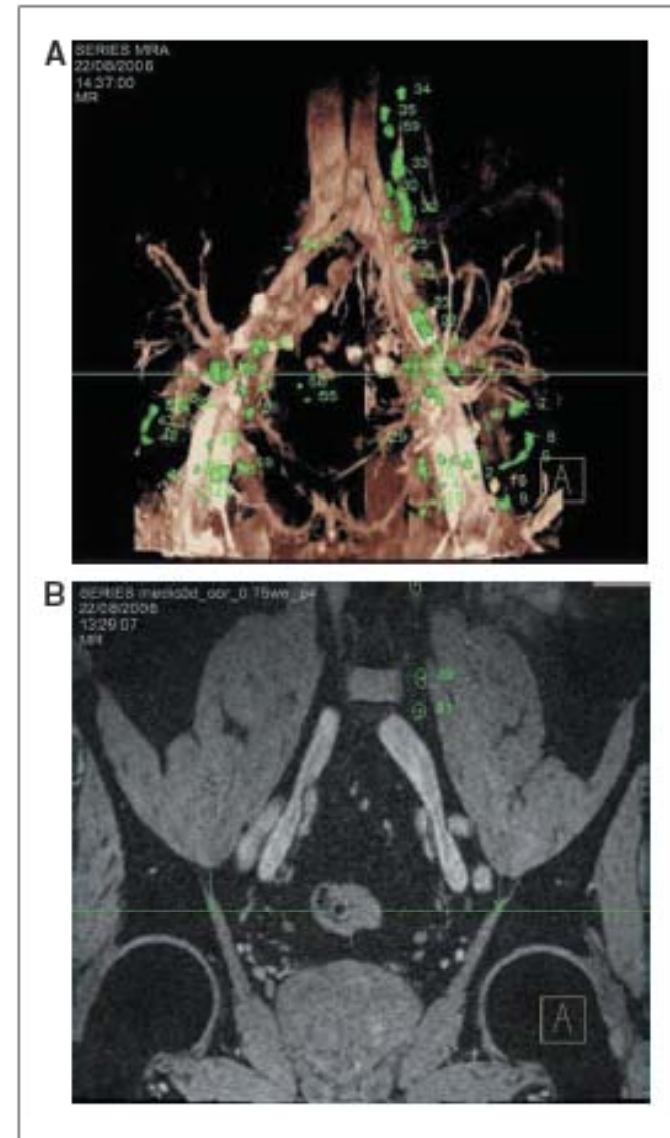
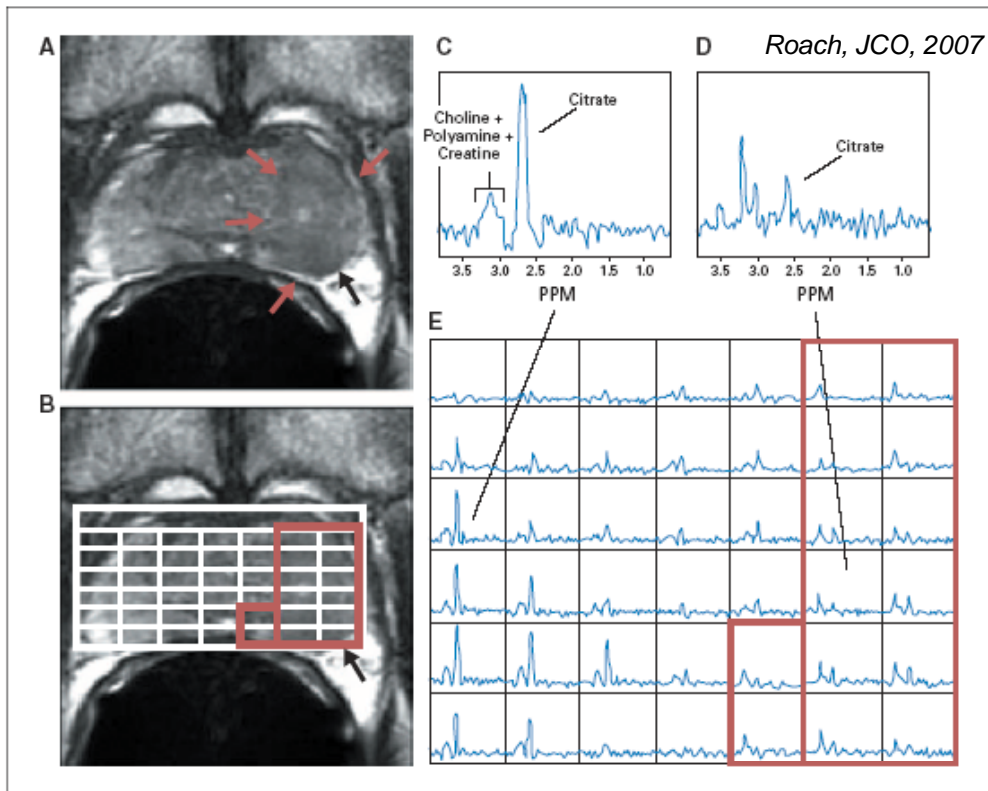
Precision-Guided Radiotherapy to Kill Cancer Cells and Protect Normal Cells



Low Dose
To Normal
Cells

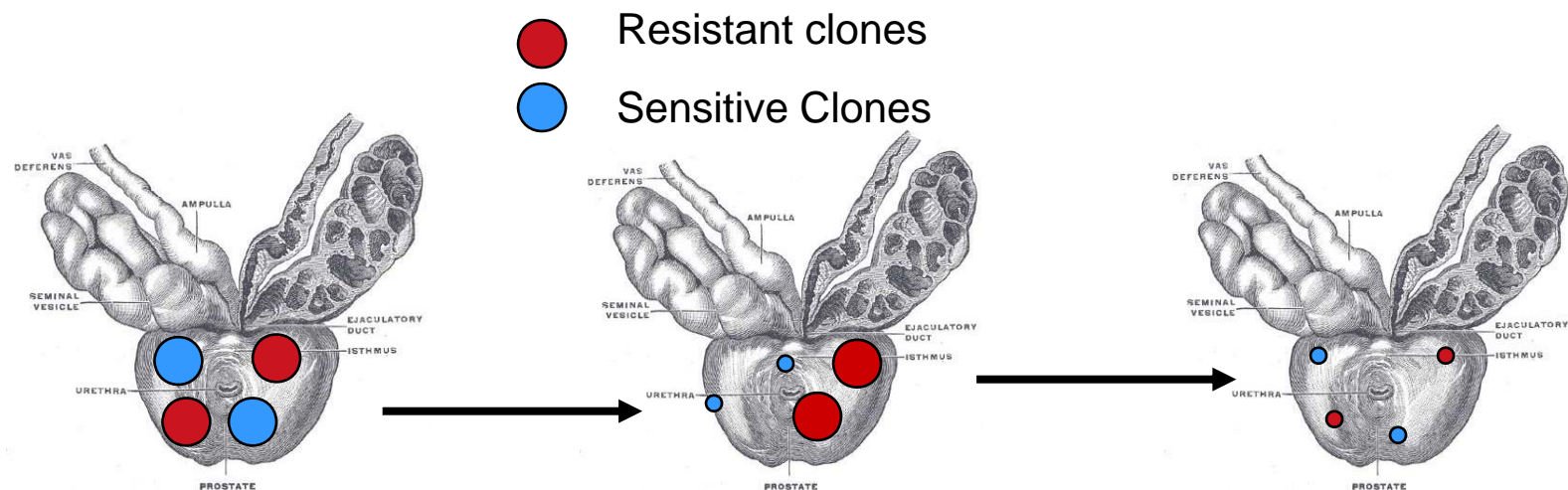
High Dose
To Cancer

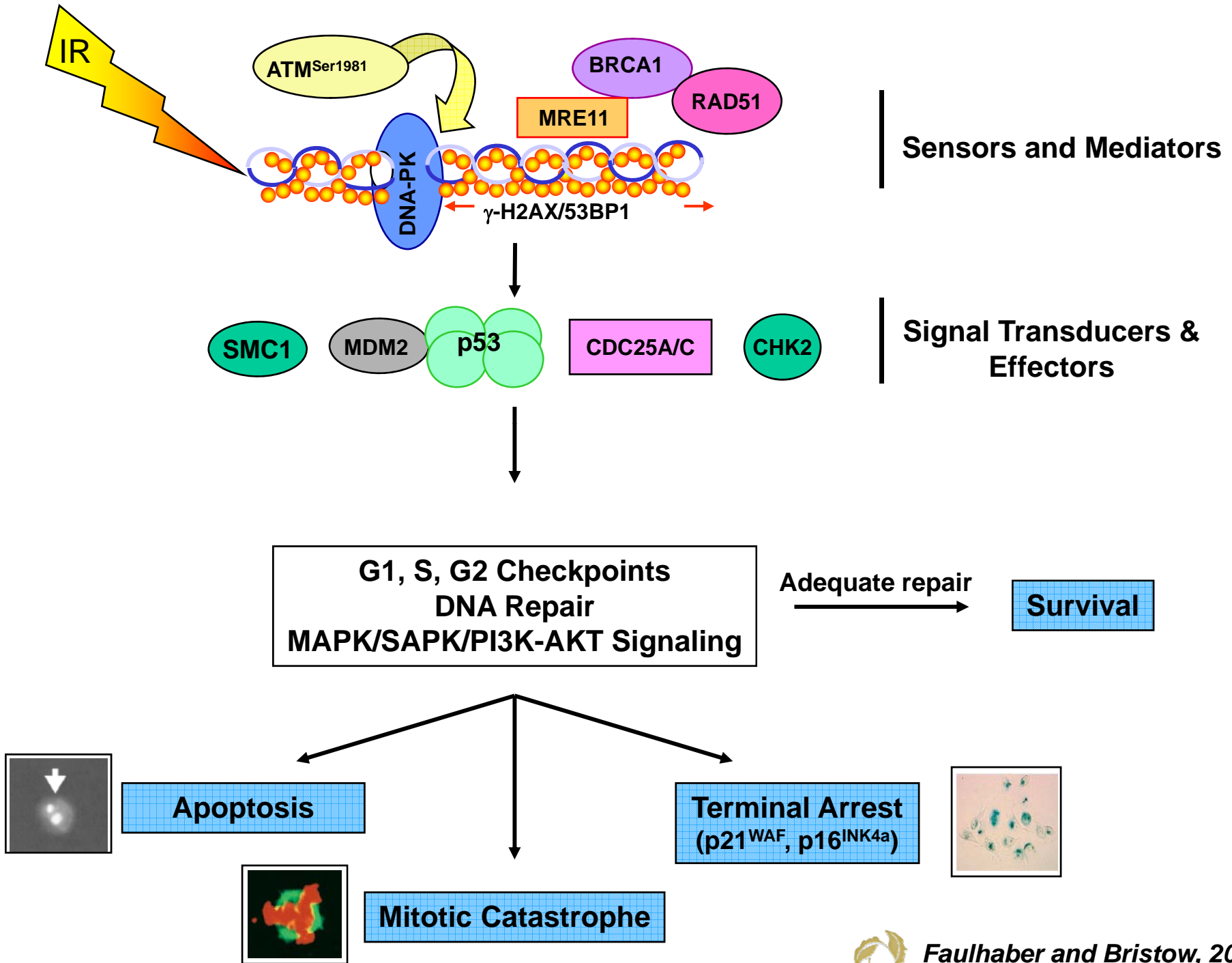
Patient-Unique Tissue Anatomy And Physiology



