

Drug-Eluting Polymer Films:

*Sustained, Local Delivery of High-Dose Chemotherapy to
the Tumor Bed*

Chandrajit P Raut, MD, MSc

TARPSWG Annual Meeting at CTOS

Vancouver, Canada

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Brigham and Women's Hospital
Founding Member, Mass General Brigham

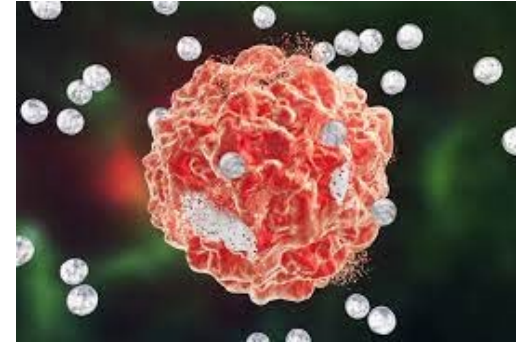


Dana-Farber
Cancer Institute

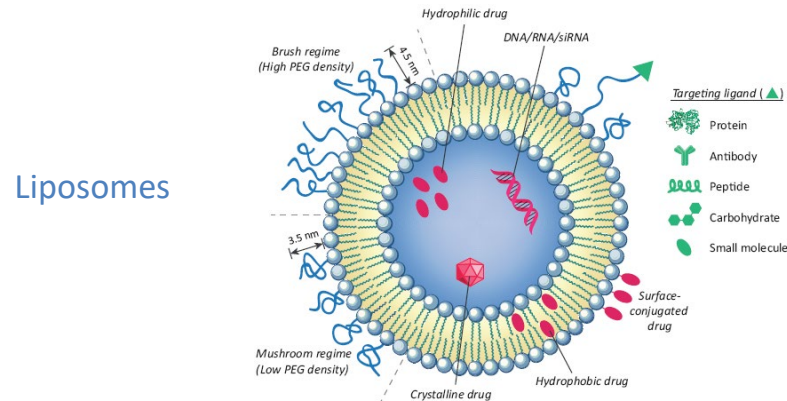


HARVARD
MEDICAL SCHOOL

Sustained Local Drug Delivery

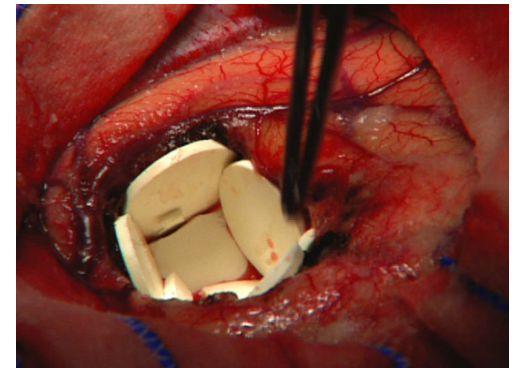


Nanoparticles and
Microspheres



Gladel®

Burst release:
50% in 4 hrs
70% in 24 hrs
100% in 5 days



Chemotherapy-Eluting Polymer Films

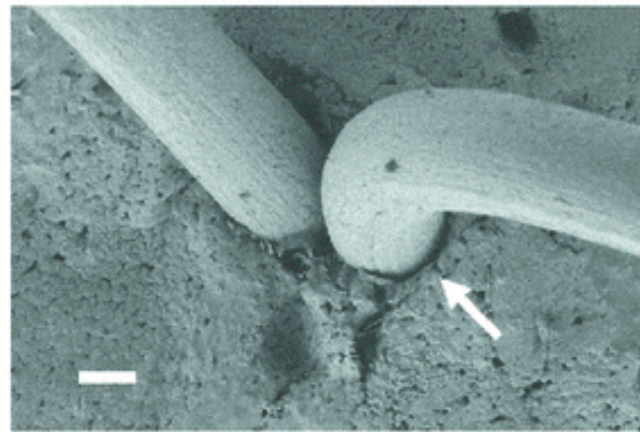
- Surgically implantable
- Established and scalable methods of manufacturing
- Safe, non-toxic, biodegradable materials
- Retained drug efficacy
- Sustained drug release > 4 wks
- Minimal burst release (< 10% cargo over 1st 3 days)
- Minimal systemic toxicity
- **Efficacy!**



Yolonda L Colson, MD, PhD

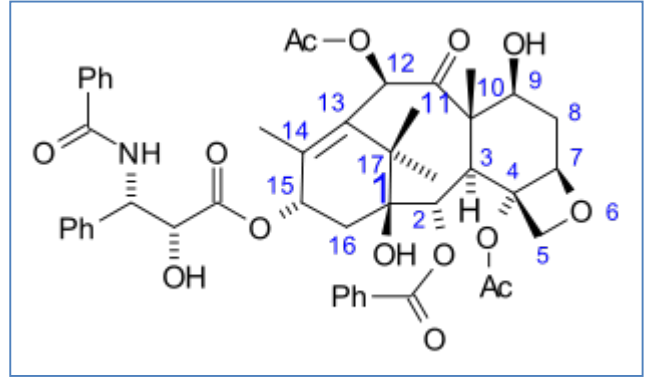
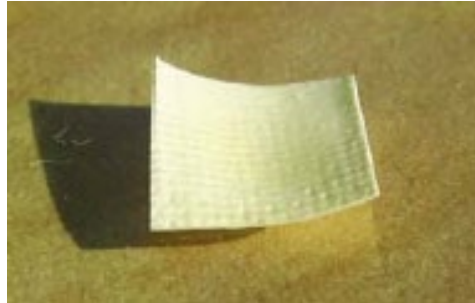
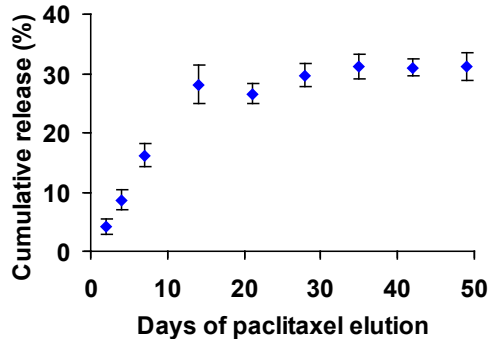
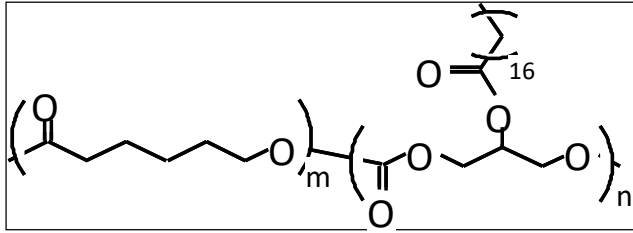


