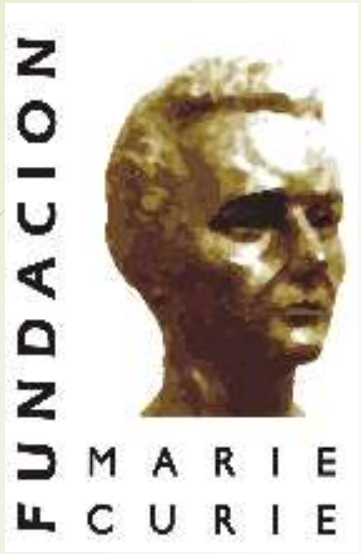

Rationale for the use of DNA repair inhibitors (PAPR inhibitors) in Cervical Cancer therapy

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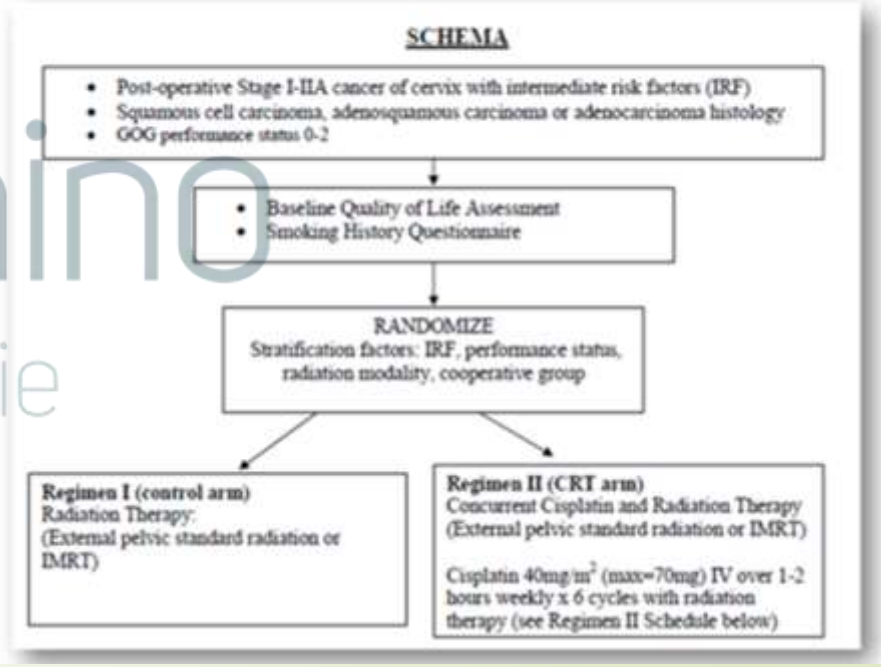
Historical Perspective – How well or bad are we doing in the management of patients with Cervical Cancer?
Early Stage Disease – Intermediate Risk

Adjuvant RT or CT+RT in St I-IIA Cervical Cancer Intermediate Risk Group

TRIAL RANDOMIZATION	RISK-GROUP # PTS	DFS	OVERALL SURVIVAL	RECURRENCE RATE	TOXICITY Grade 3-4
GOG-92	Intermediate	2y	2y		
Surgery	Risk	79%	79%	28%	2%
Surgery + RT	277 pts	88%	87%	15%	7%
				P= 0.007	
Jin, ASTRO 2016	Intermediate Risk	5y	5y		
Surgery + RT	Node Negative	84%	88%	15.3%	1.2%
Surgery + CRT	165 pts	86%	93%	12.7%	27%
		NSS	NSS	NSS	

Rational: ≈ 15% RR after RT in intermediate risk cervix cancer

NCI – Clinical Trials . GOG-0263



Historical Perspective – How well or bad are we doing in the management of patients with Cervical Cancer?
Early Stage Disease – High Risk

Adjuvant RT or CT+RT in St I-IIA Cervical Cancer High Risk Group

TRIAL RANDOMIZATION	RISK-GROUP # PTS	DFS	OVERALL SURVIVAL	RECURRENCE RATE	TOXICITY Grade 3-4
GOG-109		4 years	4 years		
S+RT	127	63%	71%	34%*	4%
S + RT + CT *[CDDP + 5-FU]*	116	80% P=0.03	81% P=0.07	16%*	**17%**