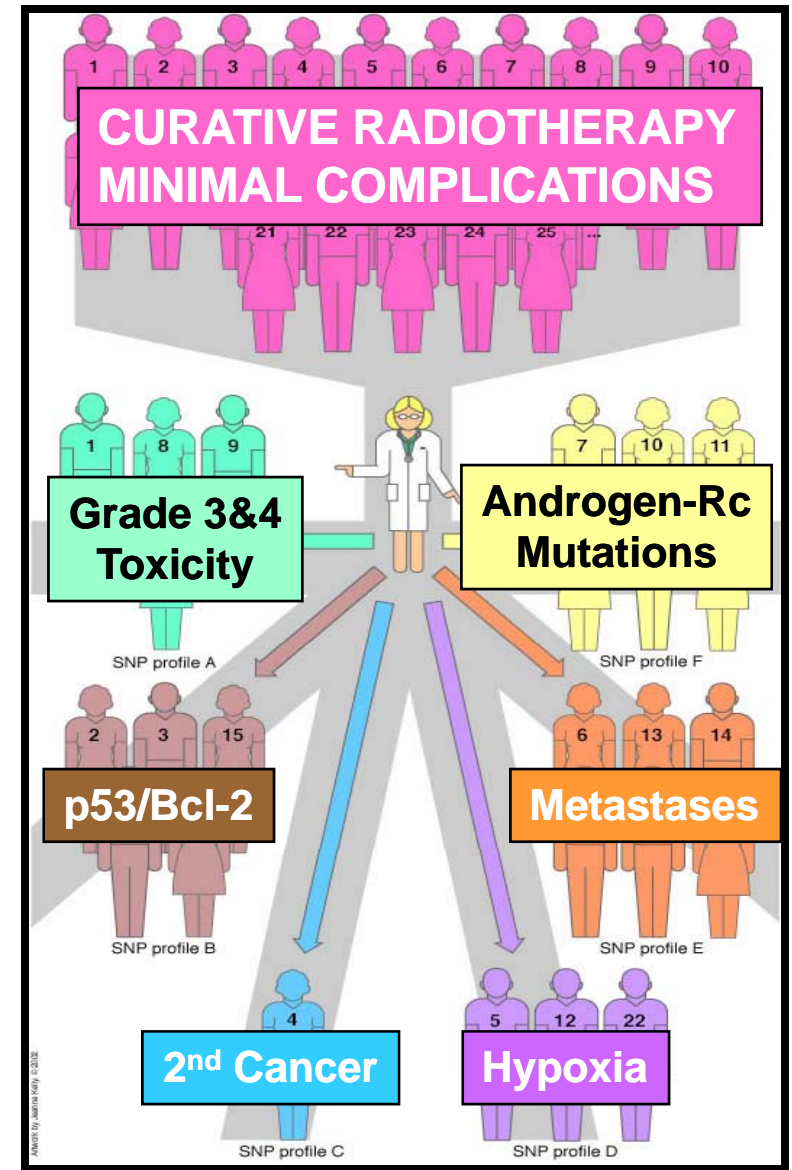
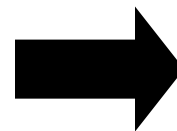
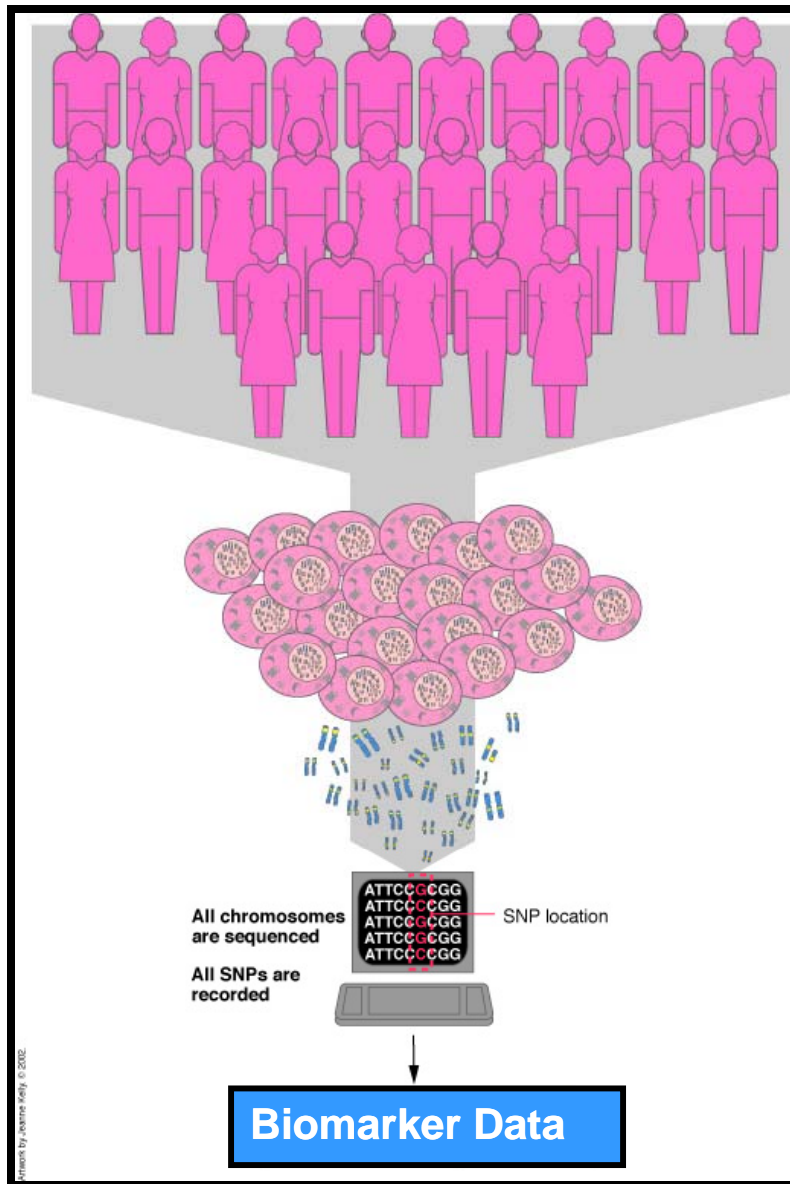
Intrinsic and Microenvironment Predictors

- Can we develop individual therapy-based decisions for precision IMRT radiotherapy ?
- Is the microenvironment a factor in this decision ?
- What biomarkers might be useful in trials to act on this information in normal/cancer tissues ?





Theragnostics: Predict and Change Treatment



RT Predictors: Complex *In Situ* Response

RT Endpoints:	Post-RT PSA, Biopsies, MRSi, proteomics
Signal to Target:	Pre-RT, Intra-RT (4-D Tracking), Post-RT (PSA nadir or DT)
Need Modern High-dose IMRT:	Dose & Local Control increasing; Toxicity decreasing
Toxicity Scoring:	PT-derived, Prospective, Biological Plausibility (Radiopathology?)
Single/Combined Treatment	Risk Groups: RT alone versus RT+ AD: need local and systemic predictors

Risk Groupings and Pre-treatment Prognostic Factors

PROGNOSTIC FACTORS

- Traditional: T-stage, PSA, Gleason Score
- Newer: Percent Positive Biopsies, Ki-67, PSA DT < 10 months
- Promising: p53, BAX-BCL2, EGFR, MDM2, SURVIVIN, p16^{INK4a}, Hypoxia

RISK GROUPS

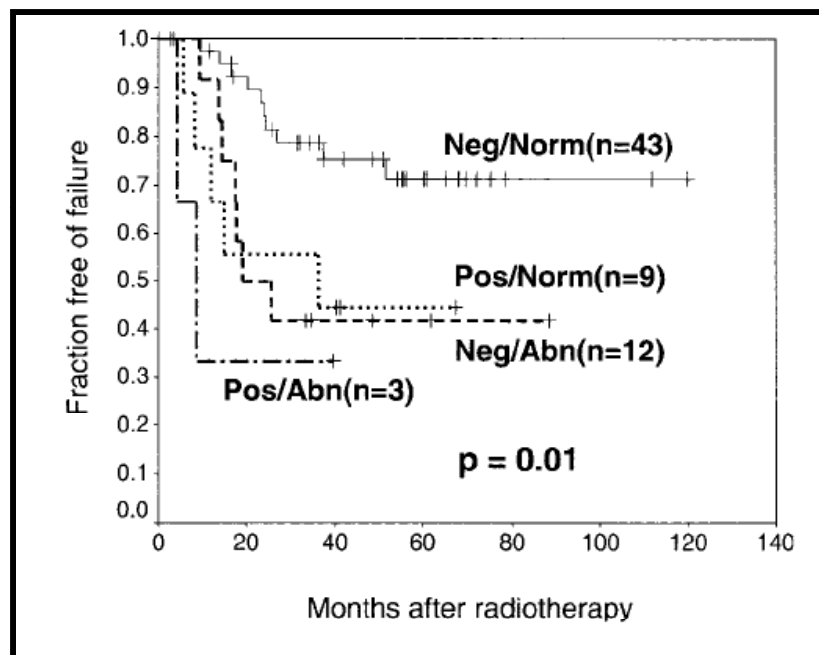
- LOW: T1/T2; PSA <10; GS 4-6 (*Brachy, EBRT*)
- INTERMEDIATE: T1/T2; GS 7; PSA 10-20 (*Brachy/EBRT +/- Hormones*)
- HIGH: PSA > 20; GS 8-10; T3-T4 (*EBRT + Hormones +/- Chemo*)

Are there signatures for radioresistance and normal toxicity ?