Mark W Grinstaff, PhD



Paclitaxel Films

Polyglycerol monostearate-co-ε-caprolactone

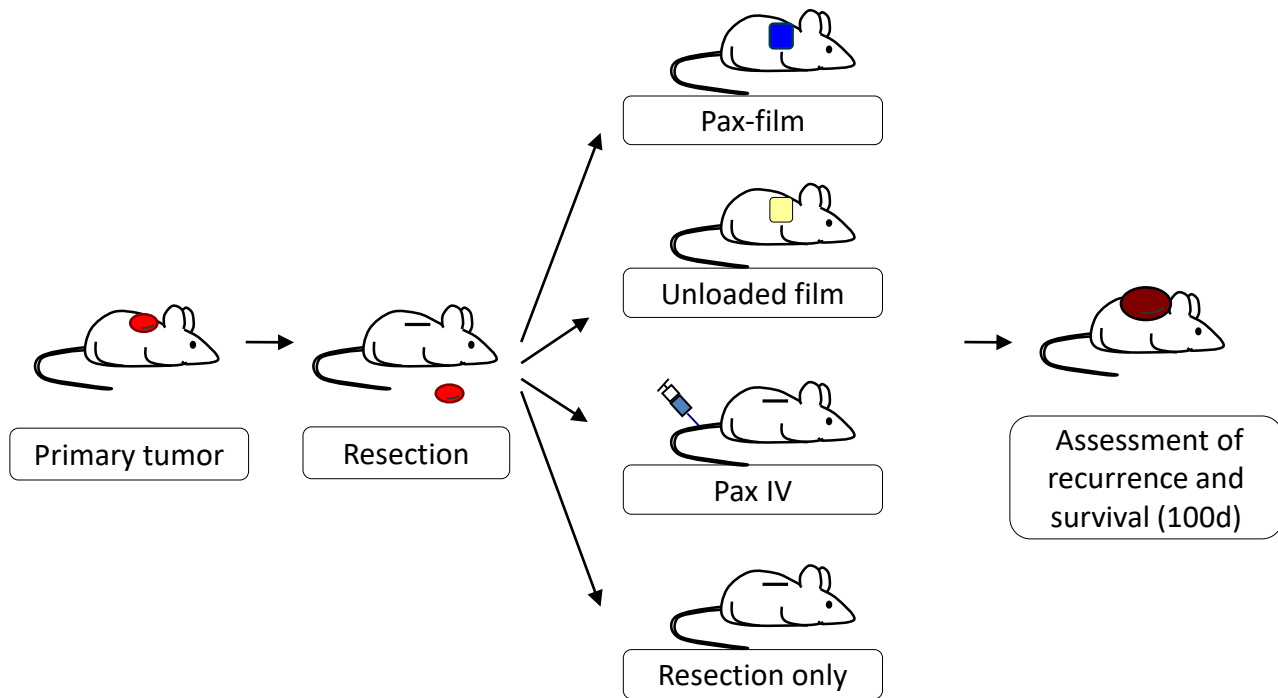


Paclitaxel

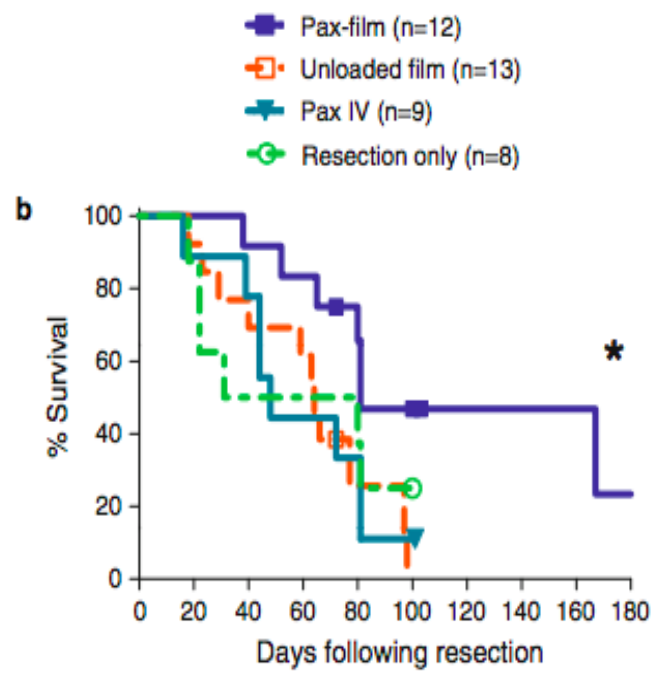
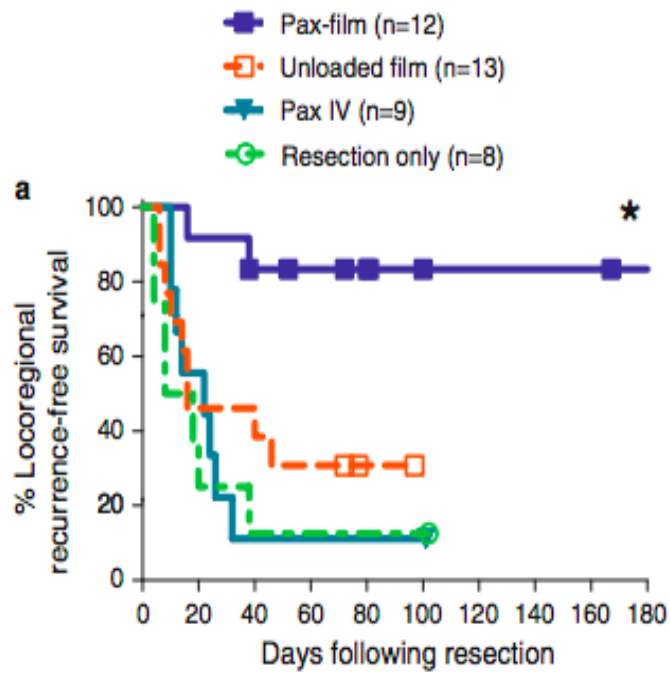
- Mitotic inhibitor
- Hydrophobic
- 300 μg paclitaxel per film (1.0 x 0.8 cm^2)

