# Some chemotherapeutics-treated cancer cells display stem-like and senescent cell features

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Warsaw

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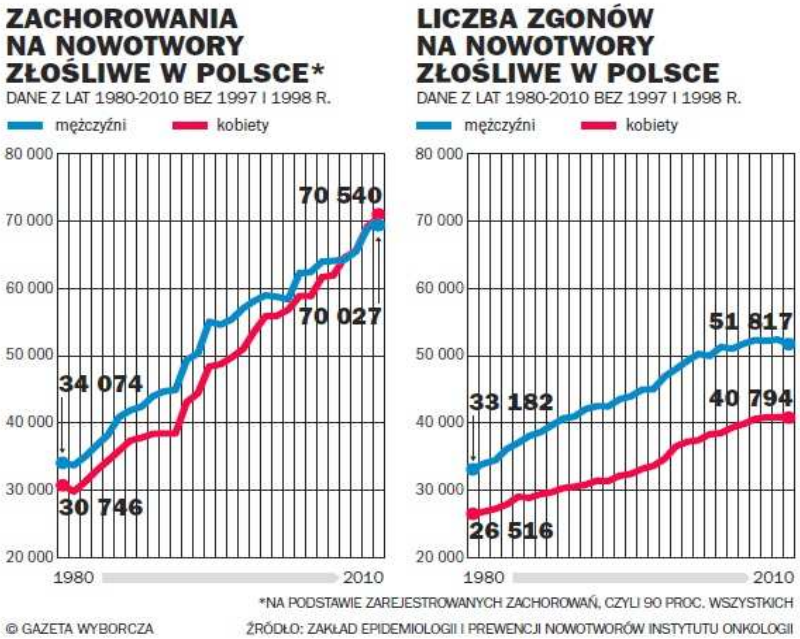
*Poznań, Poland*

# Anti-cancer therapies

Krajowy Rejestr Nowotworów

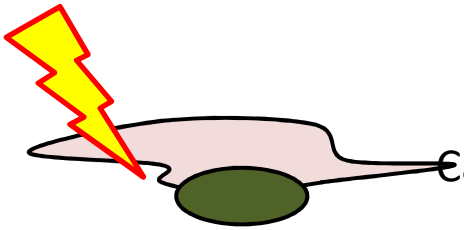



# MAIN GOAL

**Development of strategies that may prevent relapse in cancer patients after chemotherapy.**

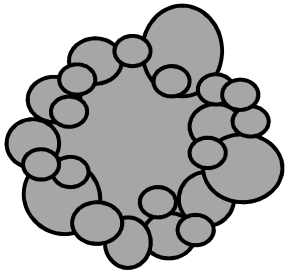
# CANCER CELL FATE
## UPON ANTI-CANCER TREATMENT

**Chemotherapy**
**Radiotherapy**

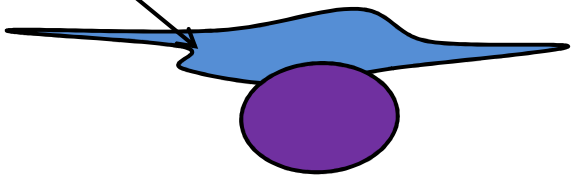


Cancer cell

Primary aim of existing anti-cancer therapies



**CELL DEATH**



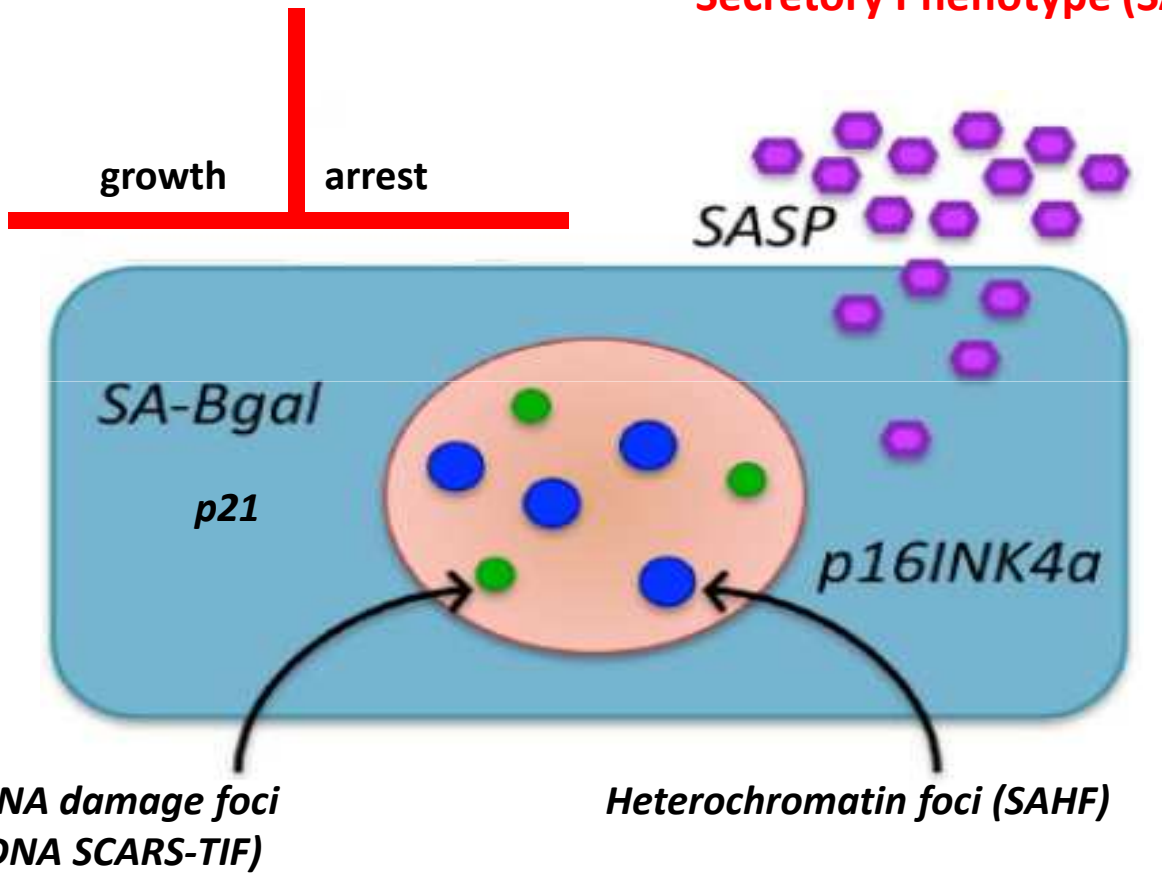
**CELLULAR SENESCENCE**

**STRESS-INDUCED PREMATURE SENESCENCE**

- oncogenes activation, DNA damaging agents, oxidative stress
- independant on telomere shortening

