

第29回日本遺伝子細胞治療学会学術集会  
JSGCT教育プログラム2023

## 腫瘍融解ウイルス製剤の 臨床開発の経験

岡山大学学術研究院 医歯薬学域  
消化器外科学

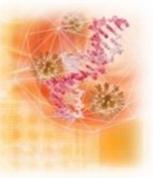
藤原 俊義

2023年9月10日（日）  
大阪国際会議場10F

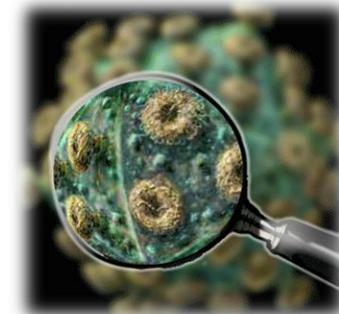


# Today's Topics

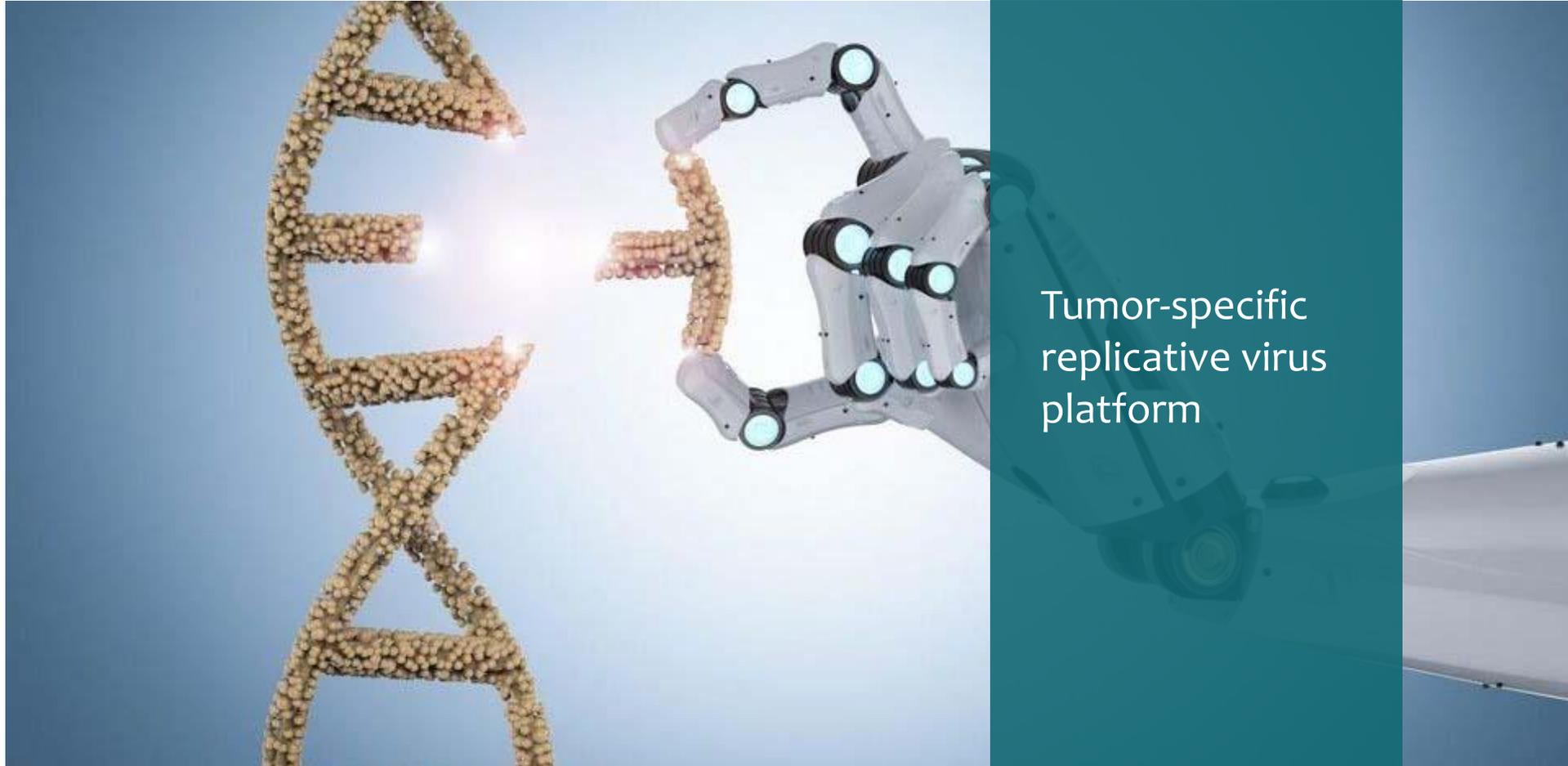
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- Tumor-specific replicative adenovirus platform
- Telomerase-specific oncolytic virotherapy for cancer cure
- Next-generation oncolytic virotherapy armed with p53 gene

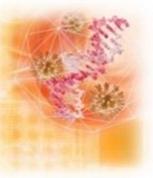


■ Topics 1

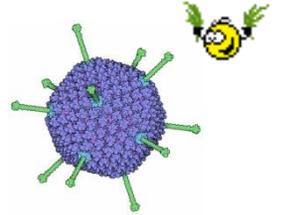


Tumor-specific  
replicative virus  
platform

# “Smart drug”としてのウイルス (virus) の特徴



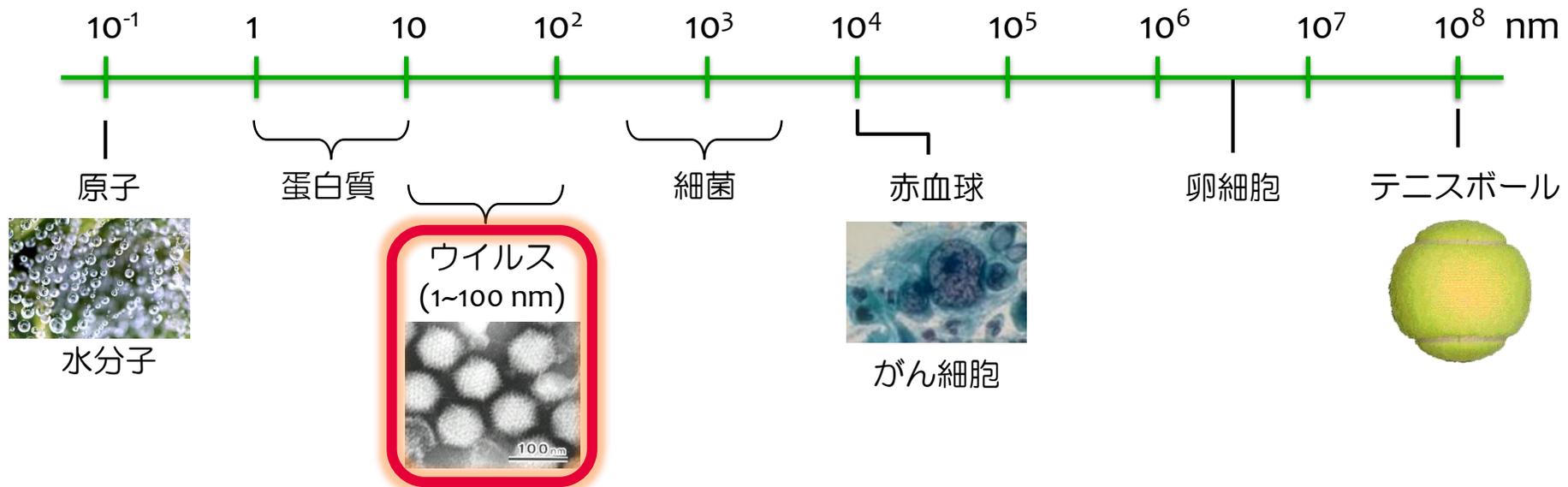
- ウイルスはタンパク質と核酸からなる粒子である。
- ウイルスは外来性にDNAやRNAを宿主細胞に持ち込む。
- ウイルスは単独では増殖できず、他の細胞に寄生したときのみ増殖できる。
- ウイルスは増殖すると宿主細胞を破壊（融解・溶解）する。
- ウイルスは全身的な免疫反応を惹起する。



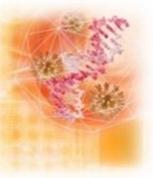
Gene delivery

Oncolysis

Immunotherapy



# Virus can kill human tumor cells



## Regression of Burkitt's Lymphoma in Association with Measles Infection

Bluming AZ, and Ziegler JL  
Lancet, 2 (7715):105-106, 1971

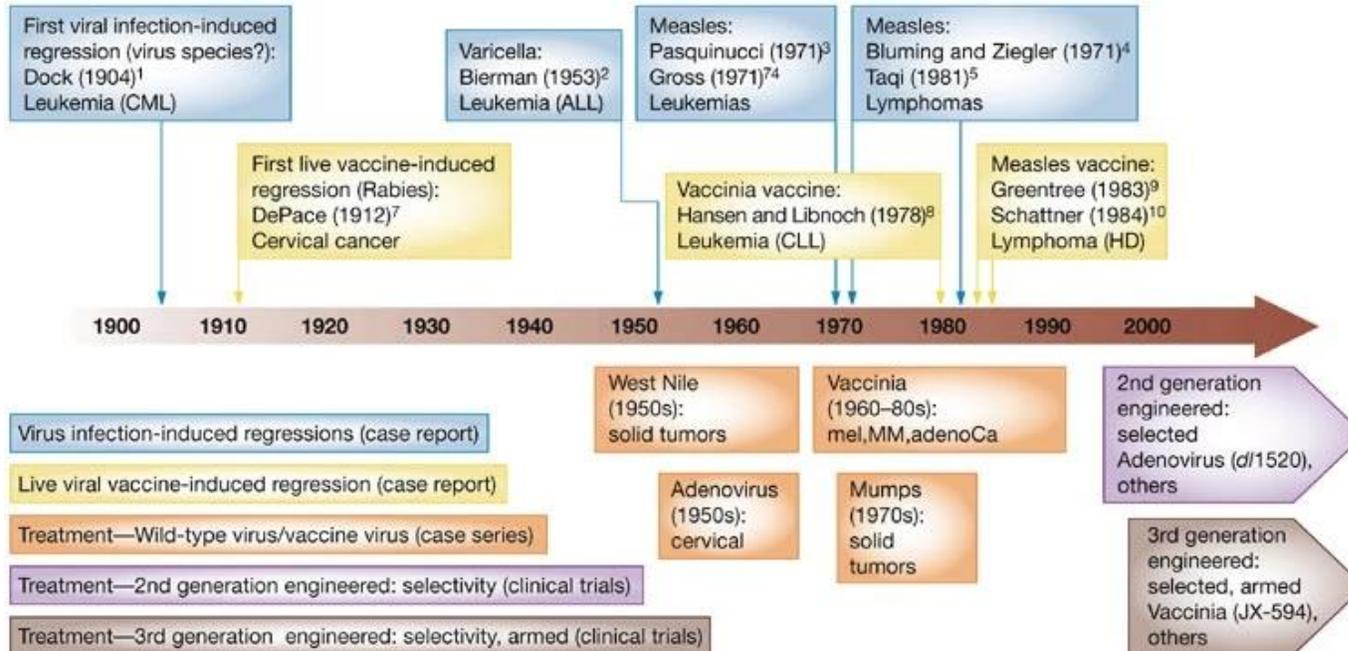
バーキットリンパ腫のアフリカの少年が  
はしか（麻疹）にかかって高熱を出した後  
リンパ腫が治癒した報告



Fig. 1—Patient on admission, Dec. 1, 1970.

Fig. 2—Patient on Dec. 21, 1970, with resolving measles exanthem.

Fig. 3—Patient on Jan. 6, 1971. Tumour and measles have resolved completely.



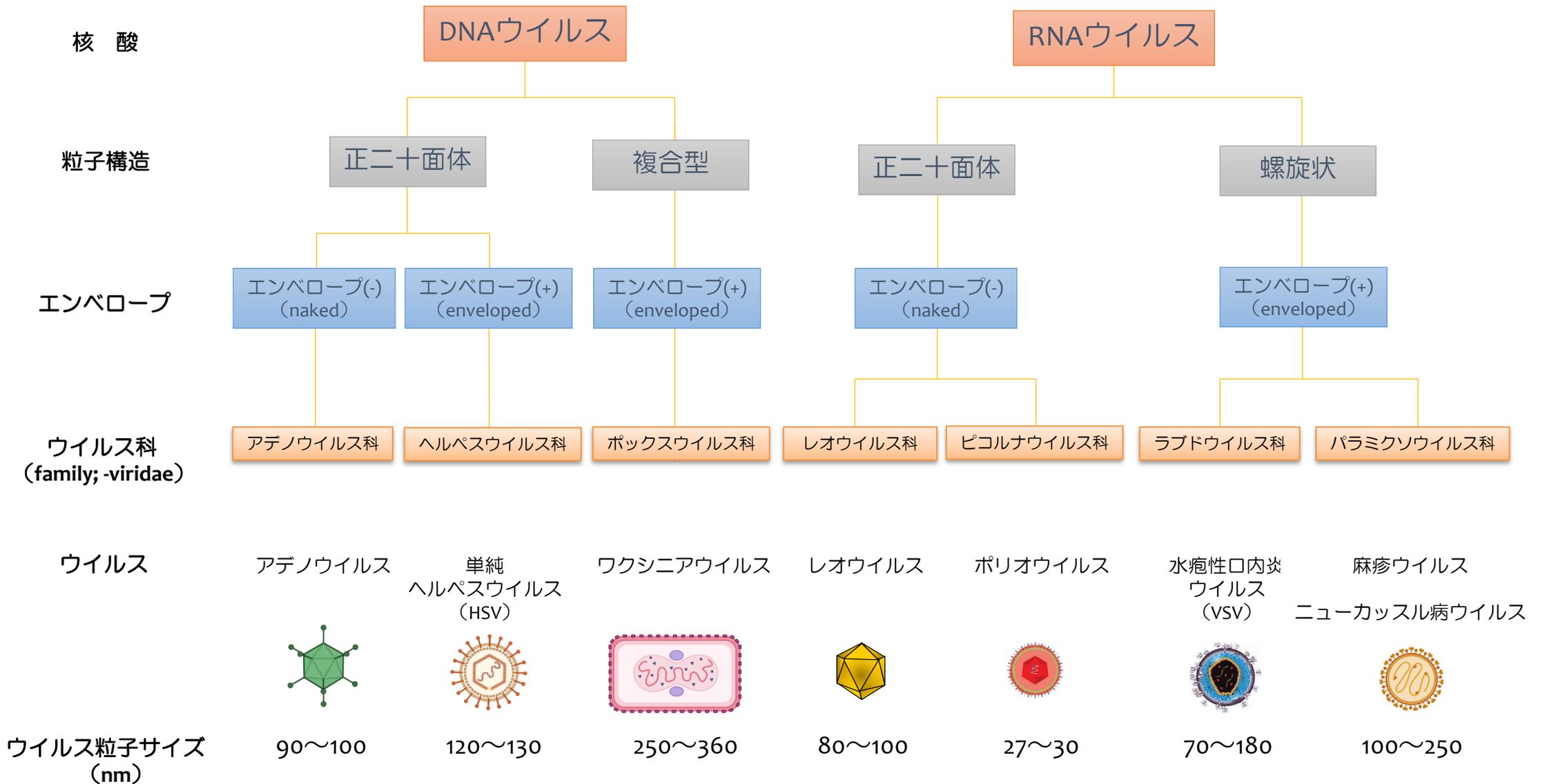
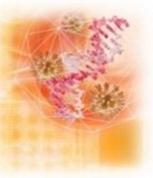
欧米で承認

