Recurrence: hard to code, hard to treat, hard to research.

~An update~

September 20, 2019

2019 Carolinas Cancers Registrar's Fall Regional Meeting

Charlotte, NC

Shai White-Gilbertson, PhD, MSCR, CTR, Dipl Ac

We all know some of the challenges of recurrence

Date of First Recurrence

Item #	Length	Column #	Allowable Values	Required Status	Date Revised
1860	8	2867-2874	CCYYMMDD	All Years	06/05, 01/10, 01/11, 01/12

Description

Records the date of the first recurrence.

Rationale

This data item is used to measure the efficacy of the first course of treatment.

Coding Instructions

- Record the date the physician diagnoses the first progression, metastasis, or recurrence of disease after a disease-free period.

Type of First Recurrence

Item #	Length	Column #	Allowable Values	Required Status	Date Revised
1880	2	2877-2878	00, 04, 06, 10, 13-17, 20-22, 25-27, 30, 36, 40, 46, 51-59, 60, 62, 70, 88, 99	All Years	06/05, 01/10, 01/11, 01/13, 01/15, 01/18

Description

Identifies the type of first recurrence after a period of documented disease-free intermission or remission.

Rationale

This item is used to evaluate treatment efficacy and as a long-term prognostic factor.

Coding Instructions

- Code the type of first recurrence. First recurrence may occur well after completion of the first course of treatment or after subsequent treatment.
- Check the SEER *Multiple Primary and Histology Coding Rules Manual* or the 2018 Solid Tumor Rules to determine which subsequent tumors should be coded as recurrences.
- If the patient has never been disease-free (code 70), continue to track for disease-free status which may occur after subsequent treatment has been completed.
- If the patient is disease-free (code 00), continue to track until a recurrence occurs. First recurrence may occur well after completion of the first course of treatment.
- Once a recurrence has been recorded (code 04-62 or 88), subsequent recurrences are NOT to be recorded.
- Codes 00 through 70 are hierarchical; record the highest-numbered applicable response, with the following limits. The first time a patient converts from disease status (70) to disease-free, change the code to 00. Then the first time a patient converts from 00 to a recurrence, then record the proper code for the recurrence. No further changes (other than corrections) should be made.
- If the tumor was originally diagnosed as in situ, code recurrence to 06, 16, 17, 26, 27, 36, or 46 only. Do not use those codes for any other tumors. Codes 00, 88, or 99 may apply to any tumor.
- Codes 51–59 (organ or organ system of distant recurrence) apply only if all first occurrences were in a single category. There may be multiple metastases (or "seeding") within the distant location.
- Code lymphomas or leukemias that are in remission 00. If the patient relapses, then code recurrence as 59. If one of these is controlled by drugs (for example, Gleevec for CML), the patient is in remission.
- If there is more than one primary tumor and the physician is unable to decide which has recurred, code the recurrent disease for each tumor. If the recurrent primary is identified later, revise the codes appropriately.

Journal of Surgical Research
Volume 235, March 2019, Pages 551-559

Oncology

Lack of Cancer Recurrence Data in Large Databases: A National Survey of Hospital Cancer Registries

Haejin In MD, MPH, MBA [a, b], Ian Solsky MD, MPH [a], Cassie A. Simon CTR [c], David P. Winchester MD, FACS [b, d]

Conclusions

Those tasked with collecting recurrence information report significant barriers concerning data access, data quality, adequate resources, and coding variability. A unified effort is needed to improve collection.

Abstract

Background

Cancer recurrence information is not routinely collected by the US cancer registries. Prior research suggests hospital characteristics, staff qualifications, and chart access may be contributing factors but this has not been explored nationally. This study aimed to understand issues underlying poor collection of recurrence information and to identify targets for improvement.

Methods

A survey was sent to Commission on Cancer hospitals to investigate reasons for variations in recurrence data collection, examine resources allocated, and assess coding variability. Descriptive and multivariate analyses were performed.

Results

Eight hundred and forty-five of 1417 surveys to Commission on Cancer hospitals were analyzed. Sixty-nine percent reported annually examining charts for recurrence ("investigating" hospitals). They more likely had experienced registrars (91% *versus* 84%, $P < 0.05$), integrated electronic medical records (75% *versus* 68%, $P < 0.05$) and chart access to in-network hospitals (80% *versus* 73%, $P < 0.05$). Thirty-seven percent reported ability to follow-up using medical records on <50% of patients. Reasons for noncollection included inability to accurately collect (37%), limited resources (44%), and low priority (18%). Odds of being an investigating hospital increased with the percentage of patients who could be followed up with medical records (90%-100% OR = 6.72). There were minimal differences among hospitals in registry caseload and resources. 79.5% reported that without prior recurrence documentation, they would code the patient as not having a recurrence, 8.8% would change all recurrence variables to "unknown," and 7.2% would leave them blank.

Recurrence rates for selected cancers

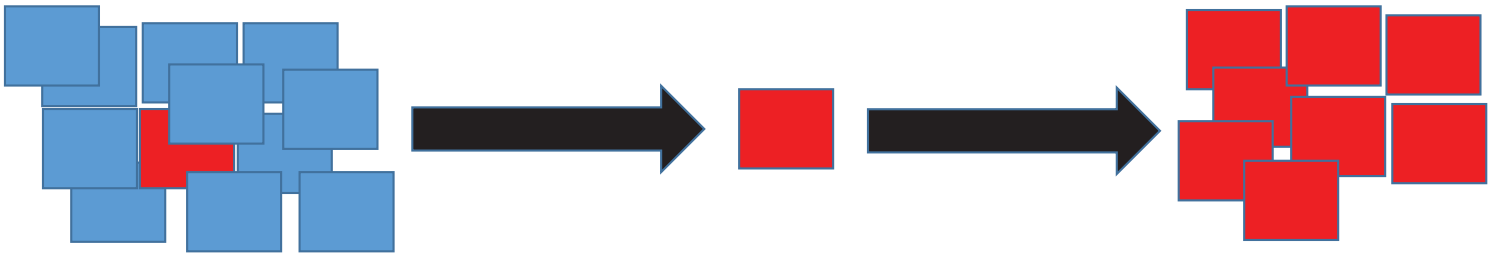
Cancer Type	Recurrence Rate
NSCLC[22,23]	26% after curative surgery 27% after chemoradiotherapy for locally advanced disease
Osteosarcoma[12]	11%-12% local recurrence 5%-45% metastasis
Ovarian[3]	85%
Pancreas[6,7]	36% within 1 year after curative surgery 38% local recurrence after adjuvant chemotherapy 46% distant metastasis after adjuvant chemotherapy
Prostate[24]	After prostatectomy at 10 years: 24% low-risk disease 40% intermediate-risk disease 48% high-risk disease
Soft tissue sarcoma[4]	50% after adjuvant chemotherapy Nearly 100% for advanced disease
Thyroid[25,26]	Up to 30% for differentiated thyroid carcinoma 8%-14% after surgery for medullary thyroid carcinoma

https://www.cancertherapyadvisor.com/home/tools/fact-sheets/cancer-recurrence-statistics/

Cancer Type	Recurrence Rate
Bladder[5]	50% after cystectomy
Breast[10,16]	30% overall 5% to 9% with letrozole or placebo during median 10.6 years
Colorectal[17]	17% after curative surgical resection with microscopically clear margins
Glioblastoma[2]	Nearly 100%
Head and neck, stage IV[18]	After intensified, split-course, hyperfractionated multiagent chemoradiotherapy: 17%, locoregional 22%, distant
Hodgkin lymphoma[13,14]	10% to 13% after primary treatment 20% to 50% after second-line treatment
Kidney[11,19]	13% 49% after complete response to tyrosine kinase inhibitor therapy
Leukemia, childhood ALL[20]	15% to 20%
Leukemia, childhood AML[15]	9% to 29%, depending on risk
Lymphoma, DLBCL[8]	30% to 40%
Lymphoma, PTCL[9]	75%
Melanoma[21]	15% to 41%, depending on stage 87%, metastatic disease

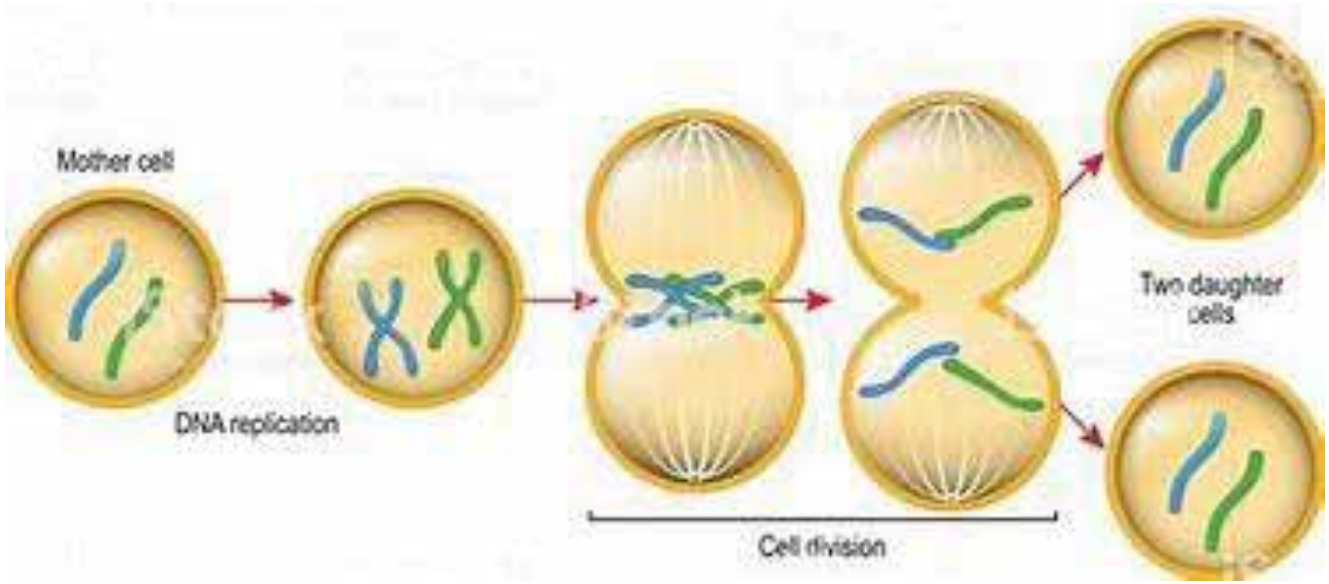
Recurrence is a big deal because it's typically more aggressive and more resistant to treatment

A common way to think about treatment selecting for resistant cells, which remain and repopulate the tumor bed:



This is part of the reason that second line therapies are different from first line therapies. The time frame and the difference between the original tumor cells and the recurrent tumor cells creates a real challenge from a research point of view. Almost any combination of traits could be hiding in that one red box…how do you design experiments for almost anything? But it turns out there is a very strange mechanism underlying the survival of that one red cell.

