



遺伝子治療臨床試験トレーニングコース Session III. ケース・スタディ

臨床研究の経験：テロメライシン

～ Clinical Study of Telomelysin ～

Hiroshi Tazawa

Associate Professor

Center for Innovative Clinical Medicine
Okayama University Hospital



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東京慈恵会医科大学

COI (Conflict of Interest) Disclosure Information

Hiroshi Tazawa

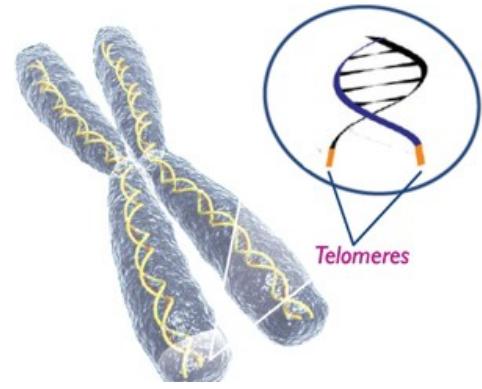
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Telomerase-Specific Oncolytic Virotherapy



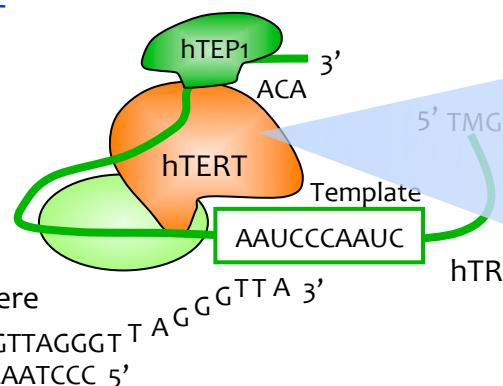
Telomerase

- Telomerase is a ribonucleoprotein complex that is responsible for adding TTAGGG repeats onto the 3' ends of chromosomes.
- The majority of malignant tumors express telomerase activity, whereas telomerase is strongly repressed in most normal somatic tissues.
- Telomerase may be a plausible target for cancer diagnosis and therapy.

