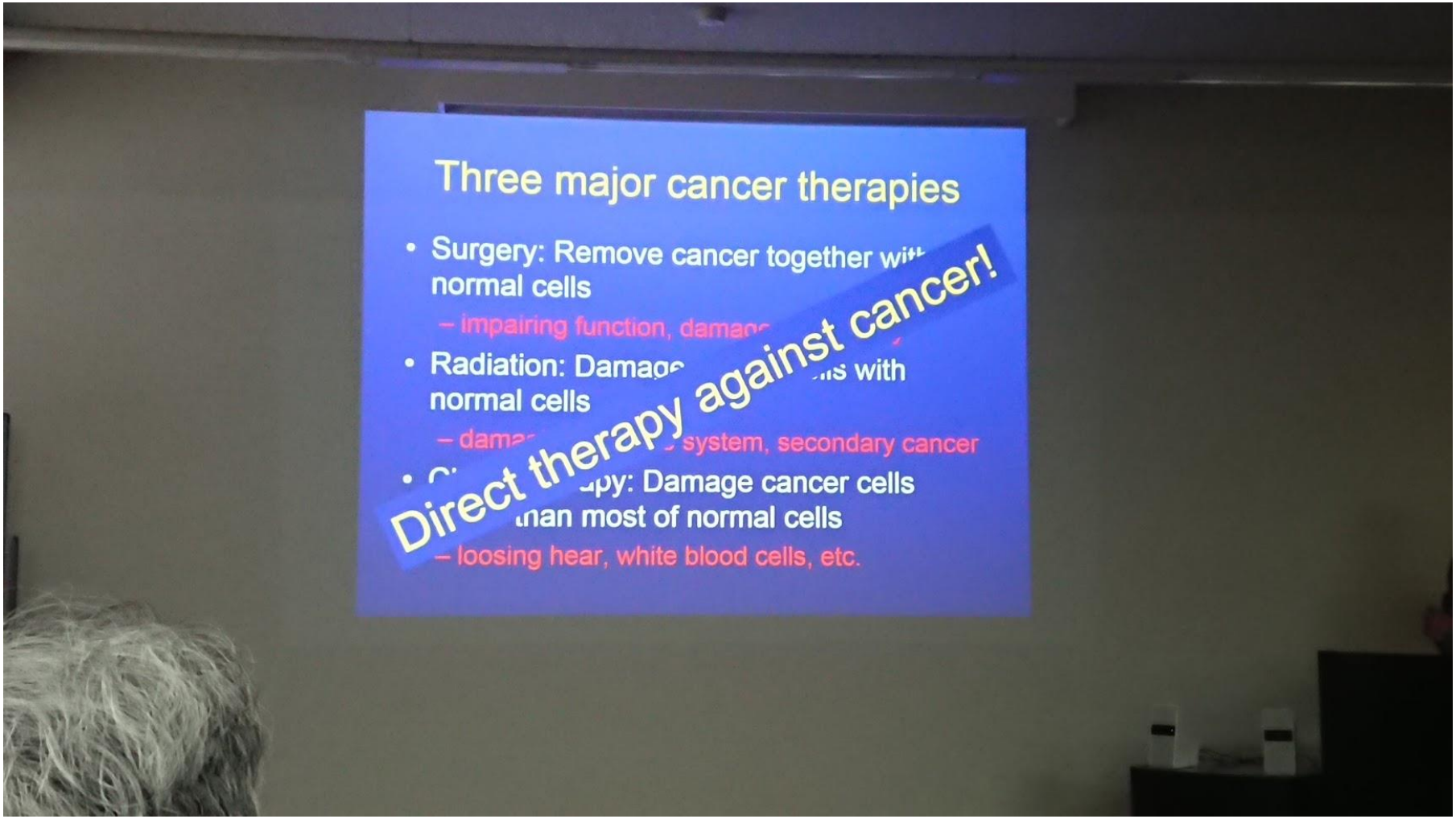
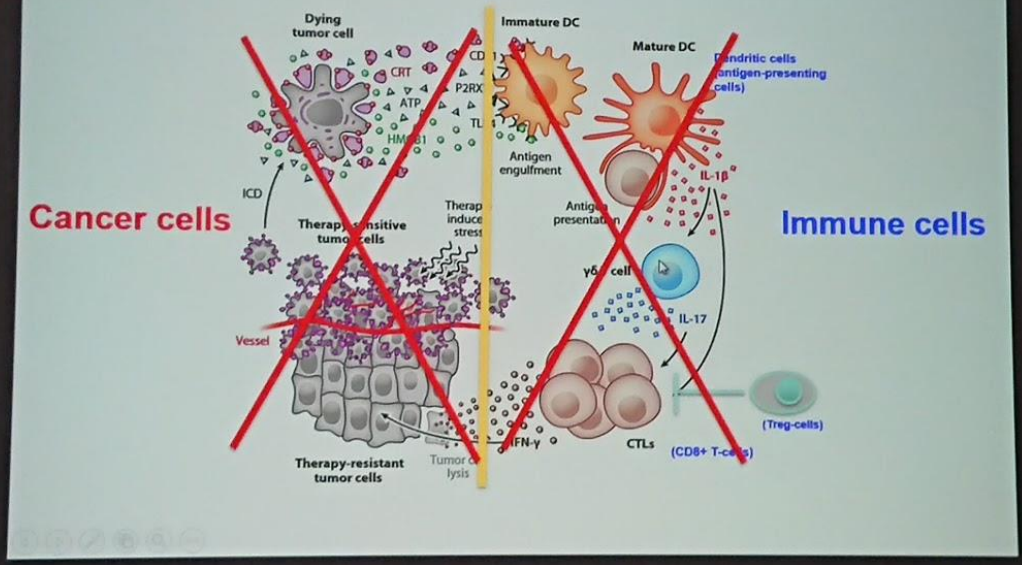

Near infrared photoimmunotherapy for cancer
Hisataka Kobayashi, MD, PhD
Molecular Imaging Program,
NCI /NIH, Bethesda, MD
関西研講演 (2018/03/20, Nara, Japan)

Three major cancer therapies

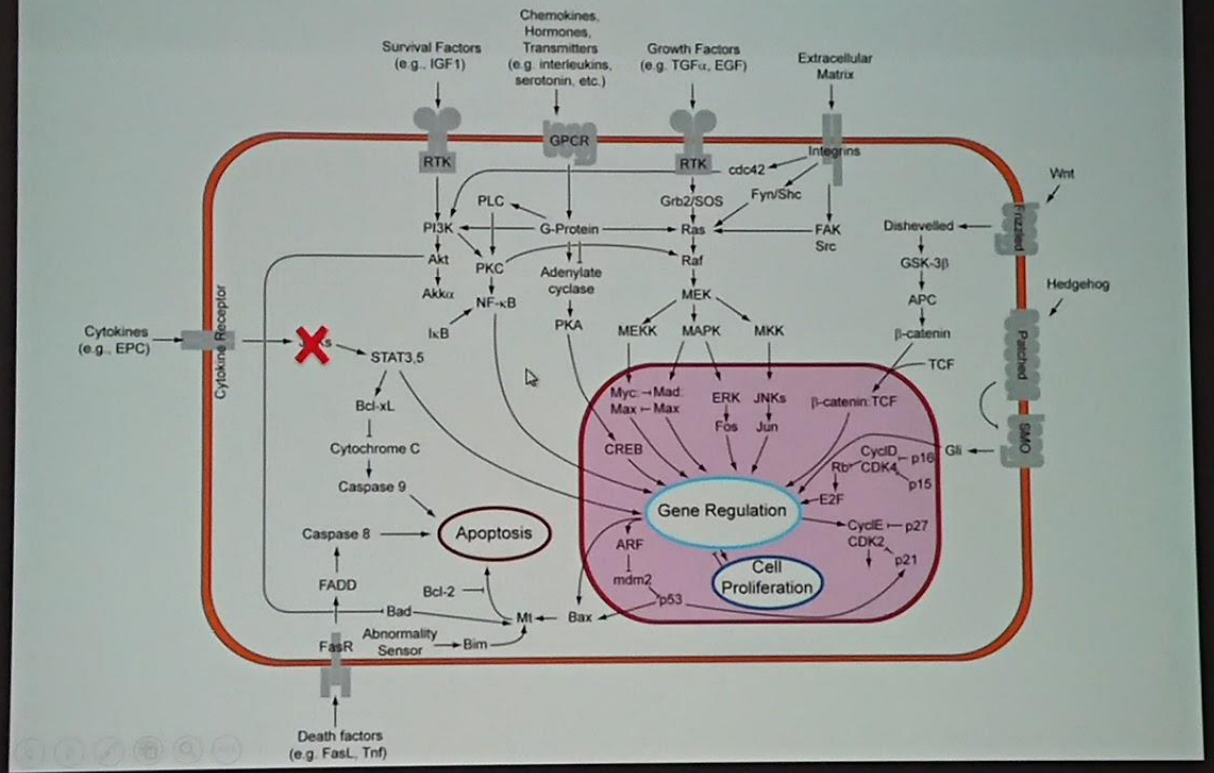
- Surgery: Remove cancer together with normal cells
  - impairing function, damage to the body
- Radiation: Damage cancer cells with normal cells
  - damaging immune system, secondary cancer
- Chemotherapy: Damage cancer cells better than most of normal cells
  - loosing hear, white blood cells, etc.


Three major cancer therapies
• Surgery: Remove cancer together wit
normal cells
– impairing function, damag
• Radiation: Damag
normal cells
– dama
system, secondary cancer
• C
apy: Damage cancer cells
nan most of normal cells
– loosing hear, white blood cells, etc.
Direct therapy against cancer!