日本で承認

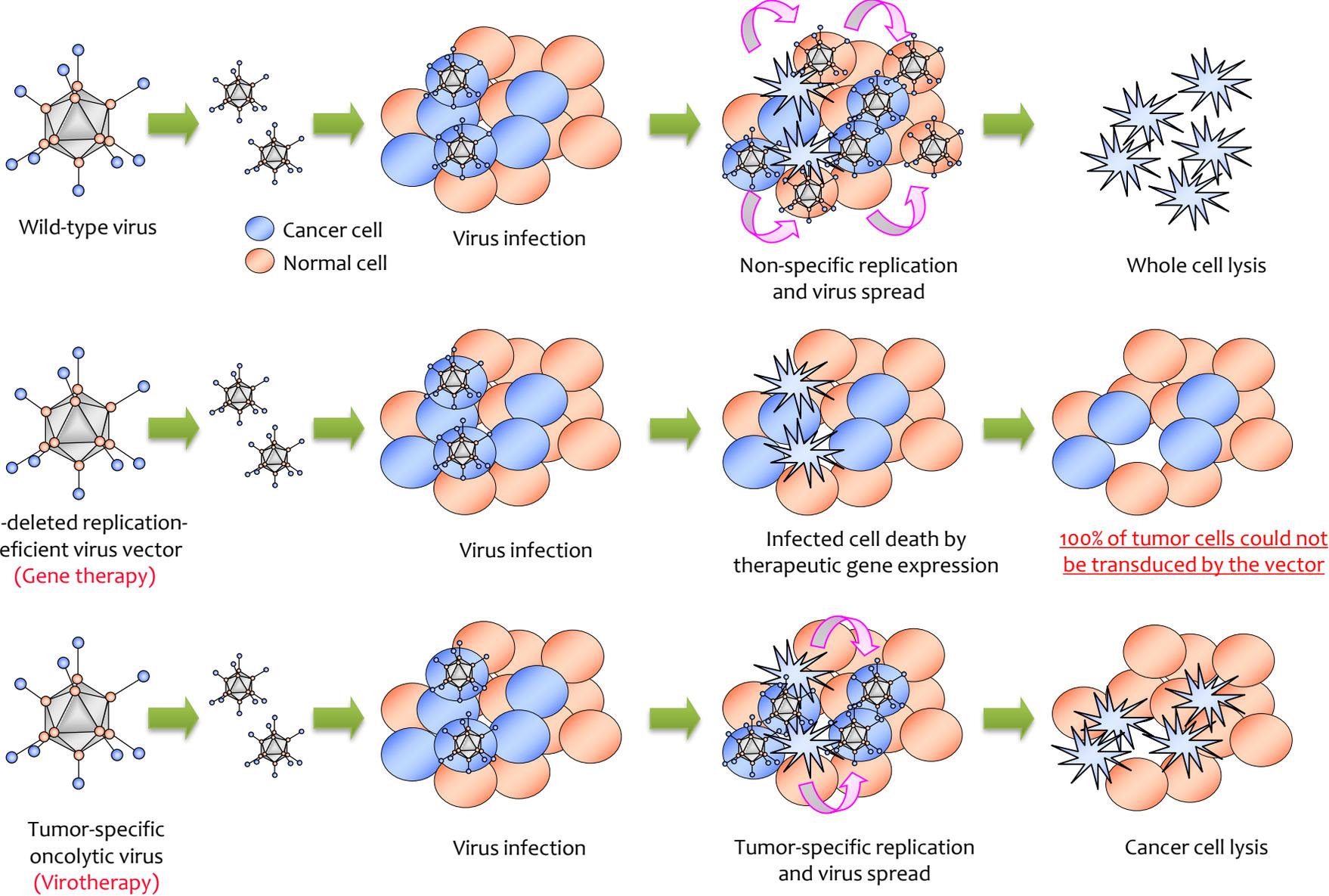
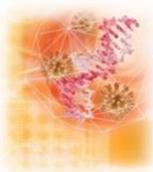


- 悪性黒色腫に対する **talimogene laherparepvec (T-VEC、IMLYGIC)**
- 脳腫瘍に対する **テセルパツレブ (G47Δ、デリタクト注)**

# Viruses used in oncolytic virotherapy



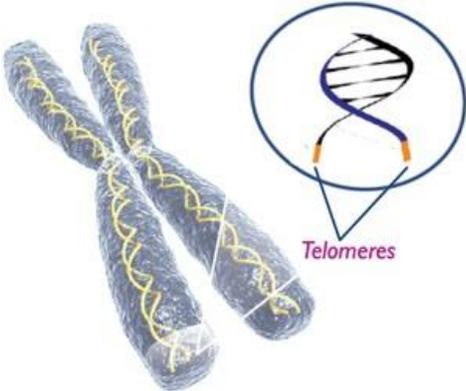
# Viral replication and oncolysis



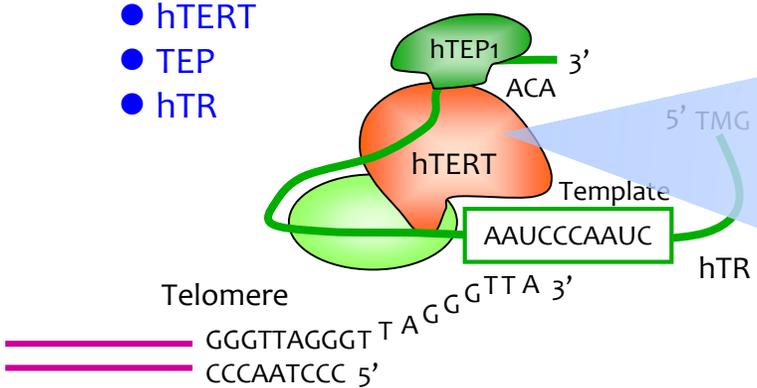
# Telomerase



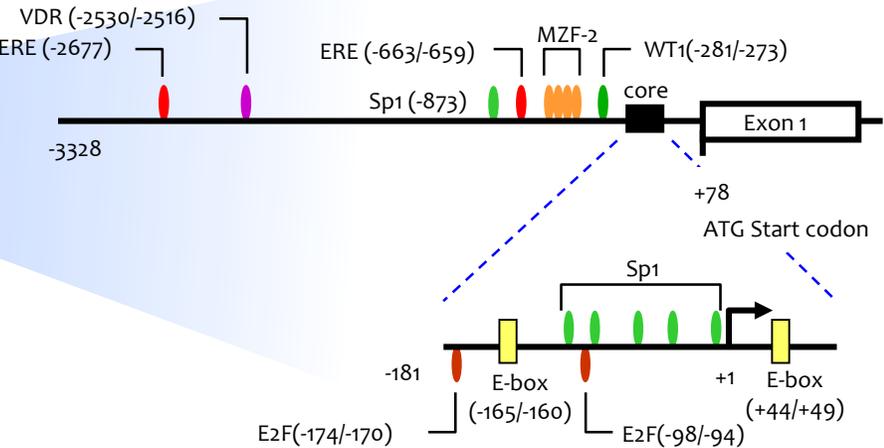
- Telomerase is a ribonucleoprotein complex that is responsible for adding TTAGGG repeats onto the 3' ends of chromosomes.
- The majority of malignant tumors express telomerase activity, whereas telomerase is strongly repressed in most normal somatic tissues.
- Telomerase may be a plausible target for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



### ■ Telomerase protein complex



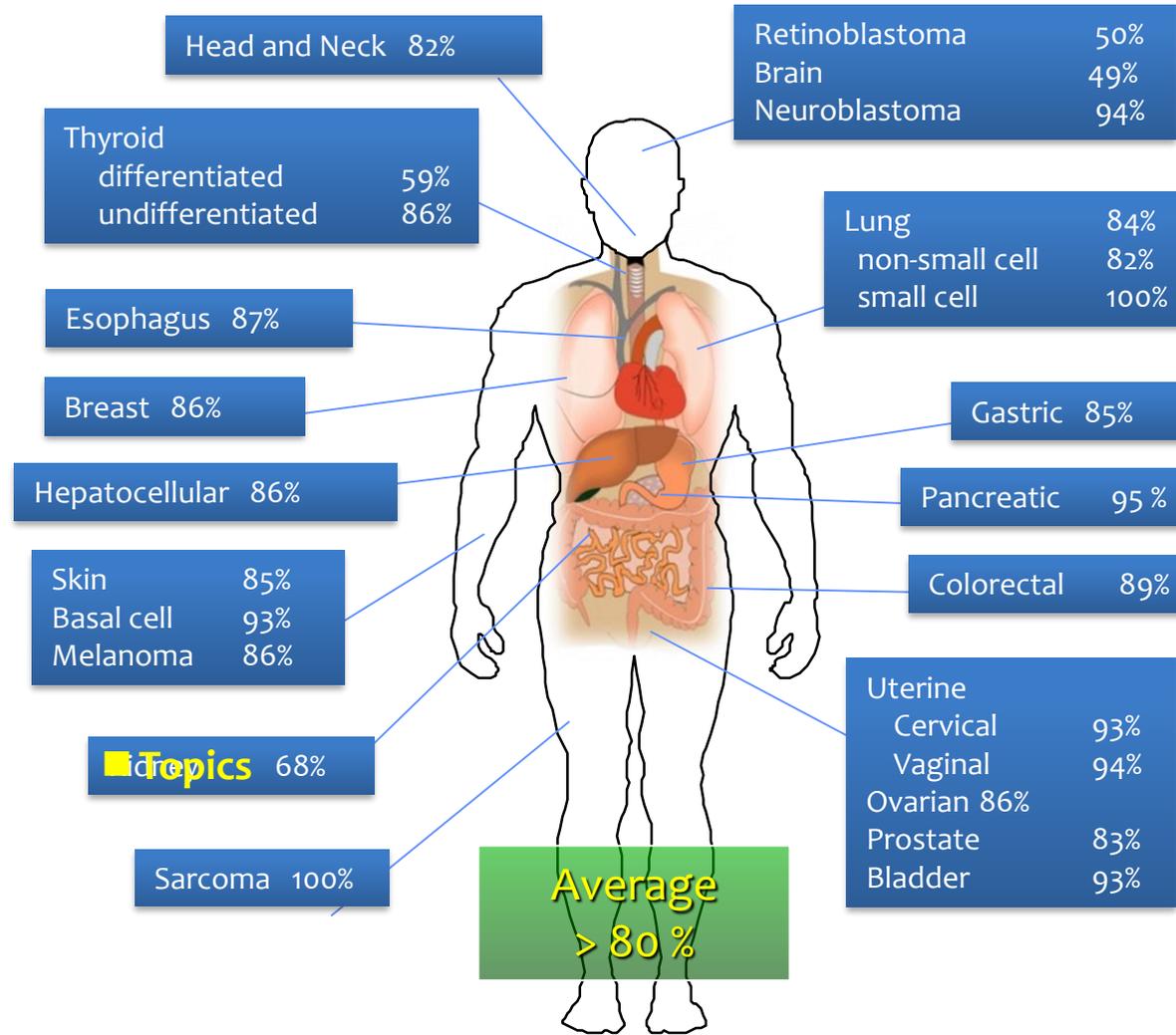
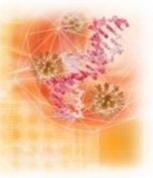
### ■ hTERT promoter



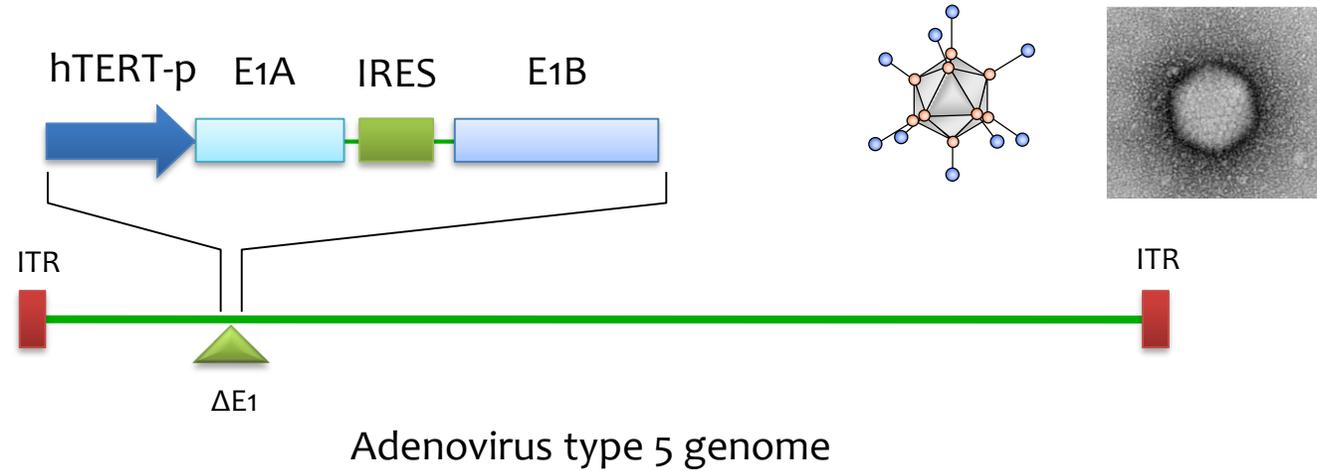
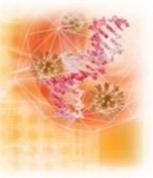
- hTERT promoter can be used as a **molecular switch** for human cancer

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

# Telomerase activity in human cancers



# OBP-301 (telomelysin)



hTERT-p



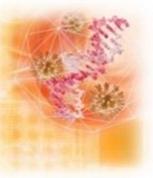
The hTERT promoter was used as a **molecular switch** for telomerase-positive human cancers

IRES

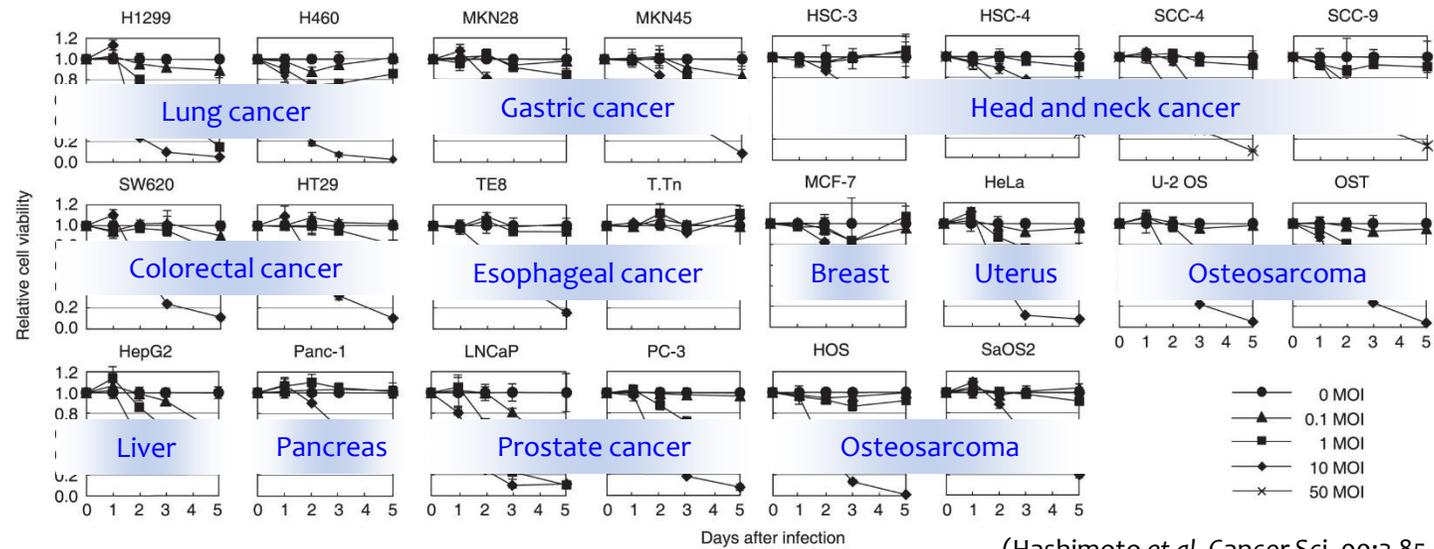


An IRES sequence allows expression of **two genes** from a single promoter

# Viral replication and oncolysis

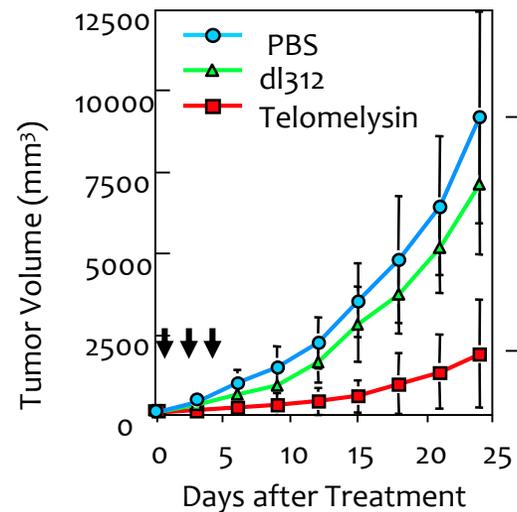


## ■ Preclinical study of telomelysin (*in vitro*)



(Hashimoto *et al*, *Cancer Sci*, 99:3 85-390, 2008)

## ■ Preclinical study of telomelysin (*in vivo*)



(Kawashima *et al*, *Clin Cancer Res*, 10: 285-292, 2004)

# Broad molecular functions of OBP-301 (telomelysin)



- *In vivo* imaging of **lymph node metastasis** with telomerase-specific replication-selective adenovirus.

*Kishimoto H et al. Nat Med. 2006*

Telomelysin traffics to **the regional lymphatic area**.

- Virus-mediated oncolysis induces danger signal and stimulates cytotoxic T-lymphocyte activity via proteasome activator upregulation.

*Endo Y, et al. Oncogene. 2009*

Telomelysin induces **immunogenic cell death (ICD)**.

- A novel **antiangiogenic effect** for telomerase-specific virotherapy through host immune system.

*Ikeda Y, et al. J Immunol. 2009*

Telomelysin exhibits **antiangiogenic activities**.

- Genetically engineered oncolytic adenovirus induces **autophagic cell death** through an E2F1-microRNA-7-epidermal growth factor receptor axis..