Let’s start with mitosis, which is driving most cancer growth



https://media.istockphoto.com/vectors/mitosis-cell-division-vector-id687251074

Oncogenesis. 2016 Dec; 5(12): e281. **Linking genomic reorganization to tumor initiation via the giant cell cycle**

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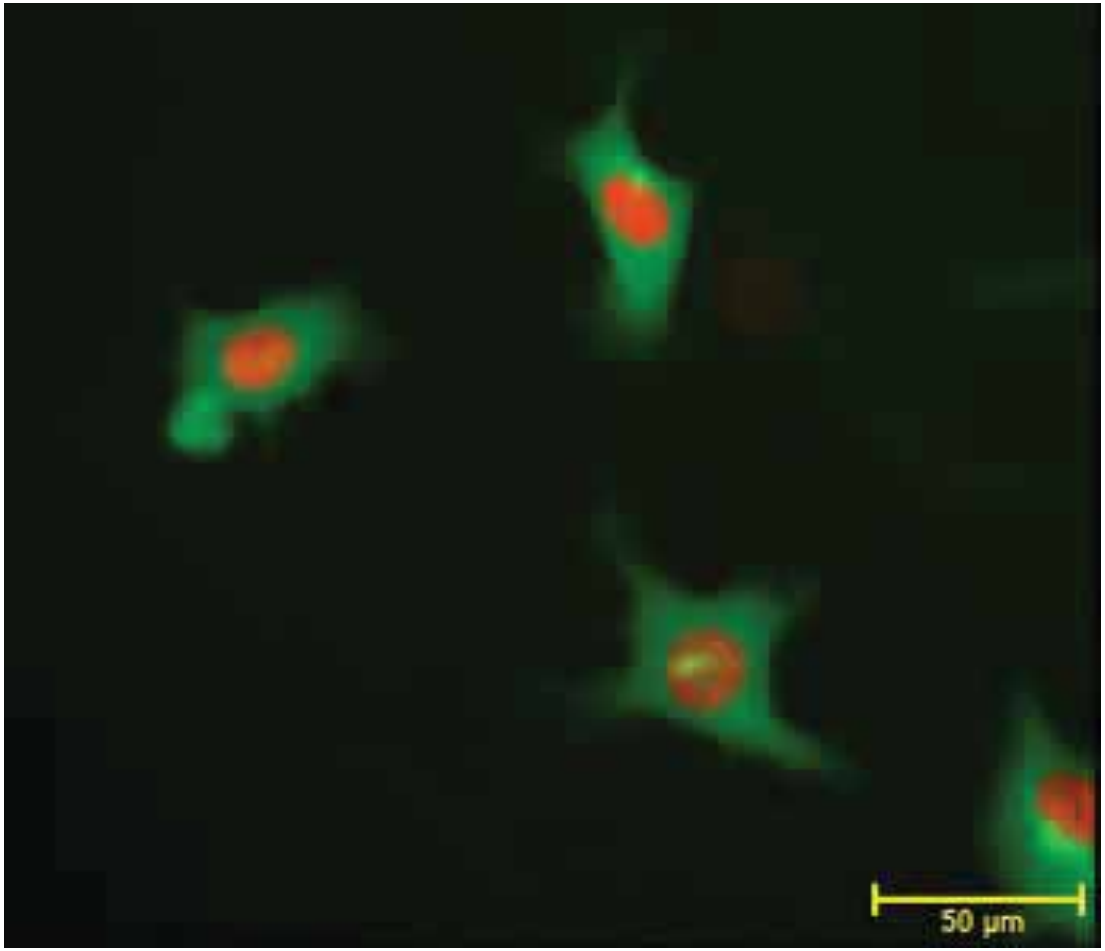
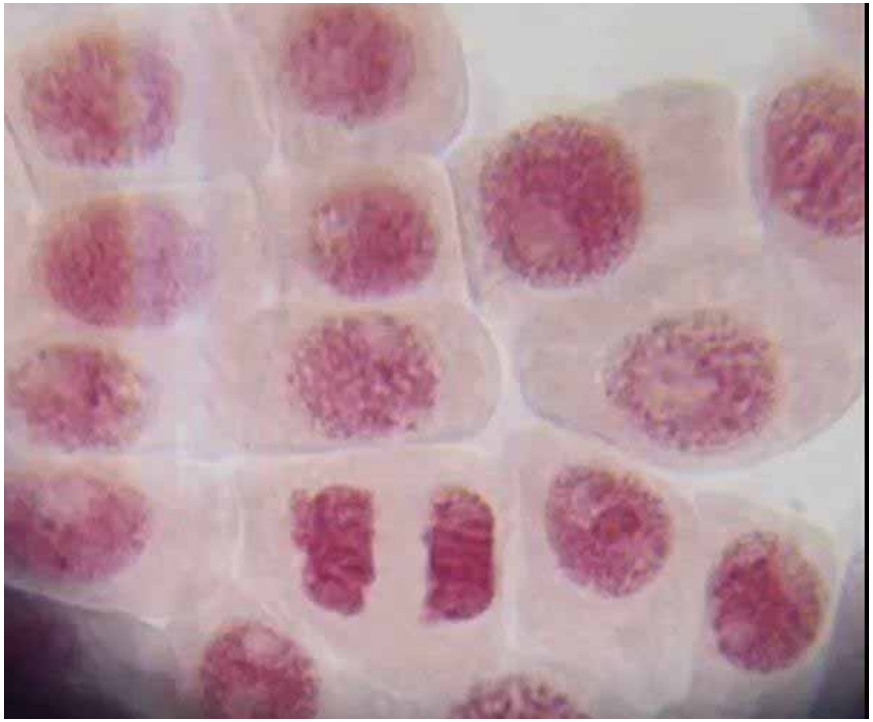


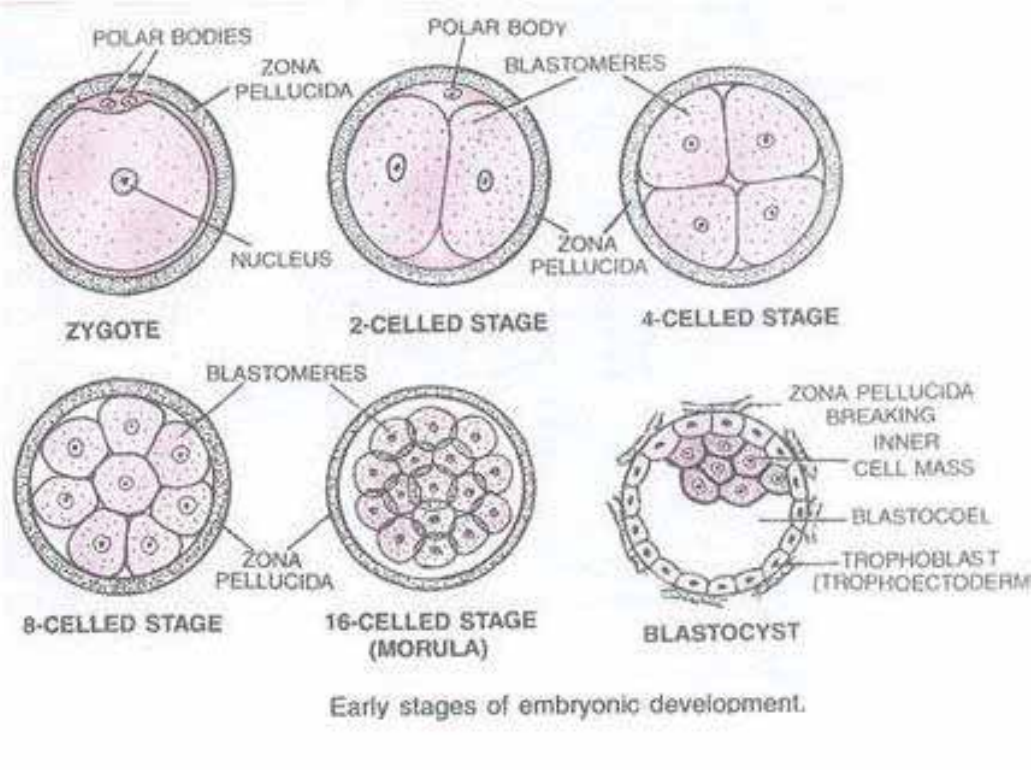


https://www.youtube.com/watch?v=GBV0o7nydPY

Chemotherapy and radiation are mitosis poisons

- Radiation causes nicks and breaks in the DNA, making it impossible for the replication machinery to ride the strands
- Chemotherapies have a wide range of mechanisms
  - Taxols lock up the microtubules
  - Vincristine inhibits spindle formation
  - Doxorubicin intercalates into the DNA and de-rails the replication machinery
  - Platins cross-link DNA molecules with the same effect
  - Temozolomide methylates DNA with the same effect
  - Capecitabine inhibits the formation of new DNA

Cancer cells who cannot perform their central obsession (mitosis) occasionally look back in their history for some non-mitosis option



Early stages of embryonic development.

