

Photodynamic Priming Mitigates Chemoresistance and Mitochondrial Enhancements in Ovarian Cancer Cells with a History of Chronic Per- and Polyfluoroalkyl Substances (PFAS) Exposure

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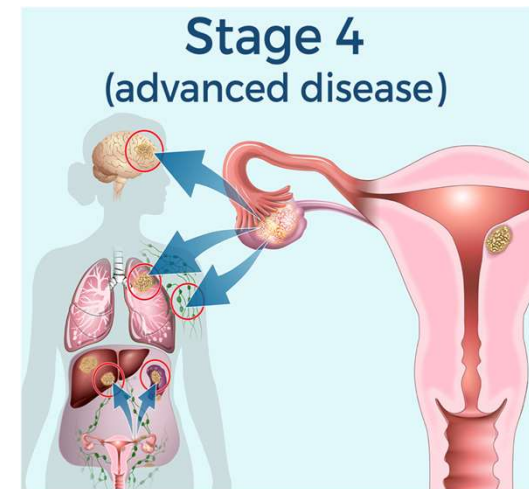
RASS Webinar, 10/14/26

Overview of Ovarian Cancer

- Ovarian cancer is the most lethal gynecologic malignancy with a mortality rate of ~65%
 - 2026: ~21,000 new cases, ~12,500 deaths¹
- Lack of early detection results in advanced-stage diagnoses



5-year survival: 89%

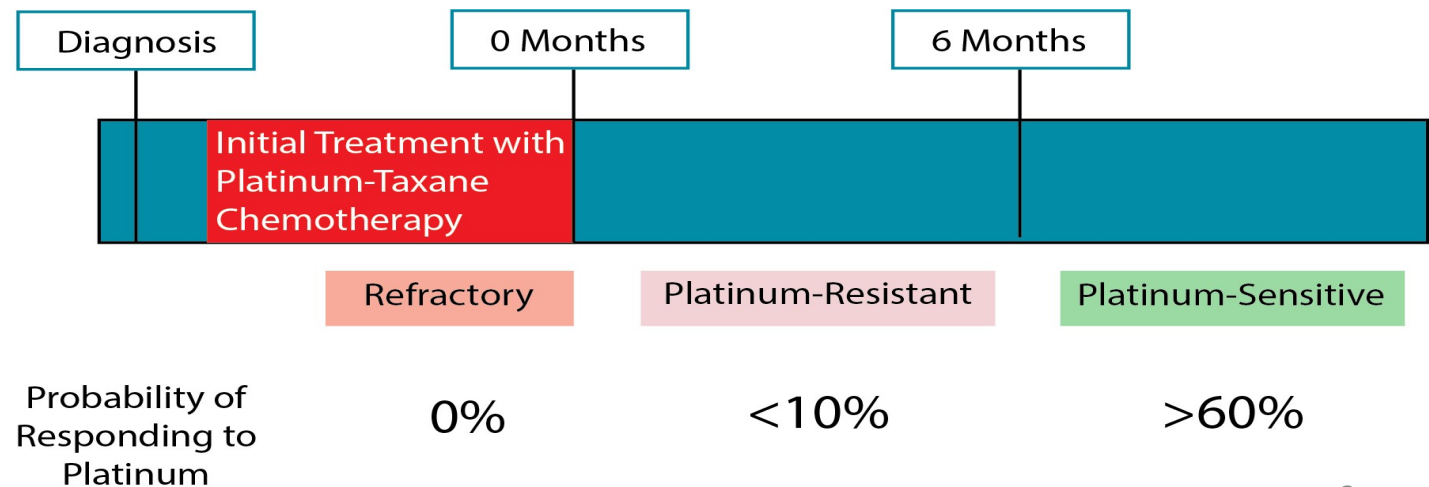


20%

¹ Siegel et al. ACS, 2026
Photos courtesy of ovarian.org

Treatment of Ovarian Cancer

- With advanced-stage ovarian cancer:
 - Patients receive debulking surgery to remove macroscopic tumors
 - Combination treatment with platinum- and taxane-based chemotherapy¹
- First line therapy is often effective!
 - BUT > 80% of patients recur and develop platinum-resistant disease
 - Median survival of 9-18 months²



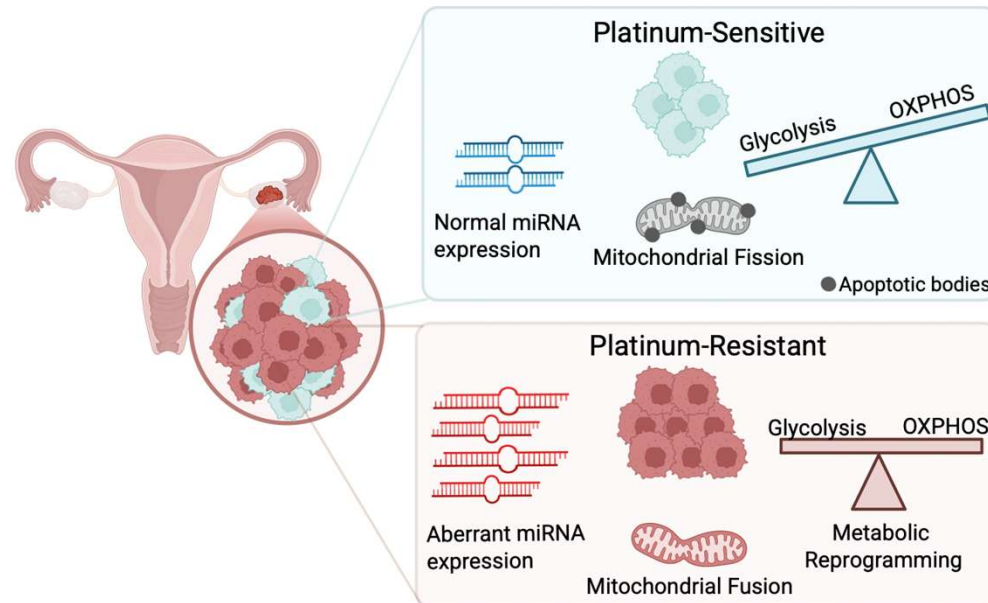
¹ Davis et al. Gyn Onc. 2014

² Nikolaidi et al. Front Onc. 2022

Timeline adapted from Colombo et al. Crit Rev Onc. 2014.

Causes of Platinum Resistance

- We're not really sure!
- Multiple variables including:
 - Alterations in DNA damage repair
 - Metabolic reprogramming
 - Alterations in mitochondrial dynamics



Causes of Platinum Resistance

- We're not really sure!
- Multiple variables including:
 - Alterations in DNA damage repair
 - Metabolic reprogramming
 - Alterations in mitochondrial dynamics
 - **Environmental stressors**

> [Int J Mol Sci.](#) 2022 May 5;23(9):5176. doi: 10.3390/ijms23095176.

Select Per- and Polyfluoroalkyl Substances (PFAS) Induce Resistance to Carboplatin in Ovarian Cancer Cell Lines

Brittany P Rickard ¹, Xianming Tan ^{2, 3}, Suzanne E Fenton ^{1, 4}, Imran Rizvi ^{1, 3, 5, 6}

> [Environ Res.](#) 2025 Nov 1;284:122211. doi: 10.1016/j.envres.2025.122211. Epub 2025 Jun 21.

Chronic PFAS exposure induces chemotherapy resistance by promoting mitochondria-related alterations in ovarian cancer cells

Brittany P Rickard ¹, Lauren A Sapienza-Lundie ², Marta Overchuk ³, Justin Tulino ³, Mateus Prates Mori ⁴, James P McCord ⁵, Vesna A Chappell ⁴, Carl D Bortner ⁶, Victoria L Bae-Jump ⁷, Janine H Santos ⁴, Suzanne E Fenton ⁸, Imran Rizvi ⁹

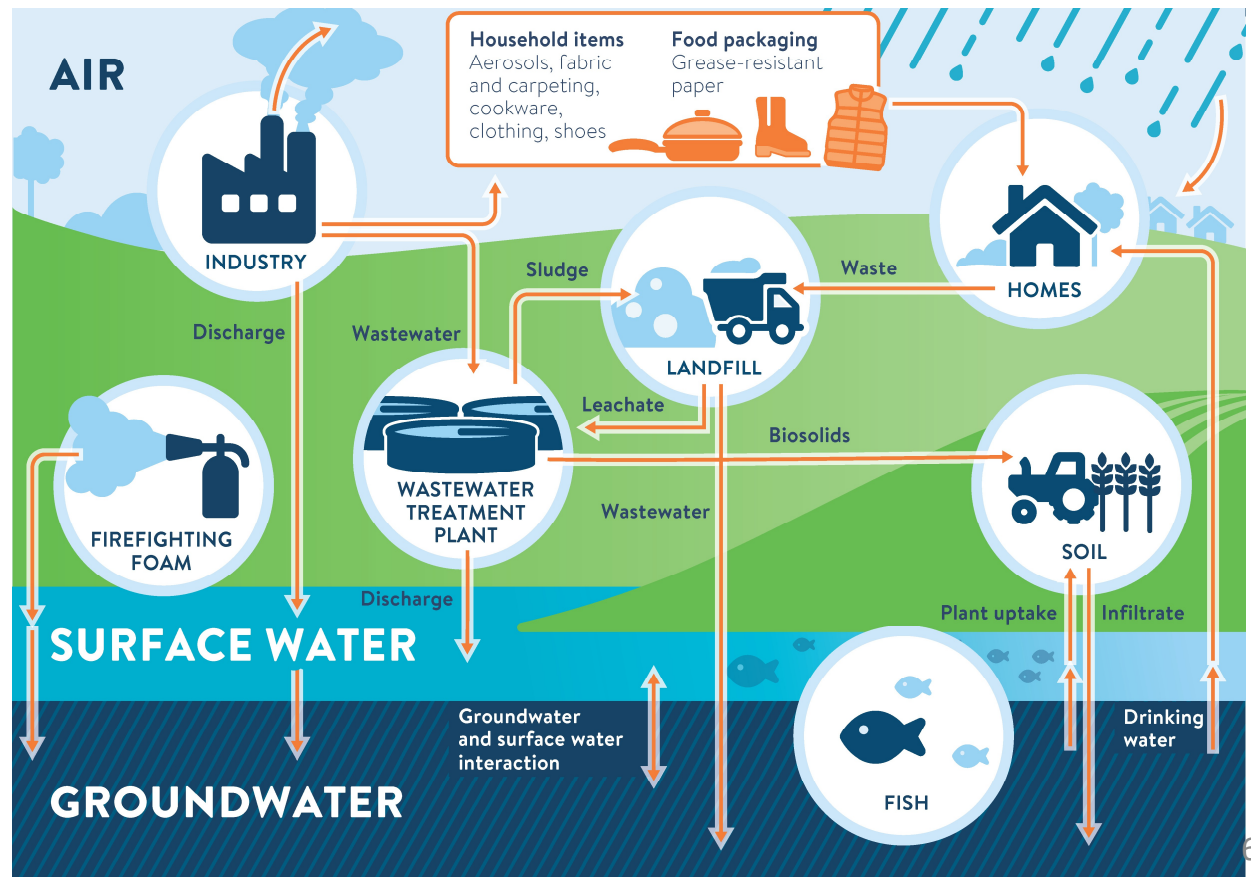
> [Environ Health.](#) 2023 Dec 14;22(1):87. doi: 10.1186/s12940-023-01034-2.