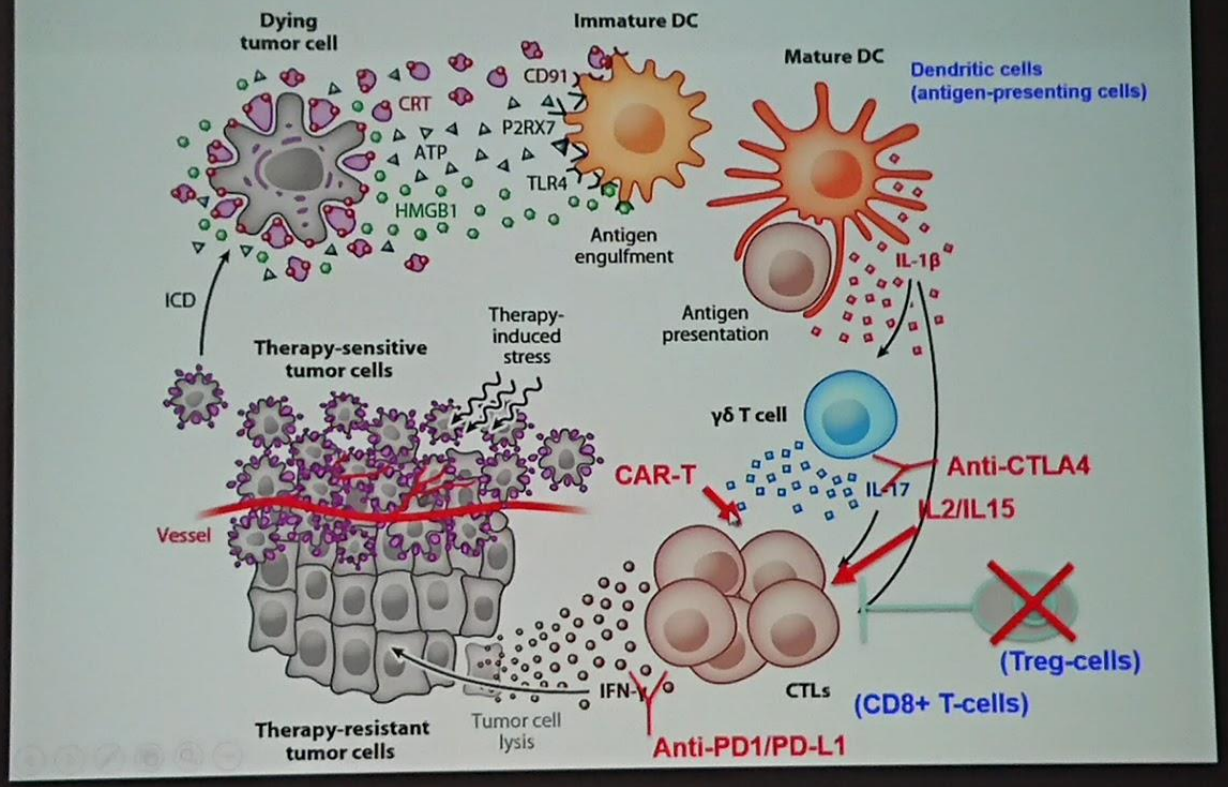
Three major cancer therapies



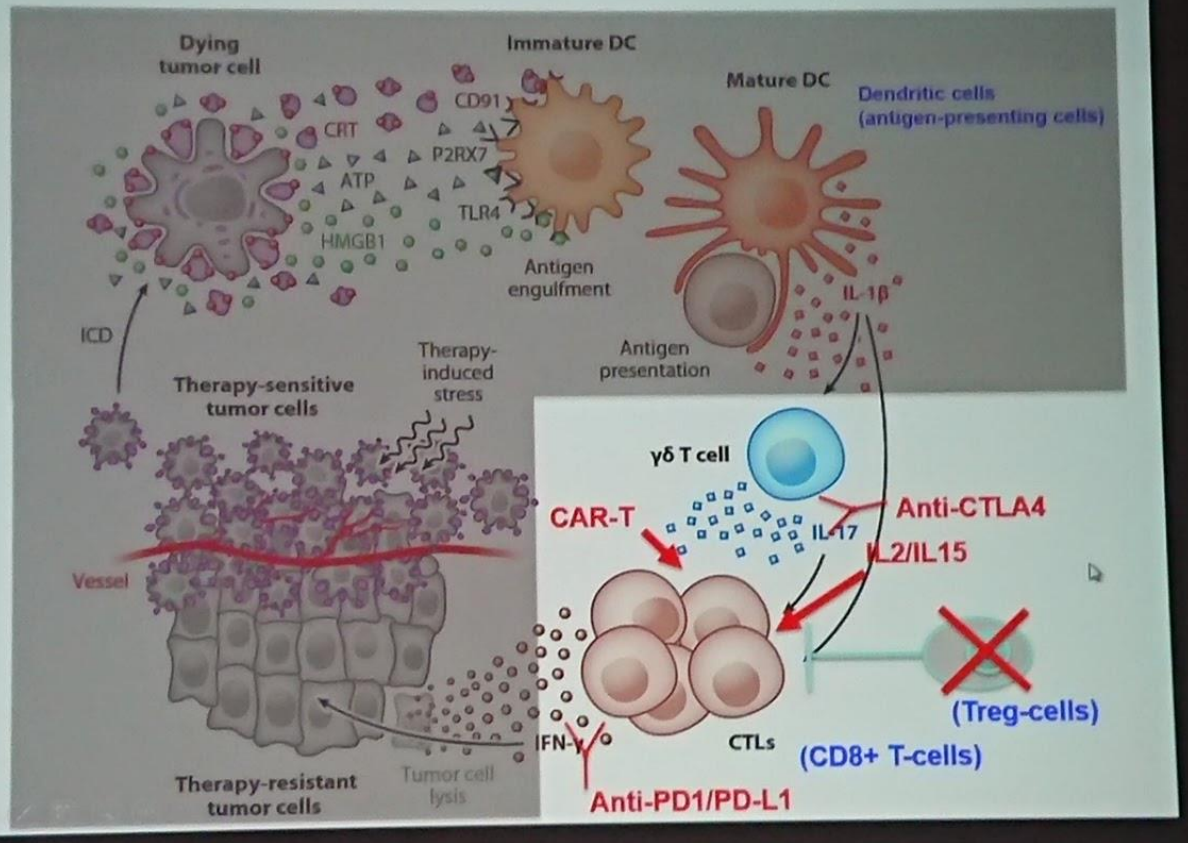
Molecular-target therapy



Cancer immunotherapies

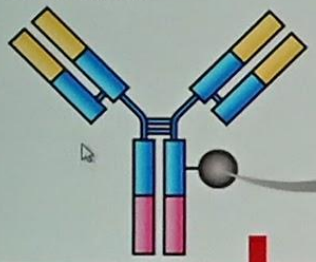


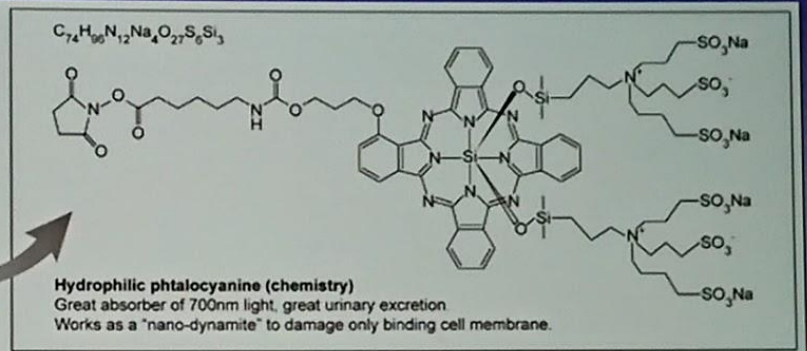
Cancer immunotherapies



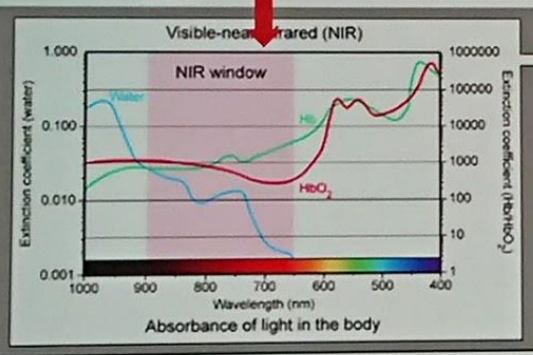
Near infrared photo-immunotherapy (NIR-PIT)

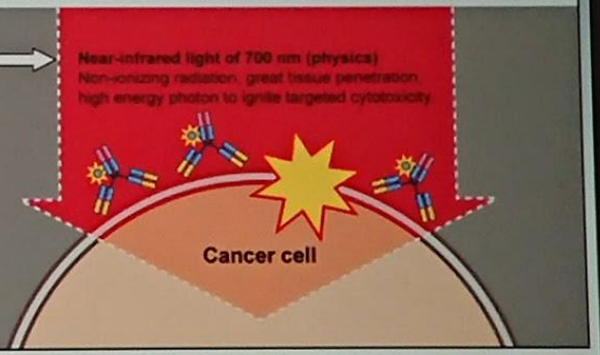
Humanized monoclonal antibody (biology/medicine)
Highest binding specificity, greatest *in vivo* target delivery, applicable to the clinical practice.



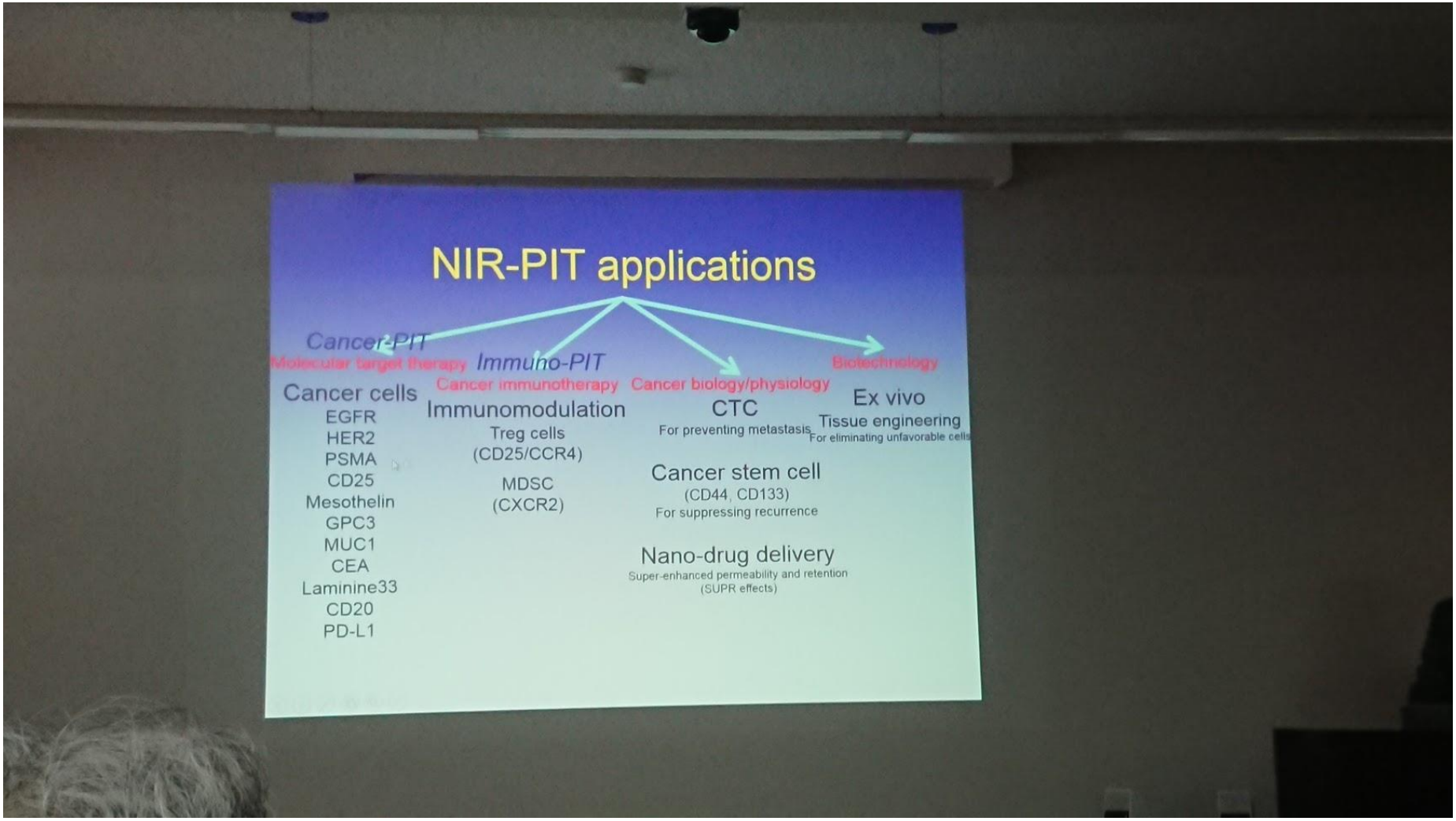


Hydrophilic phtalocyanine (chemistry)
Great absorber of 700nm light, great urinary excretion
Works as a "nano-dynamite" to damage only binding cell membrane.

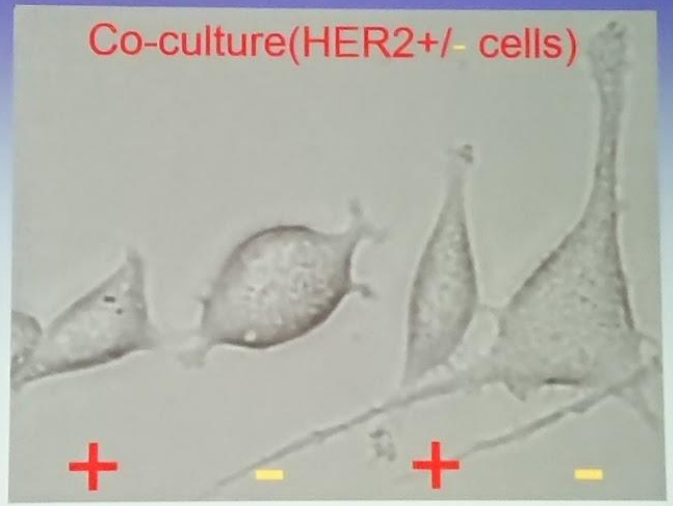




Mitsunaga , Kobayashi, Nature Med, 2011/12


NIR-PIT applications
Cancer-PIT
Molecular target therapy
Cancer cells
EGFR
HER2
PSMA
CD25
Mesothelin
GPC3
MUC1
CEA
Laminine33
CD20
PD-L1
Immuno-PIT
Cancer immunotherapy
Immunomodulation
Treg cells
(CD25/CCR4)
MDSC
(CXCR2)
Cancer biology/physiology
CTC
For preventing metastasis
Cancer stem cell
(CD44, CD133)
For suppressing recurrence
Nano-drug delivery
Super-enhanced permeability and retention
(SUPR effects)
Biotechnology
Ex vivo
Tissue engineering
For eliminating unfavorable cells

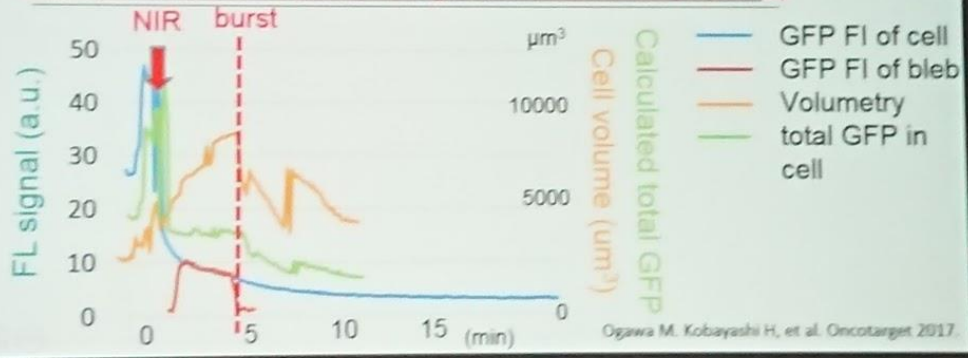
NIR-PIT selectively killed only target-expressing cells



Target:
HER2

Direct killing with release of cellular contents by NIR-PIT

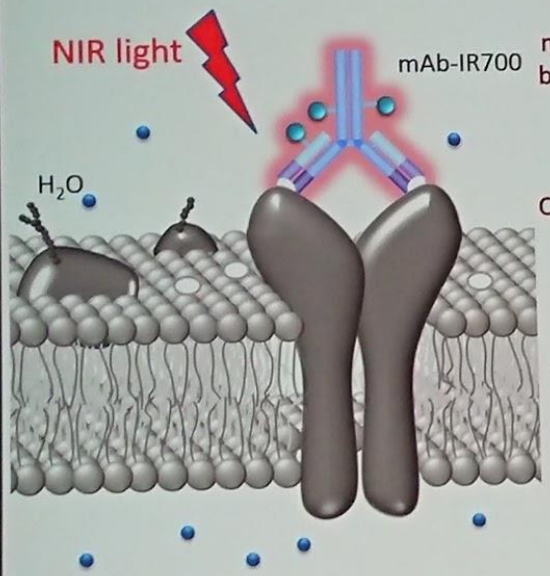
Dynamic 3D-image of 3T3/HER2 cell expressing GFP in the cytoplasm (Stereo view)
Dual-view inverted selective plane (sheet light) illumination microscope (diSPIM)



Target:
HER2

Ogawa M. Kobayashi H, et al. Oncotarget 2017.

NIR-PIT induced cell swelling and release of intracellular contents



mAb-IR700 specifically binds to the target cell.

↓

NIR irradiation

↓

Cell membrane damage to make "holes".

↓

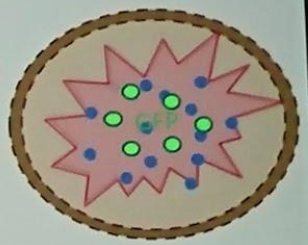
Flowing water molecules into cells through the damaged cell membrane.