Cleavage: the process in early development when a fertilized egg (zygote) multiplied its DNA content and “pinches off” to make new, smaller cells called blastomeres.

http://www.yourarticlelibrary.com/wp-content/uploads/2013/10/image50.png

The paper we reference the most

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

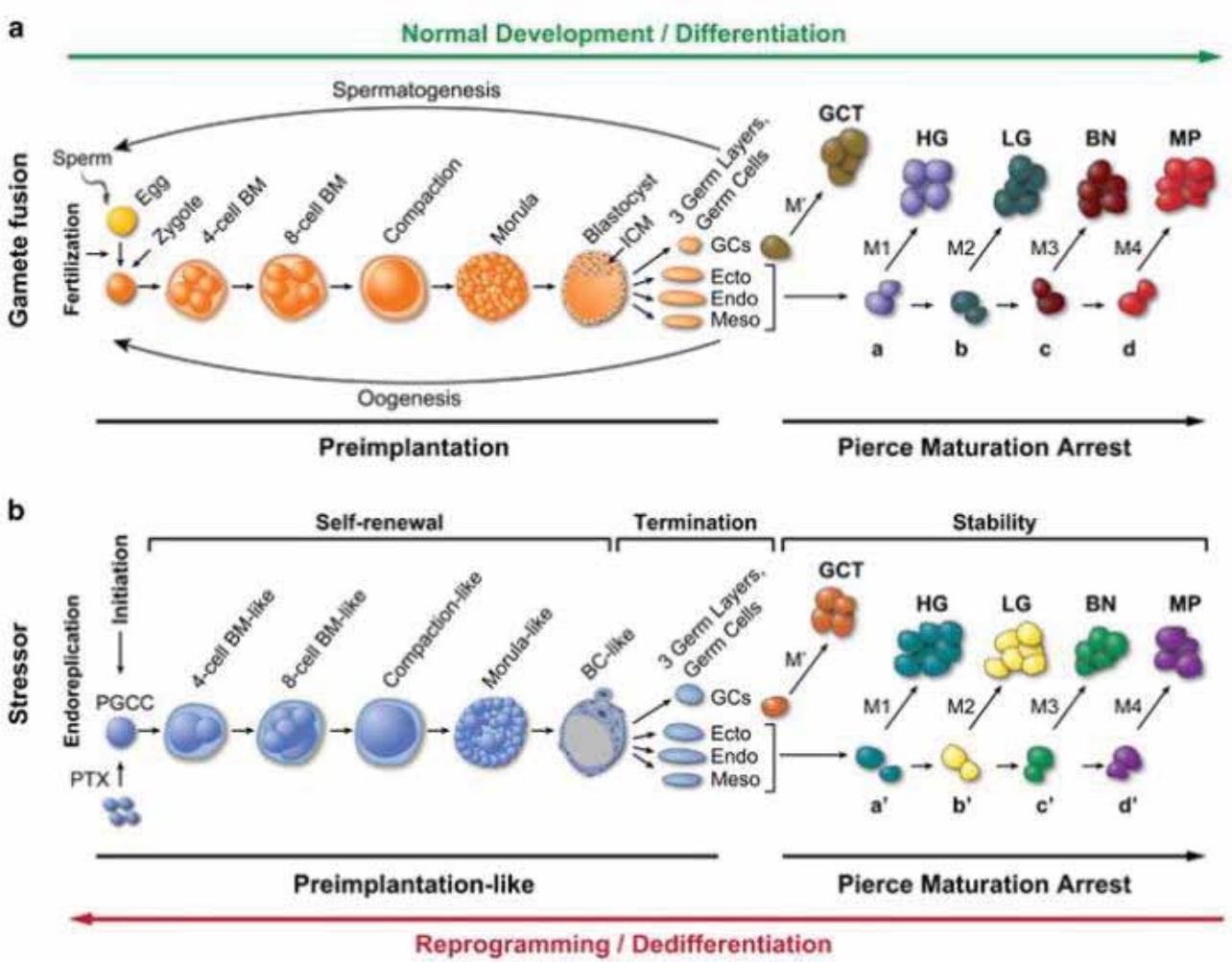
Home Profiles Research Units Equipment **Research Output** Activities Prizes

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

Na Niu, I. Mercado-Uribe, Jinsong Liu

Pathology

Research output: Contribution to journal › Article



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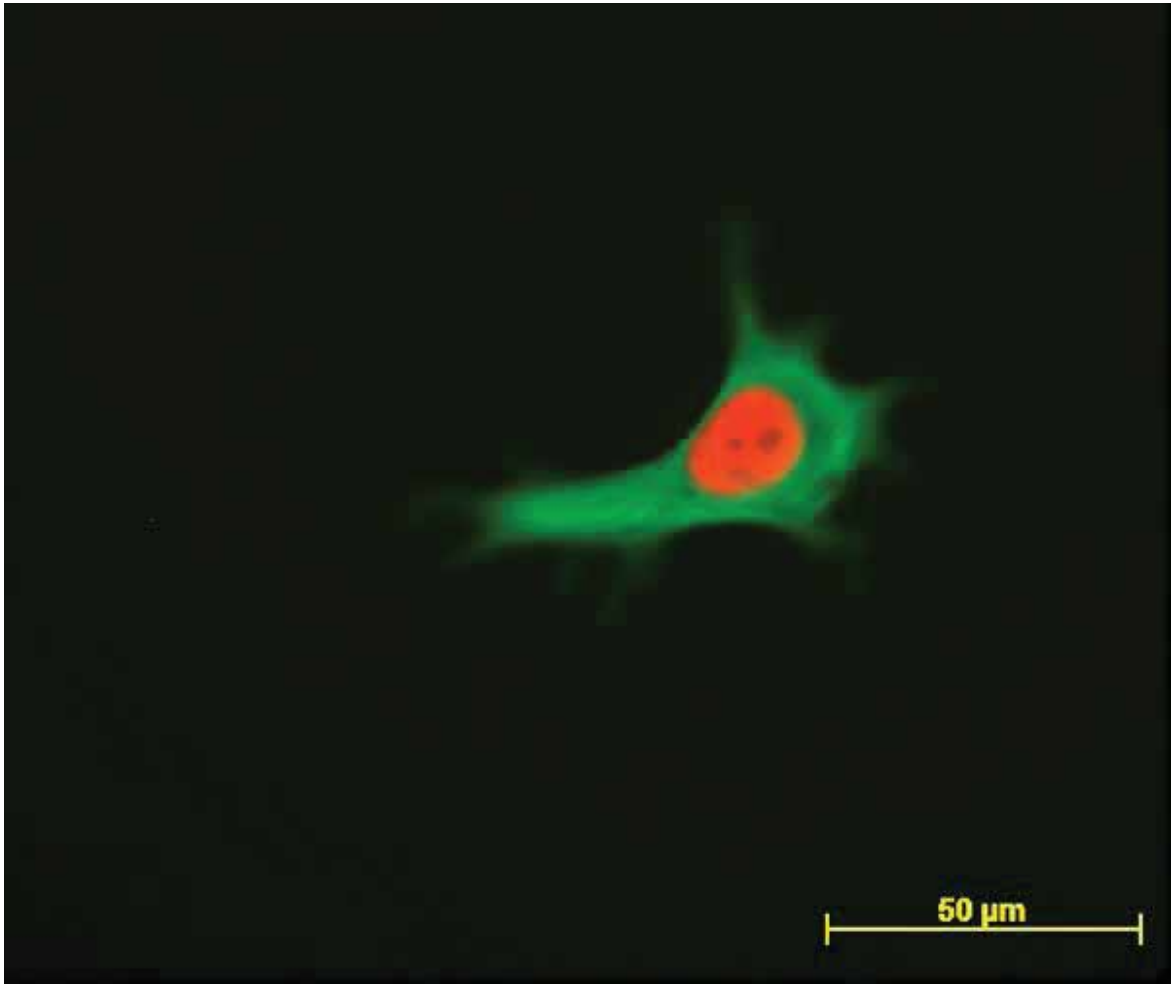
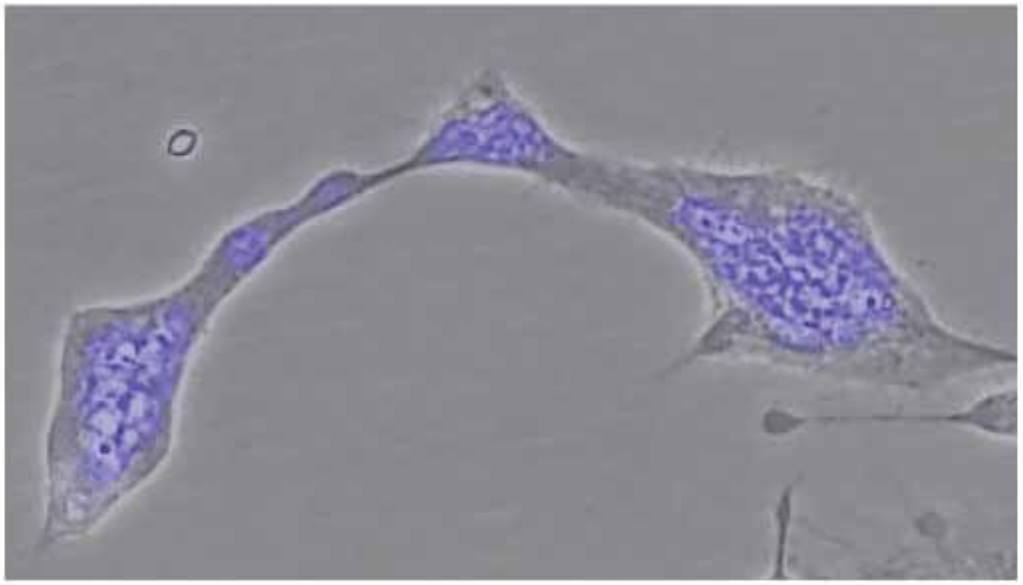


PGCC Polynuclear giant cancer cells: Warehouses formed under mitotic stress

- Once the stress is gone, something even stranger happens, something cribbed from an even earlier evolutionary moment.
- This process is called NEOSIS
- Could be budding
- Could be extrusion
- Could be a burst
- The PGCC dies
- The next generation multiplies