*= 55-60% Local recurrences

NCI – Clinical Trials

RTOG-0724

Adjuvant therapy high risk patients after radical hysterectomy and pelvic LND

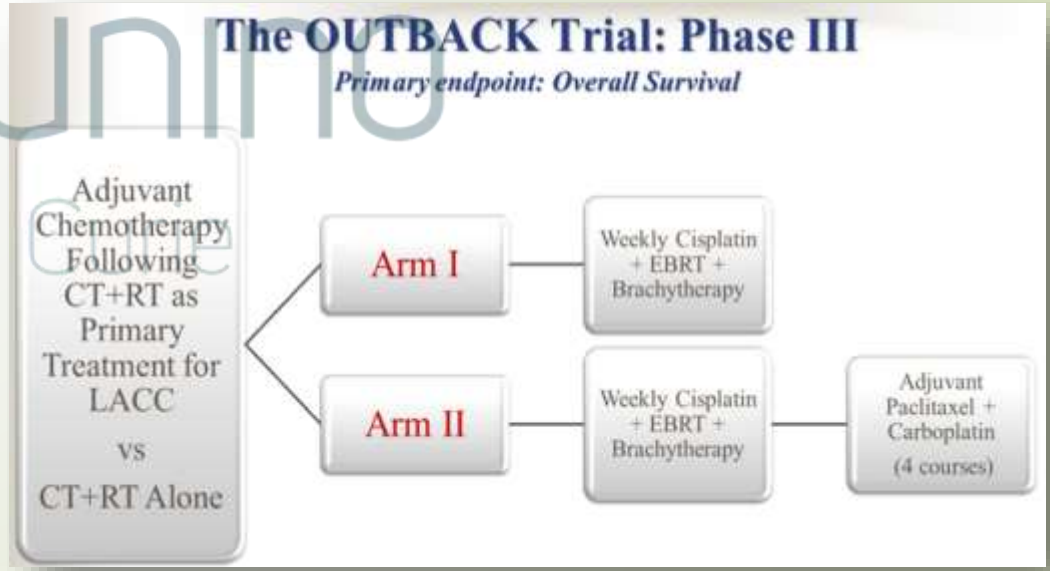
CDDP+RT (3DCRT or IMRT) +/- Vaginal brachytherapy

- **Adjuvant Chemotherapy**
- **Observation**

Historical Perspective – How well or bad are we doing in the management of patients with Cervical Cancer? Advanced Stage Disease

Chemo + RT in Locally or Locoregionally Advanced Cervical Cancer

TRIAL RANDOMIZATION	RISK-GROUP– FIGO cSt # PTS	DFS	OVERALL SURVIVAL
GOG-123; peters, 2000 RT + EFH RT+CT+EFH	FIGO IB2, High Risk - Adjuvant 186 183	4 years 63% 79%, P<0.001	4 years 74% 83%, P=0.008
RTOG- 90 01; Morris, 1999 Pelvic RT + [5FU+CDDP] Pelvic + PA-RT	FIGO Stage: IB, IIA [≥ 5cm or (+) Pelvic LNs], IIB, III & IVA. (-) PA - LN's 195 193 Grade ≥ 3 Acute Toxicity – 45%	5 years 67% 40%, P<0.001	5 years 73% 58%, P=0.004
NCI – Canada; Pearcey, 2000 Pelvic RT + [Weekly CDDP] Pelvic RT	FIGO Stage: IB, IIA bulky; IIB, III & IVA 126 123		5 years 62% 58%, P=0.42
Duenas-Gonzalez, 2011 Pelvic RT + Weekly [CDDP+GEM] + [CDDP+GEM] x 2 Pelvic RT + Weekly CDDP	259 256 Grade ≥ 3 Acute Toxicity – 85%	5 years (estimate) 74% 65%, P=0.029	5 years (estimate) 76% 65%, P=NS