Exposure to select PFAS and PFAS mixtures alters response to platinum-based chemotherapy in endometrial cancer cell lines

Brittany P Rickard ^{1, 2}, Marta Overchuk ³, Justin Tulino ³, Xianming Tan ⁴, Frances S Ligler ⁵, Victoria L Bae-Jump ^{6, 7}, Suzanne E Fenton ^{1, 2}, Imran Rizvi ^{8, 9, 10, 11}

PFAS are Widespread Environmental Contaminants

- ~200 million Americans are living in a community with PFAS-contaminated drinking water



¹ Rickard et al. Toxicology (2022).
² Sunderland et al. J Expo Sci Environ Epidemiol (2019).

- ~200 million Americans are living in a community with PFAS-contaminated drinking water
- PFAS levels change across the life span (especially in women)

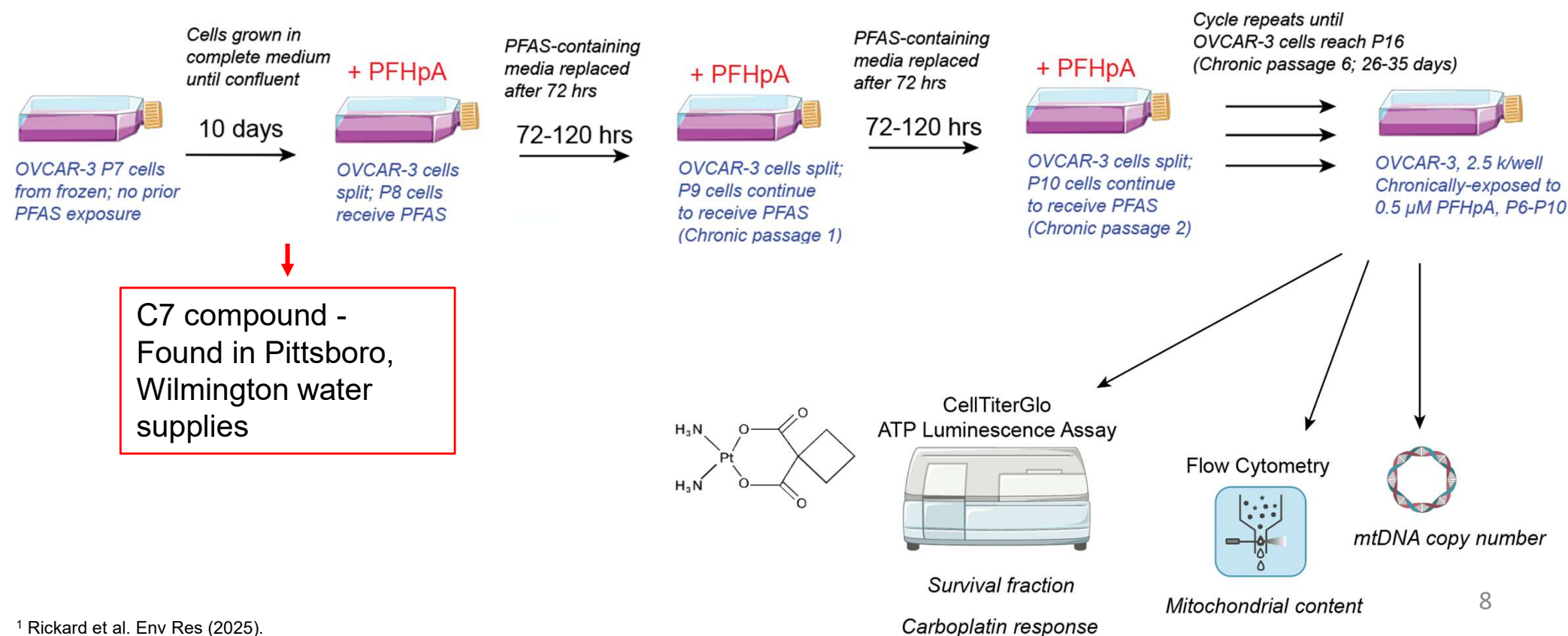
PFAS are Widespread Contaminants



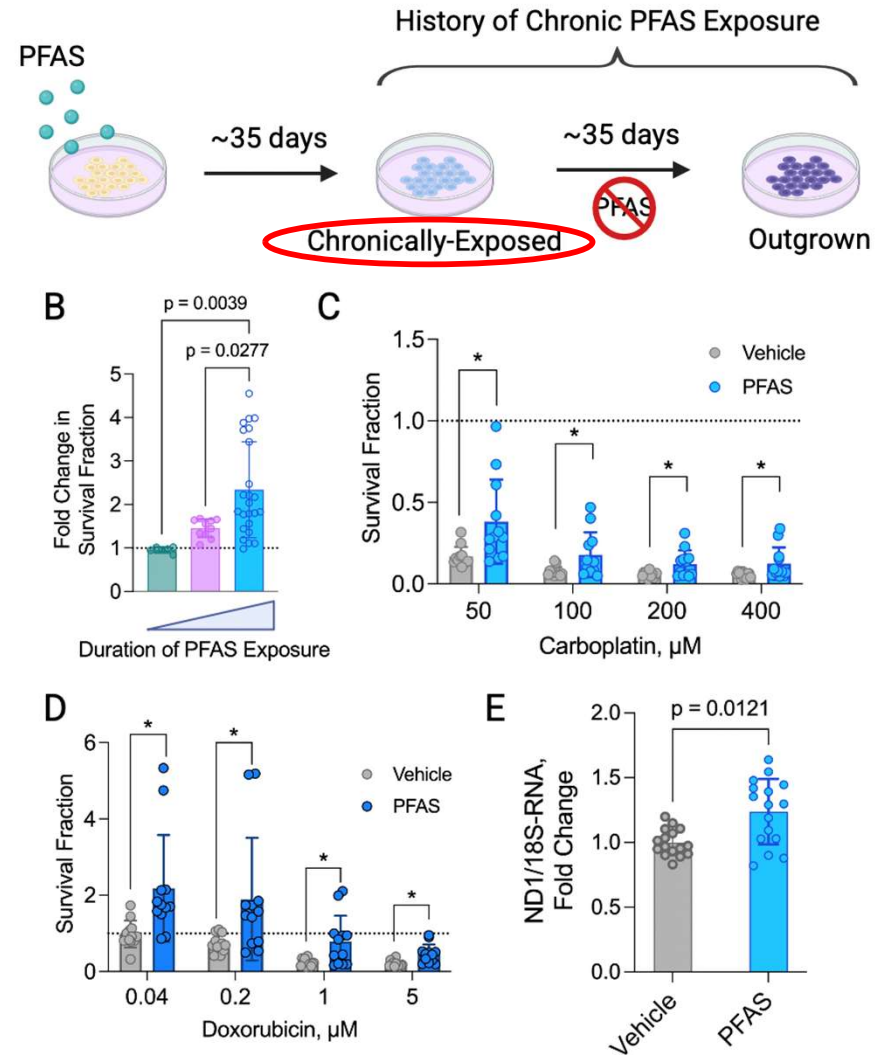
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Modeling Chronic PFAS Exposure in Ovarian Cancer Cell Lines

