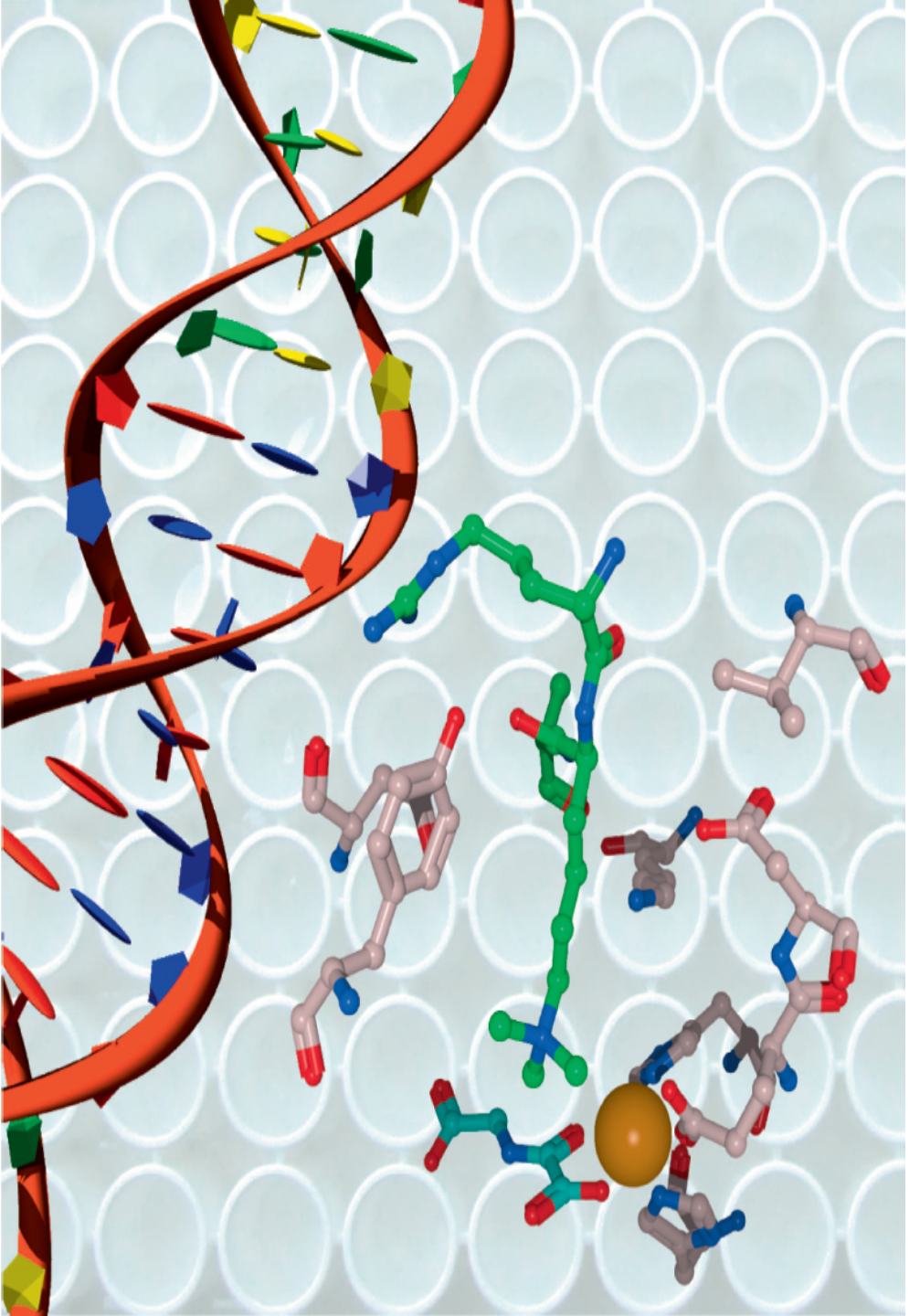

Il razionale biologico dell'uso di agenti epigenetici nei processi di radiosensibilizzazione dei tumori solidi

Giovanni Luca Gravina

Importance of Epigenetics

1. DNA methylation
2. Imprinting
3. X-chromosome inactivation
4 Development/Reprogramming of somatic nucleus
5. Cancer
6. Rett syndrome
7. Non-coding RNAs & heterochromatin

Molecular Mechanisms Mediating Epigenetic Phenomena

Gravina *et al. Molecular Cancer* 2010, **9**:305
http://www.molecular-cancer.com/content/9/1/305

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MOLECULAR CANCER

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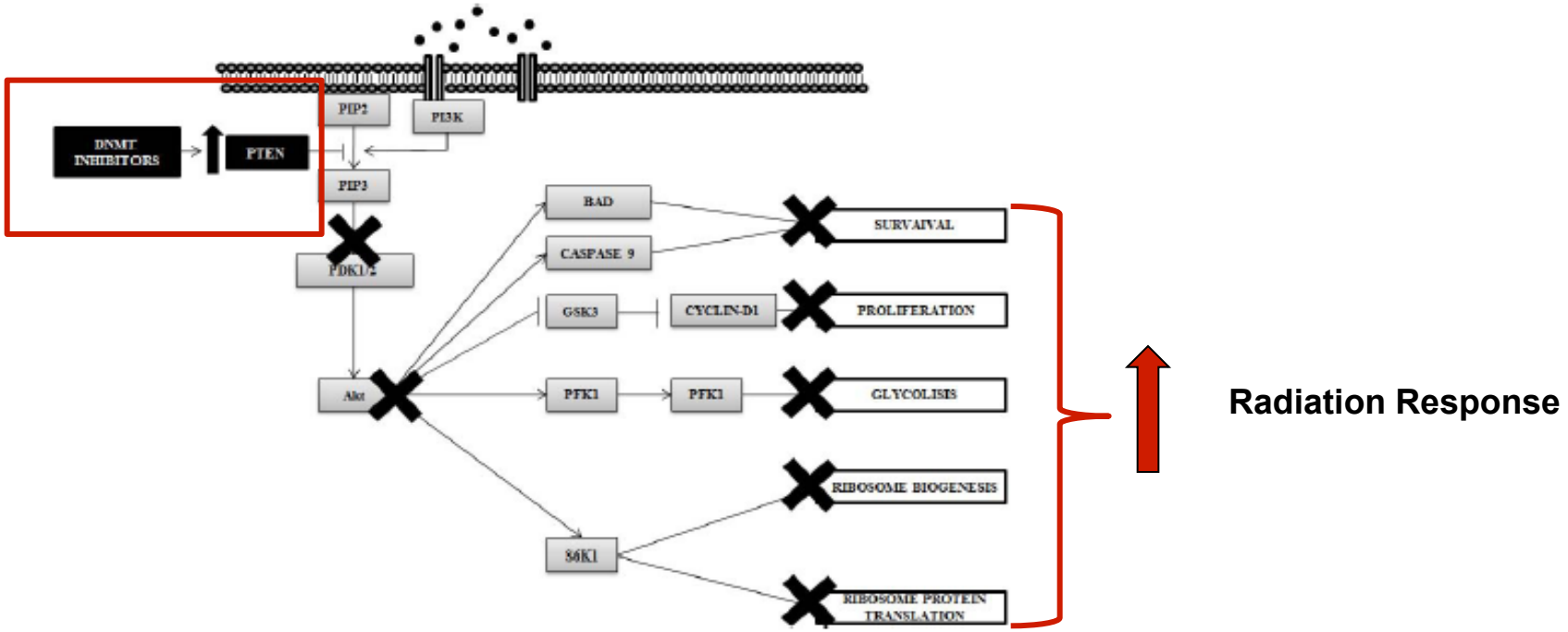
Biological rationale for the use of DNA methyltransferase inhibitors as new strategy for modulation of tumor response to chemotherapy and radiation

