OncoTherapy Science, Inc.

OncoTherapy Science, Inc.
R&D Day meeting

President & CEO, Masaharu Mori

Dec .18th, 2015

Our Mission

“To develop

anti-cancer medicine and cancer therapy

with high efficacy

and minimum risk of adverse events,

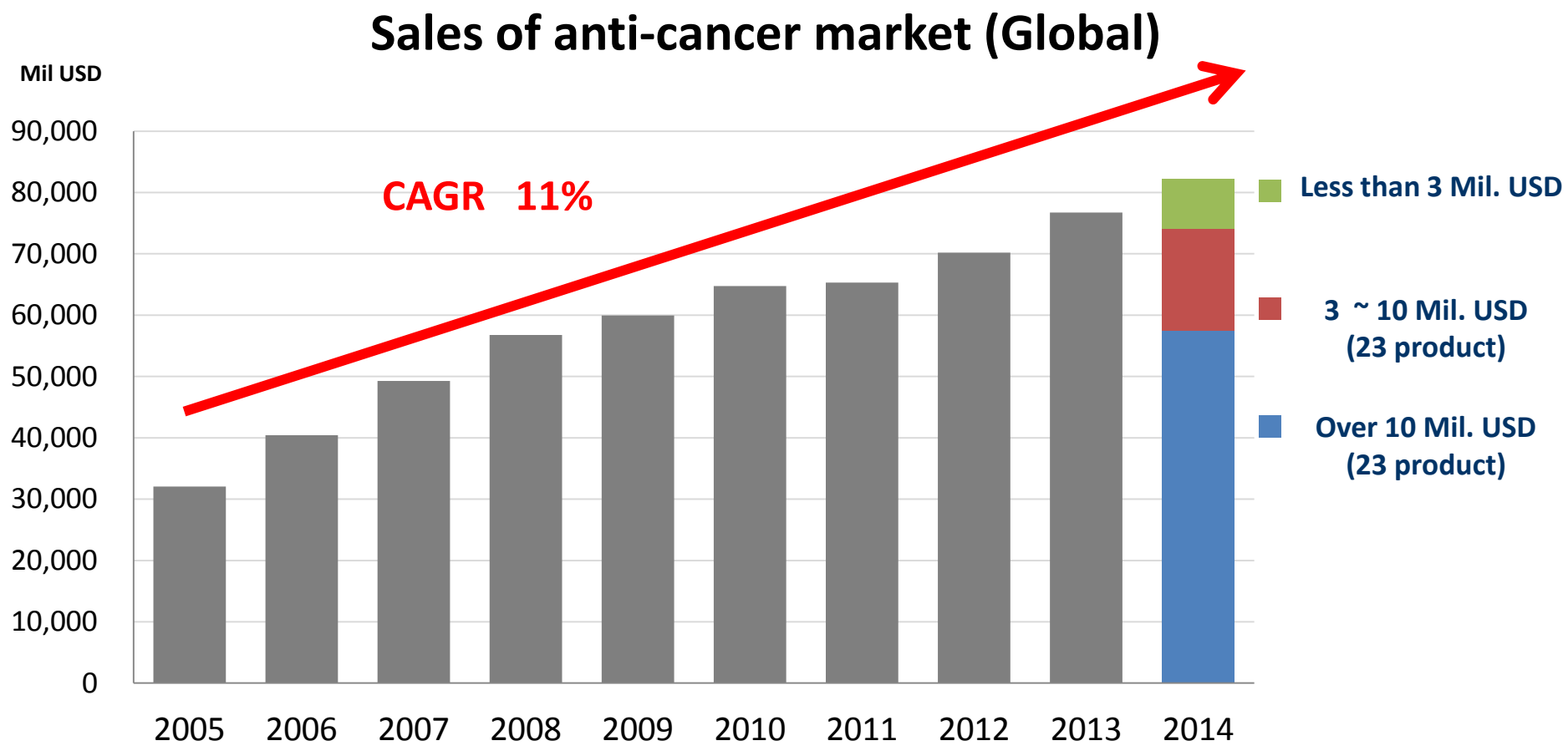
and

to win the war against cancer”

