

Near infrared photoimmunotherapy:

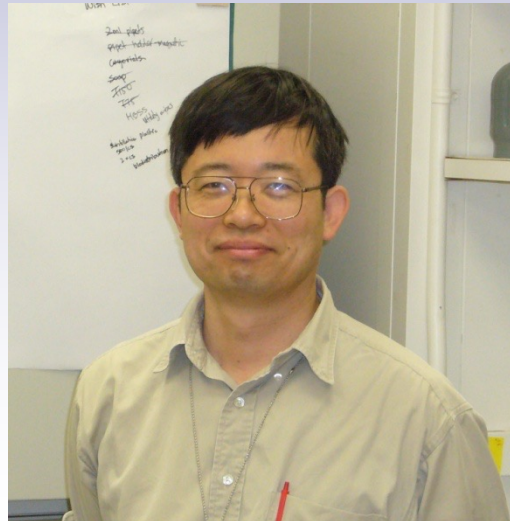
A new light-based treatment for cancer

Peter Choyke, MD

*Laboratory of Molecular Theranostics
Molecular Imaging Program,
NCI /NIH, Bethesda, MD*

Disclosures

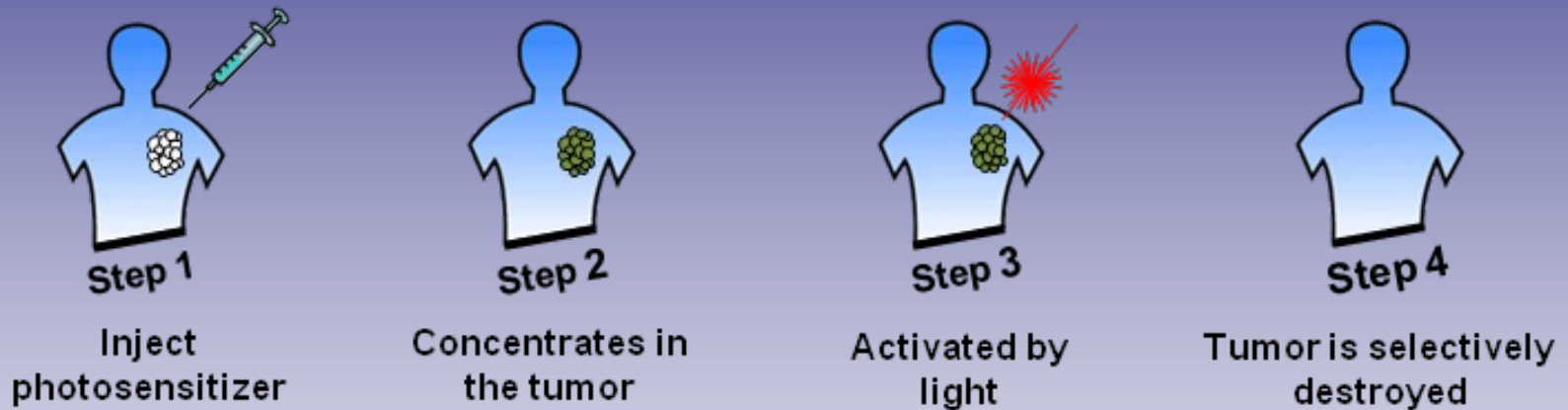
- No financial conflict of interest
- Patents on photoimmunotherapy
- Licensed to Rakuten Asypirian.com
- Indebted to Hisataka Kobayashi (HK)



Brief History of Light Therapy

- Laser Ablation
 - Thermally burns tissue
 - In plastic surgery laser light can be tuned to selectively ablate discolored lesions
 - Requires expert control of laser.
- Photodynamic therapy
 - Inject a photo-porphyrin
 - Slightly greater uptake in tumors than normal
 - Narrow therapeutic window

Photodynamic therapy (PDT)



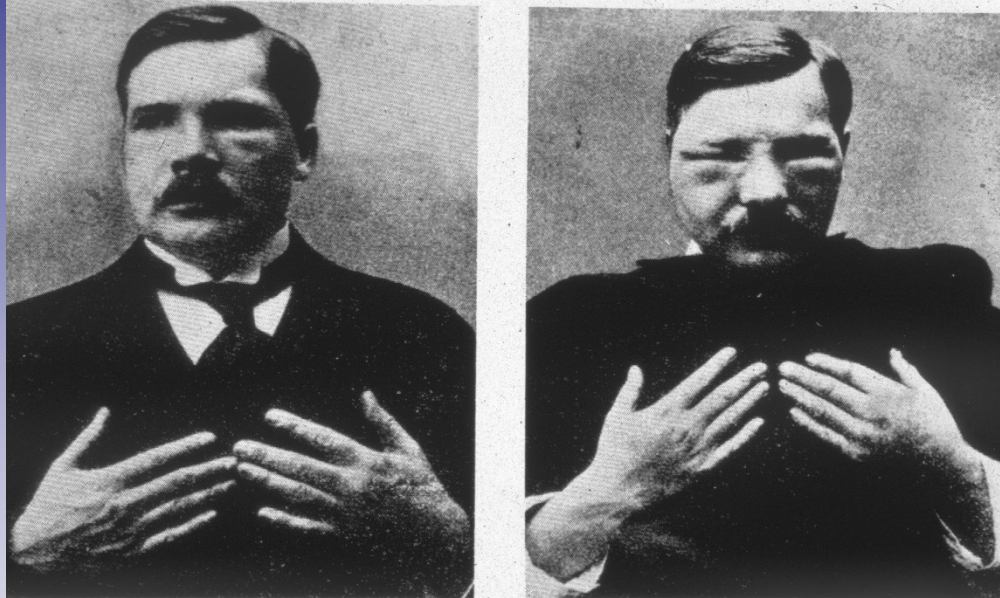
Non specific uptake (normal tissue accumulates)

- Side effects limit efficacy

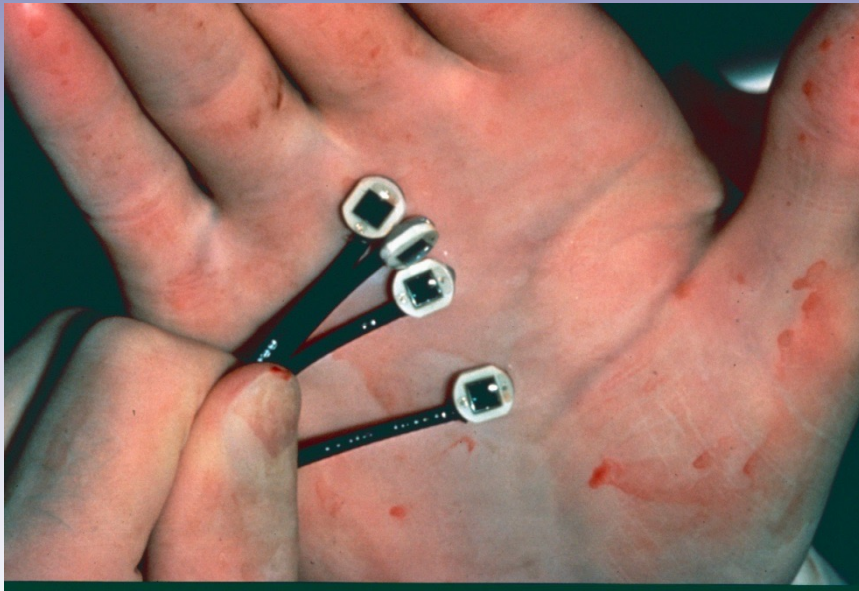
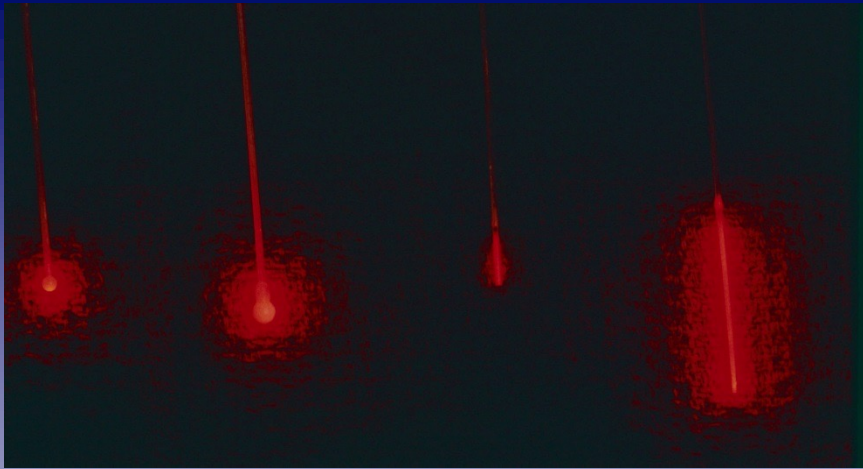
Kills by apoptosis-non immunogenic

Photosensitivity for 2-8 weeks post injection

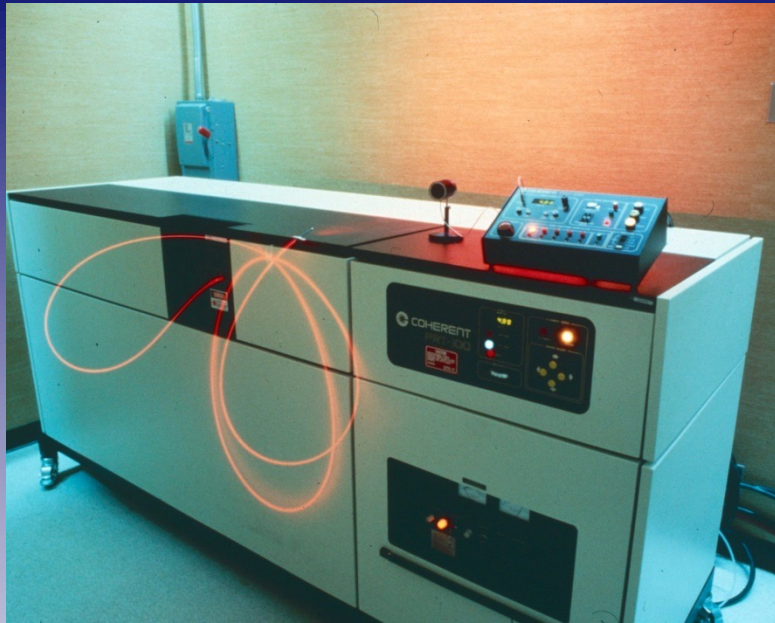
First Person to Receive PDT



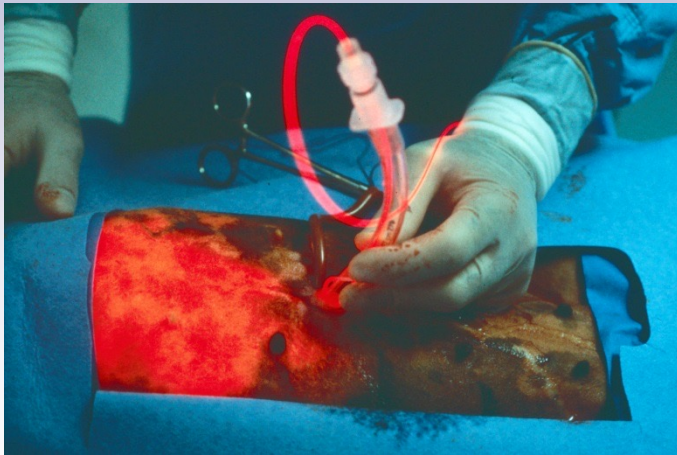
Inject hematoporphyrin derivative (HPD),
wait 10 min, move to direct sunlight
From: Meyer-Betz *Deutsches Klin Med* 112: 476, 1913



ROB PDT Laser



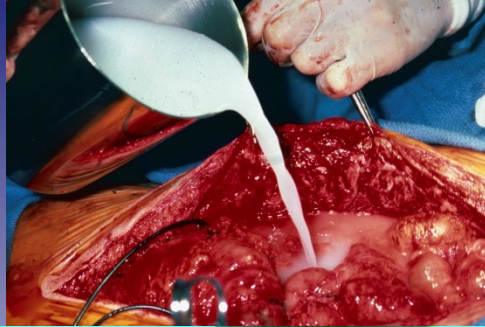
Pre-Clinical Canine Studies



Surgery Conducted by Dr. William Sindelar, Surgery Branch NCI (mid 1980s to early 1990s)

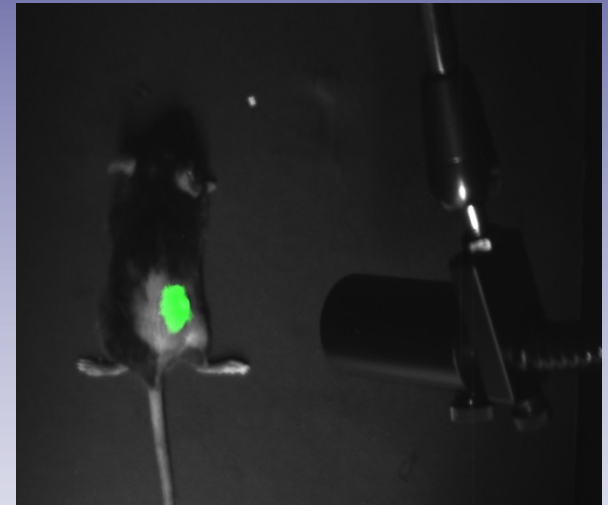
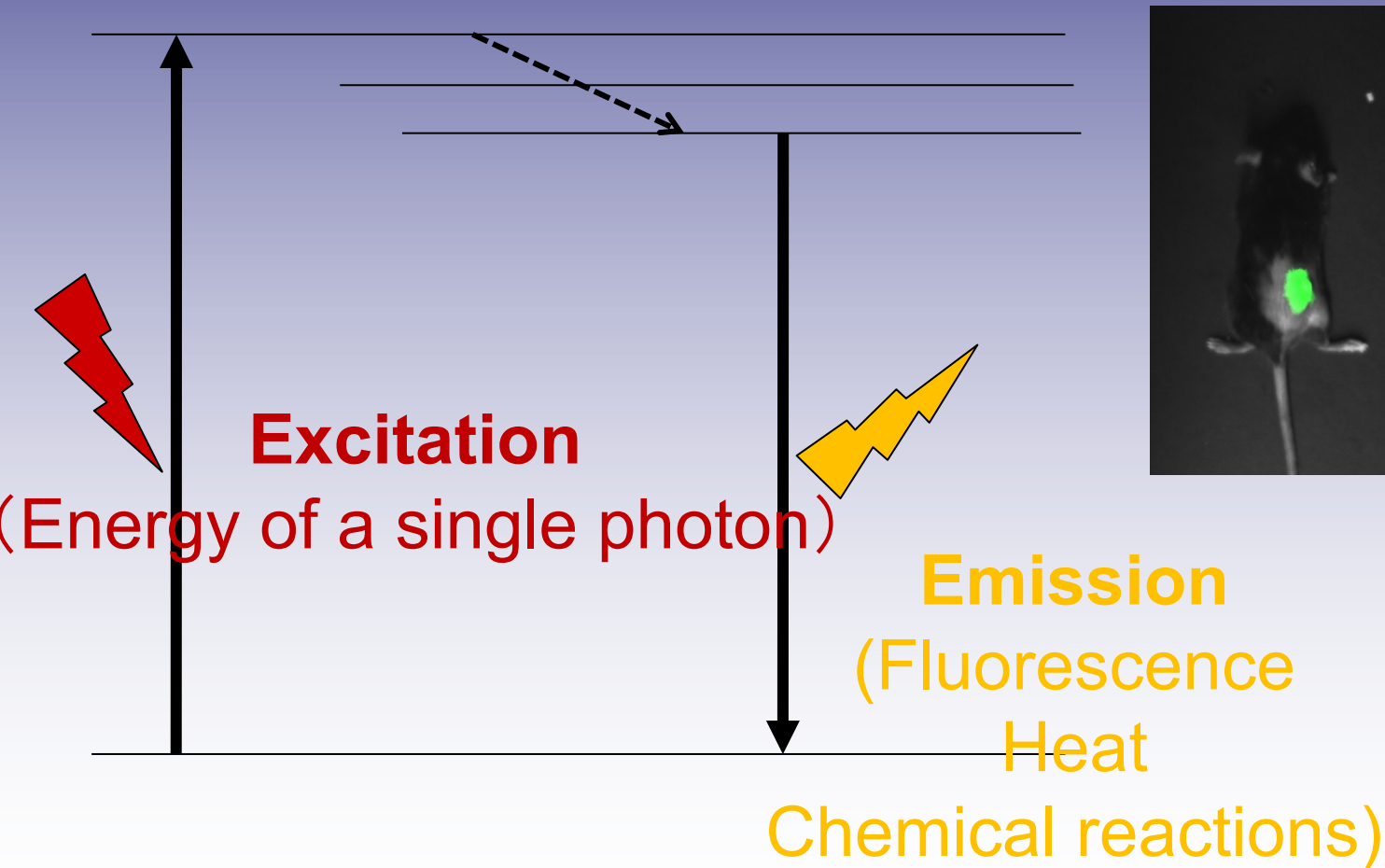
Clinical PDT Studies