Other RT + CT combinations

TRIAL	Agent	Study Phase	# Pts	Results	Comments
GOG 98-03 DiSilvestro P. 2006	Paclitaxel + CDDP	I	35, FIGO St IB-IVA	Well tolerated MTD: CDDP 40 mg/m2/wk + Taxol 40 mg/m2/wk	COT: 8 wks, 52%; 9 wks, 79%
GOG 99-12 Rose P. 2007	Gemcitabine + CDDP	I	13, FIGO St IB-IVA	MTD: Gemcitabine 50 mg/m2/wk + Cisplatin 40 mg/m2/wk	At this dose level severe chronic toxicity was observed
RTOG C-0116 Small W. 2005	CDDP+ EFRT	Arm I	27 pts without Amifostine (+) common or PA nodes	Acute grade 3-4 toxicity: 81%	
RTOG C-0116 Small W. 2011	CDDP+ EFRT + Amifostine	Arm II	18 pts treated with Amifostine (+) common or PA nodes	Acute grade 3-4 toxicity: 87%	Amifostine did not reduce acute toxicity
GOG 191 Thomas G. 2008	RT+ CDDP+/- Erythropoietin	Phase III	109 pts, FIGO St IIB-IVA	Median FU 37 months 3 y PFS: CT+RT, 65%; CT+RT+Epo, 58% 3 y OS: CT+RT, 75%; CT+RT+Epo, 61%	Trial stopped prematurely because of concerns regarding TEE with Epo (19%)
GOG-219 DiSilvestro P. 2014	RT+CDDP+/- Tirapazamine	Phase III	387 pts, FIGO St IB2-IVA	Median follow-up 28.3 months, 3 y PFS: TPZ/CIS/RT, 63%; CIS/RT, 64% 3y OS: TPZ/CIS/RT, 70.5%; CIS/RT, 70.6%	Trial stopped prematurely because of the lack of TPZ supply and lack of superiority

Targeted Therapy

Trial, Author, Year	Patients – FU	DFS	OS	G ≥ 3 Toxicity
RTOG 0128 - Phase I-II. Gaffney, 2007 COX-2 inhibitor, Celebrex ® + [CDDP + 5-FU] + RT	84 pts, FIGO St IIB-IVA and IB-IIA with (+) pelvic nodes or T ≥ 5cm	----	----	48% Regimen excessively toxic not recommended for further evaluation
GOG 99-18 – Phase I. Moore, 2012 CDDP + RT + Cetuximab	20 pts, FIGO St IB-IVA with/without (+) pelvic and/or PA nodes	----	----	Severe toxicity in the PA node group
RTOG 0417 – Phase II. Schefter, 2014 CDDP + RT + Bev [10 mg/kg, q2 wks x 3 cycles]	49 pts, FIGO St IB-IIIB 46 months	69% LRF, 23% Distant +/- PA, 38%	81%	36.7%

Why do we need New Agents in the management of Cervical Cancer?

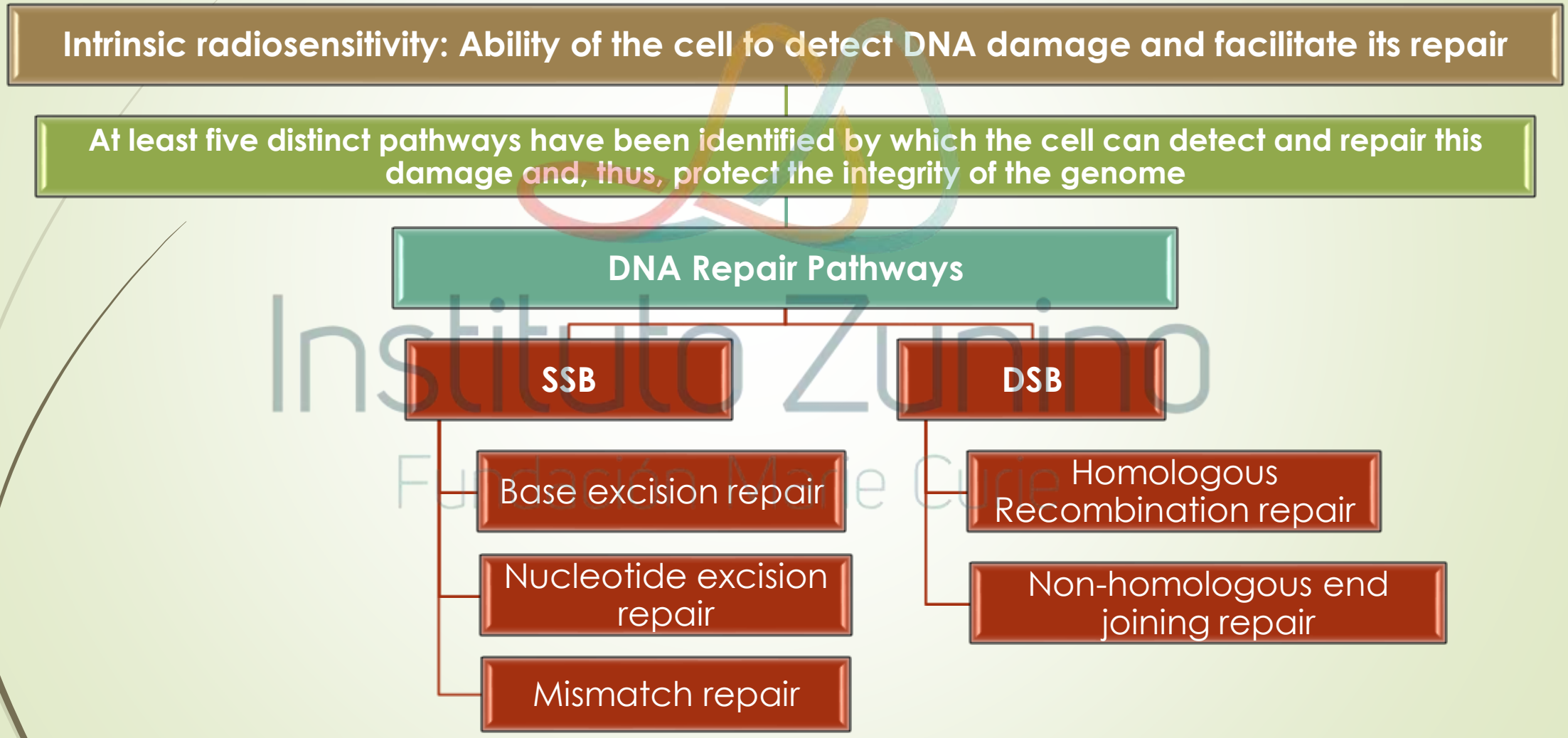
Treatment with ionizing radiation and/or chemotherapy, does deliver clinical benefit, so tumors in general must deal with DNA damage less efficiently than normal tissues.