Giovanni L Gravina[1,2*], Claudio Festuccia[2], Francesco Marampon[1,2,3], Vladimir M Popov[3], Richard G Pestell[3], Bianca M Zani[2], Vincenzo Tombolini[1,2]



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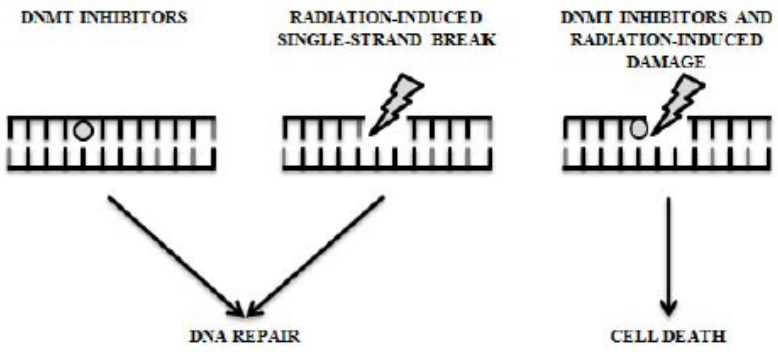
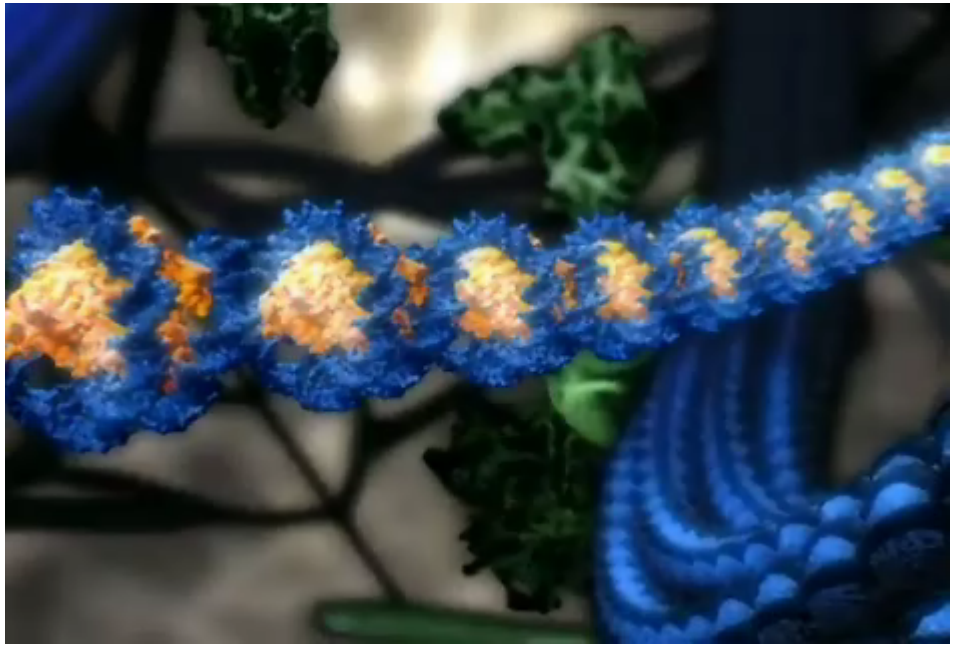


Figure 4 Cooperative cytotoxic mechanism between DNMT inhibitors and radiation. Ionizing radiation induces DNA base damage, single-strand breaks, and double-strand breaks (DSBs). All of these errors can be rapidly repaired except for DSBs, which if not repaired are considered lethal. The cytotoxic effect of DNMT inhibitors in close proximity to a radiation-induced single-strand break can act synergistically to make the defect significantly more difficult to repair, consequently resulting in the induction of cellular death.