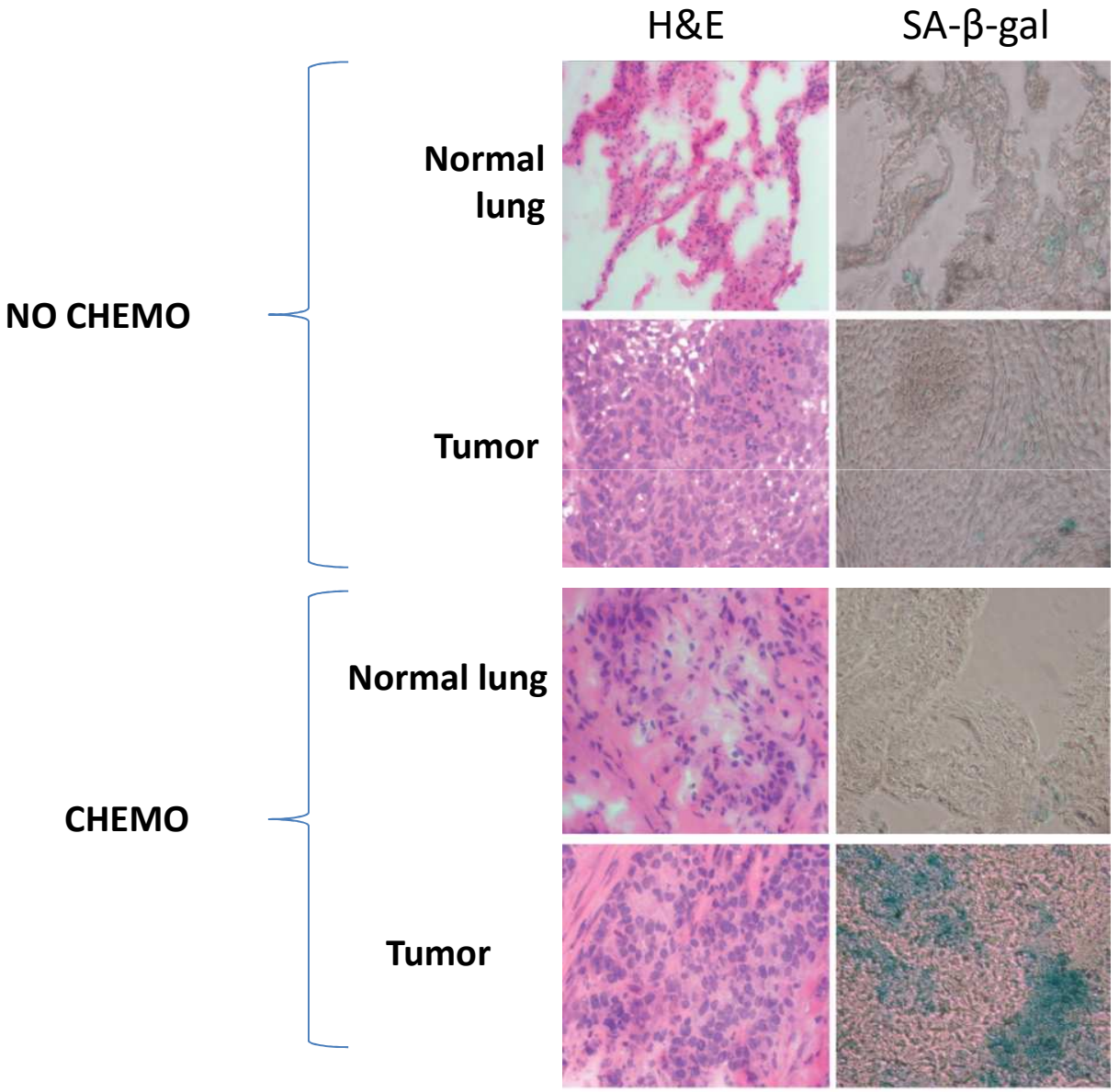
# HALLMARKS OF SENESCENCE

**Senescence Associated Secretory Phenotype (SASP)**




**SA-β-galactosidaze**
**marker of senescent cells**

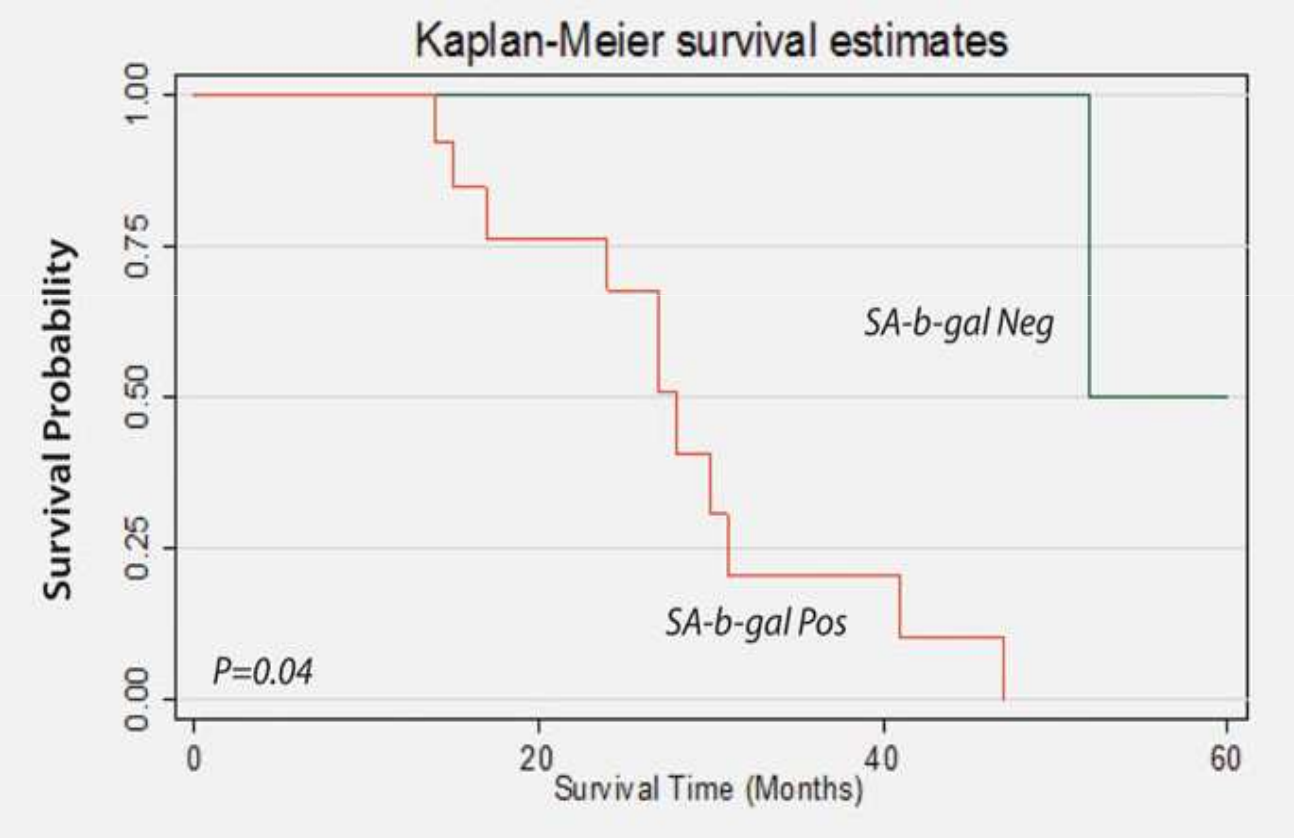
# THERAPY-INDUCED SENESCENCE IN PATIENTS