Contents

Anti-cancer market with double digit growth

Anti-cancer market becomes 3 times bigger due to launch of molecular target drug blockbusters during last decade



Source: Uto Brain 2015

High Attention to Cancer Immunotherapy

Big success of immune checkpoint inhibitors attract attention to cancer immunotherapy, with the advent of NGS* genome analysis

Target		Specific（pin point）	Non specific
Cancer Cell		●Molecular target drug - Small molecule - Antibody	●Cytotoxic chemotherapy （Poisonous for both cancer and healthy cells）
Immune system	Press the accelera-tor	●Cancer Vaccine - Oncoantigen vaccine - Neoantigen vaccine	●Non-specific immunotherapy
	Release the brake	●Immune checkpoint inhibitor - High efficacy on cancers with lots of mutations, such as melanoma	

Cancer genome analysis by utilizing NGS（Immunopharmacogenomics）

* **NGS**: Next Generation Sequencer

Contents

Platform Technologies
→ Genome-based Drug Discovery

With our platform technologies, **providing comprehensive gene expression profile analyses and gene function analyses**, we have identified suitable target genes to develop new anti-cancer medicines with a minimal risk of adverse events.

1. A large number of fresh clinical specimen (samples)

- More than 1000 clinical samples (20～80 patients /cancer type)

2. Identified gene groups over-expressed in cancer cells

- Laser Microbeam Microdissection (LMM) system
- Our original cDNA microarray system
  Gene expression database of cancer and normal cells

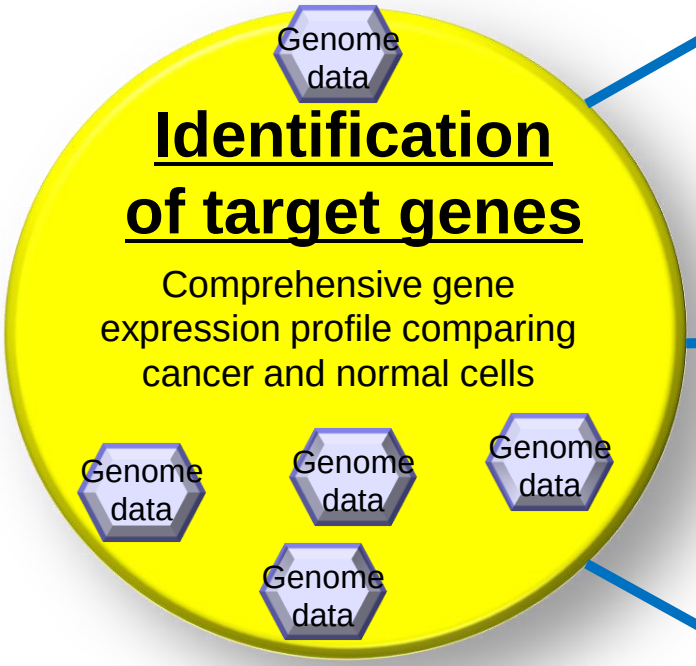
3. Validate the effect of selected genes on the growth or survival of cancer cells

- A gene function inhibiting experiment using the RNA interference technology

4. Examine expression in 31 normal organs

- Absent or hardly detectable in any normal and important vital organs

Genome-based Drug Discovery and Development of Novel Anti-Cancer Drugs



Small Molecule Drugs

OTS167
Phase I study in US.

OTS964 etc.
Pre-clinical study.

Cancer Peptide Vaccines

OTSGC-A24 etc.
Clinical study in Japan and Asian countries.
Other peptide vaccines have been licensed out.

Antibody Drugs

OTSA101
Phase I study in France.

OTS's R&D strategy

Basic policy

•Create a series of innovative new drugs using our novel platform technologies ⇒ Genome-based drug discovery

Three develop-ment strategy

•Small molecule drug: Gather good clinical data at global clinical studies, while closely cooperating with top-tier researchers in the University of Chicago and other renowned research institutes in US.

•Cancer vaccine: Contribute to cancer immune therapy by conducting cancer peptide vaccines and newly launched TCR analysis business.

•Antibody drug: Prepare for phase II study by completing OTSA101phase I study in France.

