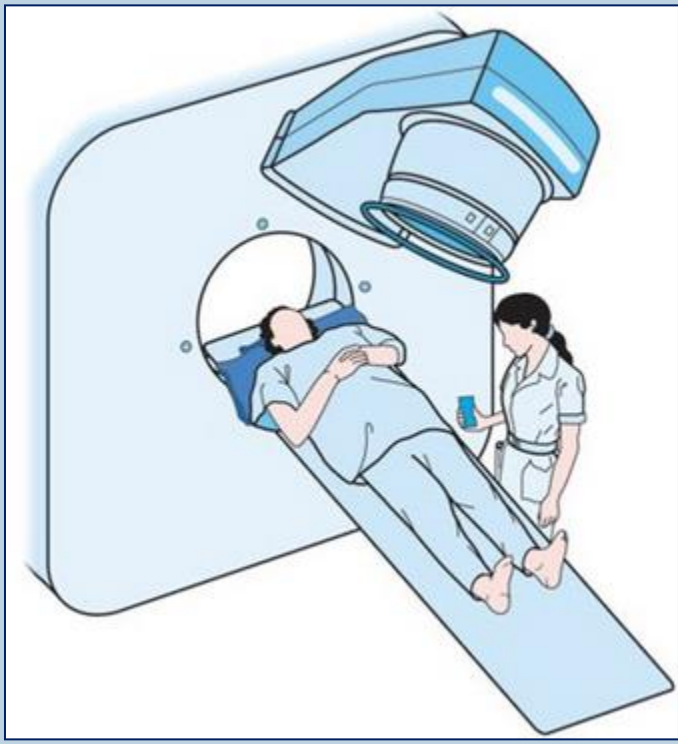
Importance of ATM in Radiotherapy

Radiology and Physical Medicine

María Trinidad Rueda Cáceres

Radiotherapy

- One of the standard treatment options for various malignant cancers
- Multidisciplinary treatment of cancer:
  - Systemic treatment:
    - Chemotherapy
  - Local treatments:
    - Surgery
    - <u>Radiotherapy</u>
- RT
  - ↓ systemic effects than chemotherapy
  - severe local adverse effects
    - Thecniques to improve RT:
      - Stereotactic RT
      - Fractionated RT
      - <u>Radiosensitizing agents</u> (↑*cytotoxic effects on cancer cells*)
      - Radioprotective agents (↓*adverse effects on normal cells*)



Radiosensitizers

- ↓ Hypoxia
- Hyperthermia
- Chemotherapeutic agents
  - *5-FU, Cisplatin, Gemcitabine…*
- <u>Molecularly targeted therapy</u>
  - Promising therapy in treatment of cancer:
    - In cancer cells: ↑effectiveness of RT
    - In normal cells: ↓ harmfulness of RT