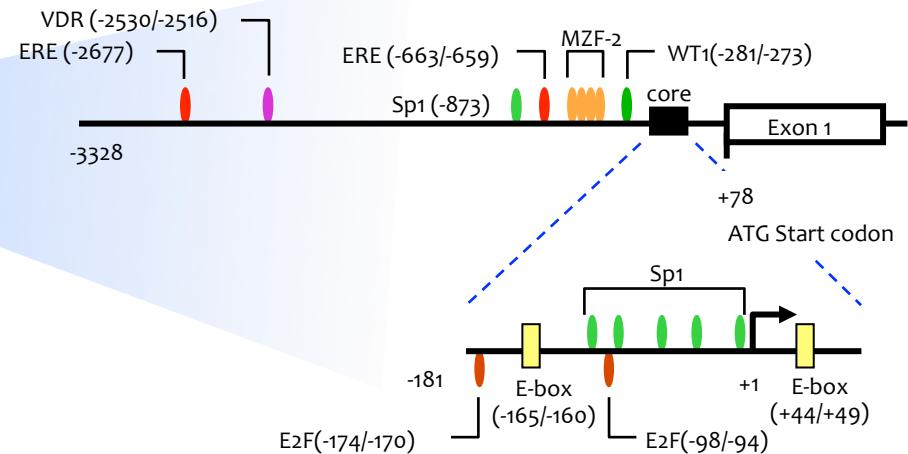


■ Telomerase protein complex

- hTERT
- TEP
- hTR

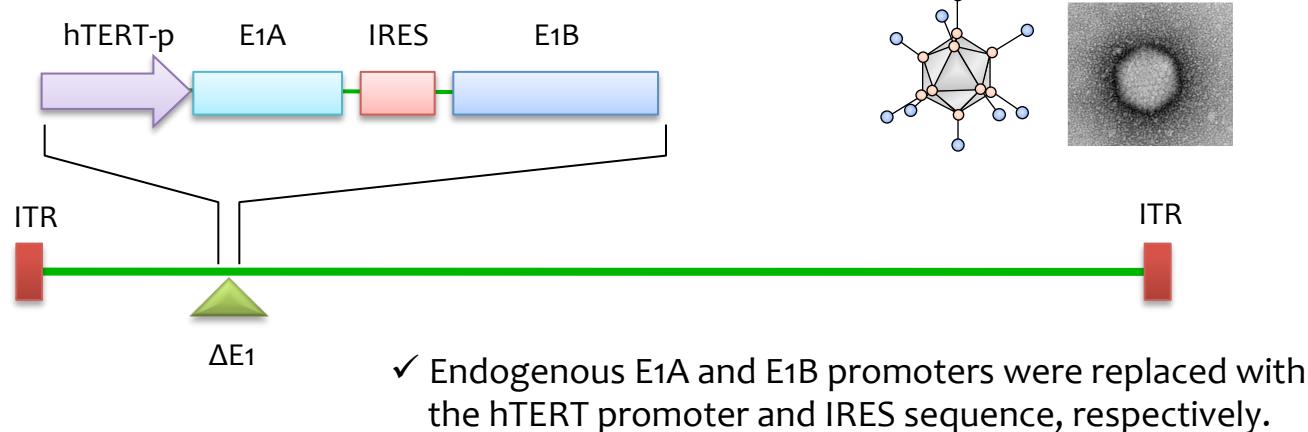


■ hTERT promoter

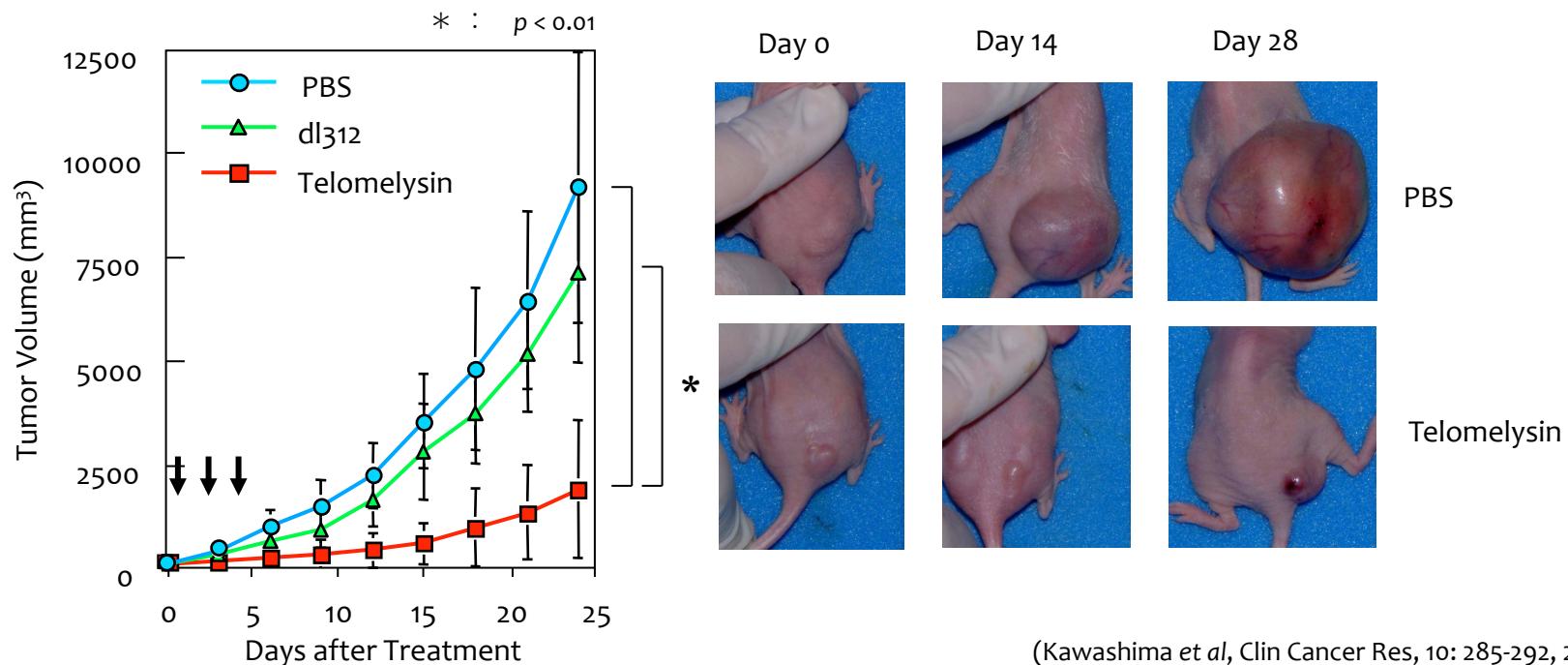


(Takakura, Kyo et al, Cancer Res, 59: 551-557, 1999)

Telomelysin (OBP-301)



■ Preclinical study of Telomelysin (*in vivo*)



Clinical Trial of Telomelysin in the U.S.

Nemunaitis et al., Mol. Ther., 18: 429-34, 2010

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original article

A Phase I Study of Telomerase-specific Replication Competent Oncolytic Adenovirus (Telomelysin) for Various Solid Tumors

John Nemunaitis¹⁻⁴, Alex W Tong^{3,4}, Michael Nemunaitis¹, Neil Senzer¹⁻⁴, Anagha P Phadke⁴, Cynthia Bedell¹, Ned Adams¹, Yu-An Zhang^{3,4}, Phillip B Maples⁴, Salina Chen⁴, Beena Pappen⁴, James Burke⁵, Daiju Ichimaru⁶, Yasuo Urata⁶ and Toshiyoshi Fujiwara⁷

¹Mary Crowley Cancer Research Centers, Dallas, Texas, USA; ²Texas Oncology PA, Dallas, Texas, USA; ³Baylor Sammons Cancer Center, Dallas, Texas, USA; ⁴Gradalis, Inc., Dallas, Texas, USA; ⁵Billings Clinic, Billings, Montana, USA; ⁶Oncolys BioPharma, Tokyo, Japan; ⁷Center for Gene and Cell Therapy, Okayama University Hospital, Okayama, Japan

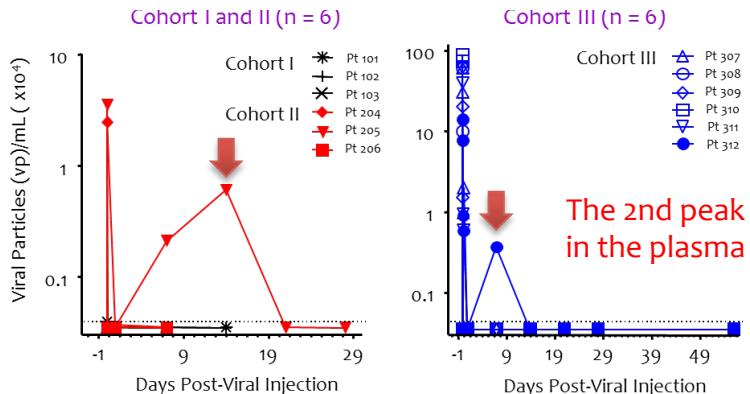


Table 1 Patient demographics

Patient	Age	Sex	Histological diagnosis	Prior treatments
1 (101)	57	F	Squamous cell ca unknown primary	XRT, carboplatin, docetaxel, anastrozole