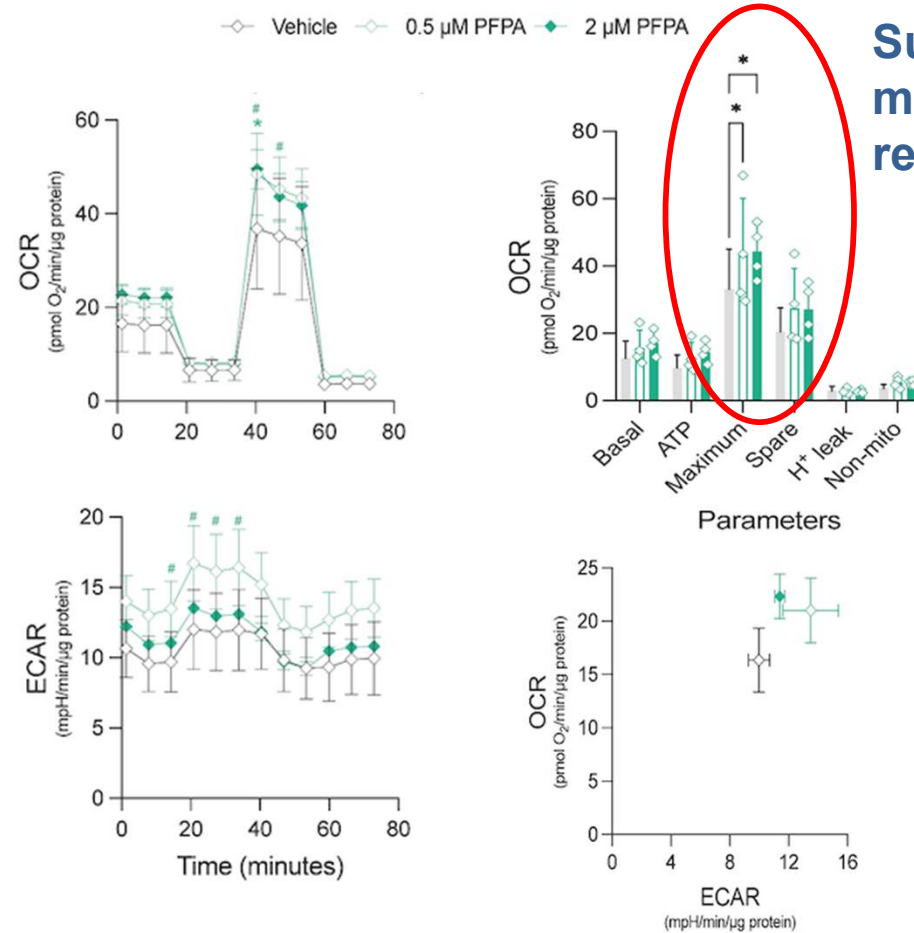


Chronic PFAS Exposure Induces Aggressive Ovarian Cancer Phenotypes



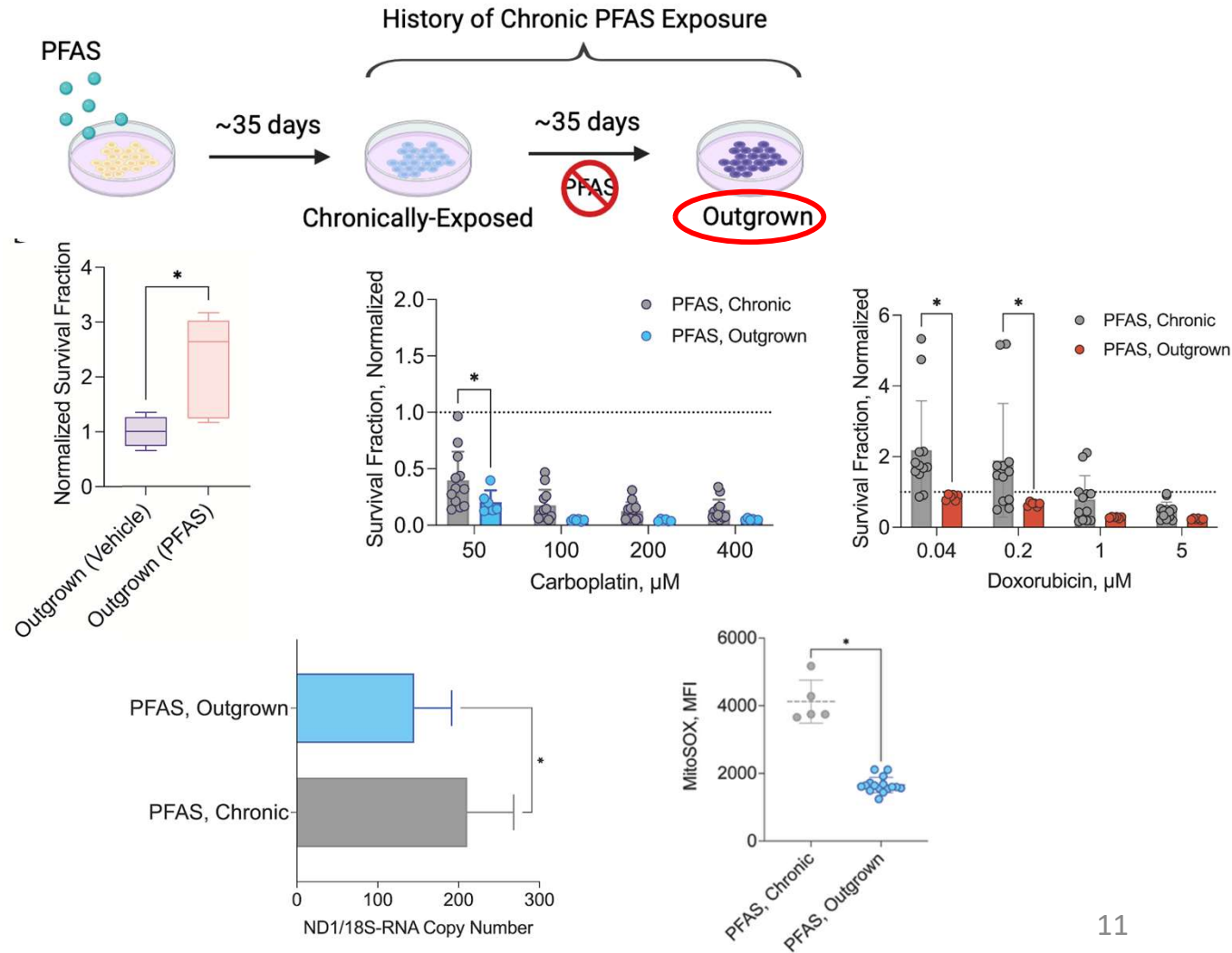
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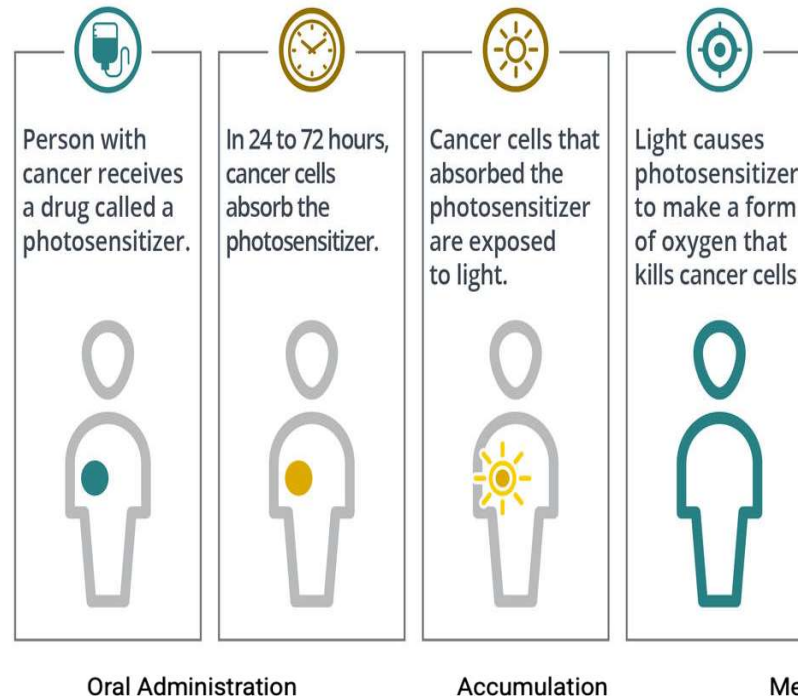


Suggestive of metabolic reprogramming!

Cells Allowed to “Recover” from PFAS Exposure Can Revert to Baseline Phenotypes

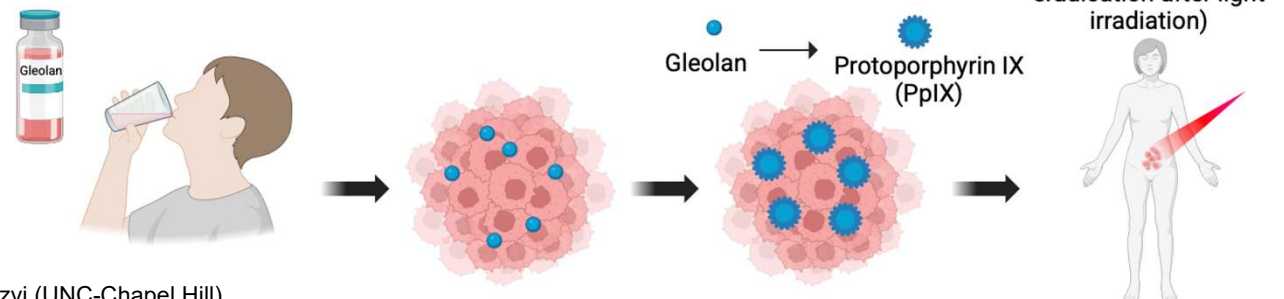


Harnessing Visible Light to **Kill** Chemoresistant Cell Populations

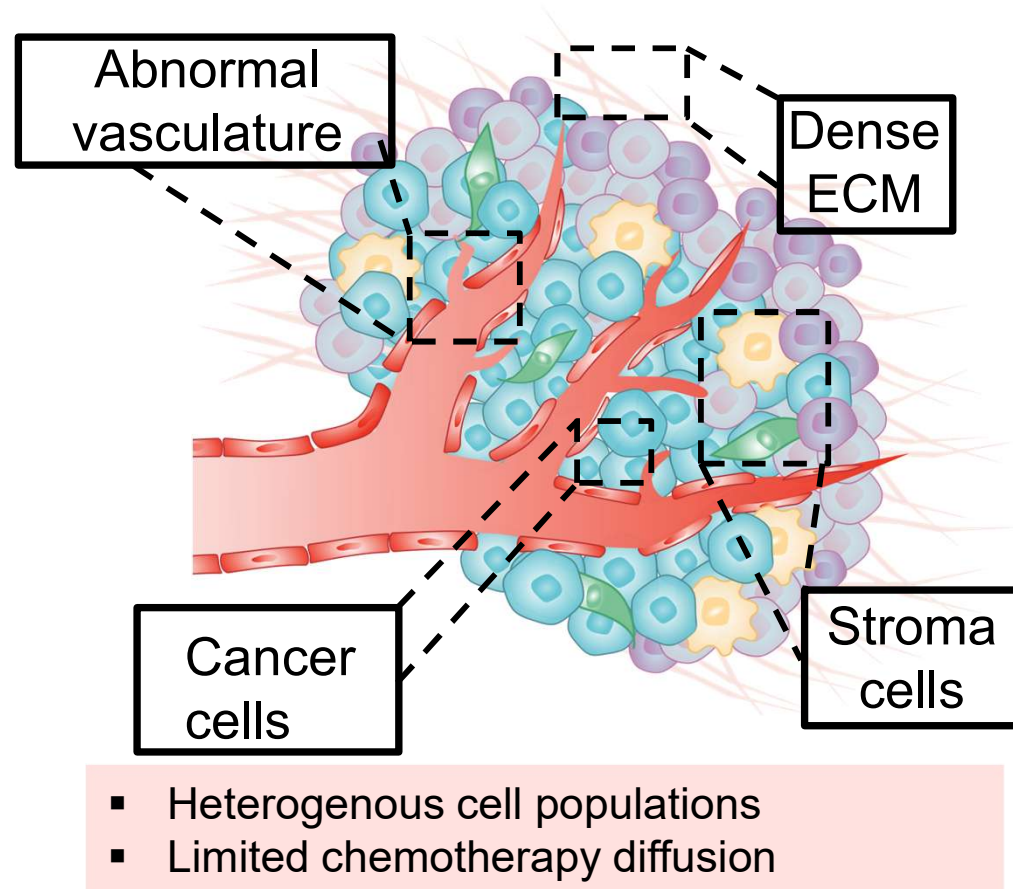


Photosensitizers used:

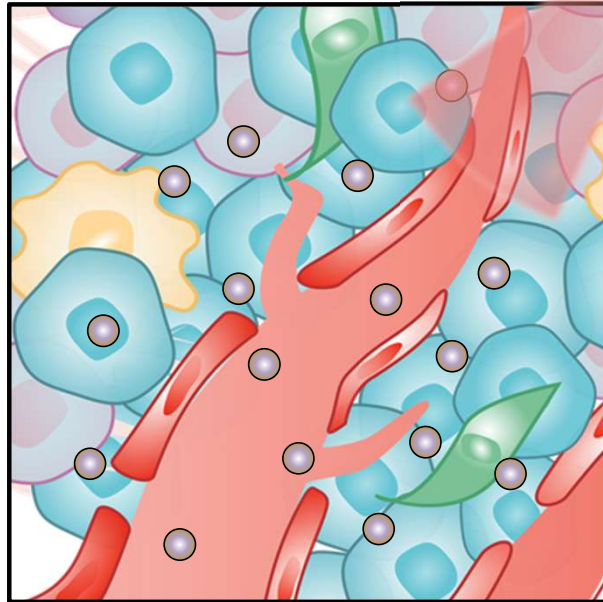
- **Benzoporphyrin derivative (BPD)**
- **Aminolevulinic acid-induced protoporphyrin IX (ALA-PpIX)**



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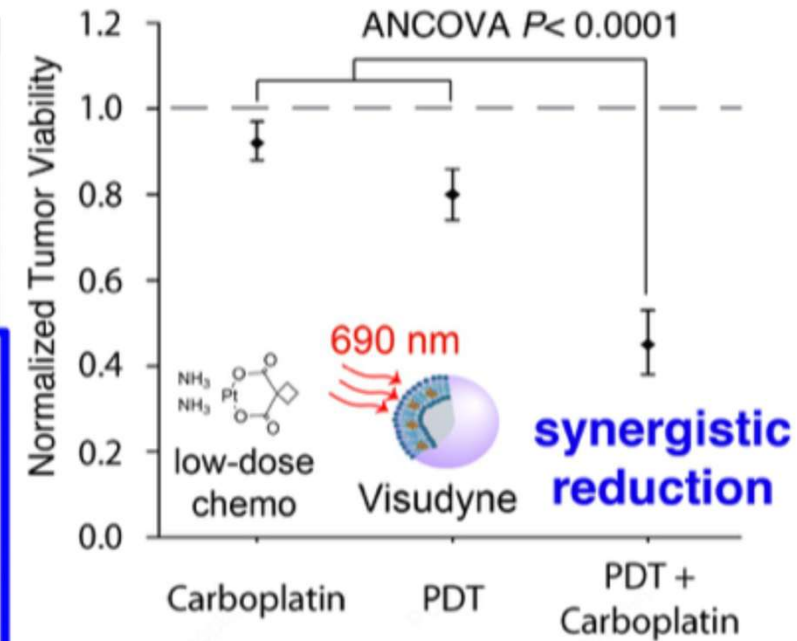
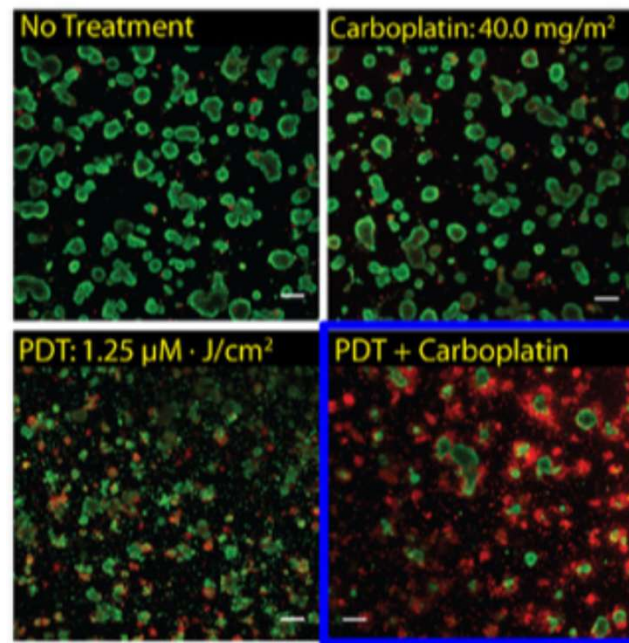


- **↑ vessel leakiness**
(Snyder, Cancer Res, 2003)
- **↓ solid stress**
(Sano, ACS Nano, 2013)
- **↑ mitochondrial photodamage** (Kessel, Photochem Photobiol, 2014)

Therapeutic PDT doses have been shown to decrease tumor microenvironmental barriers and enhance chemotherapy accumulation & efficacy.

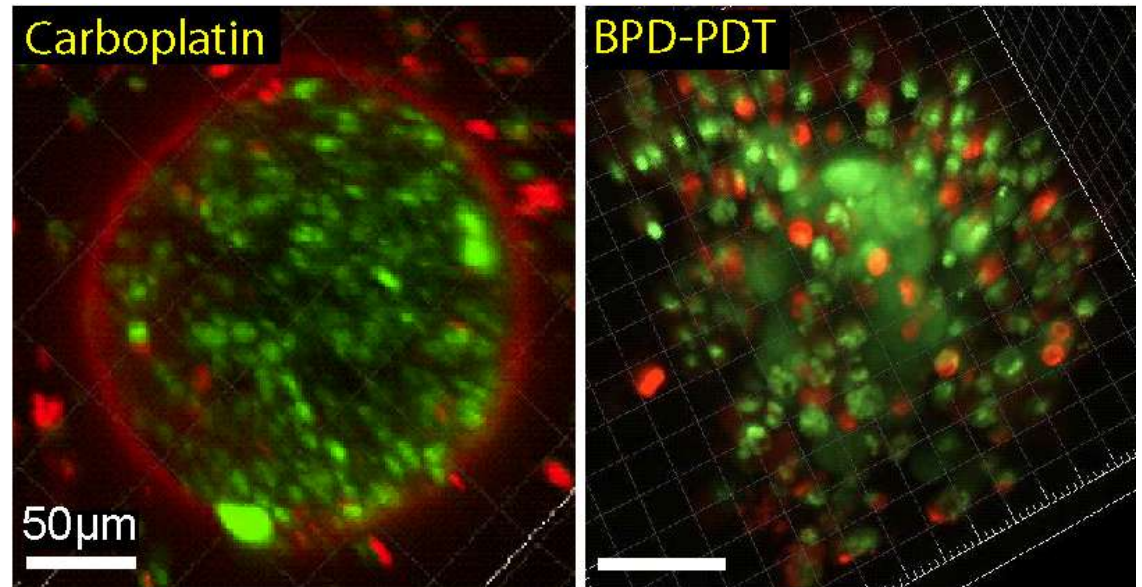
¹ Overchuk et al, Biomaterials (2018).

PDT Overcomes Chemoresistance in Ovarian Cancer



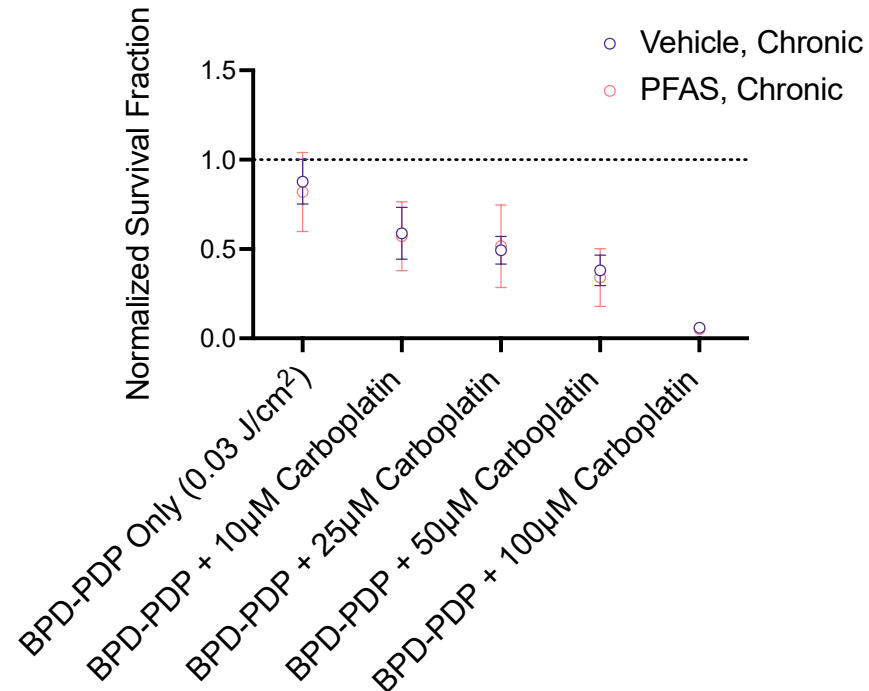
PDT synergizes with chemotherapy to induce cell death.

PDT Penetrates Ovarian Cancer Spheroids to Kill Tumor Cells



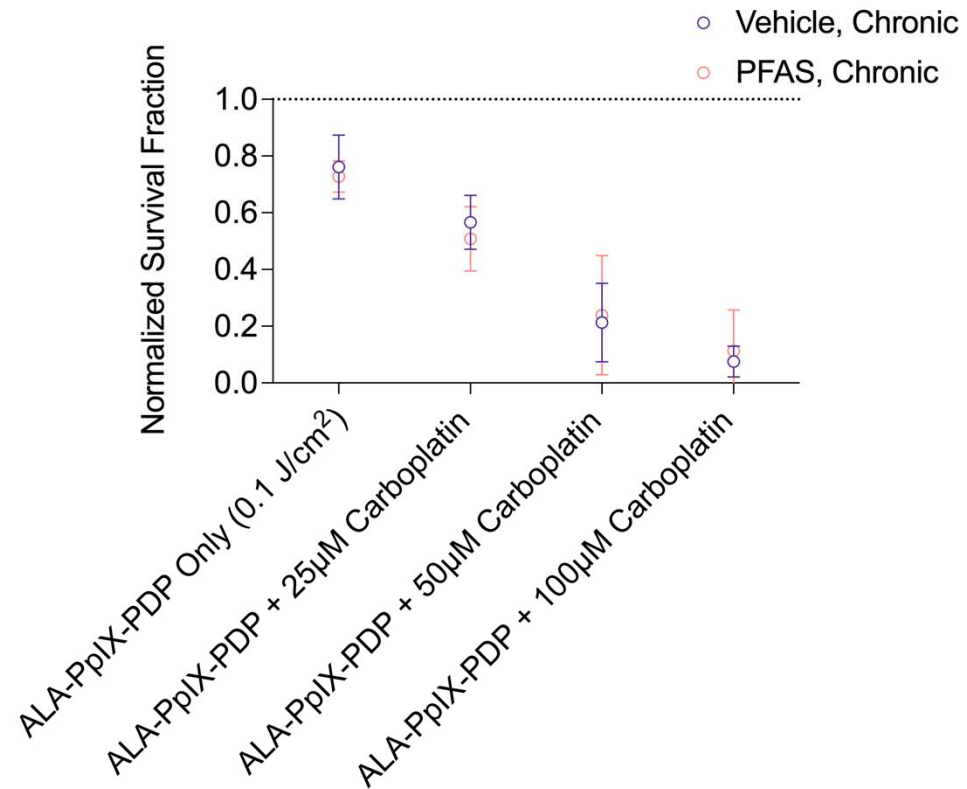
PDT toxicity penetrates through 3D nodules, while carboplatin toxicity is limited to tumor edge.