Murine Chondrosarcoma Recurrence Model

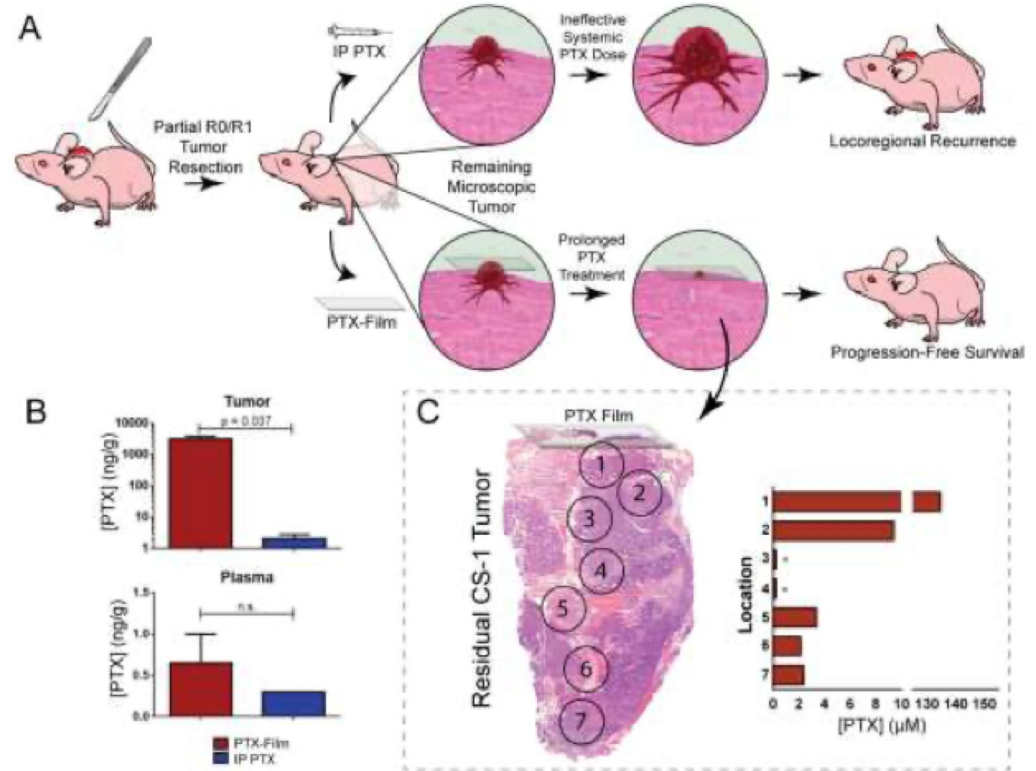
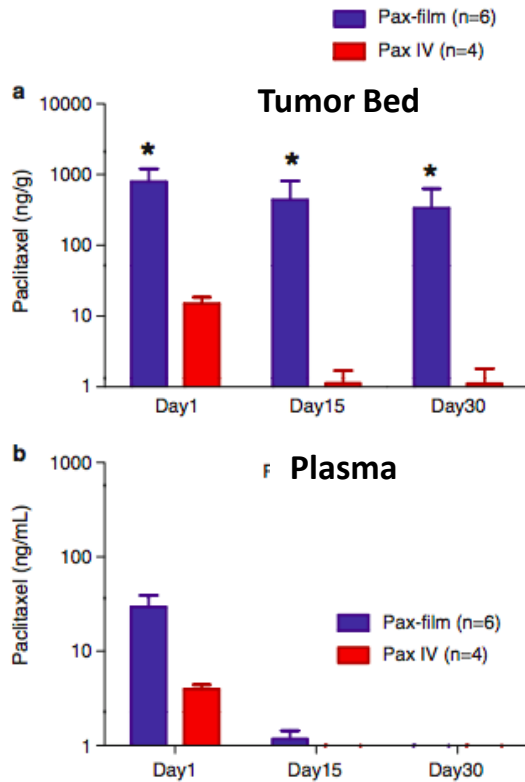
Derived from High-Grade Chondrosarcoma



Survival

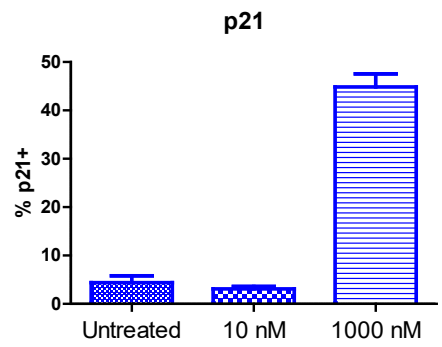
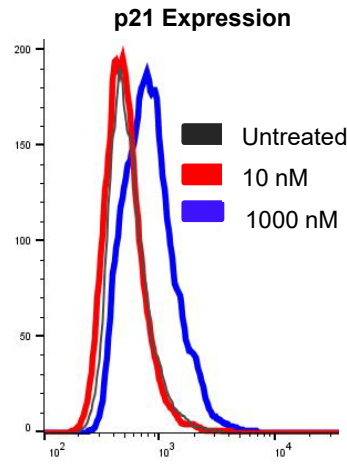