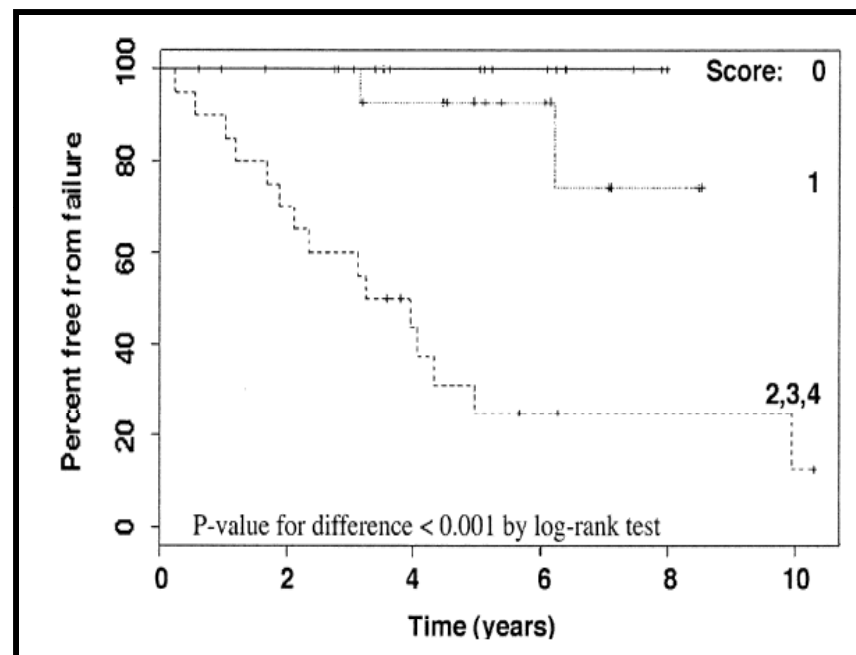
MDM2, p53, BAX-BCL2 and Radioresponse

BCL2/BAX RATIO

p53



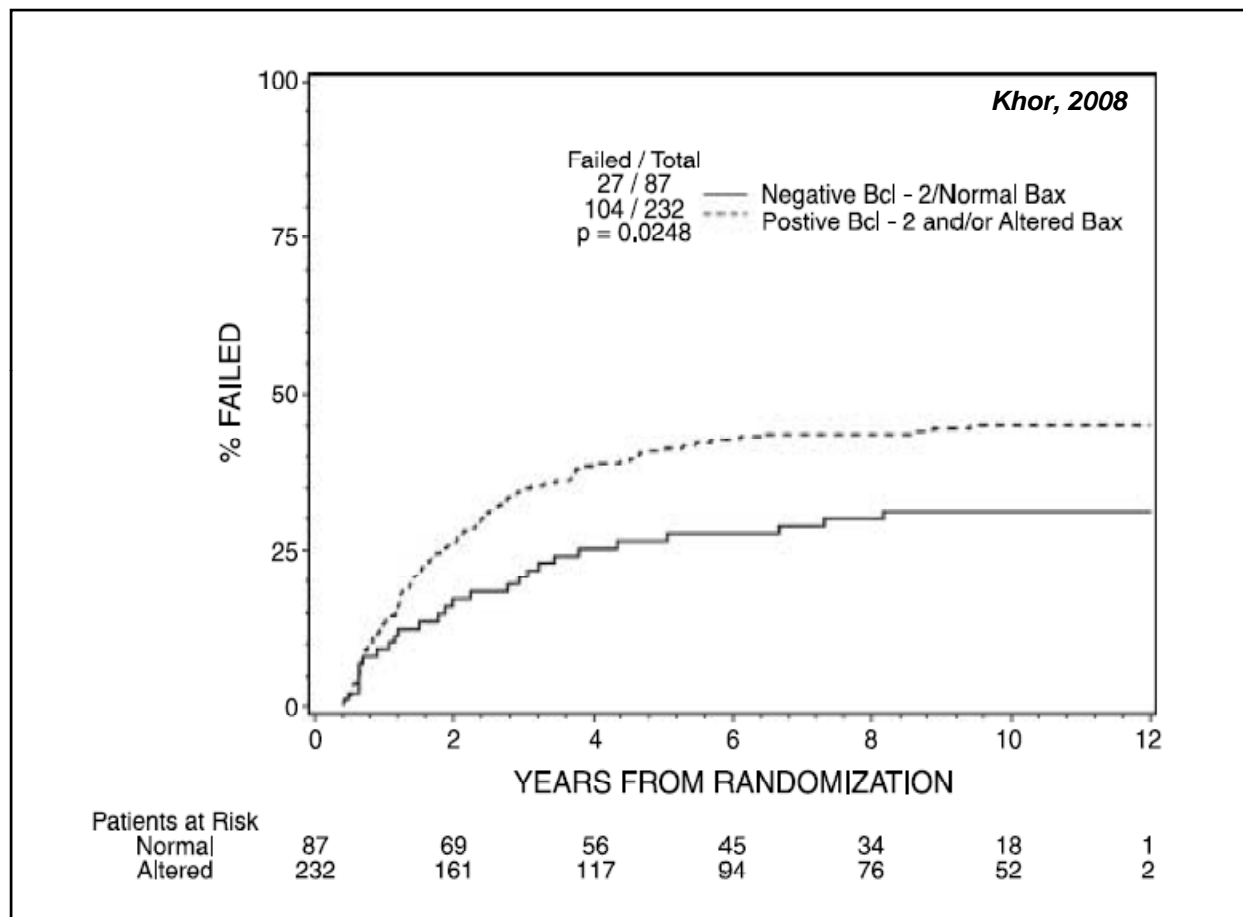
Pollack, JCO-2003



Ritter-IJROBP-2002

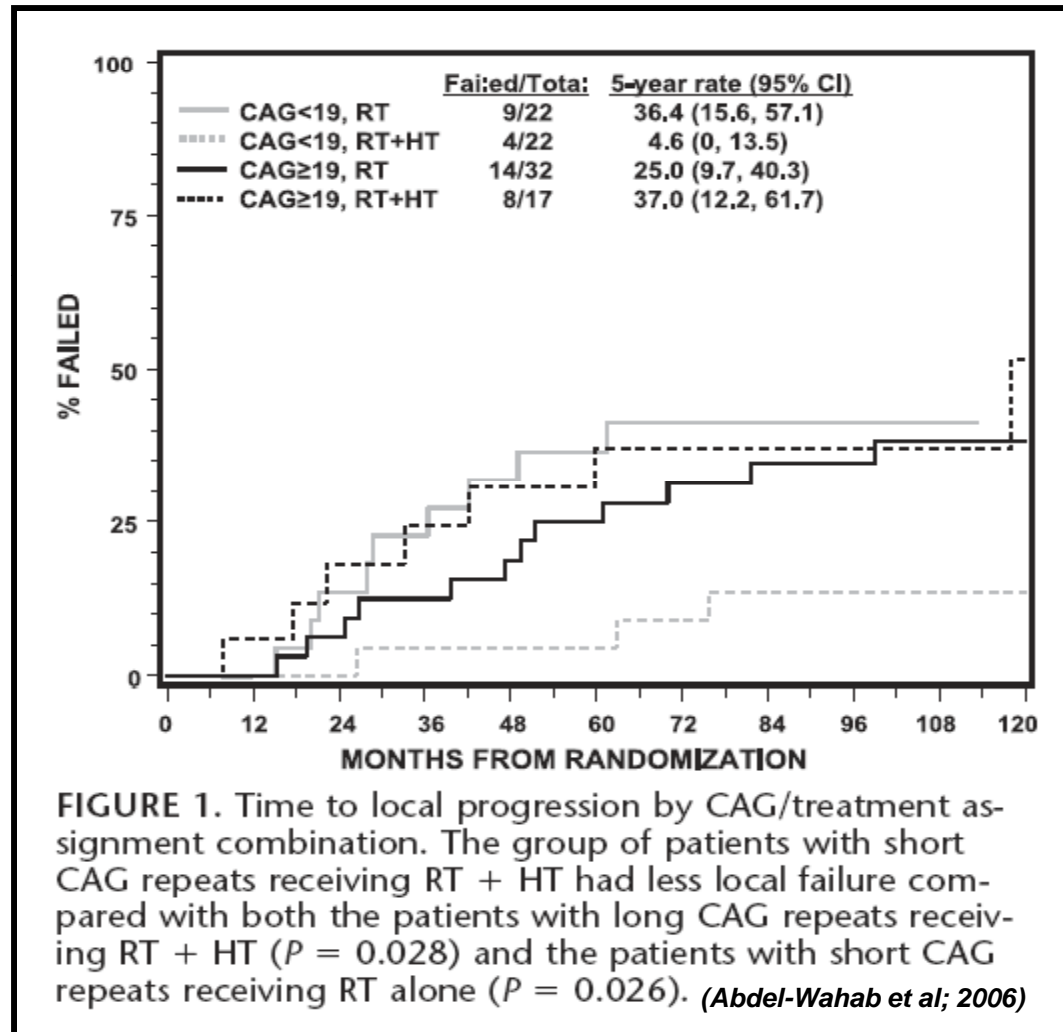
Similar data for MDM2 Over-expression in RTOG 86-10 (Khor, 2005)