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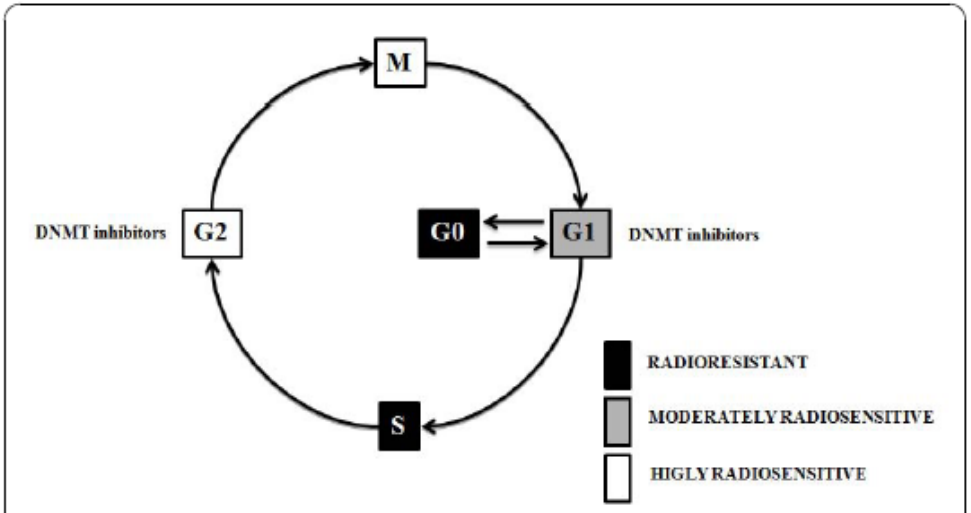
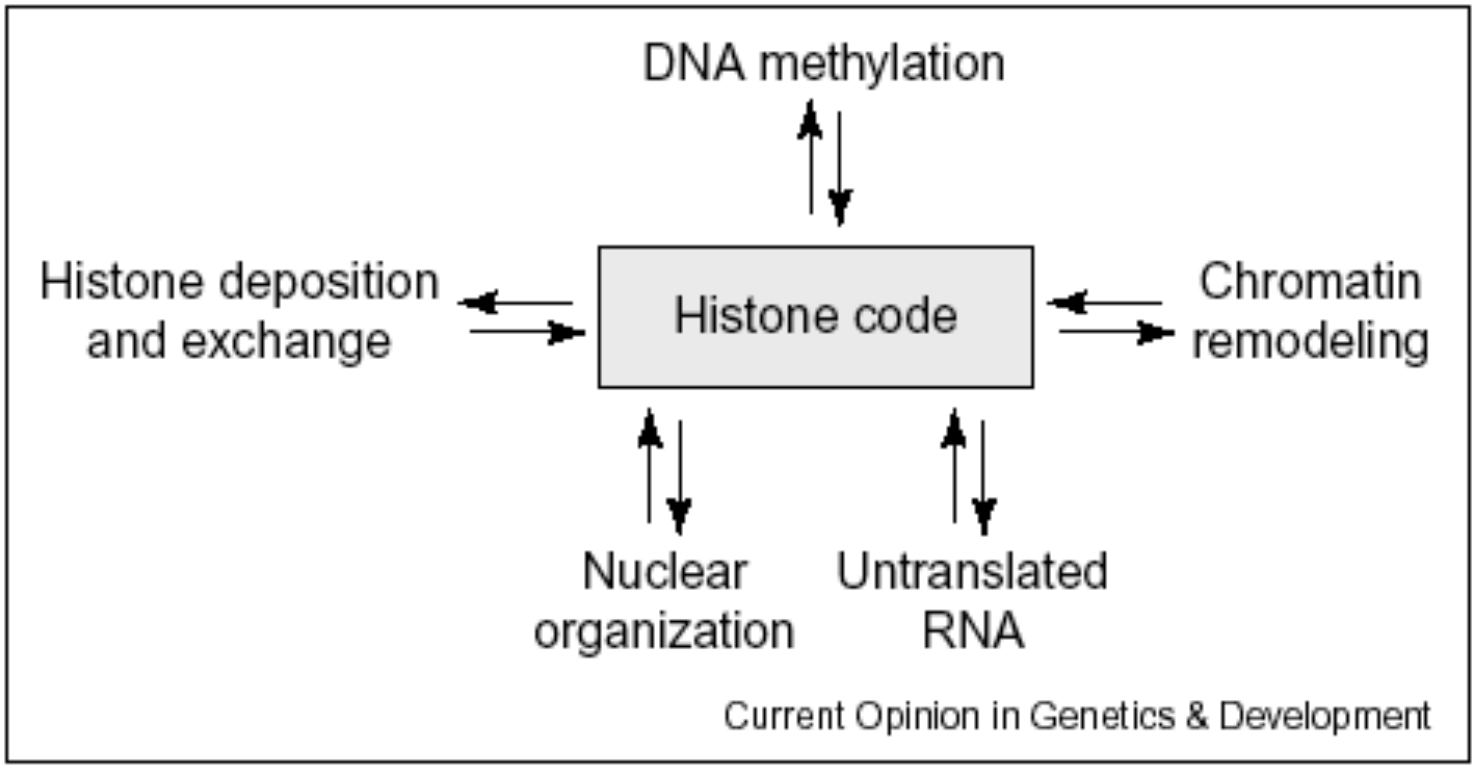


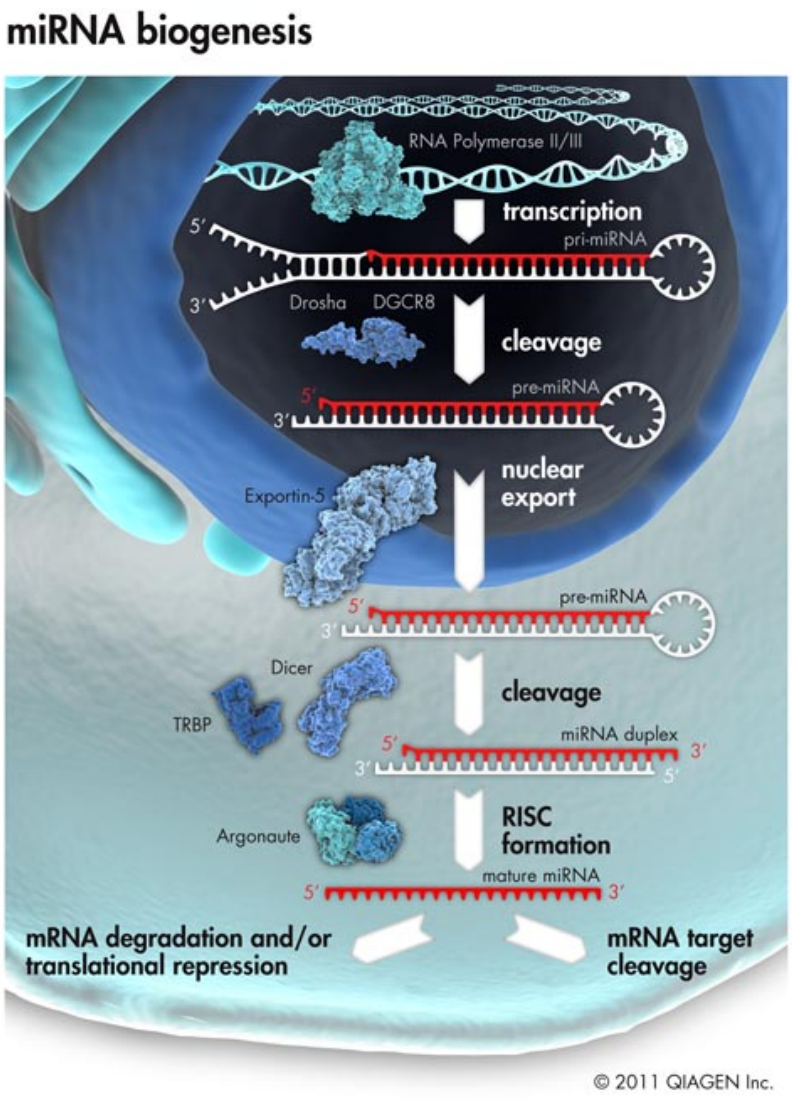
Figure 5 Cell cycle, DNMT inhibitors and radiosensitivity. The radiosensitivity of cells is dependent on the phase of the cell cycle. Cells in the S phase are the most radio resistant, and cells in the G2-M phase of the cell cycle are the most radiosensitive. DNMT inhibitors synchronize with the cell cycle of tumor cells increasing the efficacy of subsequent radiotherapy.