Tissue and Plasma Concentration

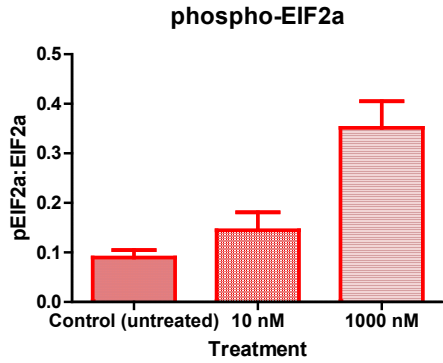




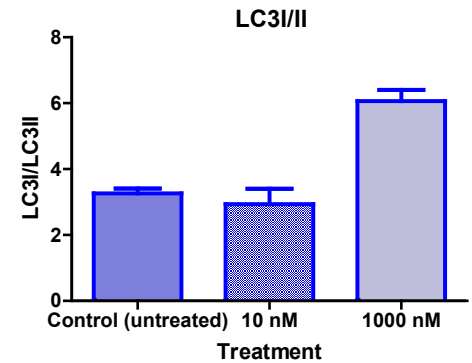
High-Dose Paclitaxel Induces Multiple Cell Death Pathways



Apoptosis



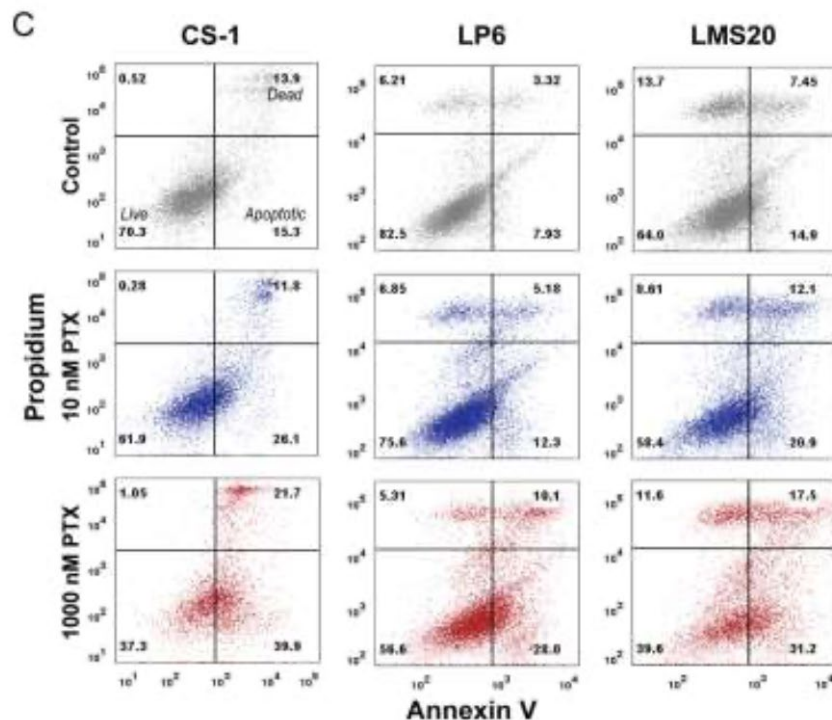
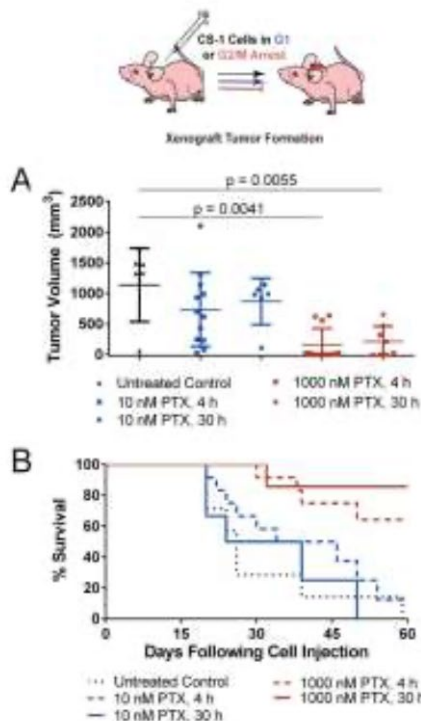
ER Stress



Autophagy

High-Dose Paclitaxel Pretreatment

Higher Proportion of Apoptotic and Dead Cells Across 3 Cell Lines



8-month-old micro-
Yucatan swine (26-29
kg)