MDM2, p53, BAX-BCL2 and Radioresponse

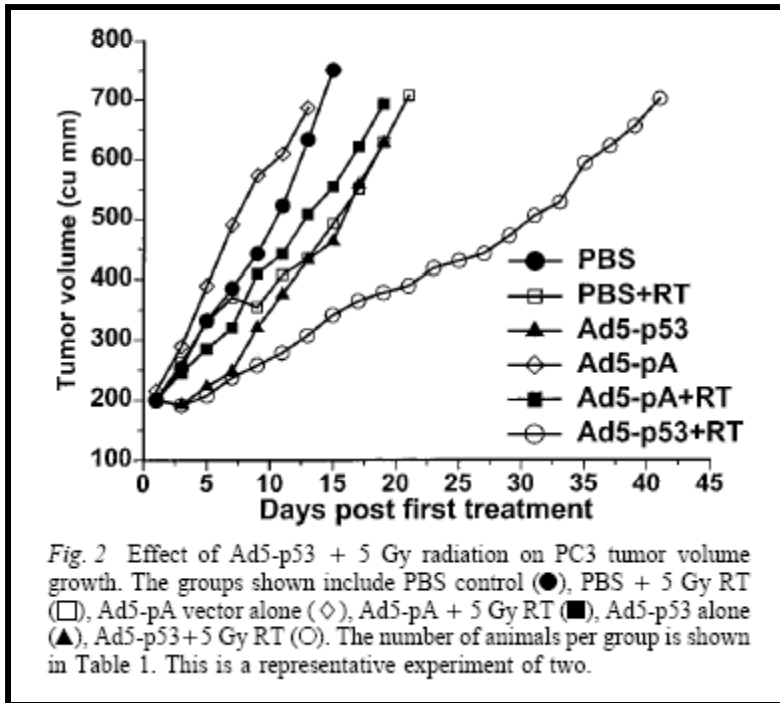


Also suggested that LTAD (2y) vs STAD (4m) when BCL-2+

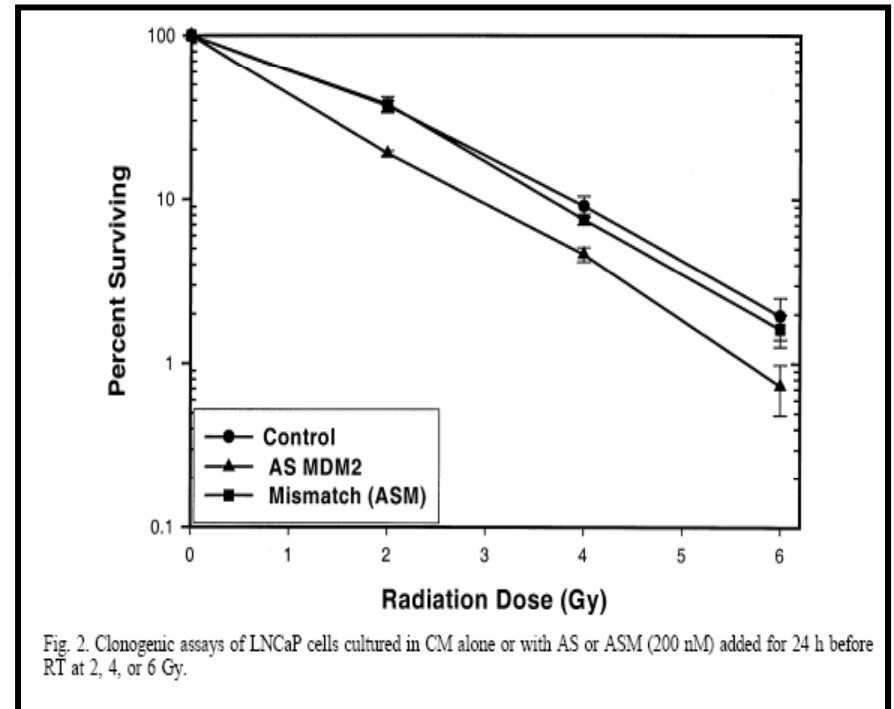
Hormone-RT Responders: Number of AR-CAG Repeats & Failure



P53, MDM2, BCL-2: Experimental Therapy



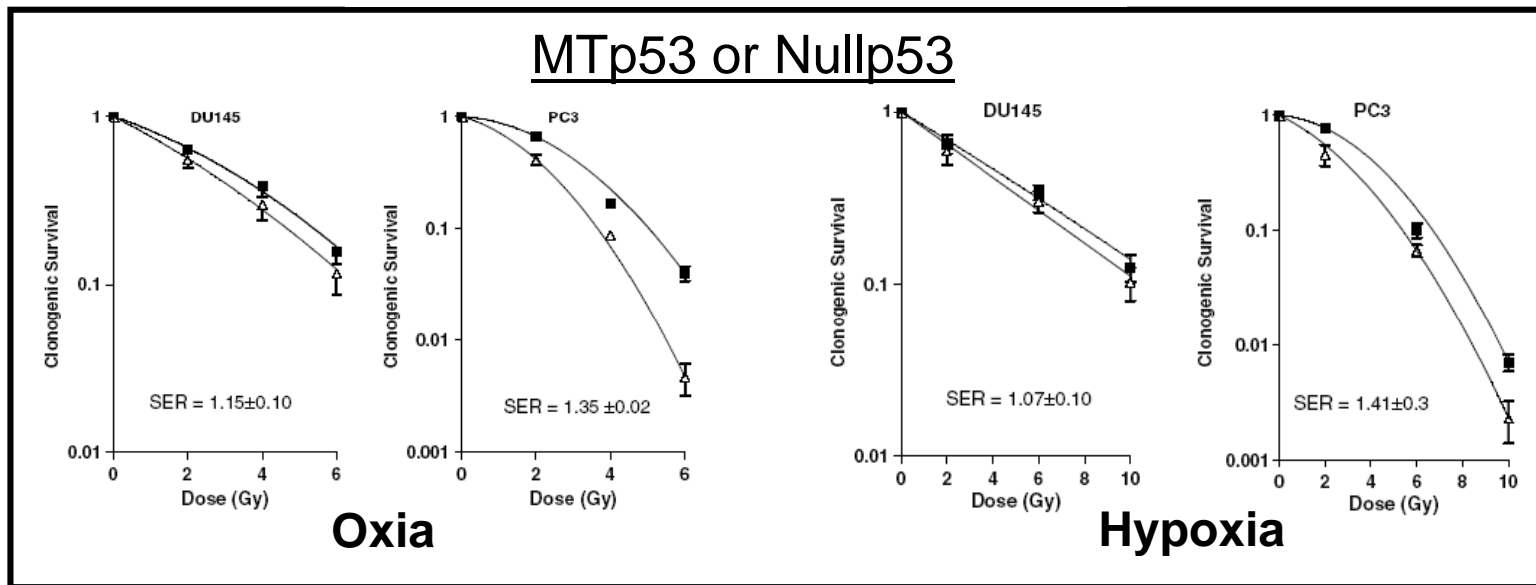
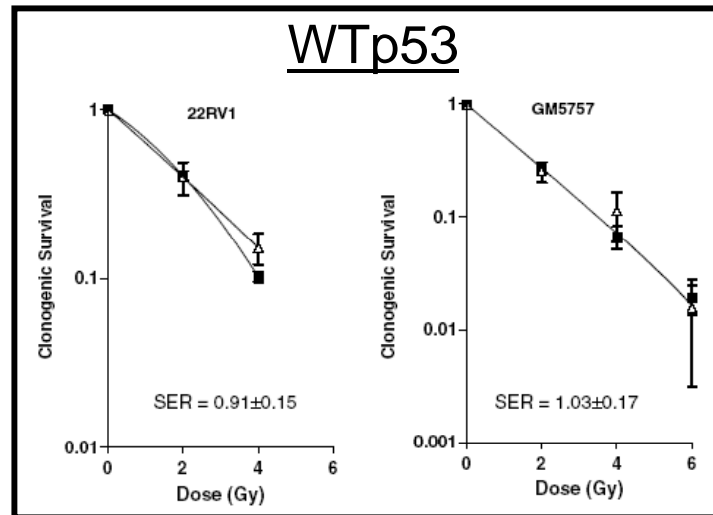
Cowan, Meyn, Pollack, 2000



Mu and Pollack, 2004

Similar Effects for anti-BCL-2 (Genasense) In Vitro-PC3/LNCAP

Anti-p53 Therapies As Nutlin/PRIMA-1: p53-specific ?