*Roberson et al. 2005*

# THERAPY-INDUCED SENESCENCE IN PATIENTS

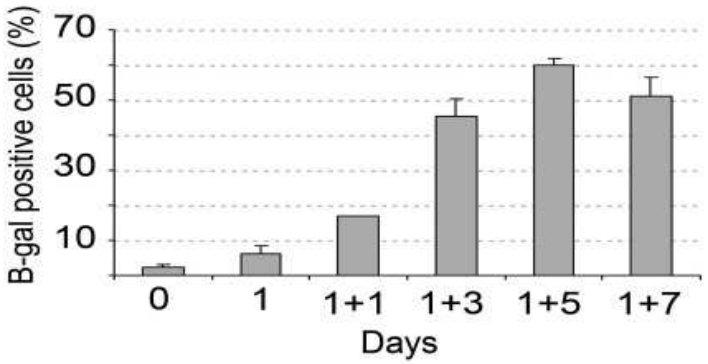
**Locally advanced non-small cell lung cancer following neoadjuvant chemoradiotherapy (CMT) or chemotherapy (carboplatin/ paclitaxel 3).**

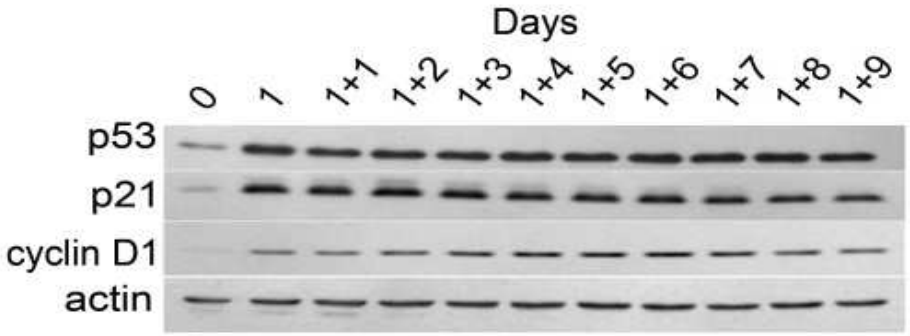


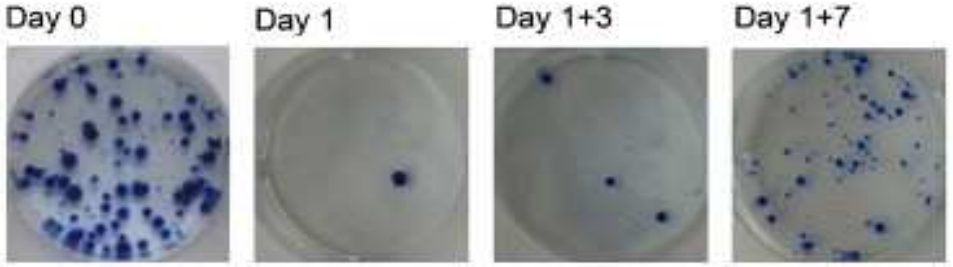

**SA-β-galactosidaze (SA-β-gal)**
**marker of senescent cells**

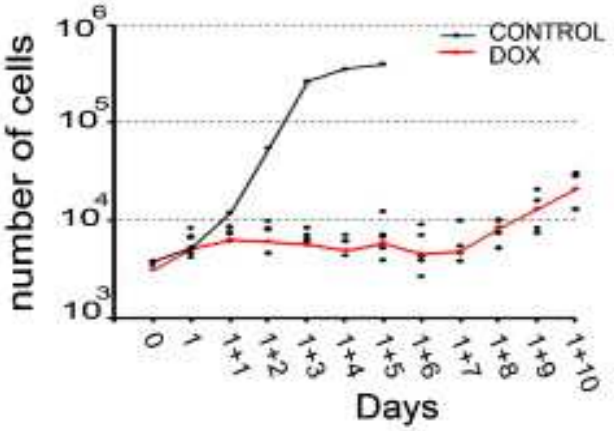
*Wang et al. 2012*

# DOXORUBICIN INDUCES SENESCENCE OF HCT116 CELLS AND THE PROCESS IS REVERSIBLE

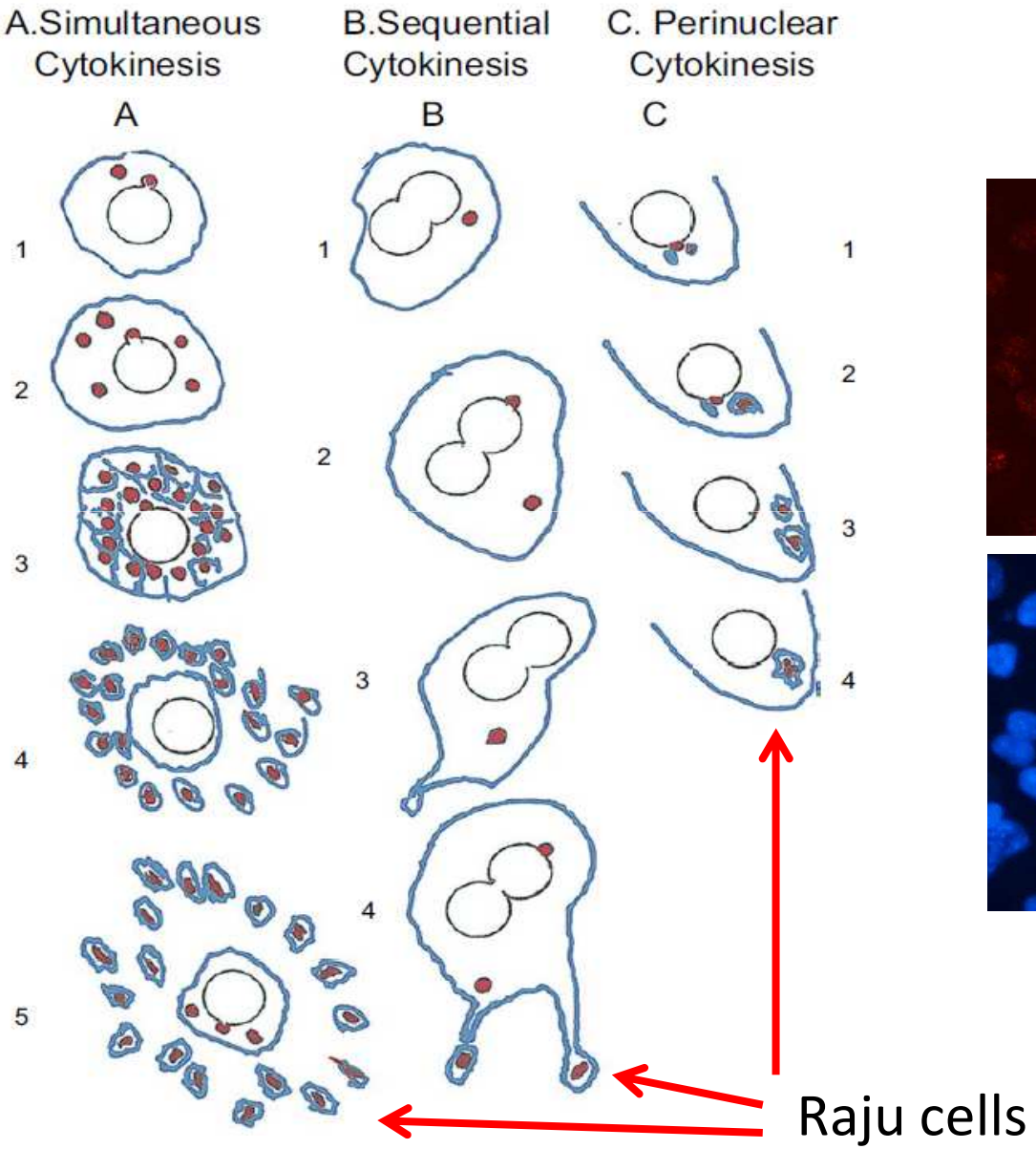