2 (102)	54	M	Melanoma	Interferon, dacarbazine
3 (103)	34	F	Melanoma	Lenalidomide, dacarbazine, vinblastine, cisplatin, IL-2, interferon
4 (204)	60	M	Salivary gland tumor	XRT, perifosine
5 (205)	69	M	Squamous cell ca base of tongue	Cisplatin, XRT
6 (206)	60	F	Leiomyosarcoma	Doxorubicin, ifosfamide, gemcitabine, docetaxel, perifosine
7 (307)	52	F	Neuroendocrine tumor	Irinotecan, cisplatin, topotecan, docetaxel, pemetrexed, CT 2103, XRT
8 (308)	78	F	Melanoma	Interferon
9 (309)	54	M	NSCLC	Paclitaxel, carboplatin, pemetrexed, XRT
10 (310)	49	M	Squamous cell ca base of tongue	Paclitaxel, carboplatin, cisplatin, fluorouracil, cetuximab, XRT
11 (311)	60	M	Squamous cell ca floor of mouth	Cisplatin, XRT
12 (312)	48	M	Melanoma	Interferon, melphalan, actinomycin-D
13 (313)	54	F	Sarcoma	None
14 (314)	38	M	Basal cell carcinoma	Cisplatin, fluorouracil
15 (315)	54	F	Squamous cell ca of gall bladder	Capecitabine, gemcitabine
16 (316)	46	F	Breast cancer	Doxorubicin, cyclophosphamide, paclitaxol, herceptin, tamoxifen, anastrozole, capecitabine, docetaxel

M, male; F, Female.

Safety

- Telomelysin was well tolerated (up to 5×10^{12} vp).
- Most Adverse Events were mild to moderate.

Pharmacokinetics

- Measurable levels in plasma after 1 – 3 hours.
- Virus shedding was evident at 7 and 14 days after treatment.

Clinical Benefit

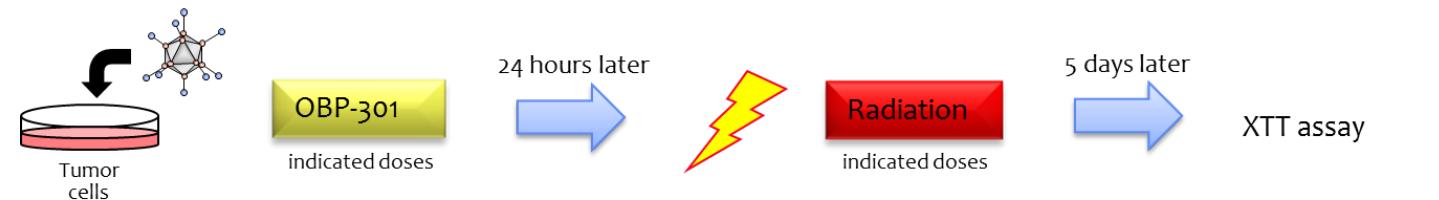
- Indication of reduction in treated tumor in some patients.