By understanding how cellular responses to DNA damage differ between malignant and healthy cells, it may be possible to accentuate these differences and enhance the therapeutic ratio.

Factors affecting cancer cell radiosensitivity The 5 "Rs" of Radiobiology

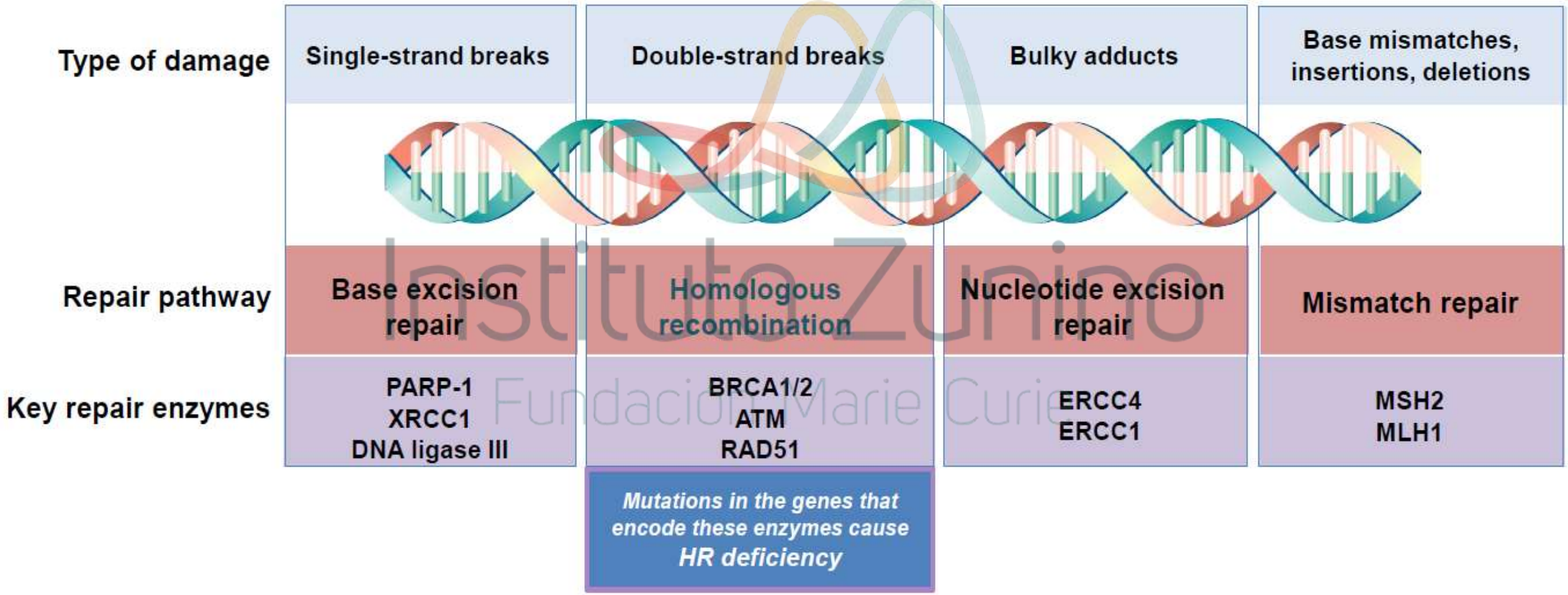
- When tumors are treated with RT, the TCP is governed by a number of factors:
  - the ability to repair DNA damage
  - the number of clonogenic cells and their rate of repopulation
  - their redistribution in the cell cycle over time
  - their intrinsic radiosensitivity
  - the presence of tissue hypoxia