Disseminated
Intra-peritoneal
Malignant
Neoplasms

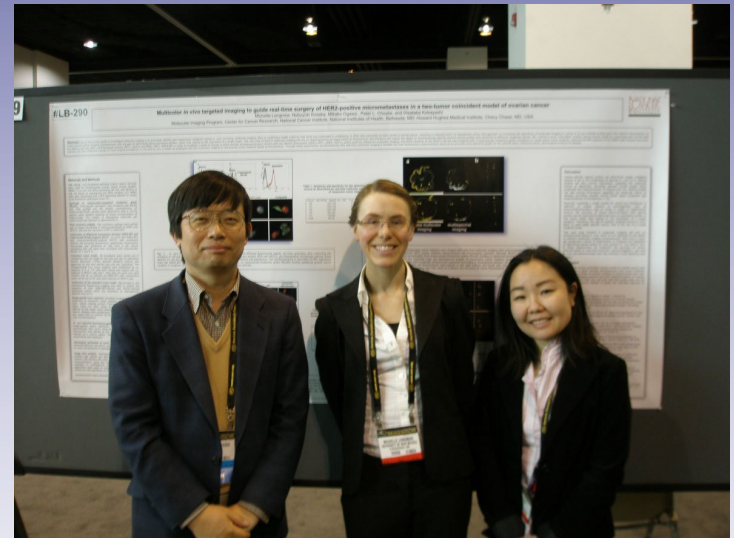
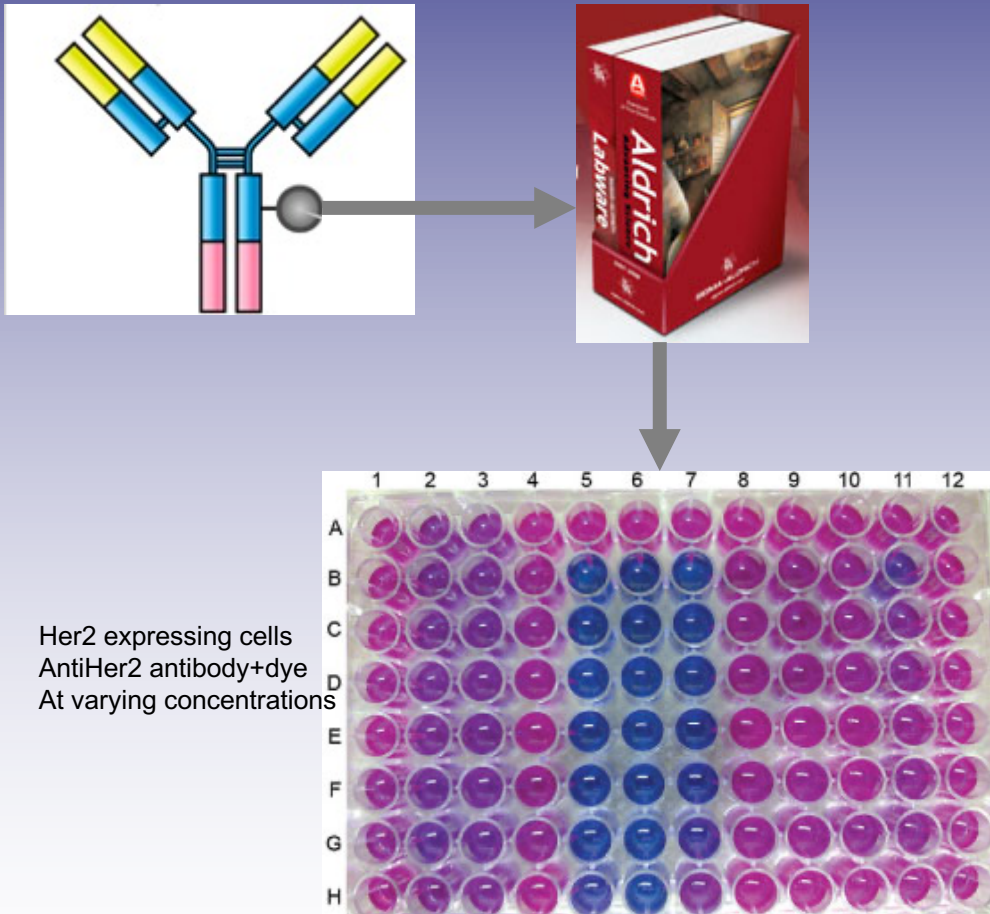


Thoracic Malignancies PDT: Dr. Harvey
Pass, Surgery Branch NCI (late 1980s
to early 1990s)

Light Therapy: Is there a better way?

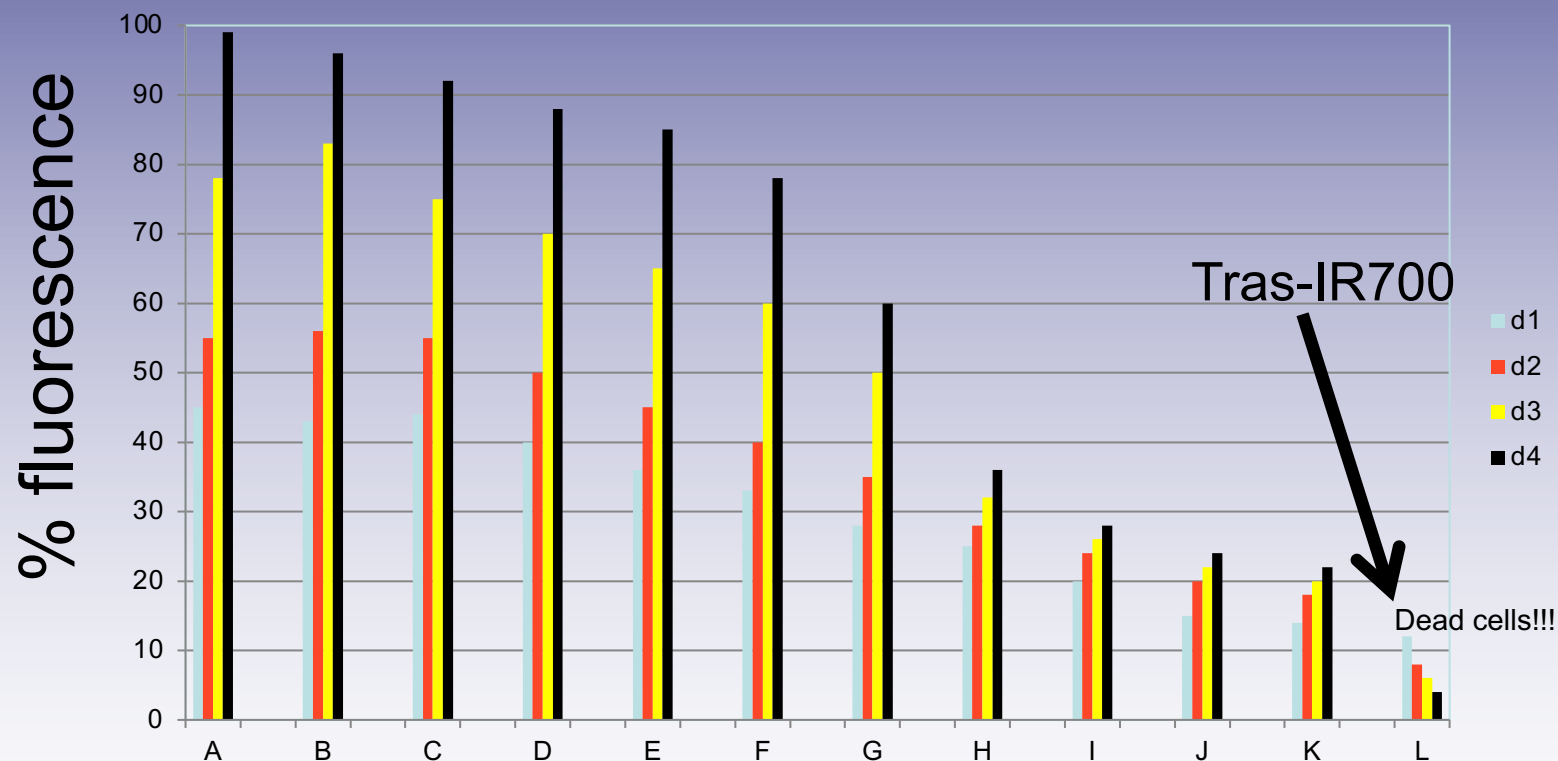


Targeted imaging with fluorescent dyes



L→R: Hisataka Kobayashi
Michele Longmire
Mikako Ogawa

Trastuzumab –NIR dyes

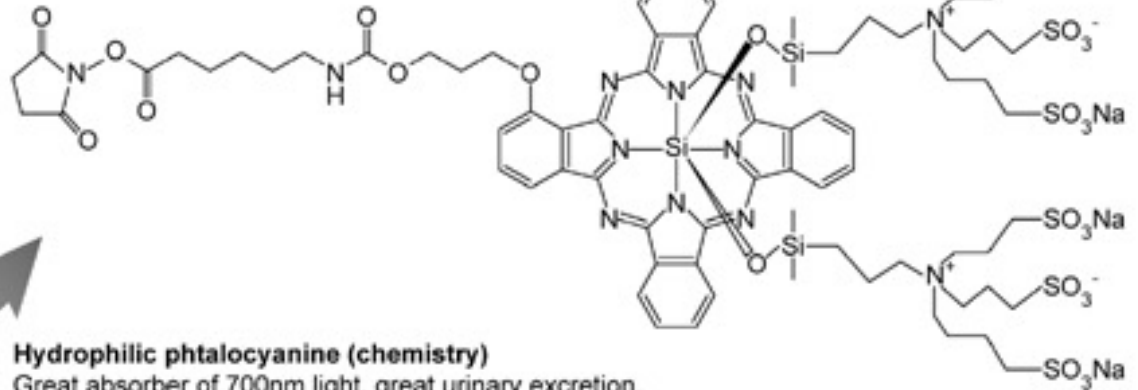
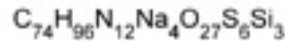
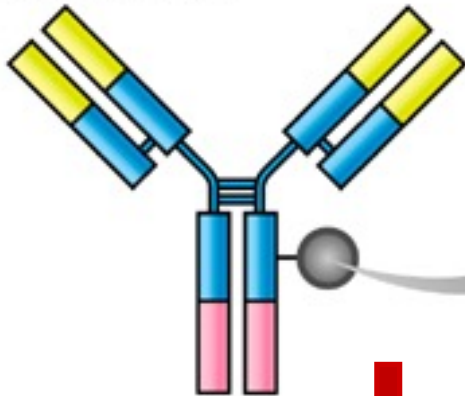


Tras-dye combination

Near infrared photo-immunotherapy (NIR-PIT)

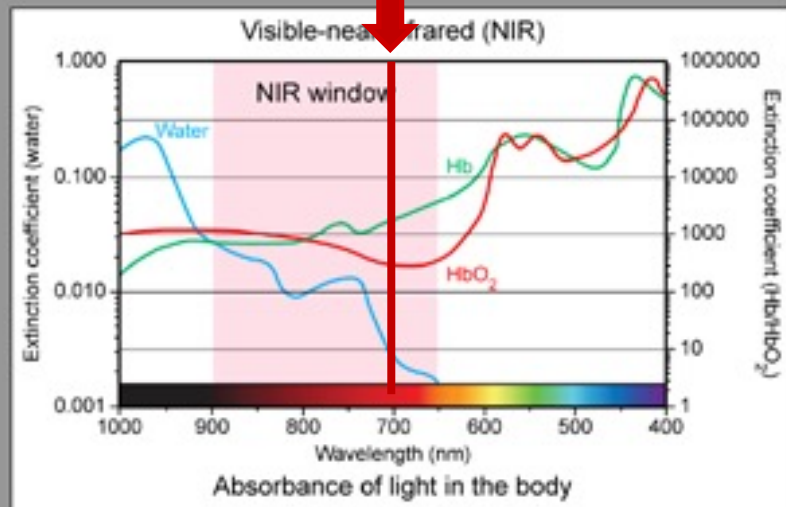
Humanized monoclonal antibody (biology/medicine)

Highest binding specificity, greatest *in vivo* target delivery, applicable to the clinical practice.



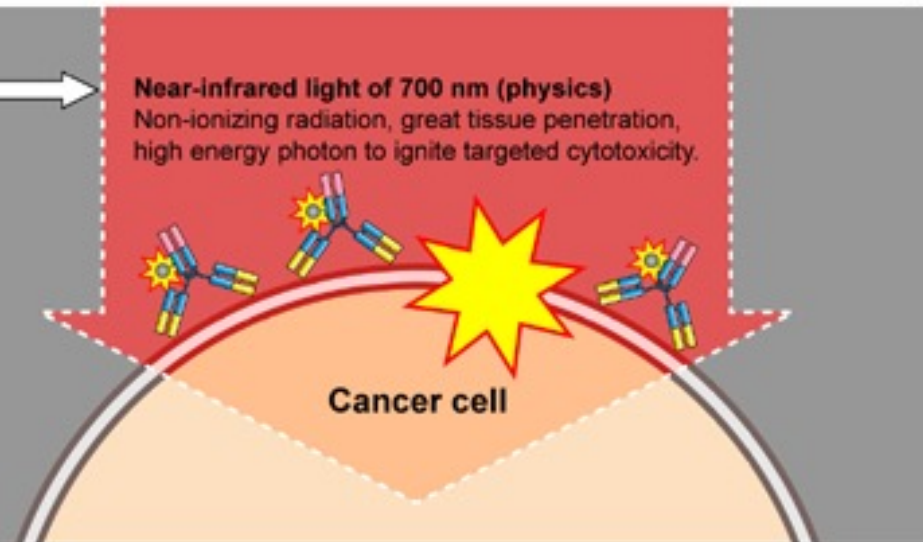
Hydrophilic phthalocyanine (chemistry)

Great absorber of 700nm light, great urinary excretion.
Works as a "nano-dynamite" to damage only binding cell membrane.