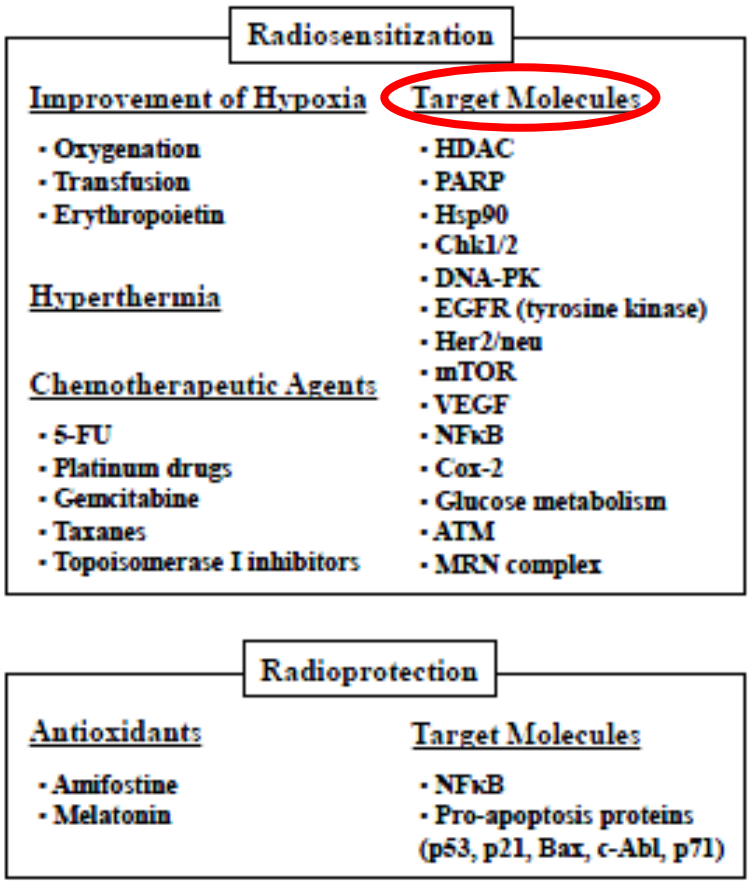


Fig. 1 Approaches to improvement of radiotherapy. Radiosensitizing agents are designed to increase the cytotoxic effects of radiation on cancer cells, and radioprotective agents are designed to decrease the adverse effects of radiation on normal cells. Hsp90, heat shock protein 90; NF-κB, nuclear factor-κB; COX-2, cyclooxygenase-2.

Radiosensitizers

Interest in Molecularly targeted therapy

↓

Understanding of **DNA repair** and

cell cycle checkpoints signaling pathways

↓

ATM central function

- Mutations in ATM gene → **Ataxia telangiectasia (AT)**
- Investigation of AT ↔ **ATM functions**

Radiosensitization

Improvement of Hypoxia	Target Molecules
• Oxygenation	• HDAC
• Transfusion	• PARP
• Erythropoietin	• Hsp90
	• Chk1/2
Hyperthermia	• DNA-PK
	• EGFR (tyrosine kinase)
	• Her2/neu
Chemotherapeutic Agents	• mTOR
	• VEGF
• 5-FU	• NFκB
• Platinum drugs	• Cox-2
• Gemcitabine	• Glucose metabolism
• Taxanes	• ATM
• Topoisomerase I inhibitors	• MRN complex