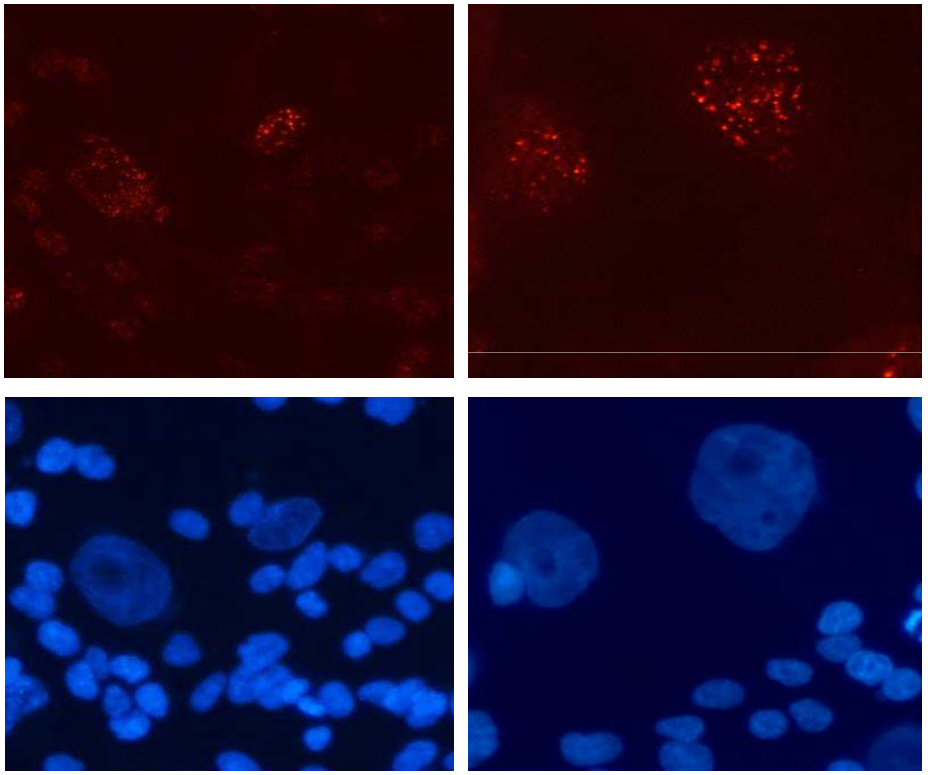




*Sliwinska et al., MAD, 2009*

# NEOSIS: A NEW TYPE OF CANCER CELL DIVISION?

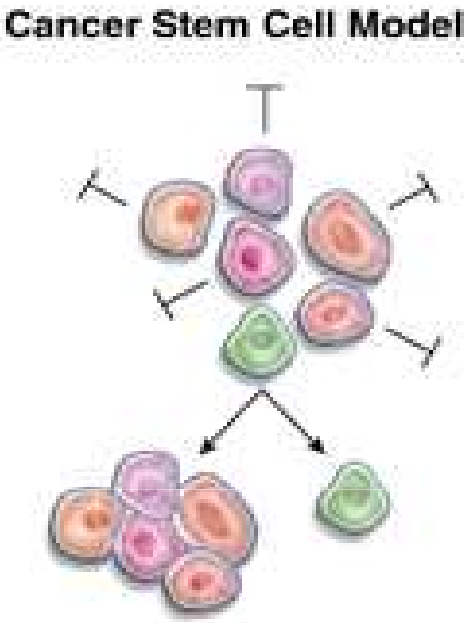


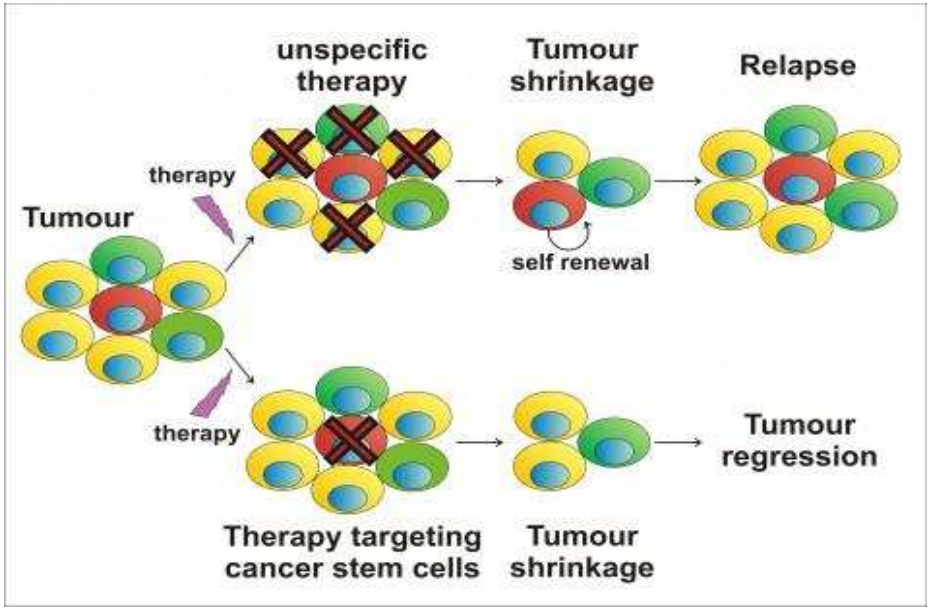

*Rajaraman et al. 2005*



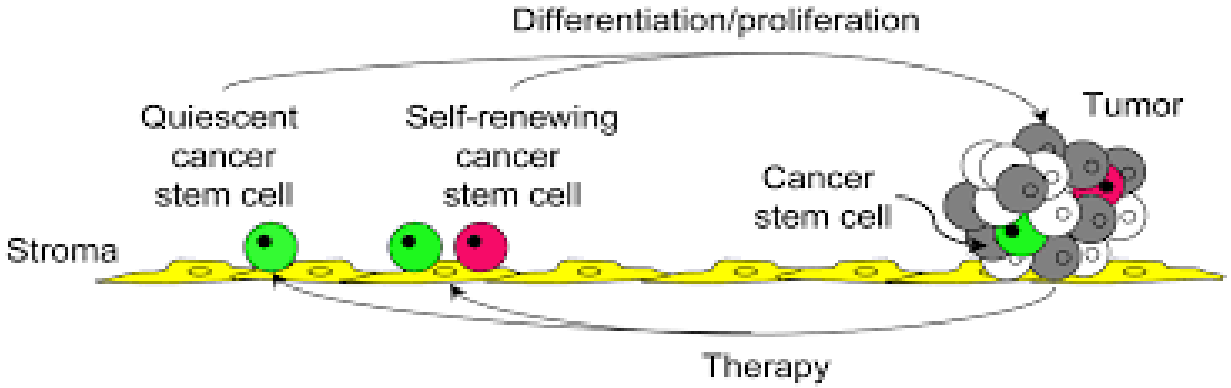

*Was et al., unpublished*

# WHY COULD WE NOT KILL ALL TUMOR CELLS?




**Cancer stem cell is a cell within a tumor that possess the capacity of self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor (*Clarke et al. Cancer Res, 2006*).**