Management Policies and Strategies

1. Continue deep basic research
   - ✓ Own research＋Collaboration with Univ. of Chicago etc.

2. Promote genome-based drug discovery
   - ✓ Small molecule drug, Cancer peptide vaccine, Antibody

3. Promote development by well designed clinical studies
   - ✓ Our own activity＋Partner pharmaceutical company
   - ✓ Expansion of indication based on preclinical data

4. Facilitate licensing business with potential/existing partners
   - ✓ Strategic communication＋Technical assistance
   - ✓ Launch T/B cell receptor analysis business, develop novel immune therapy

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Pipelines（as of Dec., 2015）

	Product	Target / Indication	Basic Research	Lead Optimization	Pre-clinical	Phase I	Phase II	Phase III
Small Molecule	**OTS167**	MELK						
	OTS964 etc.	TOPK						
	–	First-in-class identified 5 targets						
Cancer Vaccines	**S−588410 ＊ Licensing-out to Shionogi**	Esophageal Cancer						
	(Licensing-out to Shionogi)	Bladder Cancer Head and neck Cancer						
	(Licensing-out to Ono)	Hepatocellular carcinoma						
	(Licensing-out to Otsuka)	Colorectal Cancer						
Antibodies	**OTSA101**	Synovial Sarcoma						
	(Licensing-out to Kyowa Kirin)	Alzheimer						

Note: Solid lline shows our hands-on R&D products（including development assistance for a licensing-out product, S-588410*）
Dotted line shows licensing-out products, being developed by other companies

Highlight of this year（June ~ Nov., 2015）

- Small molecular drug
  - MELK
    - ✓ Conducting phase I study of OTS167-IV in the University of Chicago. Additional oral administration study of OTS167-PO was approved .（Jun., 2015）
  - TOPK
    - ✓ Publication from collaborative group in the Univ. of Chicago shows TOPK inhibitor is effective to the FLT3-ITD mutated AML and FLT3 inhibitor-resistant AML.（Oct., 2015）
    - ✓ Acceptance of a proposal on our compound for NCL characterization program.（Nov., 2015）
  - SUV39H2
    - ✓ Publication of our collaborator at the University of Chicago indicated that AML could be a potential target disease of SUV39H2 inhibitor（Oct., 2015）
- Cancer-specific peptide vaccine
  - Out- license to Shionogi S-588410（5 peptide vaccine cocktail）
    - ✓ The completion of patient enrollment in Phase II clinical study in bladder cancer conducted by Shionogi & Co., Ltd.（Sep., 2015）
- Action for Cancer Precision Medicine
  - TCR analysis service
    - ✓ Launched our service for research institutes and pharmaceutical companies mainly in the fields of oncology.(Sep., 2015)