PDP Combinations Overcome PFAS- Induced Chemoresistance



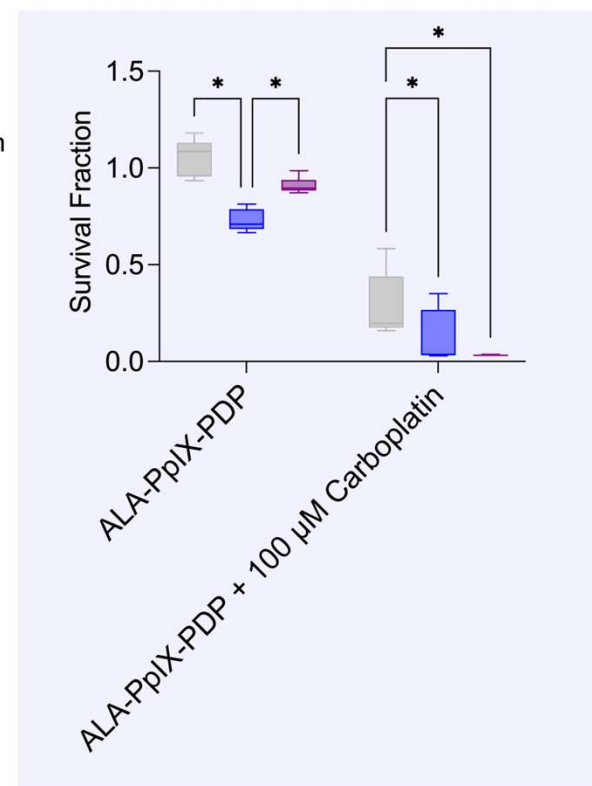
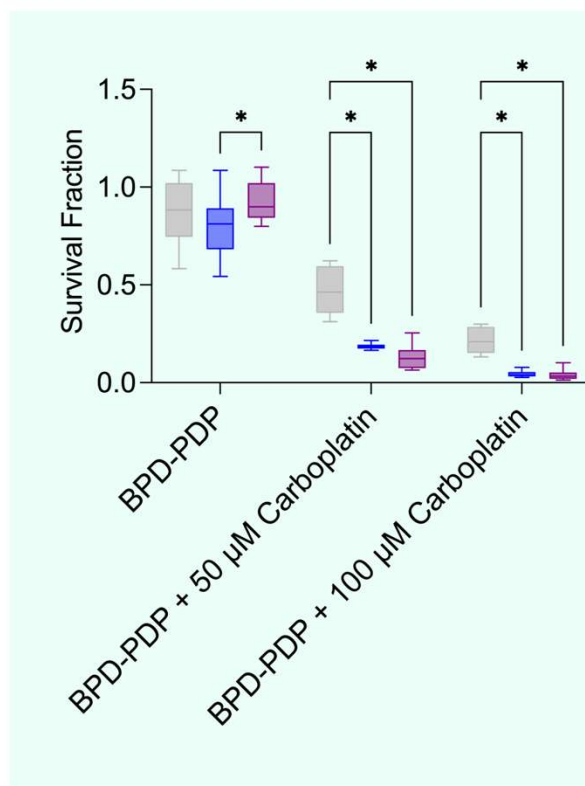
Low-dose PDT (PDP) + low-dose carboplatin overcomes chemoresistance induced by PFAS exposure.

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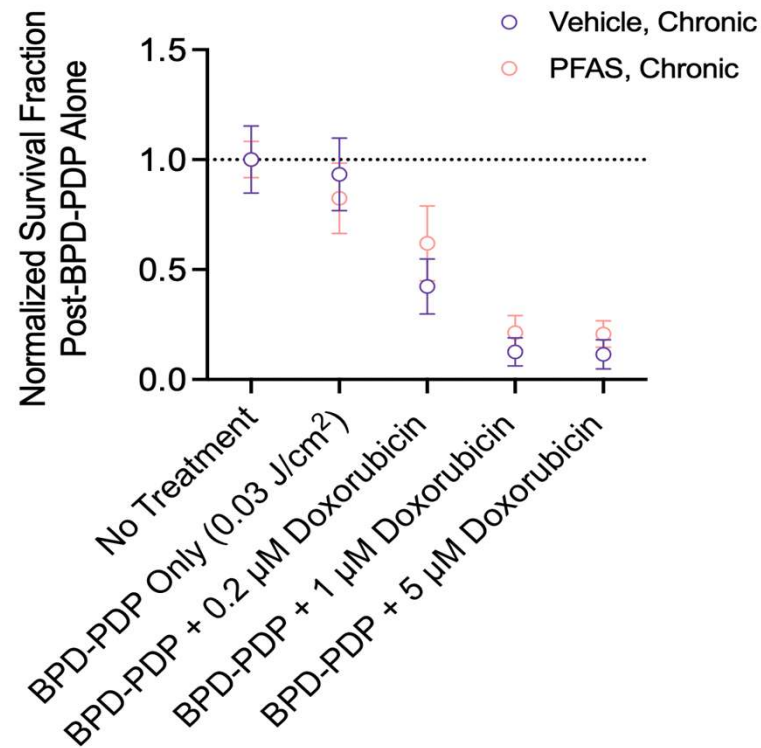
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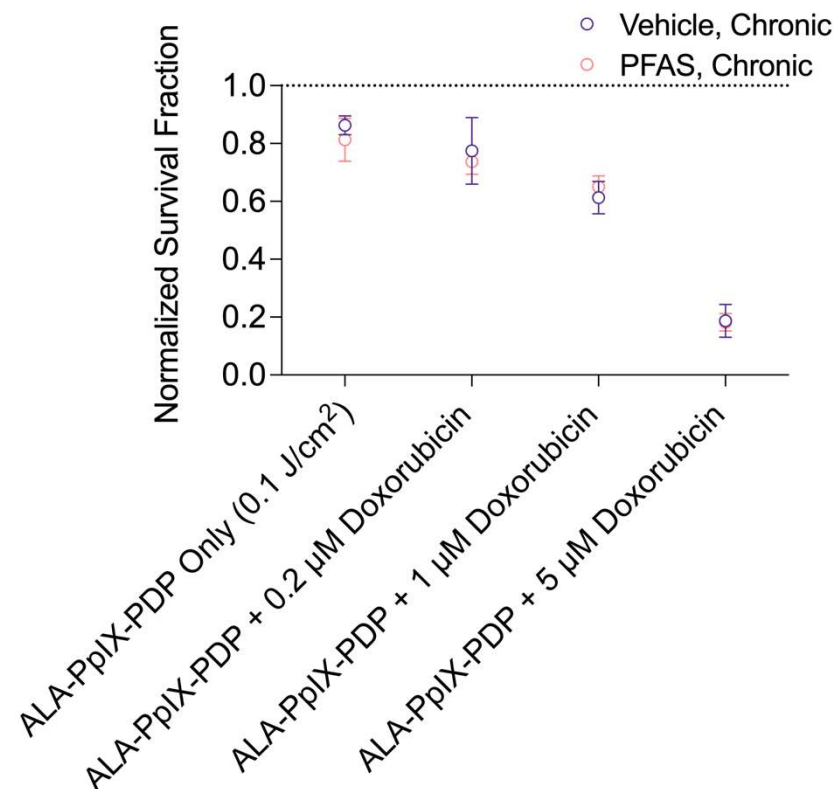
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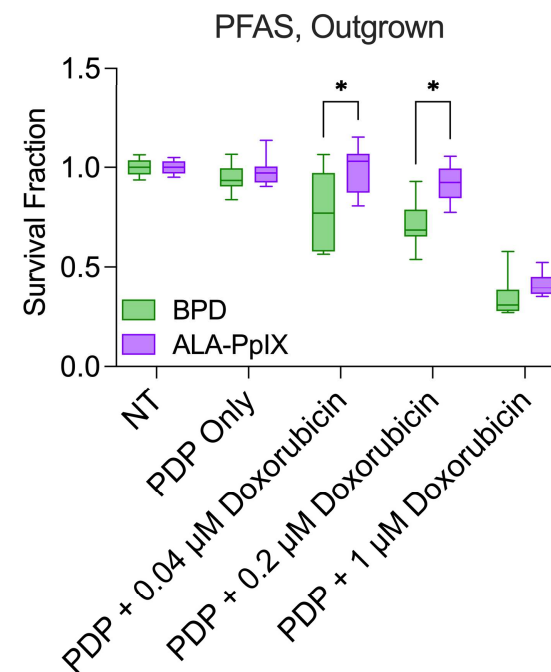
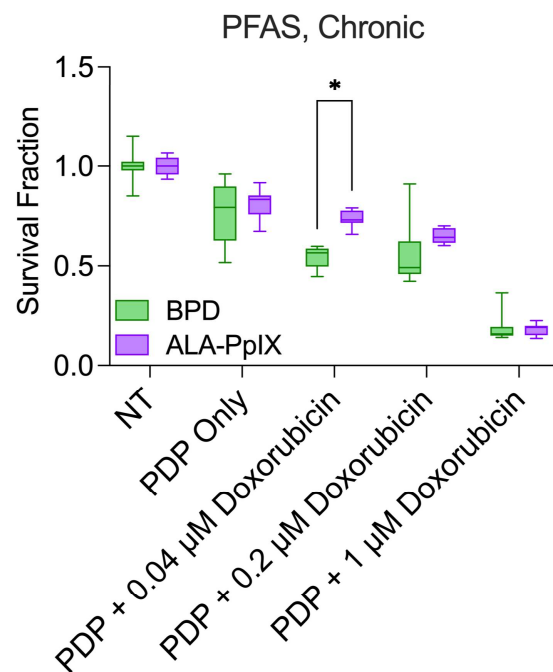
Low-dose PDT (PDP) + doxorubicin overcomes chemoresistance induced by PFAS exposure.