↓

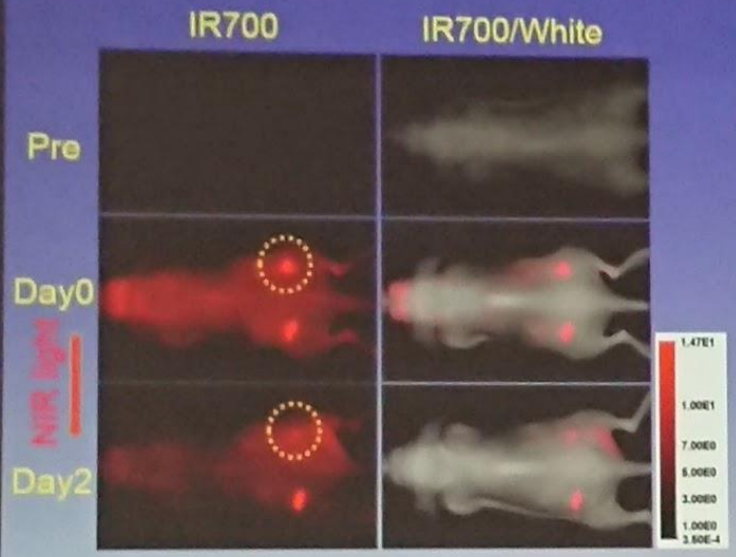
Cell expansion

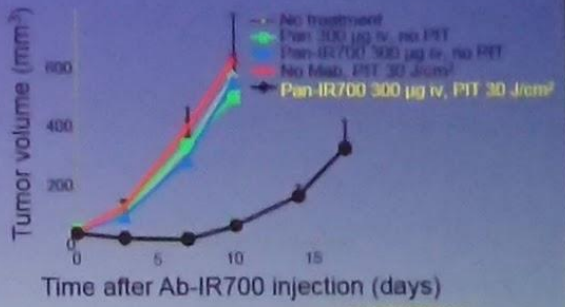
↓

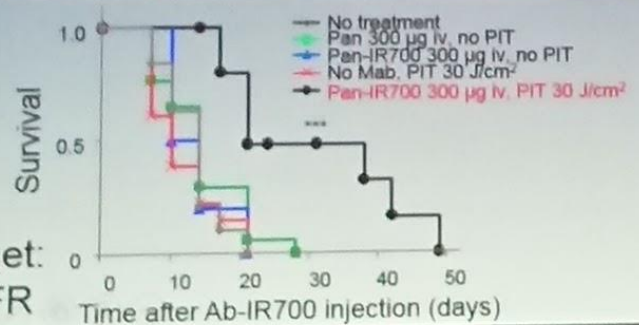
Cell death



NIR-PIT cannot cure tumors in nude mice



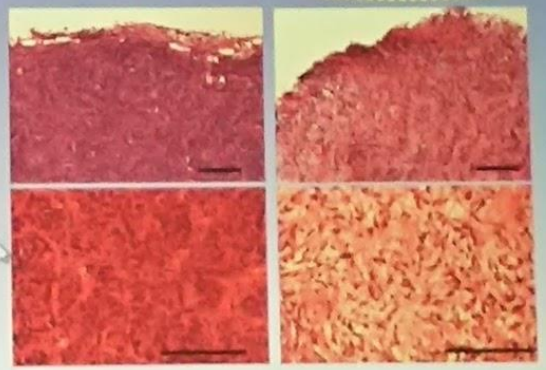




Target:
EGFR

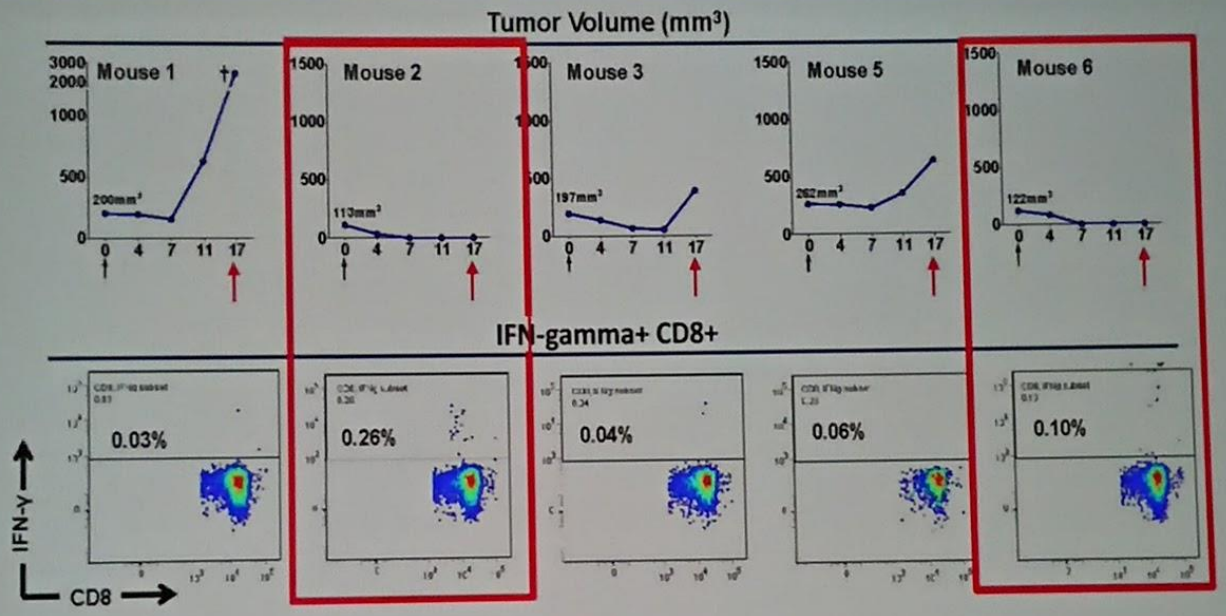
No PIT control

Pan-IR700-PIT day 2



NIR-PIT induces acquired immune response

Heparanase targeted NIR-PIT cured TC-1 tumors with 1 shot of treatment

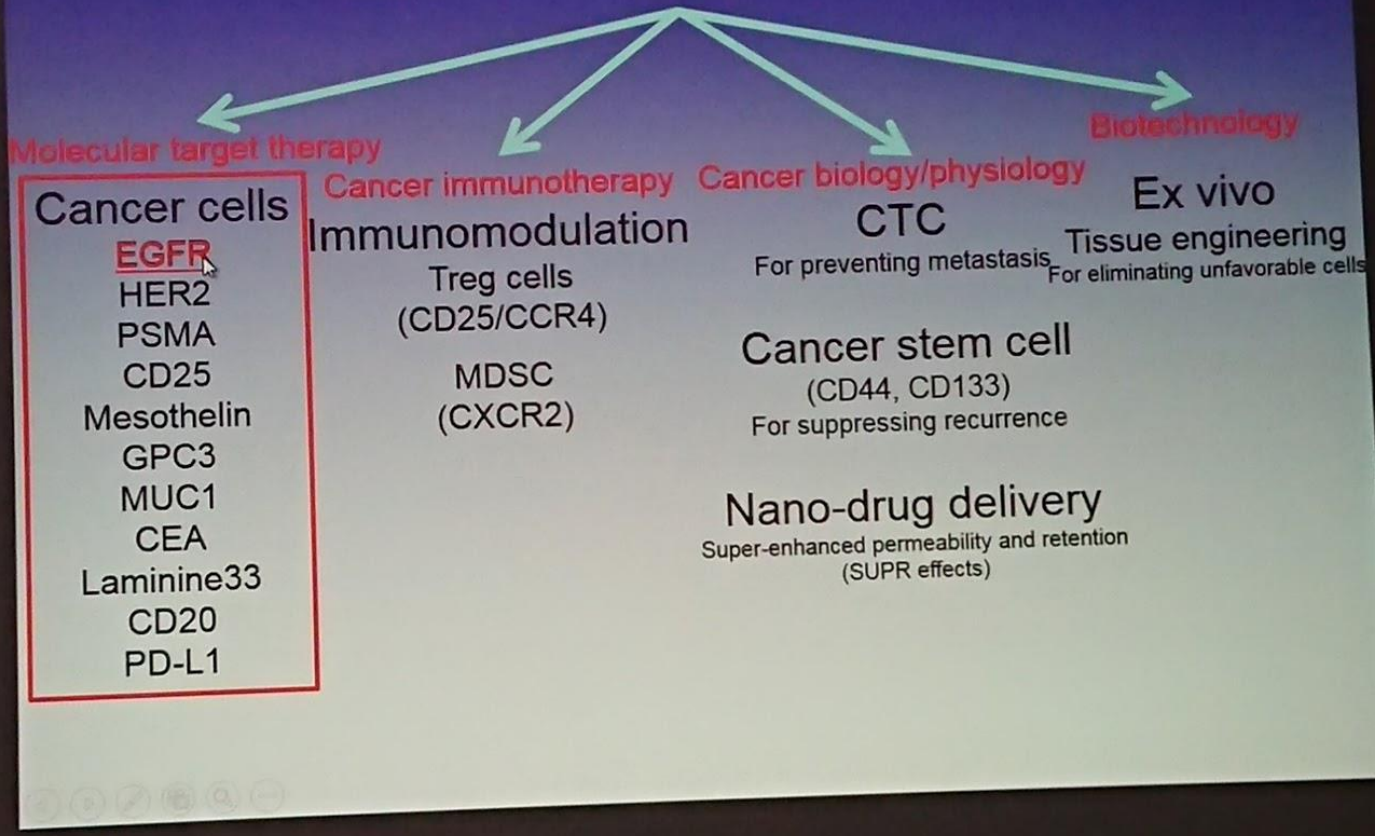


Cured mice had specific CD8+ T-cell response, therefore, re-injected TC-1 tumors did not grow in these mice.

Target:
Heparanase

Kines R, Kobayashi H, Schiller J, In Preparation

NIR-PIT applications



Phase I, Head and Neck Cancer Study Design

Phase I study, recurrent/unresectable Head and Neck Cancer that failed conventional therapies. (Antibody-conjugate dose escalation)

Step 1: RM-1929 infusion

Outpatient service

Step 2: Tumor illumination at 24 h

Phase 1 Study
RM-1929 Dose Escalation, fixed light dose
Duration: 2015/6-2016/6
Total Patients: up to 24 → 10
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***. • 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
Clinical Sites: up to 3 clinical sites in the USA

Target:
EGFR

NIR-PIT in a clinical trial

EurekAlert! The Global Source for Science News | AAAS

SEARCH ARCHIVE

ADVANCED SEARCH

HOME NEWS MULTIMEDIA MEETINGS PORTALS ABOUT LOGIN REGISTER

PUBLIC RELEASE: 15-NOV-2016

Photoimmu
spares near

Head and neck cancer c

RUSH UNIVERSITY MEDICA

Media Contact

"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.

When Kerstin Stenson, M
innovative technique she
to fight cancer, it seems li
a Tom Clancy military esp

Stenson is treating patien
photoimmunotherapy. PI
experimental technique t
immune system's ability t
cells precisely with laser energy's ability to destroy those cells. Like a high-tech weapon in a Clancy thriller, PIT delivers extremely precise, lethal payloads with minimum collateral damage.

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

KEYWORDS

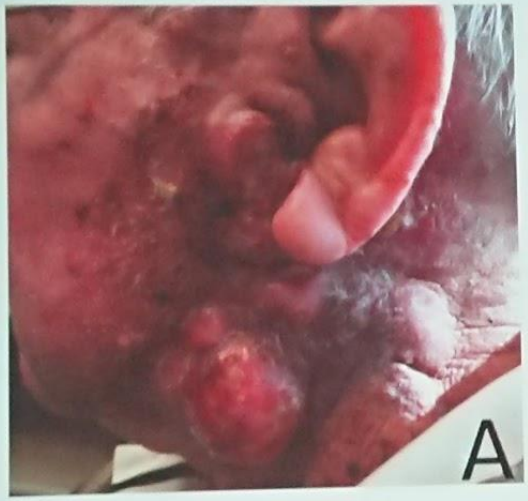
CANCER CELL BIOLOGY CLINICAL TRIALS
IMMUNOLOGY/ALLERGIES/ASTHMA
MEDICINE/HEALTH

Clear healing after NIR-PIT

Pre-treatment

During treatment

Clear healing after NIR-PIT



Pre-treatment

3 month after Tx

Phase 1: Multicenter results

9 patients (7 males, 2 females), aged 52–86 years, enrolled in to RM-1929/101 Part I study.

	Patient	Tumor site	Previous Treatment	Tumor size, CT (cm)	HPV/p16 Status
160 mg/m²	03-101	Oropharynx	Surgery, radiation×2, cisplatinum	2.6 × 1.2	+/+
	03-102	Posterior oro- and hypopharynx	Surgery, radiation	3.0 × 7.0 clinical	-/-
	03-103	Right anterior tongue	Surgery, radiation ×2, carboplatin, 5-FU, cetuximab	2.8 × 0.7 × 1.3	-/-
320 mg/m²	03-201	Right neck	Surgery, radiation, taxol, carboplatin, cetuximab, nivolumab	8.0 × 6.0 × 4.0	-/-
	03-201	Right submandi-bular, submental	Surgery, radiation, cis-platinum, paclitaxel	6.0 × 4.5 submandibular, 2.3 × 1.7 submental	-/-
	02-212	Left tongue base	Surgery, radiation, cisplatinum,docetaxel, cetuximab	2.0 × 1.1 × 0.9	-/-
640 mg/m²	02-311	Occipital mass	Surgery, radiation, PD-1 inhibitor, cetuximab, PI3K inhibitor	2.7 × 3.3	+/NA
	05-341	Pharynx and buccal mass	Surgery, radiation, 5-FU, cisplatinum, docitaxel	6.0 × 4.0 left cheek 4.0 × 4.0 left oropharynx 5.0 × 3.0 left nasopharynx	NA/NA
	03-301	Dermal meta-stases, neck nodes	Surgery, radiation, cisplatinum, cetux-imab, nivolumab	4.0 × 1.0, 2.0 × 1.0 right neck metastases, 2.0 × 1.0 right neck midline metastasis	-/+

Abbreviations: CT = computed tomography; HPV = human papilloma virus; NA = not applicable; PD-1 = programmed cell death protein 1; PI3K = phosphoinositide 3 kinase; p16 = p16 protein; 5-FU = 5-flouorouracil

7 cases at the Thomas Jefferson Univ.