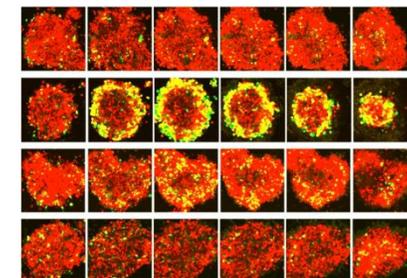
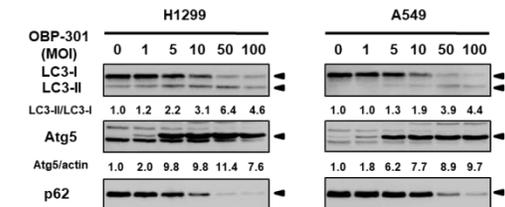
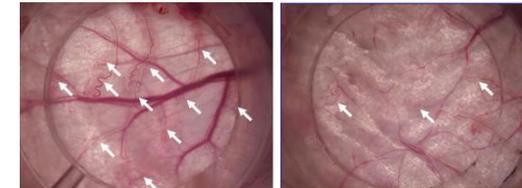
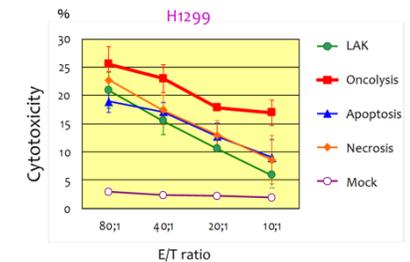
*Tazawa H, et al. Int J Cancer. 2012*

Telomelysin induces **autophagy** via a micro-RNA network.

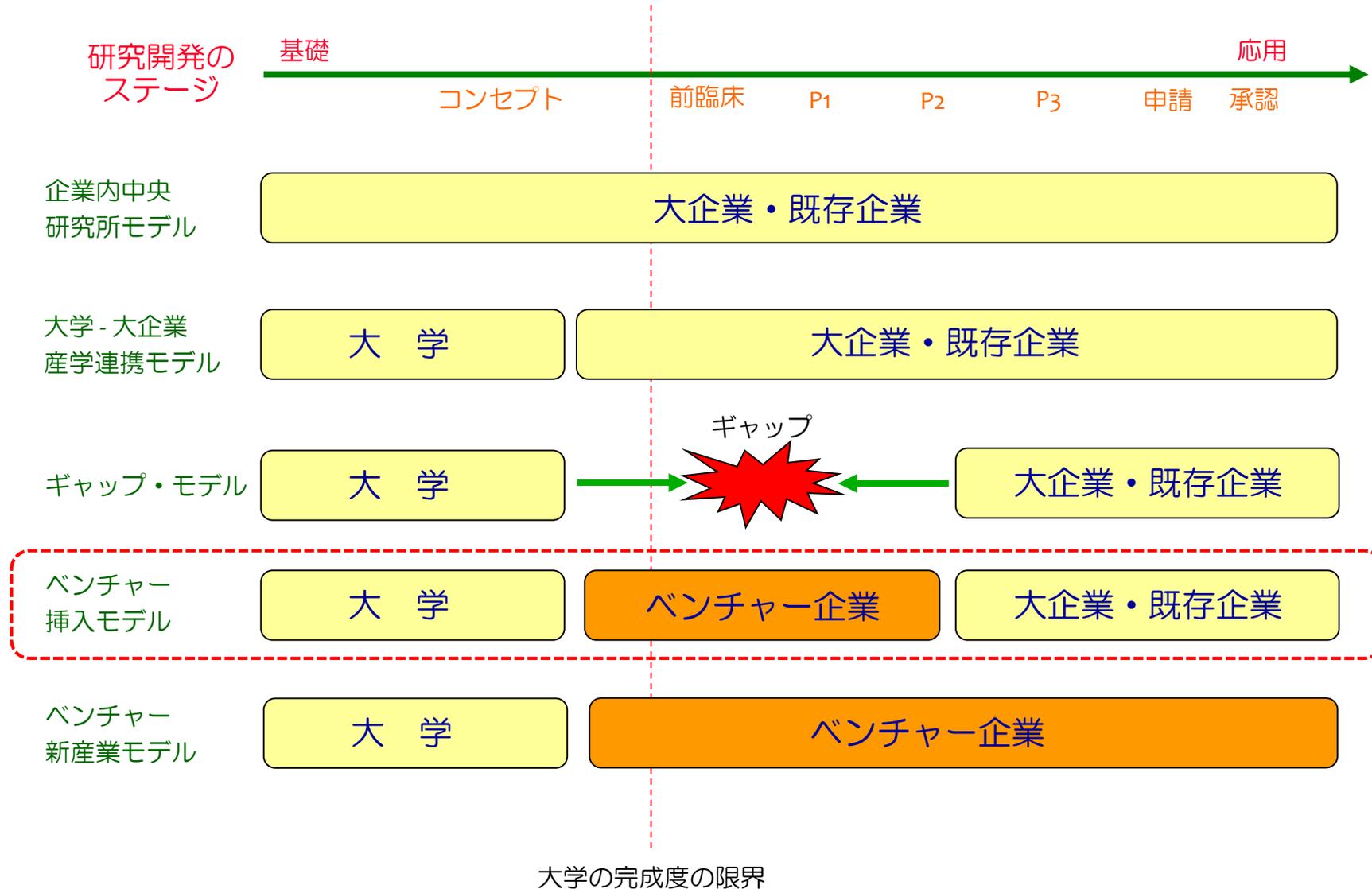
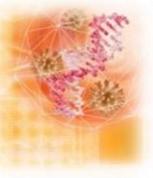
- A genetically engineered oncolytic adenovirus decoys and lethally traps quiescent **cancer stem-like cells** into S/G<sub>2</sub>/M-phases.

*Yano S, et al. Clin Cancer Res. 2013*

Telomelysin eliminates **cancer stem cells (CSCs)**.



# 技術移転：ギャップ・モデルとベンチャー企業





- がんと感染症を克服するため、独自のウイルス研究により安全で有効な新薬を開発ことを目的とする岡山大学発バイオベンチャー



創業メンバー（2004年3月28日）



## ■ GMP-grade Telomelysin Production



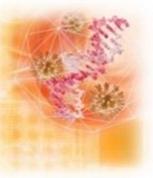
## ■ Industry-IND Application to the US FDA



### FDA/CBER members

- Product Reviewer
- Pharm/Tox Reviewer
- Pharm/Tox Branch Chief
- Clinical Reviewer
- Clinical Branch Chief
- Regulatory Management Staff

- IND (Investigational New Drug) approved (August 25, 2006)



## ■ 米国での臨床試験を選択した理由（2006年当時）

- 日本での厚生労働省の遺伝子治療臨床研究審査委員会での承認申請には時間がかかる（Advexinの開発経験から）。
- 医薬品医療機器総合機構（PMDA）の生物系審査部ではアデノウイルス製剤の製造確認申請の審査経験がなく、治験申請の審査は新薬審査第一部（抗がん剤審査担当）が担当する。
- オンコリスバイオフーマの経営陣および臨床開発担当者は日本たばこ産業（JT）医薬品事業部出身であり、FDAへの治験申請の経験を多く有する。特に、臨床開発担当者は長期の米国滞在を経験している。
- FDAの生物製剤評価・研究センター（CBER；Center for Biologics Evaluation and Research）での審査は迅速かつ的確であり、開発計画のタイムスケジュールを立てやすい。

# Clinical trial of OBP-301 (telomelysin) in the U.S.



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

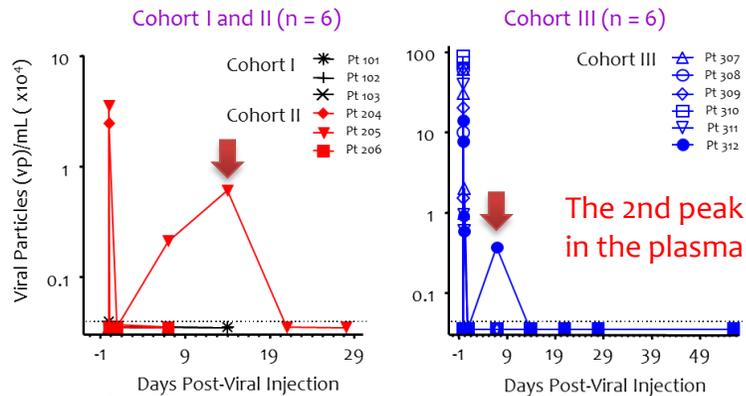
© The American Society of Gene & Cell Therapy

original article

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

John Nemunaitis<sup>1-4</sup>, Alex W Tong<sup>3,4</sup>, Michael Nemunaitis<sup>1</sup>, Neil Senzer<sup>1-4</sup>, Anagha P Phadke<sup>4</sup>, Cynthia Bedell<sup>1</sup>, Ned Adams<sup>1</sup>, Yu-An Zhang<sup>3,4</sup>, Phillip B Maples<sup>4</sup>, Salina Chen<sup>4</sup>, Beena Pappen<sup>4</sup>, James Burke<sup>5</sup>, Daiju Ichimaru<sup>6</sup>, Yasuo Urata<sup>6</sup> and Toshiyoshi Fujiwara<sup>7</sup>

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



### ■ Safety

- Telomelysin was well tolerated (up to  $5 \times 10^{12}$  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.

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, perfosine
5 (205)	69	M	Squamous cell ca base of tongue	Cisplatin, XRT
6 (206)	60	F	Leiomyosarcoma	Doxorubicin, ifosfamide, gemcitabine, docetaxel, perfosine
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

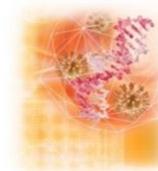
M, male; F, Female.

Cohort 1  
1x10<sup>10</sup> vp  
(1/100)

Cohort 2  
1x10<sup>11</sup> vp  
(1/10)

Cohort 3  
1x10<sup>12</sup> vp  
(Max dose)

# Local response of injected tumors



	Patient background	Pre-study (cm) (area cm <sup>2</sup> )	Day 28 (cm) (area cm <sup>2</sup> )	Local response of Day 28	Day 56 (cm) (area cm <sup>2</sup> )
Cohort 1	SCC primary unknown	2.5 x 1.5 (3.75)	2.5 x 1.6 (4.00)	SD (+6.7%)	n.a. resected
	Melanoma	4.0 x 2.8 (11.20)	3.8 x 2.5 (9.50)	<u>SD (-15.2%)</u>	4.0x2.5 (10.00, -10.7%)
	Melanoma	4.2 x 3.3 (13.86)	3.6 x 2.8 (10.08)	<u>SD (-27.3%)</u>	Not evaluable (fluid)
Cohort 2	Salivary carcinoma	4.5 x 3.2 (14.40)	4.3 x 3.2 (13.76)	<u>SD (-4.4%)</u>	4.5x3.1 (13.95, -3.1%)
	SCCHN	2.5 x 1.7 (4.25)	2.2 x 1.7 (3.74)	<u>SD (-12.0%)</u>	2.6x1.7 (4.42, 4%)
	Leiomyosarcoma	2.5 x 2.0 (5.00)	2.2 x 2.0 (4.40)	<u>SD (-12.0%)</u>	n.d.
Cohort 3	Lung cancer	1.7 x 1.5 (2.55)	1.7 x 1.4 (2.38)	<u>SD (-6.7%)</u>	1.7x1.4 (2.38, -6.7%)
	Melanoma	3.3 x 1.4 (4.62)	2.8 x 1.1 (3.08)	<u>SD (-33.3%)</u>	2.7x1.0 (2.70, -56.7%)
	NSCLC	3.5 x 4.7 (16.45)	4.8 x 3.5 (16.80)	SD (+2.1%)	4.8x3.7 (18.50, 12.5%)
	SCCHN	2.8 x 1.8 (5.04)	Not evaluable	n.a.	3.1x2.1 (6.51, 29.2%)
	SCCHN	5.8 x 2.6 (15.08)	7.2 x 3.2 (23.04)	SD (+50.0%)	—
	Melanoma	1.5 x 1.5 (2.25)	n.d.	n.a.	—
	Sarcoma	5.5 x 3.4 (18.7)	n.d. (withdraw)	n.a.	—
	Basal cell carcinoma	2.8 x 1.0 (2.8)	1.7 x 0.9 (1.53)	<u>SD (-45.4%)</u>	PD (new legion)
	Gall bladder carcinoma	4.2 x 3.4 (14.28)	4.7 x 3.7 (17.39)	SD (+21.8%)	4.4x4.3 (18.92, 32.5%)
	Breast cancer	1.0 x 0.9 (0.9)	n.d. (withdraw)	n.a.	—

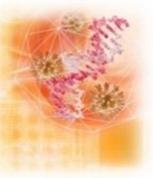
完全奏効 (CR) はなかった

■ Topics 2

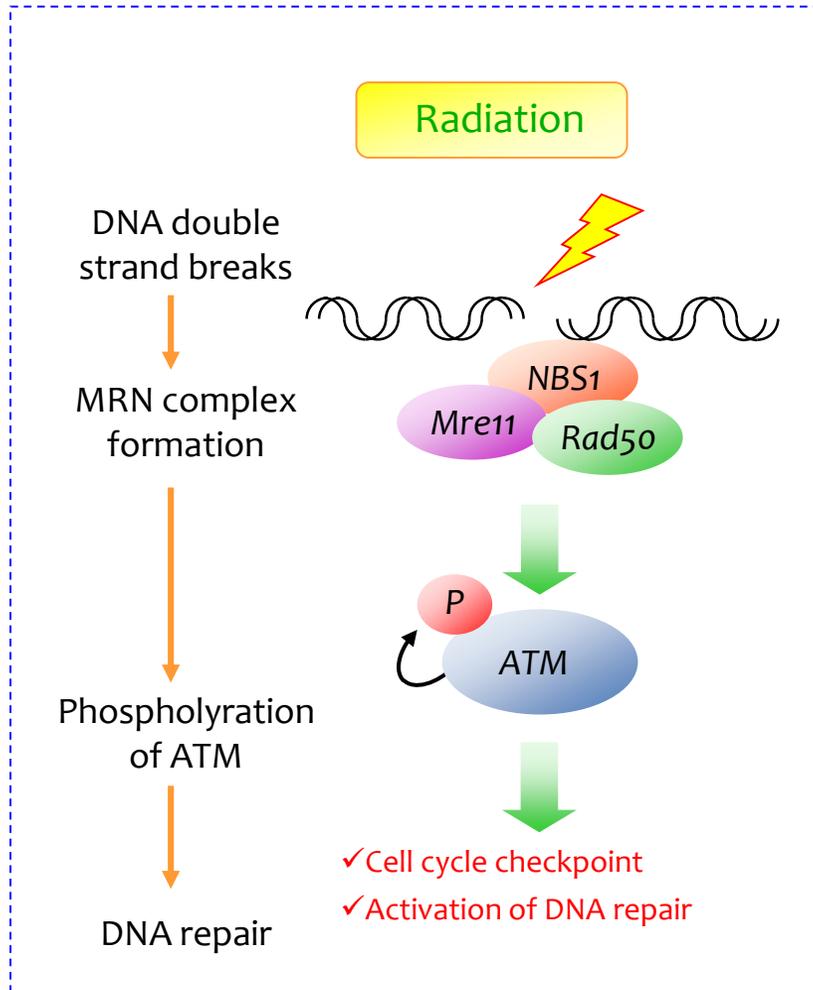


Telomerase-specific  
oncolytic virotherapy  
for cancer cure

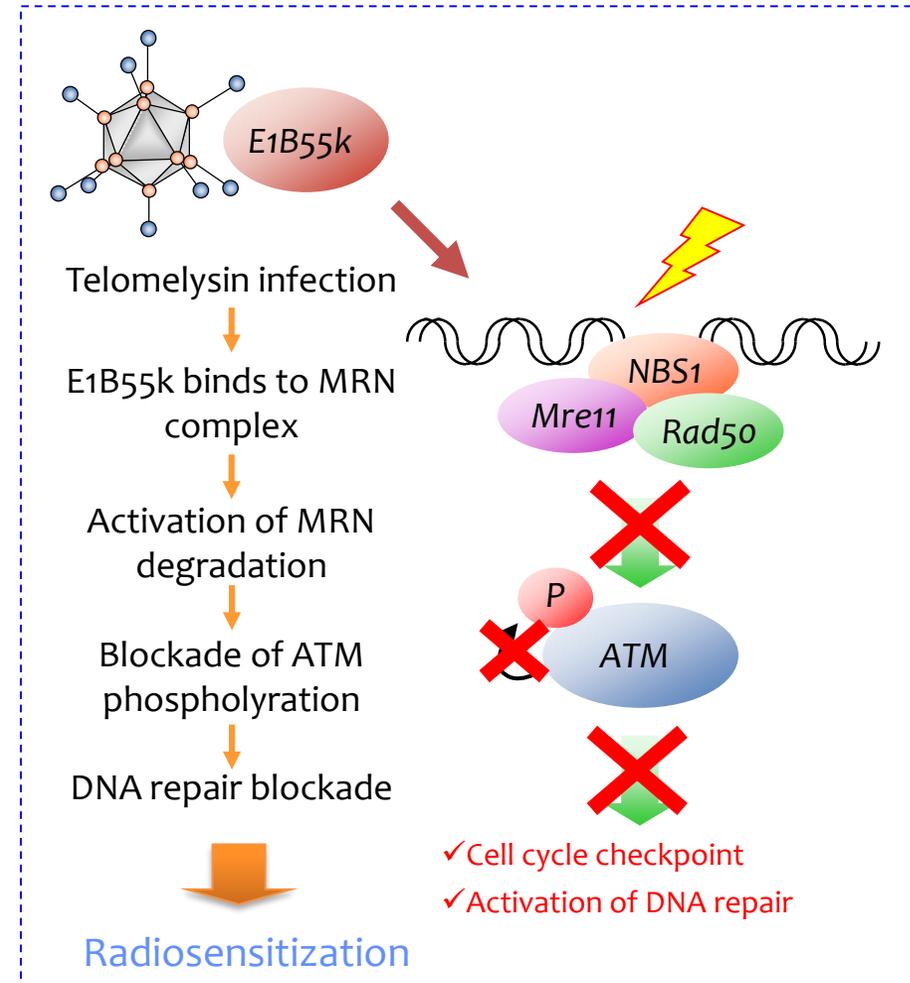
# Radiosensitization by adenoviral E1B55kD