PDP Combinations Overcome PFAS- Induced Chemoresistance



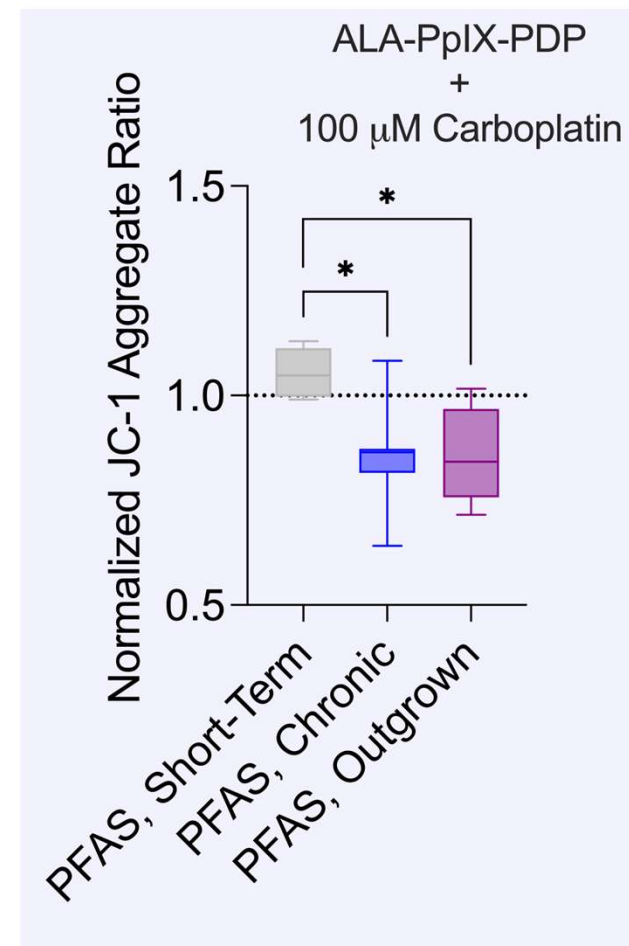
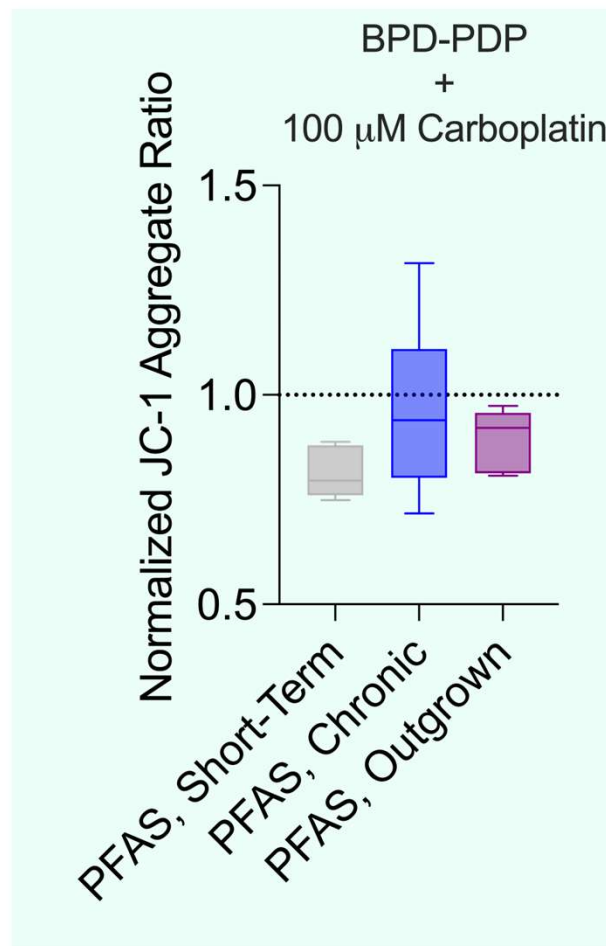
Low-dose PDT (PDP) + doxorubicin overcomes chemoresistance induced by PFAS exposure.

Efficacy of PDP-based Combinations Differ by Photosensitizer

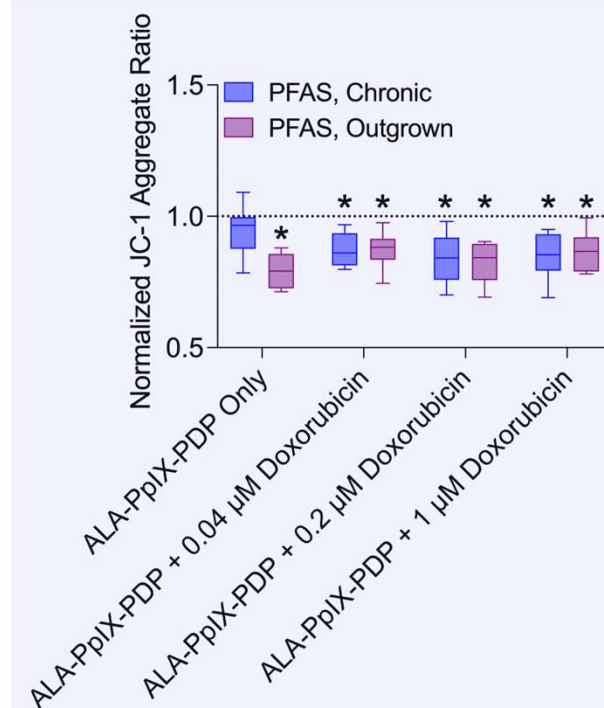
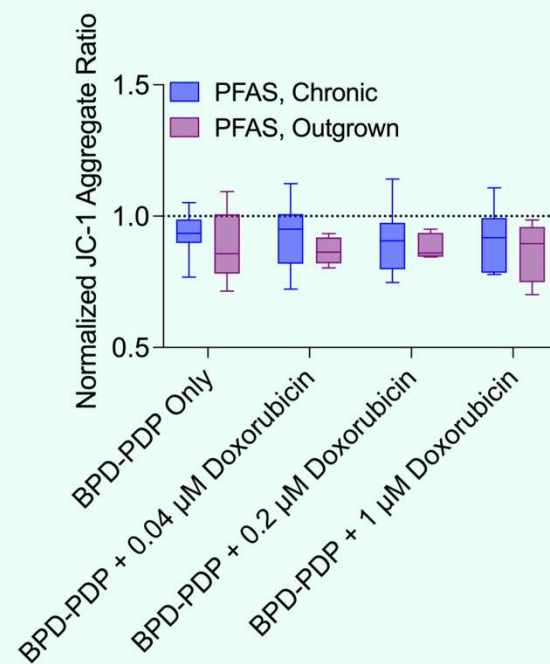


BPD-PDP, rather than ALA-PpIX-PDP, is more potent when combined with doxorubicin in cells with prior PFAS exposure.

ALA-PpIX-PDP Induces More Potent Effects on Mitochondrial Membrane Potential

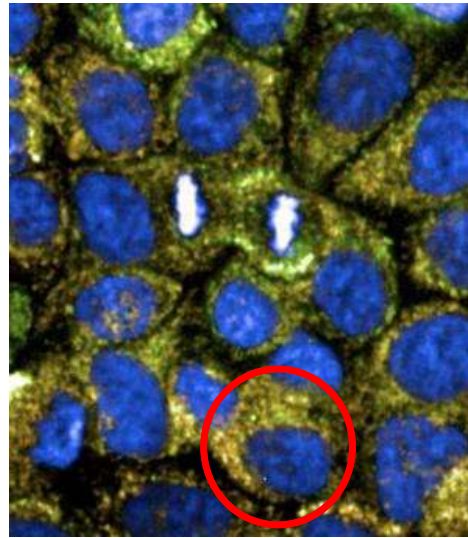


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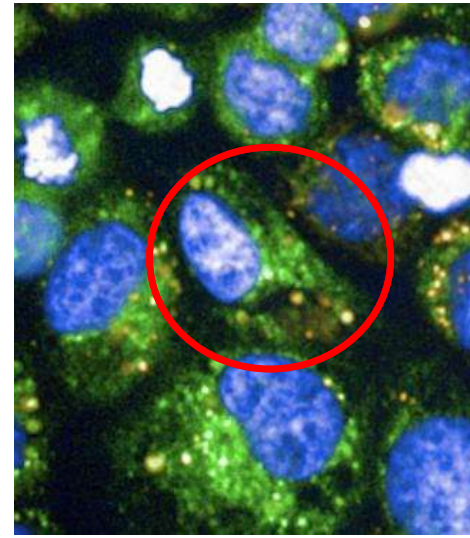


ALA-PpIX-PDP-based combinations, especially with doxorubicin, decrease mitochondrial membrane potential more than BPD-PDP.

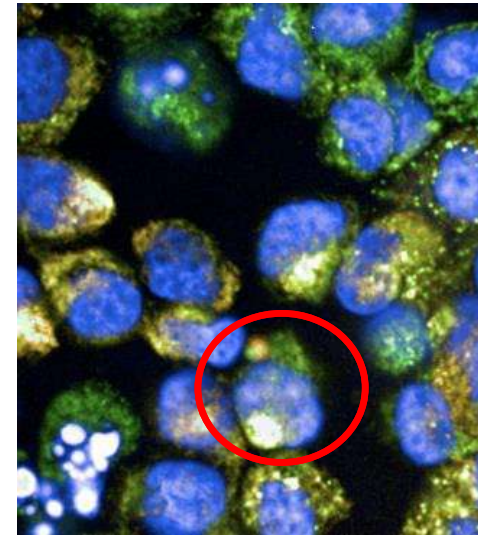
High Content Imaging Confirms Mitochondrial Damage



OVCAR-3, NT



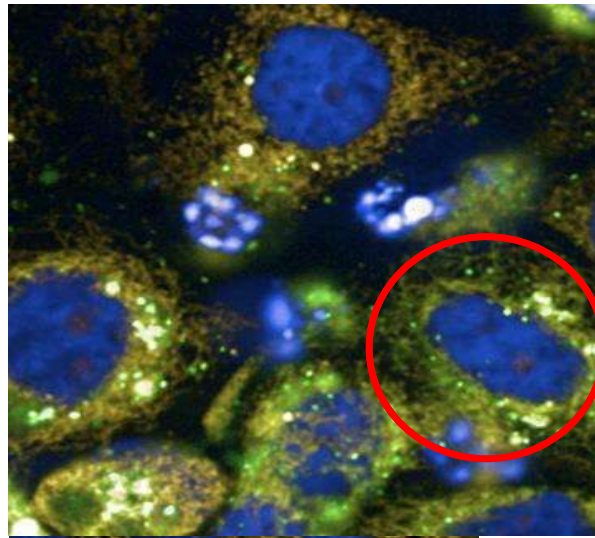
BPD-PDP,
0.03 J/cm²



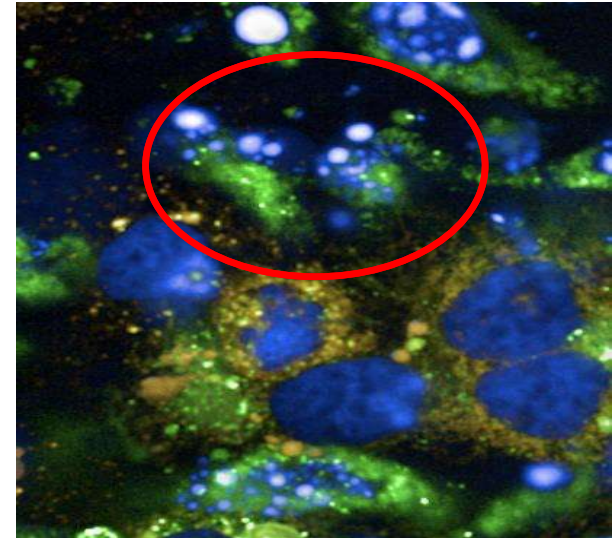
ALA-PpIX-PDP,
0.1 J/cm²

Mitochondrial membrane potential (orange) decreases in ALA- and BPD-PDP treated cells, mitochondrial content (green) decreases following both PDP types.