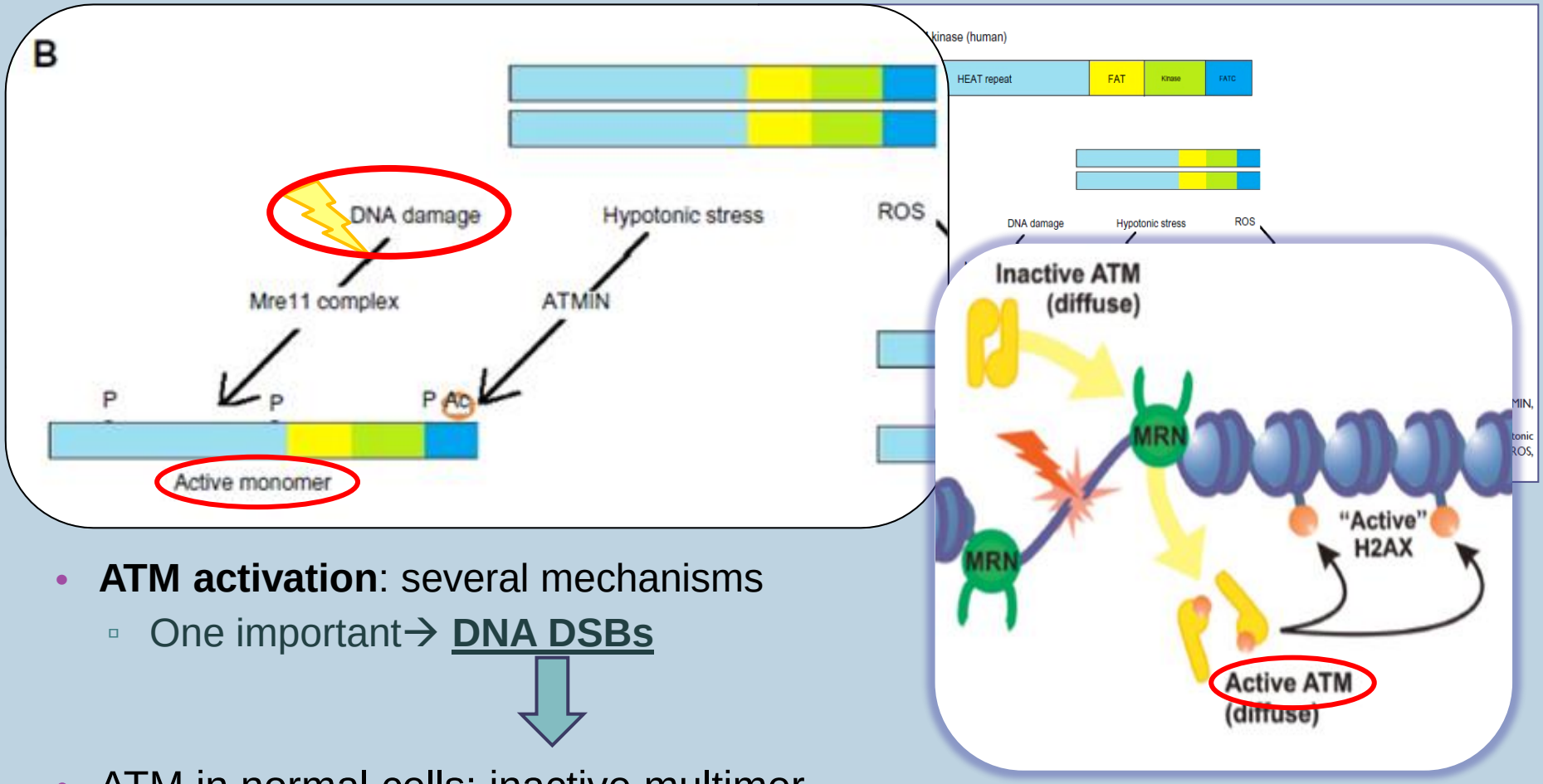
Radioprotection

Antioxidants	Target Molecules
• Amifostine	• NFκB
• Melatonin	• Pro-apoptosis proteins (p53, p21, Bax, c-Abl, p71)

Fig. 1 Approaches to improvement of radiotherapy. Radiosensitizing agents are designed to increase the cytotoxic effects of radiation on cancer cells, and radioprotective agents are designed to decrease the adverse effects of radiation on normal cells. Hsp90, heat shock protein 90; NF-κB, nuclear factor-κB; COX-2, cyclooxygenase-2.

(1)