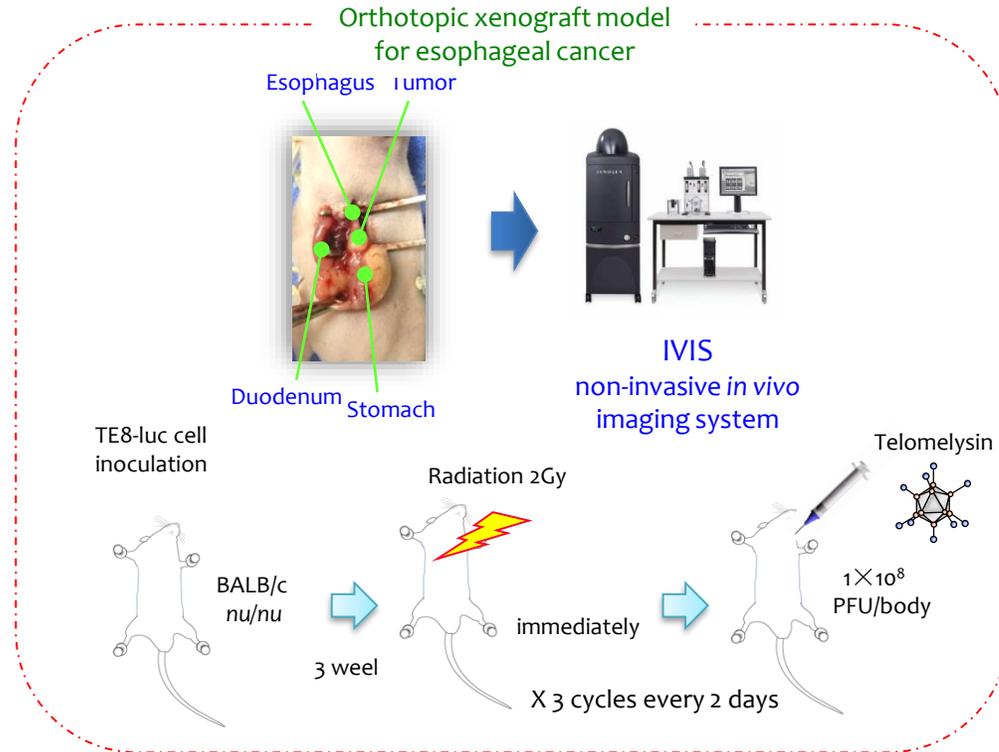
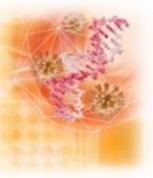
## DNA Repair Mechanism after Radiation



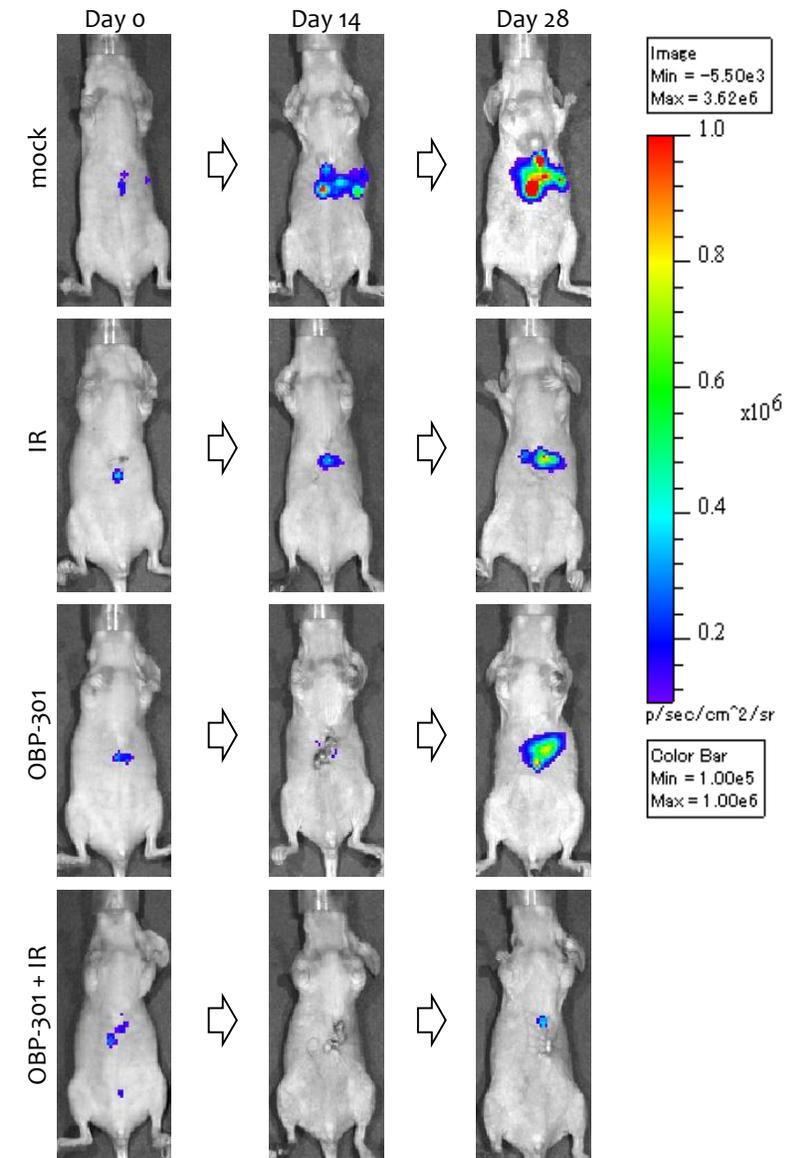
## Telomelysin Blocks the Repair of DNA Damages



# Combination with radiotherapy for esophageal cancer

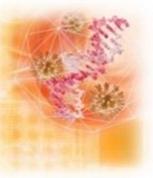


- Telomelysinは放射線によるDNA障害の修復を阻害することでがん細胞の放射線感受性を増強する。
- 放射線併用Telomelysin 療法はヒト食道癌同所性モデルで顕著な併用効果を示した。
- 放射線は**コクサッキー・アデノウイルス受容体(CAR)**の発現を増強することでウイルスの効果を強める。

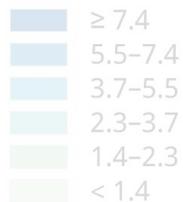


(Kuroda et al., Cancer Res., 70: 9339-9348, 2010)

# Esophageal cancer

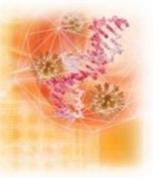


- Esophageal cancer is the seventh leading cause of cancer-related death and affects more than 45,000 people across the world<sup>1</sup>. It is classified into main histological types including squamous cell carcinoma (SCC) and adenocarcinoma.
- Overall 5-year survival rates have improved up to 20%; however, the prognosis for patients diagnosed with esophageal cancer, regardless of its histological type, remains poor<sup>2</sup>.
- Esophageal cancer increases in incidence with age, peaking in **the seventh and eighth decades** of life. In general, elderly patients may have a limit with their ability to tolerate intensive treatments such as radical surgery or definitive chemoradiotherapy<sup>3</sup>.
- It seems to be important to understand how best to treat **frail and/or elderly esophageal cancer patients**.



1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. CA 66:7-30, 2016; 2. Rustgi AK, El-Serag HB: Esophageal carcinoma. N Engl J Med 371:2499-509, 2014; 3. Bonavina L, Incarbone R, Saino G, et al: Clinical outcome and survival after esophagectomy for carcinoma in elderly patients. Dis Esophagus 16:90-3, 2003.

# Clinical protocol of telomelysin with radiotherapy

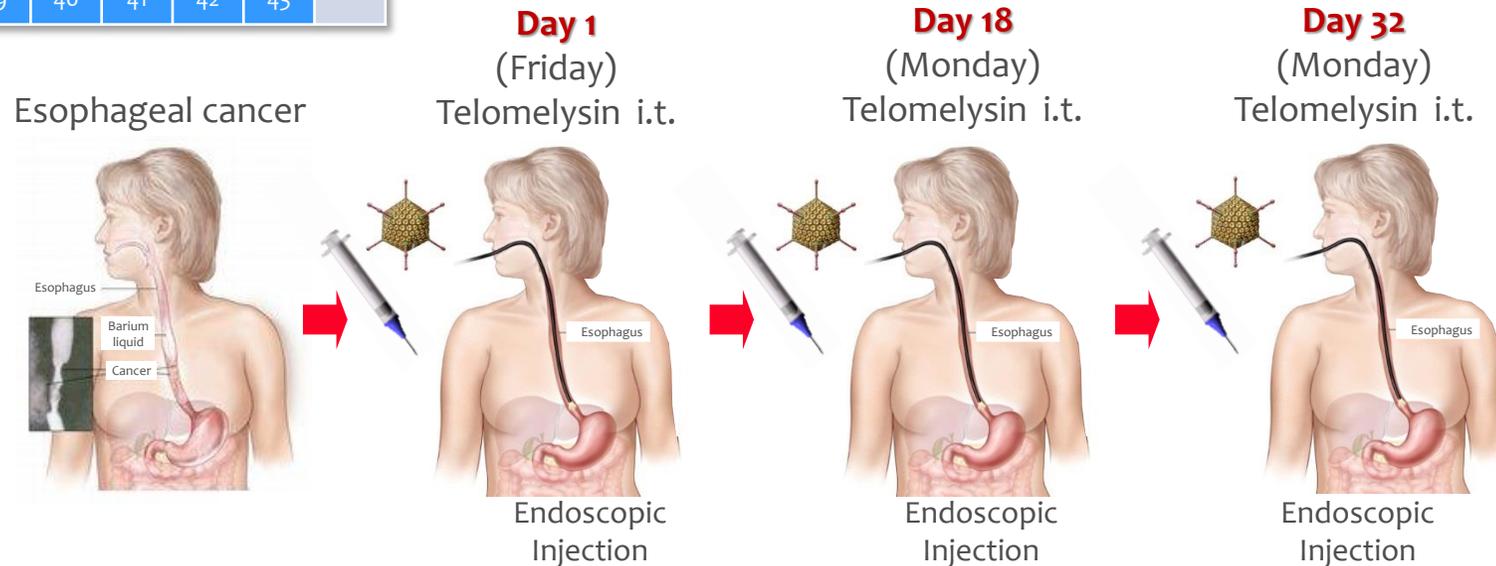
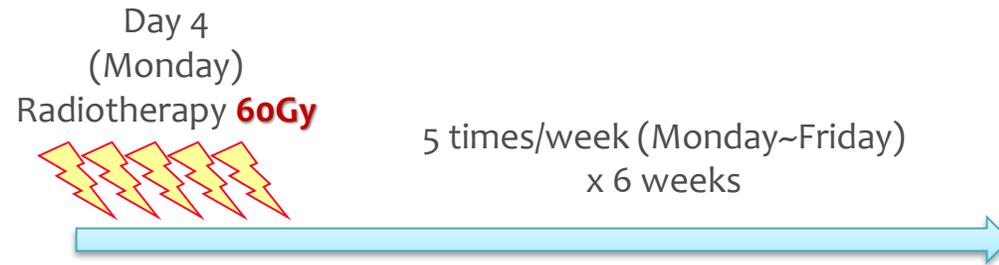


## ■ Treatment schedule

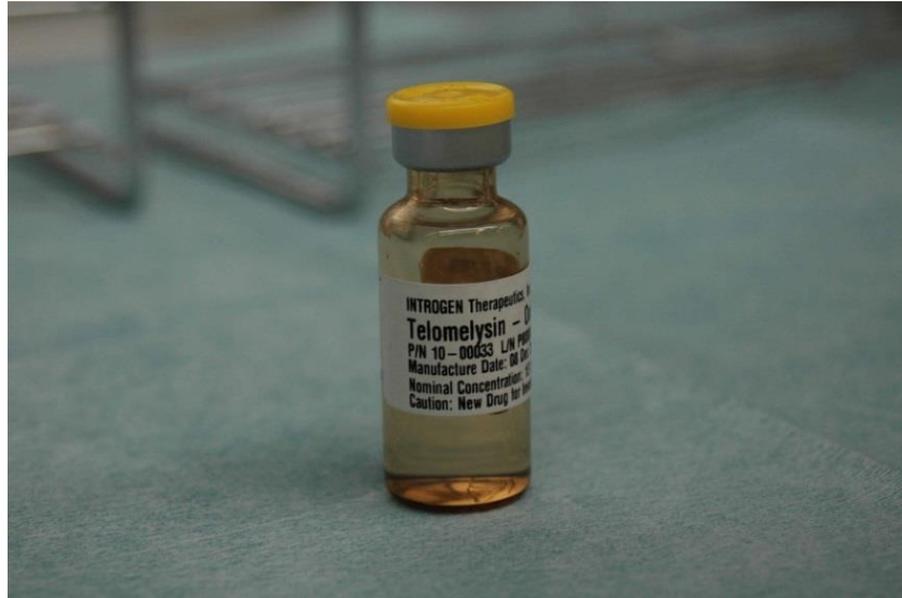
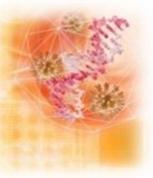
S	M	T	W	T	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31	32	33	34	35	36	37
38	39	40	41	42	43	

## Patient with esophageal cancer

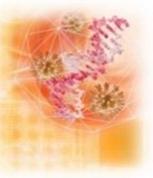
- Histologically confirmed esophageal cancer for whom effective standard therapies such as **radical surgery** or definitive **chemoradiotherapy** were not available due to the **old age** or **prevalence of frailty**



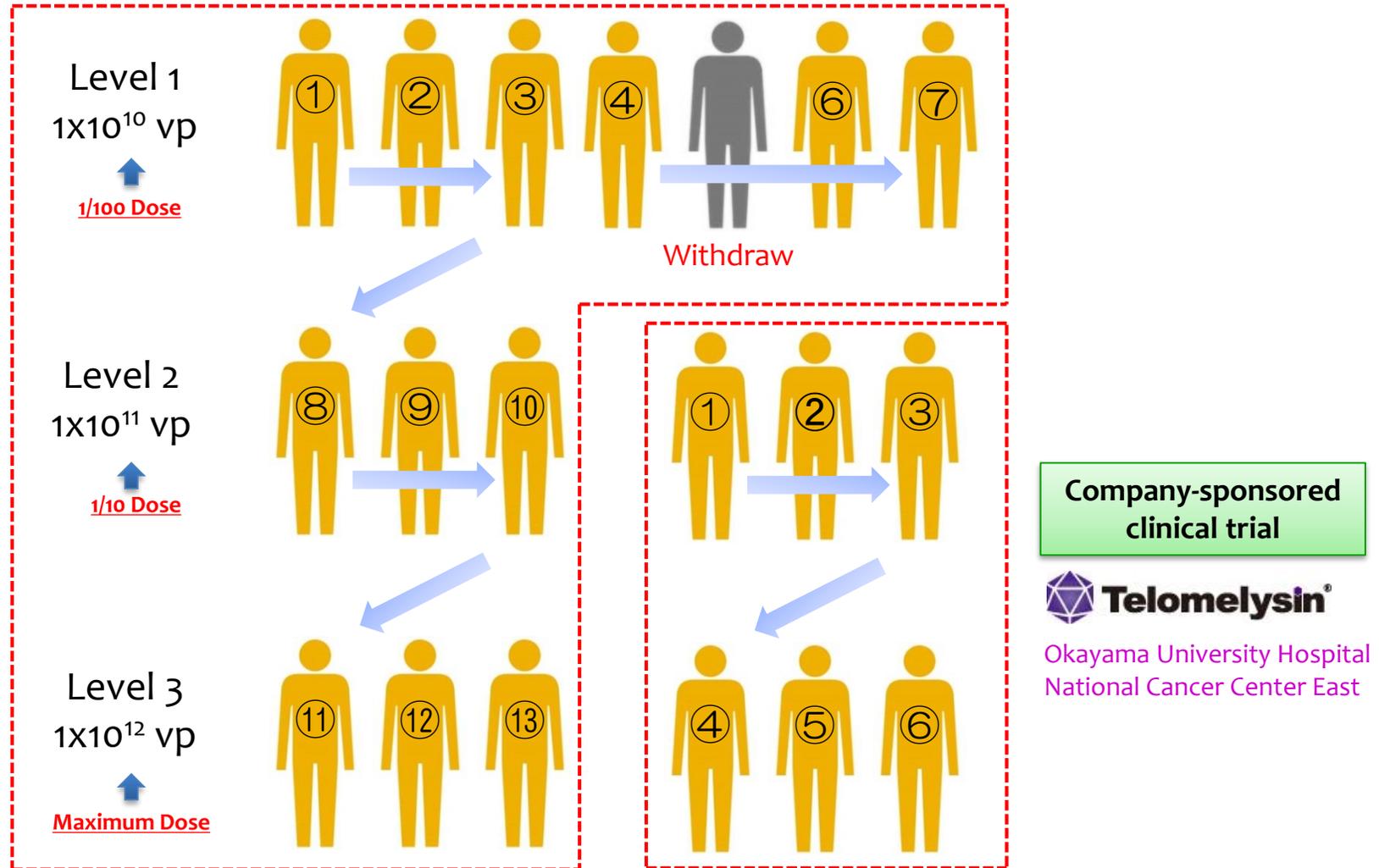
# Endoscopic injection of OBP-301 (telomelysin)