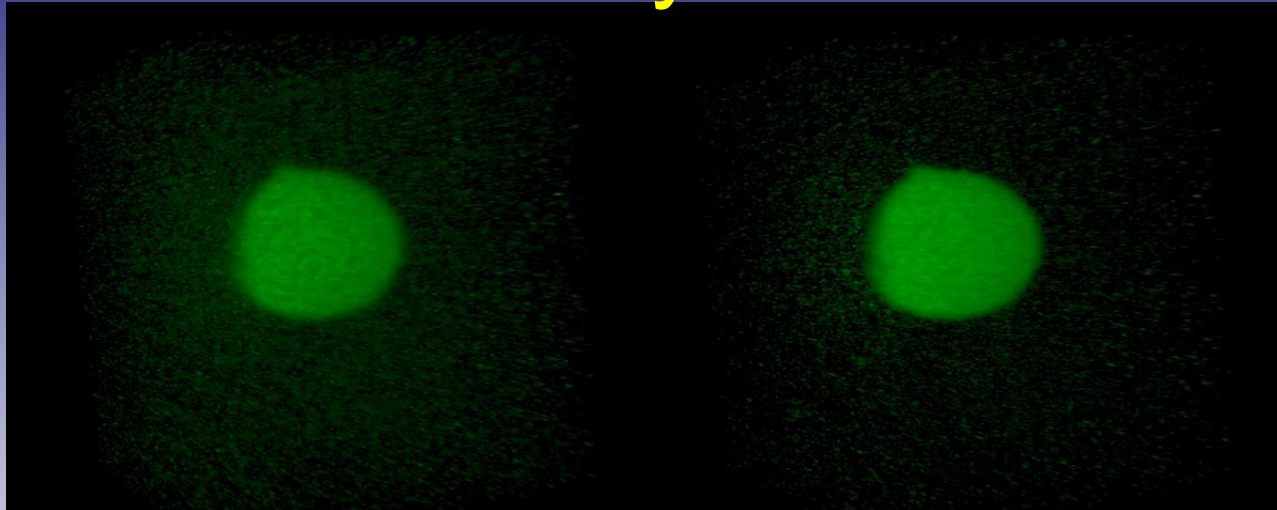


Near-infrared light of 700 nm (physics)

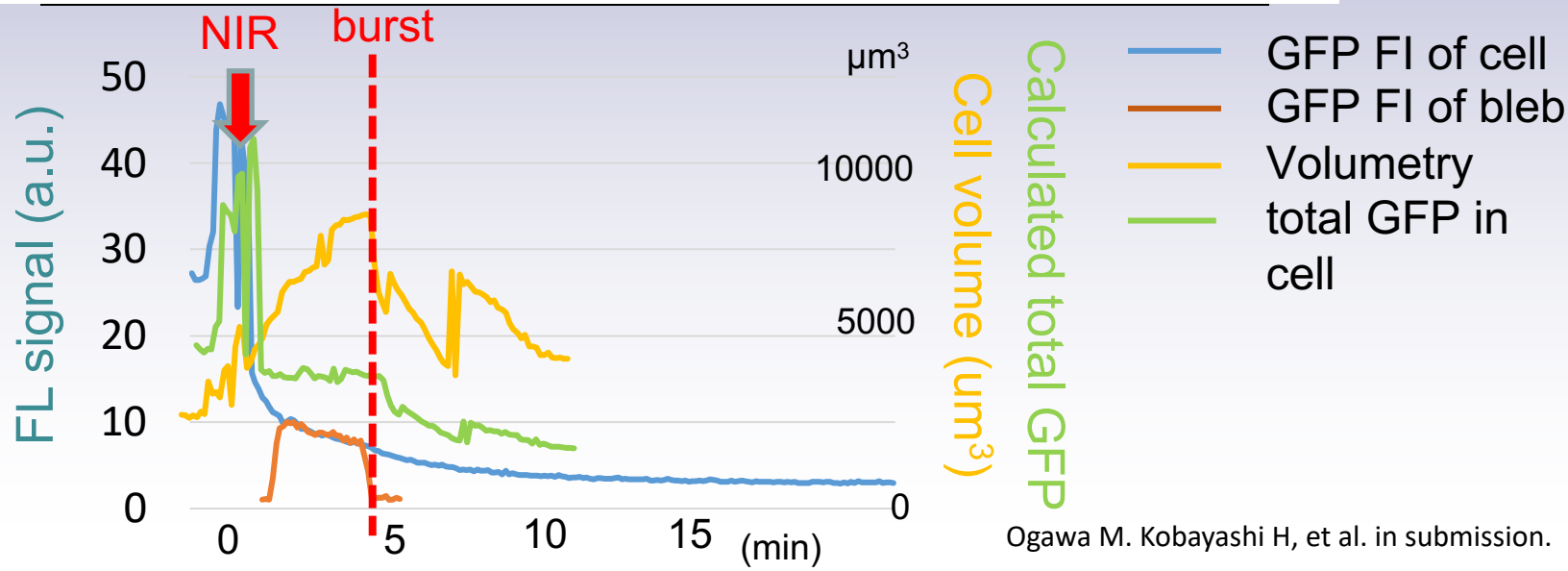
Non-ionizing radiation, great tissue penetration,
high energy photon to ignite targeted cytotoxicity.



Direct killing with release of cellular contents by NIR-PIT



Dynamic 3D-image of 3T3/HER2 cell expressing GFP in the cytoplasm (Stereo view)
Dual-view inverted selective plane (sheet light) illumination microscope (diSPIM)

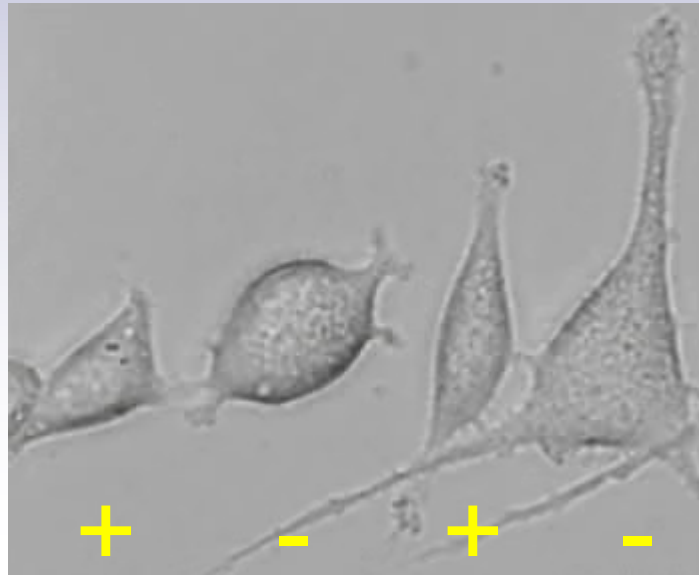


NIR-PIT works even at 4°C and selectively kills

37°C targeted cells 4°C



Her+ Her- Her+ Her-



Target:
HER2

NIR-PIT induced cell swelling and release of intracellular contents

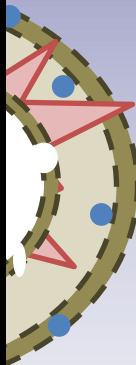
Low coherent quantitative phase microscope (QPM)

-3.6 sec.

N

H₂O

20 μ m





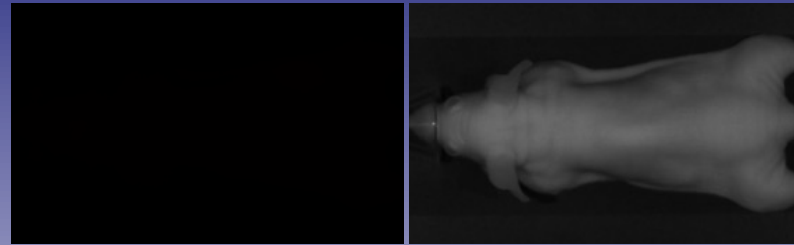
Photoimmunotherapy

NIR-PIT reduces tumors in nude mice

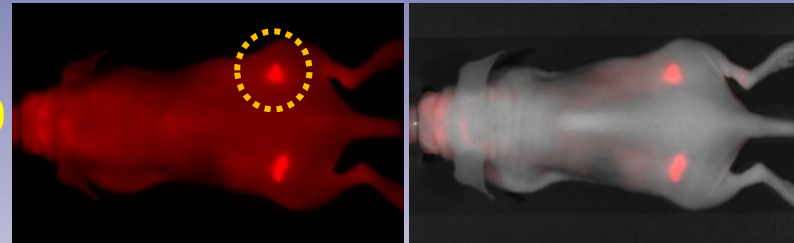
PAN-IR700

PAN-IR700/White

Pre

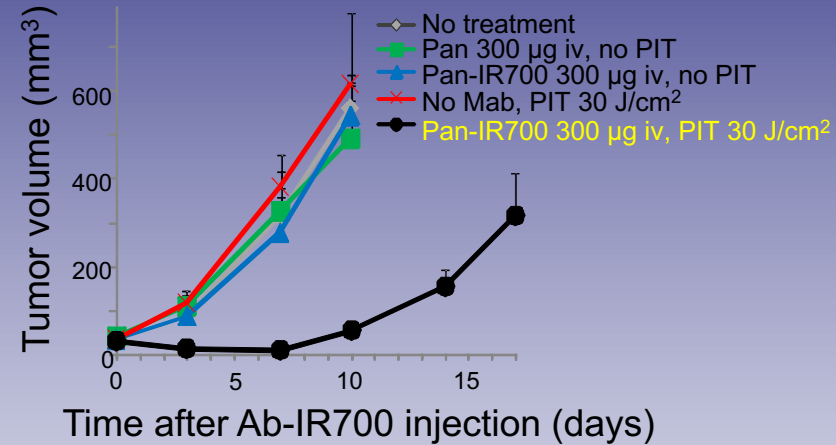
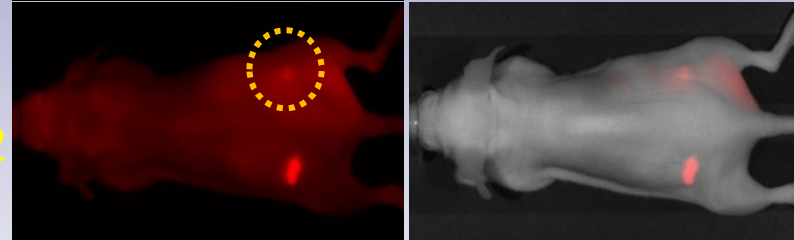


Day0



NIR light

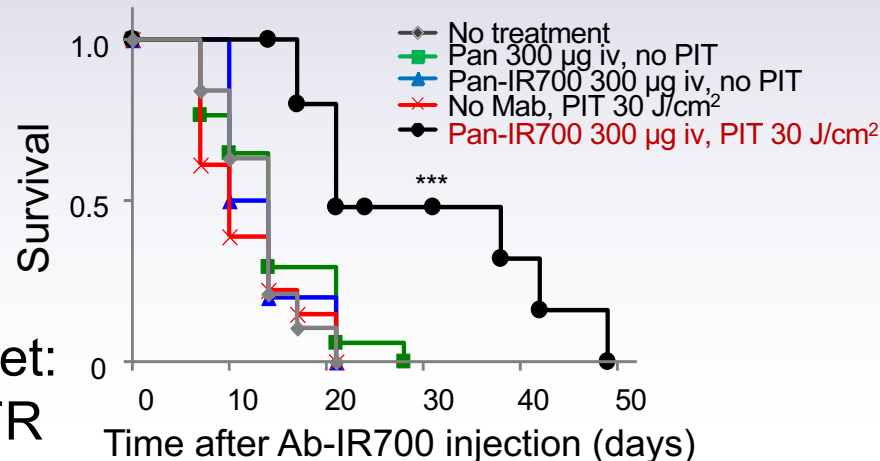
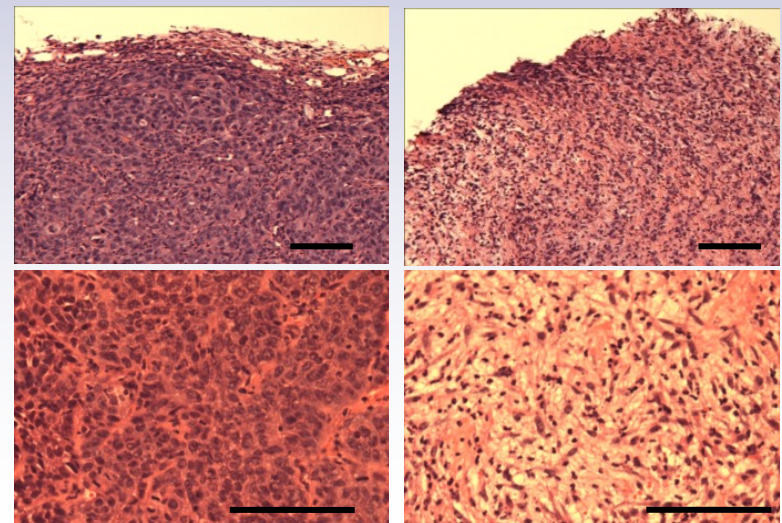
Day2



Time after Ab-IR700 injection (days)

No PIT control

Pan-IR700-PIT day 2



Target:
EGFR

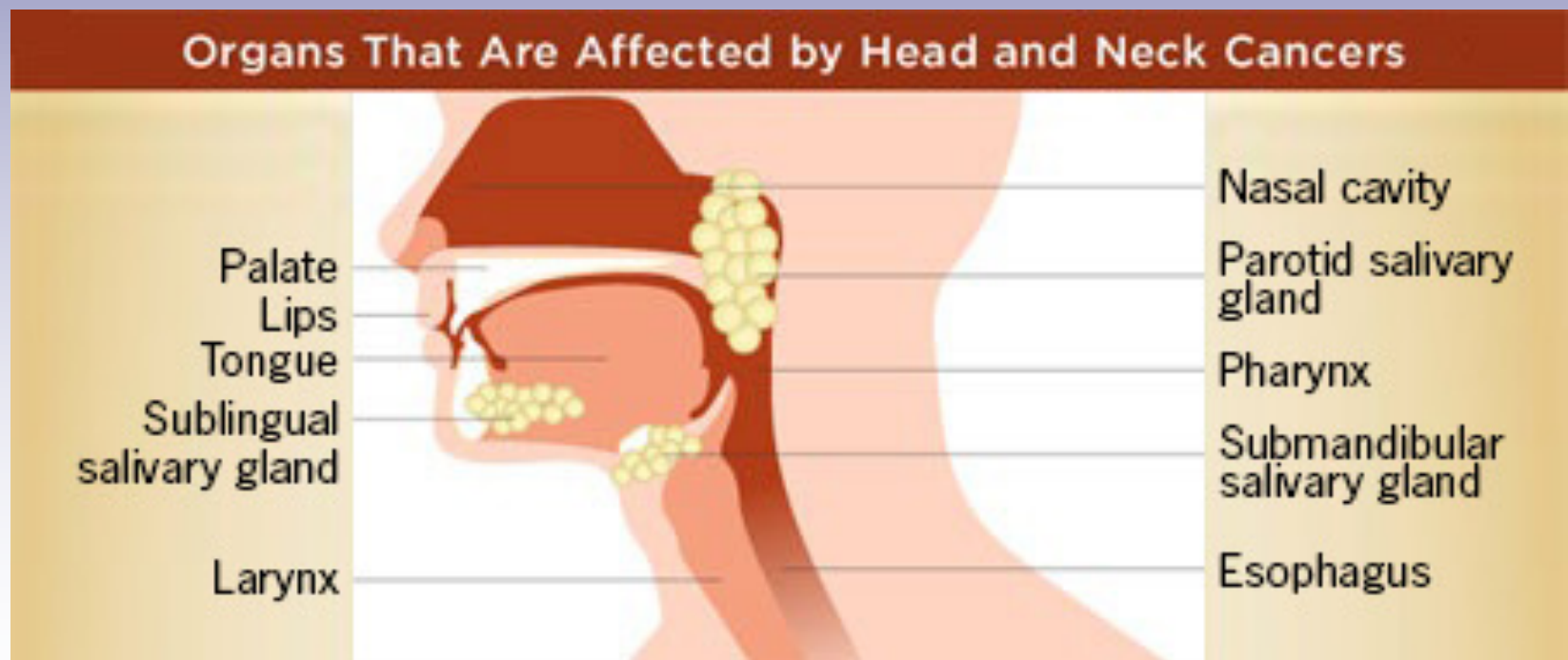
Time after Ab-IR700 injection (days)

PIT licensed to Rakuten Aspyrian

- Toxicity studies of cetuximab-IR700 in NHPs showed no cutaneous toxicity
- No systemic toxicity
- Phase 1 dose finding study in inoperable recurrent Head and Neck Cancer was approved by FDA
 - Cetuximab-IR700 dose finding
 - Light dose finding

Head and Neck Cancer

644,000 new cases each year,
Two thirds are in developing countries
In the US, 12,460 deaths per year



Treatment

- Initial: Chemoradiation and surgery
- Recurrence:
 - Combination chemotherapy: 10-36% RR
 - Duration of response: 5.5 months
 - Immunotherapy, antibody therapy
 - Re-irradiation: significant toxicity
 - Quality of life strongly affected.
 - Photodynamic therapy (Foscan)
 - Improves median survival
 - Significant side effects-normal tissue damage
 - Carotid rupture, fistulas, perforations, etc.