Results

Age	Tumor site	Treatments	Comments	RESIST
78M	oropharynx, hypopharynx	2	Clinical and radiologic improvement, no evidence of disease currently	CR
67M	retropharyngeal nodes, bilateral neck nodes	4	Moderate rash of scalp and back from drug initially, continued clinical and radiologic improvement of tumor noted	CR
59F	right and left neck, peristomal area	3	Strong tumor response leaving right carotid artery exposed, developed pharyngocutaneous fistula; died of carotid bleed after exposure	CR
66M	left neck mass	4	Partial response of tumor to treatments, underwent resection after completion	PR
65M	neopharynx	1	Progression of disease posteriorly into spine, palliative chemotherapy, died due to disease	PR
86M	left face and neck	1	Extensive tumor necrosis debrided, wound granulating with NED. Noted increased appetite, weight gain, and activity	CR
75M	right face and neck	1	Partial response on right (treated) side but progression on left, transitioned to hospice, died due to disease	PR

AHNS 2017 David Cognetti, et al.; Thomas Jefferson University

Cell death

Apoptotic cell death

- Non-immunogenic
- Biological death
- >6 hrs to days
- Death with healing
- Induced by

  (to non-selective cells)
  - Drugs/chemotherapy
  - Radiation
  - Photodynamic therapy

  (to selective cells)
  - Molecular target Txs
    - Antibodies
    - Small molecules

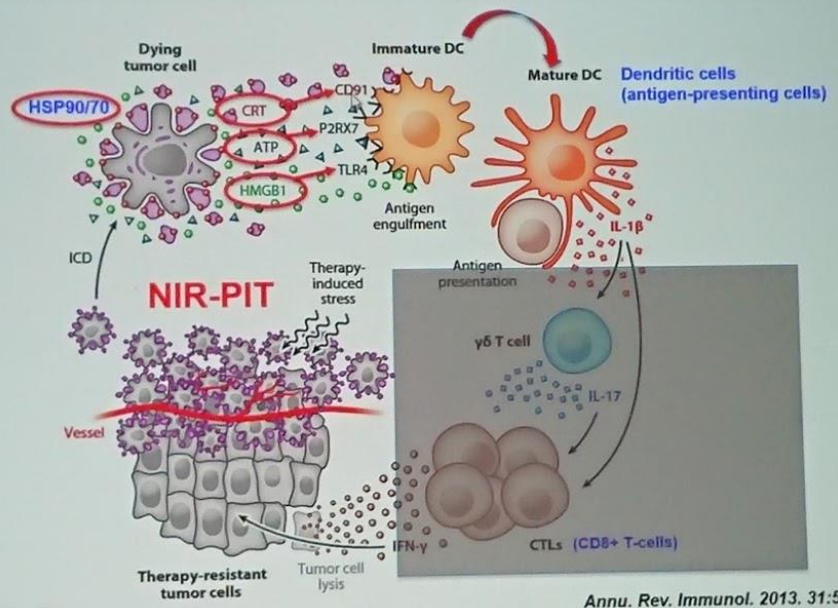
Necrotic/Immunogenic cell death

- Immunogenic
- Physical/chemical death
- Seconds to minutes
- Death without healing
- Induced by

  (to non-selective cells)
  - Heat
  - Cryotherapy
  - Focused Ultrasound

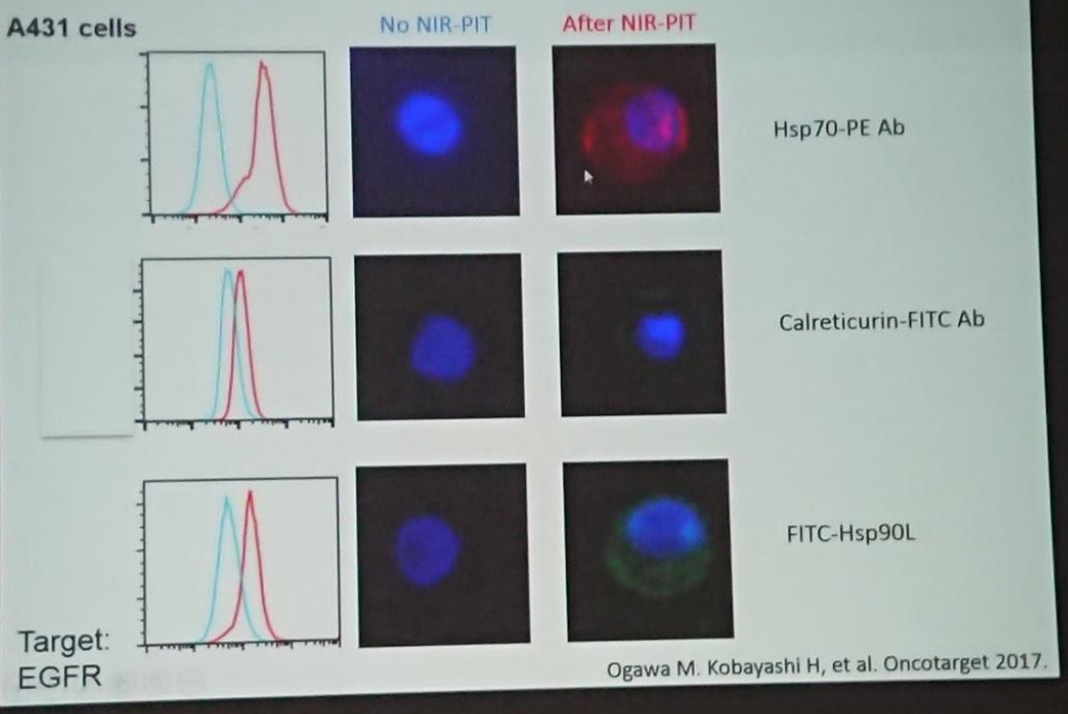
  (to selective cells)
  - NIR-PIT

Tumor immunity initiated by NIR-PIT induced Immunogenic cell death (ICD)



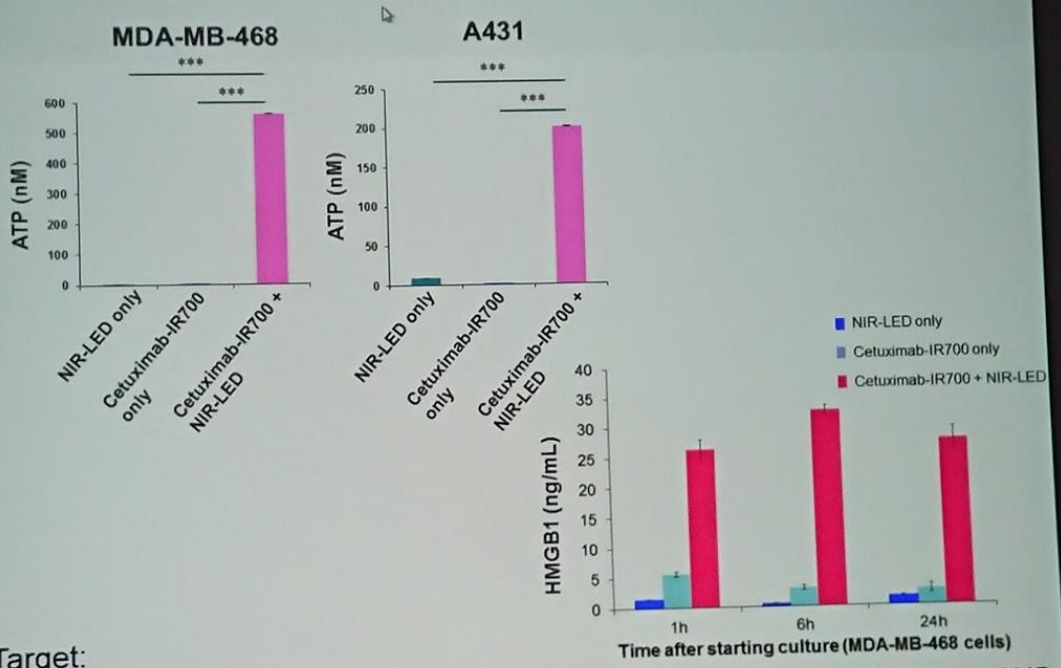
Annu. Rev. Immunol. 2013. 31:51–72

Stress markers are quickly induced by NIR-PIT



Ogawa M. Kobayashi H, et al. Oncotarget 2017.

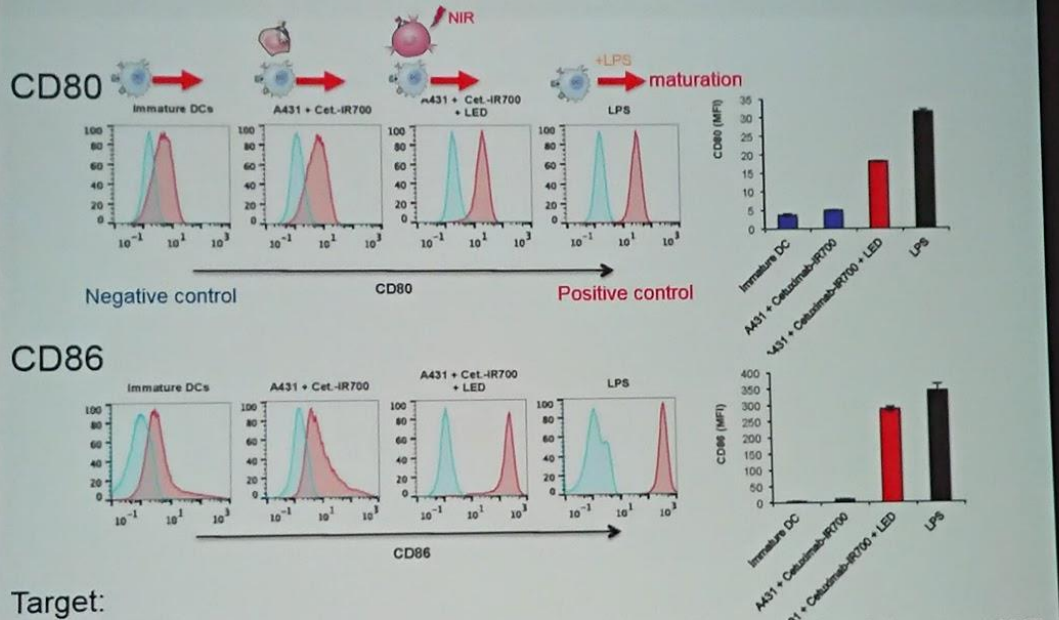
ATP and HMGB1 are released after NIR-PIT



Target:
EGFR

Ogawa M. Kobayashi H, et al. Oncotarget 2017.

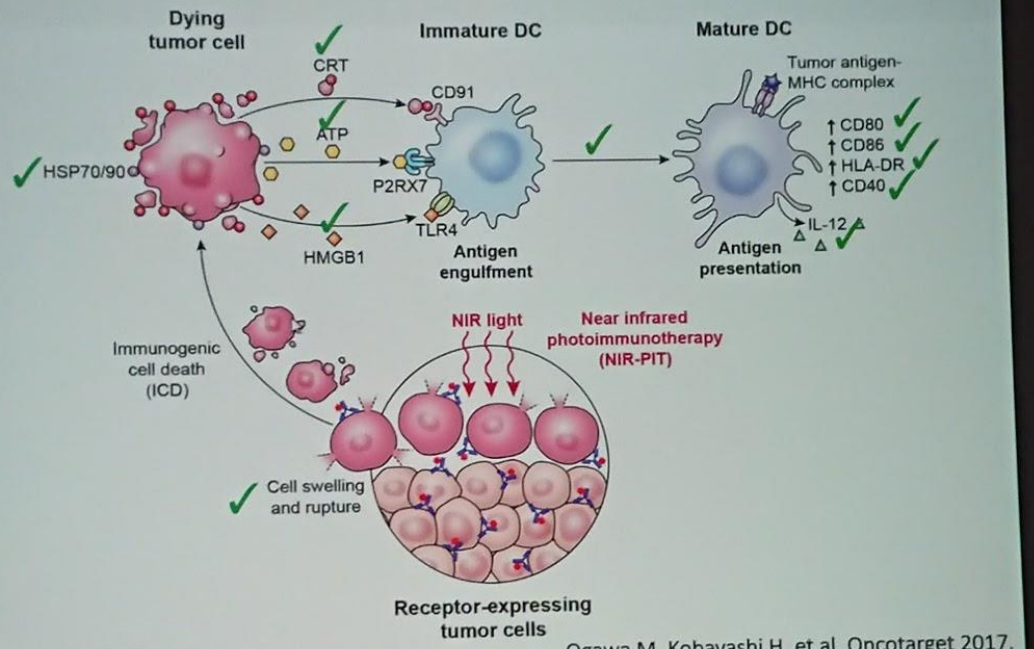
NIR-PIT induces maturation of immature dendritic cells



Target:
EGFR

Ogawa M. Kobayashi H, et al. Oncotarget 2017.

NIR-PIT induced immunogenic cell death



Ogawa M. Kobayashi H, et al. Oncotarget 2017.

Advantages of selective cancer cell killing by NIR-PIT

- Intact immune cells
  - Dendritic cells – activate initiate immunity against crashed cancer cells
  - T-cells – rapidly activate cytotoxic-$CD8^{+}$T and NK cells
- Intact tissue stem cells
  - Rapid and clear repairing process

NIR-PIT: Skin metastasis lesions

Pre-PIT

1 week after

NIR-PIT: Skin metastasis lesions

Pre-PIT

1 month after

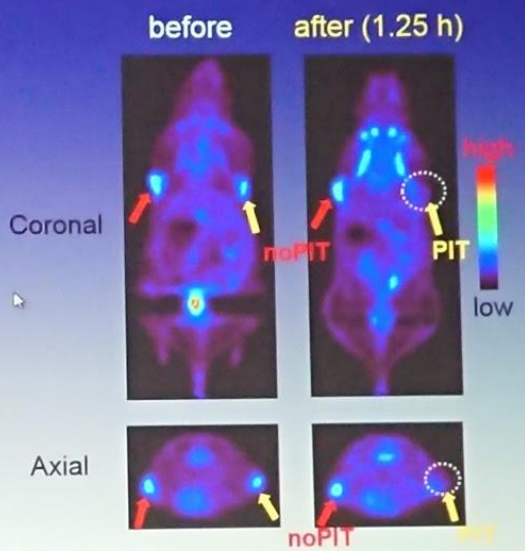
NIR-PIT: Skin metastasis lesions

Pre-PIT

2 month after

Immediate cell killing of PIT
(FDG-PET: glucose metabolism)