ATM *(Ataxia-Telangiectasia Mutated)*



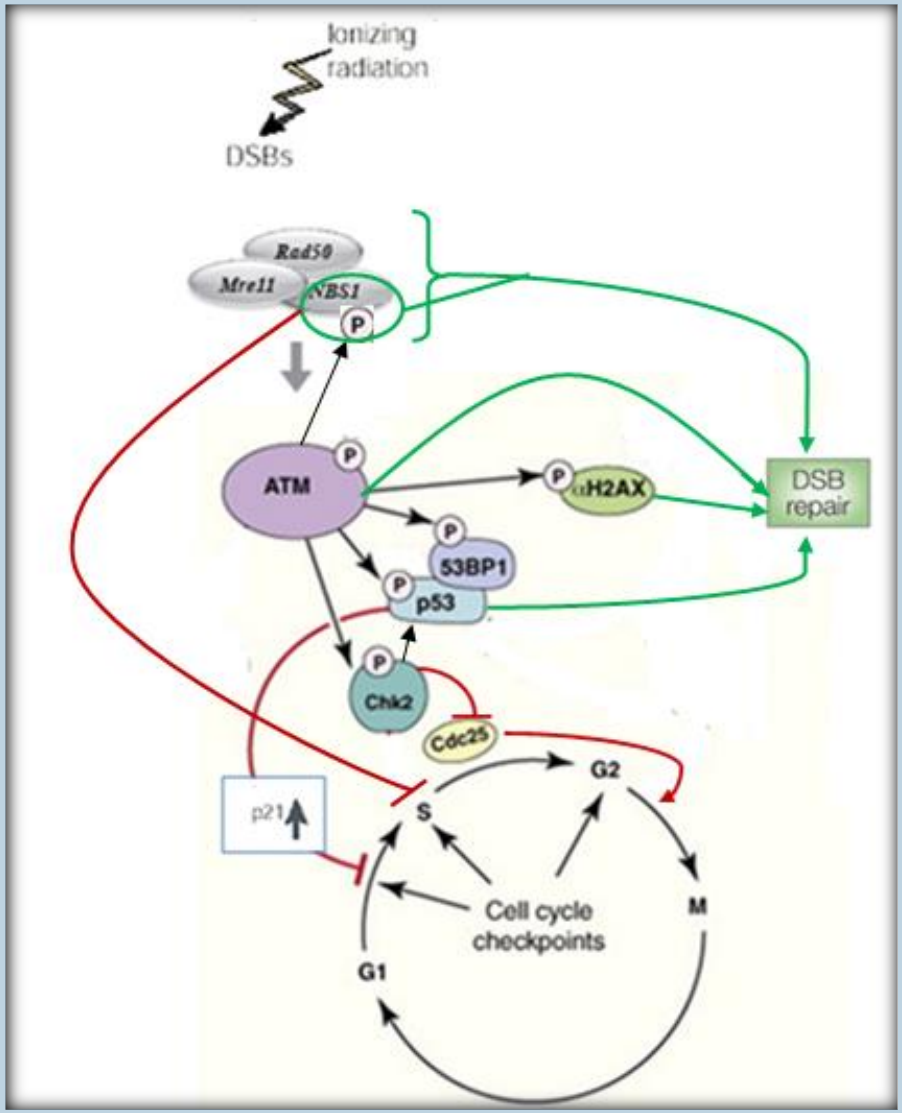
- **ATM activation**: several mechanisms
  - One important→ **DNA DSBs**

- ATM in normal cells: inactive multimer
- ATM in cells with DSBs: **MRN complex recruits ATM** to DSB site → autophosphorylation and monomerisation → **activate monomer**

ATM activated

- Kinase: phosphorylation of multiple targets
- ATM activacion effects and some ATM targets implicated:
  - Cell cycle checkpoints
    - G1-S (p53)
    - Intra-S (Nbs1)
    - G2-M (Chk2)
  - DNA repair (RH and NHEJ)
    - ATM <u>directly or indirectly</u>
    - MRN <u>directly or indirectly</u>
- Dysfunction of MRN complex or ATM → Hypersensitivity to DNA-damaging agents