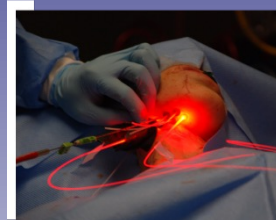
Phase I/II, Head and Neck Cancer Study Design

Phase I study, recurrent/unresectable Head and Neck Cancer that failed conventional therapies. (Two parts: part I drug dose escalation, and part II light dose escalation.)

Step 1: RM-1929 infusion



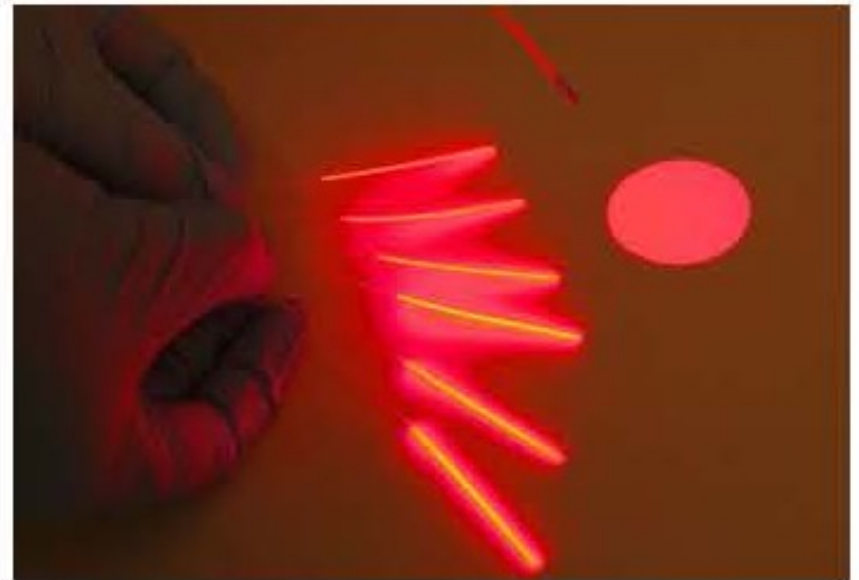
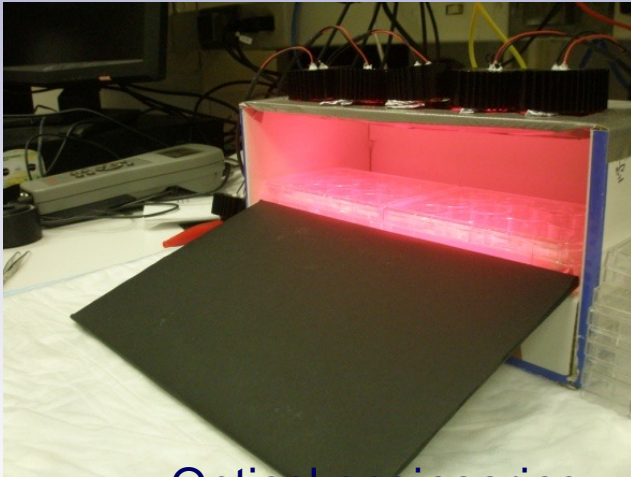
Step 2: Tumor illumination at 24 h



→
Outpatient service

Part I	Part II
RM-1929 Dose Escalation, fixed light dose	Light Energy Escalation, fixed drug dose
Expected Duration: 6 months	Expected Duration: 6 months
Total Patients: up to 24 → 12	Total Patients: up to 18 → 12
Description: dose escalation study of RM-1929 in various cohorts to determine the safety profile and the anticancer activity of the treatment with NIR light 50 J/cm² . <ul style="list-style-type: none"> Cohort 1: 160 mg/m² of RM-1929 Cohort 2: 320 mg/m² of RM-1929 Cohort 3: 640 mg/m² of RM-1929 Cohort 4: 1280 mg/m² of RM-1929 	Description: light escalation study various cohorts to determine the safety profile and the anticancer activity of the treatment <ul style="list-style-type: none"> Cohort 1: 150/200 (J/cm² or J/cm) Cohort 2: 250/300 (J/cm² or J/cm) Cohort 3: To be determined
Target: EGFR Clinical Sites: up to 5 clinical sites in the USA	Clinical Sites: up to 5 clinical sites in the USA

LED/Laser system











Optical engineering

LED of ~\$180 (~100 mW) for preclinical

→ Laser of \$30k (< 8W) for clinical

Remarkable Data from First 4 Patients

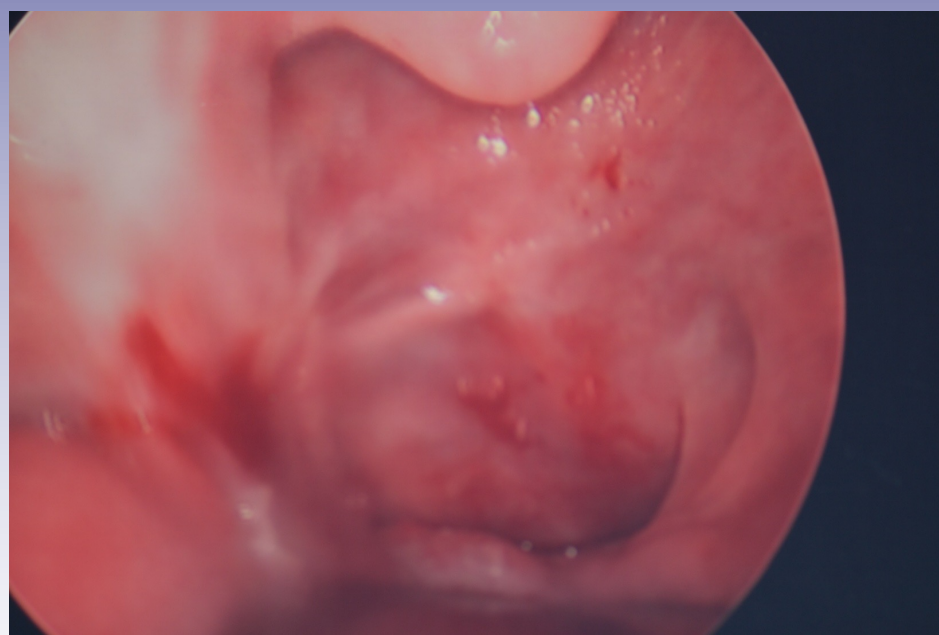
Very well tolerated, no significant AEs. No damage to normal tissue and good healing. Now >40 patients have been treated

Patient	Tumor	Safety	Anticancer Response
#1	Large cancer in the throat and nasopharynx: 3x6 cm	 No AEs	 >70% tumor reduction at 1 month
#2	Large throat cancer 3x6 cm	 No AEs	 Complete response (100% tumor death)
#3	Large 3x3x2 rapidly growing recurrent tongue cancer	 No AEs	 >70% tumor reduction at 2 weeks
#4	Large cancer in the throat: 9x4 cm	 No AEs	 Complete response (100% tumor death)

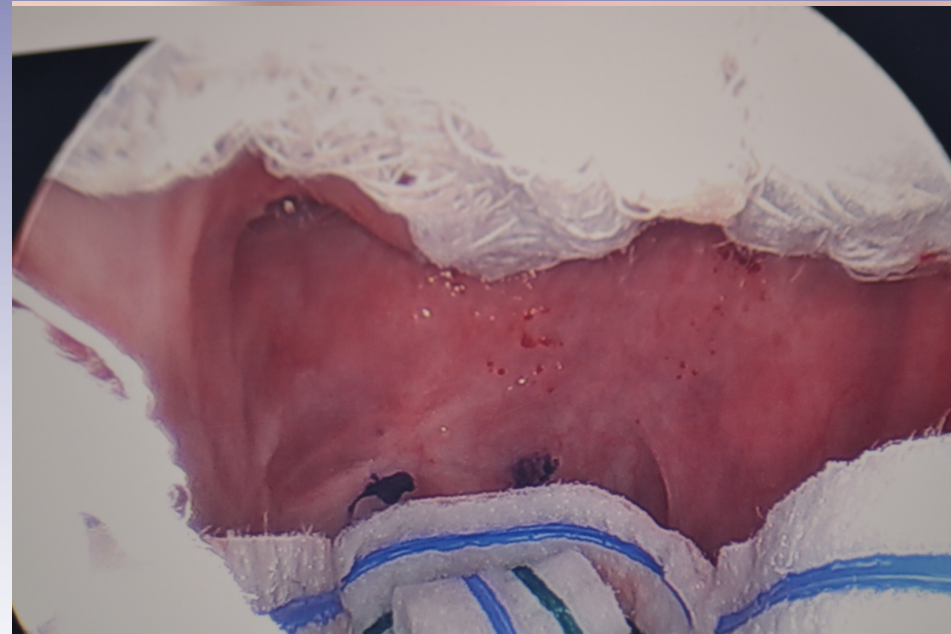
Target:
EGFR

NIR-PIT is highly effective and tissue repairs after therapy

Multiple surgeries X, chemo-radiation X, -> recurrence



Before



Immediately after

Target:
EGFR

NIR-PIT in clinical trial

PUBLIC RELEASE: 1

Photoimmunosensitizers

Head and neck

RUSH UNIVERSITY



When Kerstin Stenson, MD, describes the innovative technology to fight cancer,

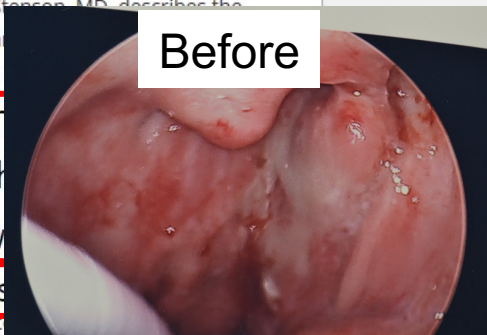
"Photoimmunosensitizers for patients who have not responded to chemotherapy," MD PhD, who

"Chemotherapy has been shown to destroy those cells,"

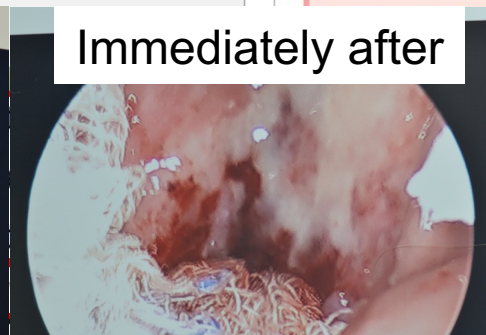
in a Clancy thriller, PIT delivers extremely precise, lethal payloads with minimum collateral damage.

"Almost immediately, you can see the tumor start dying. It turns white and melts away," Stenson says. Because the payload drug remains inert unless activated by a specific wavelength of light that doesn't damage human tissue, destroying the cancer cells causes almost no damage to surrounding cells. "The drug/dye combination (the monoclonal antibody combined with the photosensitizer) is not toxic until activated by near infrared light, thus is very safe from a systemic perspective," Stenson explains.

Before



Immediately after



1 day after

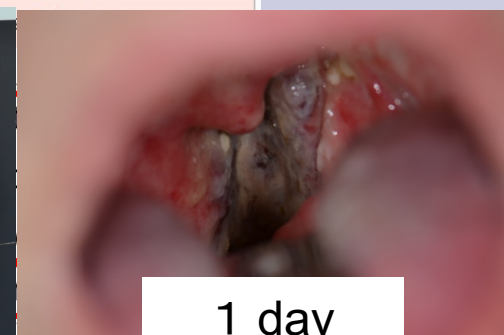


IMAGE: DR. KERSTIN STENSON READIES THE LASER OPTIC LEADS USED IN PHOTOIMMUNOTHERAPY.

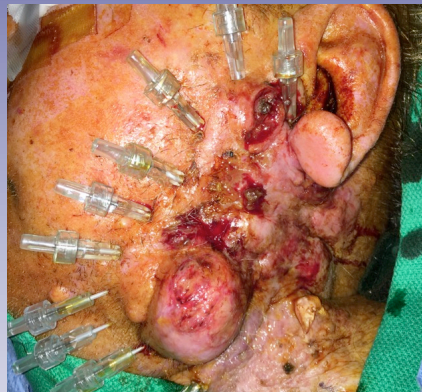
CANCER CELL BIOLOGY CLINIC
IMMUNOLOGY/ALLERGIES/ASTHMA
MEDICINE/HEALTH



Phase II study



HNSCC in 84 yo M



Intraop Fiber placement



1 month



3 months NED

Clinical Trial

Results Ph1/II

AEs have been minimal

No Photosensitivity

100% Response rate

57% Durable response rate

NCI Trial in the Clinical Center:

Optical/PET/MRI imaging after PIT

PI: Valia Saloura MD ACI

To start in 1st quarter 2019

Overall response rates (Phase 2: NIR-PIT RM-1929)

Best overall response (n=29)	RM 1929 (640mg/m ²): n (%)
Complete response	4 (13.8)
Partial response	9 (31)
Stable disease	11 (37.9)
Progressive disease	5 (17.2)
CR+PR	13 (44.8)
CR+PR+SD	24 (82.8)

Outcome in 10 patients who previously failed anti-PD1 Rx

Confirmed objective response rate	Complete responses	Disease control rate
3/10 (30%) Best ORR 40%	1/10	9/10 (90%)