■ Our Clinical Proposal

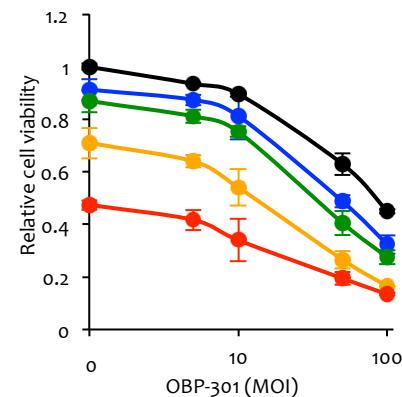
Telomelysin and Radiotherapy for Esophageal Cancer



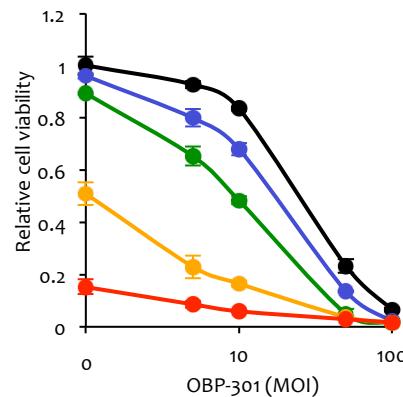
Synergistic Effect of Telomelysin and Ionizing Radiation



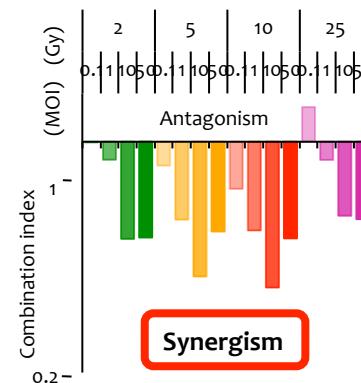
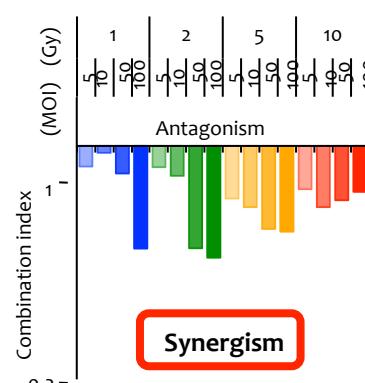
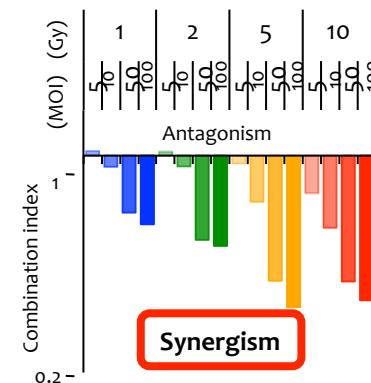
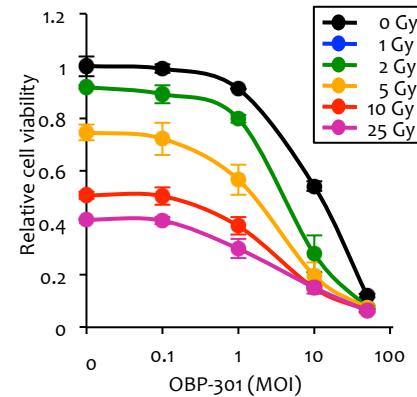
**Esophageal
Squamous Cell Carcinoma
TE8**



**Esophageal
Adenocarcinoma
SEG1**



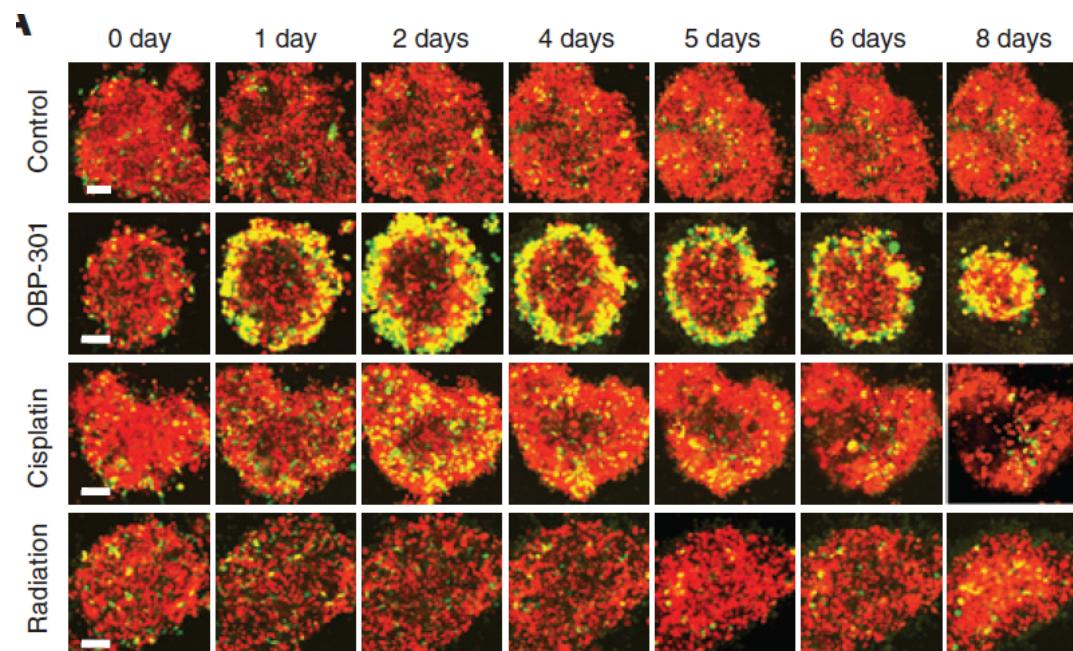
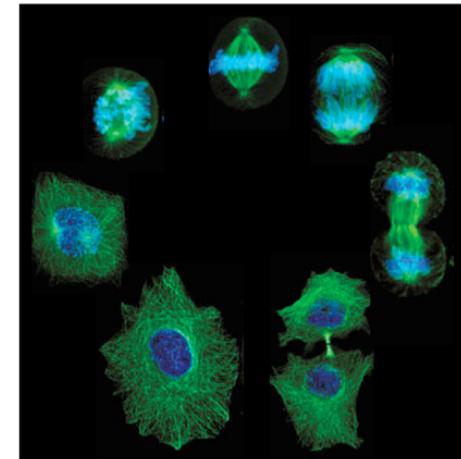
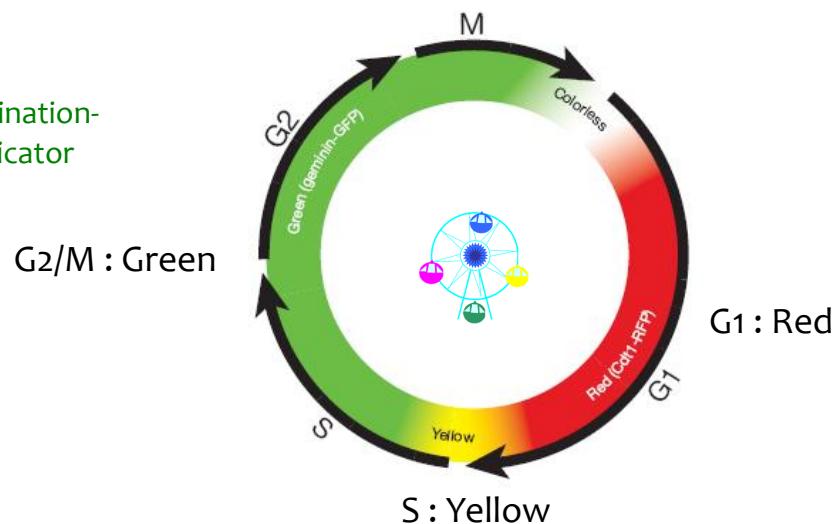
**Non-small Cell
Lung Cancer
A549**