# Clinical protocol of telomelysin with radiotherapy



## ■ Dose-escalation schedule



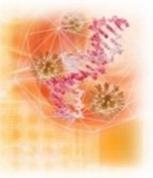
Phase I dose-escalation study of OBP-301 (telomelysin) with radiotherapy in esophageal cancer patients who are not suitable for standard therapies

# Adverse events (Level 1~3)

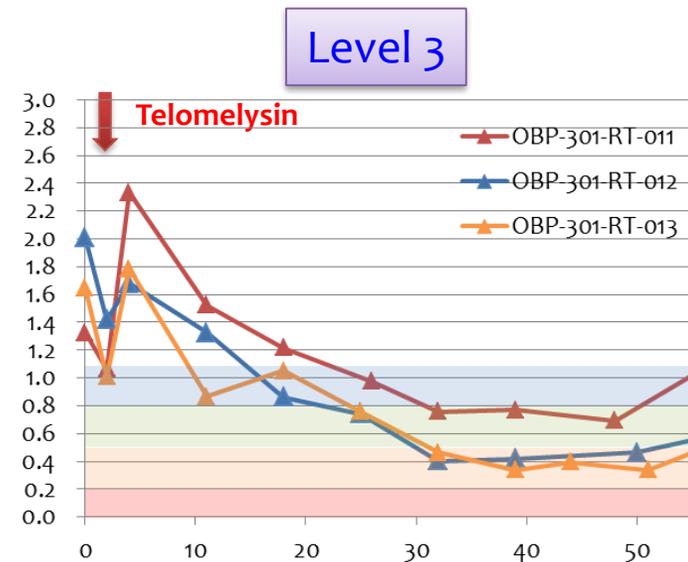
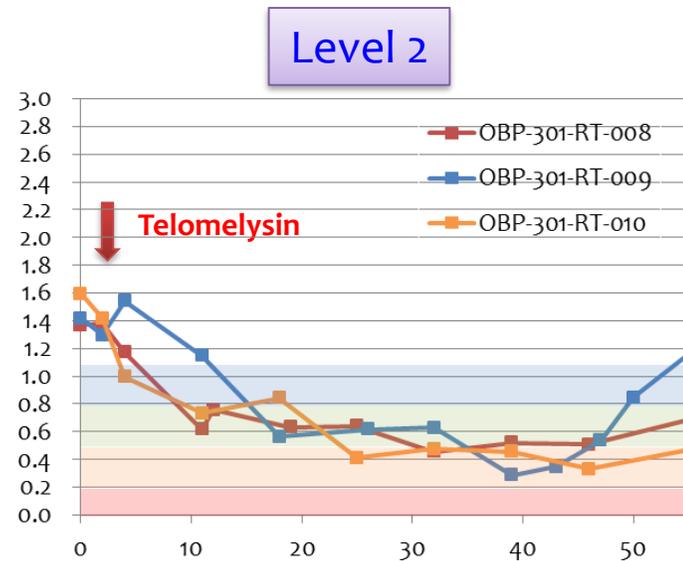
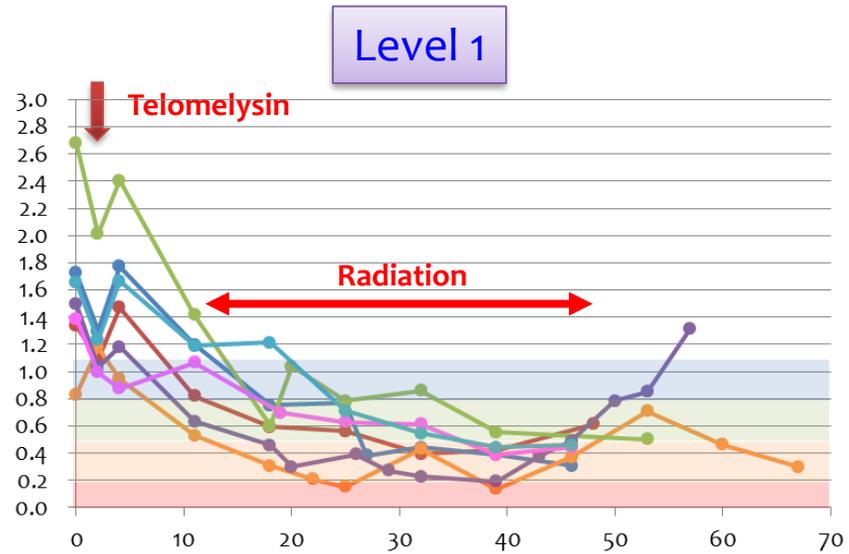


	Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Total (n=13)
General disorders and administration site conditions	Fever	5 (38.5%)	3 (23.1%)	0	0	8 (61.5%)
	Chills	2 (15.4%)	0	0	0	2 (15.4%)
	Edema limbs	2 (15.4%)	0	0	0	2 (15.4%)
	Malaise	2 (15.4%)	0	0	0	2 (15.4%)
	Non-cardiac chest pain	2 (15.4%)	0	0	0	2 (15.4%)
Gastrointestinal disorders	Nausea	2 (15.4%)	0	0	0	2 (15.4%)
	Esophagitis	3 (23.1%)	1 (8.3%)	0	0	4 (30.8%)
	Dysphagia	1 (7.7%)	0	0	0	1 (7.7%)
	Gastroesophageal reflux disease	2 (15.4%)	2 (15.4%)	0	0	4 (30.8%)
	Gastric hemorrhage	1 (7.7%)	0	0	0	1 (7.7%)
	Dyspepsia	2 (15.4%)	0	0	0	2 (15.4%)
	Constipation	3 (23.1%)	0	0	0	3 (23.1%)
Laboratory examination	Leukocytopenia	5 (38.5%)	3 (23.1%)	1 (7.7%)	0	9 (69.2%)
	Lymphocytopenia	0	3 (23.1%)	8 (61.5%)	2 (15.4%)	13 (100%)
Metabolism and nutrition disorders	Anorexia	4 (30.8%)	1 (7.7%)	0	0	5 (38.5%)
Musculoskeletal and connective tissue disorders	Arthritis	1 (7.7%)	1 (7.7%)	0	0	2 (15.4%)
	Back pain	3 (23.1%)	0	0	0	3 (23.1%)
	Buttock pain	2 (15.4%)	0	0	0	2 (15.4%)
Nervous system disorders	Headache	1 (7.7%)	0	0	0	1 (7.7%)
Respiratory, thoracic and mediastinal disorders	Aspiration	0	2 (15.4%)	0	0	2 (15.4%)
	Cough	2 (15.4%)	1 (7.7%)	0	0	3 (23.1%)
	Dyspnea	1 (7.7%)	0	0	0	1 (7.7%)
	Hoarseness	1 (7.7%)	0	0	0	1 (7.7%)
	Pharyngeal mucositis	1 (7.7%)	0	0	0	1 (7.7%)
	Pleural effusion	0	1 (7.7%)	0	0	1 (7.7%)
	Pneumonitis	2 (15.4%)	1 (7.7%)	0	0	3 (23.1%)
	Pulmonary fistula	0	1 (7.7%)	0	0	1 (7.7%)
Wheezing	0	1 (7.7%)	0	0	1 (7.7%)	
Injury, poisoning and procedural complications	Postoperative hemorrhage	1 (7.7%)	0	0	0	1 (7.7%)
Skin and subcutaneous tissue disorders	Erythema multiforme	0	1 (7.7%)	0	0	1 (7.7%)
	Rash	1 (7.7%)	0	0	0	1 (7.7%)
	Dermatitis	1 (7.7%)	0	0	0	1 (7.7%)

# Hematologic examination



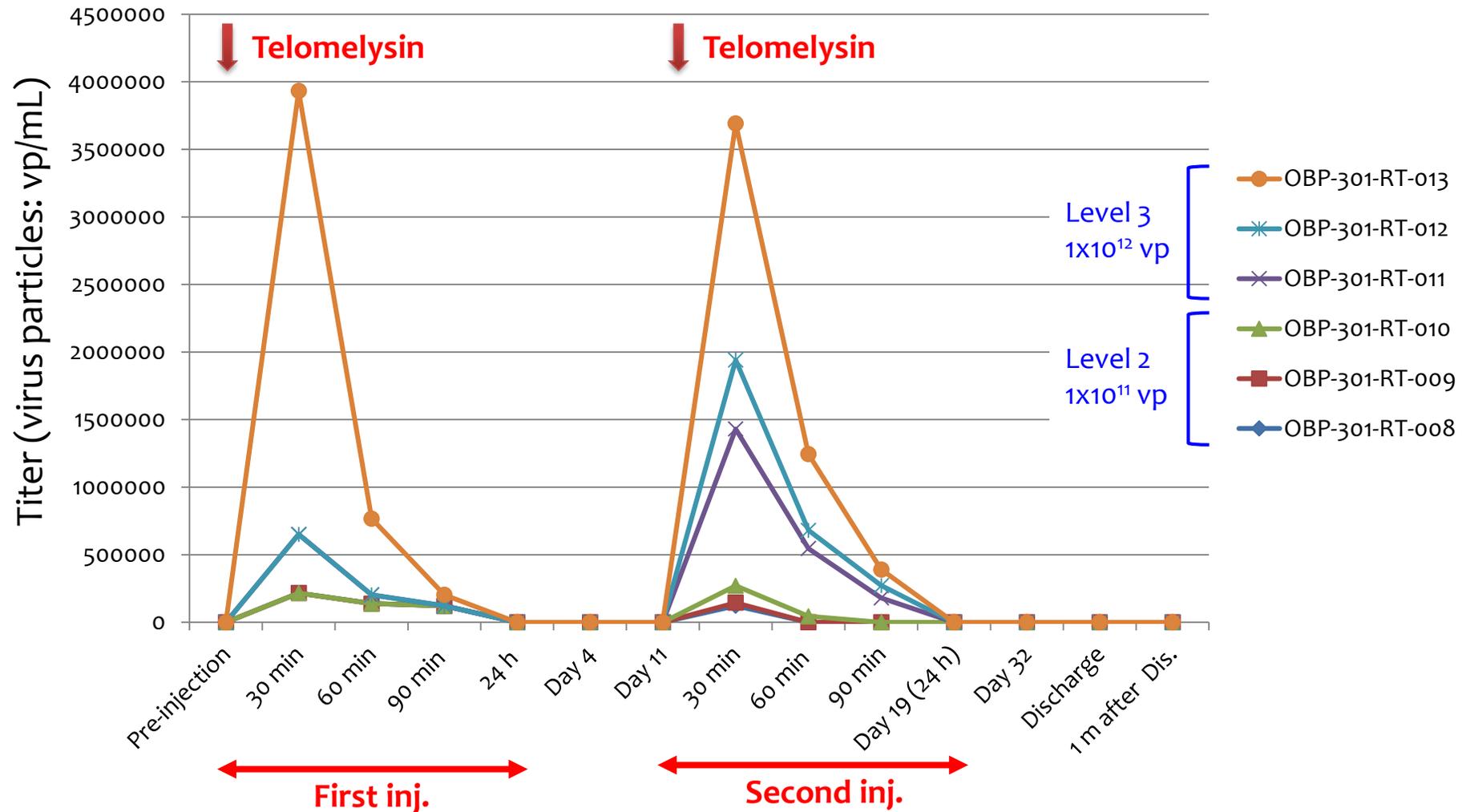
## ■ Lymphocyte counts



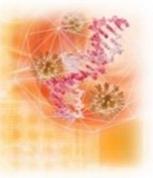
# Bio-distribution data of OBP-301 (telomelysin) (Level 2 & 3)



## Quantitative Determination of OBP-301 (telomelysin) DNA in Human Plasma

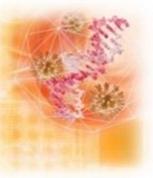


# Clinical response of injected tumors



Dose	Pt #	Age	M/F	Reason for Enrollment	Histology	Stage	Local Response	Post Injection Biopsy	Prognosis	Survival
Level 1 1x10 <sup>10</sup> vp	001	82	F	High age	SCC	cStage I	CR	3 months: No viable malignant cells	Died due to metastasis	1 y 10 m
	002	85	M	High age	SCC	cStage I	CR	3 months: Necrotic tissues No viable malignant cells	Died due to other disease	2 y 11 m
	003	92	F	High age	SCC	cStage II	PR	N/A	Died due to decrepitude	132 days
	004	68	M	Chemo-refractory	SCC	cStage IVa	SD	N/A	Died due to PD	131 days
	005	70	M	Chemo-refractory	SCC	cStage III	PD	N/A	Died due to PD	110 days
	006	88	M	High age	SCC	cStage I	CR	1 month at autopsy: No viable malignant cells	Died due to COPD	92 days
	007	53	F	Liver cirrohsis	SCC	cStage II	CR	1 month: No viable malignant cells	Alive	7 y 9 m
Level 2 1x10 <sup>11</sup> vp	008	89	M	High age	SCC	cStage I	PR	3 months: Superficial cancer > ESD	Alive	6 y 3 m
	009	74	M	Neural disease	SCC	cStage I	CR	3 months: No viable malignant cells	Died due to other disease	201 days
	010	85	M	High age	SCC	cStage I	CR	3 months: No viable malignant cells	Alive	5 y 11 m
Level 3 1x10 <sup>12</sup> vp	011	78	M	Renal dysfunction	SCC	cStage III	CR	3 months: No viable malignant cells	Died due to metastasis	173 days
	012	82	M	High age, Cardio-vascular disease	Adeno ca	cStage II	CR	1 months: No viable malignant cells	Alive	4 y 11 m
	013	81	M	High age, Cardio-vascular disease	SCC	cStage II	PR	1 months: Viable malignant cells	Died due to metastasis	10 m

# Clinical response of injected tumors

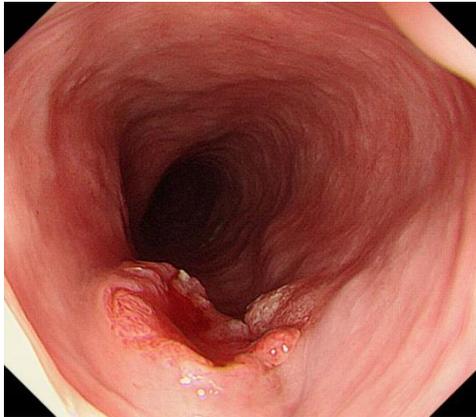


## Case 7 :

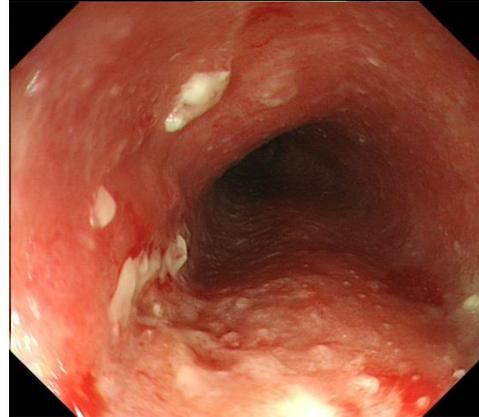
53 y. o., female Thoracic esophageal cancer