Therapeutic Options for Recurrent HNSCC

- 30-50K new patients per year (EU, USA)+ 10K Japan

First Line Recurrent

Platinum based Chemo

ORR 16%, CR 0%
PFS 3.3 m
OS 7.4 m

Erbix + Platinum
ORR 36% CR 0%
PFS 5.6m
OS 10.1 m

2nd Line Recurrent

Erbix single agent

ORR 13%, CR 0%
PFS 2.8m
OS 6.1 m

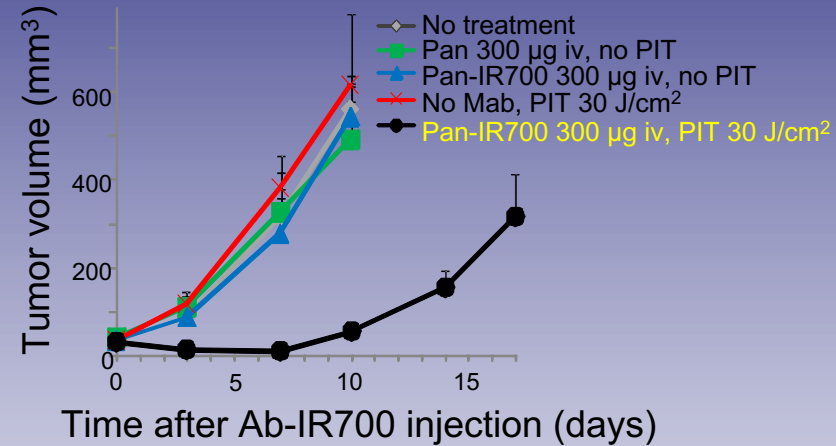
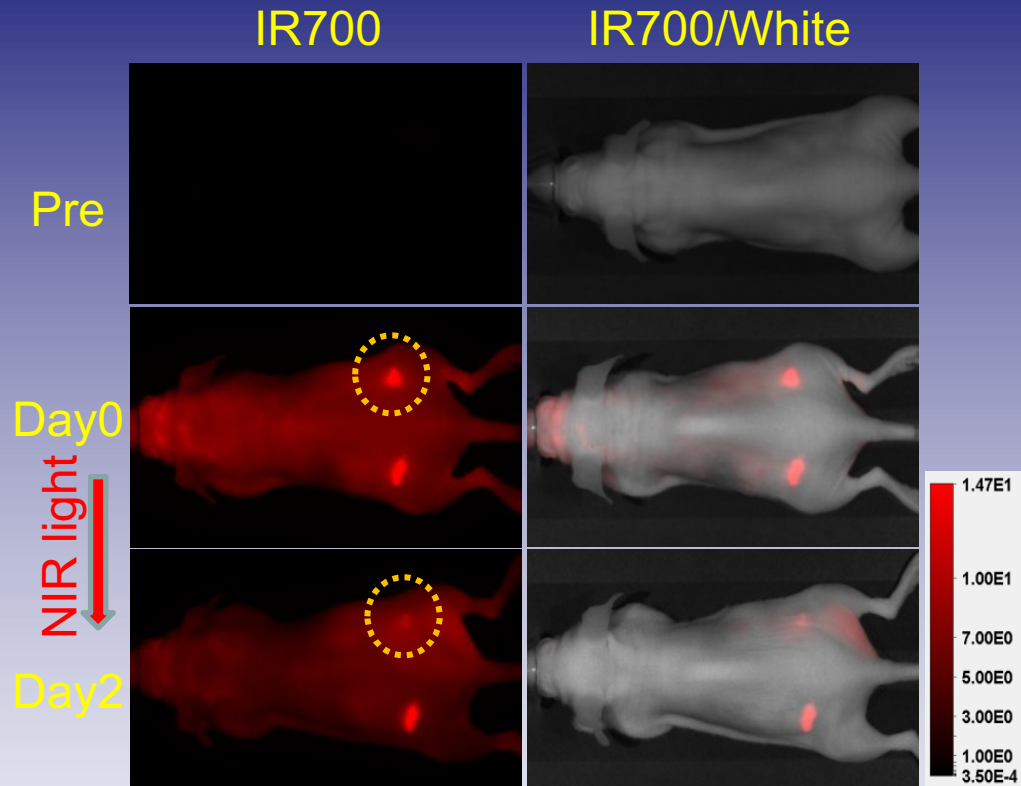
Opdivo single agent
ORR 13.3 % CR 2.5%
PFS 2m
OS 7.5 m

3rd Line Recurrent

RM 1929 single agent

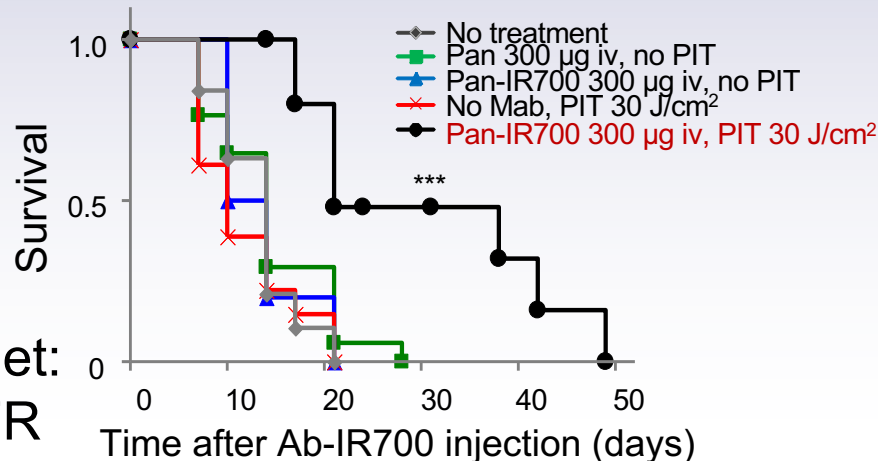
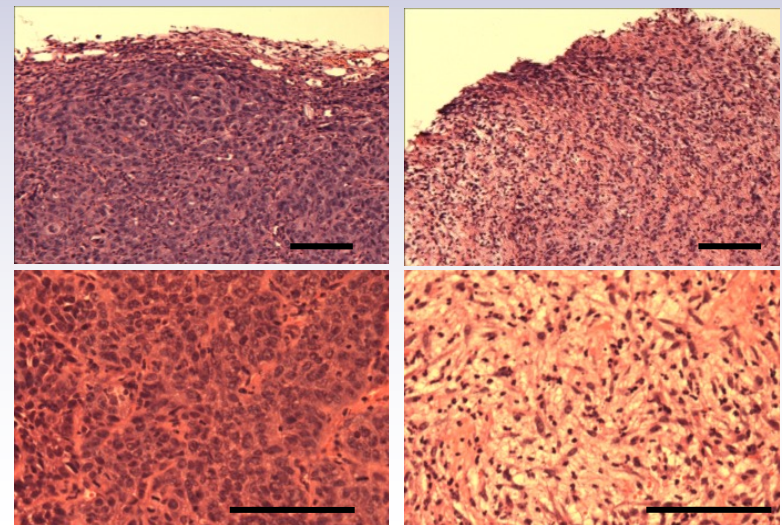
ORR 45%, CR 14%
PFS 5.7 m
OS 9.5 m

NIR-PIT cannot cure tumors in nude mice



No PIT control

Pan-IR700-PIT day 2



Target:
EGFR

NIR-PIT in humans-better than mice!

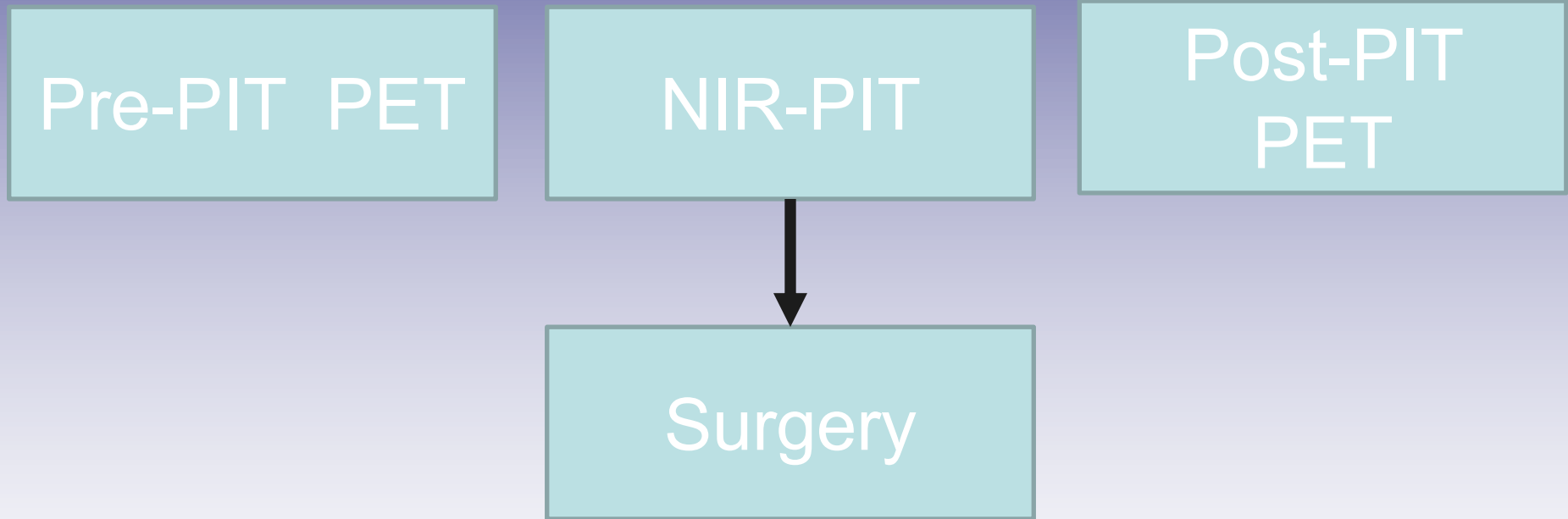
Pre-PIT



2 month after



Neoadjuvant trial at NIH



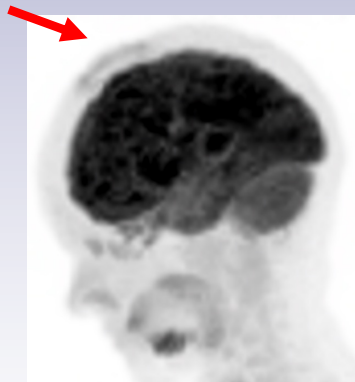
54 yo caucasian F with cT2N0M0 scalp SCC diagnosed in December 2021. She had a SCCA removed from the left posterior shoulder 15-20 years ago. Had closed cranial suture and cranioplasty as an infant. Scheduled for surgical resection . Underwent IR700-ab infusion 3-2-2022 and NIR illumination 3-3-2022.