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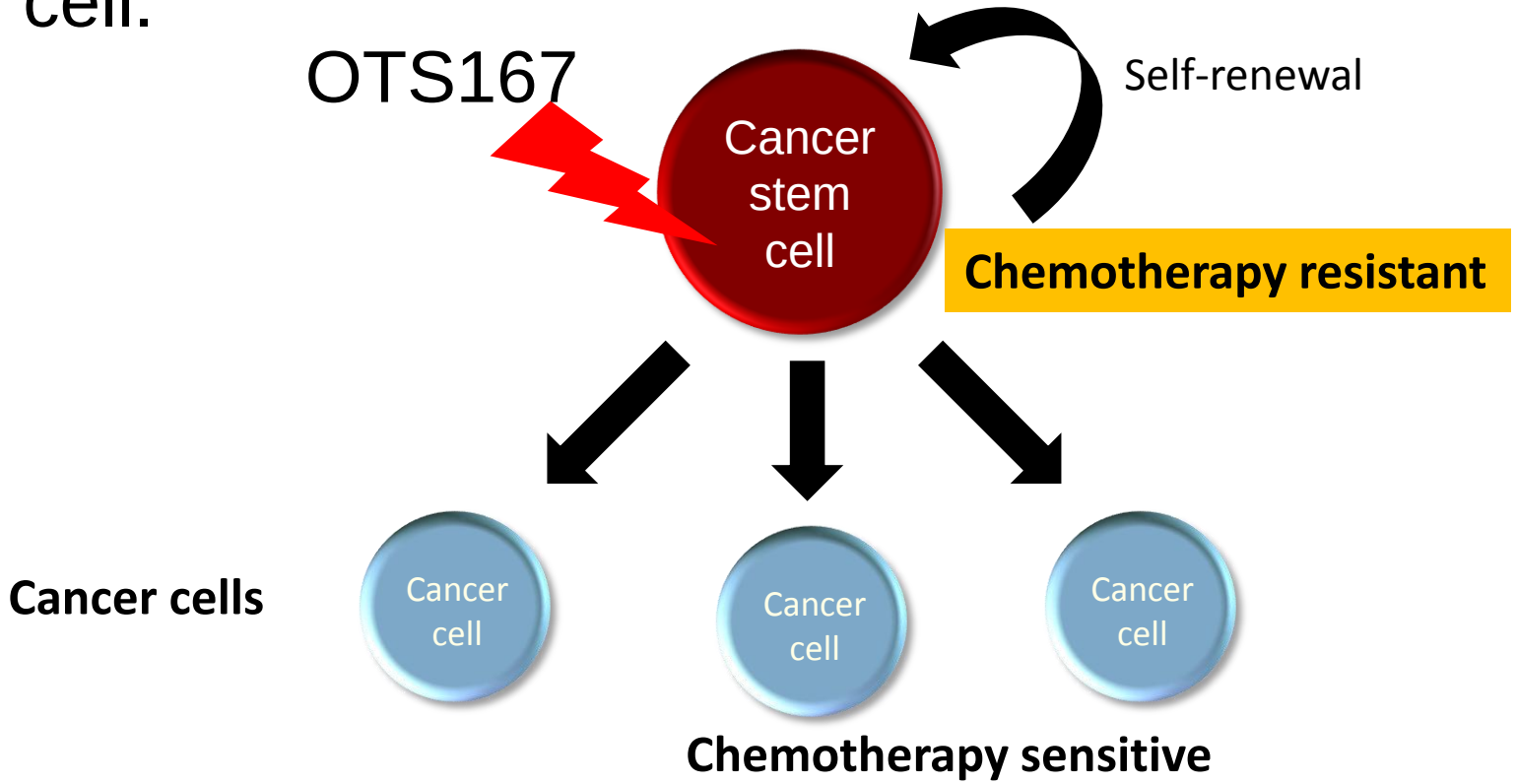
Clinical Study of OTS167(MELK inhibitor ）

- **On-going Phase I Clinical study（Univ. of Chicago）**
  - **Indication:　Refractory advanced/metastatic solid tumors**
  - **Route of Administration：**
    - ✓ **On-going; Intravenous (IV)**
    - ✓ **Additional; Oral administration（approved June, 2015）**
  - **Objective:**
    - ✓ **Primary endpoint: To determine safety and tolerability**
    - ✓ **Secondary endpoint: To check pharmacokinetics ,such as blood drug concentration, and to search and evaluation of biomarker**

- **Develop clinical studies for leukemia and solid tumor**
  - **Accelerate clinical development by choosing the most suitable area for clinical study globally.**

New Anti-Cancer Drug Target: MELK

Highly expressed MELK contributes to maintain cancer stem cell.



MELK

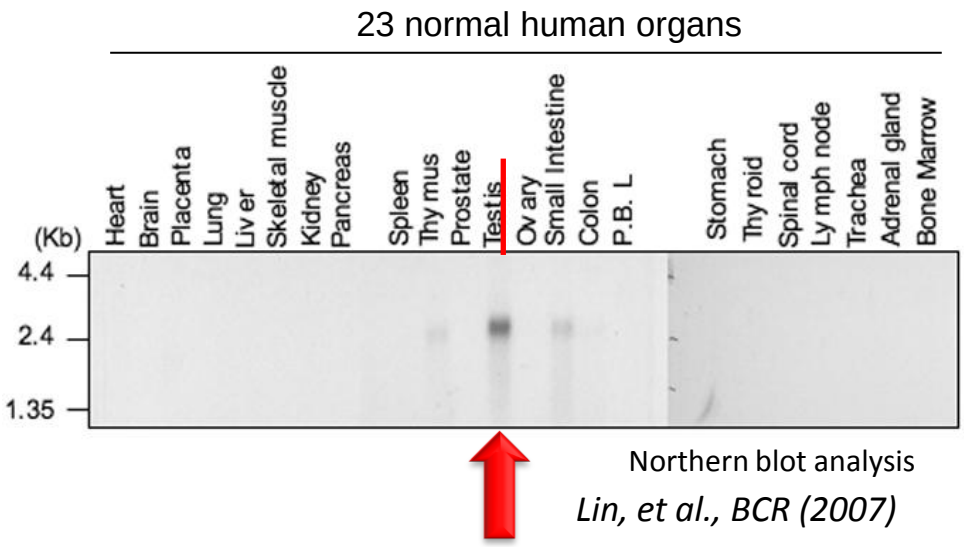
- New Anti-cancer drug target.
- OTS167(MELK inhibitor) is effective to cancer stem cell which is one of the cause of the recurrence.