Interplay between different epigenetic strategies

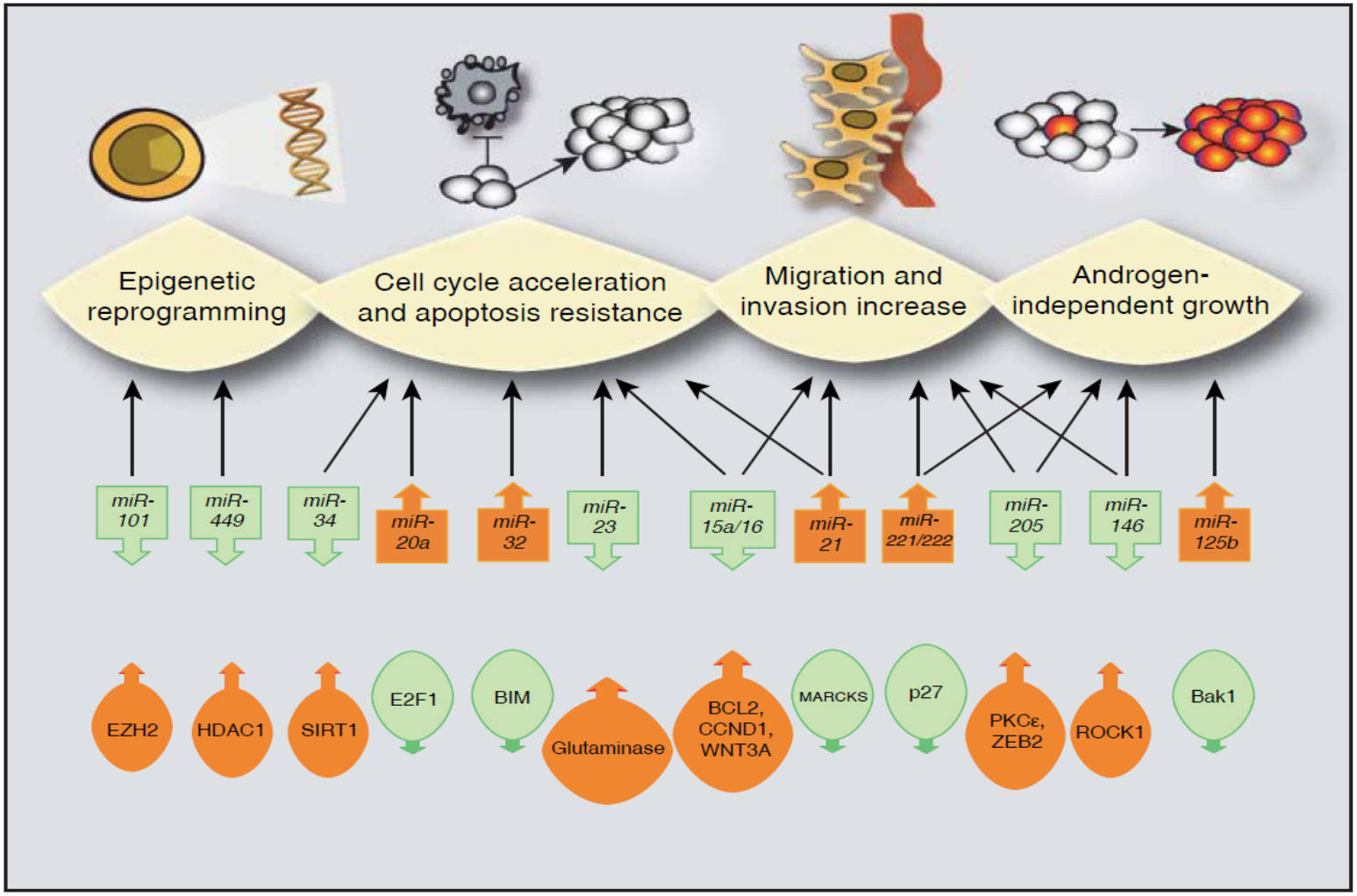


Margueron ,Current Opinion in Genetics & Development (2005)

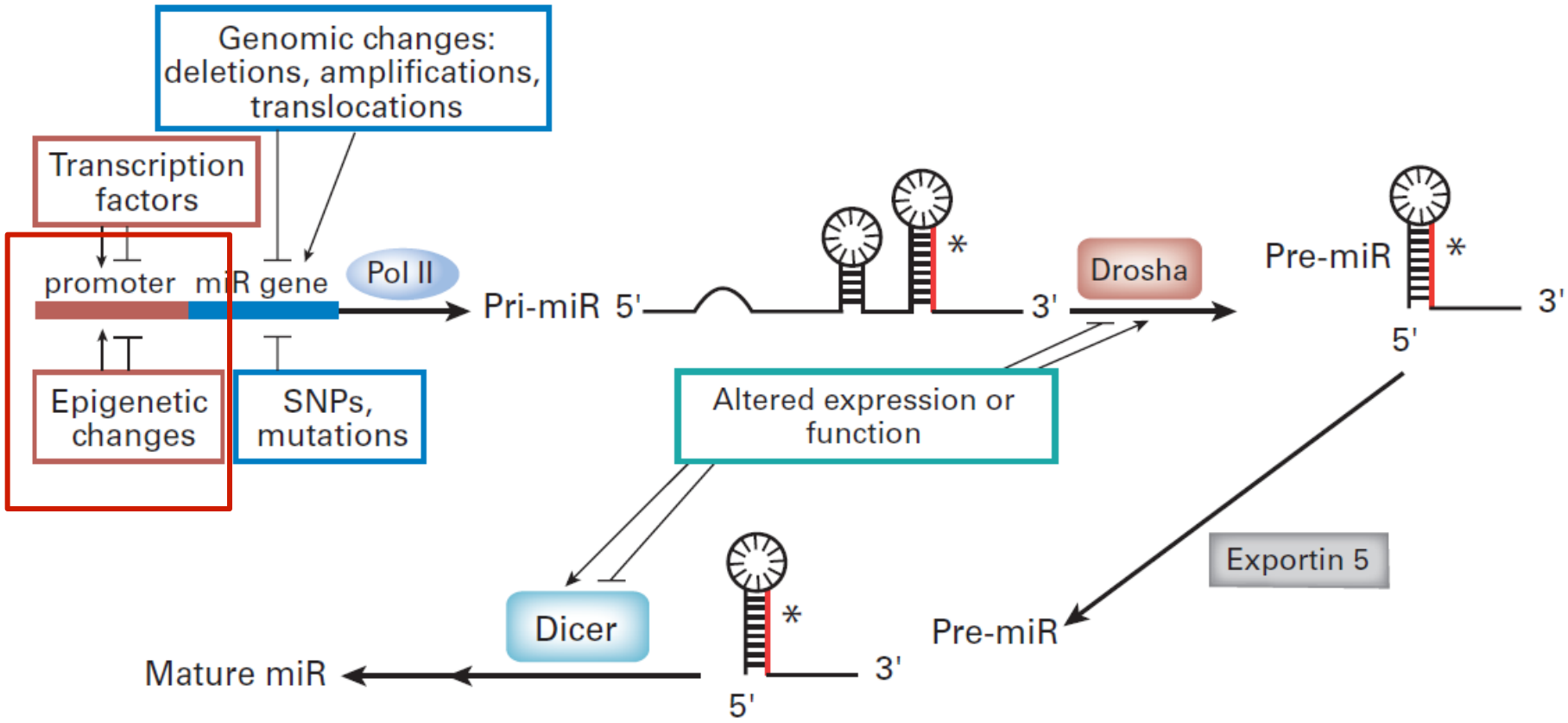
miRs: Biogenesis, processing and maturation