High Content Imaging Confirms Mitochondrial Damage and Cell Death

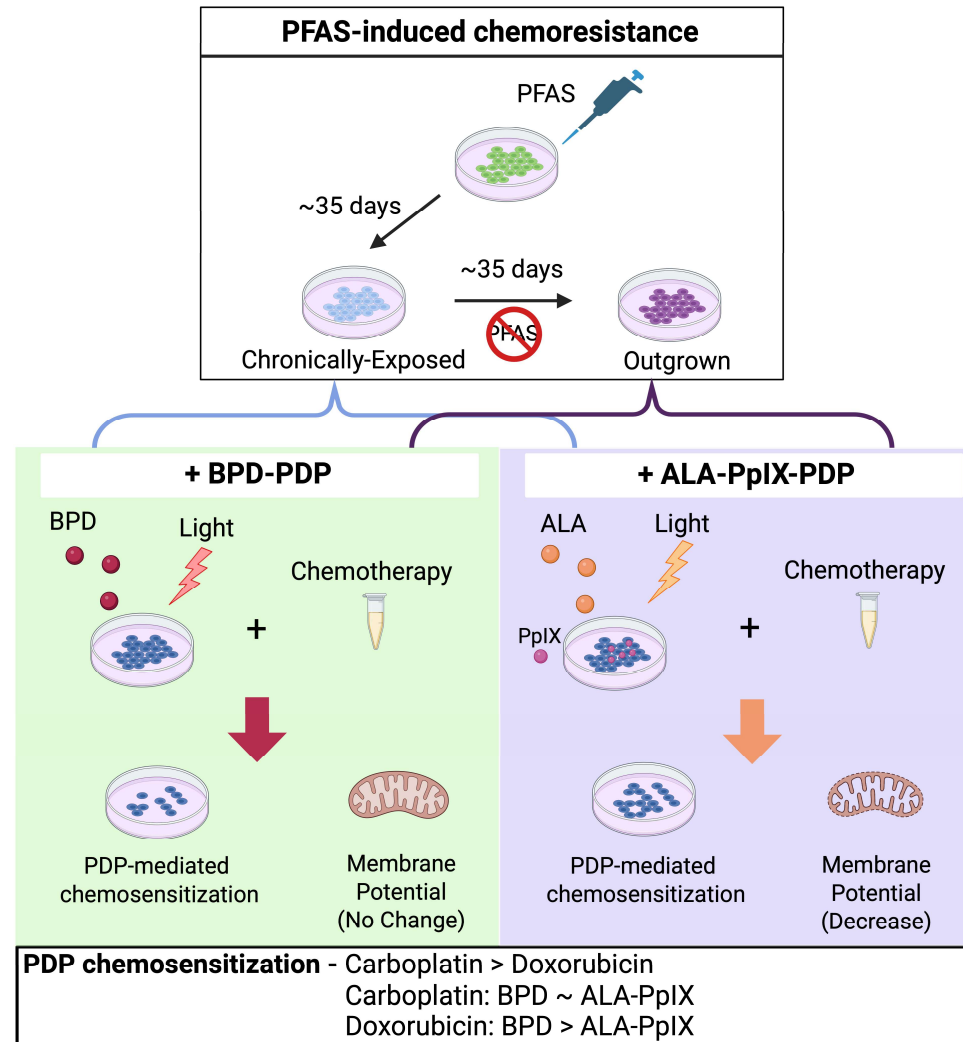


Carboplatin,
50 μ M



BPD-PDP +
12.5 μ M
Carboplatin,

Summary



Big Picture:

- Promote clinical integration of PFAS blood testing for women prior to receiving chemotherapy
- Promote clinical integration of mitochondria-localized PDP for the treatment of platinum-resistant ovarian cancer

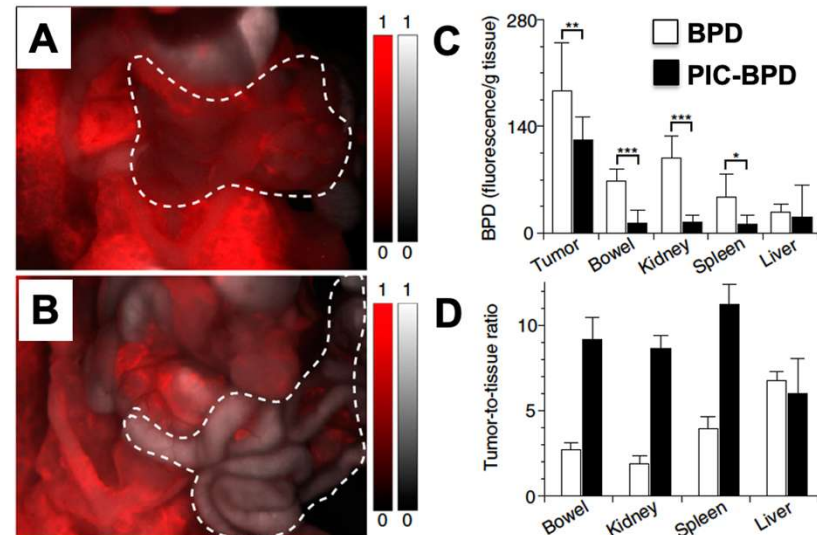
Next Steps (Targeted Photosensitizers)

- Untargeted photosensitizers pose off-target toxicity issues in preclinical and clinical studies
- PS-antibody conjugates, or photoimmunoconjugates (PICs) enable specific binding and receptor-mediated internalization via antigens overexpressed on the surface of cancer cells

BPD
(non-targeted)

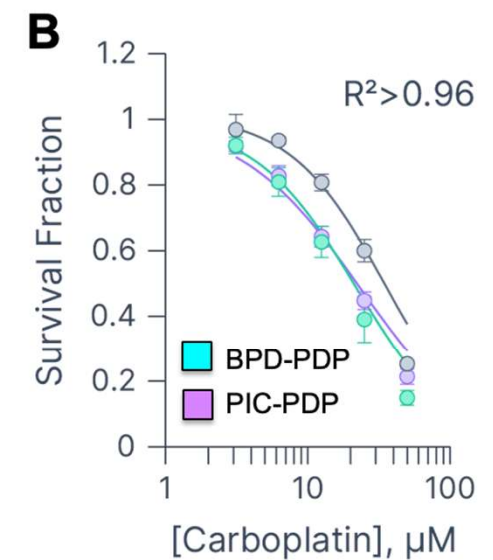
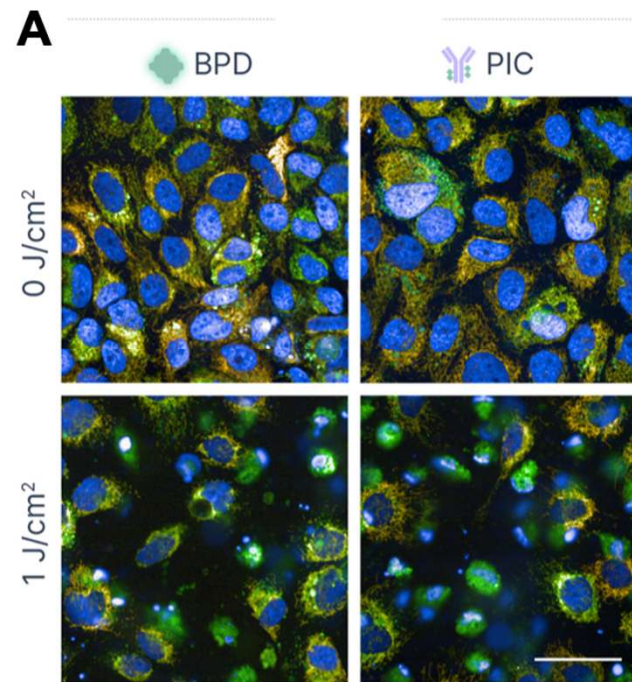


PIC-BPD
(targeted)



- When intracellular BPD concentrations are matched, BPD- and PIC-PDP efficacies align
- BPD-PDP appears to induce quicker, more potent mitochondrial toxicity than PIC-PDP