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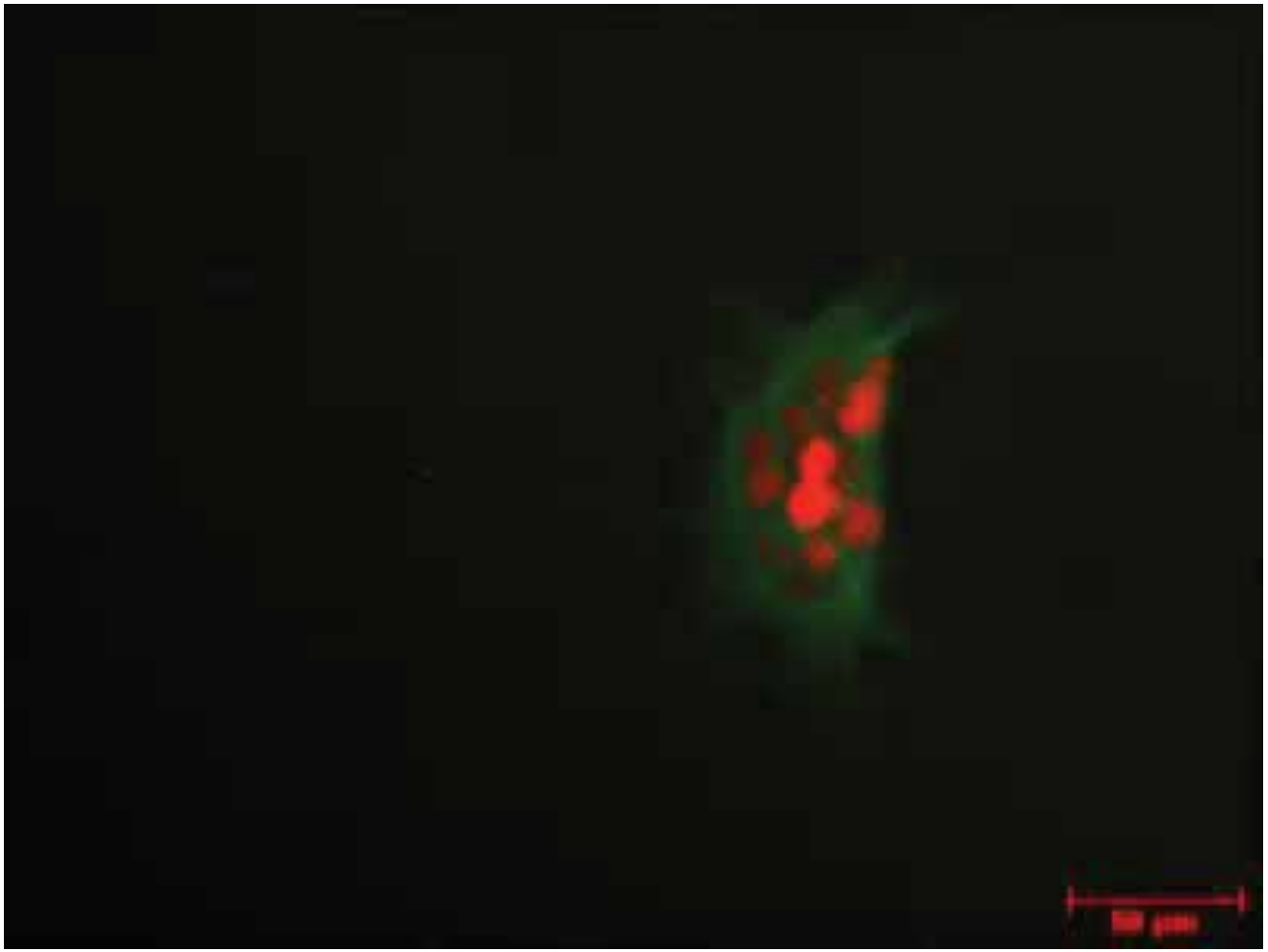
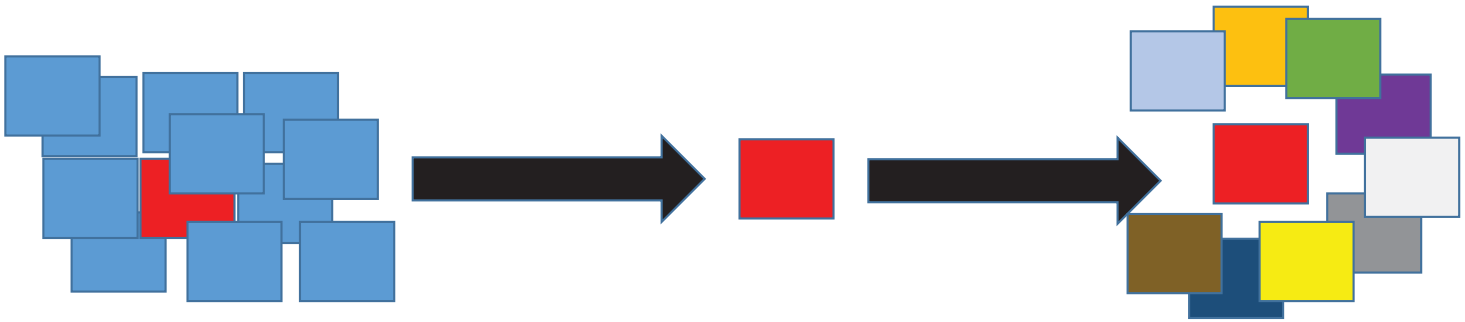
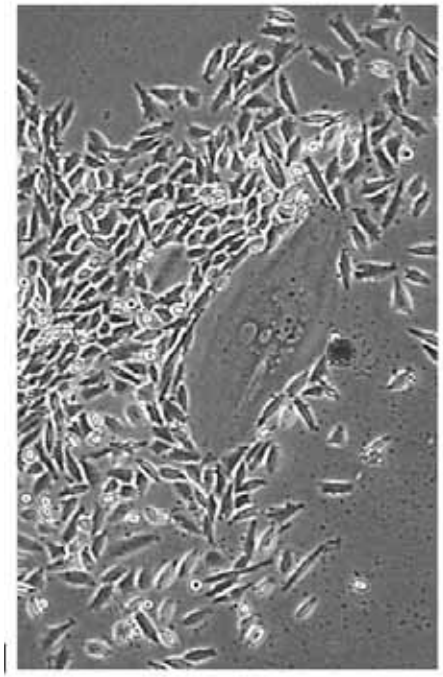


So the cells that repopulate the tumor bed are not just resistant to the one treatment they were exposed to, but have been through a genetic windmill. They could be basically anything.

This is really bad news.



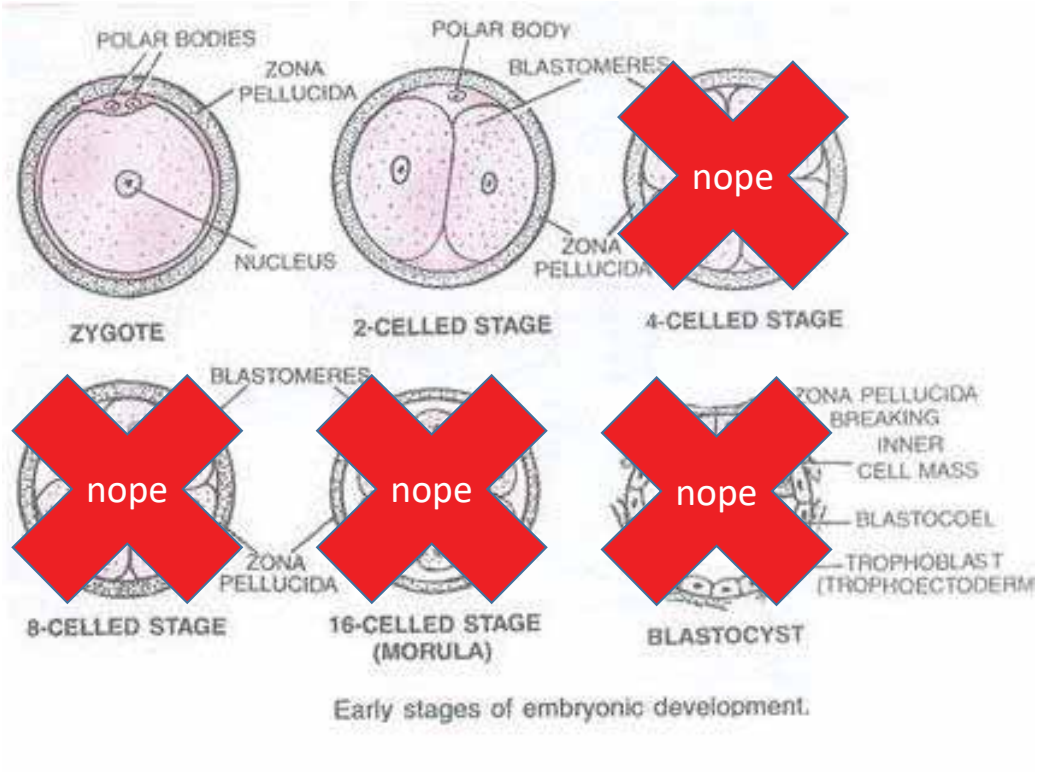


- This is an important insight. If only anti-mitotic therapies are used, PGCC could remain and re-populated the tumor bed. Optimally, anti-mitotic therapies would be used along with ***anti-neotic*** therapies to take out both populations, so that the new population would never arise.

- The problem: neosis is only known by a small number of basic researchers and where do we start in finding a target for PGCC?

- The coincidence: our lab happens to research an enzyme called acid ceramidase. The enzyme converts one sphingolipid into another sphingolipid.