Telomelysin Kills CD133⁺ Human Cancer Stem Cells (CSC)

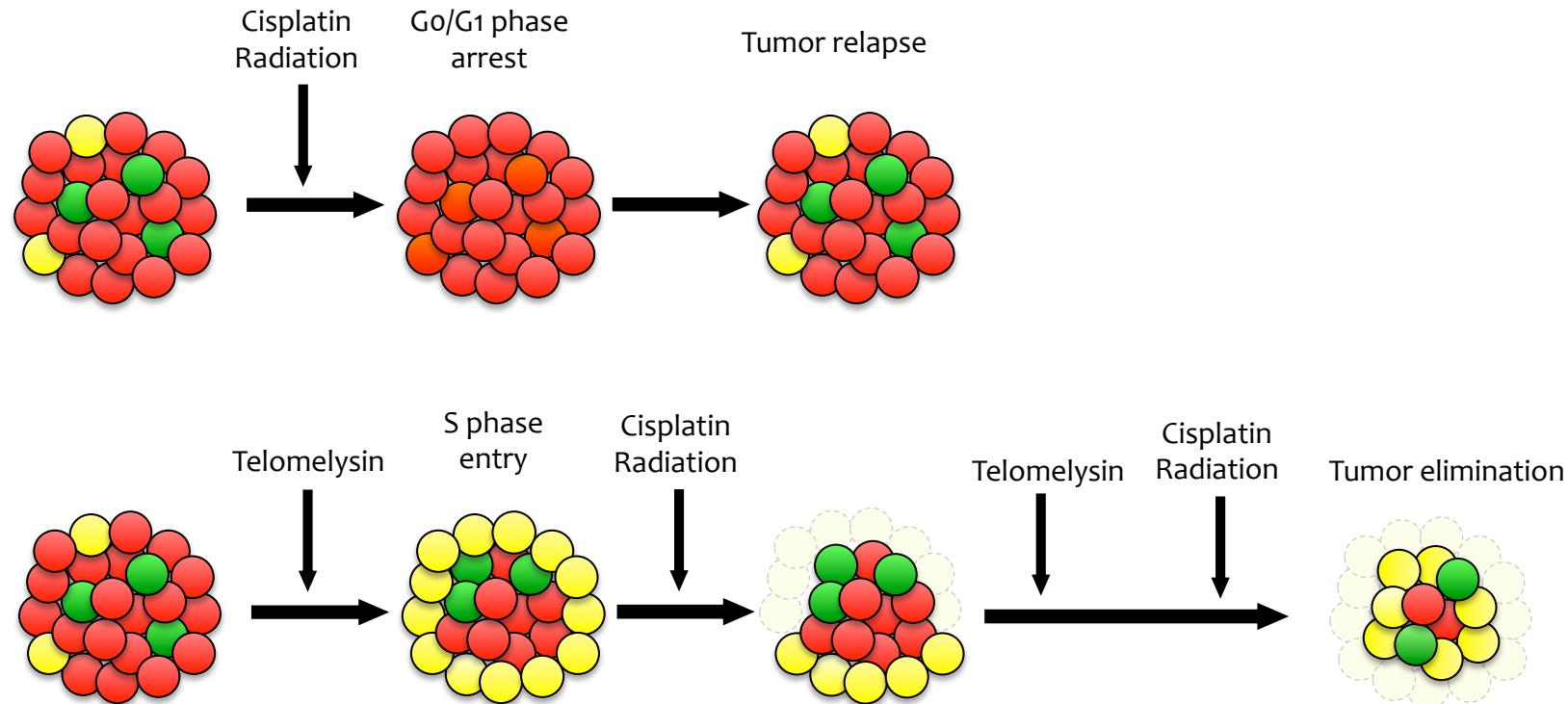
Fucci

Fluorescent Ubiquitination-based Cell Cycle Indicator



Molecular Mechanism of Multidisciplinary Therapy with Telomelysin

■ Telomelysin targets radio (chemo)-resistant human CSCs

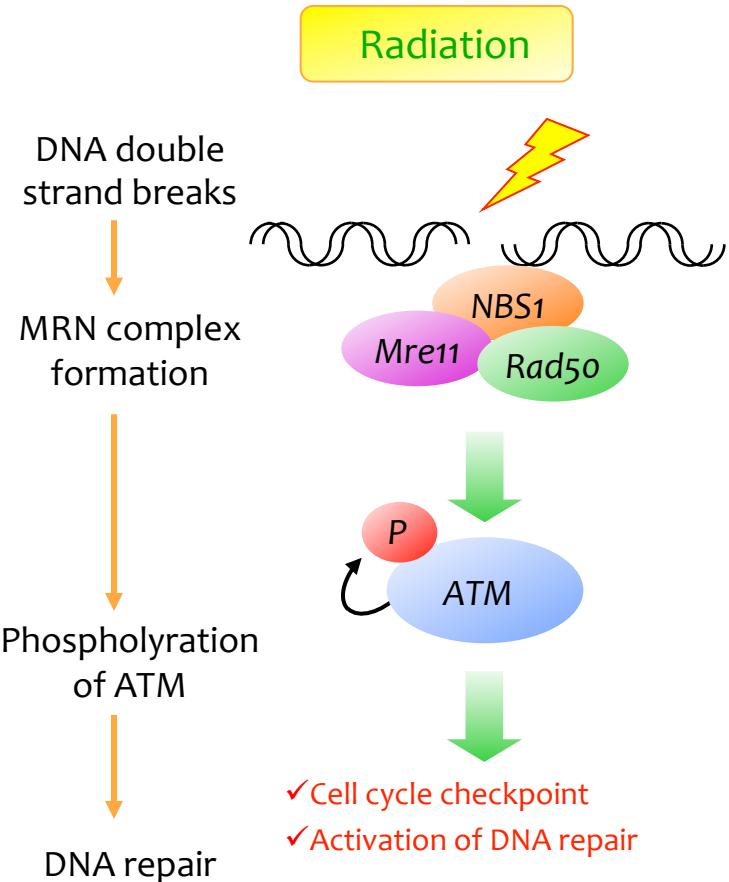


- Telomelysin sensitizes human CSCs to the conventional therapies such as chemotherapy and radiotherapy.