18

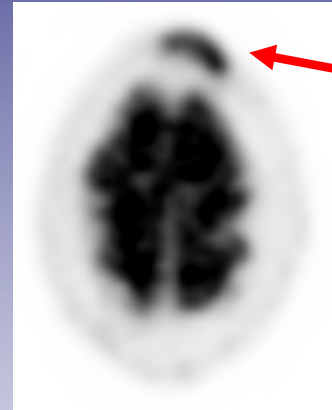
Pre
PIT 3-
1-2022



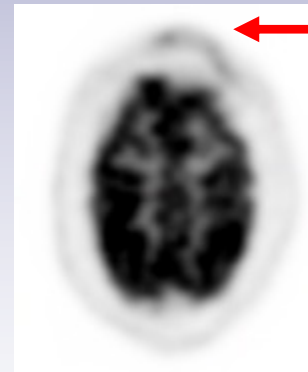
Post
PIT 3-
4-2022



Sagittal
MIP



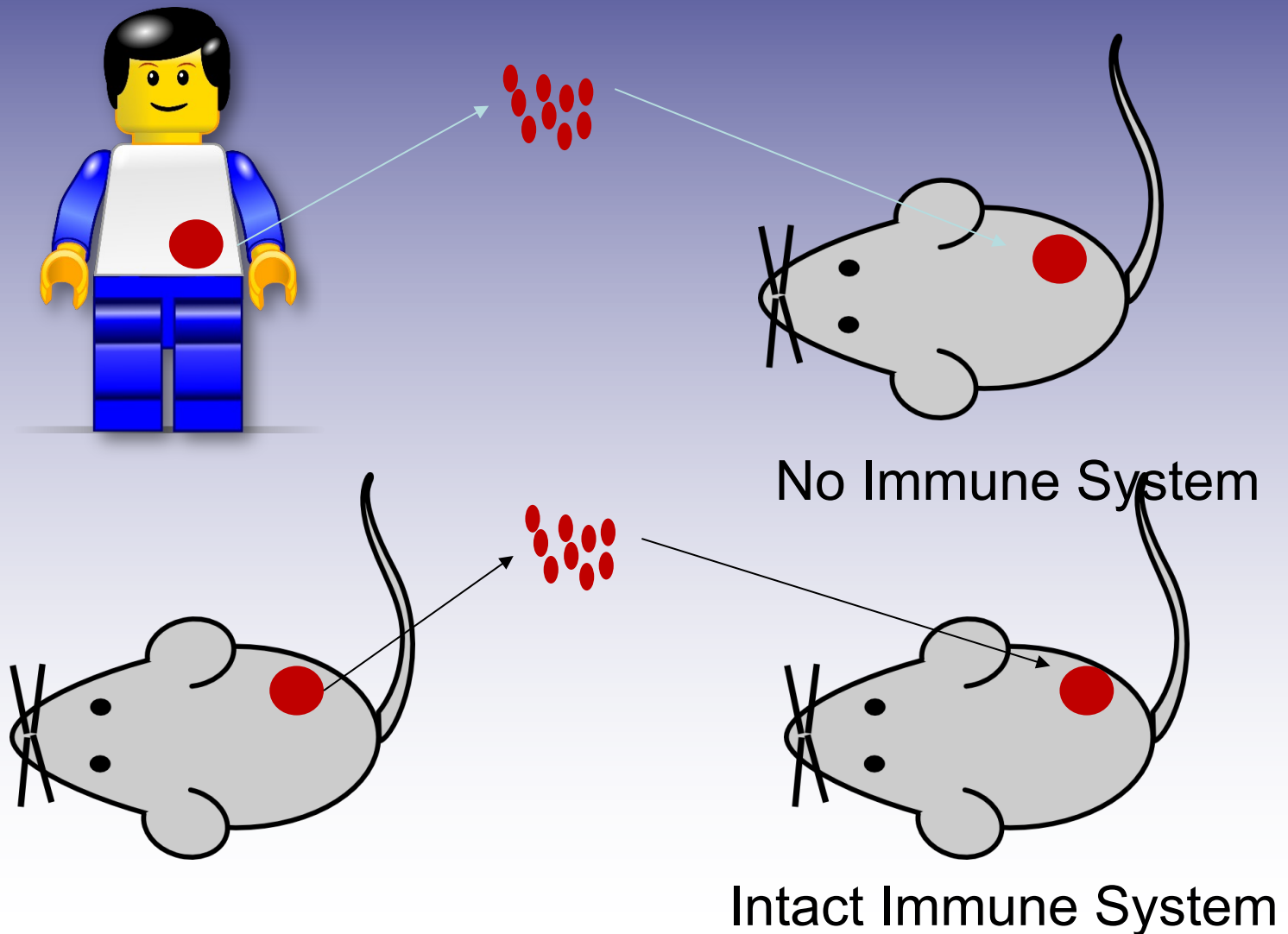
SUV
max
7.3



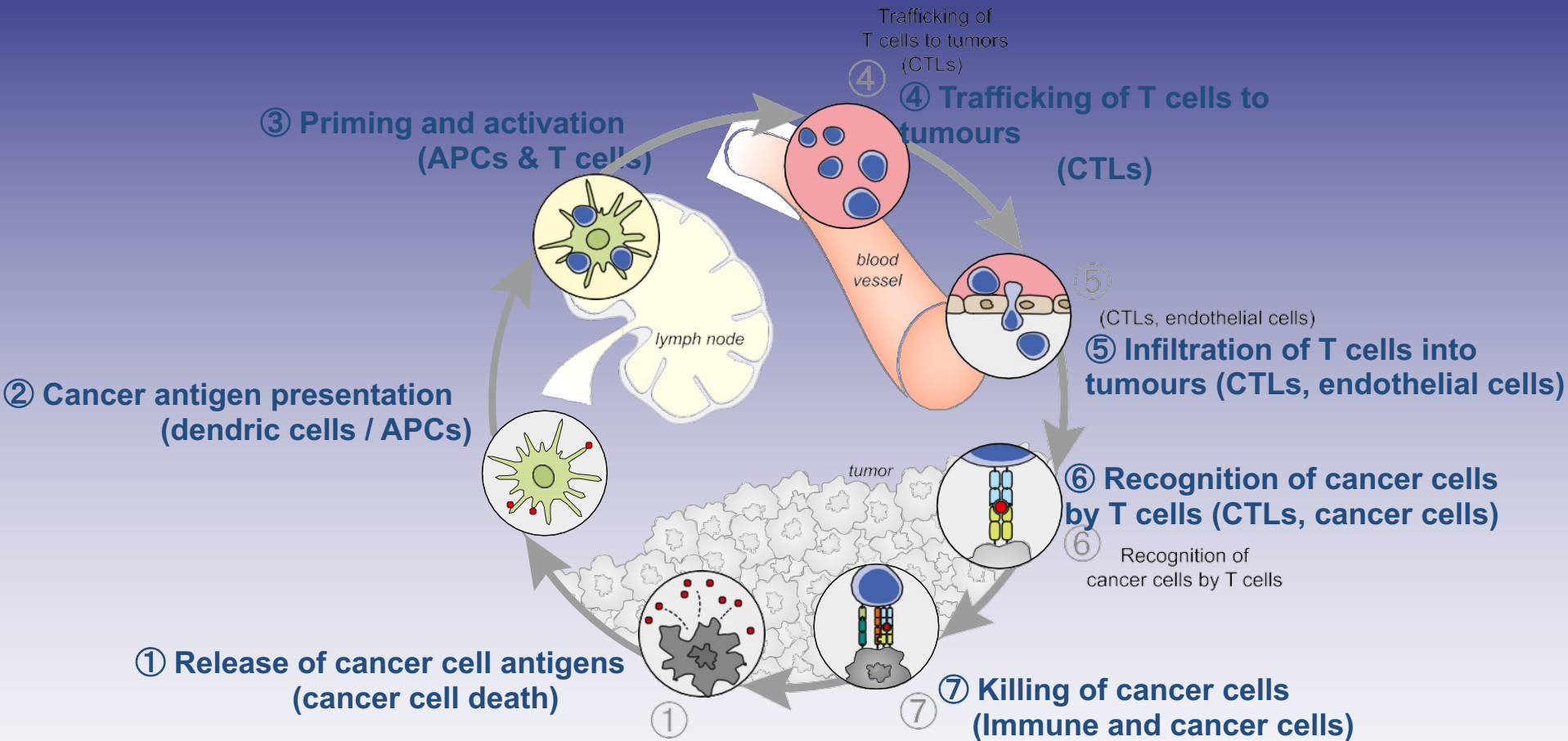
SUVm
ax 3.4

Axial
PET

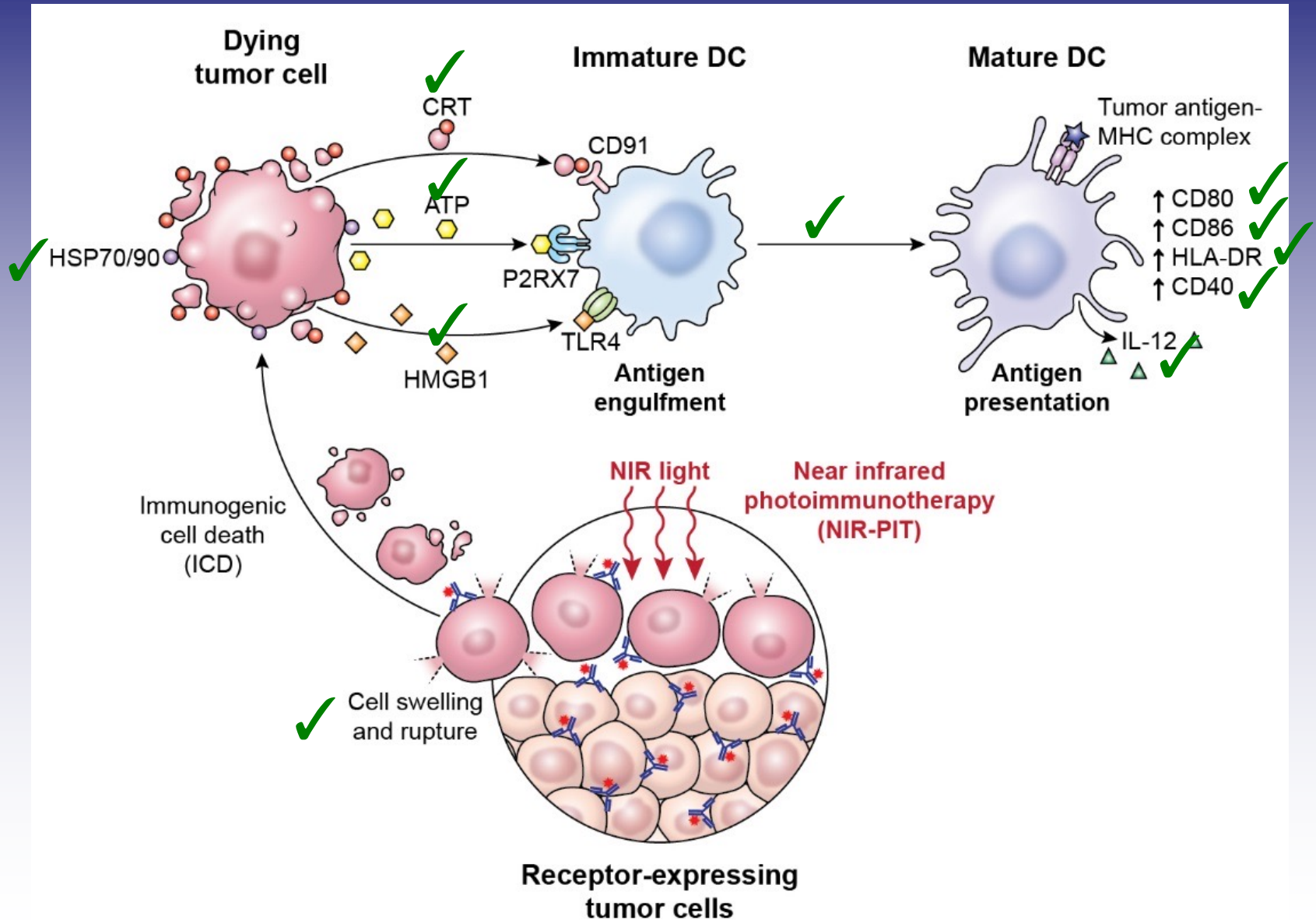
Xenograft vs. Syngeneic Model



The Cancer-Immunity cycle

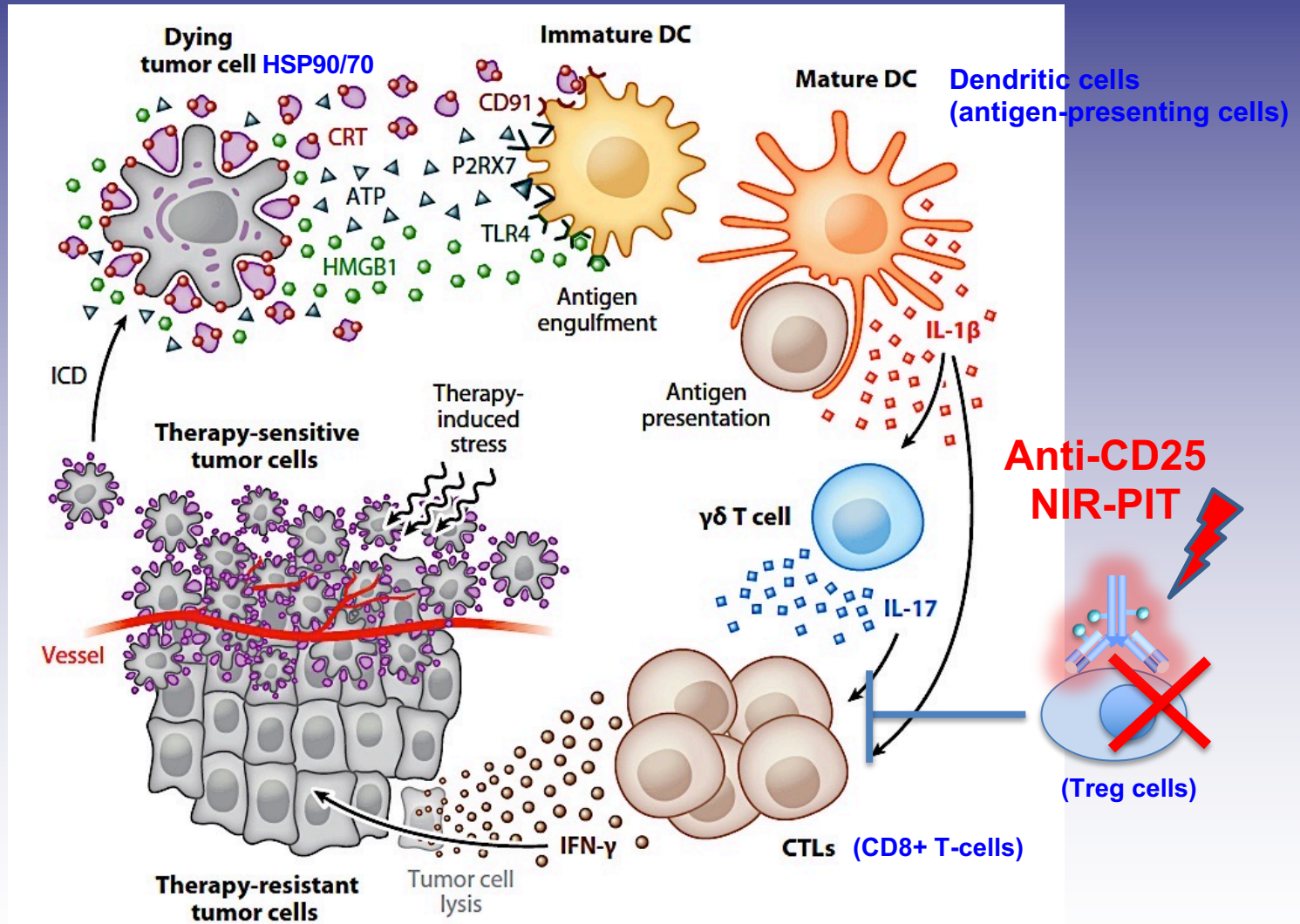


NIR-PIT induced immunogenic cell death

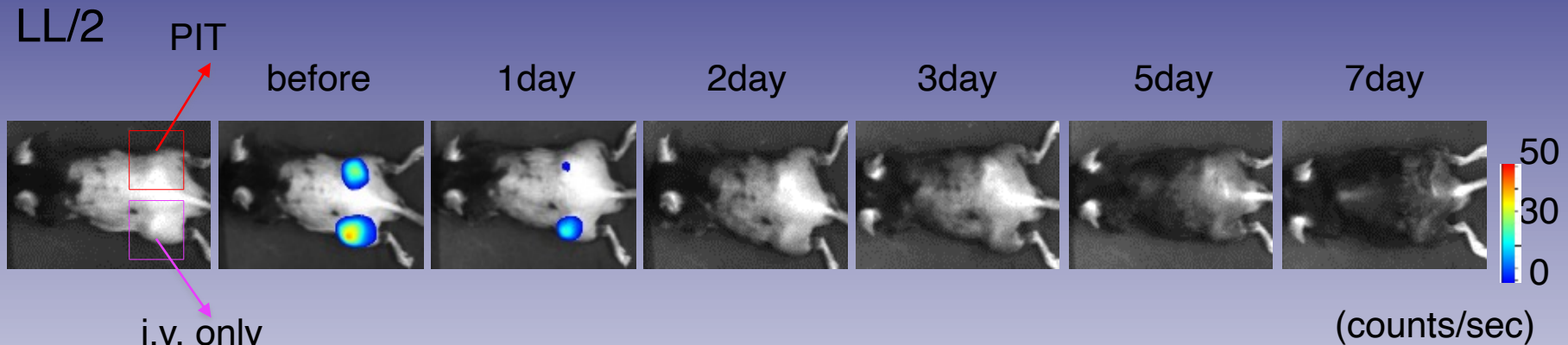


Immunomodulation with NIR-PIT

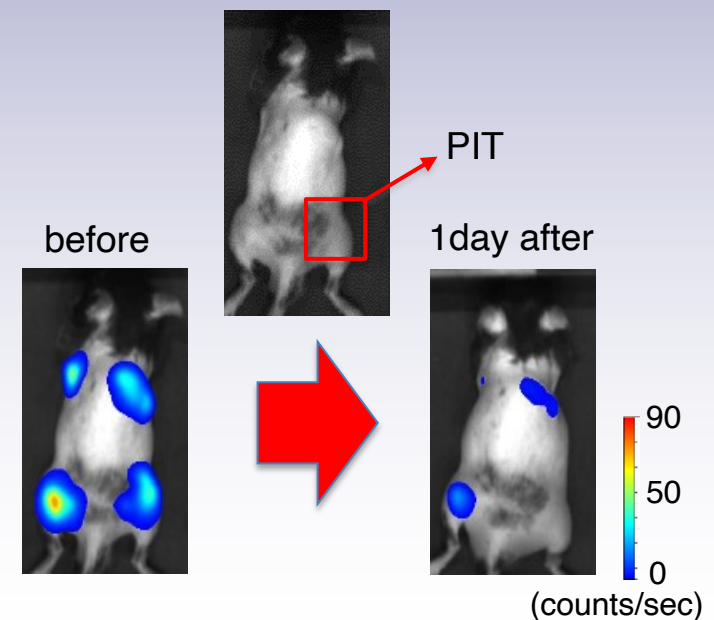
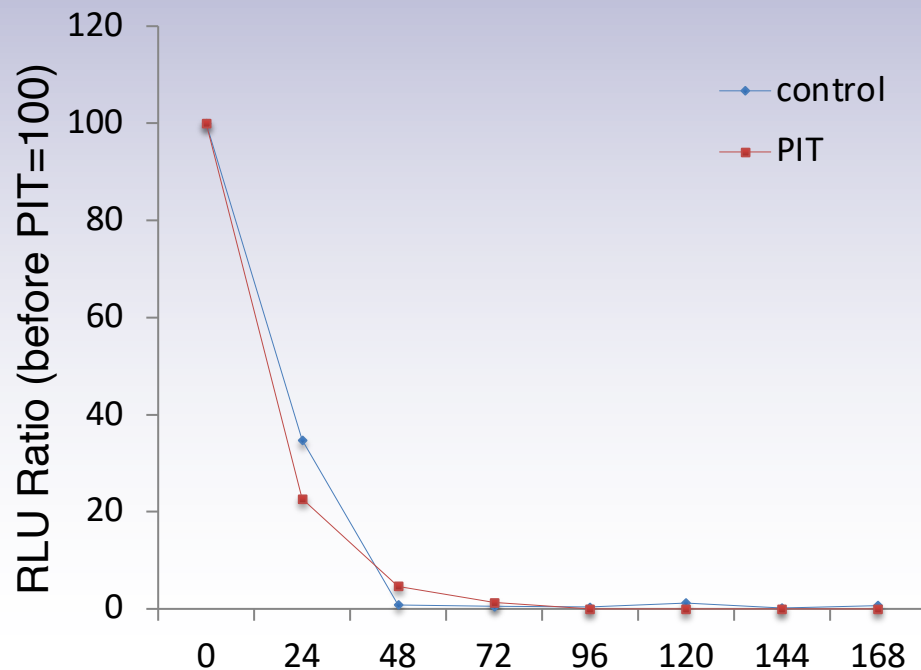
(NIR-PIT can activate acquired immunity and destroy cancer cells)