Acid ceramidase and sphingolipids



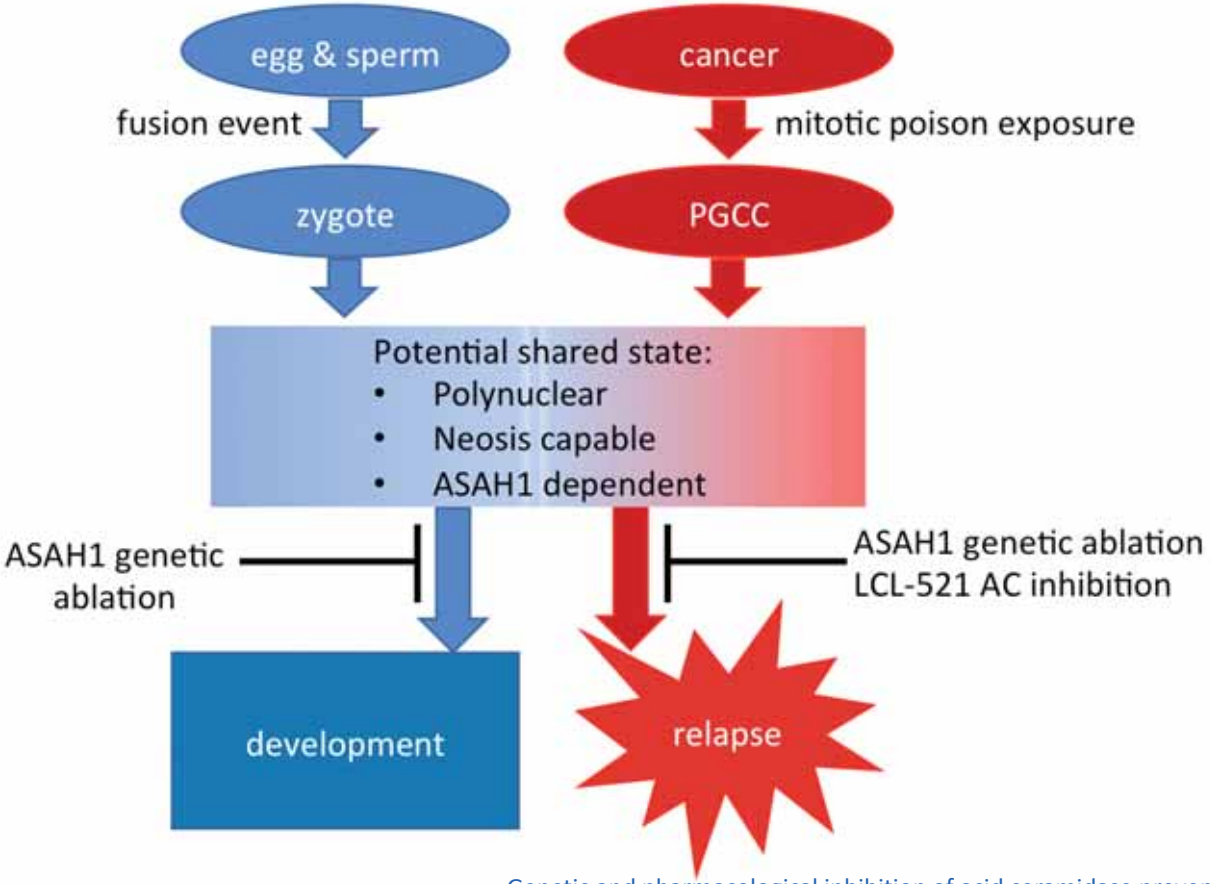
Embryonic lethal

(+) acid ceramidase

(-) acid ceramidase

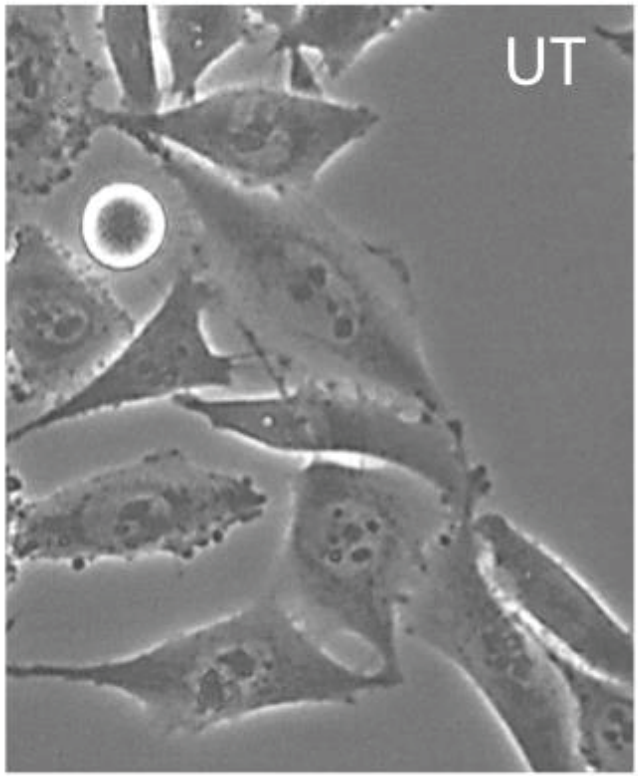
Conditional knock out is fine

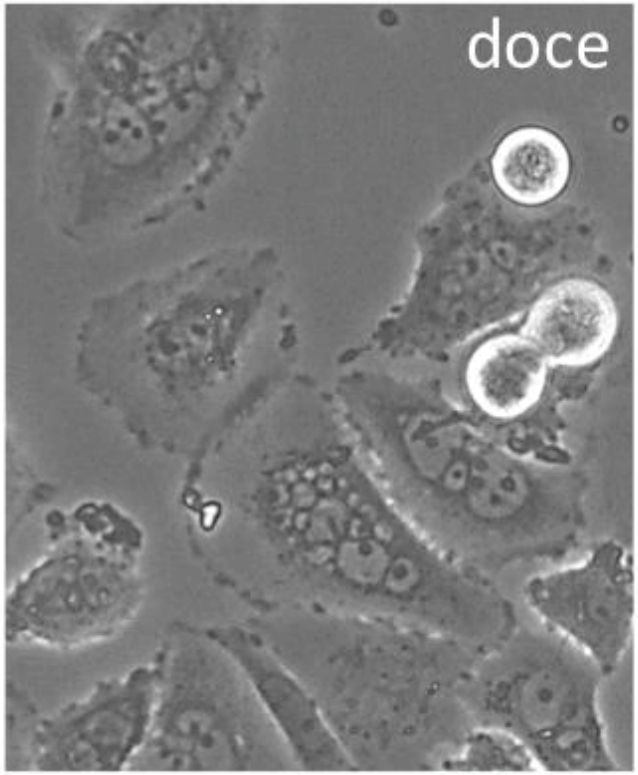
The hypothesis

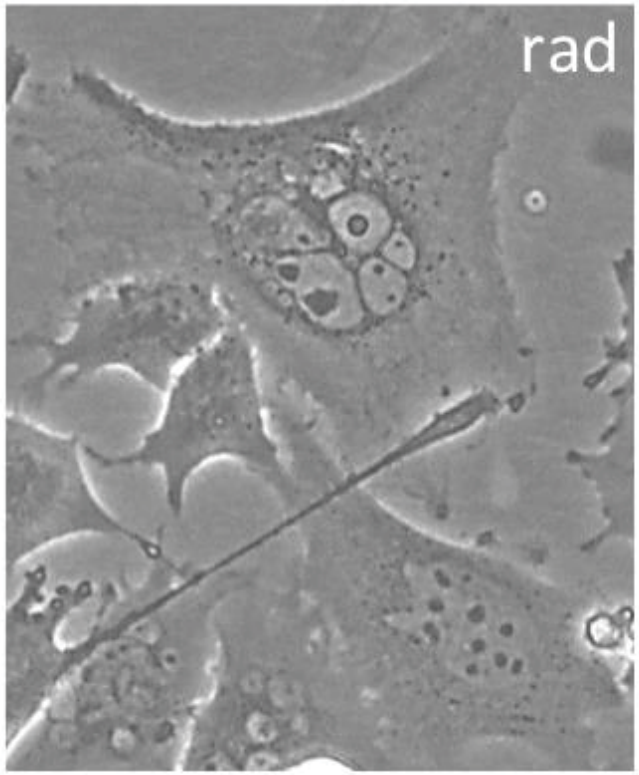


Genetic and pharmacological inhibition of acid ceramidase prevents asymmetric cell division by neosis.
White-Gilbertson S, Lu P, Norris JS, Voelkel-Johnson C.
J Lipid Res. 2019 Jul;60(7):1225-1235

Model system: prostate cancer cells PPC1







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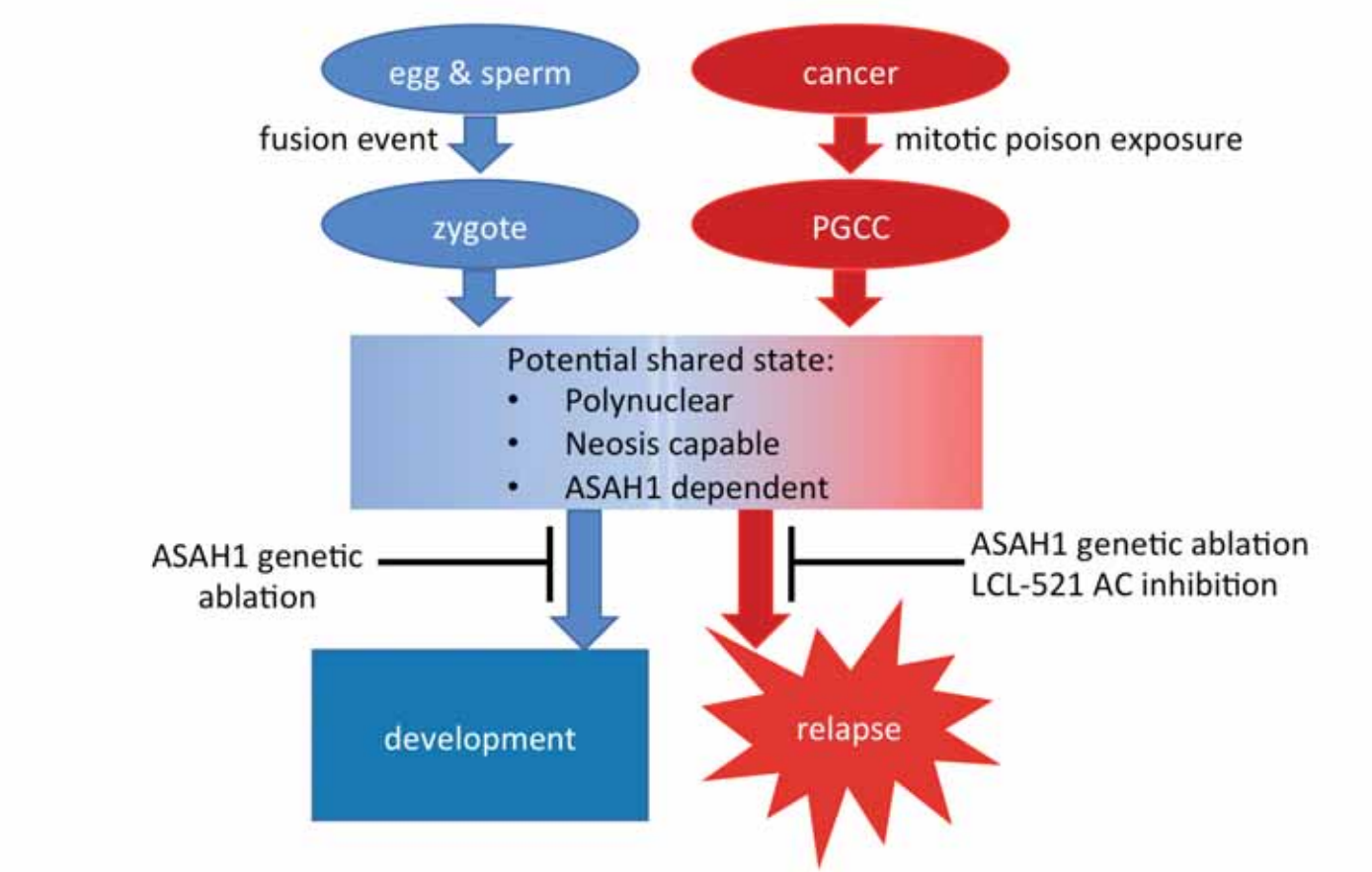
The hypothesis