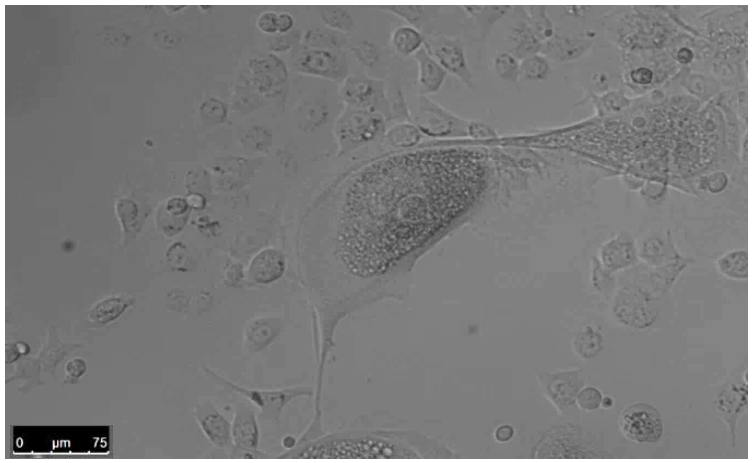


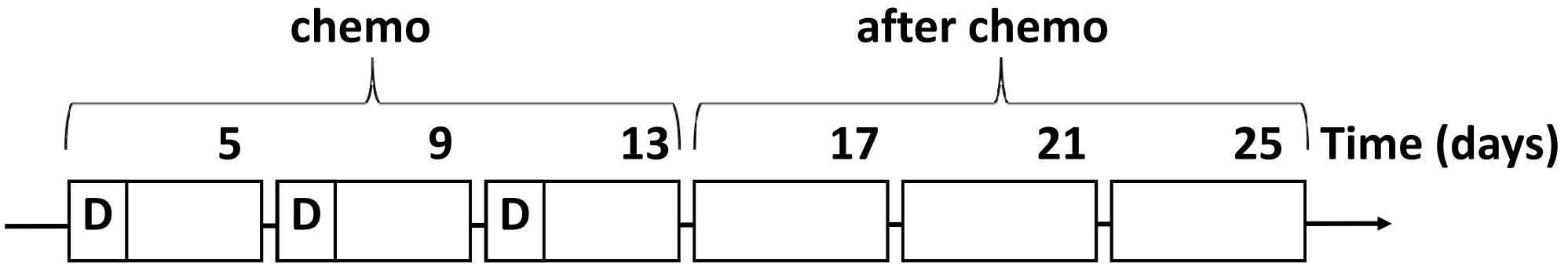
# A SENESCENT CANCER CELL IS A TUMOR-INITIATING CELL.