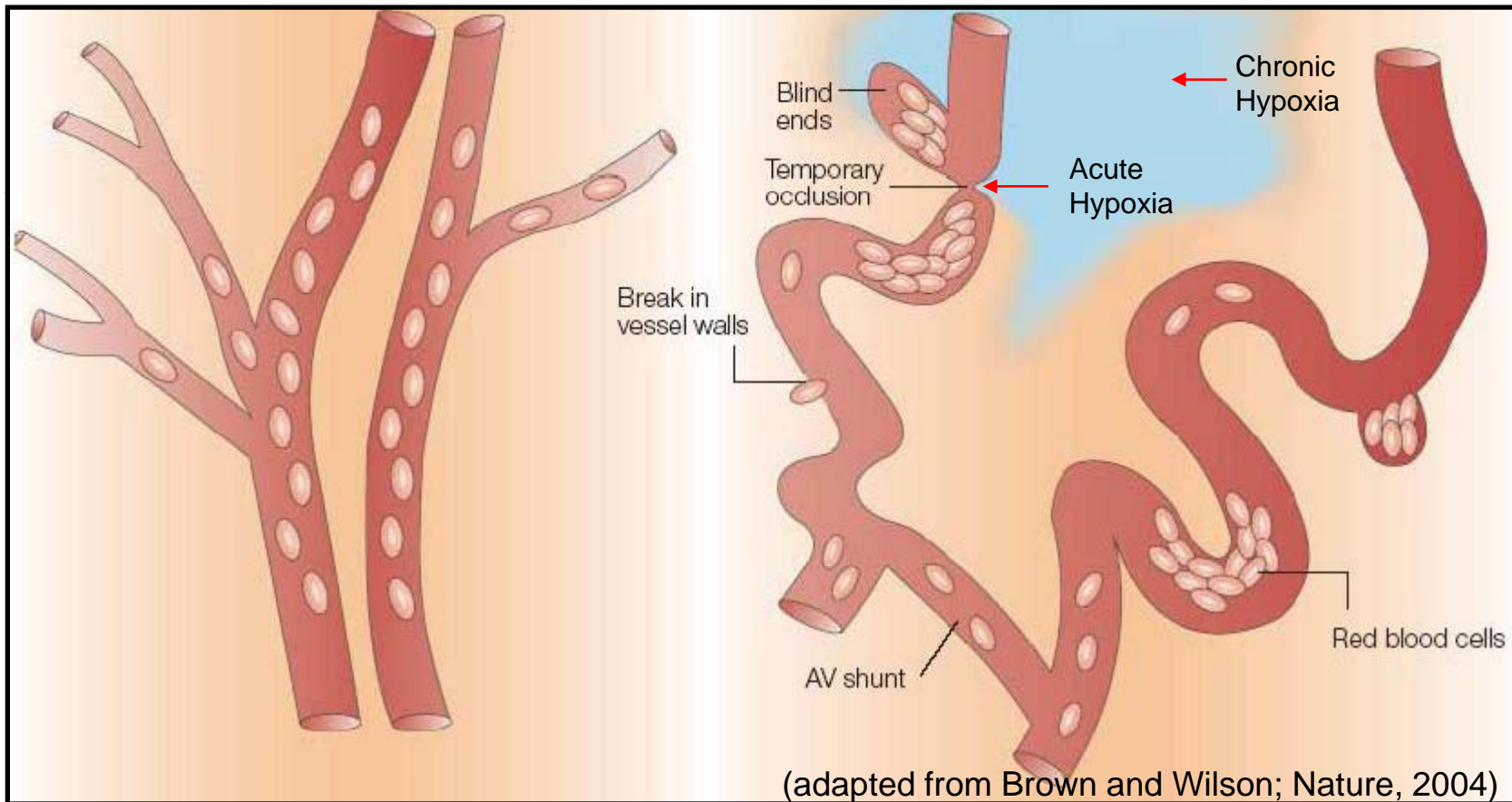


Supiot et al; Mol Can Ther 2008; Rad&Oncol 2008

Microenvironment: Tumour Hypoxia

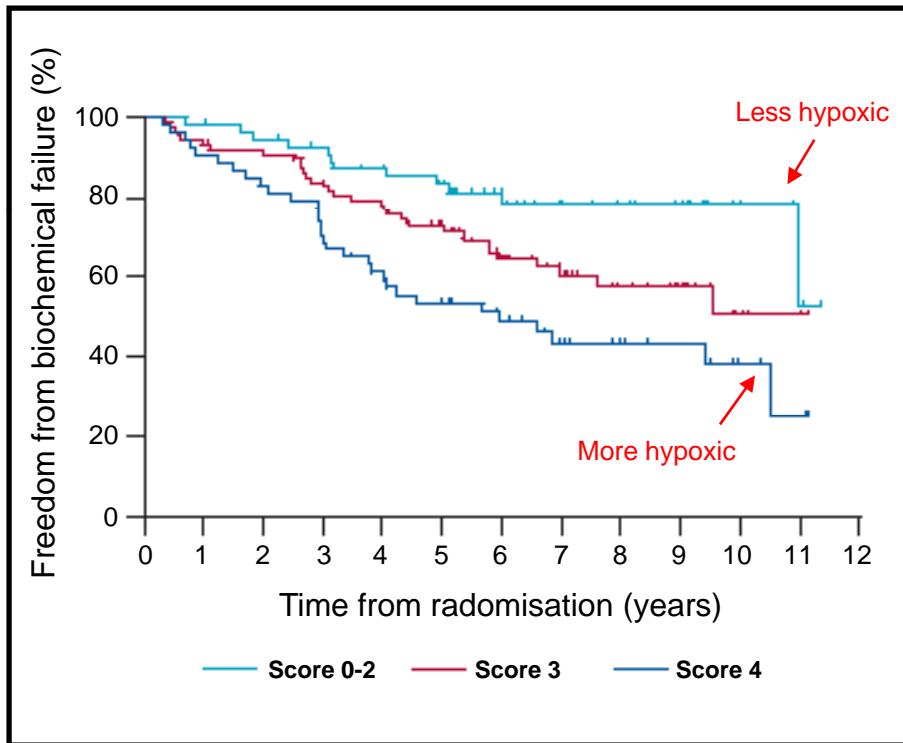
Normal

Tumour

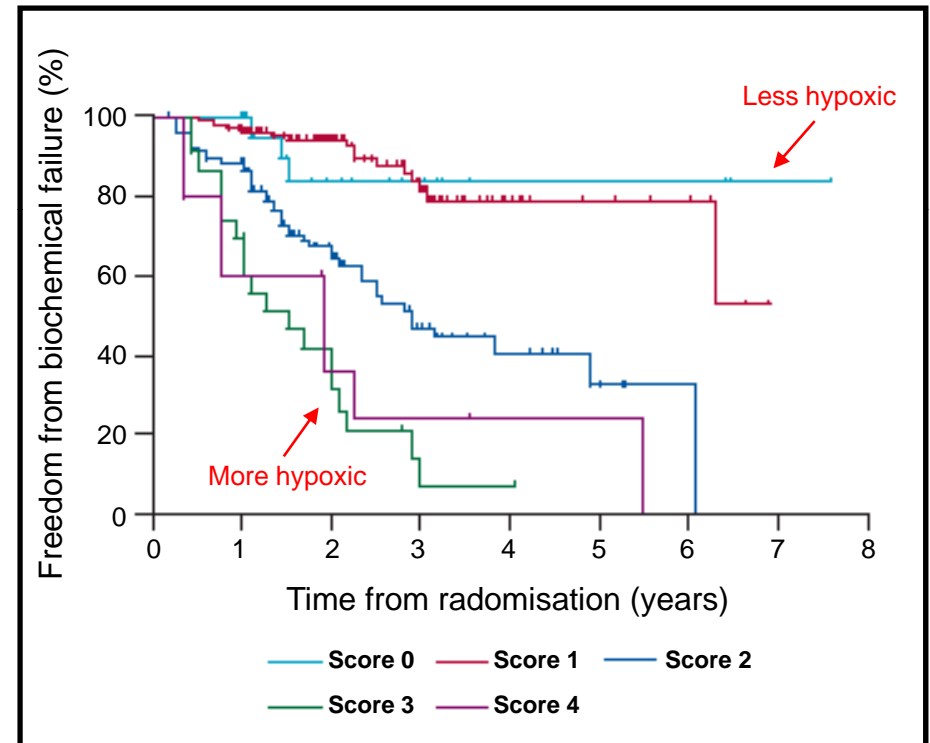


Intratumoural hypoxia is a negative clinical prognostic factor

Radiotherapy



Radical Prostatectomy

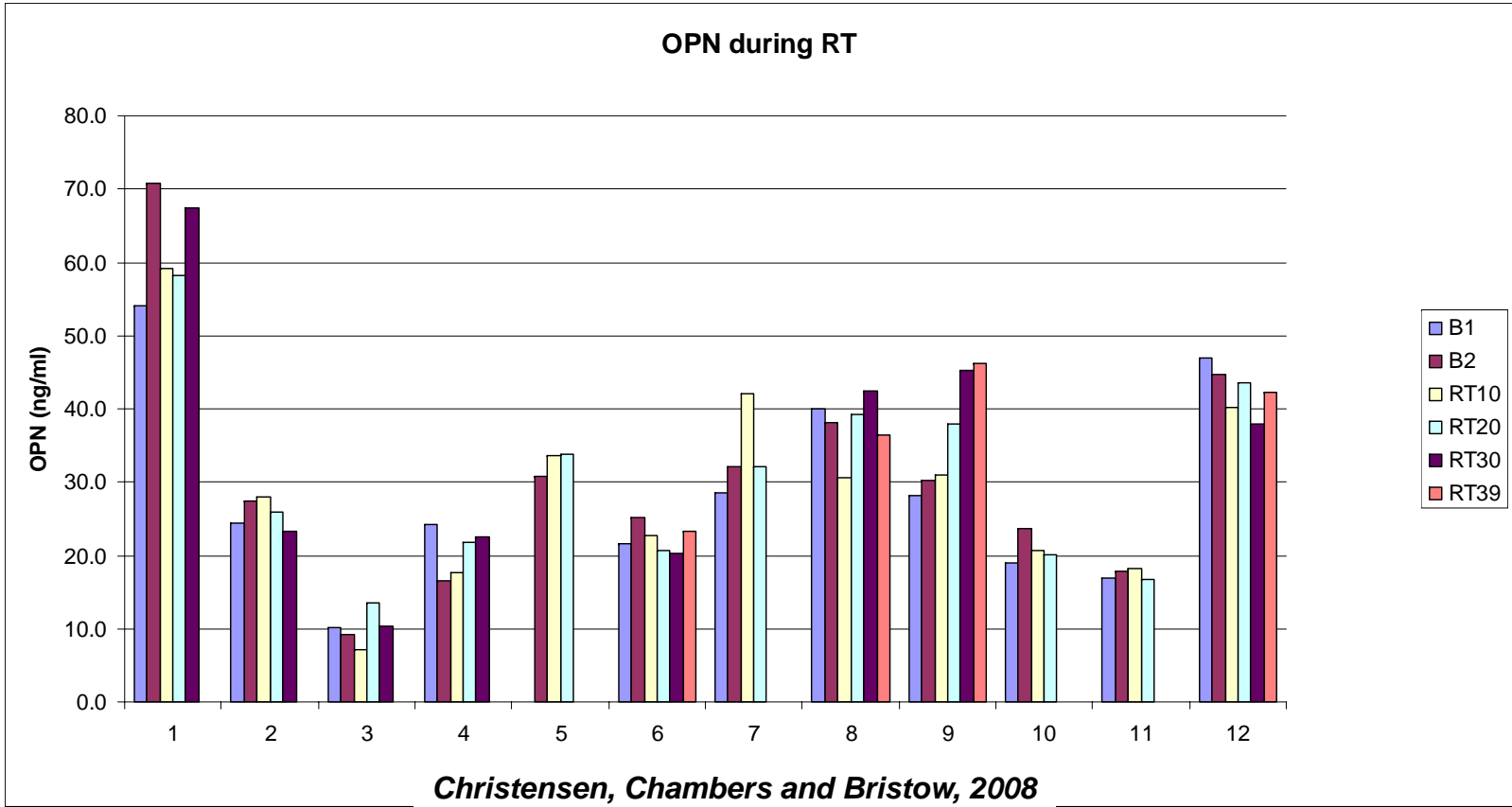