Liver dysfunction: Child-Pugh score 8, K-GSA=0.054

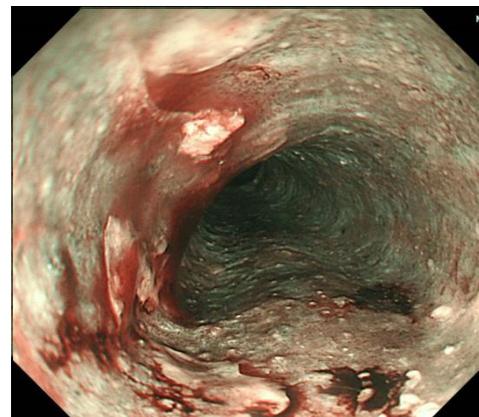
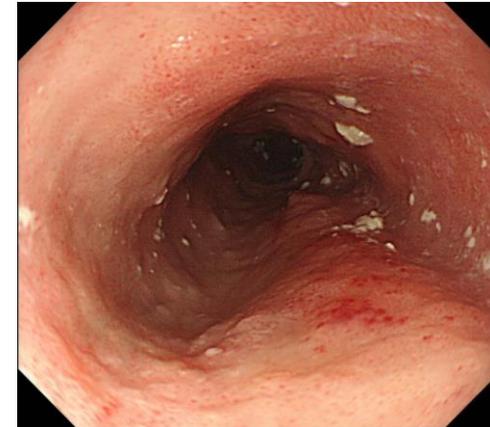
Pre-therapy



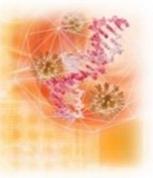
Day 18 (2/9/15)



1 month (4/9/15)



# Clinical responses on lymph node metastasis



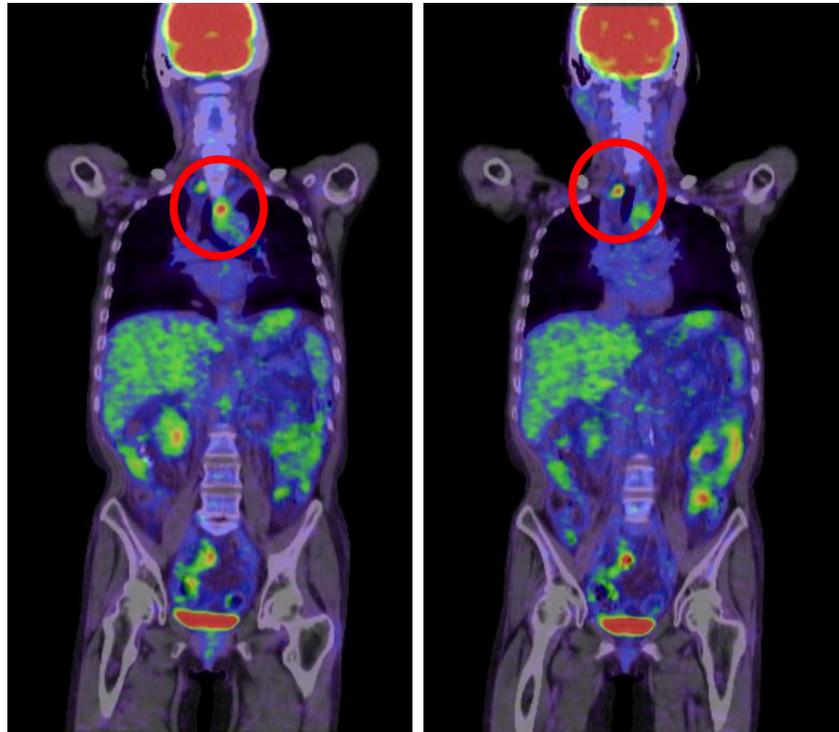
Case 7 :

Pre-therapy (10/24/14)

Post-therapy (8 months) (11/9/15)

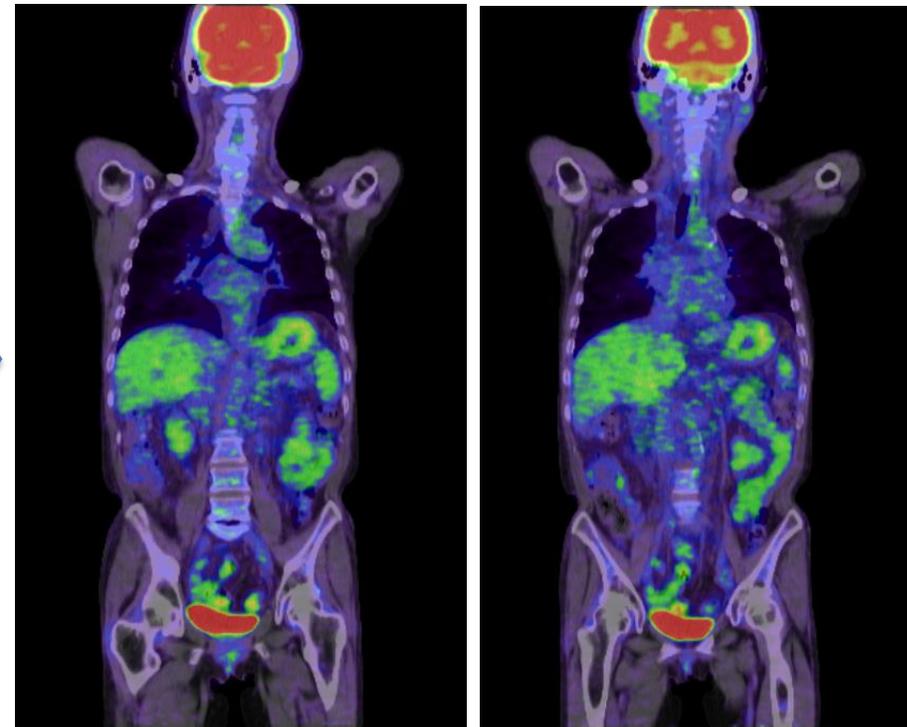
Primary tumor

#106recR



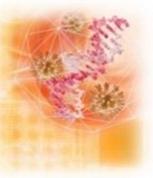
Primary tumor

#106recR



Telomelysin plus radiotherapy is also effective for lymph node metastasis.

# Clinical response of esophageal adenocarcinoma



## Case 12 :

82 y. o., male Thoracic esophageal cancer

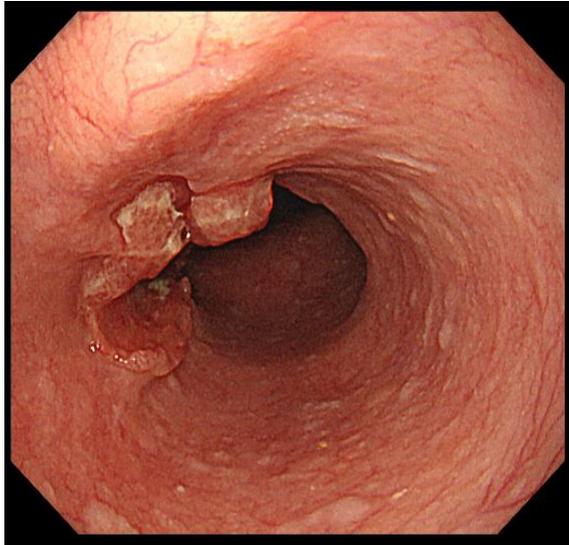
After treatment of angina pectoris

Thoracic esophageal cancer (**Adenocarcinoma**) cT2NoMo cStage II

Telomelysin: First injection (11/17/17), second (12/4/17), third (12/18/17)

Radiotherapy: 60Gy (11/20/17~1/5/18)

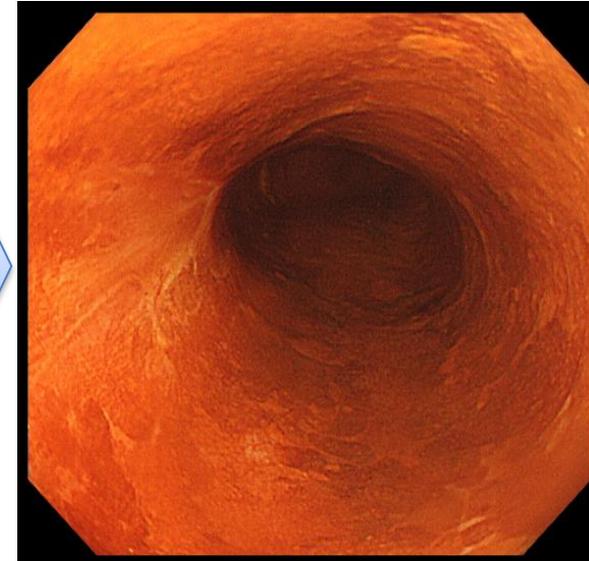
Pre-therapy



Day 18 (12/4/17)

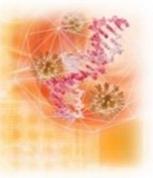


3 months



Pathology of biopsy: No viable malignant cells.

# Summary



## ■ Safety

- Most Adverse Events were mild to moderate in severity and transient.
- Transient lymphocytopenia was seen in all patients.

## ■ Pharmacokinetics

- Sputum, saliva, and urine samples had no detectable virus gene copies.
- Viral DNA could be transiently detected in the plasma at levels 2 and 3.

## ■ Clinical Benefit

	Current study (n=11)	JES data (n=123)
Stage I	83.3%	56.7%
Stage II/III	60.0%	26.8%



~~"Cure"?~~

\*Japan Esophageal Society data: Clinical CR rate by radiation alone (2009~2011: 123/2352 cases) was **56.7%** and **26.8%** for stage I and II/III, respectively. (日本食道学会 食道癌全国登録データベース)

# Acceleration to regulatory approval for practical use



- 食道癌を対象として国内で開発を進めているTelomelysin（OBP301）が、厚生労働省の定める **先駆け審査指定制度** の対象品目に指定された。薬事承認にかかわる相談、審査において医薬品医療機器総合機構（PMDA）により優先的な取り扱いを受けることができ、今回の指定による利点を最大限に活用し、早期の実用化が期待される。



- Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your **orphan-drug designation** request of telomerase specific replication-competent oncolytic adenovirus is granted for treatment of esophageal cancer.



Phase II 参加施設（進行中）			
1	岡山大学病院	10	秋田大学病院
2	国立がん研究センター東病院	11	北海道大学病院
3	国立がん研究センター中央病院	12	愛知県がんセンター
4	がん研究会有明病院	13	佐久医療センター
5	埼玉県立がんセンター	14	北里大学病院
6	東邦大学大森病院	15	群馬大学病院
7	大阪国際がんセンター	16	国立病院機構 四国がんセンター
8	熊本大学病院	17	広島市立広島市民病院
9	東北大学病院		



# 国内でのTelomelysinの臨床開発



## ● 再生医療等医薬品として条件・期限付製造販売承認を目指す。

＜再生医療等製品に従来の承認制度を適用する場合の問題点＞

### 【従来の承認までの道筋】

人の細胞を用いることから、個人差を反映して品質が不均一となるため、有効性を確認するためのデータの収集・評価に長時間を要する。



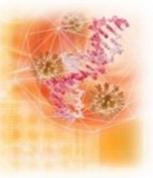
### 【再生医療等製品の早期の実用化に対応した承認制度】

患者のアクセスをより早く！



- 有効性については、一定数の限られた症例から、従来より短期間で有効性を推定。
- 安全性については、急性期の副作用等は短期間で評価を行うことが可能。

# Radiotherapy-induced abscopal effects



THE LANCET  
Oncology

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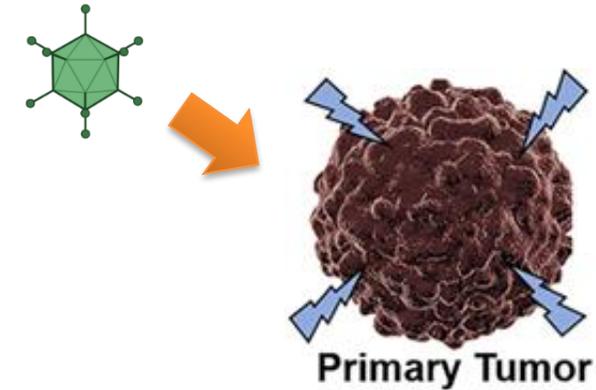
Articles

**Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate **abscopal responses** in patients with metastatic solid tumours: a proof-of-principle trial**

Encouse B Golden, MD, Arpit Chhabra, MD, Prof Abraham Chachoua, MD, Sylvia Adams, MD, Martin Donach, MD, Maria Fenton-Kerimian, NP, Kent Friedman, MD, Fabio Ponzio, MD, James S Babb, PhD, Prof Judith Goldberg, ScD, Prof Sandra Demaria, MD, Dr Prof Silvia C Formenti, MD

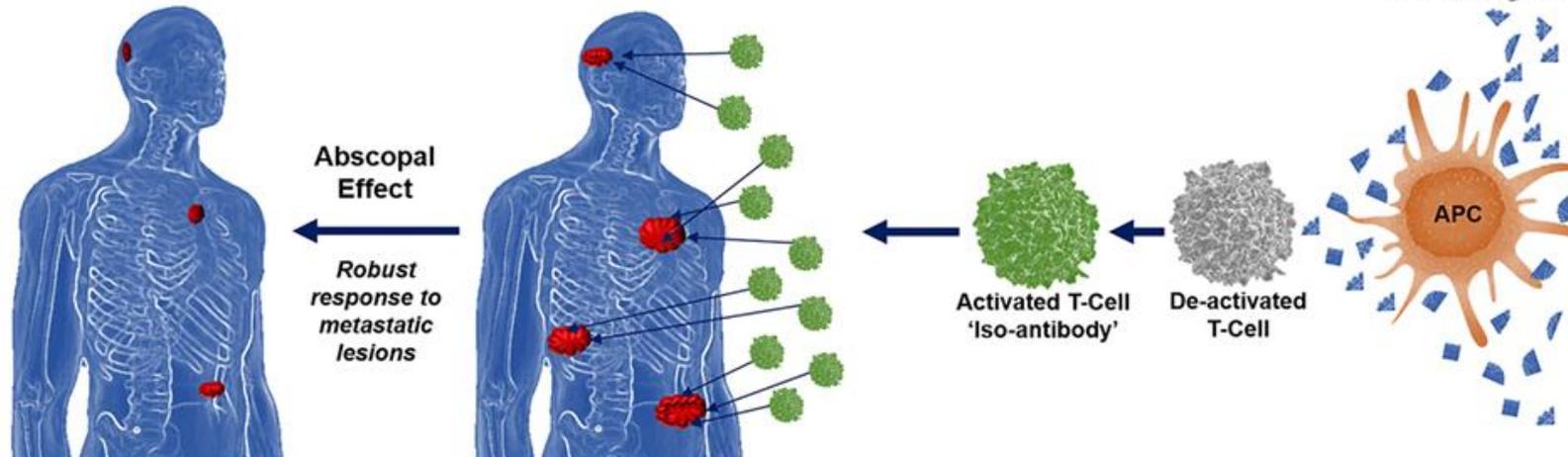
Local priming:

- Intratumoral injection of **OV**
- **Radiotherapy**

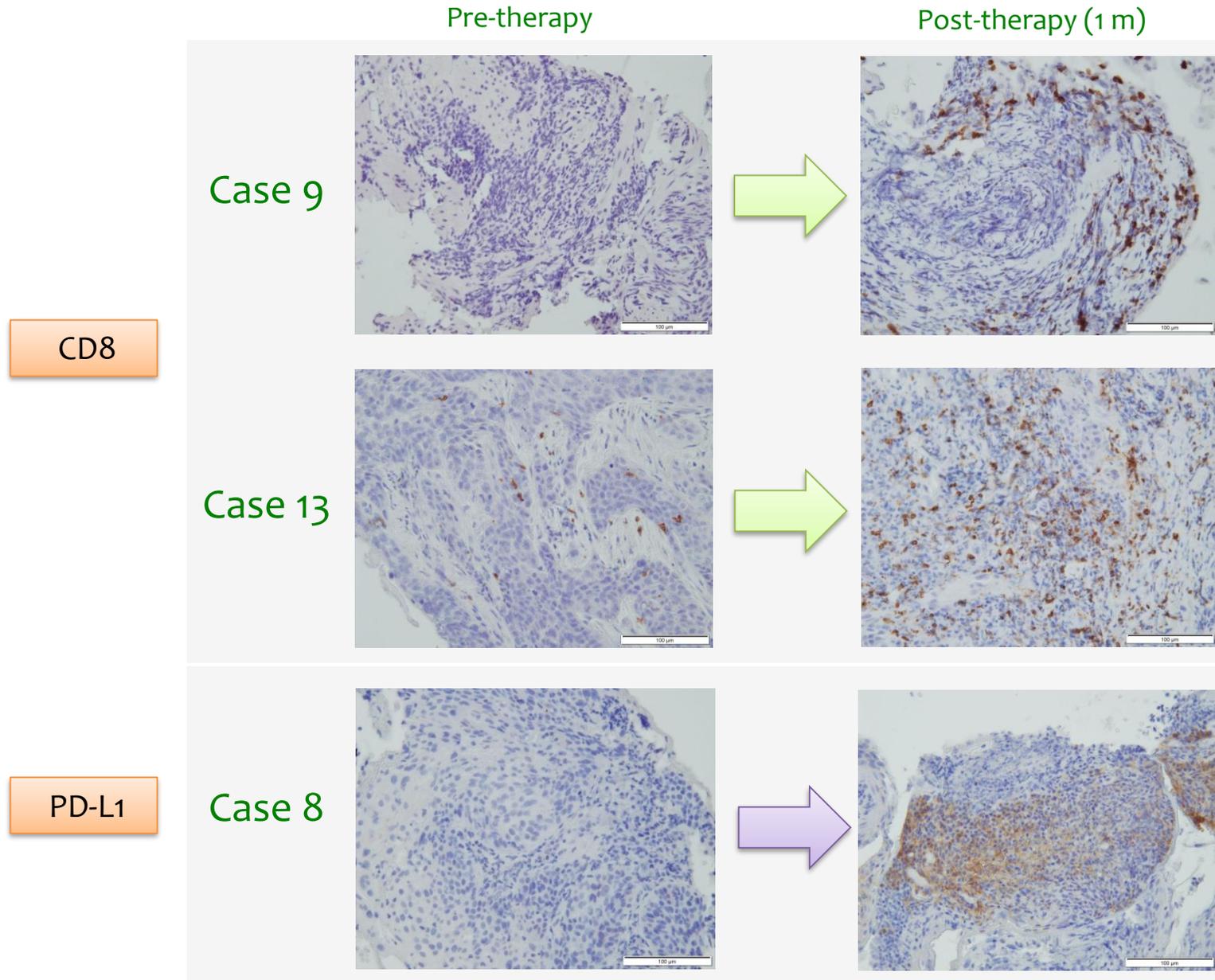


Distant effects:

- Systemic anti-tumor immunity against non-treated tumor sites

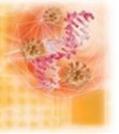


# Immunological reactions in biopsied tissues from partially responded patients





# Global expansion of OBP-301 (telomelysin)



## ■ Combination with anti-PD-1 antibody

進行性又は転移性固形がん患者を対象とした OBP 301 と Pembrolizumab 併用療法の第 I 相臨床試験（医師主導治験）



- National Cancer Center East
- Advanced or metastatic solid tumors
- OBP-301 plus **Pembrolizumab**



Phase II study of Telomelysin (OBP-301) in combination with pembrolizumab in esophagogastric adenocarcinoma



Manish Shah, MD

- Weill Cornell Medicine (New York)
- Advanced gastric and esophageal cancer
- OBP-301 plus **Pembrolizumab**

## ■ Combination with anti-PD-1 antibody and radiotherapy

Phase II study of OBP-301 (Telomelysin™) in combination with pembrolizumab and Stereotactic Body Radiation Therapy [SBRT] in advanced/metastatic head and neck squamous cell carcinoma

- Weill Cornell Medical Center
- Advanced/metastatic head and neck squamous cell carcinoma
- OBP-301 plus **Pembrolizumab & Stereotactic radiotherapy**

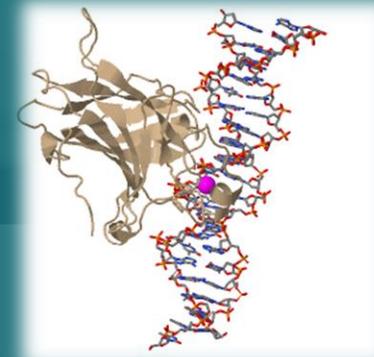


Doru M Paul, MD, PhD

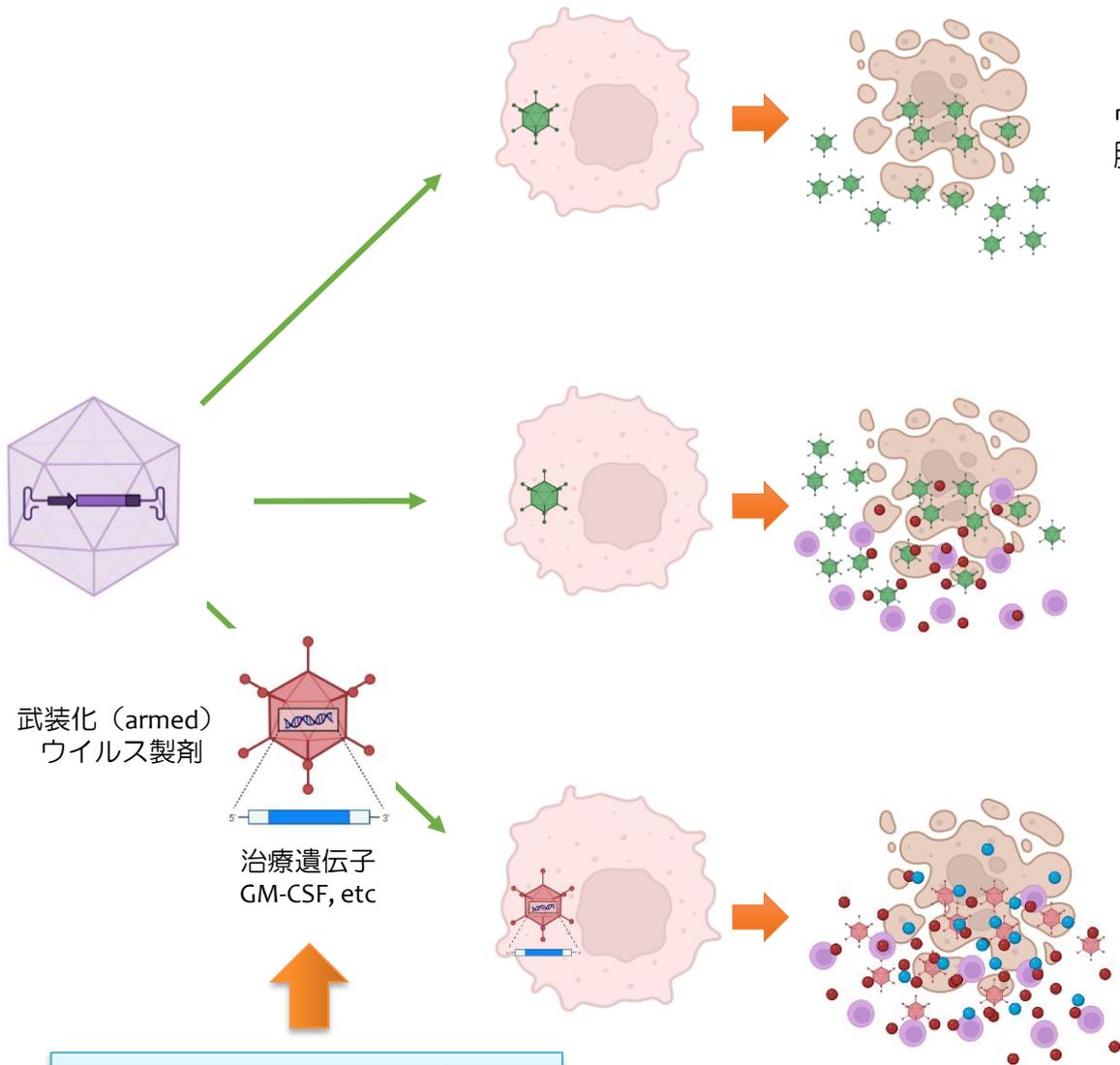
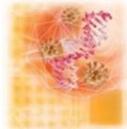
■ Topics 3



Next-generation  
oncolytic virotherapy  
armed with p53 gene



# Anti-tumor activity of oncolytic viruses by various mechanisms of action



ウイルス増殖による  
腫瘍融解 (oncolysis)

腫瘍融解 (oncolysis) と  
ICDによるDAMPs放出

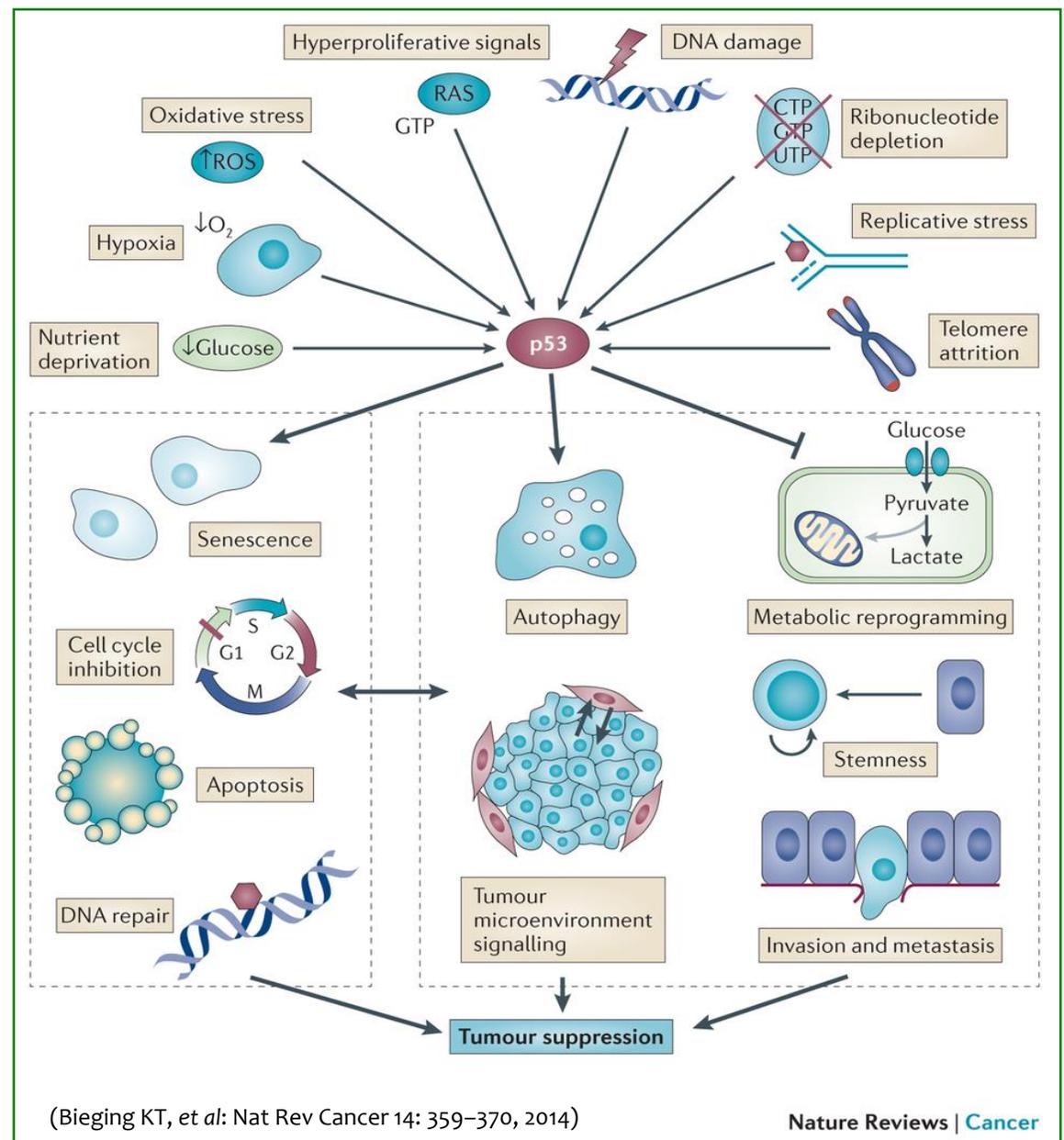
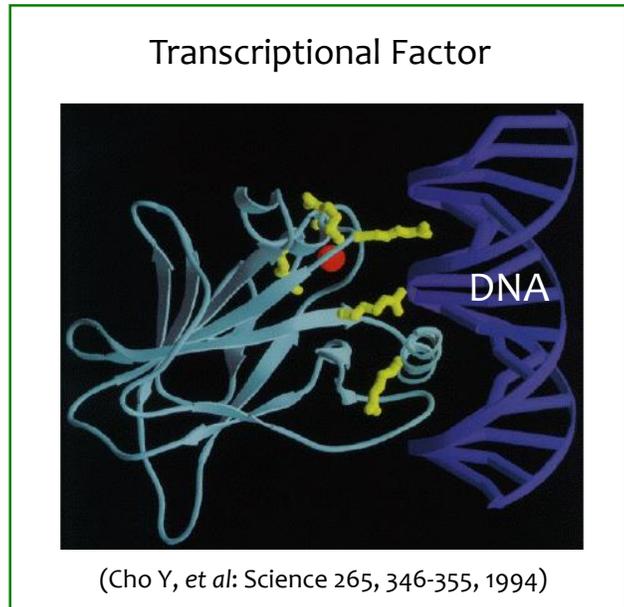
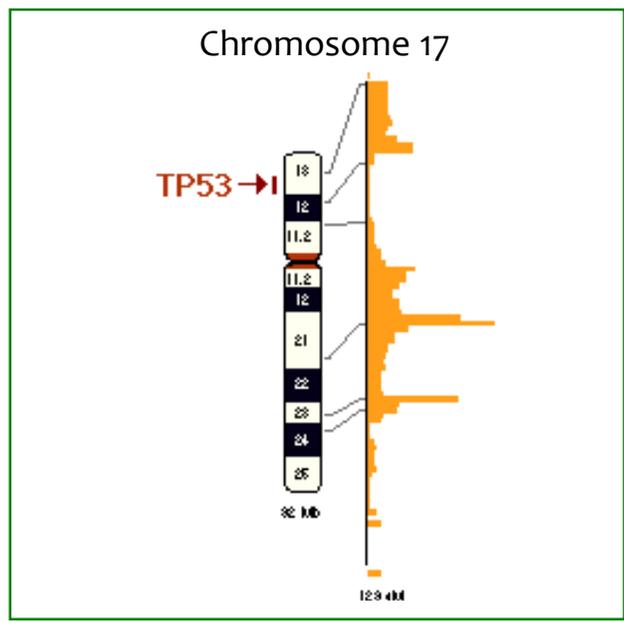
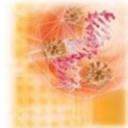
● CD8陽性T細胞  
● 起炎症因子DAMPs