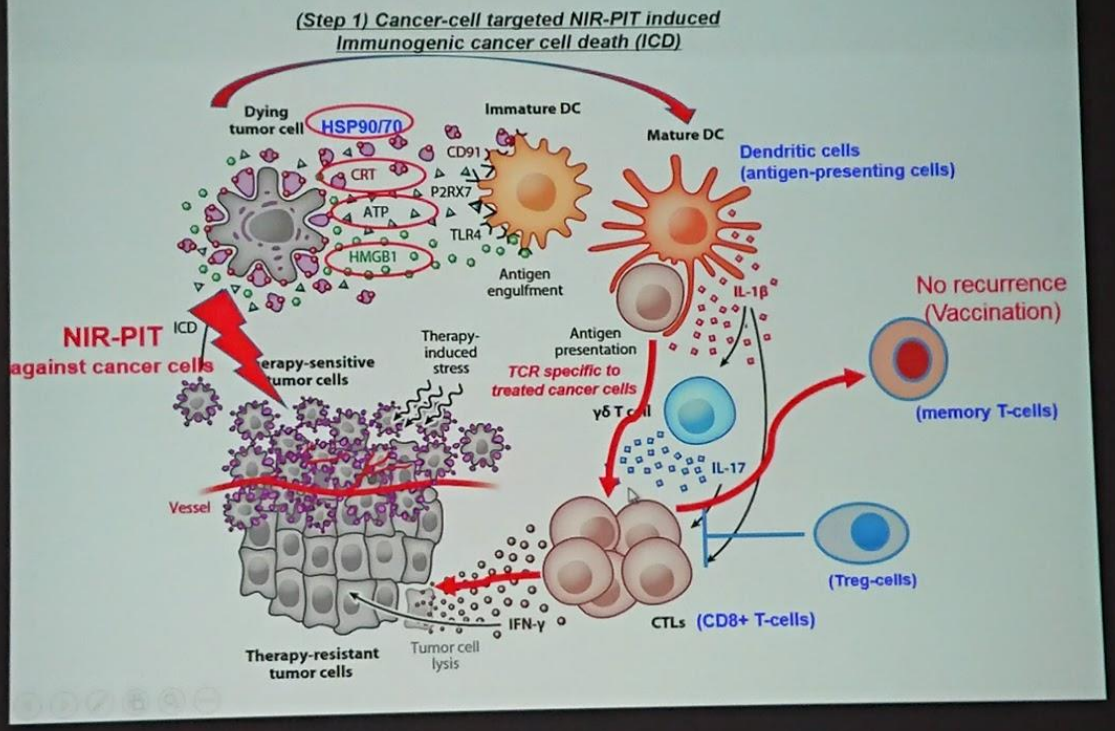
White light + IR700 FL

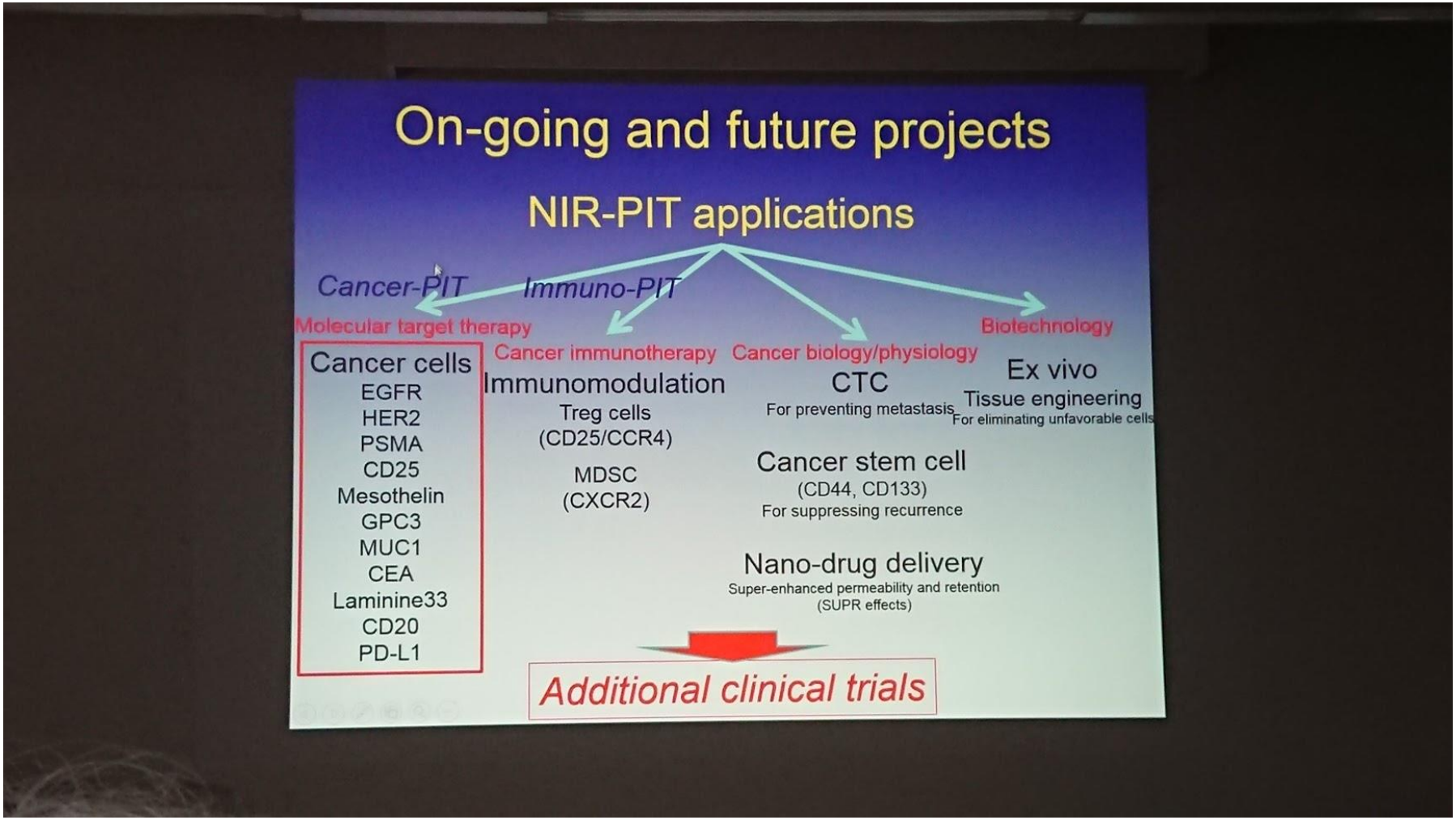


^{18}F-FDG PET

Sano , Kobayashi, J Nucl Med 2013

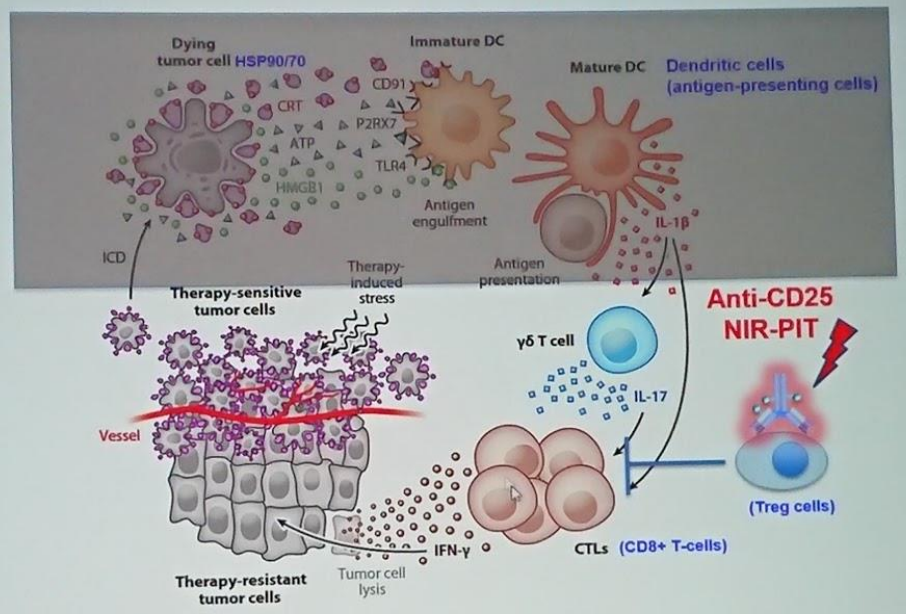
Cancer target NIR-PIT only crashes cancer cells




On-going and future projects
NIR-PIT applications
Cancer-PIT
Immuno-PIT
Molecular target therapy
Cancer immunotherapy
Cancer biology/physiology
Biotechnology
Cancer cells
EGFR
HER2
PSMA
CD25
Mesothelin
GPC3
MUC1
CEA
Laminine33
CD20
PD-L1
Immunomodulation
Treg cells
(CD25/CCR4)
MDSC
(CXCR2)
CTC
For preventing metastasis
Cancer stem cell
(CD44, CD133)
For suppressing recurrence
Nano-drug delivery
Super-enhanced permeability and retention
(SUPR effects)
Ex vivo
Tissue engineering
For eliminating unfavorable cells
Additional clinical trials

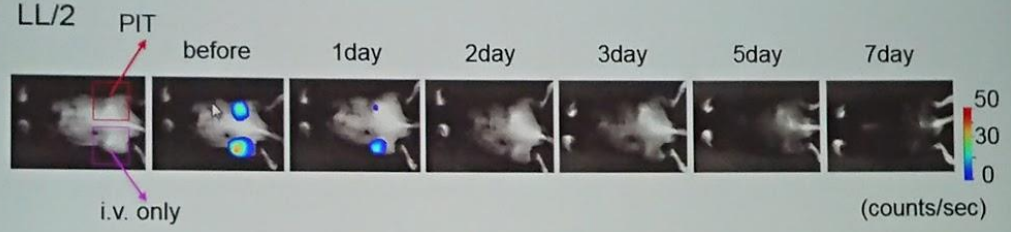
Immunomodulation with NIR-PIT

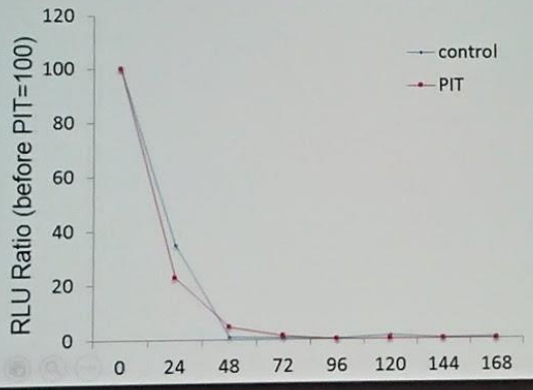
(NIR-PIT can activate acquired immunity and destroy cancer cells)



Annu. Rev. Immunol. 2013. 31:51–72

NIR-PIT-induced local knockdown of Treg cells cure both treated and non-treated tumors



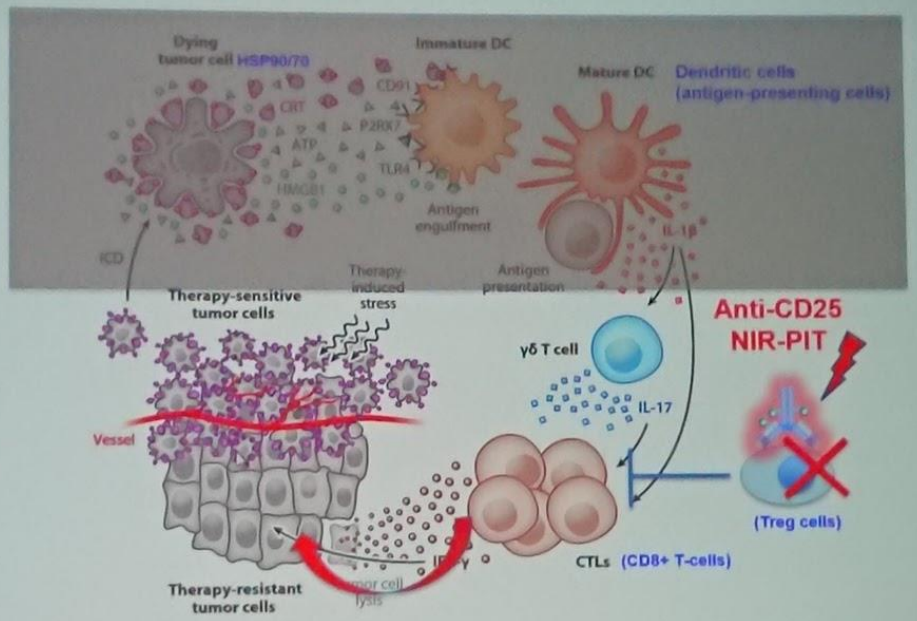


Target: CD25

Sato K. Kobayashi H, et al. Science Trans Med 2016.

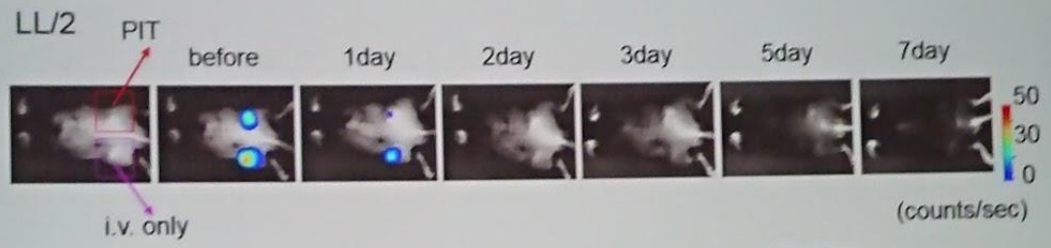
Immunomodulation with NIR-PIT

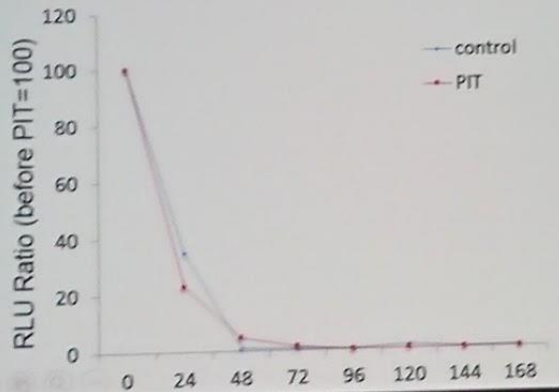
(NIR-PIT can activate acquired immunity and destroy cancer cells)

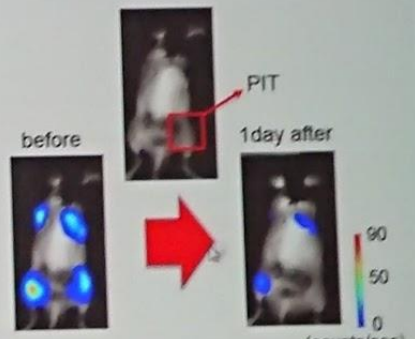


Annu. Rev. Immunol. 2013. 31:51–72

NIR-PIT-induced local knockdown of Treg cells cure both treated and non-treated tumors







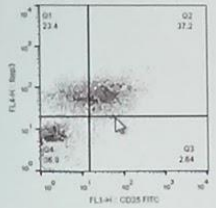
Target: CD25

Sato K, Kobayashi H, et al. Science Trans Med 2016.