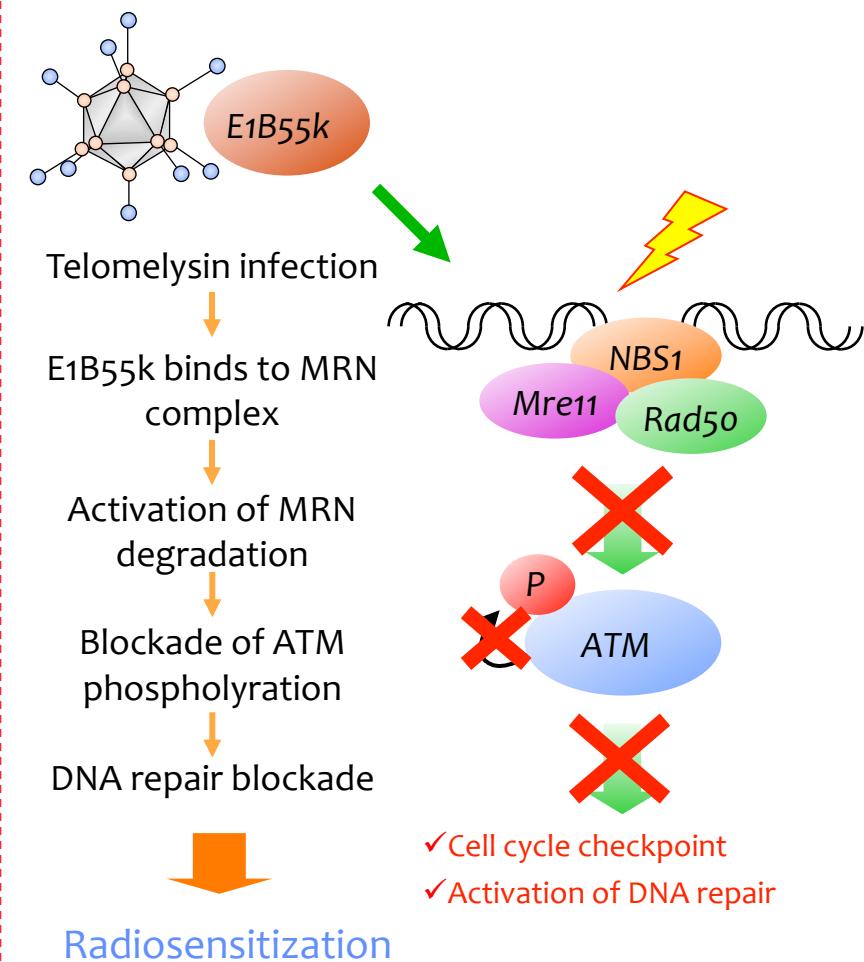


Effect of Telomelysin on DNA Repair Induced by Ionizing Radiation

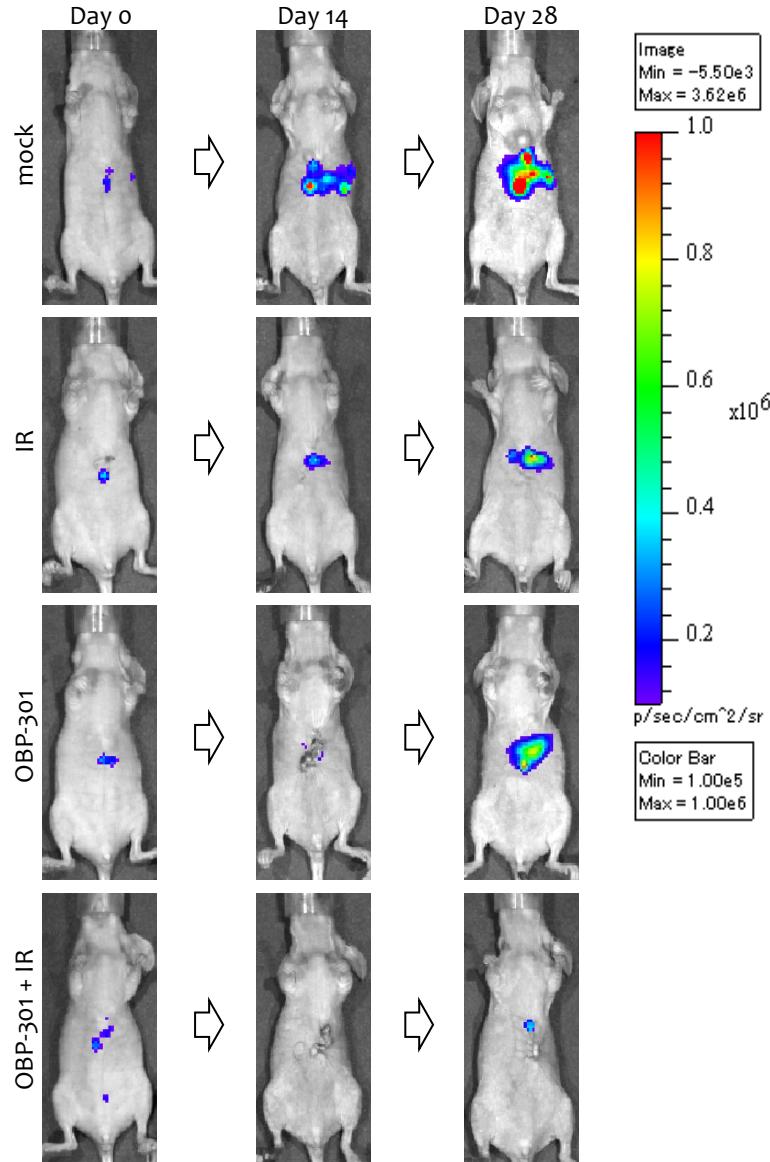
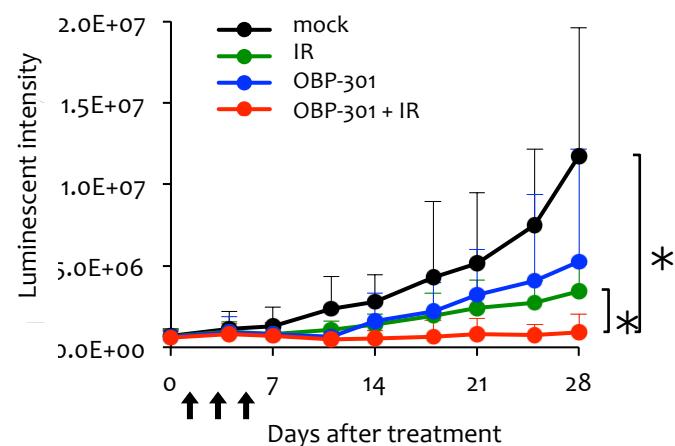
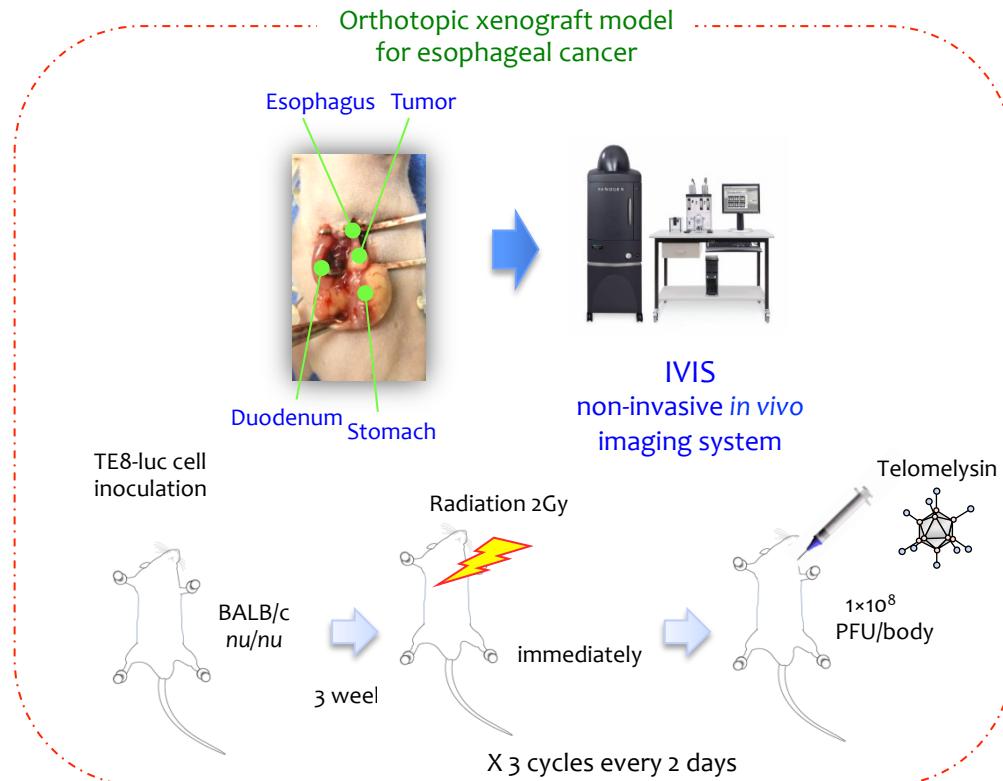
DNA Repair Mechanism after Radiation