MELK Selectively Overexpressed in Various Cancer Cells

- MELK (maternal embryonic leucine zipper kinase) is highly and selectively overexpressed in various human cancer cells.
- No or low expression in normal human organs except testis.

Expression of MELK (cDNA microarray)

Tumor type	Positive rate (%)
Non Small Cell Lung Cancer	100
Small Cell Lung Cancer	100
Bladder Cancer	100
Cholangiocellular Carcinoma	100
Cervical Cancer	93
Lymphoma	93
Breast Cancer	91
Prostate Cancer	86
ColorectalCancer	80
Osteosarcoma	78
CML	77



Expressed only in testis

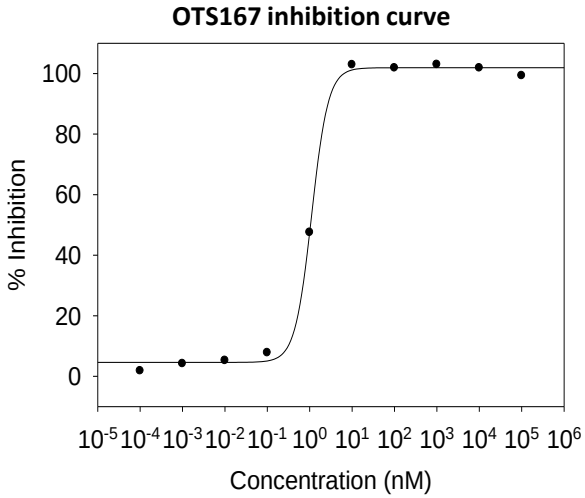
Positive rate : % of cases where Tumor/Normal > 2
(Data from collaborator (U Tokyo))

OTS167 - MELK specific inhibitor -

- **High inhibition activity against MELK**
  - IC_{50}* = 1.1 nM

IC50 of approved kinase inhibitor

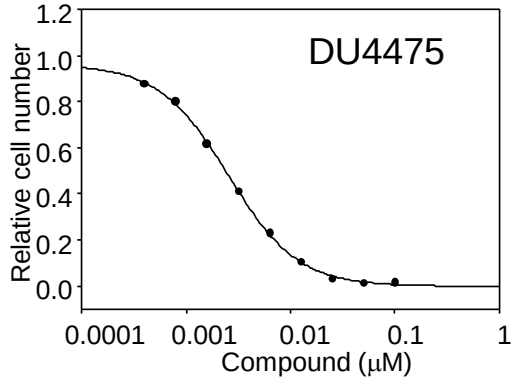
Erlotinib; Tarceva ®(CHUGAI PHARMA.)	2 nM (EGFR)
Sorafenib; Nexavar® (Bayer)	6 nM (c-Raf)
Sunitinib; Sutent® (Pfizer)	9 nM (VEGFR-2)
Imatinib; Glivec®(Novartis)	25 nM (Bcr-Abl)