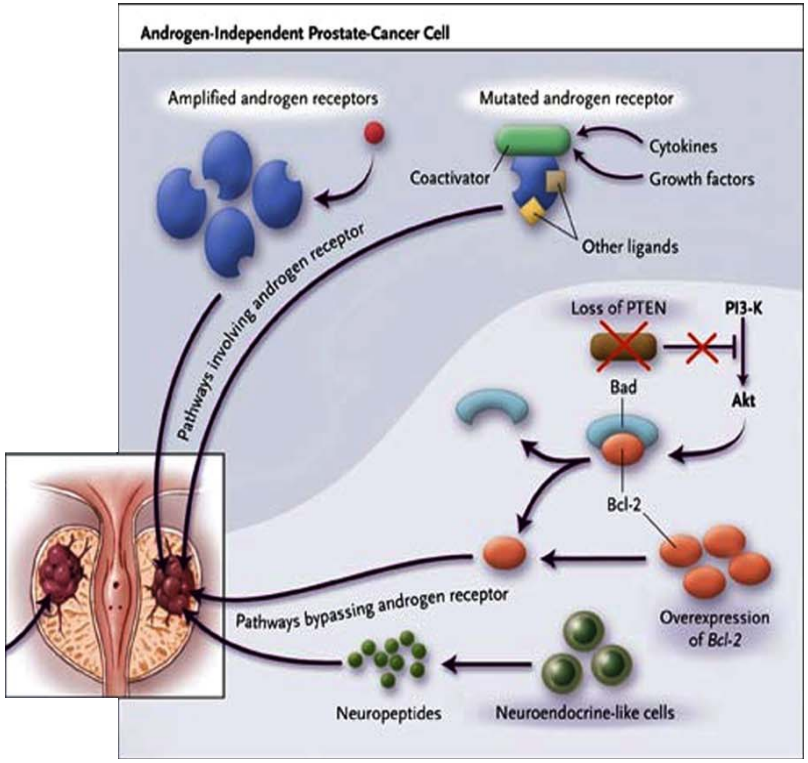
MicroRNA (miR) Biological Function



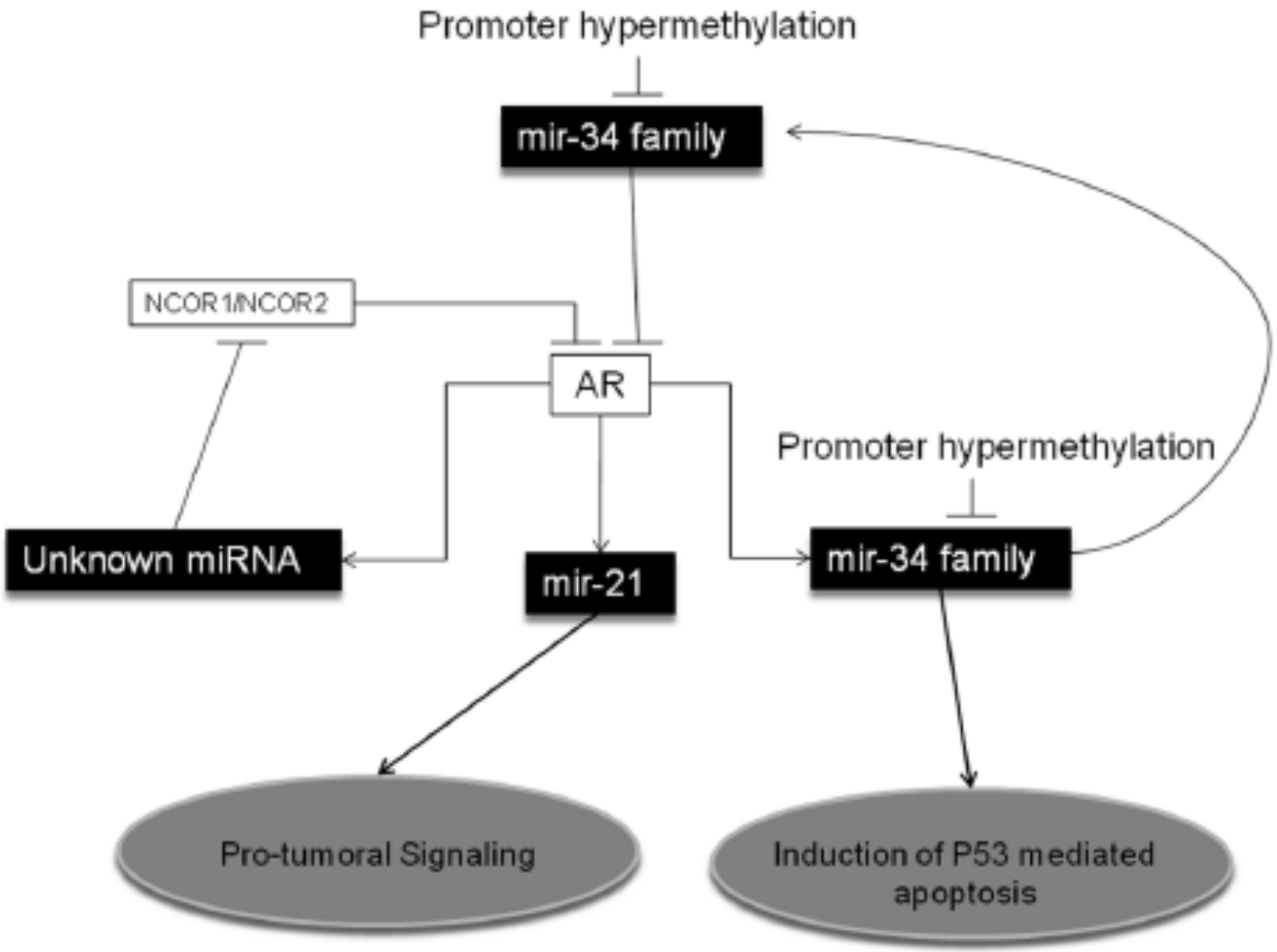
Mechanisms of microRNA (miR) regulation



Androgen Receptor
Hormone refractory and radioresistant phenotype



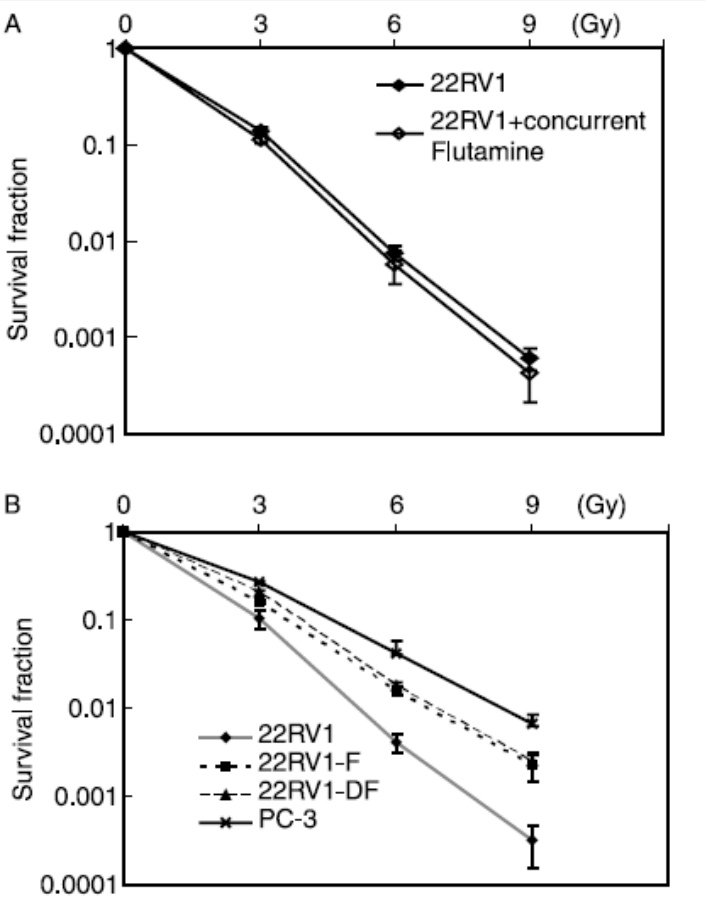
miRNA and Epigenetic regulation of AR



Endocrine-Related Cancer (2007) **14** 633–643

The radiation response of hormone-resistant prostate cancer induced by long-term hormone therapy