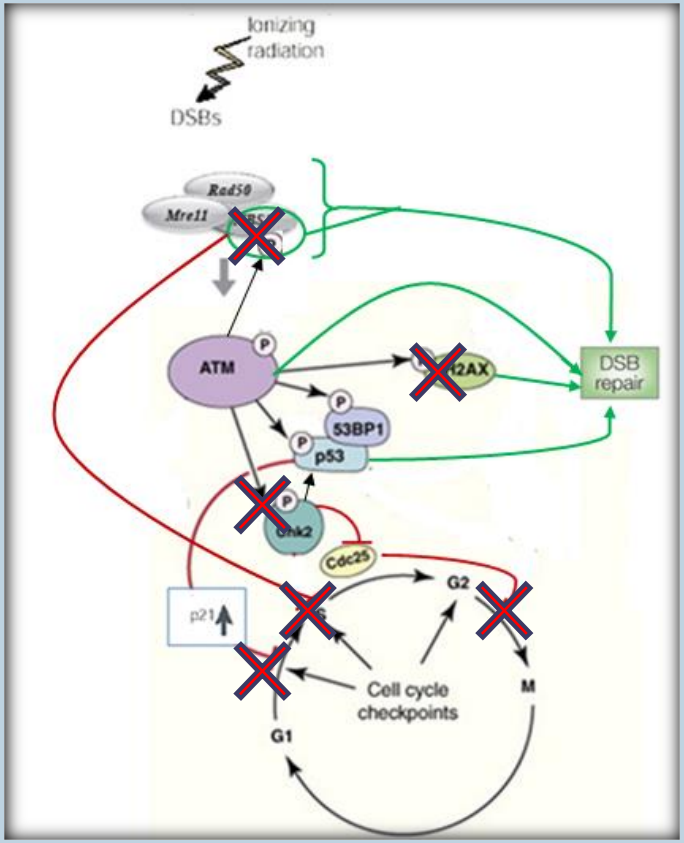
<u>ATM</u> and the <u>MRN complex:</u> targets for radiosensitization



(2) (3)

ATM inhibitors and MRN complex inhibitors

- Recent specific inhibitors with great potencial in preclinical studies
- ATM inhibitors
  - KU-55933
    - Inhibit ATM *(Blocks phosphorylation of H2AX, NBS1 and Chk1)*
  - CGK733
    - Inhibit ATM and ATR *(Blocks checkpoints pathways)*
  - CP466722
    - Inhibit ATM *and its targets*
- MRN complex inhibitors
  - Mirin
    - Inhibit MRN complex-dependent ATM activation

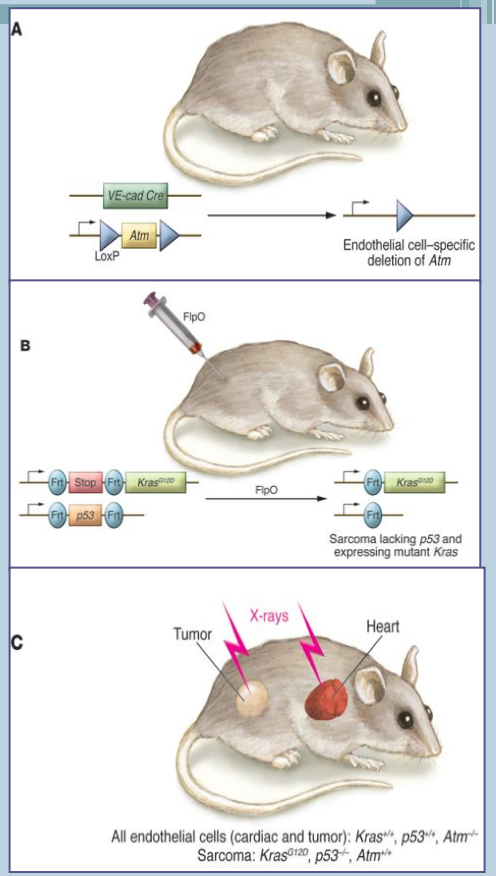


Terrible response to XRT of patients with AT

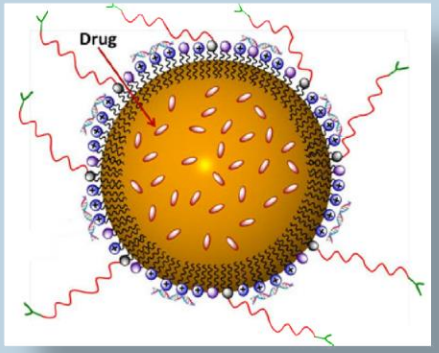
PROBLEM: normal tissues could sensitize as well and get damaged