Treg cell targeted NIR-PIT induces rapid activation of CD8+ T and NK cells

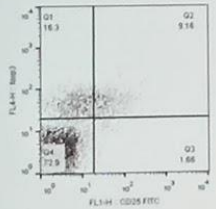
30 min after PIT

CD3+/CD4+/CD25+/Foxp3+ control tumor



37.2

CD3+/CD4+/CD25+/Foxp3+ PIT treated tumor

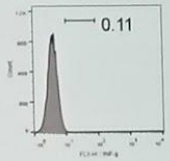


9.16

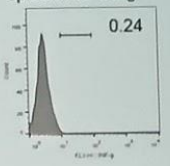
Target:
CD25

1.5 hrs after PIT

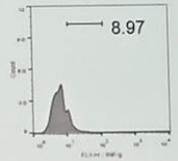
spleen:CD8+INFg



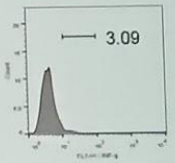
spleen:NK+INFg



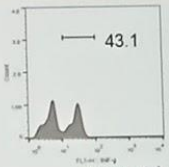
cont tumor:CD8+INFg



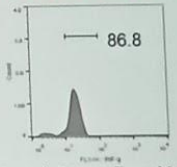
cont tumor:NK+INFg



PIT treated tumor:CD8+INFg



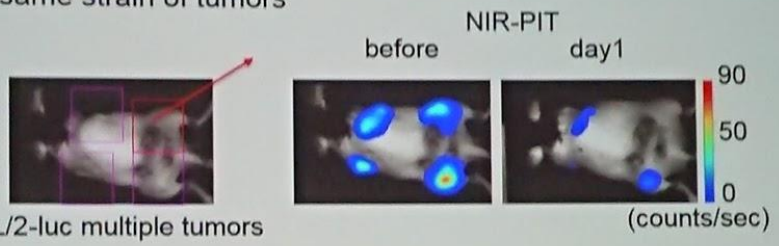
PIT treated tumor NK+INFg



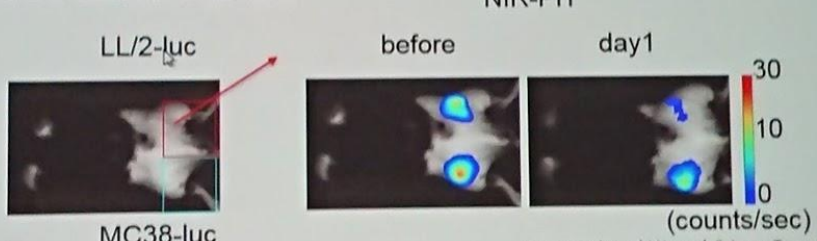
Sato K. Kobayashi H, et al. Science Trans Med 2016.

Specificity of tumor immunity

The same strain of tumors



Different strains of tumors

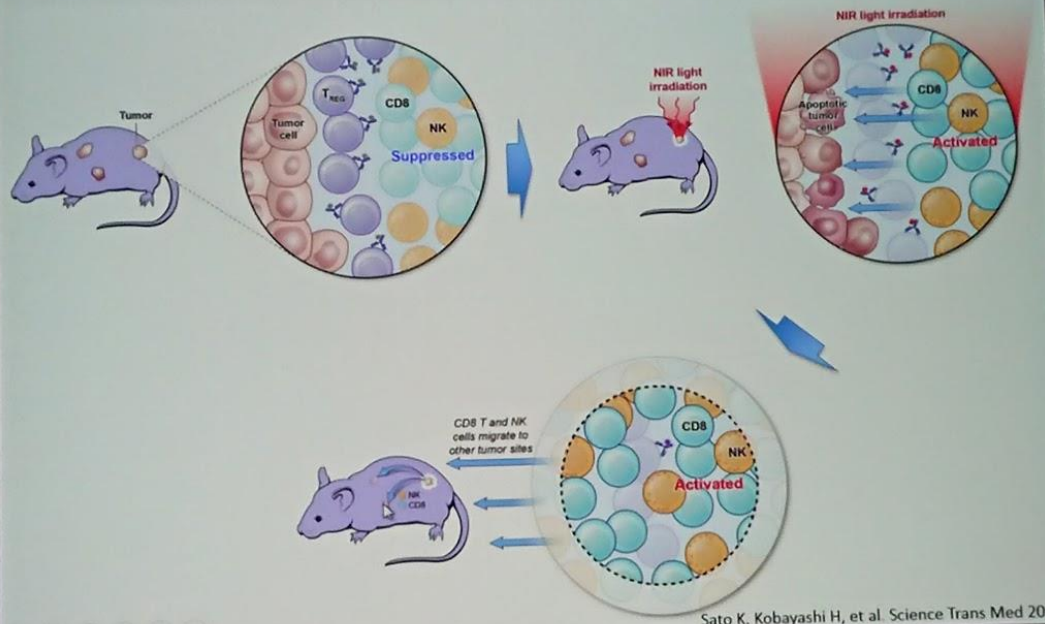


Target:
CD25

Sato K. Kobayashi H, et al. Science Trans Med 2016.

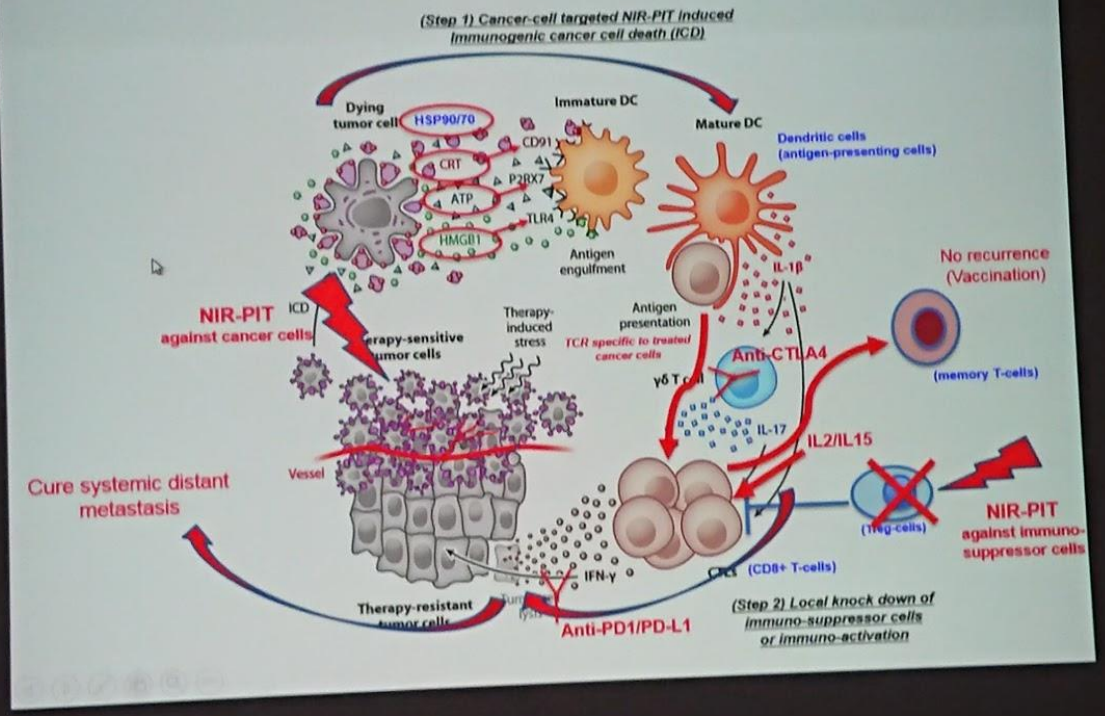
NIR-PIT induced acquired immunity

by local knockdown of Treg cells

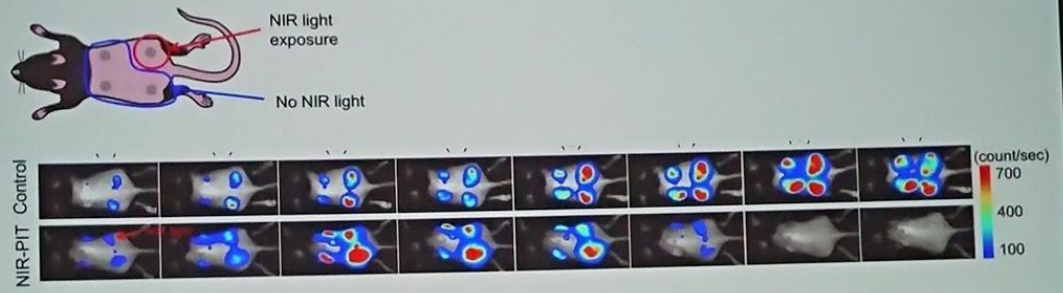


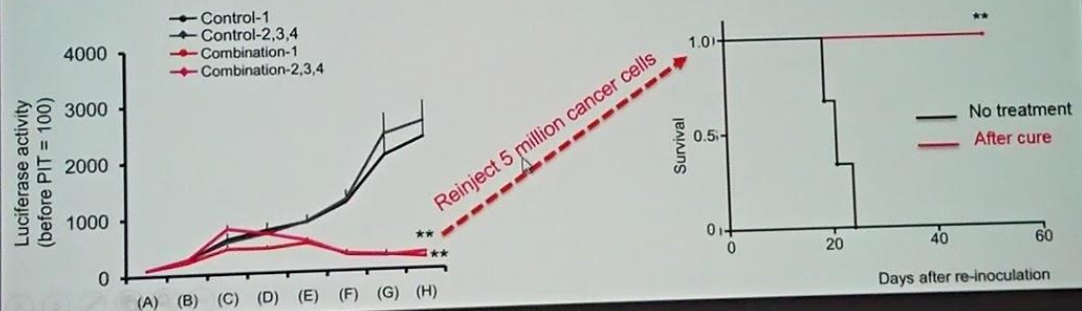
Sato K. Kobayashi H, et al. Science Trans Med 2016.

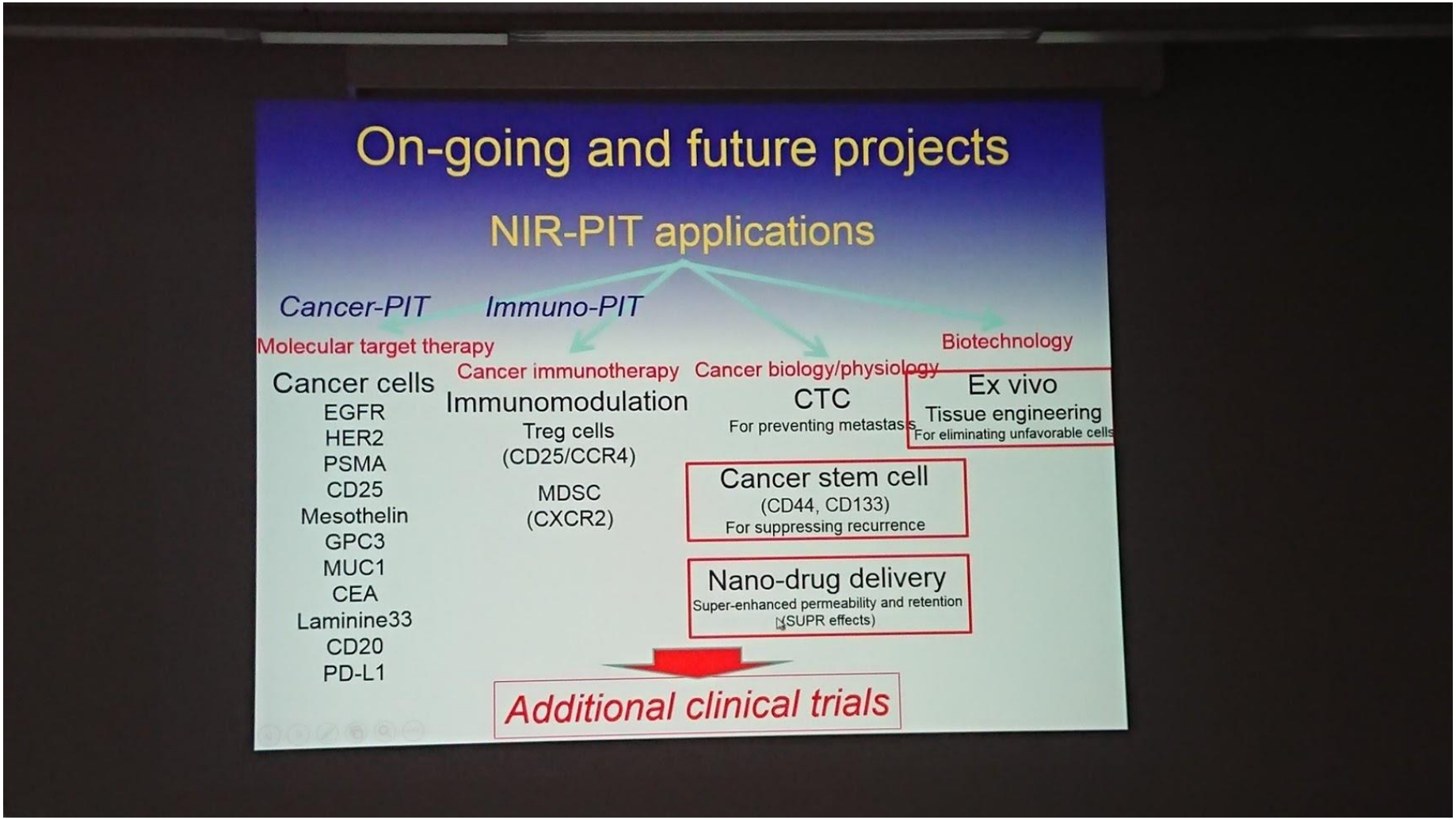
Final form of NIR-PIT therapy



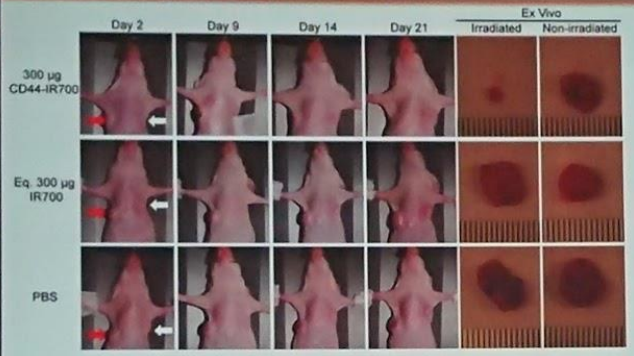
Cancer-PIT combined with immuno-activation cure local and distant cancers without recurrence

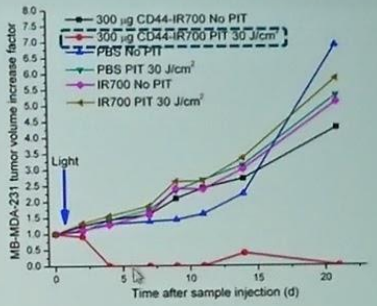





On-going and future projects
NIR-PIT applications
Cancer-PIT
Immuno-PIT
Molecular target therapy
Cancer immunotherapy
Cancer biology/physiology
Biotechnology
Cancer cells
EGFR
HER2
PSMA
CD25
Mesothelin
GPC3
MUC1
CEA
Laminine33
CD20
PD-L1
Immunomodulation
Treg cells
(CD25/CCR4)
MDSC
(CXCR2)
CTC
For preventing metastasis
Ex vivo
Tissue engineering
For eliminating unfavorable cells
Cancer stem cell
(CD44, CD133)
For suppressing recurrence
Nano-drug delivery
Super-enhanced permeability and retention
(SUPR effects)
Additional clinical trials

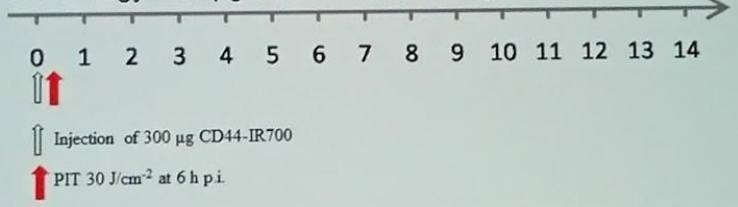
Application of NIR-PIT targeting cancer stem cells





➡ 30 J/cm^{-2} White arrow denotes no PIT

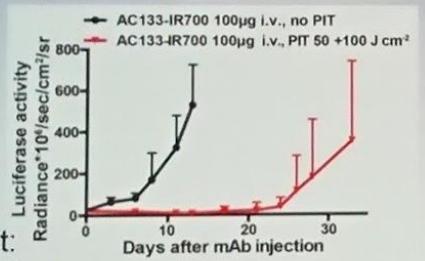
Treatment strategy: 300 μg CD44-IR700, one injection, one PIT at 6 h p.i.