Surgery

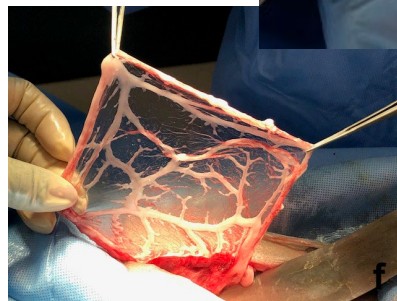
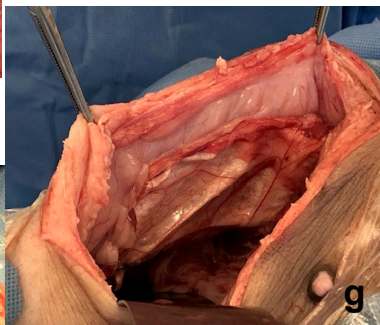
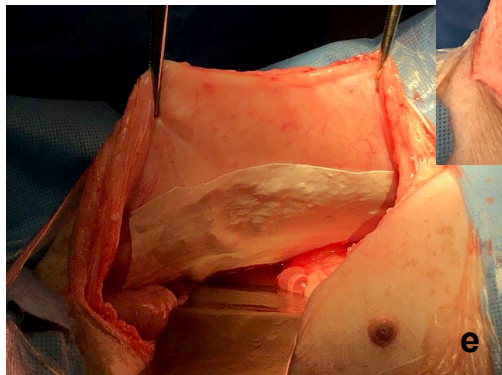
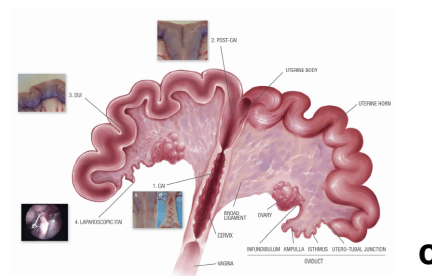
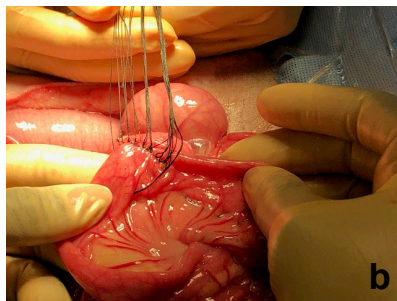
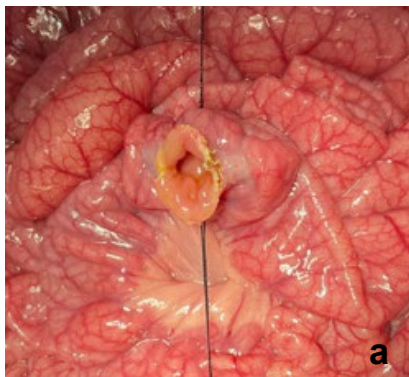
Exploratory laparotomy, enterotomy and
repair, partial hysterectomy

Treatment

- 1) Pax-film (300 ug/cm²) +
contralateral unloaded film (n=5)
- 2) IV Paclitaxel (one-time infusion of
100mg/m²) (n=1)

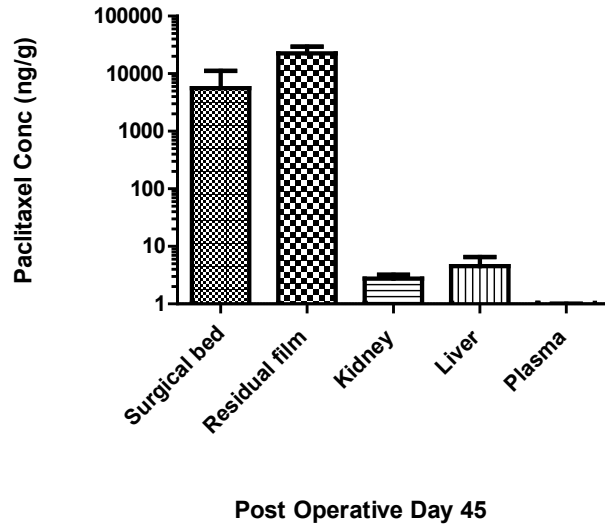
Weekly labs

**IV paclitaxel animal monitored for 35 days
AND
Pax-film animals were monitored for 45 days**



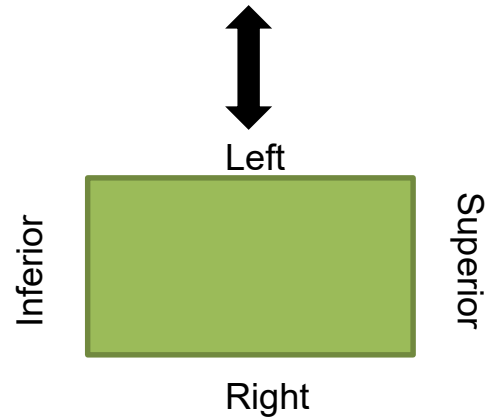
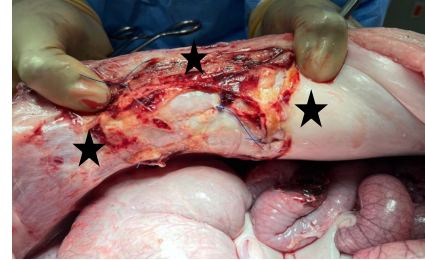
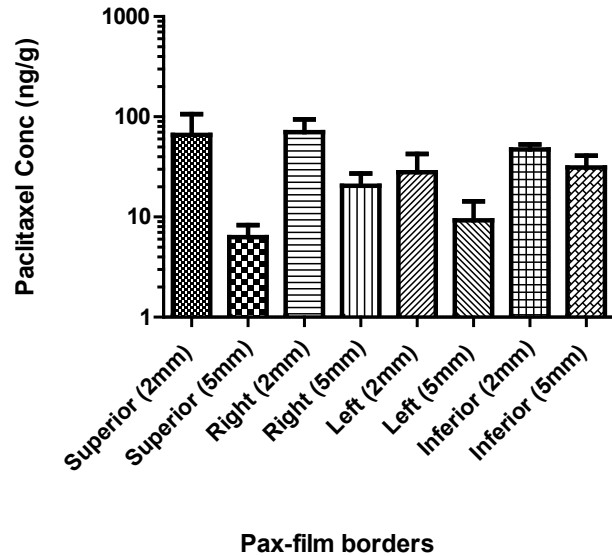
Rojas-Alexandre et al, unpublished data
Mahvi et al, unpublished data