About ATM inhibition…

- RECENT STUDIES:
  - **Murine model of sarcoma:**
    - Result: Deletion of ATM gene: much less radiosensitizing effect on normal cardiac endothelia than on tumor endothelia:
    - Hypothesis: PROLIFERATION differences ?
    - After inhibition of proliferation *(via SCH72765 treatment)* + irradiation: "*ATM deficiency in endothelial cells was irrelevant if cell cycle block was present in the moment of irradiation*"
    - **CONCLUSIONS**
      - **Different tissues →different response** to ATM inhibition
      - ¿this is only due to proliferation or there are **other additional factors**?



- SOLUTIONS / ALTERNATIVES:
  - Development in drug delivery: Nanomedicine
    - Carriers with tumor-targeting potencial
  - **Telomelysin** *(oncolytic adenovirotherapy)*



(1) (4)

Telomelysin / OBP-301

Adenoviral E1B55kDa protein inhibit MRN complex

⇩

Inhibition of ATM activation

⇩

Inhibition of DNA repair

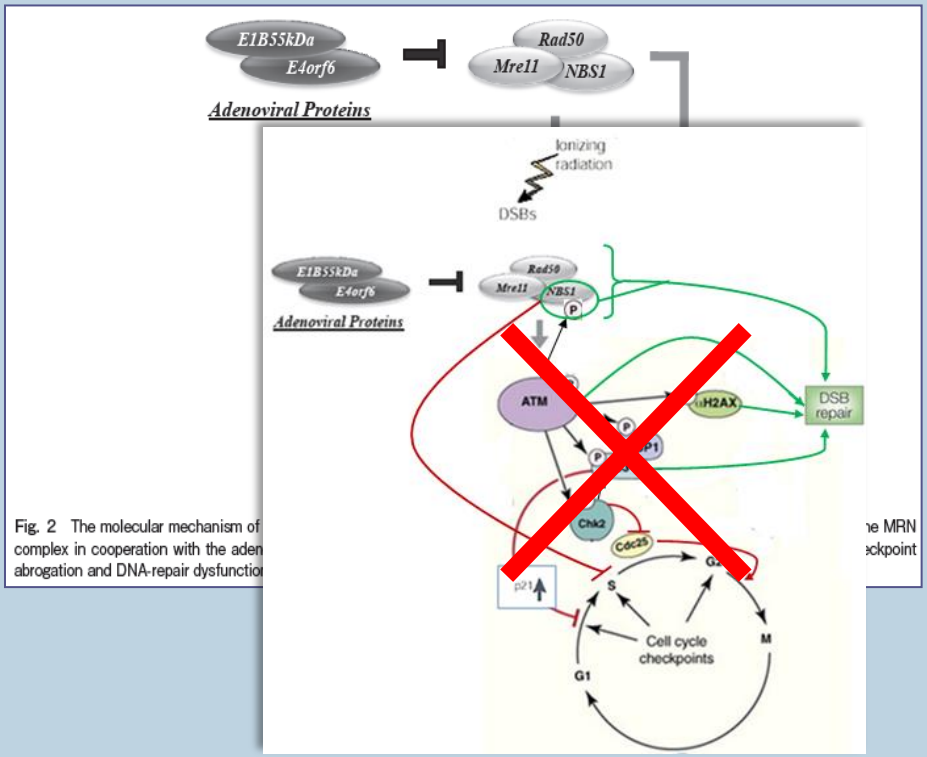
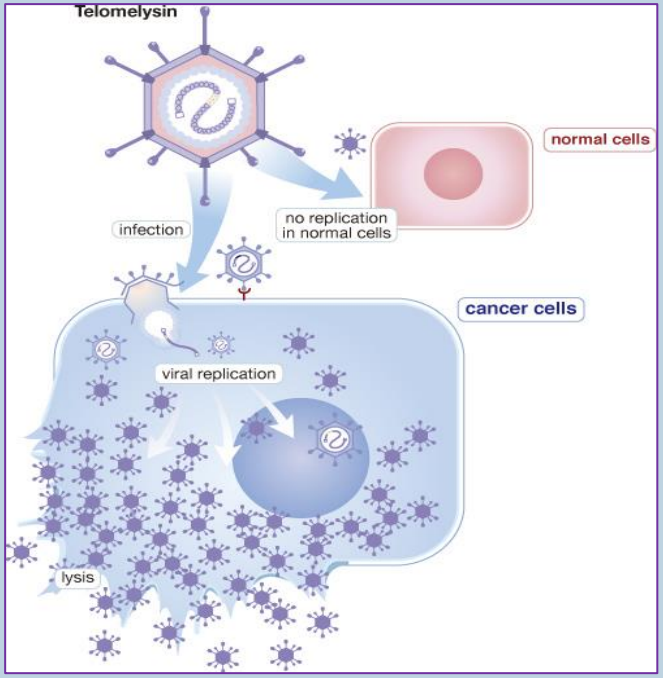