# *IN VITRO* EXPERIMENTAL MODELS

- **Human colon cancer cell line HCT116**

- **Drugs: doxorubicin, 5-FU, oxaliplatin, irinotecan**

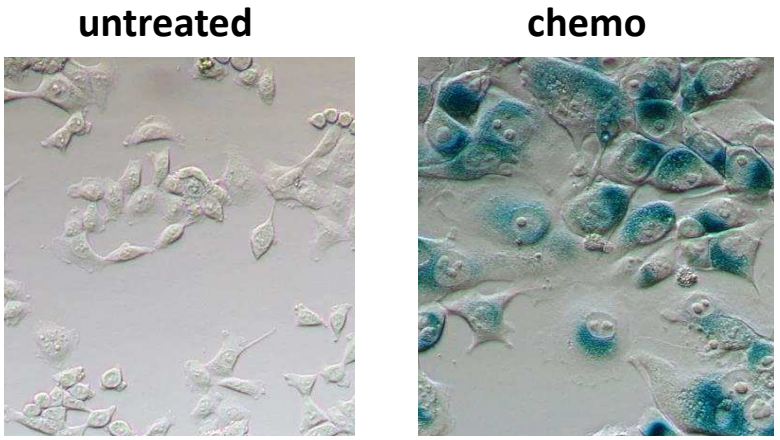


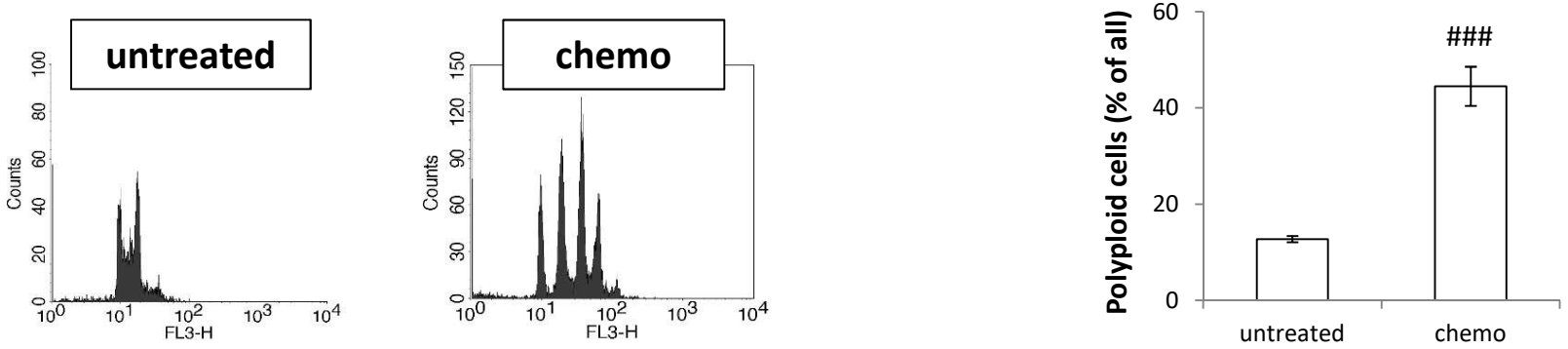

*Was et al., Oncotarget, 2017*
*Was et al., Can Biol Ther, 2018*

# HCT116 CELLS UNDERGO SENESCENCE IN RESPONSE TO REPEATED DOXO TREATMENT

- **Cell morphology and SA-β-gal activity**




- **Polyploidization**

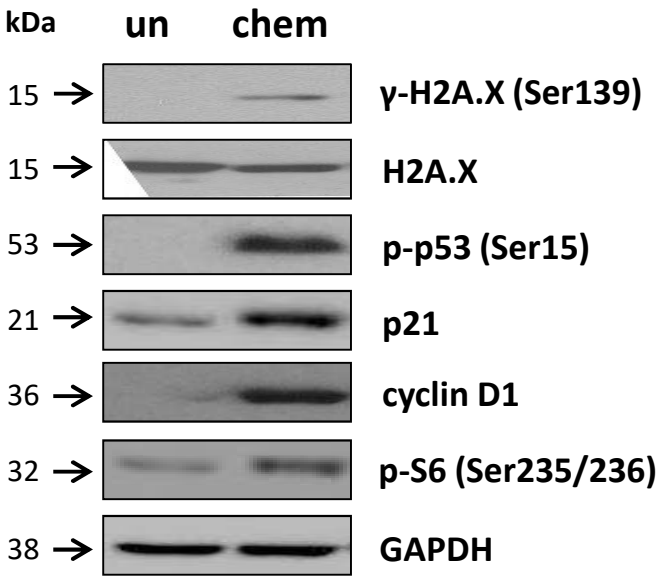



# - p < 0,05, ## - p<0,01, ### - p<0,001 - untreated vs. CHEMO, N≥3

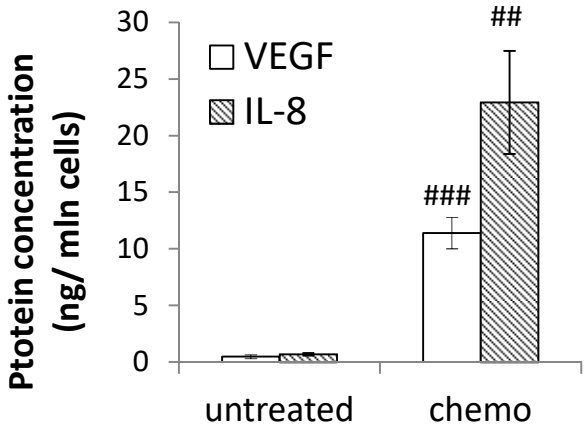
*Was et al., Oncotarget, 2017*

# HCT116 CELLS UNDERGO SENESCENCE IN RESPONSE TO REPEATED DOXO TREATMENT

- **Cell cycle inhibitors**




- **Secretory phenotype**

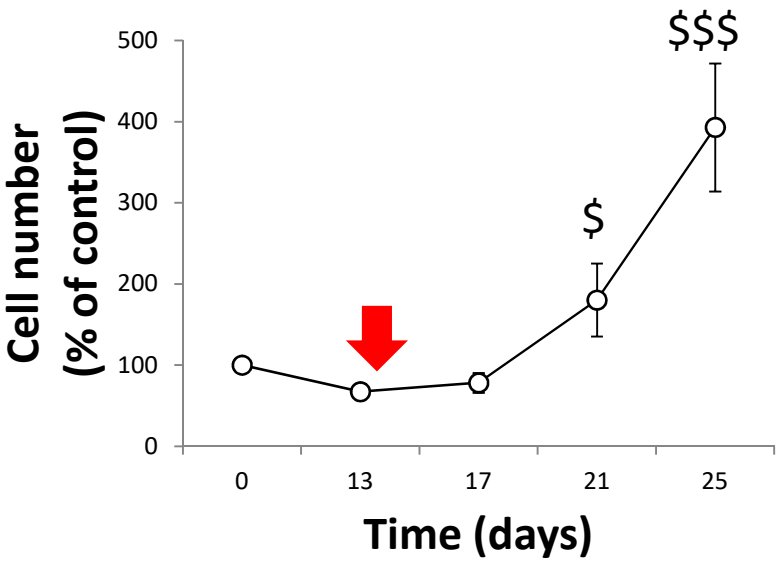


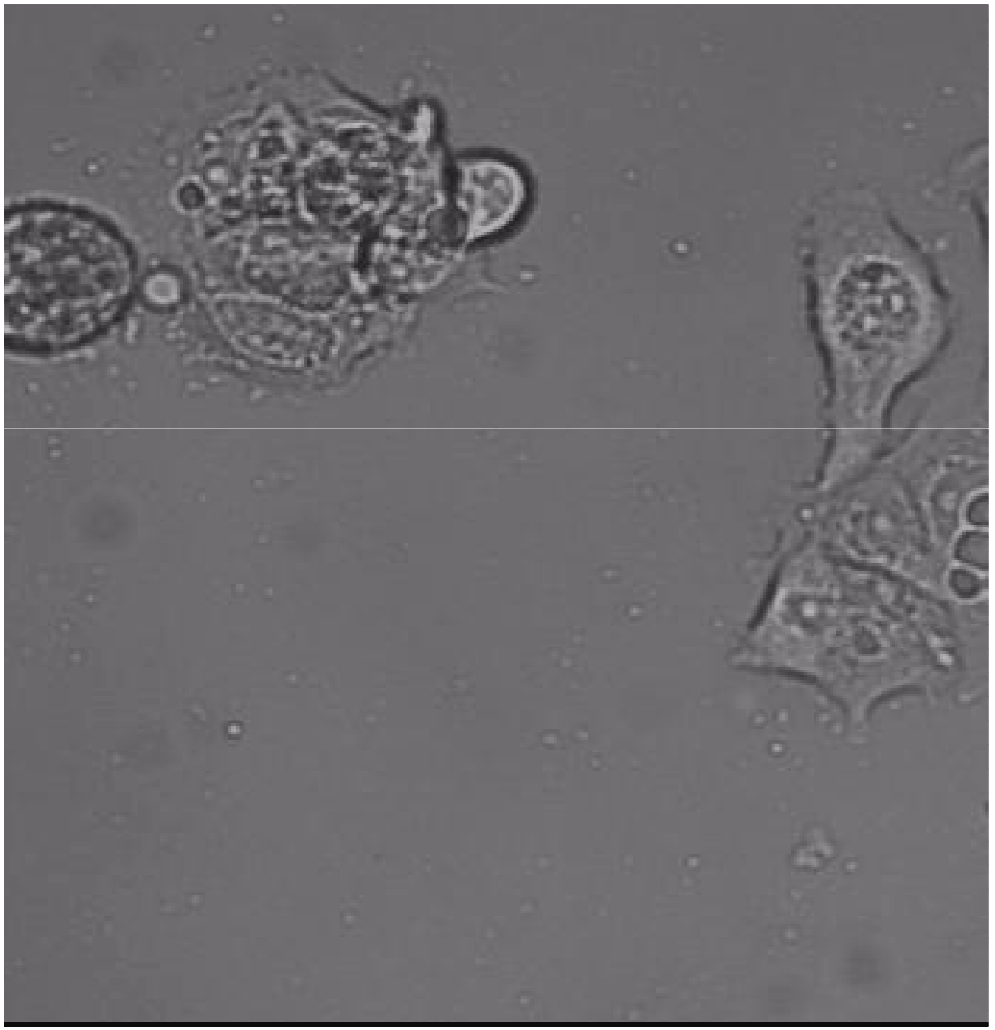

# - p < 0,05, ## - p<0,01, ### - p<0,001 - untreated vs. CHEMO, N≥3

*Was et al., Oncotarget, 2017*

# DIVISION OF SENESCENT CANCER CELLS – CAUGHT RED-HANDED?

- **Cell number**



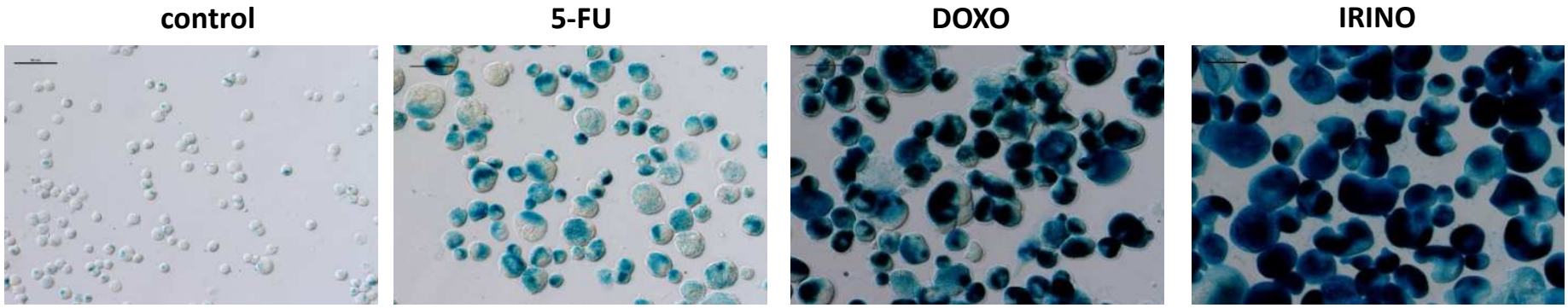



$ - p < 0,05, $$ - p<0,01, $$$ - p<0,001 - vs. CHEMO (day 13th), N≥3