(adapted from Vergis et al.; Lancet Oncol, 2008)

- Prostate tumours with increased HIF1, VEGF and OPN have higher relapse
- Potentially a local and systemic problem (cervix, HEENT, breast, sarcoma, etc.)



Osteopontin

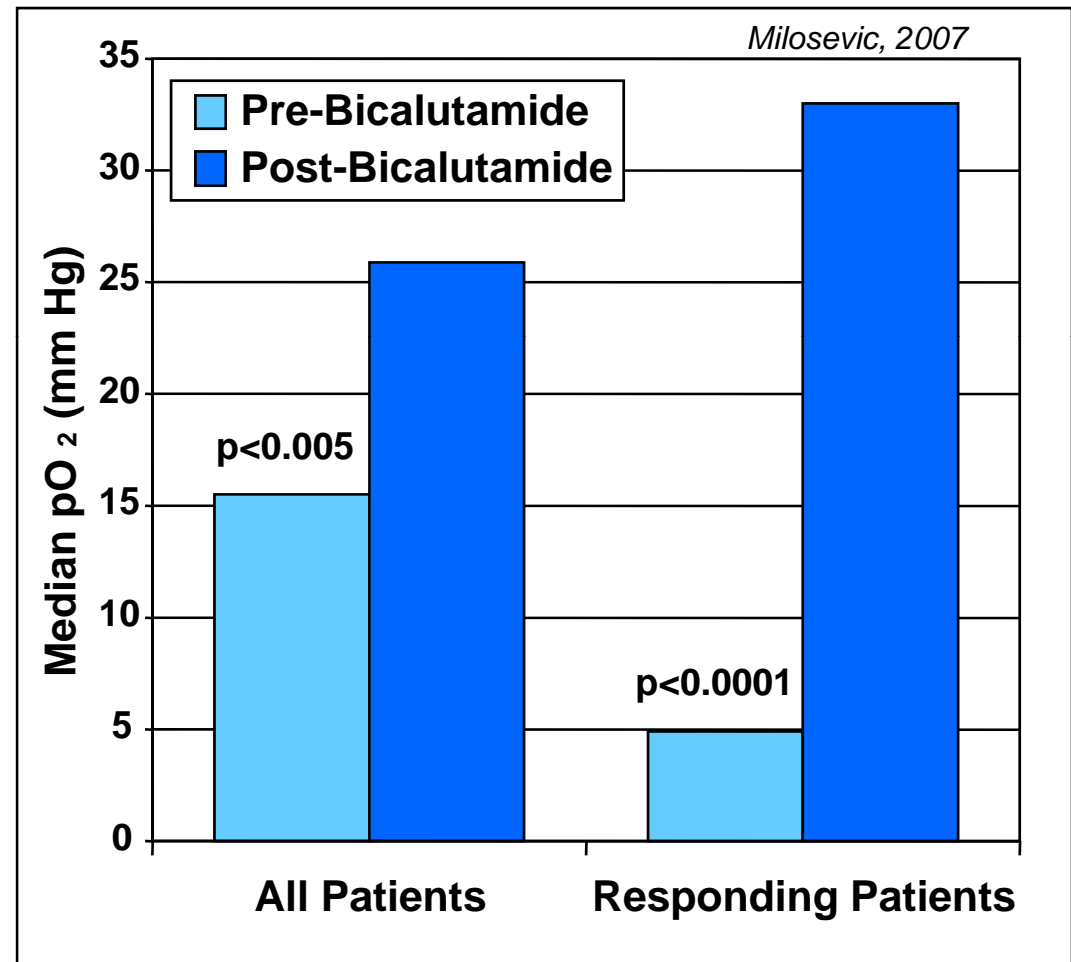


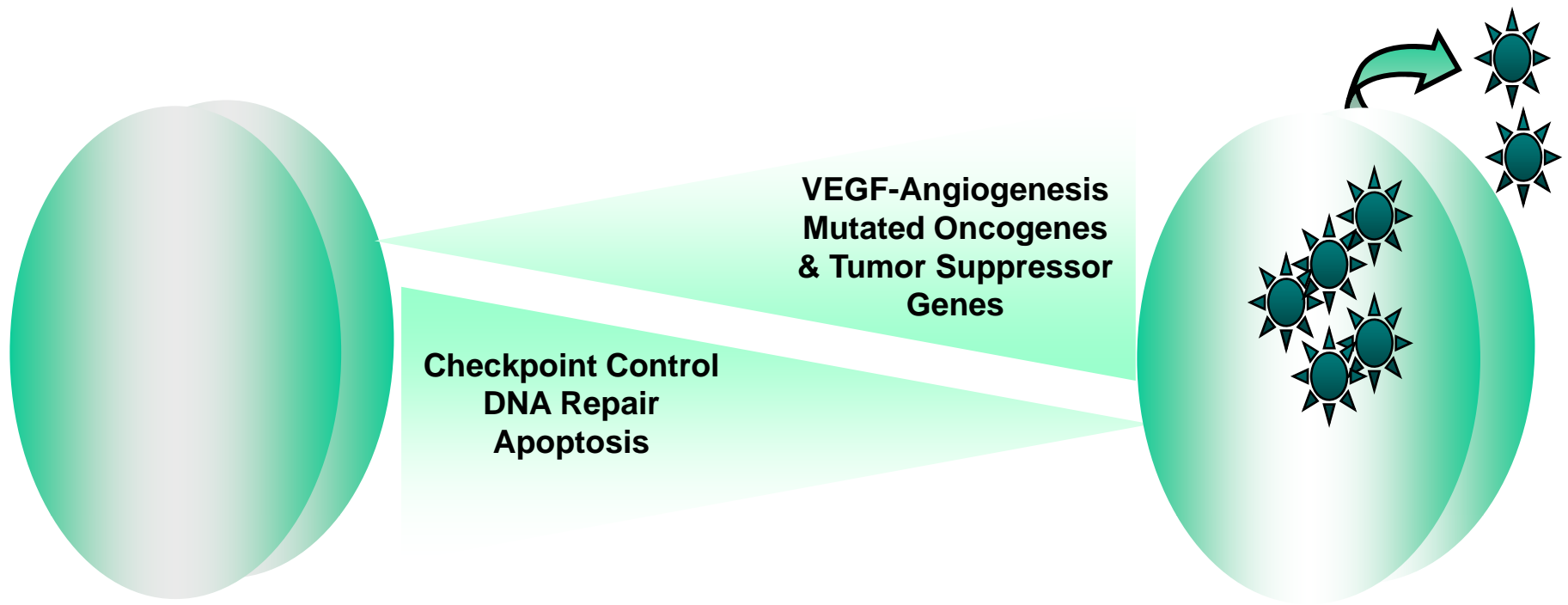
-plasma OPN predicts for advanced disease; triage high-risk patients ?