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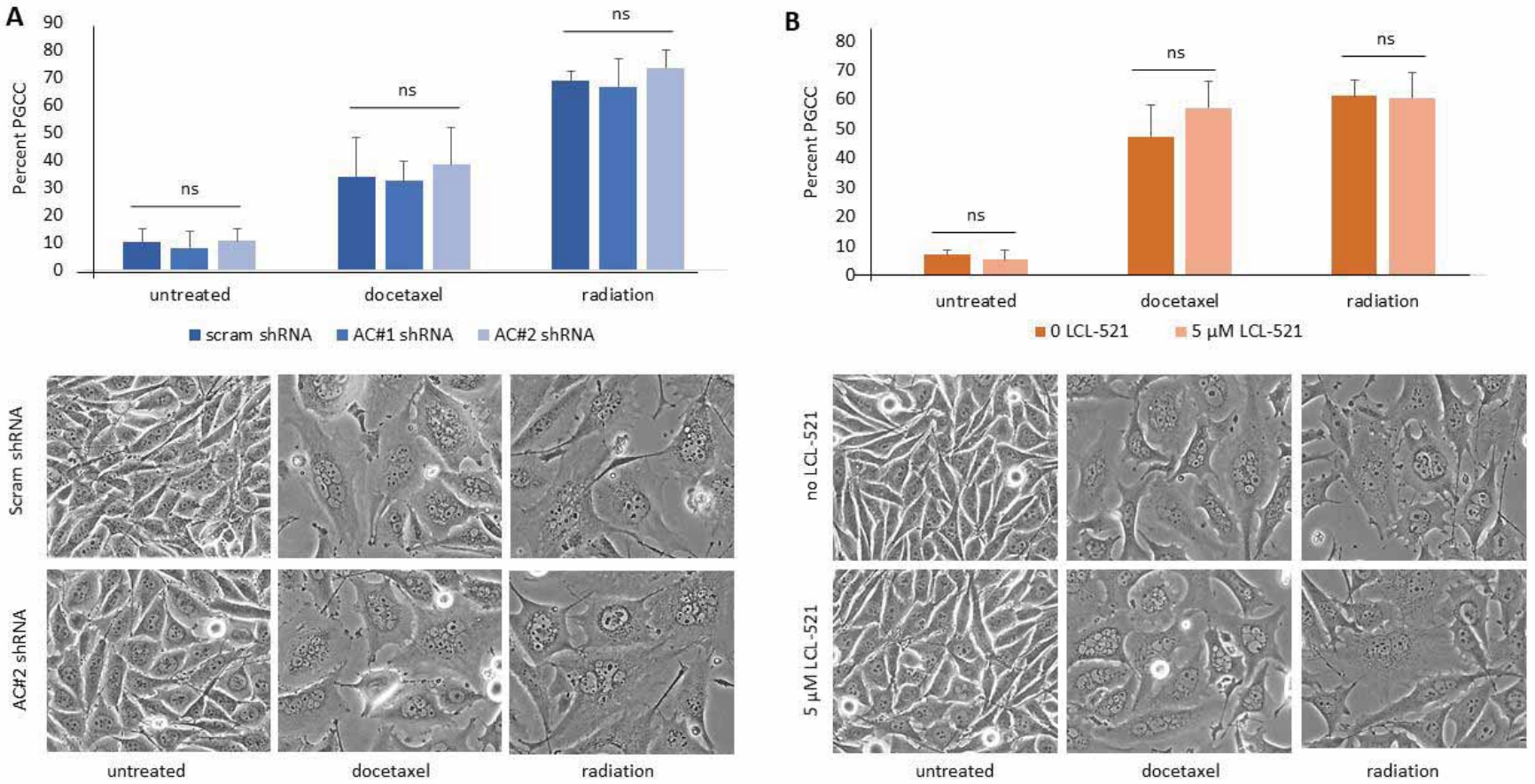
Inhibiting acid ceramidase does not stop PGCC formation

Figure 3



[Genetic and pharmacological inhibition of acid ceramidase prevents asymmetric cell division by neosis.](#)
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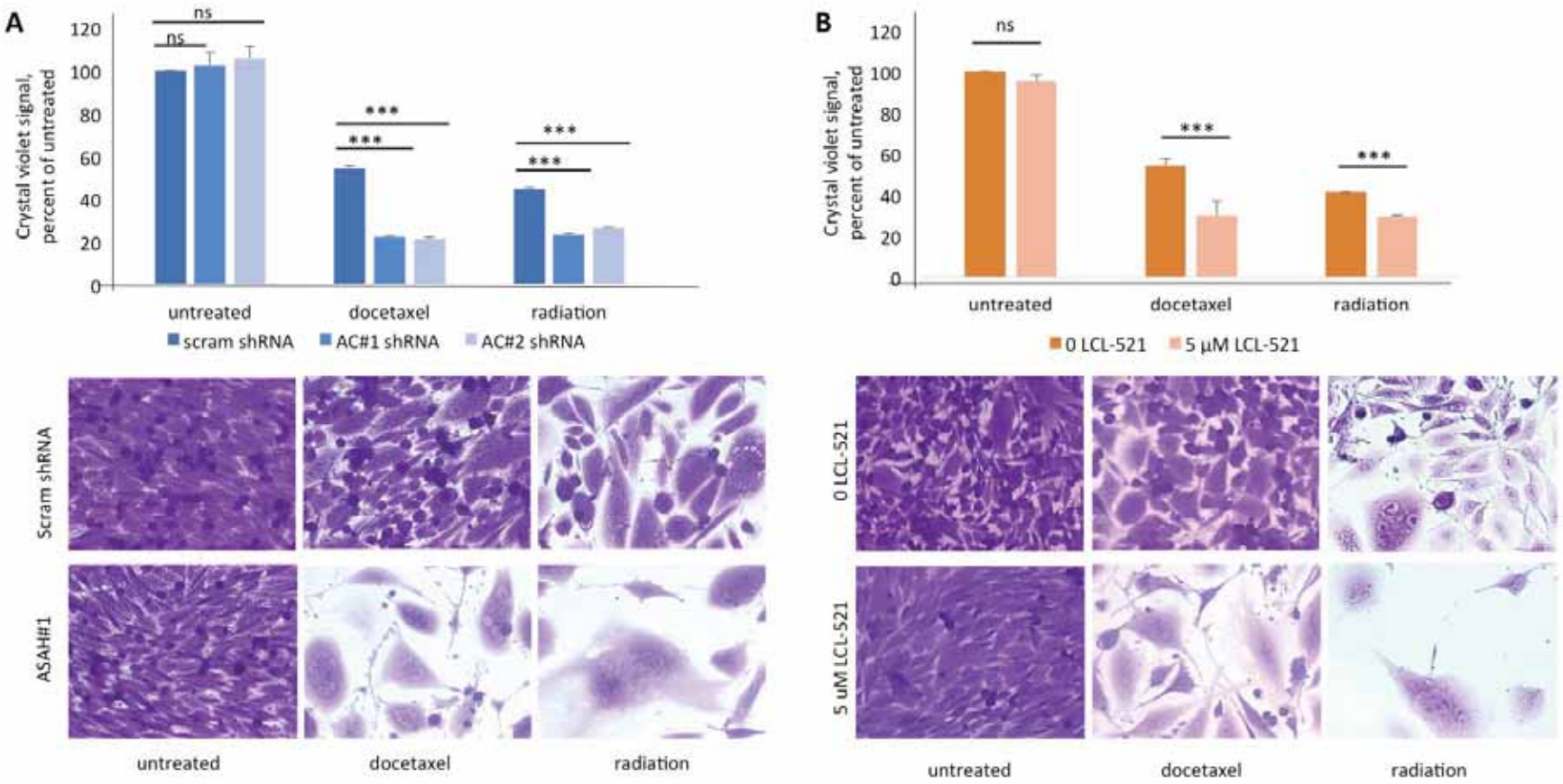
Inhibiting acid ceramidase stops neosis

Figure 4



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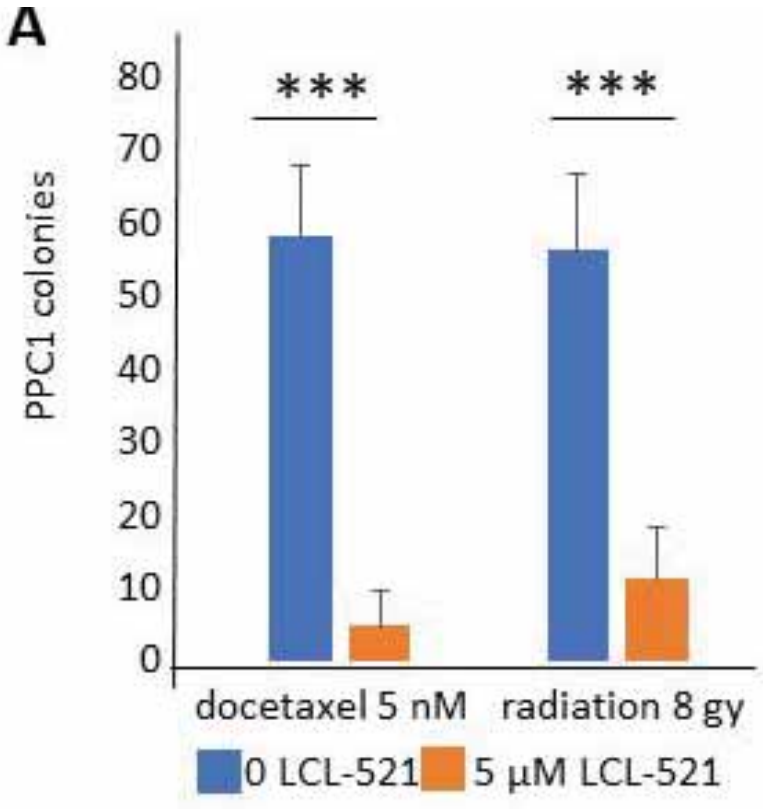
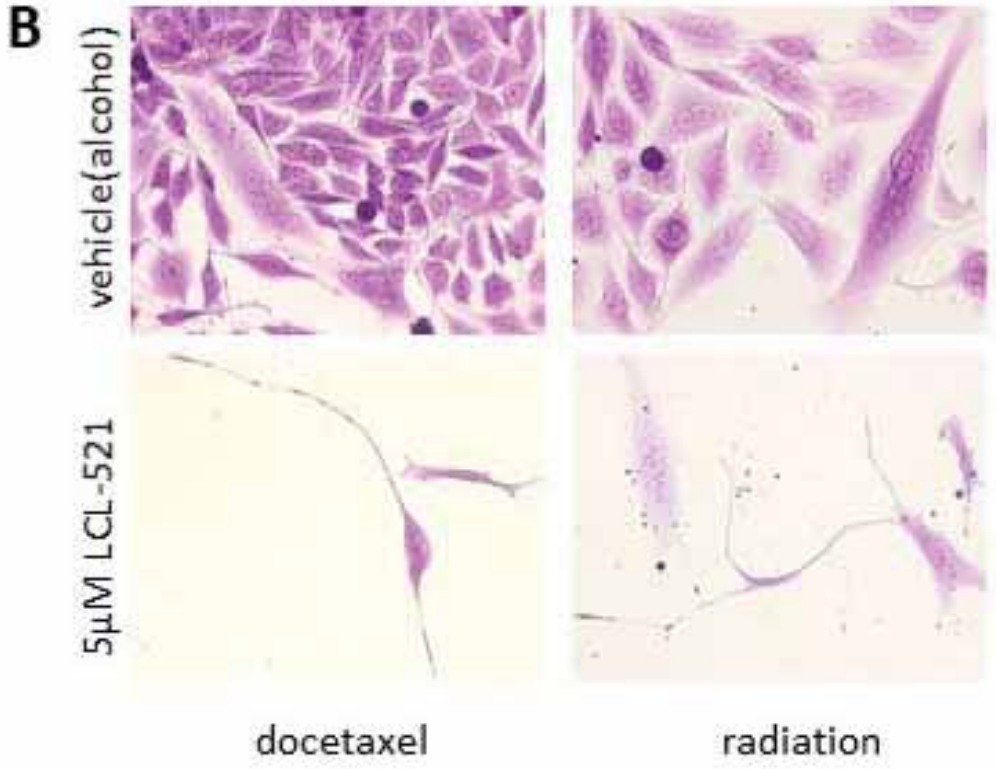
Colony counting prostate cancer cells