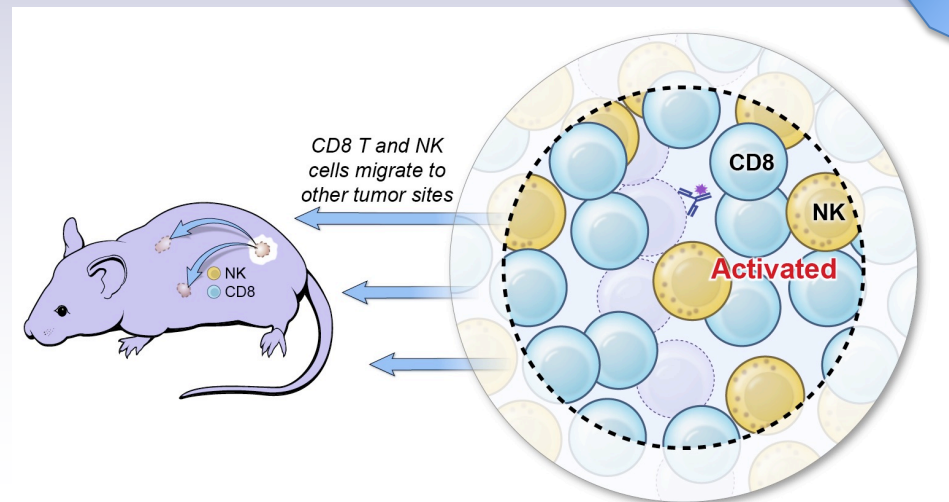
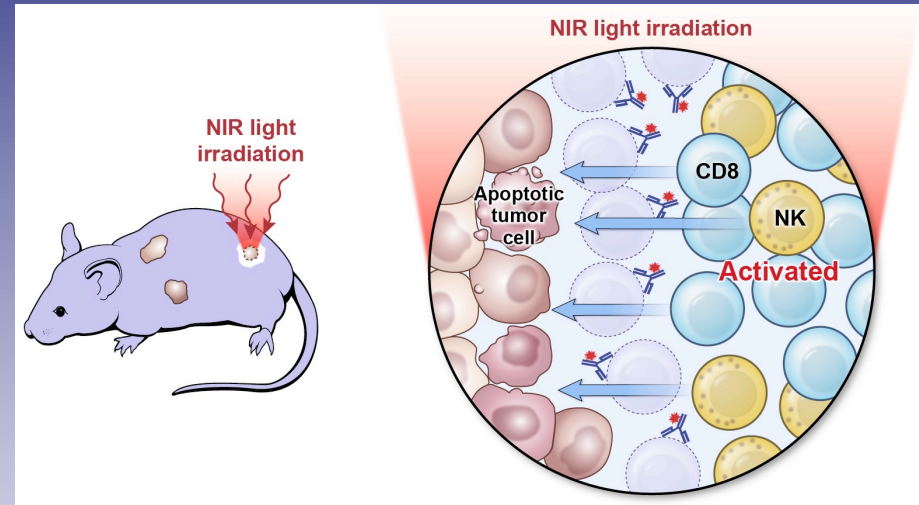
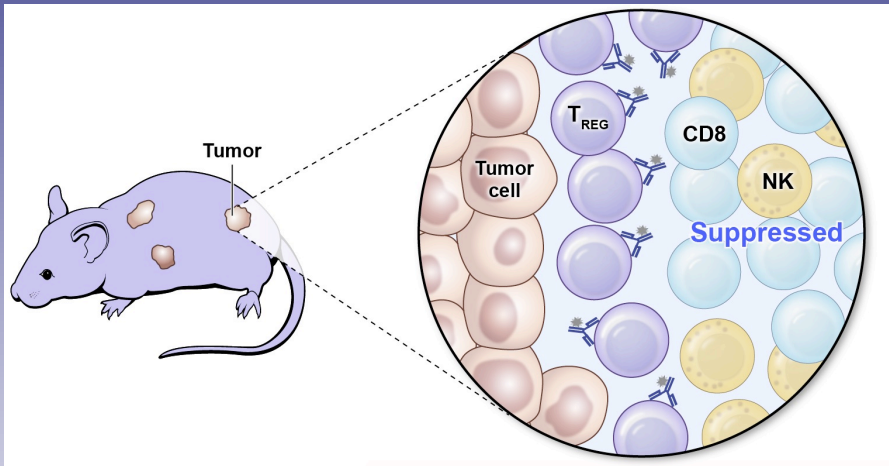
NIR-PIT-induced local knockdown of Treg cells with Fab'(2)-IR700 antiCD25



i.v. only

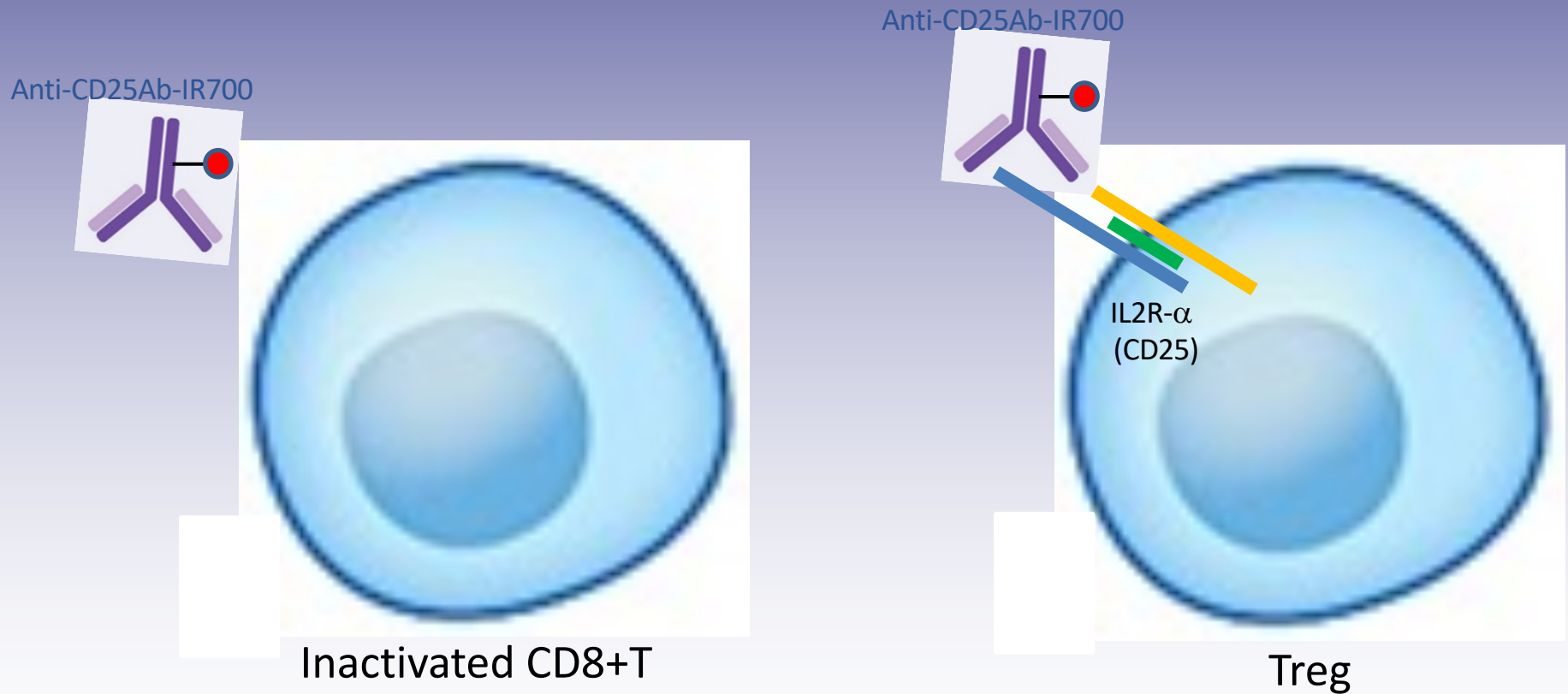


NIR-PIT induced acquired immunity by local knockdown of Treg cells

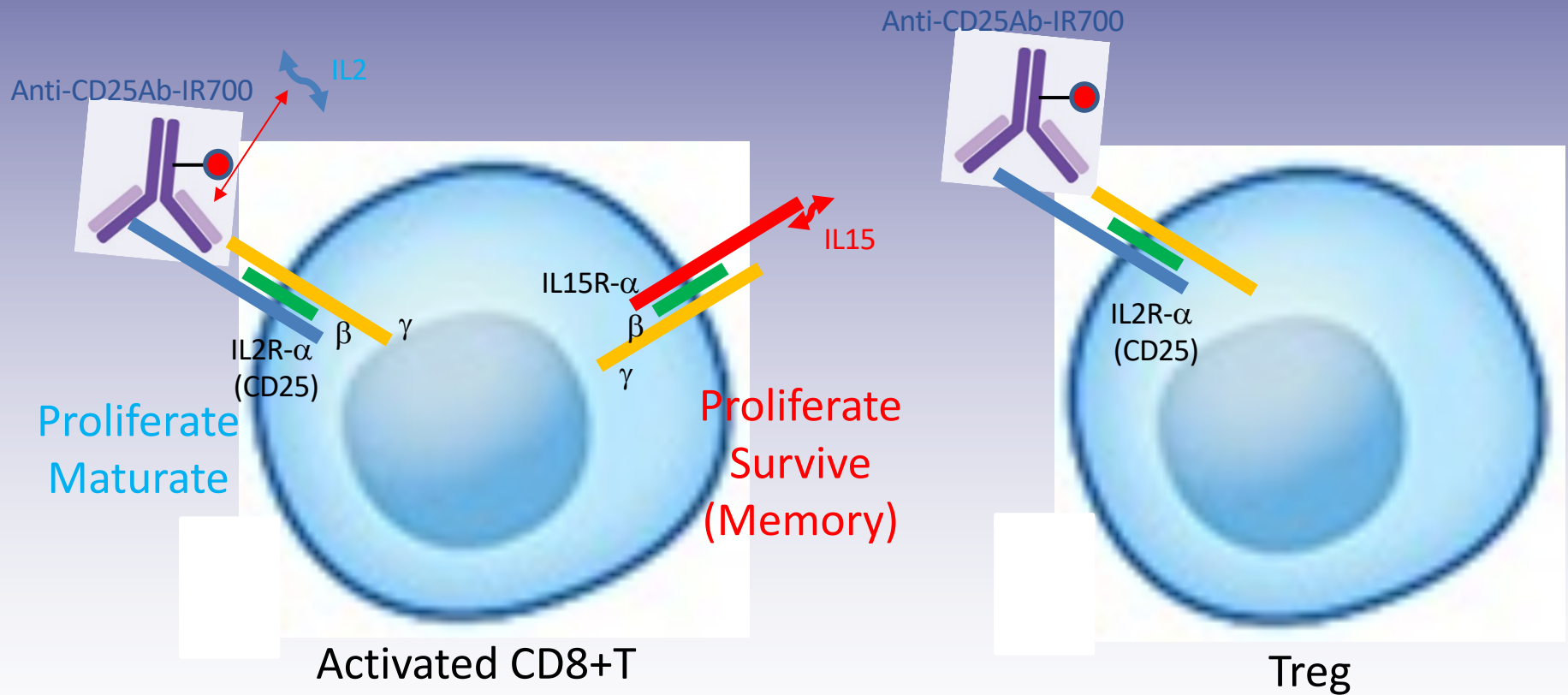


T-reg cell elimination process/ PIT

Why Fab'(2)?