Chun-Te Wu[1,2], Wen-Cheng Chen[3], Shuen-Kuei Liao[2], Cheng-Lung Hsu[2,4], Kuan-Der Lee[2,5] and Miao-Fen Chen[2,3]

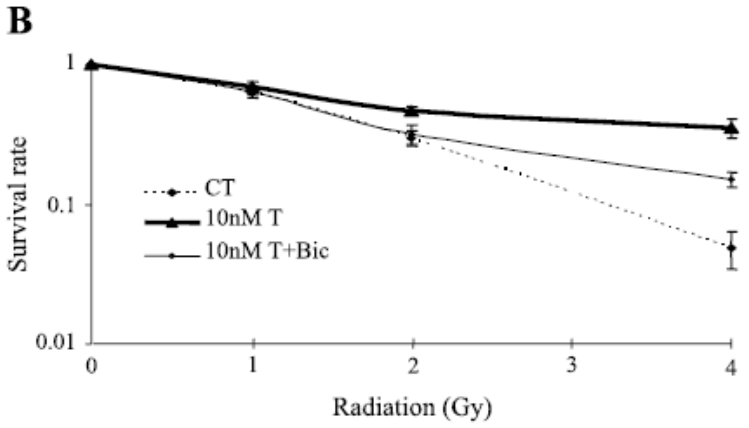


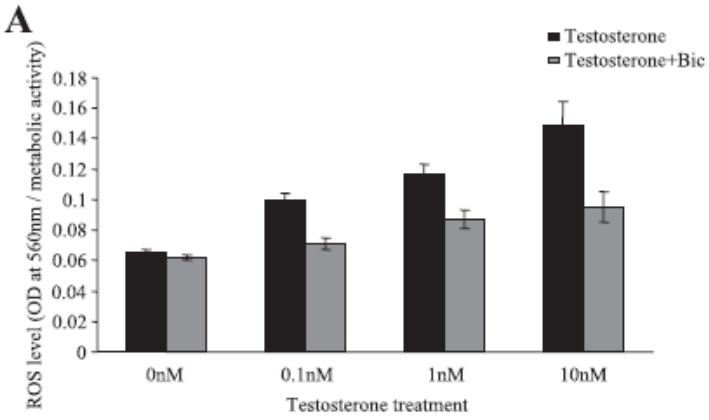
Neoplasia • Vol. 9, No. 1, January 2007, pp. 68–80 68

www.neoplasia.com

Androgen Induces Adaptation to Oxidative Stress in Prostate Cancer: Implications for Treatment with Radiation Therapy[1]

Jehonathan H. Pinthus[*,†,‡], *Inna Bryskin*[†], *John Trachtenberg*[*], *Jiang-Ping Lu*[‡], *Gurmit Singh*[§], *Eduard Fridman*[‡] *and Brian C. Wilson*[†]