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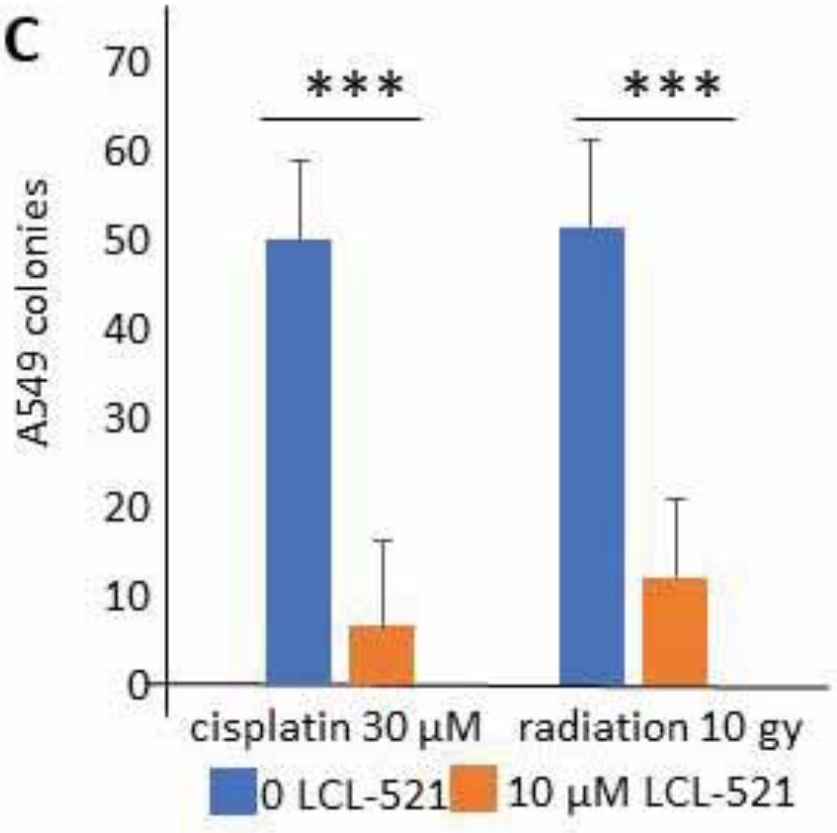
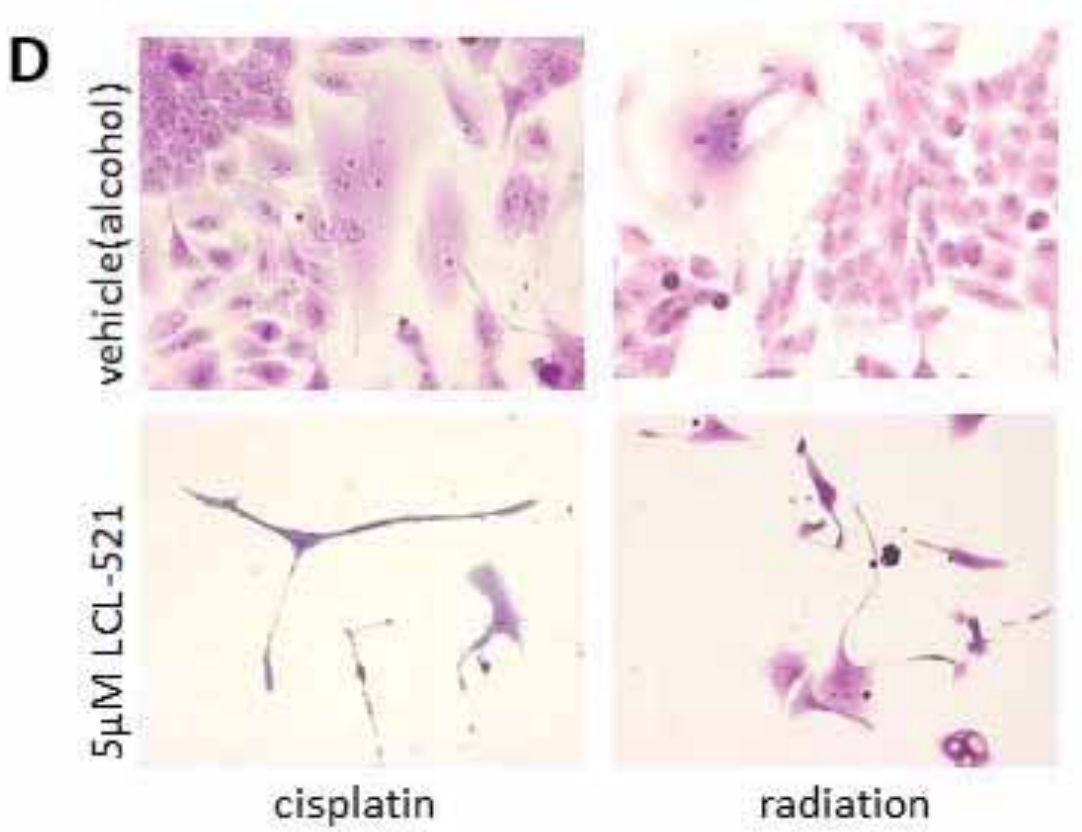
Colony counting lung cancer cells





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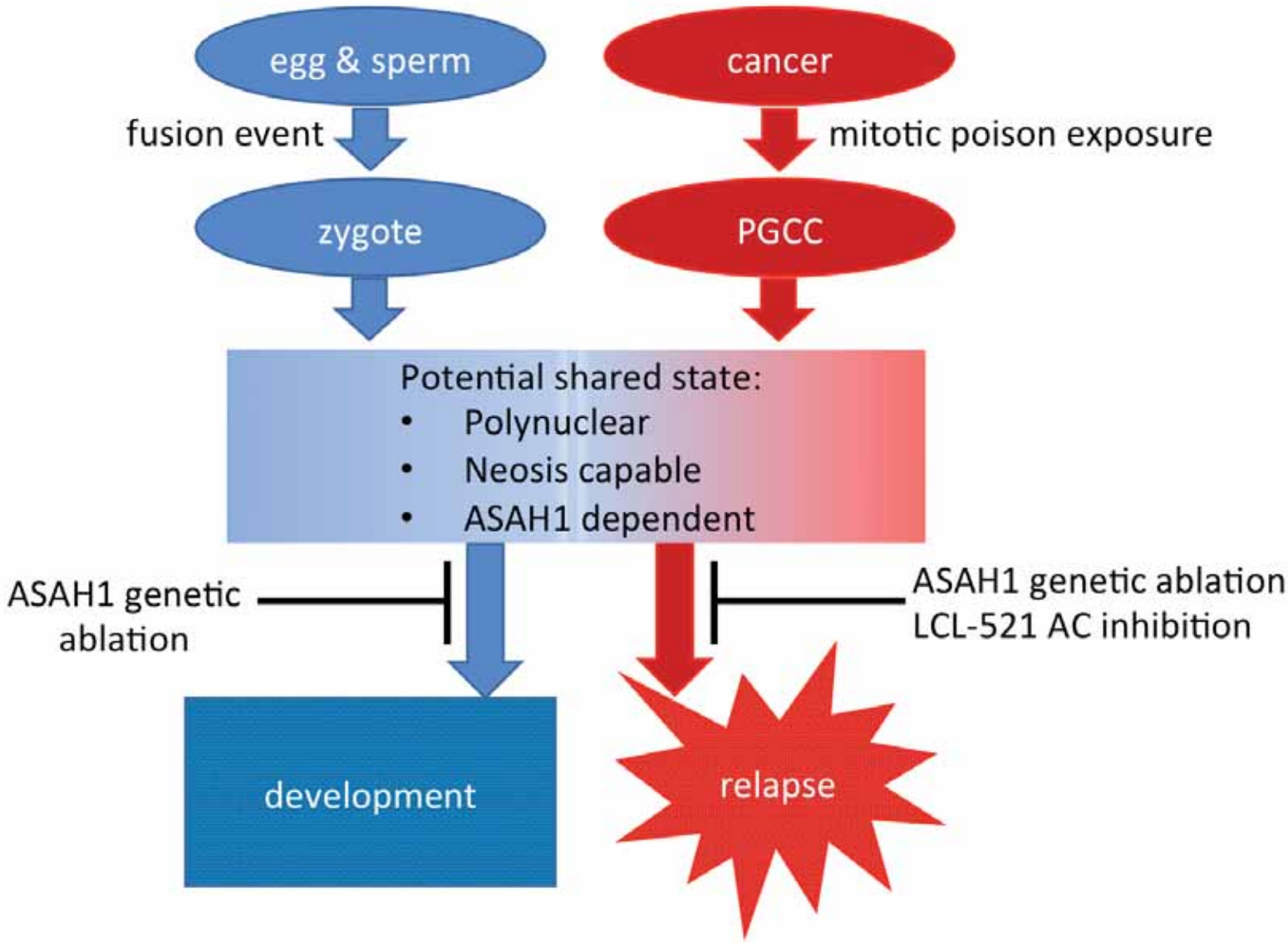
egg & sperm
cancer
fusion event
mitotic poison exposure
zygote
PGCC
Potential shared state:
• Polynuclear
• Neosis capable
• ASAH1 dependent
ASAH1 genetic ablation
ASAH1 genetic ablation
LCL-521 AC inhibition
development
relapse