The basis of radiosensitisation is an alteration in some aspect of DNA repair



DNA Repair Involves a Complex Protein Network

- **Many enzymes mediate repair of multiple forms of DNA damage via several key pathways**



Lord CJ, et al. *Nature*. 2012;481(7381):287-294. Hosoya N, et al. *Cancer Sci*. 2014;105(4):370-388.

DNA Repair Defects

The Achilles' Heel in Cancer Cells

- **Normal Cells:**
  - Complete Repair [minor defects]

- **Cancer Cell:**
  - Highly Defective Repair but still sufficient repair capability
  - Defects in multiple repair processes
  - Common Mutations
    - **Loss of function of TP53** (*Guardian of the Genome*)
    - **Loss of Cell Cycle Inhibitors/Checkpoints**: p15, p16, p21, p27, CHEK1, CHECK2
    - **Mismatch Repair Defects**: MSH2, MSH6, MLH1, PMS2
    - **HR Repair Defects**: BRCA1 & 2, ATM, PALB2, RAD51
    - **Loss of DNA damage Sensors**

Mehta A, Haber JE. *Cold Spring Harb Perspect Biol.* 2014;6:a016428.
Cerrato A, et al. *J Exp Clin Cancer Res.* 2016;35:179.

Taking Advantage of DNA Repair Defects in Cancer

[Poly(ADP-ribose) polymerase (PARP) Inhibitors]

The Achilles' Heel in Cancer Cells

PARP proteins

Family of 17 enzymes involved in a wide range of cellular functions

- DNA transcription
- DNA damage response
- Genomic stability maintenance
- Cell cycle regulation
- Cell death

PARP

Overall Function

- **DNA damage sensors**: bind rapidly to sites of DNA damage
- **DNA damage signalers**: modulate a wide range of proteins involved in the DNA damage response

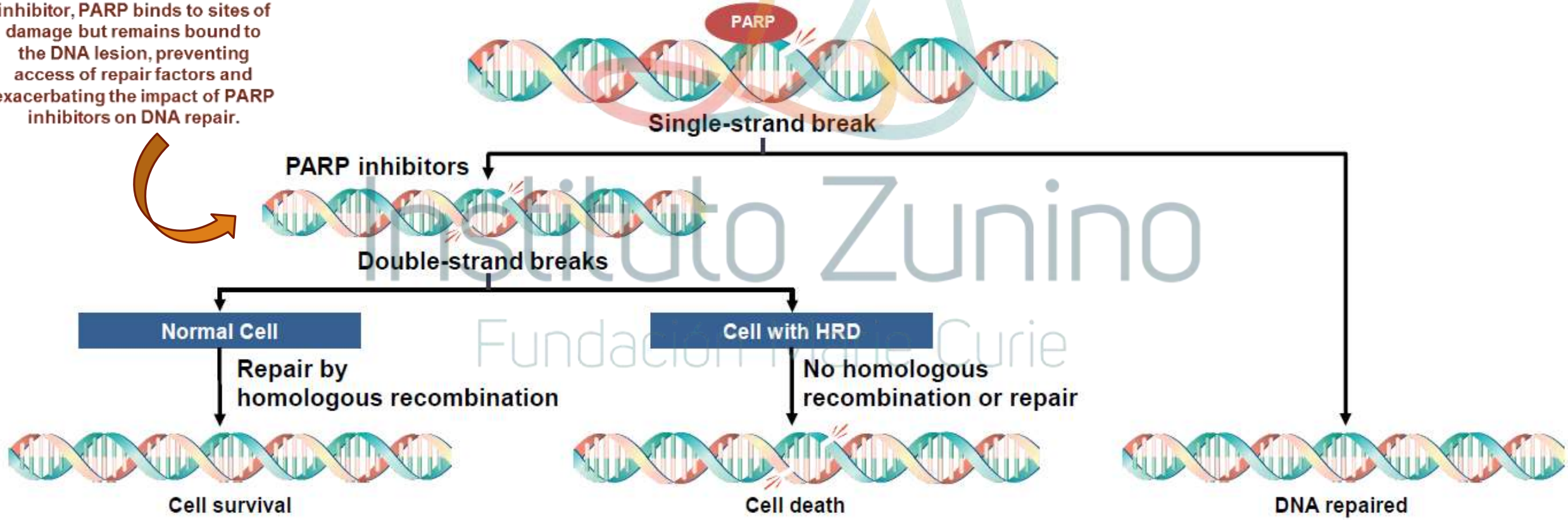
Pharmacological Inhibition- modulation of DNA repair pathways [PARP Inhibition] is lethal to cancer cells, but spare normal cells