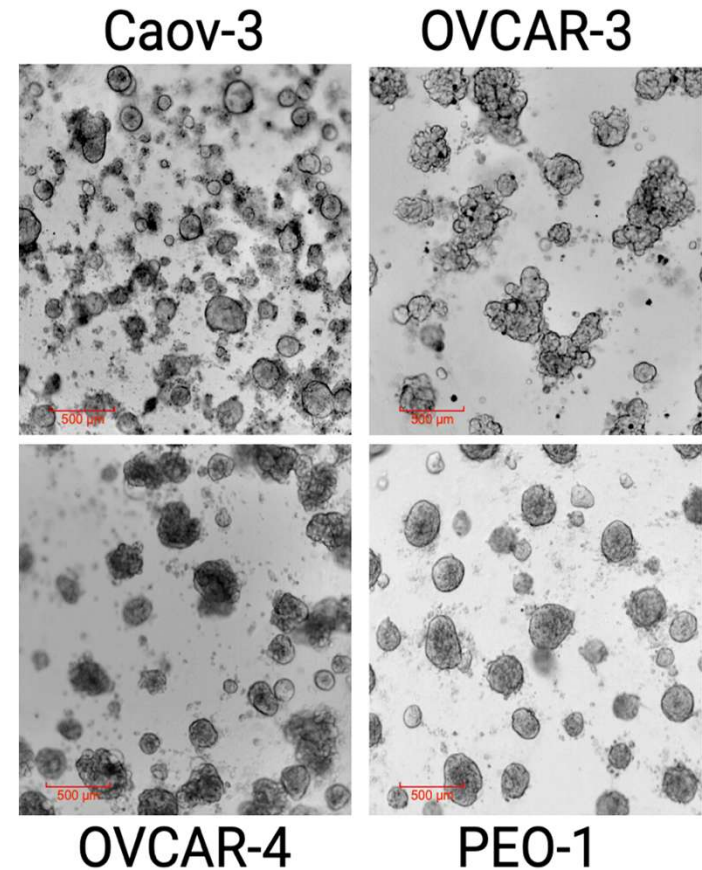
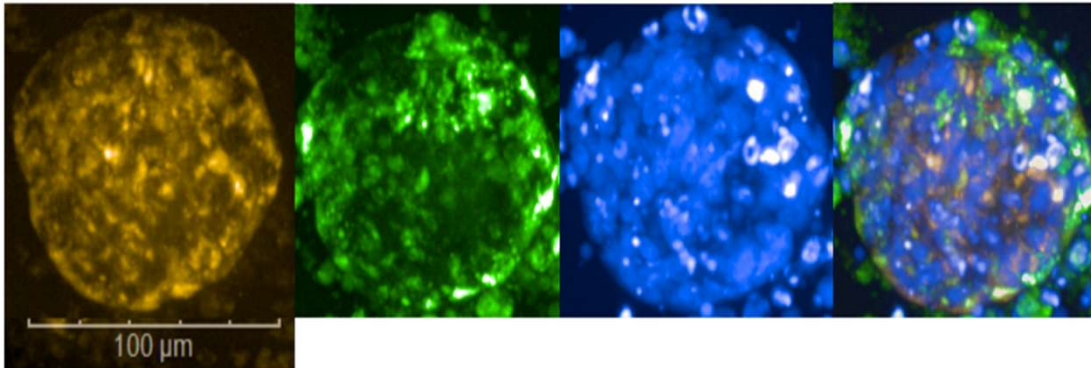
Next Steps (Targeted Photosensitizers)



	No PDP	BPD-PDP	PIC-PDP
IC50	35.7	22.0	23.6

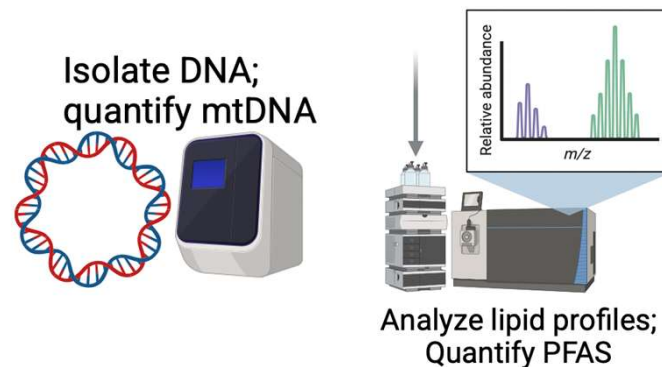
- Better represents physiological growth conditions (i.e. nodular structure)
- Resistance selection
- Longitudinal staining

Next Steps (Spheroids)



Next Steps (Patient Samples)

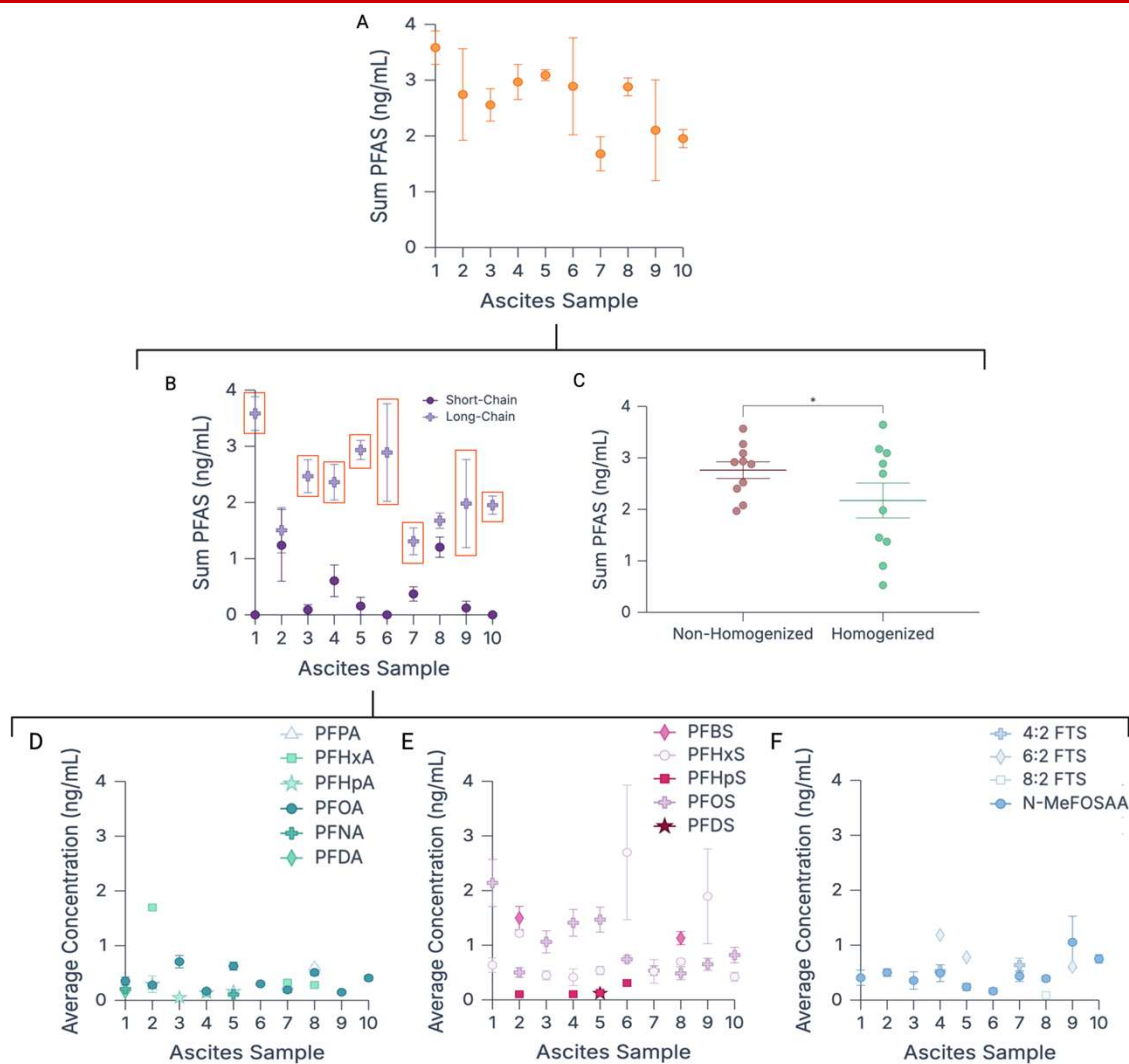
- Ascites samples
 - Collected at the University of Chicago
 - PIs: Hilary Kenny, Ernst Lengyel
 - 10 pilot samples sent so far
- Venous blood samples
 - Collected at the University of North Carolina
 - PI: Victoria Bae-Jump
 - 70 samples available and acquired
 - **Chemotherapy response data known**



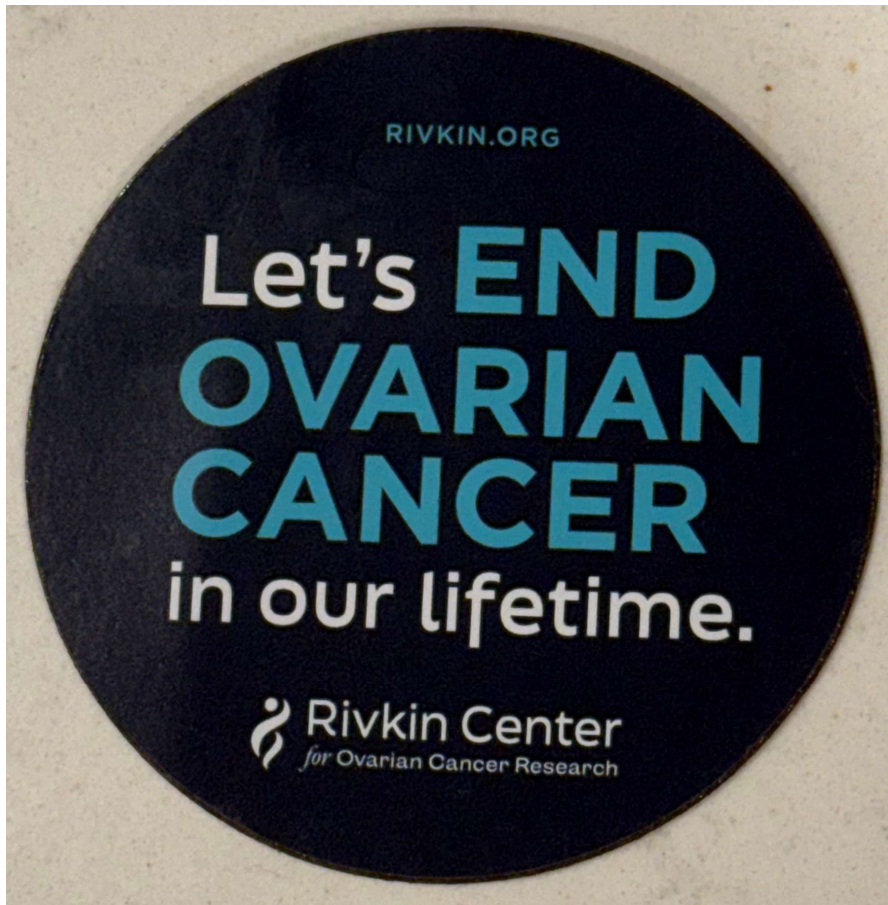
Next Steps (Patient Samples)

- Hot off the press!
 - PFAS are **universally detectable** in ascites fluid
 - Legacy compounds are the most prevalent
 - Levels are comparable to serum, based on previous studies
 - Levels are higher than other biological fluids, like urine or breast milk (also based on previous studies)

Next Steps (Patient Samples)



Acknowledgements



- **Fenton Lab (NC State):**
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 - Marta Overchuk, Ph.D.
 - Lauren A. Sapienza-Lundie, B.S.
 - Justin Tulino, B.S.
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- **University of Chicago:**
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