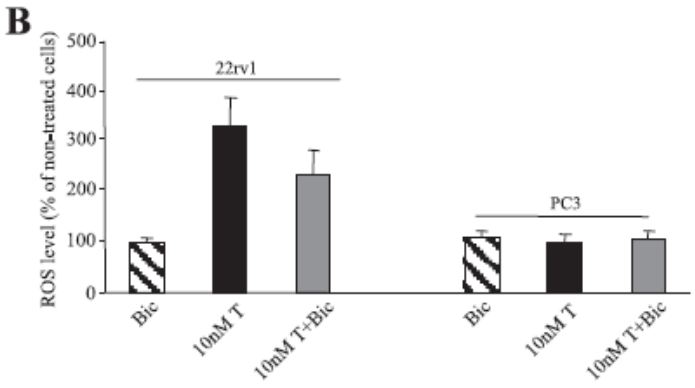


Figure 1. *Androgens induce relative resistance to oxidative stress challenge in 22rv1 human PC cells that can be reversed by AD. (A) Survival of 22rv1 cells in response to 24 hours of incubation with increasing doses of hydrogen peroxide, as determined by neutral red viability assay. LD = lethal dose. (B) Survival of 22rv1 cells in response to γ-radiation, as determined by colony formation assay. CT = control cells growing in a culture medium with CSFCS and without phenol red; T = cells growing in the same medium but with the addition of 10 nM R1881; T + Bic = cells growing in the same medium but with the addition of both 10 nM R1881 and 10 μM bicalutamide. Results are derived from at least three experiments and are expressed as mean ± SD.*

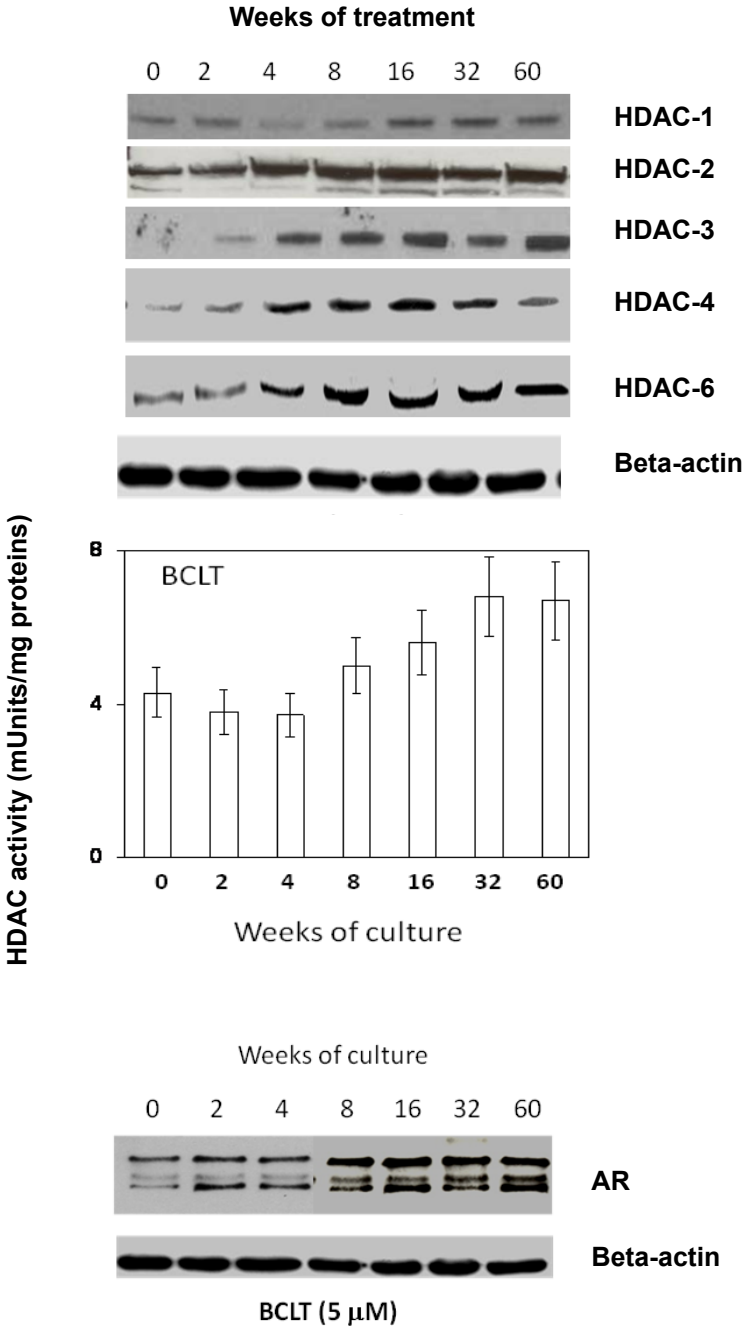
cells treated with increasing doses of R1881. To avoid po-

Endocrinology. First published ahead of print October 11, 2011 as doi:10.1210/en.2011-1056

Hormonal Therapy Promotes Hormone-Resistant Phenotype by Increasing DNMT Activity and Expression in Prostate Cancer Models

Giovanni Luca Gravina,* Francesco Marampon,* Margherita Piccolella, Marcella Motta, Luca Ventura, Roberto Pomante, Vladimir M. Popov, Bianca M. Zani, Richard G. Pestell, Vincenzo Tombolini, Emmanuele A. Jannini, and Claudio Festuccia

Department of Experimental Medicine (G.L.G., F.M., B.M.Z., C.F.); Division of Radiotherapy (G.L.G., F.M.), Laboratory of Radiobiology; and Course of Endocrinology and Medical Sexology (E.A.J.), Department of Experimental Medicine, University of L'Aquila, and Department of Pathology (L.V.), San Salvatore Hospital, 67100 L'Aquila, Italy; Department of Endocrinology (M.P., M.M.), Center of Endocrinological Oncology, University of Milano, 20122 Milan, Italy; Department of Cancer Biology (F.M., V.M.P., R.G.P.), Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19107; and Department of Pathology (R.P.), Mazzini Hospital, 64100 Teramo, Italy; Department of Radiological Sciences, University of Rome "La Sapienza" Spencer-Lorillard Fondation (V.T.), 00100 Rome, Italy