- **"Synthetic Lethality"**

PARP Inhibitors Yield Synthetic Lethality in Patients With HRD

- PARP inhibitors prevent repair of single-strand breaks, which accumulate and generate double-strand breaks
- People with HRD cannot repair double-strand breaks, which triggers cell death

In the presence of a PARP inhibitor, PARP binds to sites of damage but remains bound to the DNA lesion, preventing access of repair factors and exacerbating the impact of PARP inhibitors on DNA repair.



HRD, homologous recombination deficiency

Sonnenblick A, et al. *Nat Rev Clin Oncol.* 2015;12(1):27-41.

Synthetic Lethality

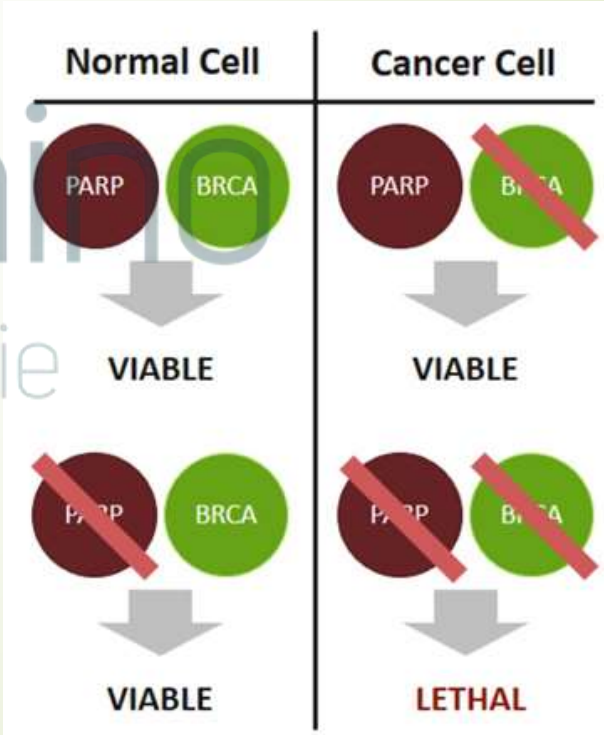
Redundancy in the DNA repair network

Deficiency of one DNA repair component renders tumor cells highly sensitive to specific inhibition of a backup pathway that would otherwise be non-essential

Because of SL, PARP-inh may be highly effective in pts with tumors harboring a germline or somatic defects in DNA damage and repair genes (eg, BRCA1, BRCA2)

- Two genes are "synthetic lethal" if:
  - Mutation of either gene A or B alone is compatible with viability, but
  - Simultaneous mutation of both genes A and B causes death
- "Holy Grail" of cancer care: selective tumor cell kill, sparing normal cells

Dietlein F, et al. *Clin Cancer Res.* 2014;20:5882-5887; Lupo B, Trusolino L. *Biochim Biophys Acta.* 2014;1846:201-215.