High Local Tissue Paclitaxel Levels

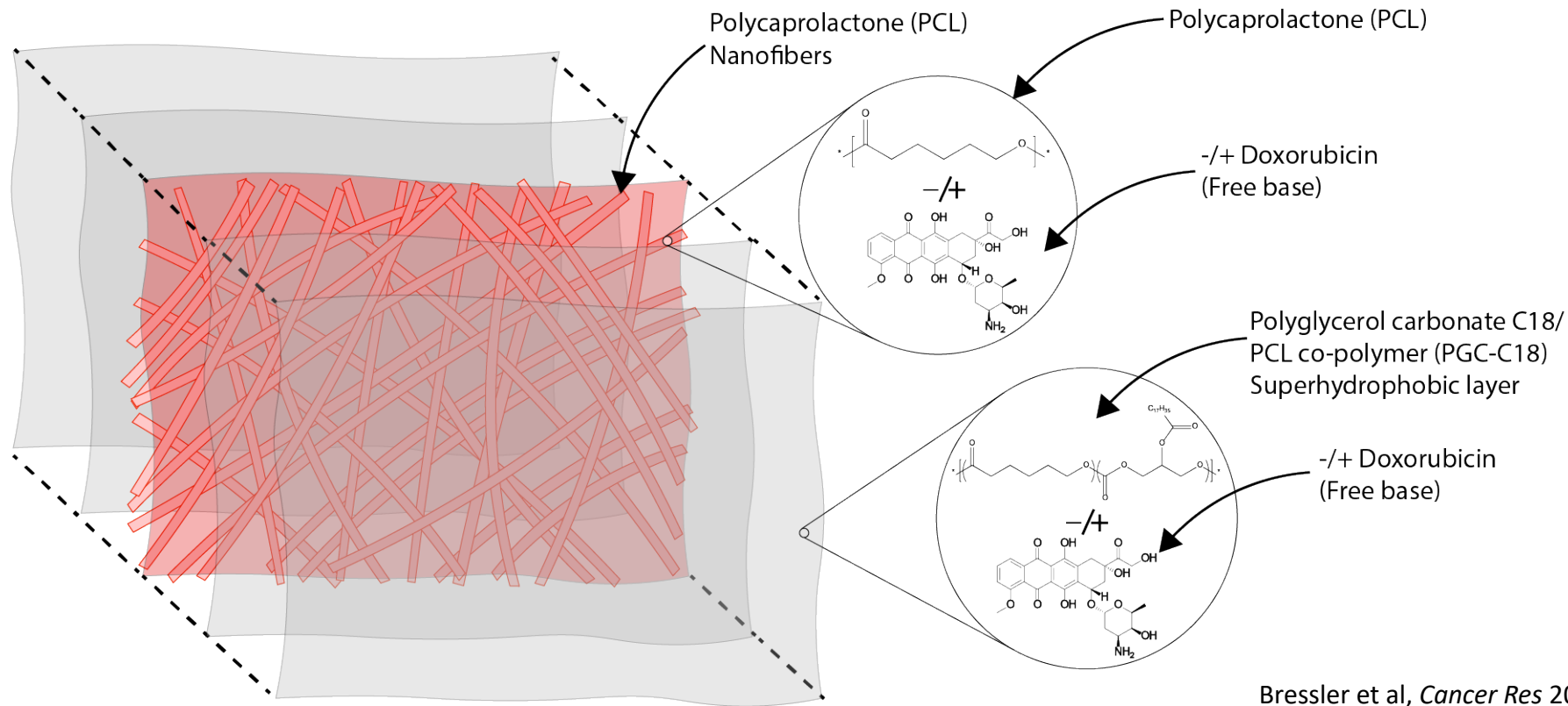


- High levels of paclitaxel detected in **surgical bed**
- High residual paclitaxel in the Pax-films
- No measurable paclitaxel levels in plasma