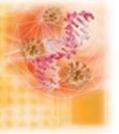
腫瘍融解 (oncolysis) と  
治療遺伝子発現・ICD

● 治療遺伝子産物

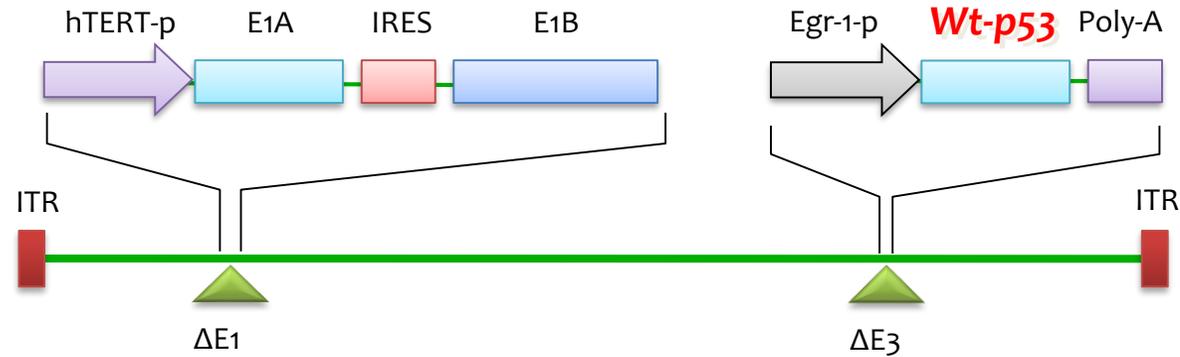
Oncolytic virusを遺伝子導入用  
ベクターとして応用

# Tumor suppressor p53 gene

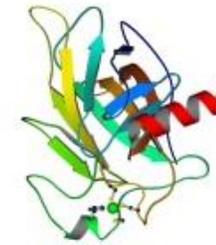




## OBP-702

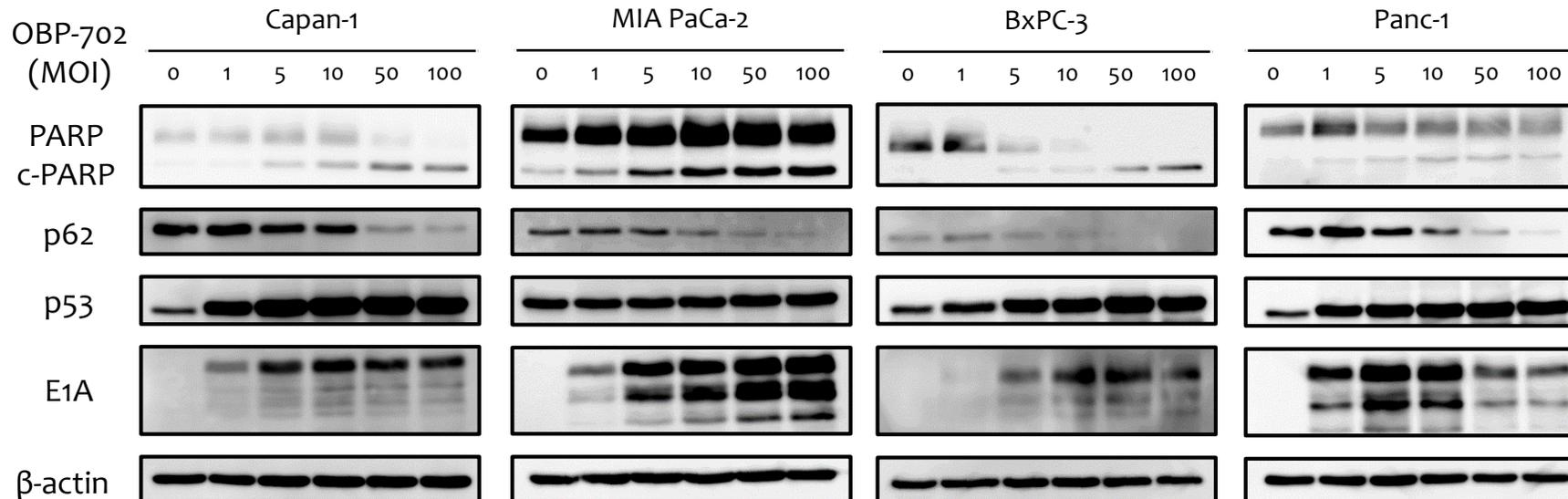


Multi-functional  
*p53* tumor suppressor



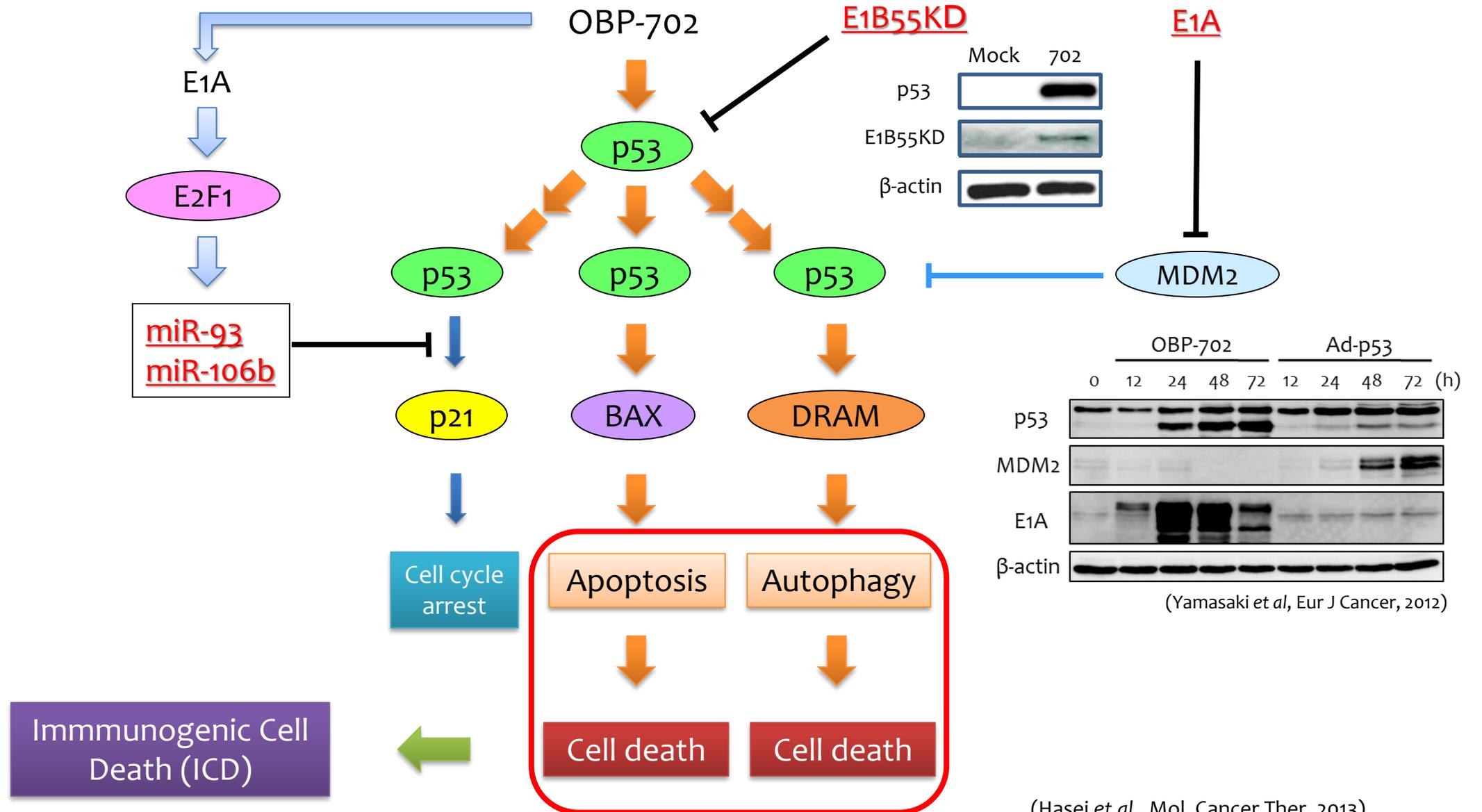
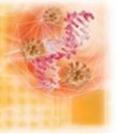
(Yamasaki *et al*, *Eur J Cancer*, 48: 2282-2291, 2012)

### Western blot

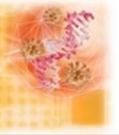


(Koujima *et al*, *Mol Ther Oncolytics*, 17: 107-117, 2020)

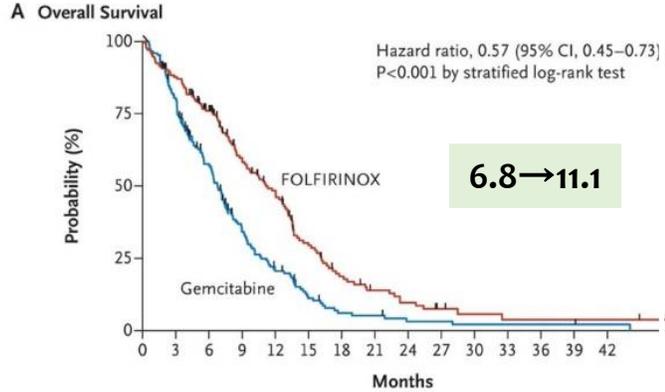
# Molecular mechanism of OBP-702



# Poor prognosis of pancreatic cancer



## FOLFIRINOX vs GEM

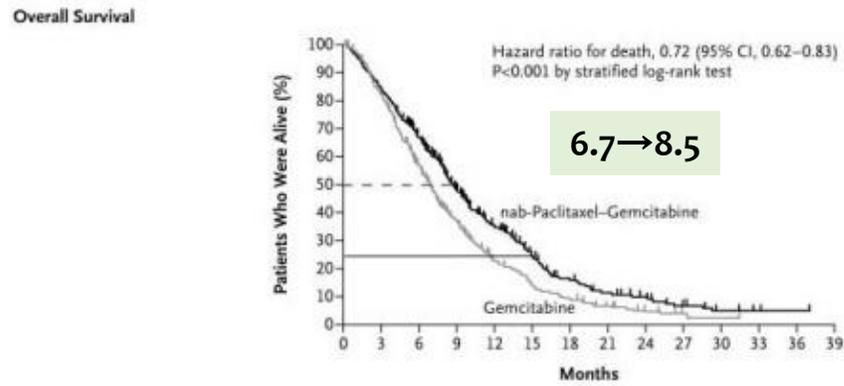


**No. at Risk**

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

(Conroy T et al, N Engl J Med, 2011)

## GEM plus Nab-paclitaxel vs GEM

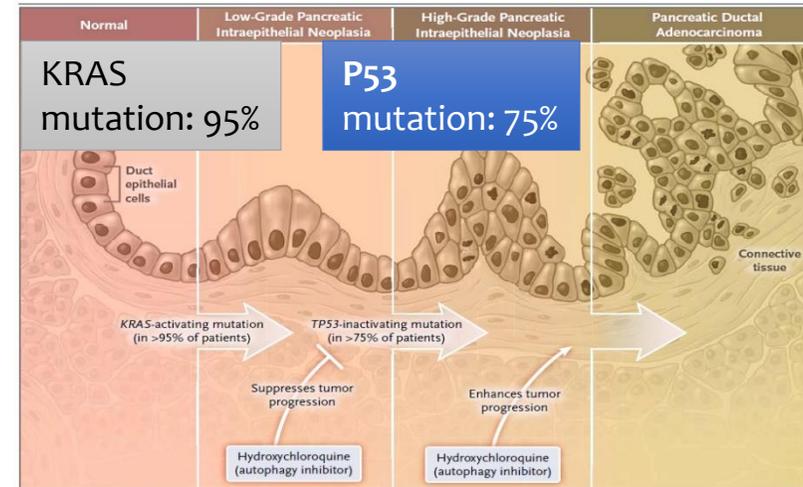
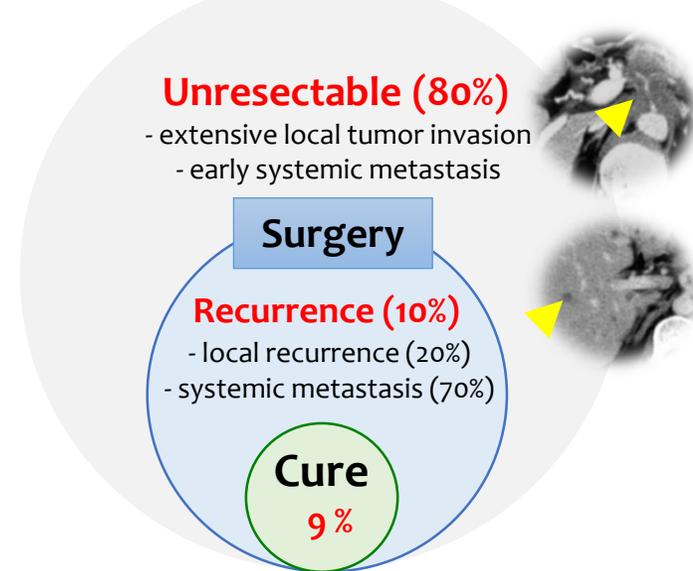


**No. at Risk**

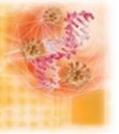
nab-Paclitaxel-Gemcitabine	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gemcitabine	430	340	220	124	69	40	26	15	7	3	1	0	0	0

(Von Hoff DD et al, N Engl J Med, 2013)

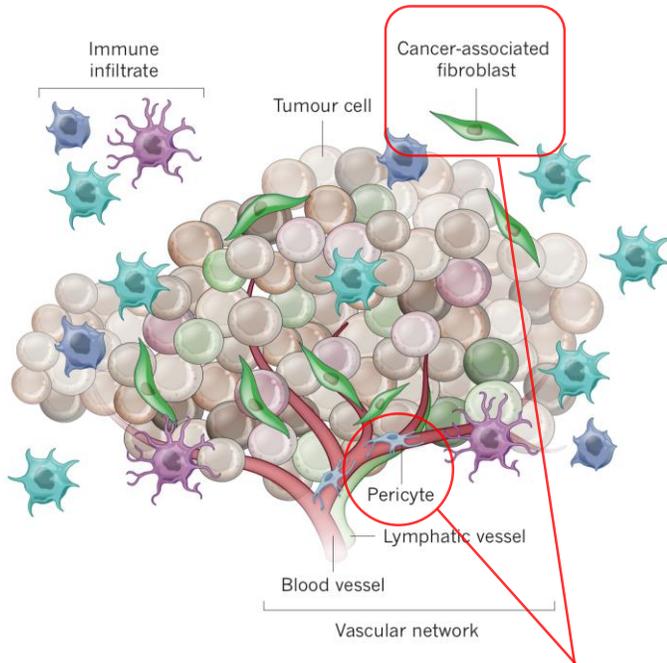
## Population at the time of diagnosis



(Christine A et al, N Engl J Med, 2014)

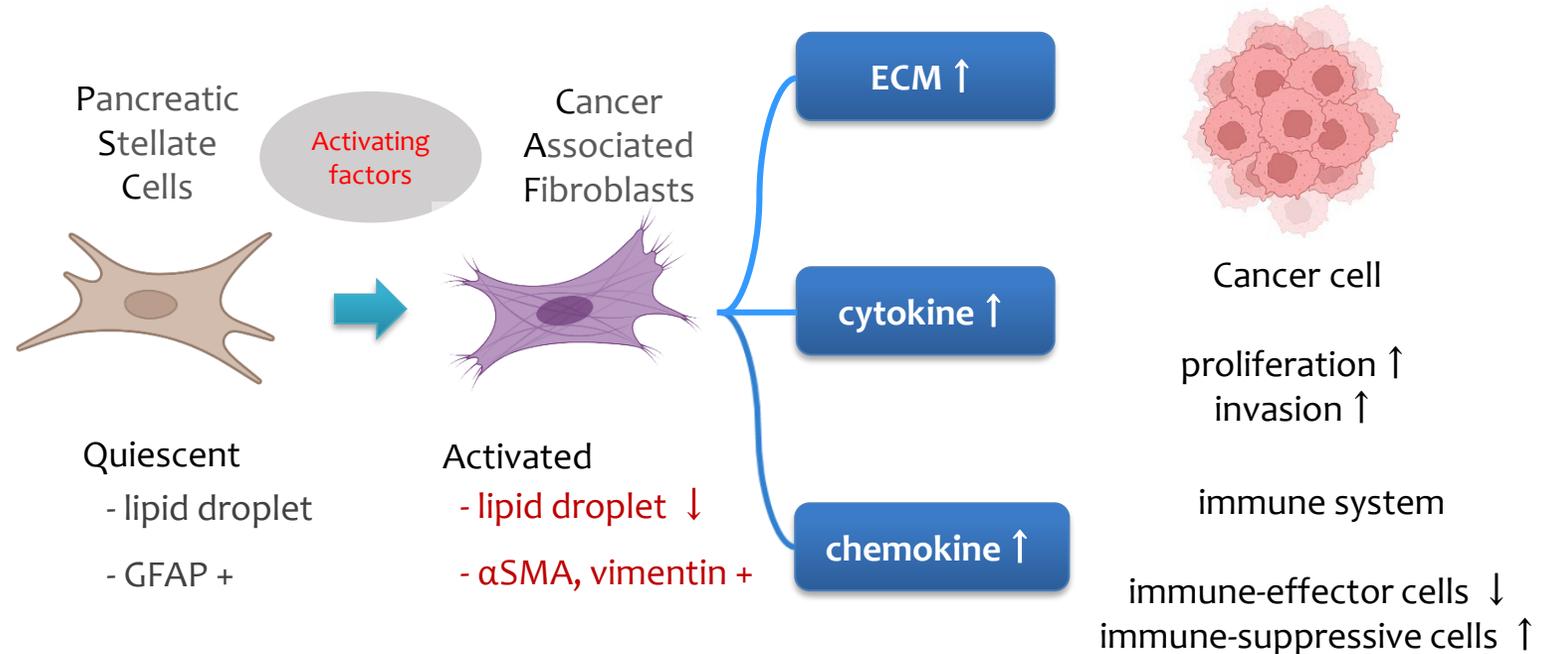


## Components of pancreatic tumor stroma

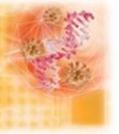


**Pancreatic stellate Cells (PSC)**  
 膵星細胞

## PSCs play a key role in desmoplasia of PDAC



- 膵星細胞（PSC）は膵癌細胞と共存することで活性化される。
- 活性化しCancer-Associated Fibroblast（CAF）化したPSCは膵癌細胞の遊走能や浸潤能を促進する。
- CAF化した膵星細胞（PSC）を除去することは膵癌微小環境の改善につながる。



## ■ Preclinical study of OBP-702 for PDAC

- OBP-702は各種ヒト膵癌細胞細胞に対して、OBP-301より強力なアポトーシスおよびオートファジー誘導能を発揮した。
- 活性化しCancer-Associated Fibroblast (CAF) 化した膵星細胞 (PSC) は膵癌細胞の遊走能や浸潤能を促進したが、OBP-702はp53遺伝子発現を介してCAF化PSCを選択的に殺傷した。
- 膵癌に標準的に使用されるゲムシタビン (GEM) 耐性膵癌細胞は、GM-CSF分泌増強により骨髄由来抑制細胞 (MDSC) を誘導することで免疫抑制微小環境を構築するが、OBP-702はGM-CSF発言を阻害することで膵癌微小環境を改善する



## ■ Clinical trial of OBP-702 for PDAC

### AMED公的資金

- 革新的がん医療実用化研究事業 (2017~2019年)
- 革新的がん医療実用化研究事業 (2020~2022年)



### OBP-702ウイルスのGMP製造



- Yuanxing Gene 社 (中国 広東省深圳 (シエンチエン) 市)

### 毒性試験・薬理動態試験

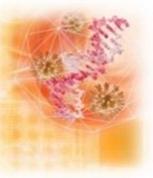


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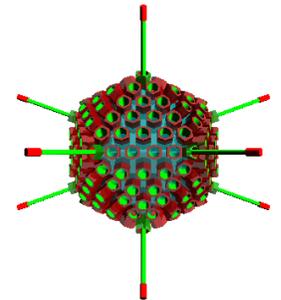
- Southern Research Institute (米国アラバマ州 バーミンガム)
- ボゾリサーチセンター (東京都新宿区)

# Today's Topics

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- Tumor-specific replicative adenovirus platform
- Telomerase-specific oncolytic virotherapy for cancer cure
- Next-generation oncolytic virotherapy armed with p53 gene



## Acknowledgements