Telomelysin Blocks the Repair of DNA Damages

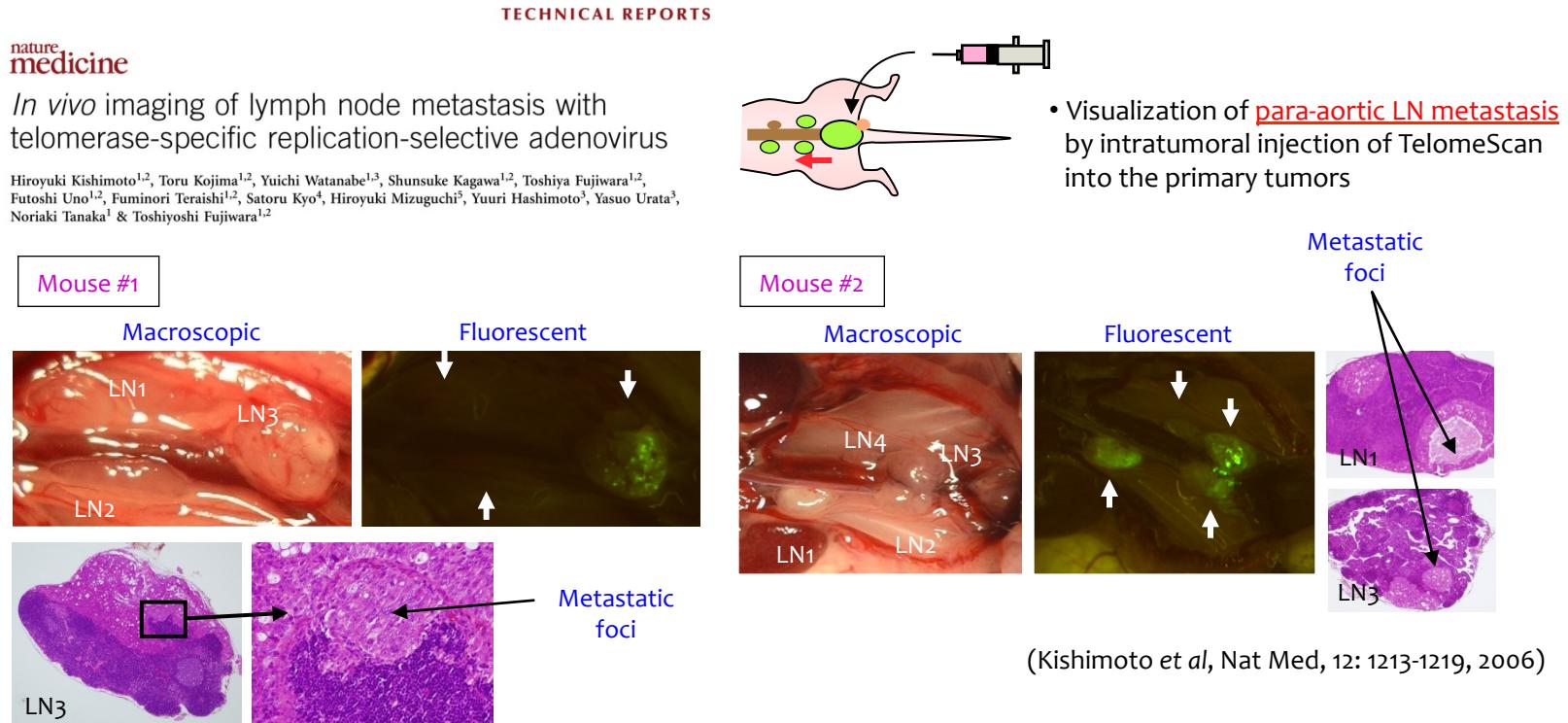


Rationale for Telomelysin with Radiotherapy for Esophageal Cancer

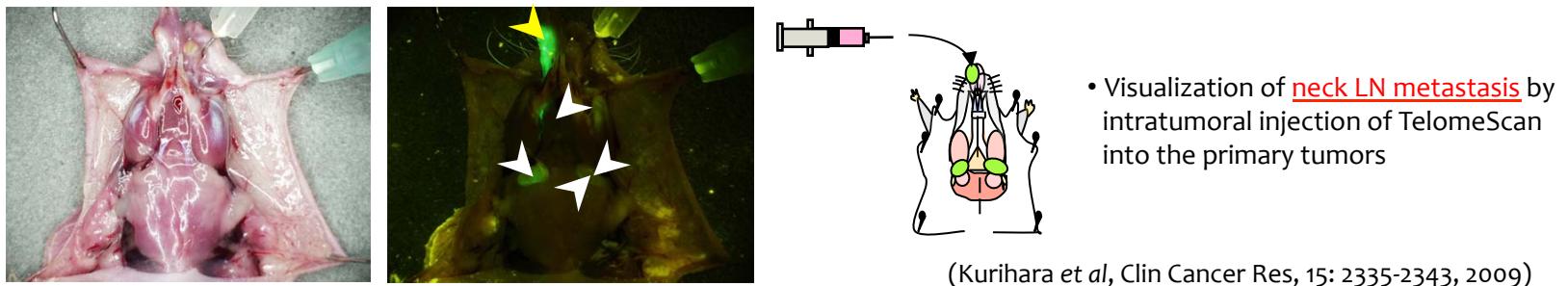


Adenovirus Traffics to the Regional Lymphatic Area

■ Orthotopic mouse model of human rectal cancer

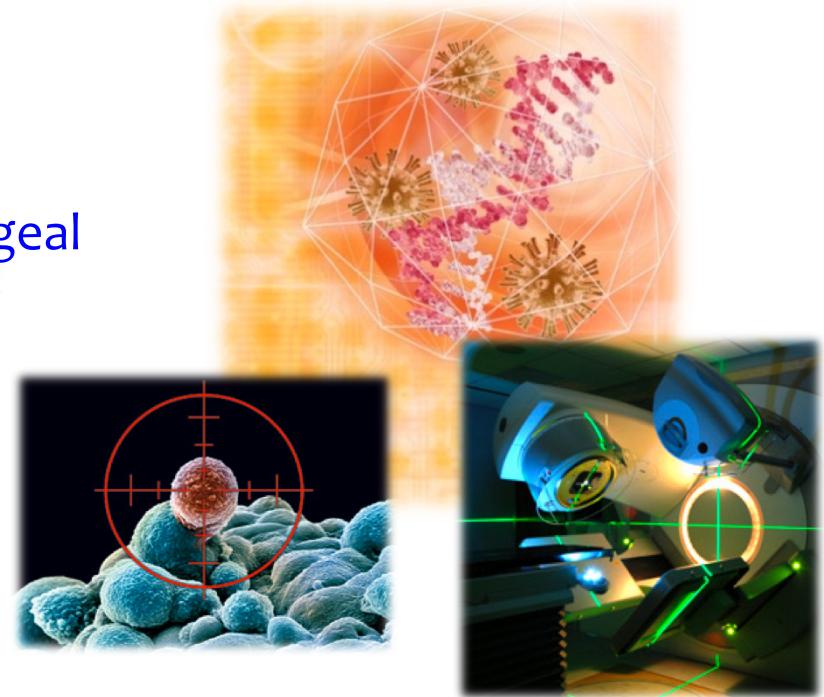


■ Orthotopic mouse model of human head & neck (tongue) cancer



■ Precision (Personalized) Medicine

Minimally Invasive Treatment for Esophageal Cancer in Elderly Patients



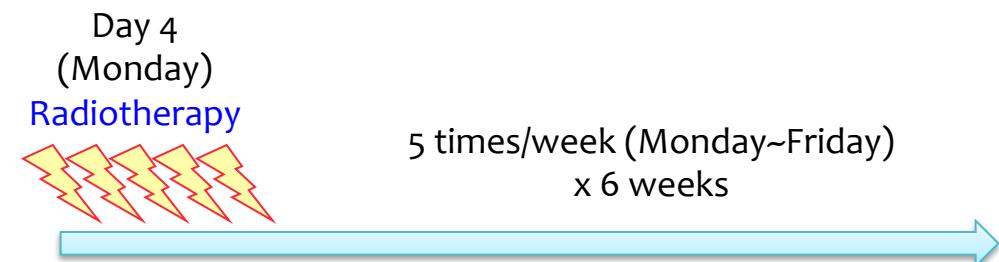
Clinical Protocol of Telomelysin with Radiotherapy

“Investigator-driven clinical research of Telomelysin in combination with radiotherapy for head and neck cancer and thoracic malignancies.”

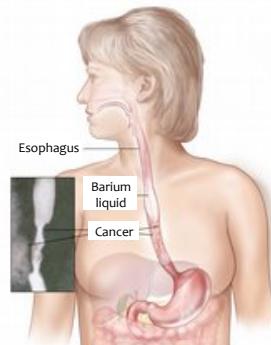
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■ Treatment schedule

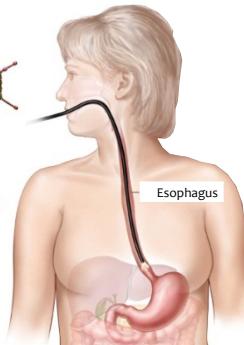
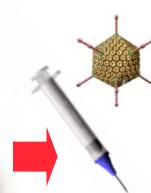
S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31	32	33	34	35	36	37
38	39	40	41	42	43	



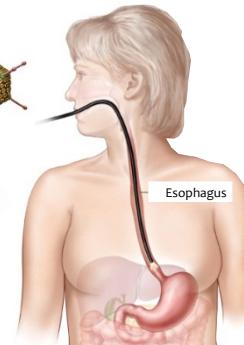
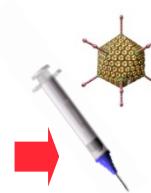
Esophageal cancer



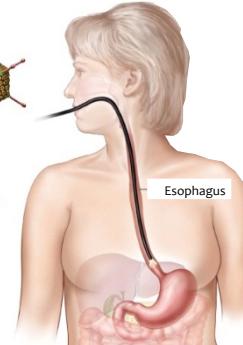
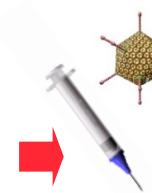
Day 1
(Friday)
Telomelysin i.t.



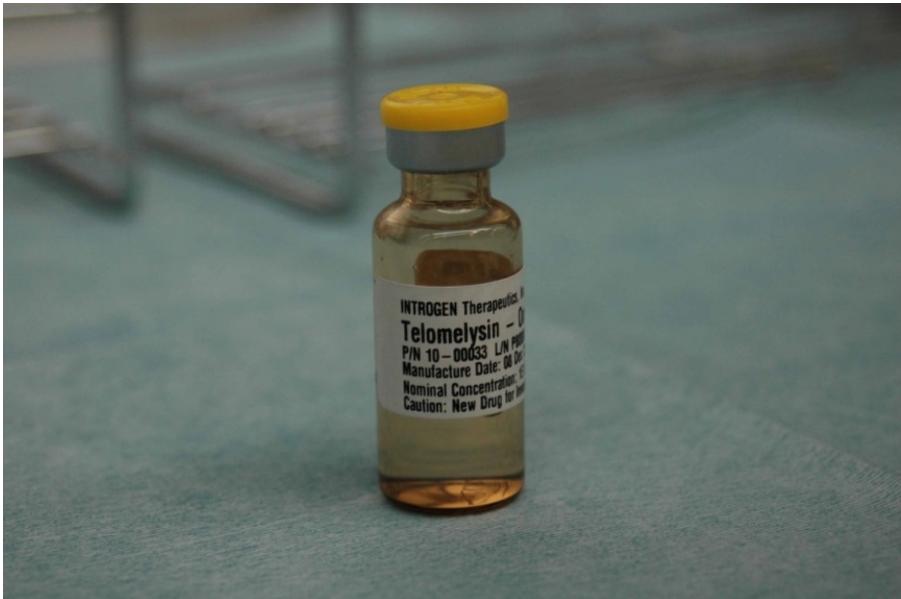
Day 18
(Monday)
Telomelysin i.t.