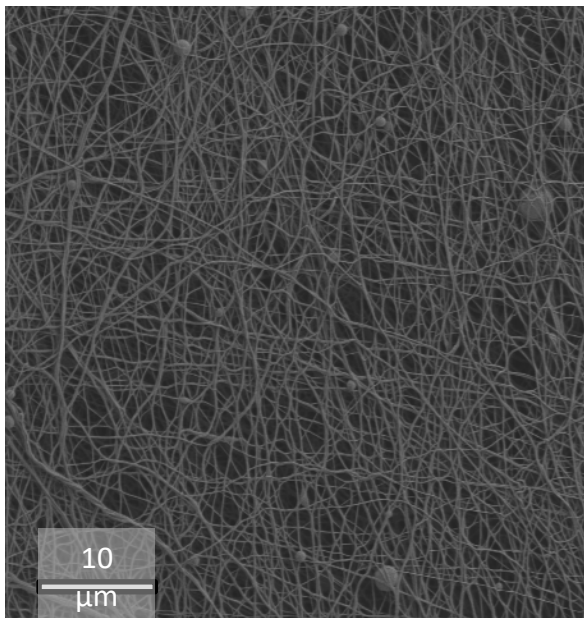
High Paclitaxel Levels Surrounding Film



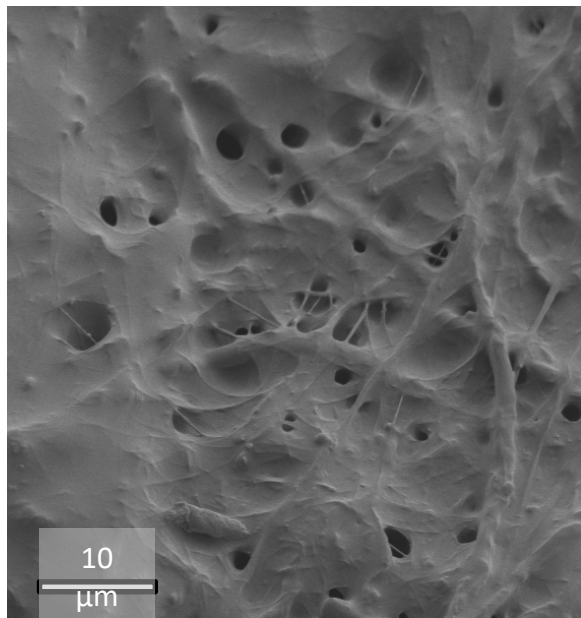
Doxorubicin-Loaded Films



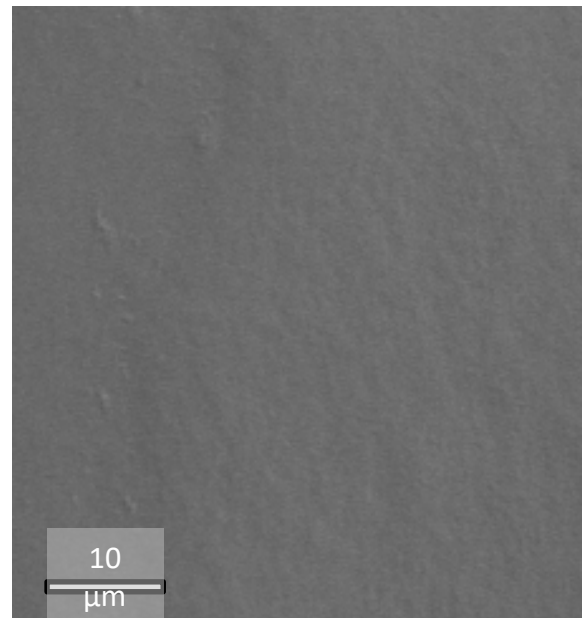
PGC-C18: Coat Doxorubicin and Delay Release



Bare Nanofibers

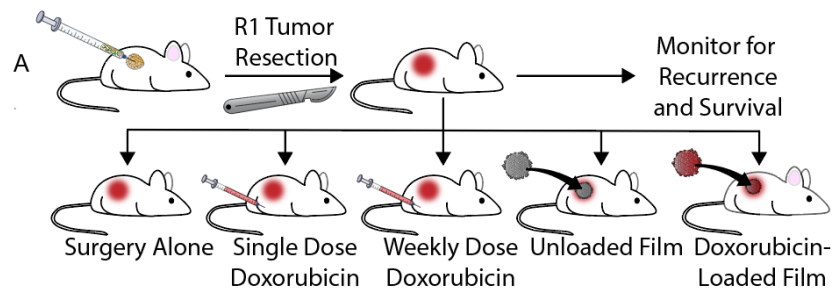


1x PGC-C18 Coating



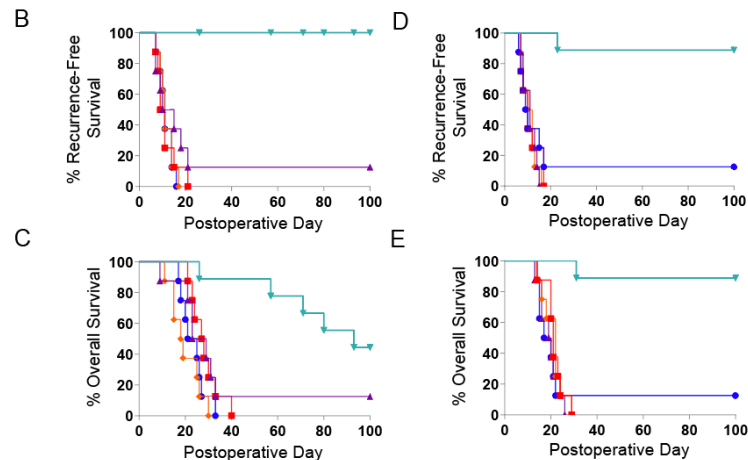
2x PGC-C18 Coating

Doxorubicin-Eluting Polymer Films



CS1 Tumors

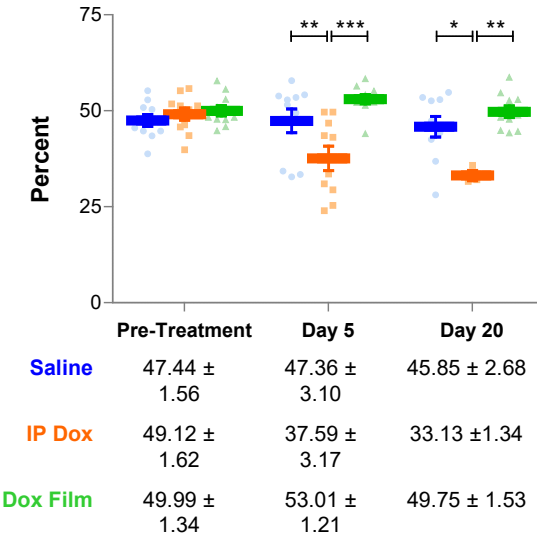
LP6 Tumors



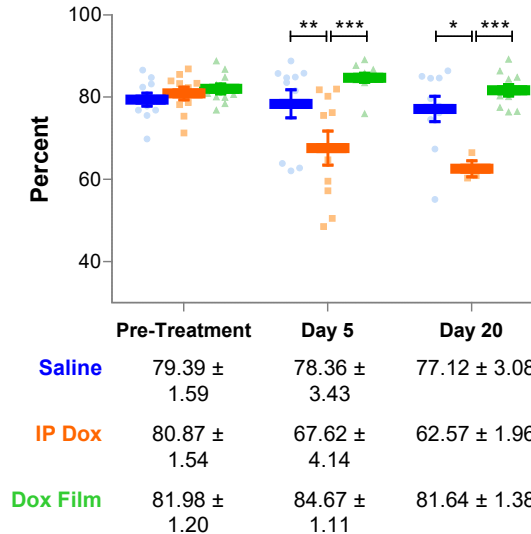
● Surgery Alone (n=8)
 ● IP Dox 20 mg/kg once (n=8)
 ● IP Dox 5 mg/kg weekly x4 (n=8)
 ● Unloaded Film (n=8)
 ● Dox Film (n=8)