Fig. 2 The molecular mechanism of … complex in cooperation with the aden… abrogation and DNA-repair dysfunctio… …e MRN …eckpoint



Telomerase-dependent

⇩

Only CANCER CELLS death

(high hTERT activity)

BUT…

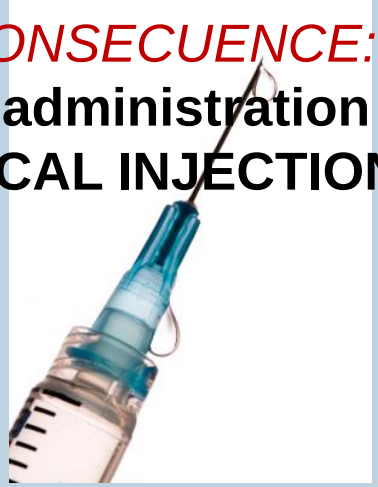
Telomelysin / OBP-301

PROBLEMS:

1. Liver trap ↑% of adenoviruses in blood
2. Adenoviruses are very common cold viruses
   ↳ we have Igs ➡ Telomelysin is removed

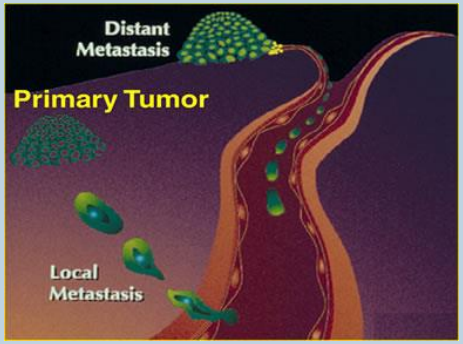
Not effective levels at tumor

CONSECUENCE:
only administration by LOCAL INJECTION



Limited to cancers confined within **locoregional areas**

Neccesity to **improve systemic delivery** to treat distant metastases



(1)

BIBLIOGRAPHY

- *(1) Ataxia-Telangiectasia Mutated and the Mre11-Rad50-NBS1 Complex: Promising Targets for Radiosensitization. Kuroda S, Urata Y, Fujiwara T. Acta Med. Okayama, 2012 66 (2): 83-92*
- *(2) Ataxia-telangiectasia: future prospects. Chaudhary MW, Al-Baradie RS. The Application of Clinical Genetics 2014 7: 159–167*
- *(3) 'A mover and a shaker': 53BP1 allows DNA doublestrand breaks a chance to dance and unite. Goodarzi AA, Jeggo PA. F1000 Biol Rep. 2009 17;1:21*
- *(4) Radiation and ATM inhibition: the heart of the matter. Hammond M. Ester, Muschel J. Ruth. J Clin Invest. 2014 124(8): 3289–3291.*