Bicalutamide Reduces Hypoxia

No relationship to:

- T-Category
- Gleason score
- PSA
- Change in PSA
- Duration of bicalutamide





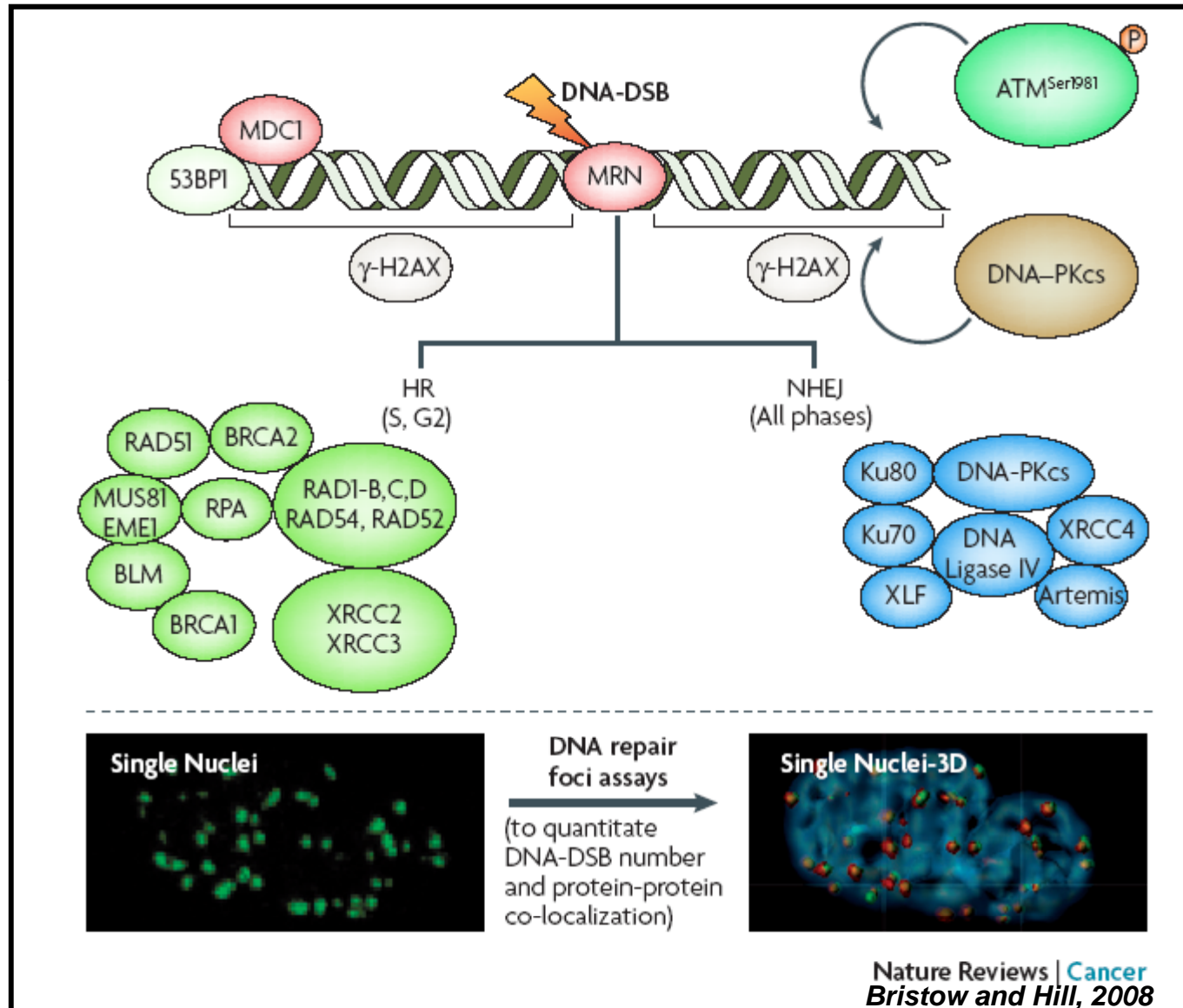
Pre-Malignant
 (Prostate
 Intraepithelial
 Neoplasia;
 Genetic
 Instability)

Increasing Hypoxia

**Aggressive
 Malignant**
 (High Proliferation;
 Androgen-Independent;
 Local Resistance and
 Metastatic)

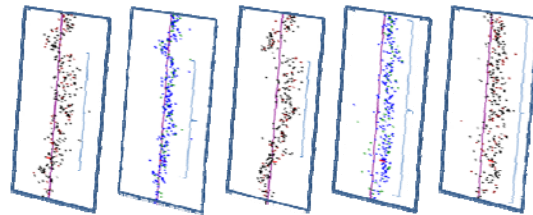
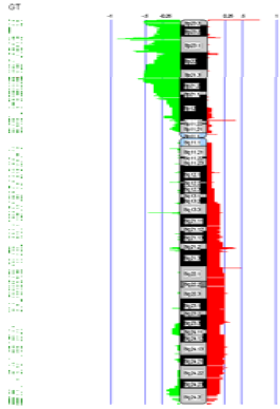
- Anti-VEGF/HIF1 α therapies
- Precision Radiotherapy to hypoxic areas
- Androgen Deprivation
- Antioxidants if PIN
- Target HR-deficient cells
- Hypoxic cell toxins
- (e.g. tirapazamine)

DNA Repair & Radiotherapy: Foci As A Biodosimeter



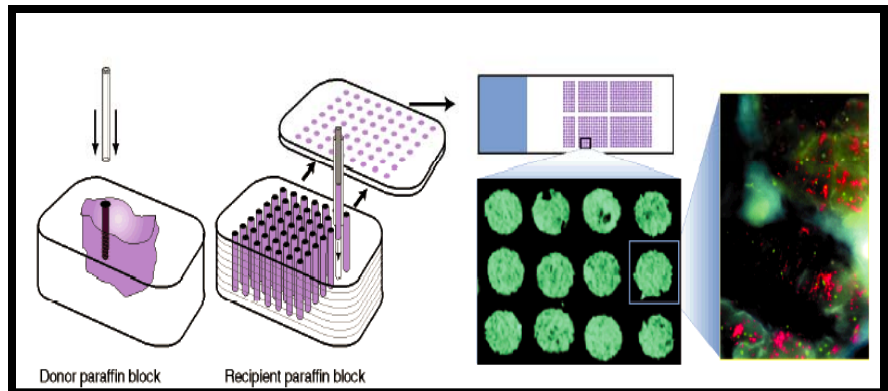
Predict Responders and Non-Responders

DNA ARRAYS



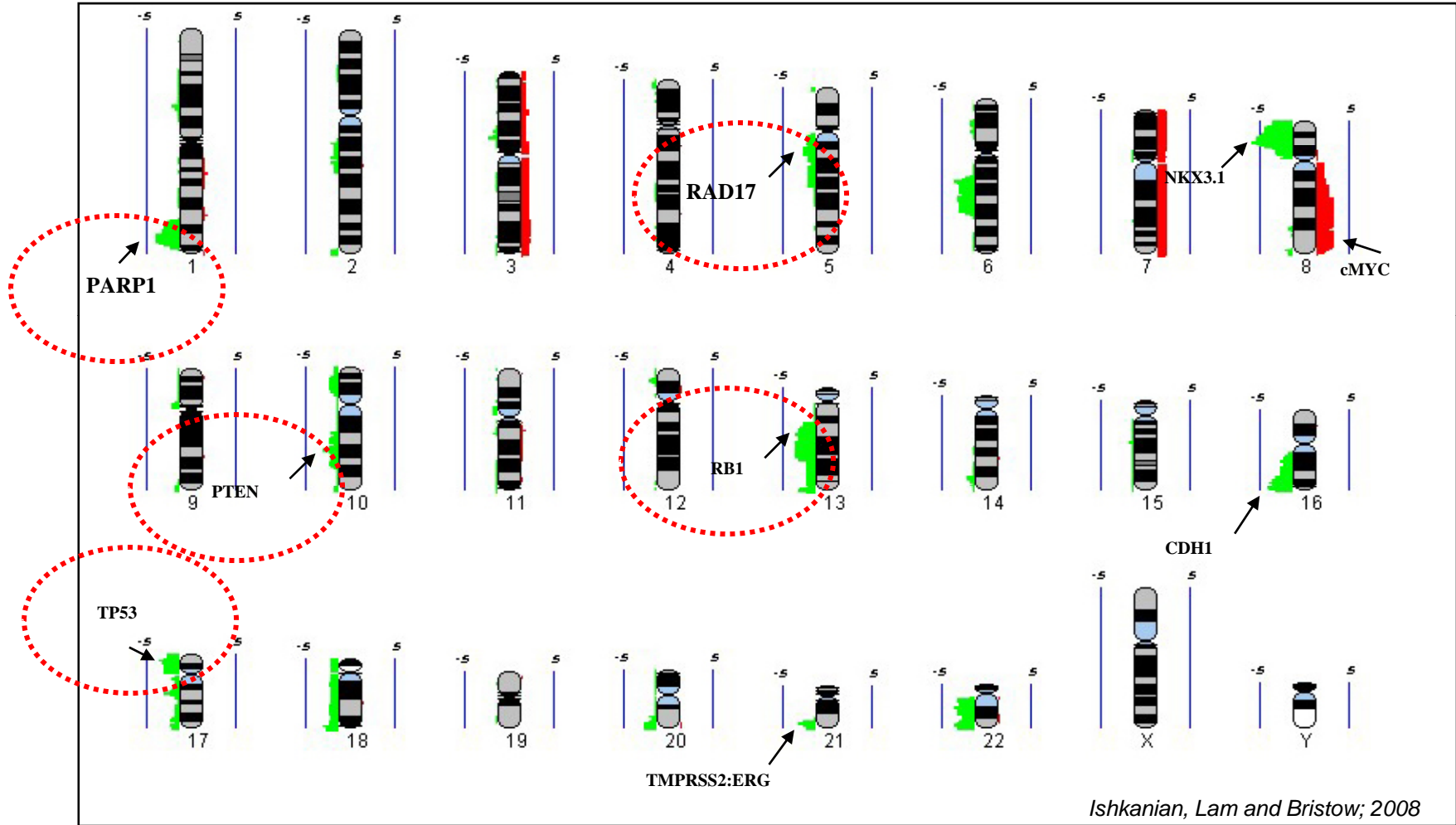
Prostate Ca Example:
Frozen biopsies from ~250 men
pO2 measurements
CGH-ATR/SSB pathways
Outcome data