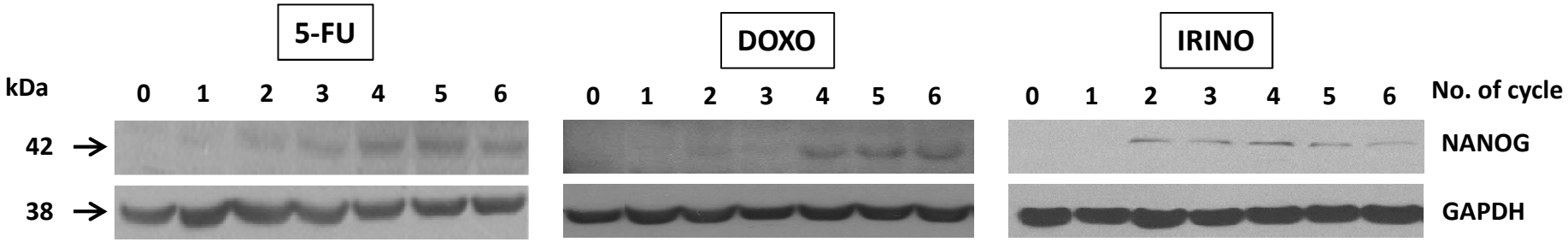
*Was et al., Oncotarget, 2017*

# SENESCENT CANCER CELLS SHOW CERTAIN FEATURES OF STEM CELLS

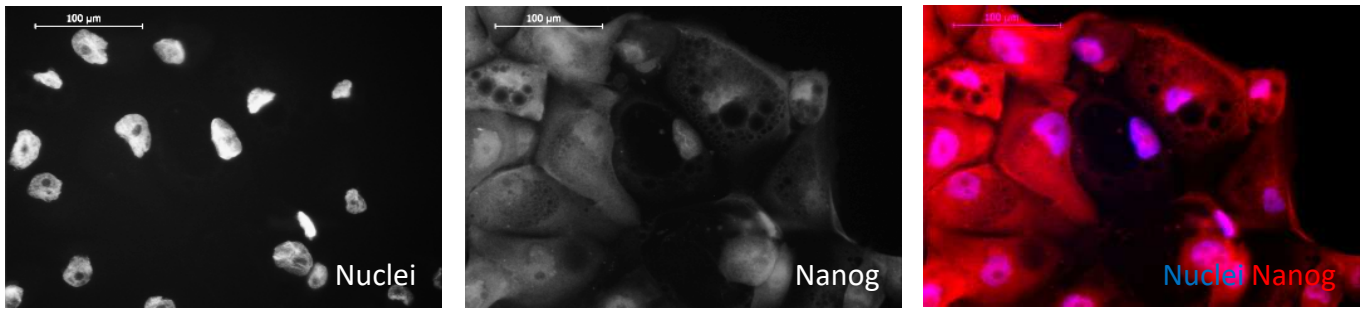
- **SA-β-gal activity**




- **Nanog expression**



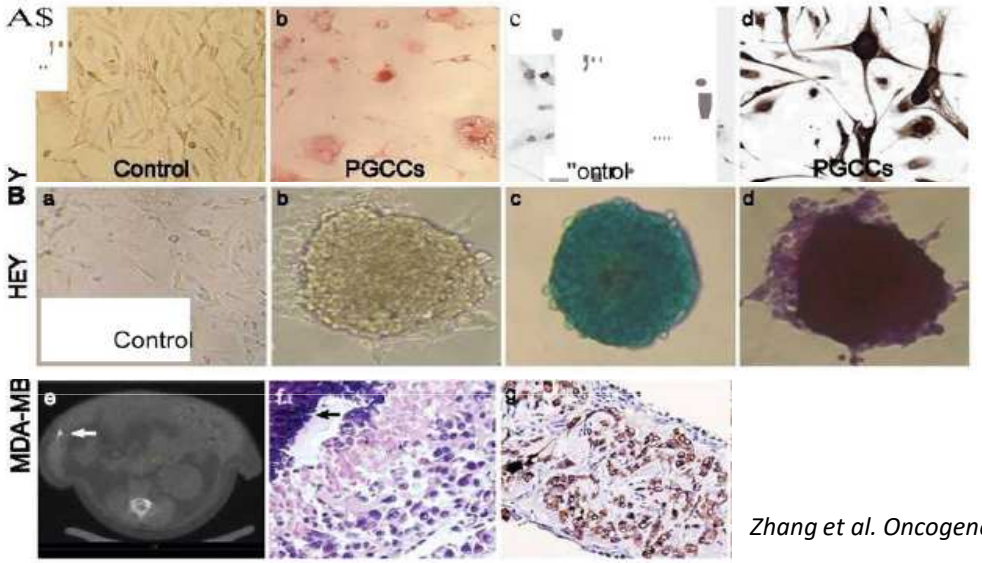

- **Nanog localization**




*Was et al., Can Biol Ther, 2018*

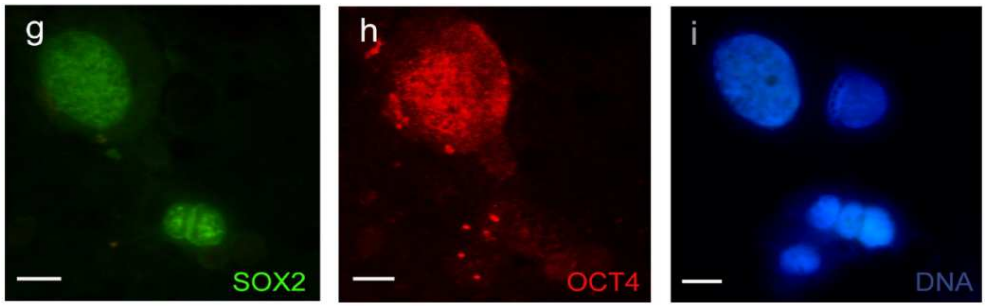
# SENESCENT CANCER CELLS SHOW FEATURES OF STEMNESS IN OTHER EXPERIMENTAL MODELS

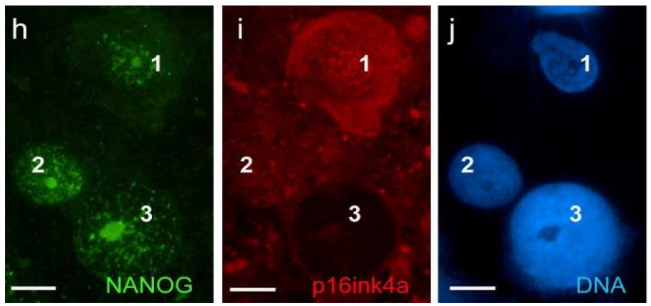
**Polyploid cancer cells may differentiate in other cell types – breast and ovarian cancers**




*Zhang et al. Oncogene 2014*

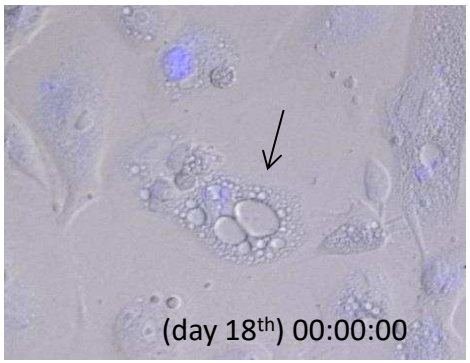
**Cancer cells present in breast tumors resistant to chemotherapy show features of senescence and stemness**

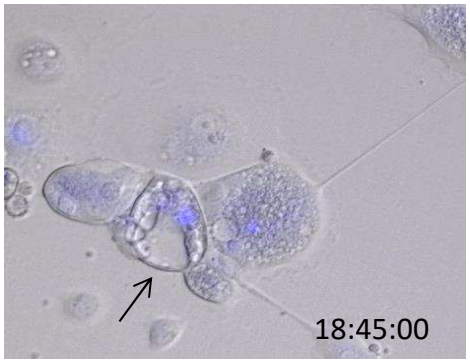


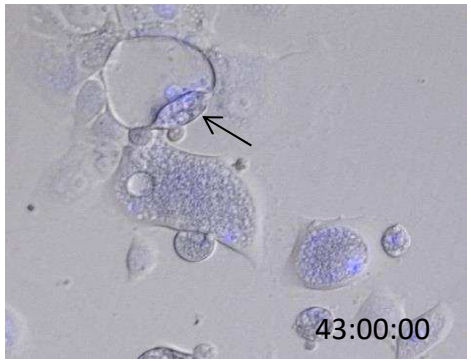




Gerashchenko et al. Histochem Cell Biol 2016

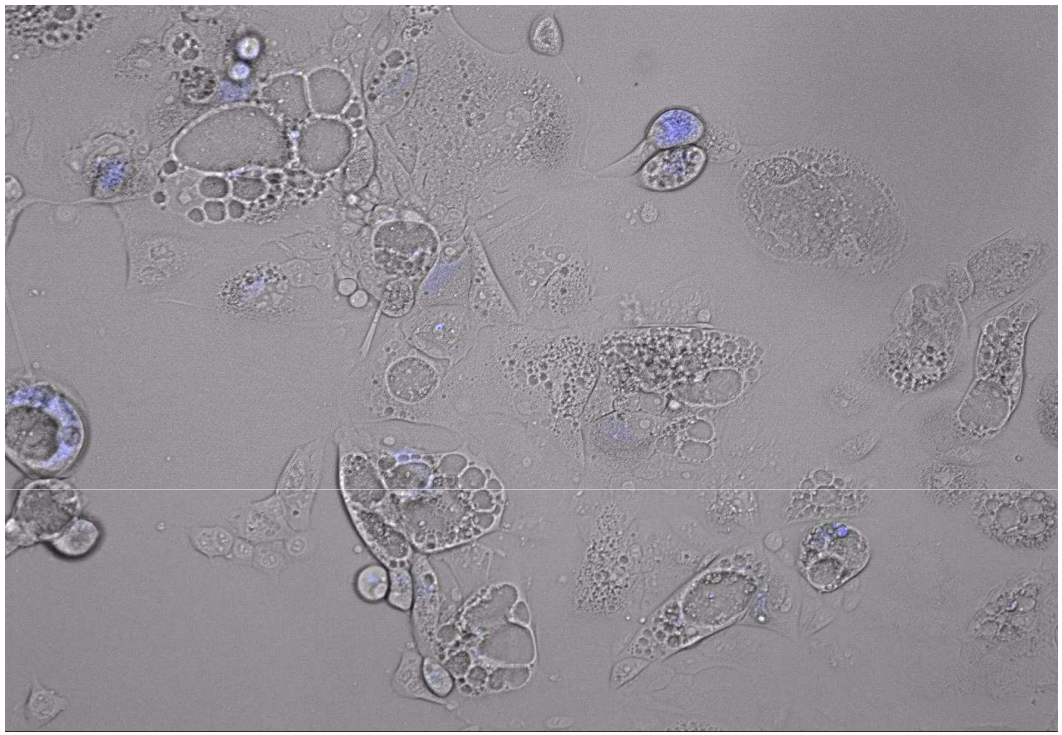
# SENESCENT CANCER CELLS SHOW BLASTOCYST-LIKE MORPHOLOGY




*Was et al., Can Biol Ther, 2018*



OPEN

Oncogene (2017), 1–14
www.nature.com/onc

ORIGINAL ARTICLE

Dedifferentiation into blastomere-like cancer stem cells via formation of polyploid giant cancer cells

N Niu, I Mercado-Uribe and J Liu

**OVARIAN CANCER**

# CONCLUSIONS

- Colon cancer cells treated with repeated cycles of chemotherapeutics exhibit hallmarks of SIPS, specifically: **hypertrophy, poliploidization,** augmented **granularity** and **SA-β-Gal activity**, elevated expression of **cell cycle inhibitors**, and **SASP**.

- Senescent cancer cells show certain features of stemness: upregulation of **Nanog**, increased numbers of **CD24$^{+}$** cells and augmented **side population.**

- Senescent cancer cells may exhibit **blastocyst-like morphology.**

- Some senescent cells carry **abnormal divisions**. After drug removal population of small and highly proliferative **progeny** appears.

# TAKE HOME MESSAGES

- **A senescent cancer cell displays a specific phenotype being a mixture of stem-like and differentiated cell features.**

- **A senescent cancer cell can be considered as a dormant, tumor-initiating cell, that contribute to cancer re-growth after chemotherapy.**

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