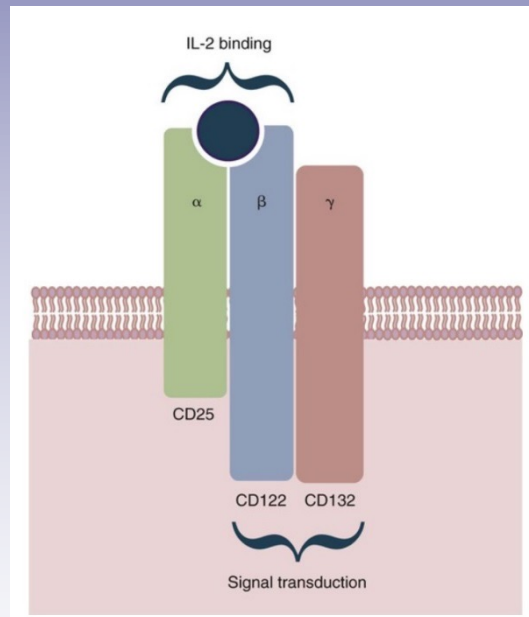


Concern: T-cell activation process/ PIT

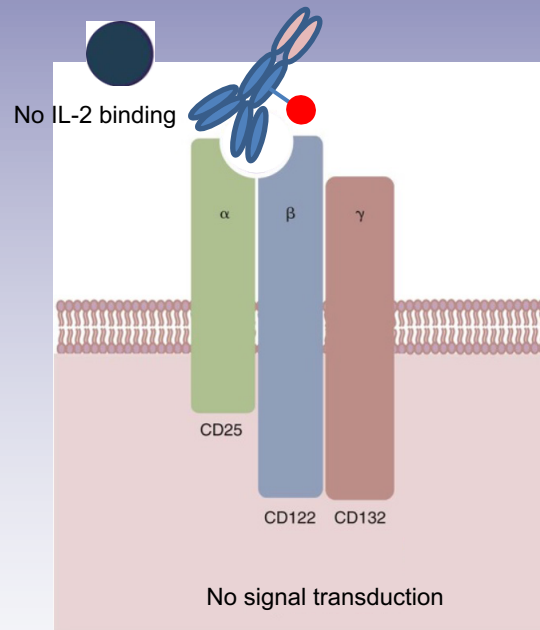


Treg targeted NIR-PIT via CD25

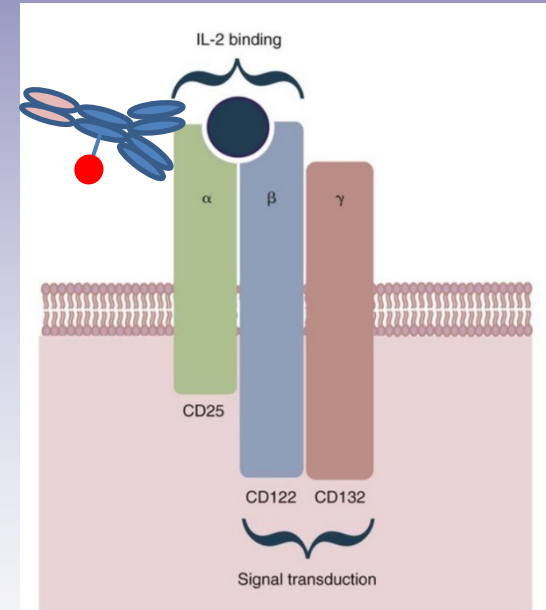
Importance of IL2 receptor



No Ab

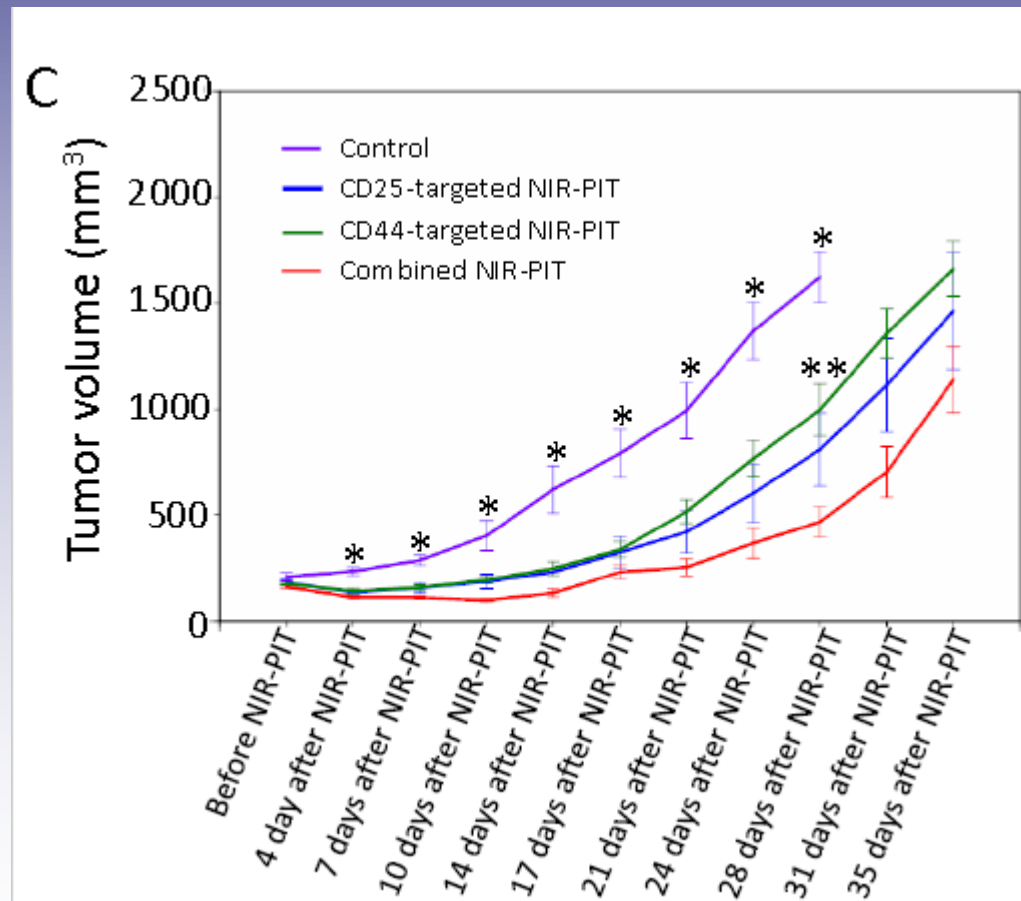


IL-2 blocking anti-CD25 Ab-IR700

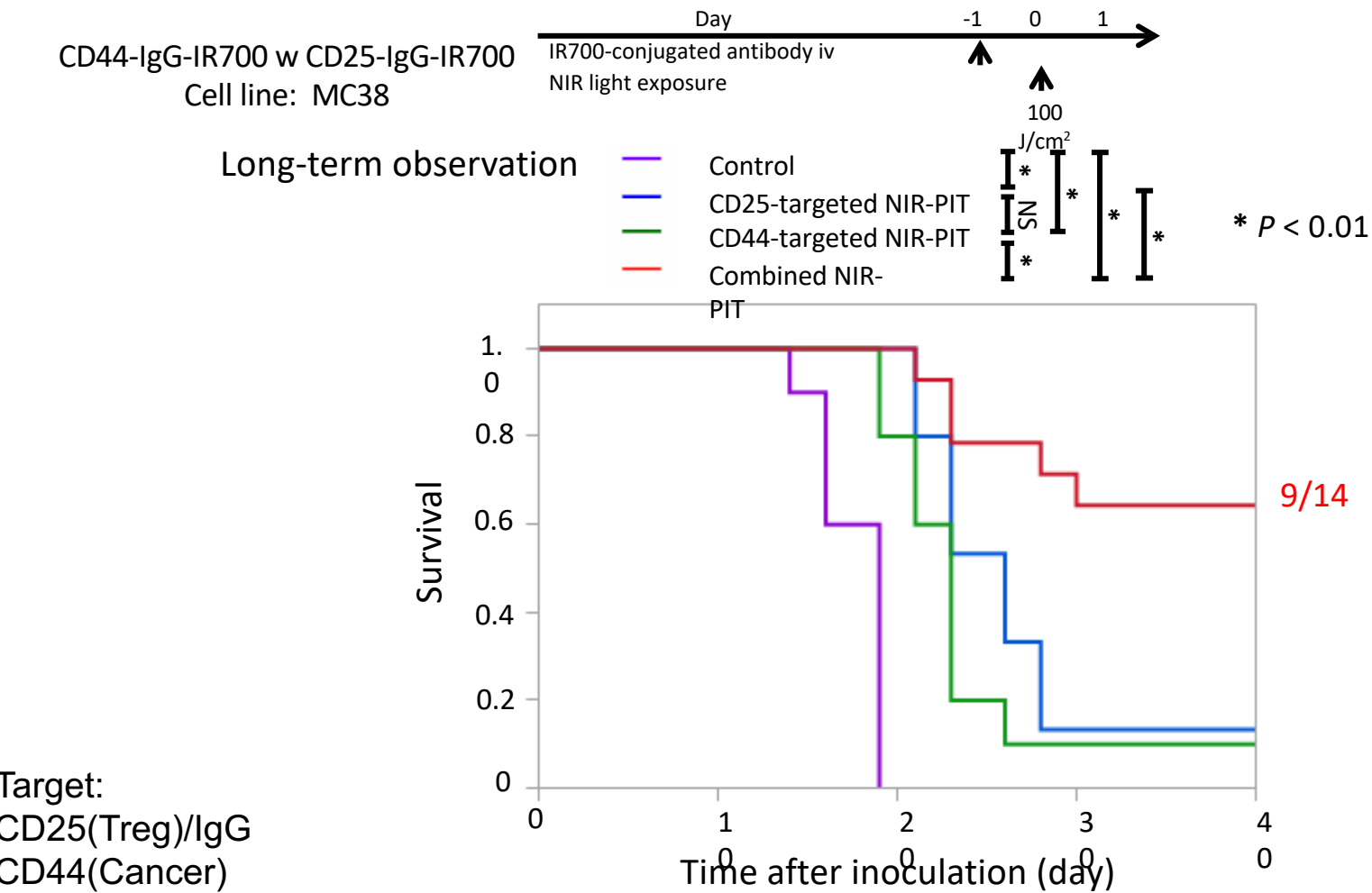


IL-2 non-blocking anti-CD25 Ab-IR700

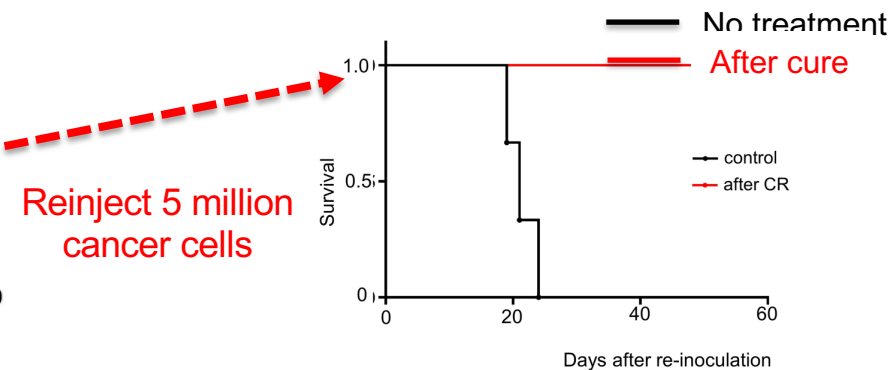
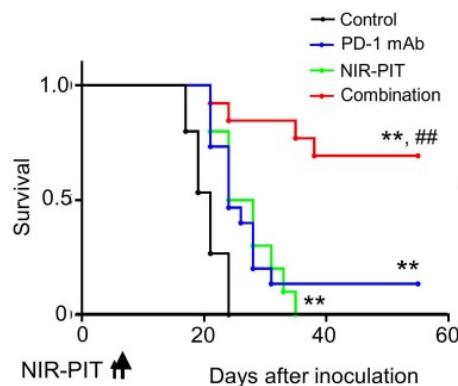
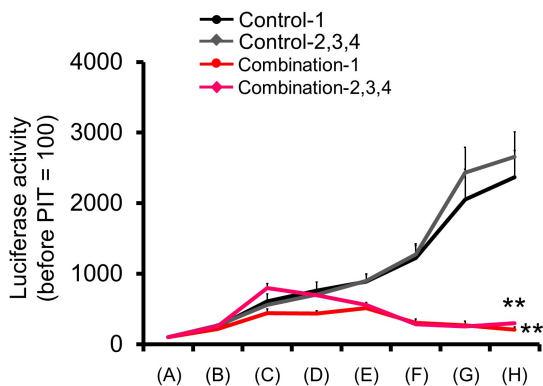
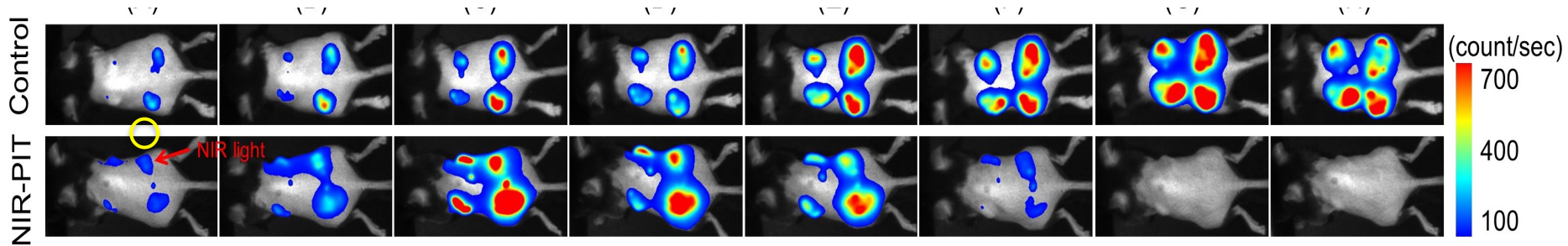
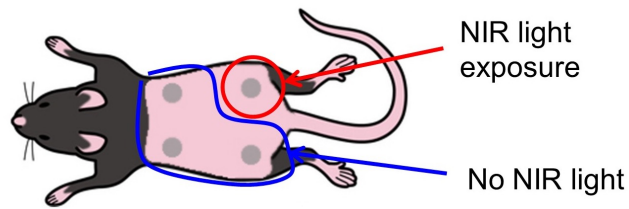
Combined tumor targeted and Treg targeted PIT:

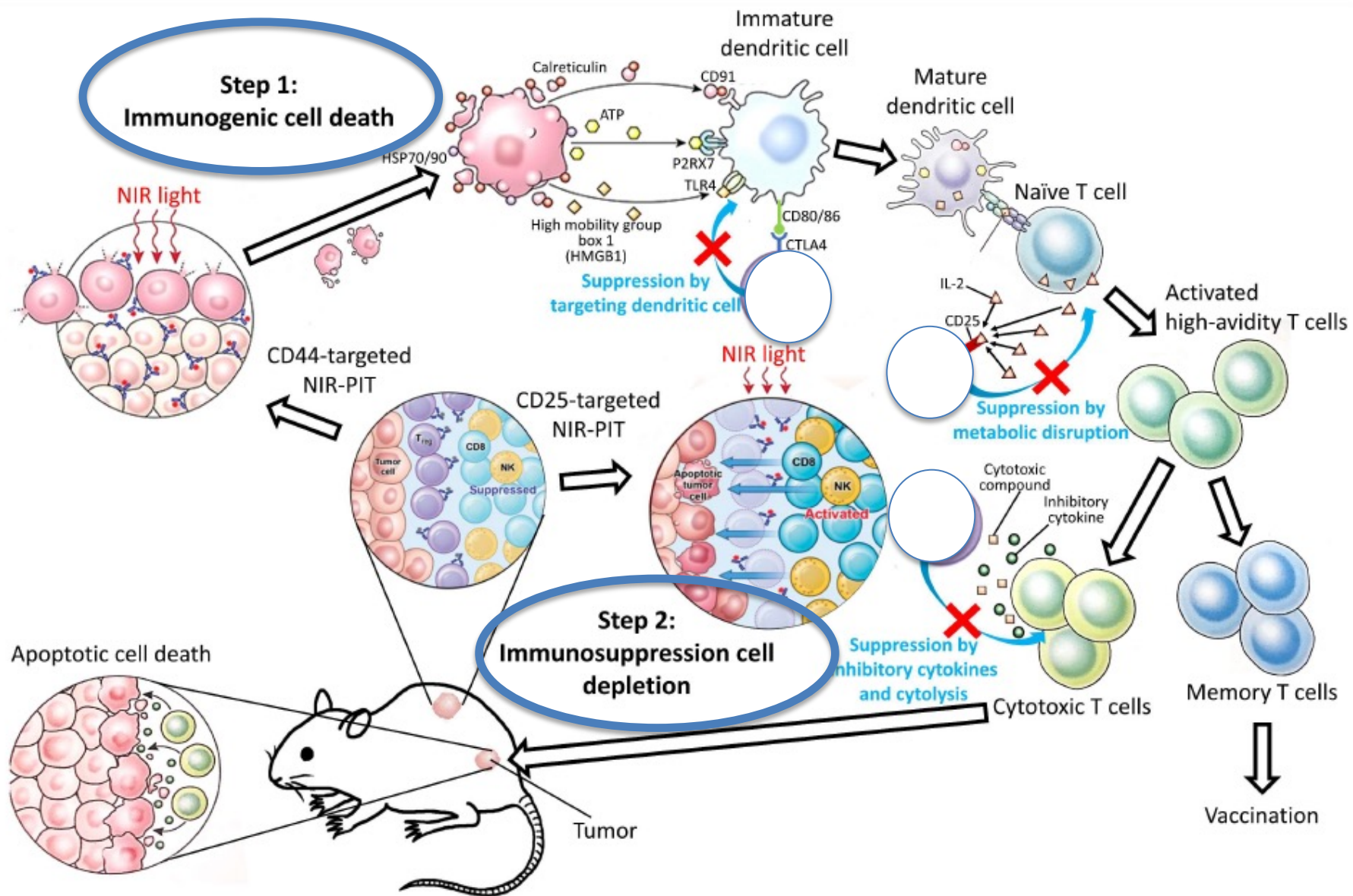


Combination with CD25(Treg)- and CD44(Cancer)-targeted NIR-PIT



Cancer-PIT combined with immuno-activation cure local and distant cancers without recurrence



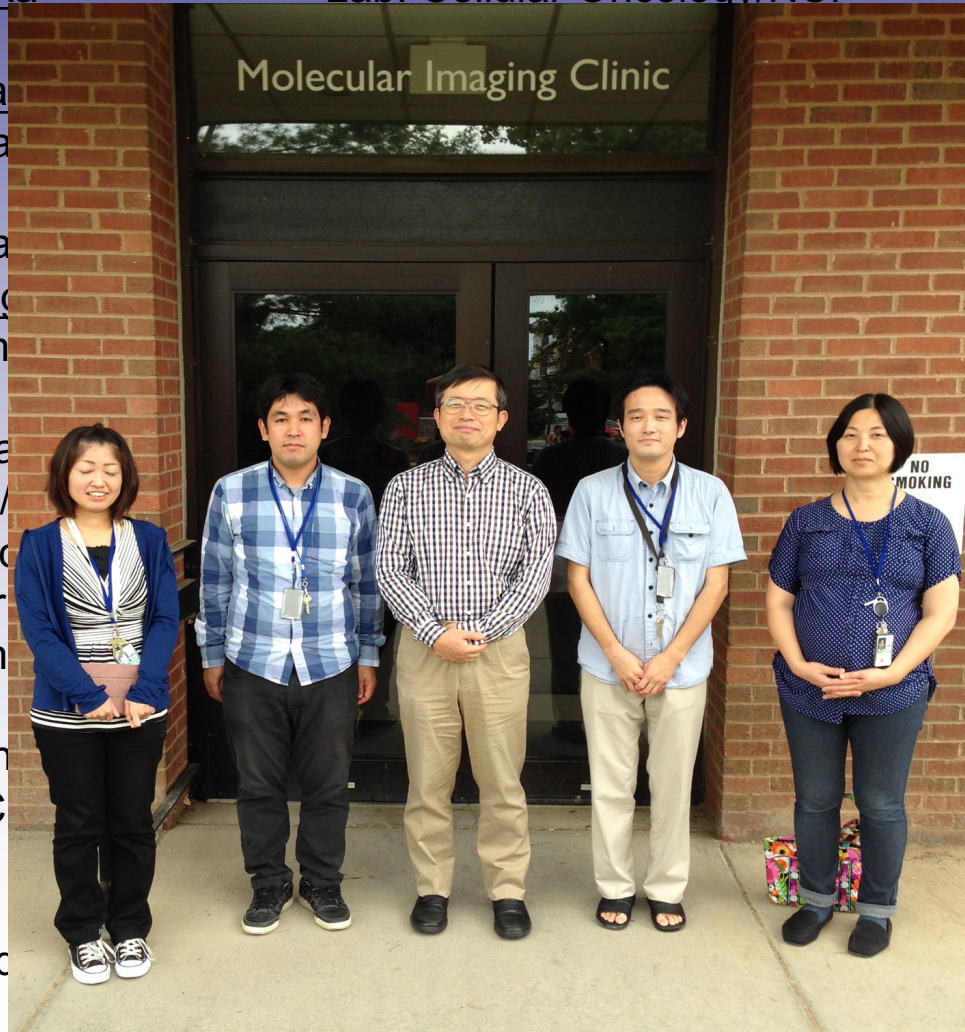


PIT: A Disruptive Technology

- Where do we go from here?
 - Combinations of tumor targeted antibodies and immune targeted antibodies
 - E.g. PSMA and MDSC PIT
 - E.g. EGFR and FGF and Treg PIT
- Who will do it?
 - Initially surgeons in ORs
 - Shift to outpatient, IR delivery
 - “A strong arm and a fiber optic catheter....”

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