PARP Inhibitors and Radiation

In vitro, PARP-inh are radiosensitizers in various cell lines with ER up to 1.7

- In both, hypoxic and euoxic conditions
- Most effective in S-phase

PARP-inh are dependent on DNA replication

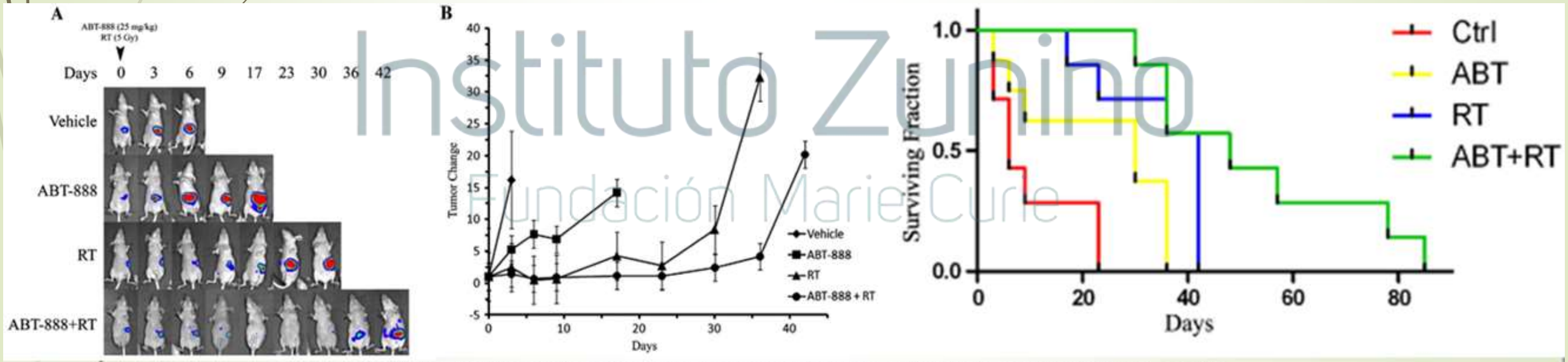
- Non-dividing cells: delay in SSB repair, no impact on DSB formation or cell survival
- Replicating cells: unrepaired SSB, collapsed replication forks, potentially lethal DSB

Potential Improvement of the Therapeutic Ratio

- Tumor-specific radiosensitization in repair-defected and highly proliferating tumor cells
- It means that PARPi may radiosensitize tumor tissue, while saving non tumoral tissue, which is one of the most important qualities of a radiosensitizing agent