Currently extending these findings

SCIENTIFIC REPORTS

Article | Open Access | Published: 07 August 2017

Complete Acid Ceramidase ablation prevents cancer-initiating cell formation in melanoma cells

Michele Lai, Natalia Realini, Marco La Ferla, Ilaria Passalacqua, Giulia Matteoli, Anand Ganesan, Mauro Pistello, Chiara Maria Mazzanti & Daniele Piomelli

melanoma

(-) acid ceramidase

ovarian

Oncotarget

Open Access Impact Journal

Oncotarget. 2017 Dec 22; 8(68): 112662–112674.
Published online 2017 Nov 7. doi: 10.18632/oncotarget.22637

PMCID: PMC5762539
PMID: 29348854

Acid ceramidase and its inhibitors: a *de novo* drug target and a new class of drugs for killing glioblastoma cancer stem cells with high efficiency

Ninh B. Doan,[1,2] Hisham Alhajala,[3] Mona M. Al-Gizawiy,[4] Wade M. Mueller,[2] Scott D. Rand,[4] Jennifer M. Connelly,[5] Elizabeth J. Cochran,[6] Christopher R. Chitambar,[3] Paul Clark,[7] John Kuo,[7] Kathleen M. Schmainda,[3,8] and Shama P. Mirza[1,9,10]

glioblastoma

Do any available drugs downregulate AC?

ELSEVIER

Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids

Volume 1831, Issue 12, December 2013, Pages 1657-1664

Novel off-target effect of tamoxifen — Inhibition of acid ceramidase activity in cancer cells

Samy A.F. Morad [a, 1, 2], Jonathan C. Levin [a], Su-Fern Tan [b], Todd E. Fox [c], David J. Feith [b], Myles C. Cabot [a] [2]

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https://doi.org/10.1016/j.bbalip.2013.07.016

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Highlights

- Tamoxifen inhibits acid ceramidase (AC) activity in intact cancer cells.

Registry based research might shed light on this

Cancer

Original Article | Free Access

Lung cancer mortality risk among breast cancer patients treated with anti-estrogens†‡

Christine Bouchardy MD, Simone Benhamou DSc, Robin Schaffar MSc, Helena M. Verkooijen MD, Gerald Fioretta MSc, Hyma Schubert MSc ... **See all authors**

Conclusions: Patients on tamoxifen did not differ in their incidence of lung cancer, but DID have better survival. Is this really because of anti-estrogen action, or could it be related to anti-acid ceramidase action? Note that this might be hard to pull apart because acid ceramidase is downstream of estrogen signaling!

Registry based research might shed light on this

Breast Cancer Research and Treatment
January 2013, Volume 137, Issue 2, pp 465–470 | Cite as

Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients

Authors Authors and affiliations

Holm Eggemann, Atanas Ignatov, Bobbie J. Smith, Udo Altmann, Gunter von Minckwitz, Freidrich W. Röhl, Mark Jahn, Serban-Dan Costa

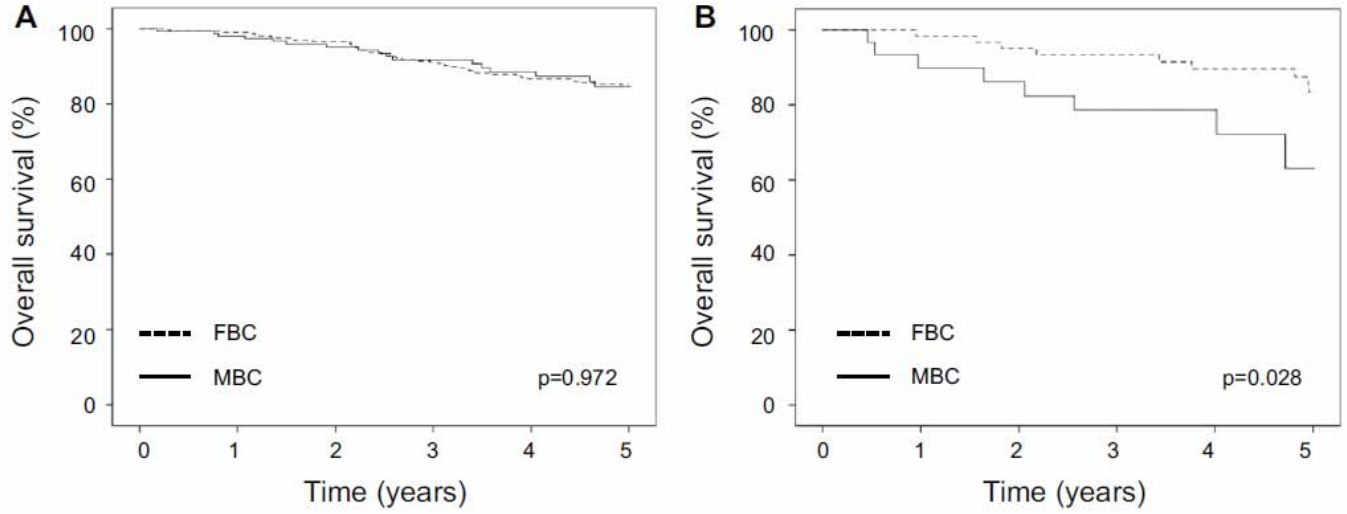
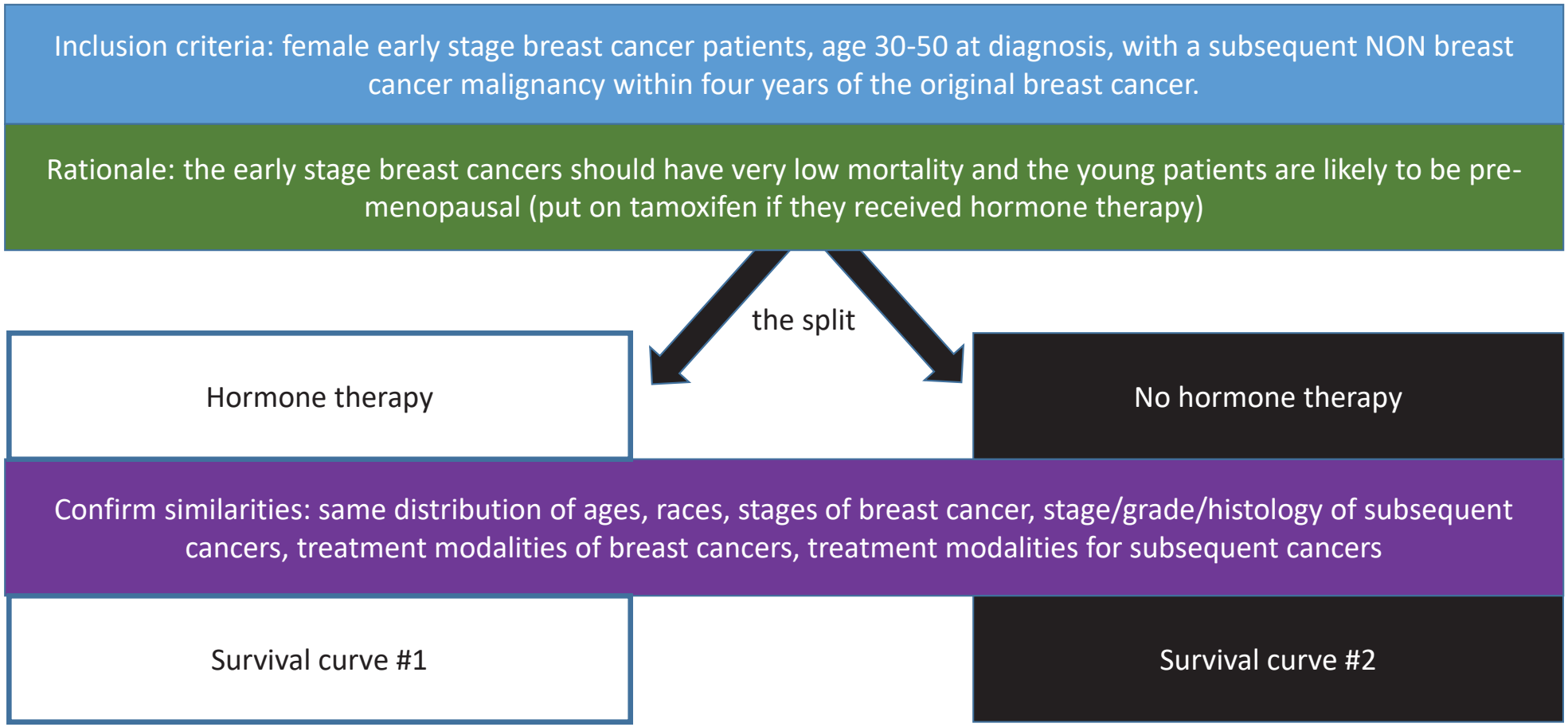


Fig. 2 Kaplan–Meier analysis of overall survival for patients treated with **a** TAM or **b** AI. *AI* aromatase inhibitor, *FBC* female breast cancer, *MBC* male breast cancer, *HER2* human epidermal growth factor receptor 2, *TAM* tamoxifen

Our current study



Conclusions

- Recurrence is by definition distant in time from the original cancer, making it harder to code and harder to study
- Recurrence is often more aggressive and resistant than the original cancer, making it harder to treat
- Recurrent cancer cells may have been through a process of de-differentiation (very early development, i.e. blastomeres)
- Recurrent tumors arising from this process may be more heterogeneous and disordered
- Acid ceramidase is required for blastomeres, and may be required for the dedifferentiation associated with recurrence
- Targeting mitosis without targeting neosis may leave behind a dangerous sub-population
- Tamoxifen may be one candidate drug to target neosis

Acknowledgements

- South Carolina State Central Cancer Registry
- North Carolina State Central Cancer Registry
- The Roper Hospital registry team
- Voelkel-Johnson lab at Hollings Cancer Center
- NIH PPG funding