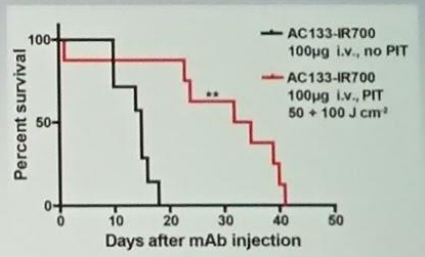


Target:
CD44

Jin J, Kobayashi H, Bhujwalla Z, Johns Hopkins Univ: Sci Rep. 2016

CD133+ GBM stem cell targeted NIR-PIT

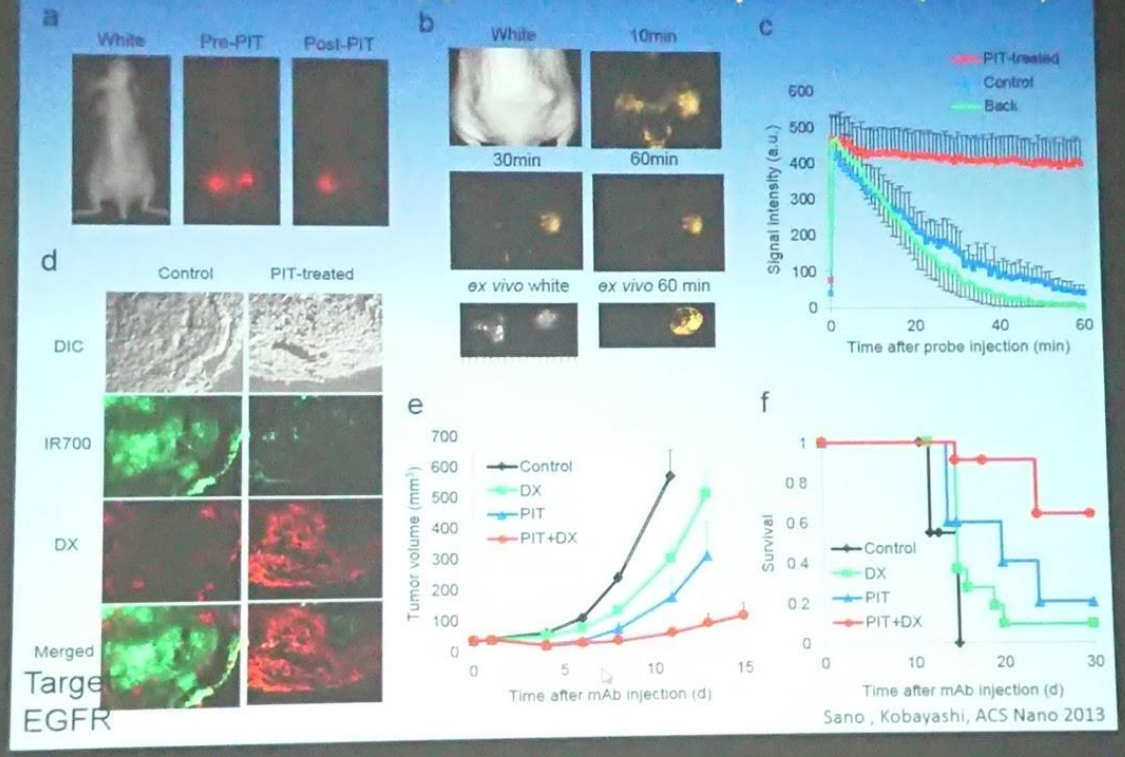




Target:
CD133

Jing H, Kobayashi H, Niedermann G, Univ. Frieberg: Theranostics 2016

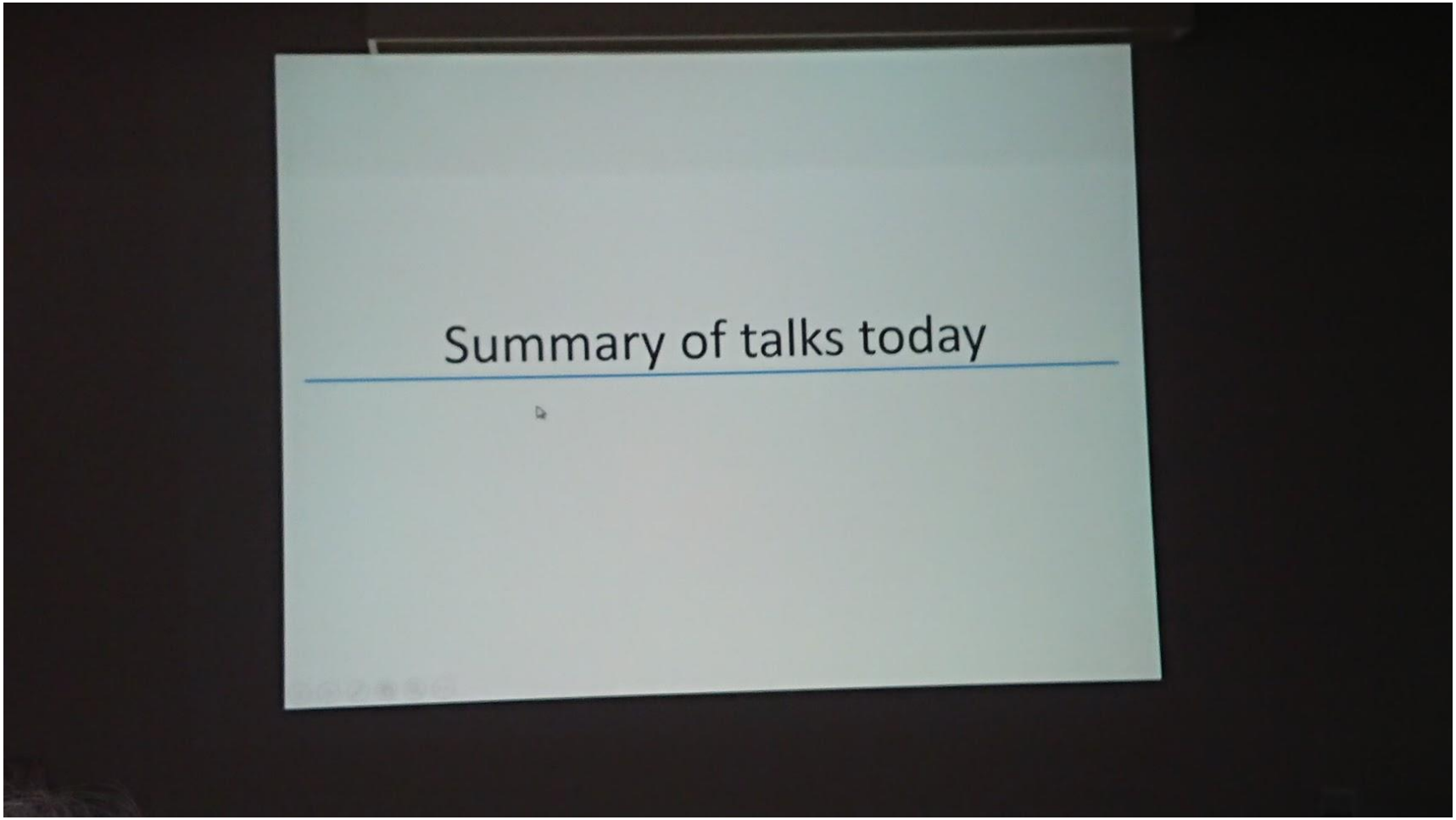
PIT/SUPR therapy with Daunoliposome (50 nm)