RNA ARRAYS

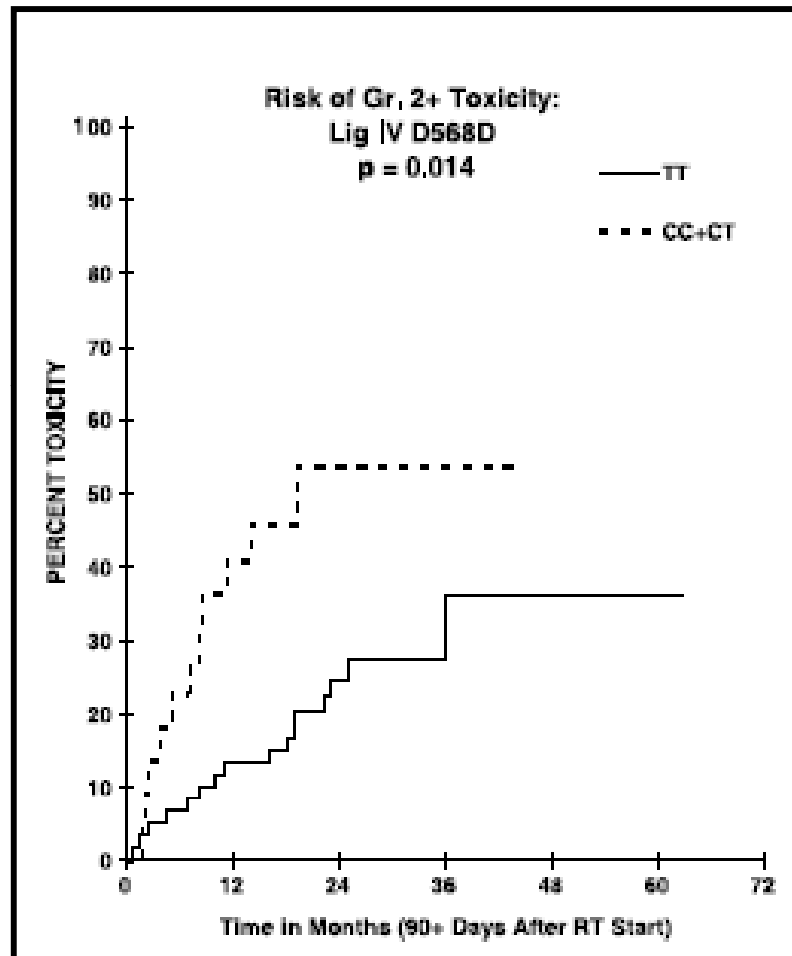


TISSUE ARRAYS

DNA REPAIR LOCI



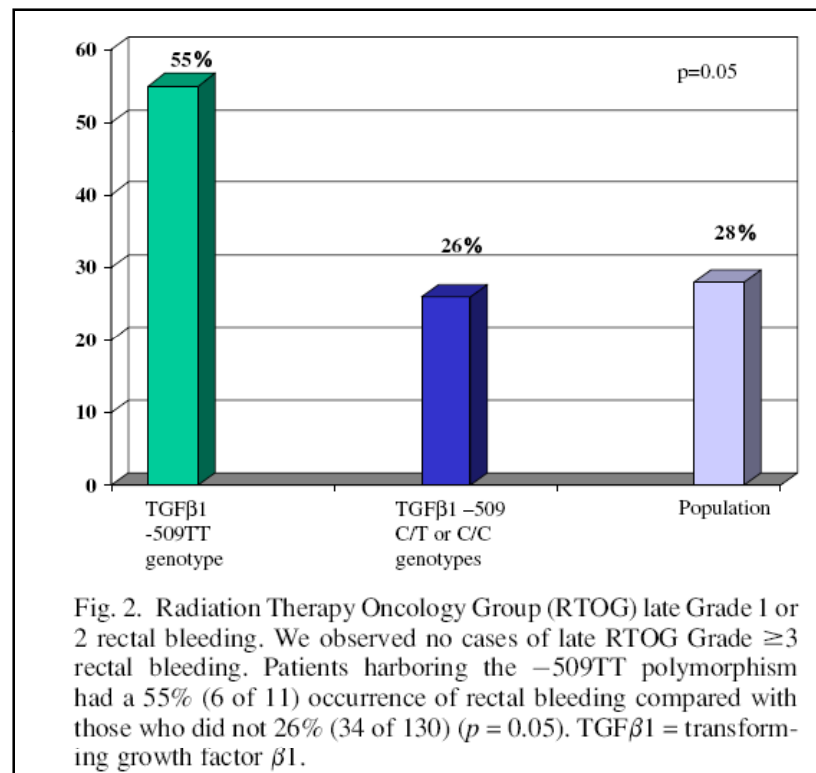
SNPs for Toxicity



Damaraju, Clin Can Res, 2006

SNPs and Normal Tissue Toxicity

-Combined SNPs of TGFB1, VEGF (growth factors) and ATM, XRCC3, XRCC1, RAD21 (DNA repair) predicts for increased ED and rectal bleeding following radical XRT ($OR = 3-4$: Moore, 2007; Langsenlehner, 2008; Cesaretti, 2007; Peters, 2008)



Molecular Therapeutic Ratio

Tumour Resistant (need surgery, RT sensitizers, Adjuvant):

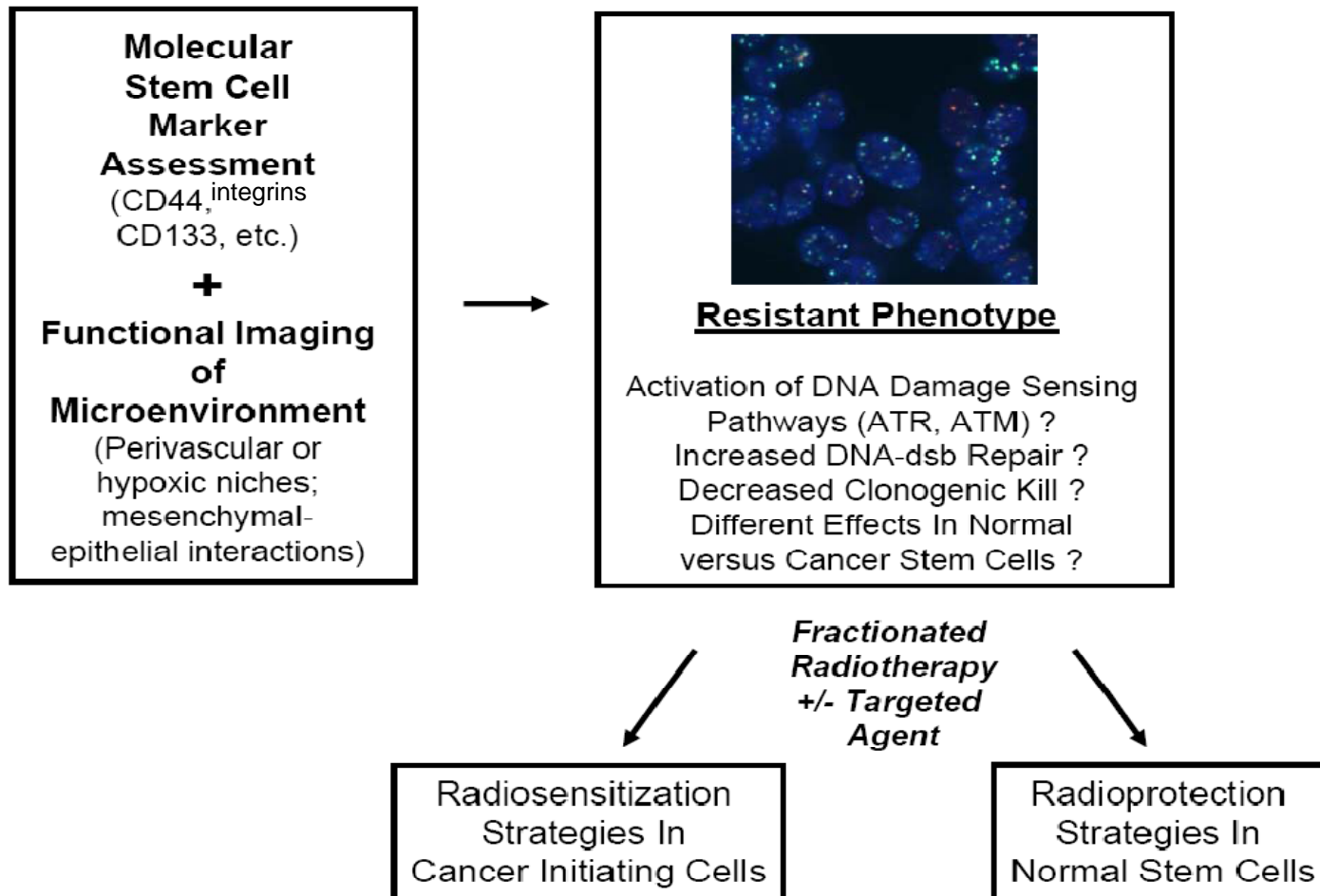
- High BCL2, p53, MDM2, P16INK4a
- High HIF1, VEGF, low pO₂
- High CTC and OPN (mets)
- Role of TMPRSS2:ERG-unknown

Normal Tissues Sensitive (need surgery, RT radioprotectors):

- Severe DNA repair disorders such as AT
(Note: BRCA1/2 probably OK and think PARP inhibitors)
- SNPs in XRCC1, XRCC2, TGFβ1

***Testable Hypotheses in Modern Cohorts With
Bioinformatic Approaches And Validation Cohorts***

Stem Cells in Prostate Cancer



Modern Prostate Radiotherapy

- Current pre-clinical approaches utilizing molecular targets based on initial clinicopathologic studies meeting with success
 - Next generation studies with agents that inhibit EGFR, HDAC, hypoxia, VEGF, proteasome and DNA repair
 - Note-multiple targets may be needed, rather than just one
- Important to understand tissue specificity of molecular pathways and derive toxicity profiles within partially irradiated organs at risk in the IMRT-conformal era
 - What is the therapeutic ratio ?
 - What about dose-escalation and hypo-fractionation ?
 - What is the specific clinical question ?
- Need to track invasively (serial biopsies) or non-invasively (PET, MRI, gene expression imaging) whether drugs are working
- Importantly, we need better pre-clinical models (cell lines are poor) especially for work on rare stem cells
 - Primary prostate xenograft program starting at PMH



PMH-Radiation Medicine Program
PMH-Prostate Clinical Research Program
CCS-NCIC Research Scientist Program
Funding Partners: NCIC, PCRFC; CIHR;
CPCRI; ACURA, CFI; US-DOD; OCRN