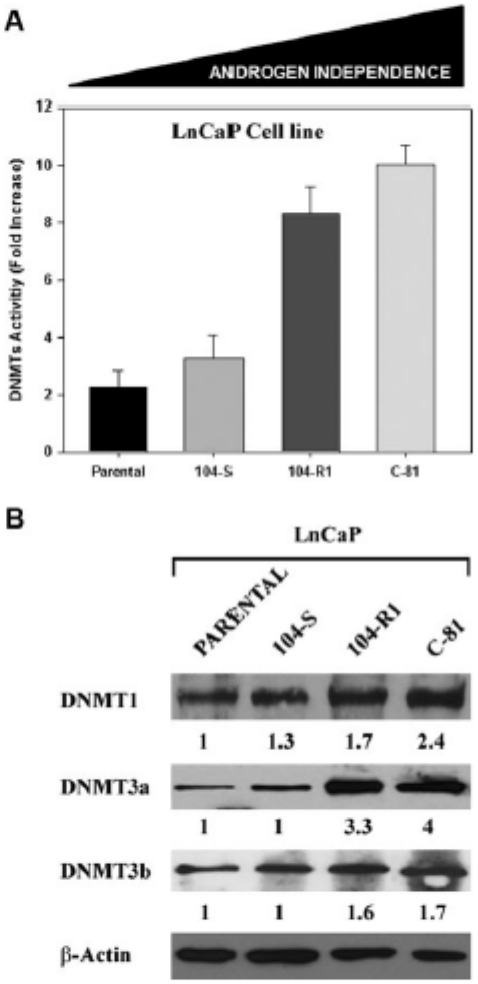
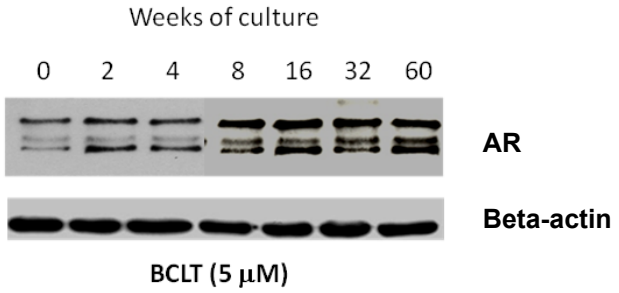
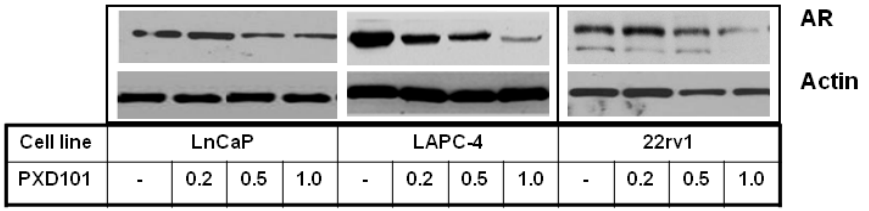
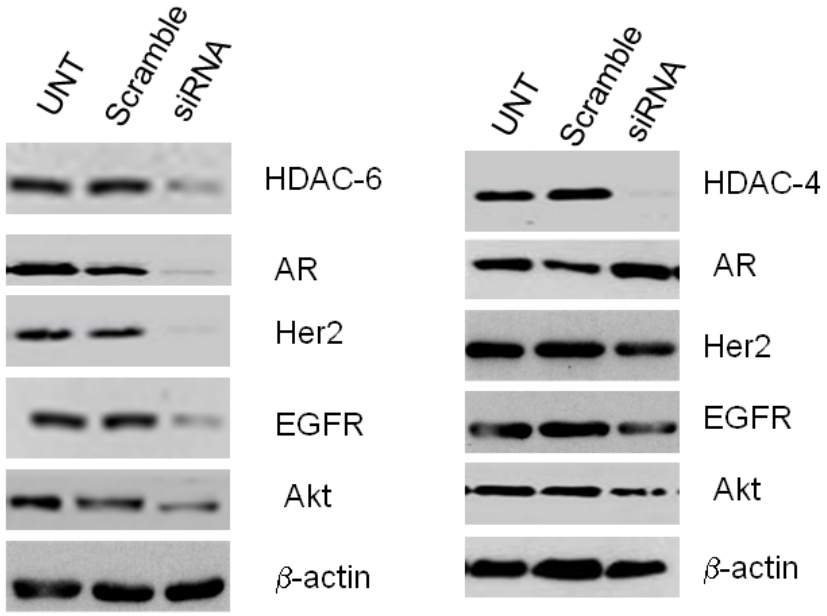
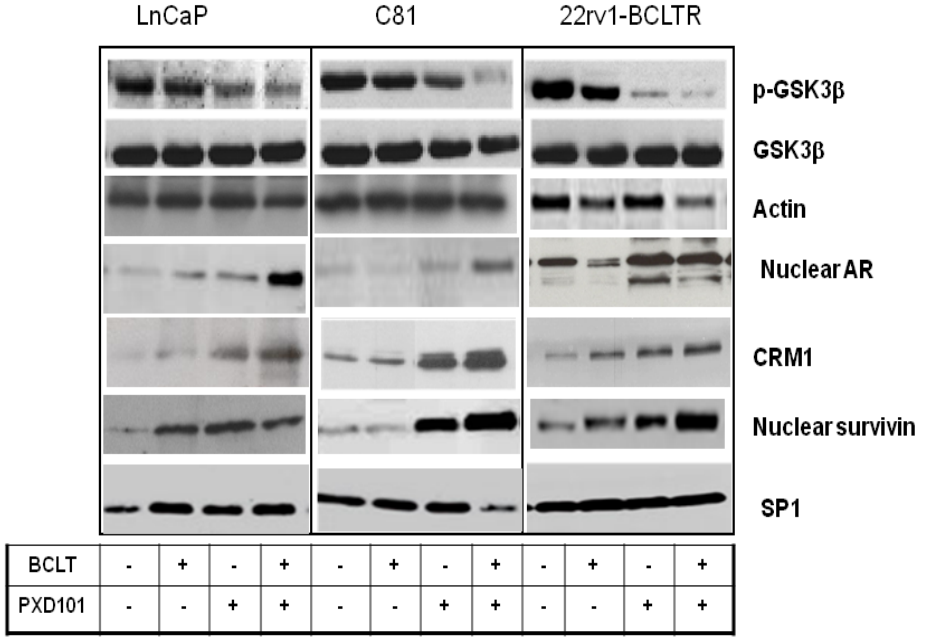


FIG. 2. DNMT activity and expression increase during the passage of Pca cells to a castration-resistant phenotype. DNMT activity (A) and expression (B) in LnCaP, LnCaP-104-S, LnCaP-104R1, and LnCaP-C81 Pca cell lines. β-Actin shows the loading of samples. The values of fold increases over the controls, arbitrarily set at 1, were obtained by densitometric analysis. Similar results were obtained in three experiments.


Weeks of culture
0
2
4
8
16
32
60
AR
Beta-actin
BCLT (5 μM)


AR
Actin
Cell line
LnCaP
LAPC-4
22rv1
PXD101
- 0.2 0.5 1.0 - 0.2 0.5 1.0 - 0.2 0.5 1.0


UNT
Scramble
siRNA
HDAC-6
AR
Her2
EGFR
Akt
β-actin
UNT
Scramble
siRNA
HDAC-4
AR
Her2
EGFR
Akt
β-actin


LnCaP
C81
22rv1-BCLTR
p-GSK3β
GSK3β
Actin
Nuclear AR
CRM1
Nuclear survivin
SP1
BCLT
PXD101
- + - + - + - + - + - +
- - + + - - + + - - + +

miRNA – Fundamental Questions