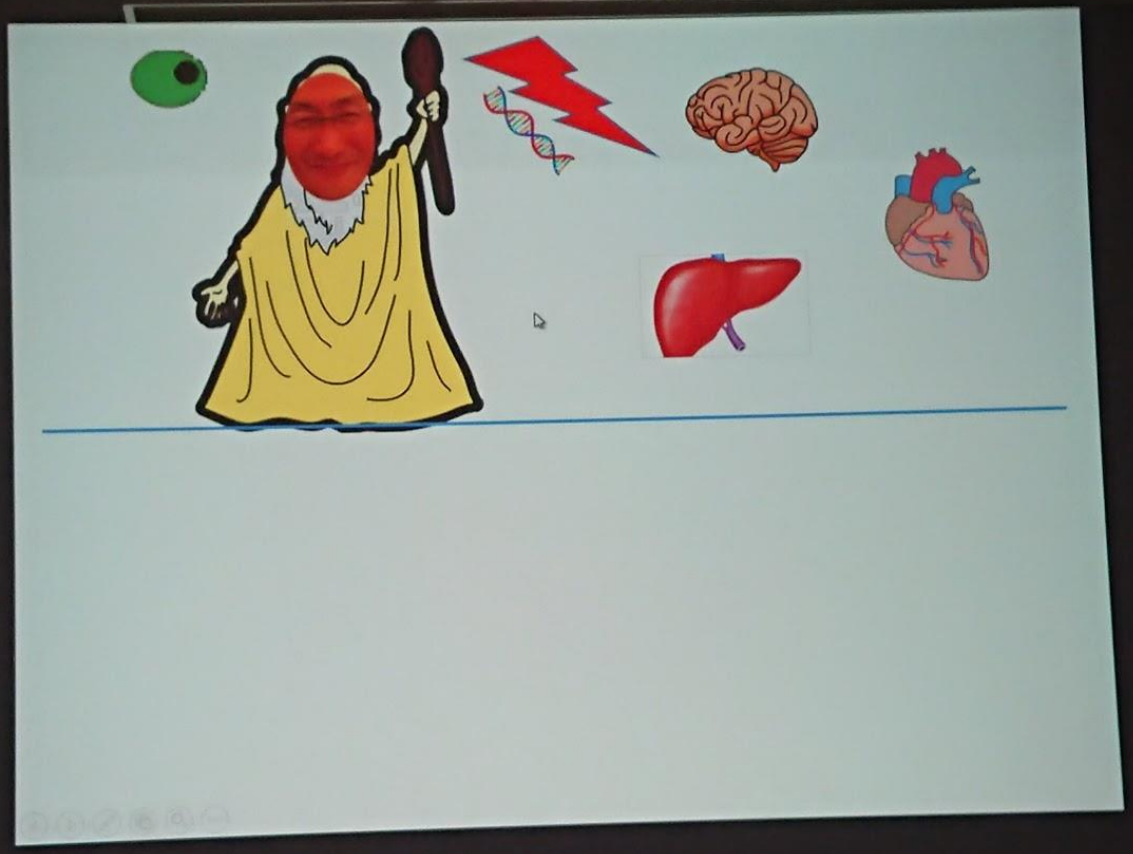


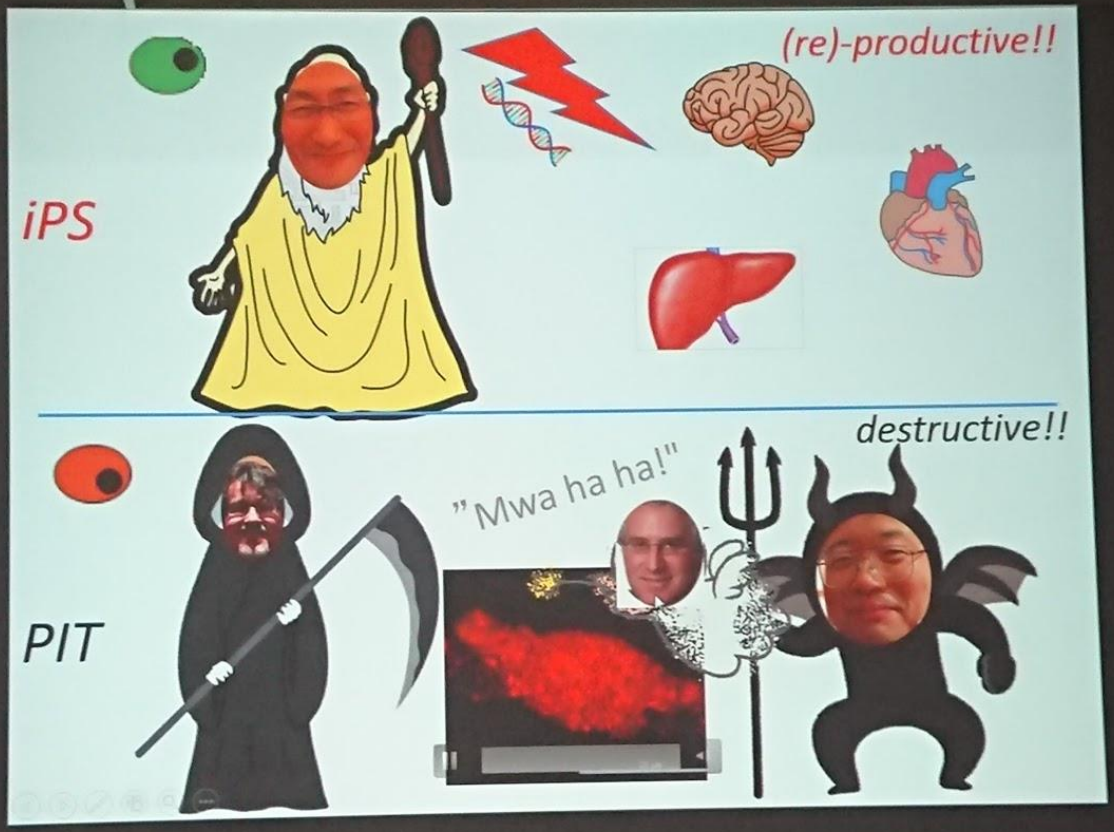
Target
EGFR

Sano , Kobayashi, ACS Nano 2013

Aspyrian-Rakuten team

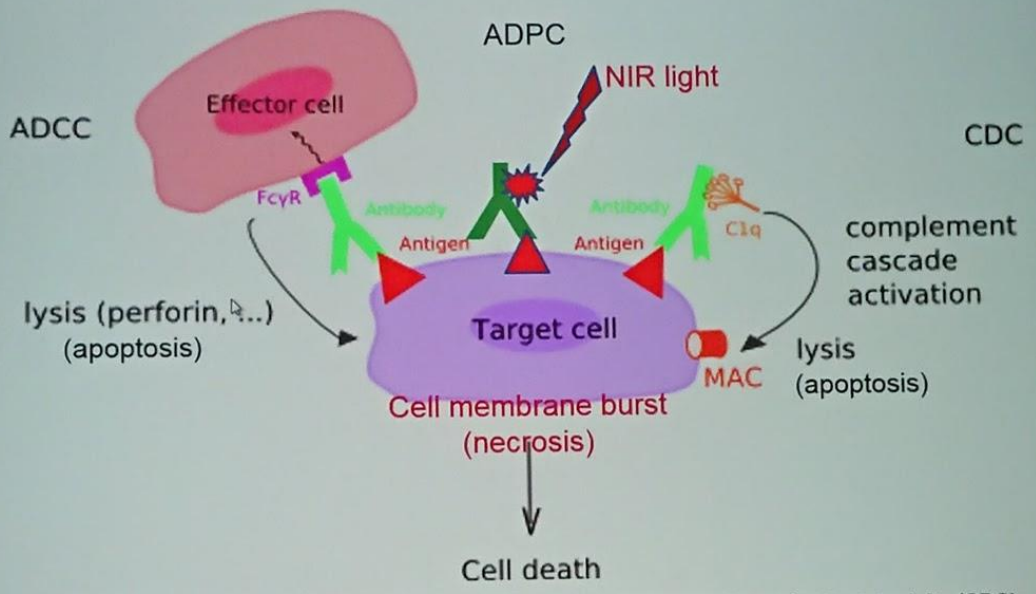

Summary of talks today




(re)-productive!!
iPS
destructive!!
"Mwa ha ha!"
PIT

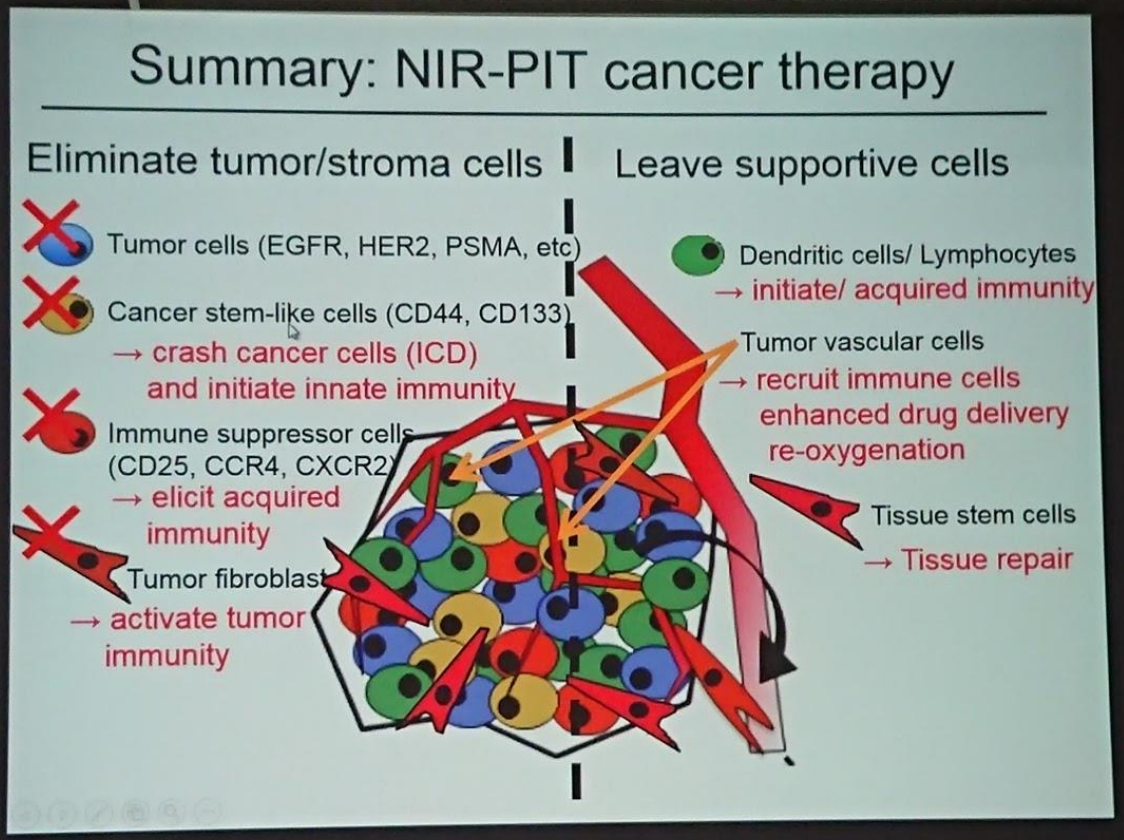

Applying NIR-PIT to tissue engineering
Eliminating selective cells from 3D culture using NIR-PIT

Antibody-photosensitizer conjugate (APC)-Dependent Photo-induced Cytotoxicity (ADPC)



Antibody-dependent cellular cytotoxicity (ADCC) and Complement-dependent cytotoxicity (CDC)

Summary: NIR-PIT cancer therapy



Phase 2 → Registration trial

STARTUPS, BIOTECH

Rakuten CEO leads $40M investment in photoimmunotherapy startup Aspyrian Th

By ME

Post

San Die
filing, t
Photoir

Photoir
immun
Institut
to keep

This $4
billiona
largest
with his

MedCity News
how the comp
$12.7 million l

Aspyrian Therapeutics Inc. announces successful advances in RM-1929 clinical development in recurrent Head and Neck Cancer, including Fast Track designation granted by the FDA, initiation of clinical studies in Japan, and plans to start pivotal studies, which will incorporate the evaluation of anti-cancer immune responses, in early 2018

Aspyrian Therapeutics, Inc.

2018-01-16

https://www.prnewswire.com/news-releases/aspyrian-therapeutics-inc-announces-successful-advances-in-rm-1929-clinical-development-in-recurrent-head-and-neck-cancer-including-fast-track-designation-granted-by-the-fda-initiation-of-clinical-studies-in-japan-and-plans-to-300583615.html

Phase 2 → Registration trial

Rakuten CEO leads $40M investment in photoimmunotherapy startup Aspyrian Th[illegible]

Aspyrian Therapeutics Inc. announces successful advances in RM-1929 clinical development in recurrent Head and Neck

KYODO

光でがん治療、国内で治験始まる

国立がんセンター東病院

2016/3/13 18:42

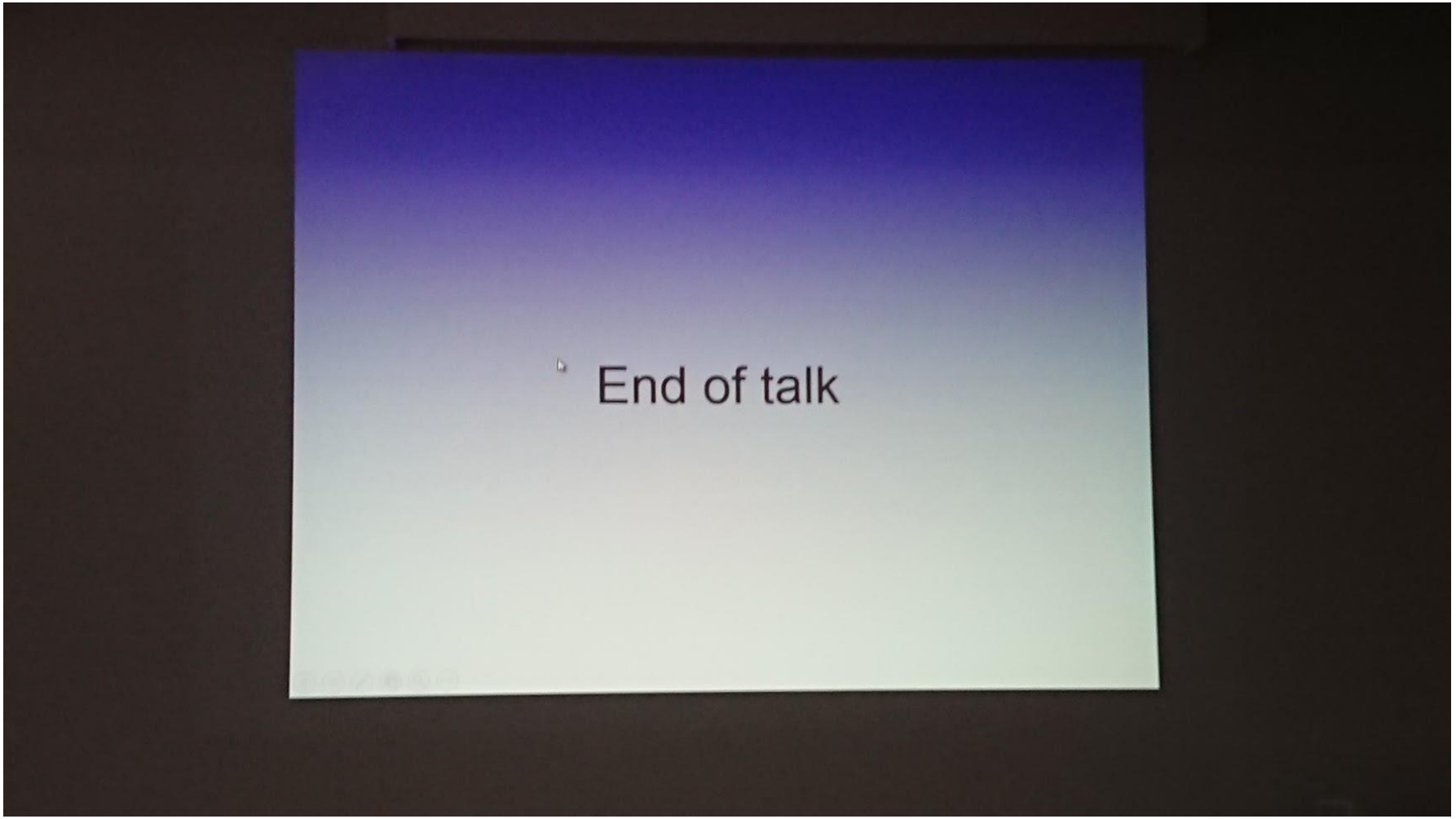
近赤外線という光を使ってがんを治療する「がん光免疫療法」の国内初の臨床試験（治験）が、国立がん研究センター東病院（千葉県柏市）で13日までに始まった。米国立衛生研究所（NIH）の小林久隆・主任研究員らが開発した手法で、米バイオベンチャーが実施。頭や首のがん患者数人を対象に安全性を確認し、数年以内の承認を目指す。

治療は、がん細胞の表面に多いタンパク質にくっつく抗体と、近赤外線に反応する物質をつなげ、薬剤として利用。この薬剤を患者に注射し、翌日にがんの部分に光を当てると、がん細胞にくっついた薬剤に化学反応が起きて、がん細胞が破裂するという。

World wide collaborations

Acknowledgements

- LMT/ MIP/ NCI/ NIH
  - Takahiro Nakajima
  - Kazuhide Sato
  - Nobuyuki Kosaka
  - Mikako Ogawa
  - Makoto Mitsunaga
  - Yuko Nakamura
  - Rira Watanabe
  - Tadanobu Nagaya
  - Michelle R. Longmire (HHMI)
  - Shuhei Okuyama
- MIP/ NCI/ NIH
  - Peter L. Choyke
  - Marcelino Bernardo
- Metabolism Branch / NCI
  - Thomas A. Waldmann
- Chemical Biology Br. /NCI
  - Martin Schnermann
- Radiation Oncology Br. /NCI
  - Martin W. Brechbiel
- Nuclear Medicine/ CC
  - Insook Kim
  - Chang H. Paik
  - Jorge A Carrasquillo (MSKCC)
- Lab. Molecular Biology/NCI
  - Ira Pastan
  - Michelle Ho
- Lab. Cellular Oncology/NCI
  - Kines C. Rhonda
  - John T. Schiller
- Univ. Maryland CP
  - Yu Chen
  - Miao Yu
  - Chia-pin Liang
- Univ. Maryland BC
  - Marcin Ptacek
- Johns Hopkins Univ.
  - Jiefu JIN,
  - Zaver Bhujwalla
- Boston Children's Hosp.
  - Steve Fishman
  - Laureen Sena
- Stanford/ Dermatology
  - Michelle R. Longmire
  - Peter Marinkovich
- UCSD
  - Michael Bouvet
  - Ali Maawy
- Univ. Groningen
  - Go van Dam
- Netherland Cancer Center
  - Fijs van Leeuwen
- Univ. Leiden
  - Maxime Slooter
  - Lowik Clemens
- Univ. Frieberg
  - Gabriele Niedermann
- Tokyo University
  - Yasuteru Urano
  - Mako Kamiya
  - Daisuke Asanuma
- Okayama University
  - Toshi Fujiwara
  - Mitsuhiro Ishida
- Hamamatsu Med/Photonics
  - Toyohiko Yamauchi
  - Mikako Ogawa
- Kyoto Univ./Shimadzu Co.
  - Ryohei Kokawa
  - Hirofumi Yamada
- NCC Singapore
  - Patricia Soo
  - Kee Chee Soo


End of talk