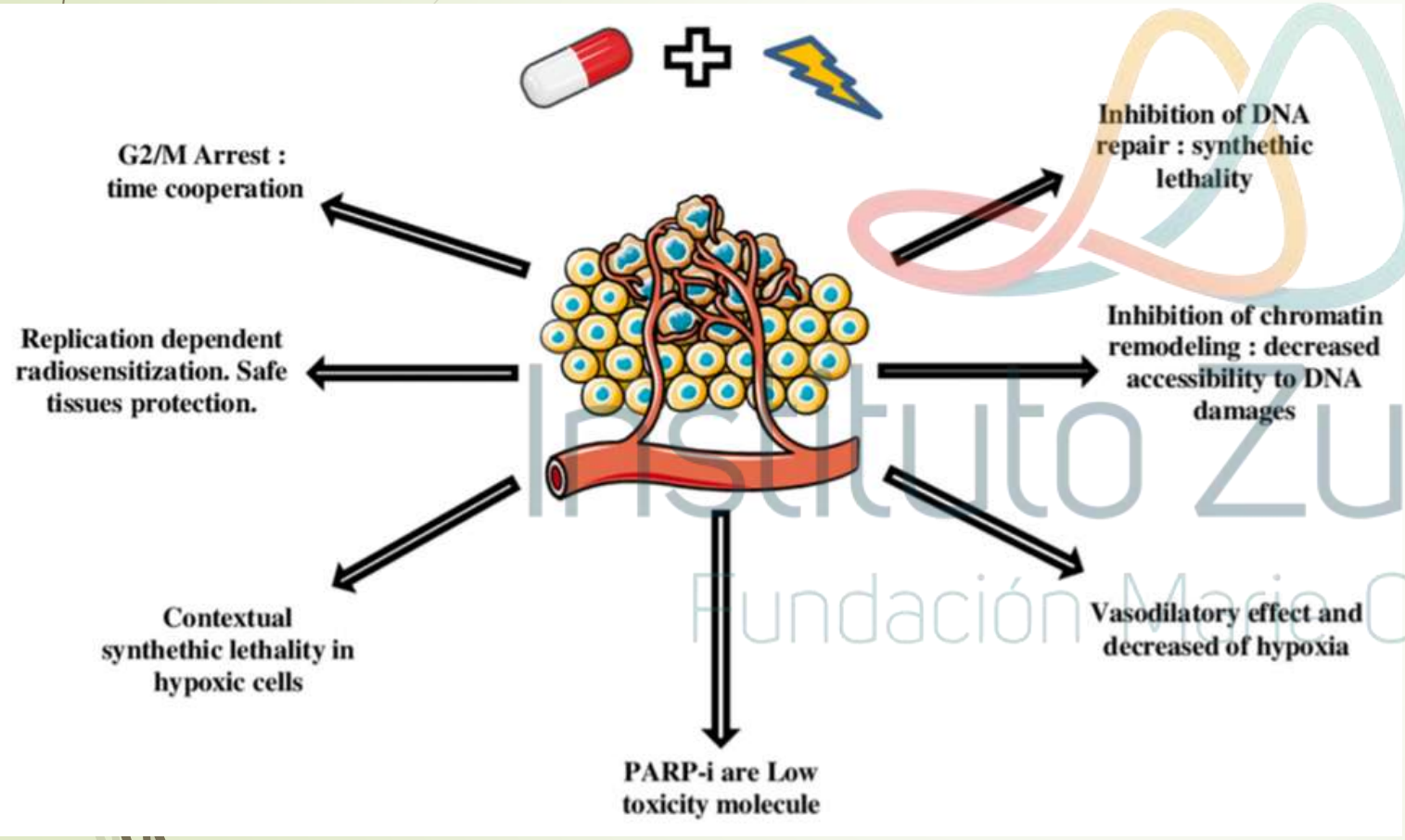
PARP Inhibitors and Radiation

- In vivo, non-toxic doses of PARP inhibitors have been shown to increase radiation-induced growth delay of xenograft tumors in mice.



Orthotopic MiaPaCa-2 tumors were treated with saline sham, ABT-888 (25 mg/kg), RT (5 Gy), or both.
Survival at 30 days for mice treated with ABT-888, RT or a combination of the two was 63%, 75% and 100%, respectively, while at 60 days, it was 0%, 0% and 29%
R. Tuli, Trasl. Oncol. 2014

Mechanisms and Advantages of PAPRi Radiosensitization



Ionizing radiation induces DNA damage – strand breaks to which PARP binds to.

Defects in specific DNA repair pathways also appear to enhance the radiosensitizing effects of PARP inhibition

Tumor cells may also be preferentially sensitized to RT by diverse mechanisms

1. Proliferation-dependent radiosensitization
2. Targeting of the endothelium and tumor vasculature
3. Increased sensitivity to PARP inhibitors within repair-deficient hypoxic cells

Because biologically active doses of PARP inhibitors caused minimal toxicity in phase I to II clinical trials, careful scheduling of these agents in combination with RT may increase the therapeutic ratio

PARP Inhibitors: What do we know?

BRCA 1 and 2 deficient cells are extremely sensitive to PARP inhibition

- Cells which lack BRCA proteins are forced to repair defects by more error prone pathways which in turn lead to genomic instability

PARP inhibition impairs the repair of SSB which, as a result, are converted to DSB during replication and this, in turn, increases the burden for repair by HR

- In BRCA-deficient cells, which are defective in HR, the damage cannot be repaired and consequently cell cycle arrest, chromosome instability and cell death results

PARP inhibitors offer great promise as radiosensitizing agents and carefully designed clinical trials are now required to evaluate their safety and efficacy in this setting

PARP Inhibitors: What don't we know?

Who to combine them with

- Chemotherapy
- Targeted Therapy
- Immunotherapy
- Radiation Therapy
  - How to schedule the PARP-inh in relation to RT
  - Sequence, Dose, Frequency

When to use them in front line and recurrent settings

How to predict benefit and assess response

How to chose between

- Veliparib
- Niraparib
- Olaparib
- Rucaparib
- Talazoparib
- Others???

PARP Inhibitors + Chemotherapy in Cervical Cancer

- Preclinical studies:
  - Cervical cancer (HeLa) cell lines resistant to cisplatin have high levels of PAR and PARP1, with PARP1 constitutively hyperactivated.
  - Exposure of the cells to pharmacologic PARP inhibition resulted in cell death.
- Clinical studies:
  - A phase I trial included patients with cervical cancer along with other gynecological malignancies to investigate the combination of Olaparib with carboplatin in refractory or recurrent disease (NCT01237067). Completed 2017
  - Another phase 1-2 trial is investigating the use of veliparib with cisplatin and paclitaxel in advanced, persistent, or recurrent cervical cancer (NCT01281852). Completed 2017

Conclusions

- PARP inhibition offers the prospect of manipulation of DDR in order to alter the intrinsic radiosensitivity of many tumors which have until now been regarded as poorly responsive to RT
- As well as being effective radiosensitizers in vitro, PARP inhibitors possess attributes which make them highly eligible candidates for clinical use, as a potential ideal radiosensitizer due to:
  - Low single agent systemic toxicity profile
  - Potential for tumor specificity
  - Ability to radiosensitize hypoxic cells
- Challenge to the introduction of PARP inhibitors as radiosensitizers: Possible increased toxicity
- How to overcome these issues
  - Adequate trial design: doses, sequencing
  - Benefits of modern radiotherapy technological advances
- Novel radiosensitizers such as PARP inhibitors have the potential to improve the therapeutic ratio


GRACIAS