Day 32
(Monday)
Telomelysin i.t.



Endoscopic Injection of Telomelysin in Esophageal Cancer Patients

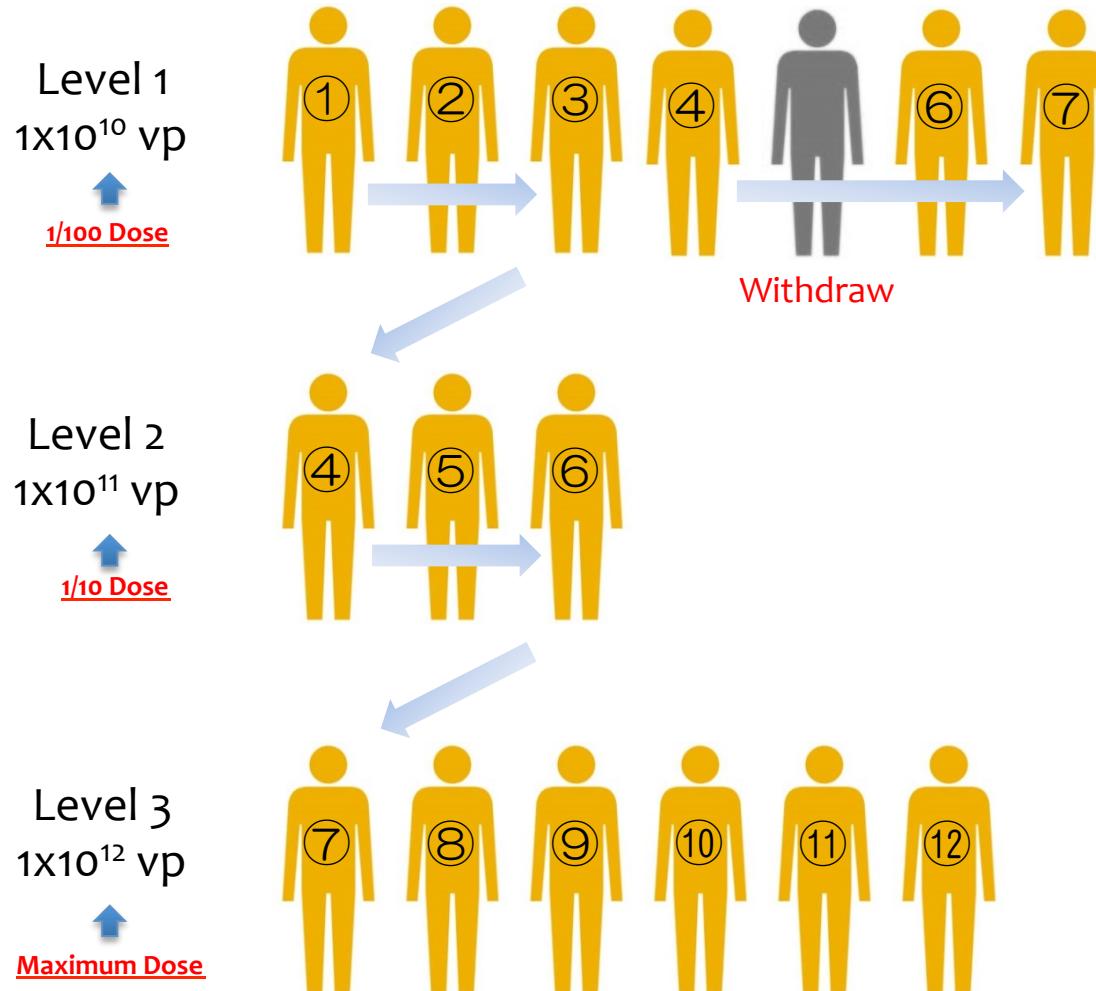


Clinical Protocol of Telomelysin with Radiotherapy

“Investigator-driven clinical research of Telomelysin in combination with radiotherapy for head and neck cancer and thoracic malignancies.”

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■ Dose-escalation schedule



Patient Characteristics

Dose	Case	Age	M/F	Histology	Location	TNM	Stage	Prior Therapy	Injection Route
<u>Cohort</u> 1×10^{10} vp	001	82	F	Squamous cell ca	Esophagus, Lt, o-IIb	cT1bNoMo	cStage I	None	Endoscopy
	002	85	M	Squamous cell ca	Esophagus, MtLt, o-IIb	cT1bNoMo	cStage I	None	Endoscopy
	003	92	F	Squamous cell ca	Esophagus, LtMtAe, Type 2	cT3NoMo	cStage II	None	Endoscopy
	004	68	M	Squamous cell ca	Esophagus, Ut, Type 3	cT4(#106rec R)N1Mo	cStage IVa	Chemotherapy (DCF)	Endoscopy
	005 (withdrawn)	79	M	Squamous cell ca	Esophagus, MtLtUt, Type 3	cT3N2Mo	cStage III	Chemotherapy (FP)	Endoscopy
	006	88	M	Squamous cell ca	Esophagus, Lt, o-IIa	cT1bNoMo	cStage I	None	Endoscopy
	007	53	F	Squamous cell ca	Esophagus, Ut, Type 2	cT2N1(#106 recR)Mo	cStage II	None	Endoscopy

Lessons learned from Ph-I study of Telomelysin in the US and Japan

■ Safety

- Single and multiple doses were well tolerated (up to 5×10^{12} vp).
- Combination with RT was also well tolerated (3×10^{10} vp).
- Most Adverse Events were mild to moderate in severity and transient.
- No liver toxicity
- Transient lymphopenia was seen 24 hours after injection.

■ Pharmacokinetics

- Measurable levels in plasma after 1 – 3 hours.
- Patients had measurable levels at 7 and 14 days after treatment.

■ Clinical Benefit

- Indication of reduction in area of treated tumor in some patients.
- No patient showed any local progressive disease.

Advantages of Telomelysin

- Telomelysin is synergistic with the DNA-damaging therapies such as chemotherapy and radiotherapy through two molecular mechanisms.
 - Eliminates cancer stem cells (CSCs) by waking CSCs from dormancy.
 - Sensitizes refractory tumor cells by inhibiting DNA repair machinery.
 - Telomelysin can traffic to the regional lymphatic area and replicate in metastatic foci in lymph nodes.
- In addition,
- Telomelysin-mediated oncolysis induces danger signal and stimulates cytotoxic T-lymphocyte activity.
(Endo Y, Fujiwara T, et al; Oncogene. 2008;27: 2375-81)
 - Telomelysin has antiangiogenic properties through the stimulation of host immune cells to produce endogenous antiangiogenic factors such as IFN- γ .
(Ikeda Y, Fujiwara T, et al; J Immunol. 2009;182:1763-9)

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