No Cardiotoxicity

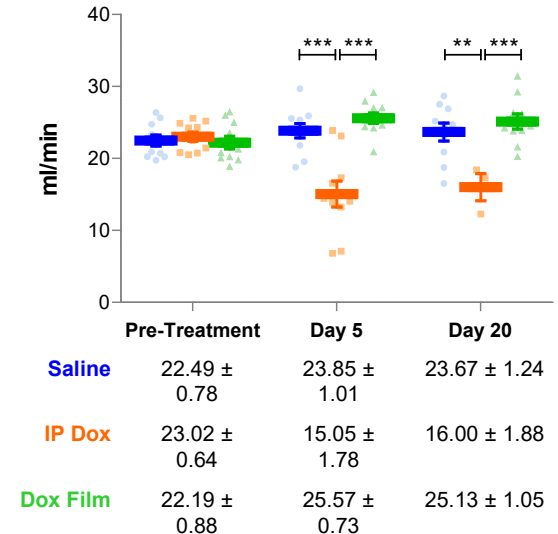
Fractional Shortening



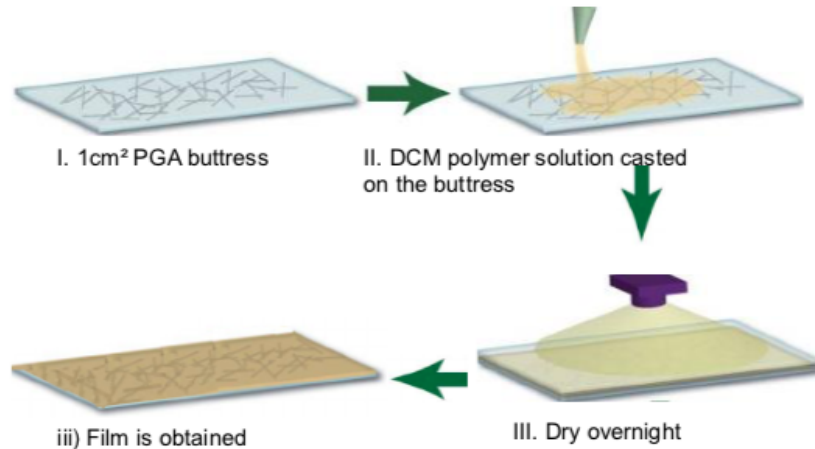
Ejection Fraction



Cardiac Output



Synthesis of *Novel* Double-Loaded Paclitaxel Film



PCL+PGC-Pax+Pax = Double-Loaded Pax Film

Composition

Concentration

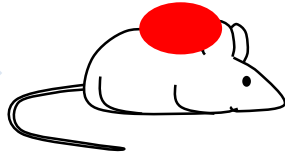
PCL	47% wt
PGC-Pax (covalently bound)	47% wt
Pax (free drug)	6% wt

Controls

- Buttress (PGA) + PCL = **Unloaded Film**
- Buttress + PCL + PGC-Pax = **Single-Loaded Pax Film**

Liposarcoma PDX Recurrence Model

LP6 Implantation



Treatment

Surgery alone

Unloaded films

Single-Pax films +
Intraperitoneal Pax

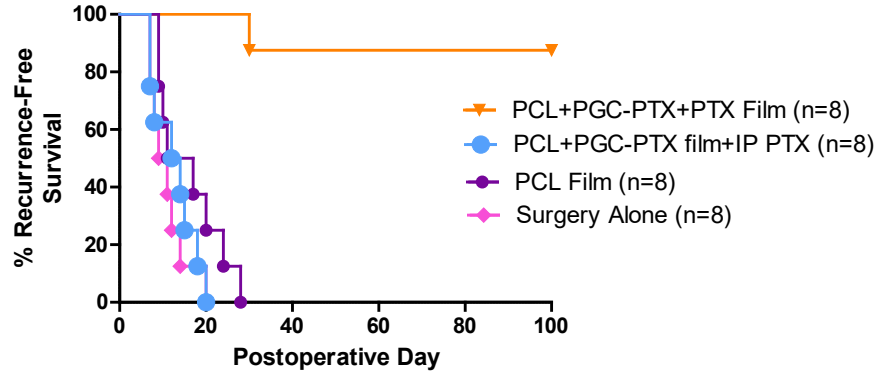
Double-Pax films



Monitor for Recurrence
and Survival

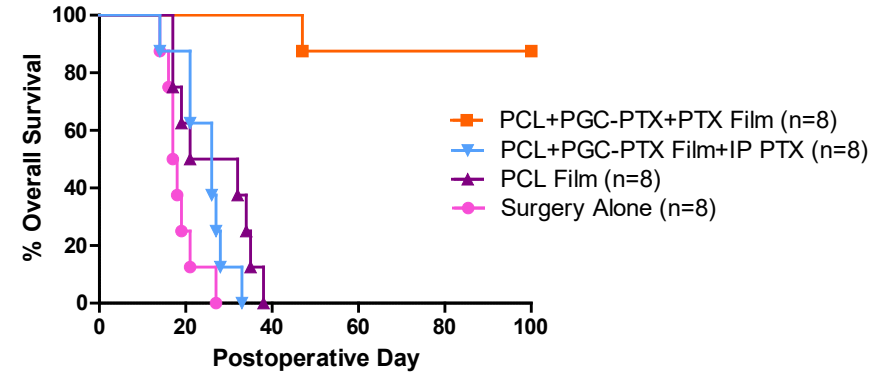
LP6 Double Pax Films

LP6 Recurrence Free Survival



$p=0.0002$

LP6 Overall Survival



$p<0.0001$



Drug-Eluting Films: Conclusions

- Reduce recurrence rates across multiple sarcoma models
- Achieve high local tissue drug concentration over a sustained period of time
- Minimize systemic toxicity
- Mechanism of action at high doses may be different than via systemic administration

Thank you

craut@bwh.harvard.edu