*IC_{50}; 50% inhibition concentration, low value means high activity

- **Selective and significant growth inhibition against cancer cells**

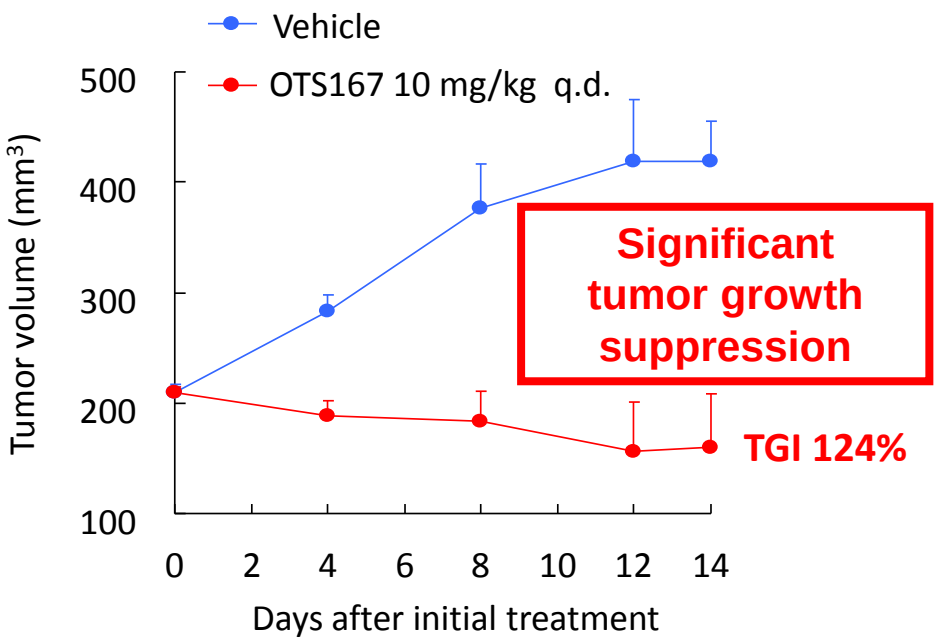
A549	IC_{50} =	8.9 nM	(lung cancer cell ; MELK positive)
T47D	IC_{50} =	5.3 nM	(breast cancer cell; MELK positive)
DU4475	IC_{50} =	3.3 nM	(triple-negative breast cancer; MELK positive)
22Rv1	IC_{50} =	5.2 nM	(prostatic carcinoma: MELK positive)
HT1197	IC_{50} =	120.0 nM	(bladder cancer cell; MELK negative)



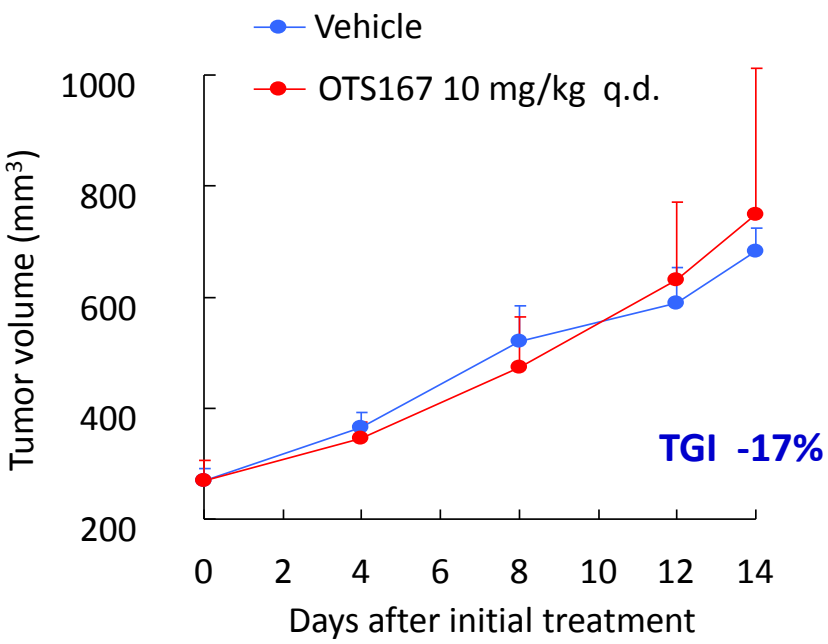
OTS167 in vivo: Tumor with MELK selectively suppress

OTS167 shows significant MELK-dependent tumor growth suppression in xenograft model by oral administration.

A549 lung cancer
(MELK high)



PC14 lung cancer
(MELK low)



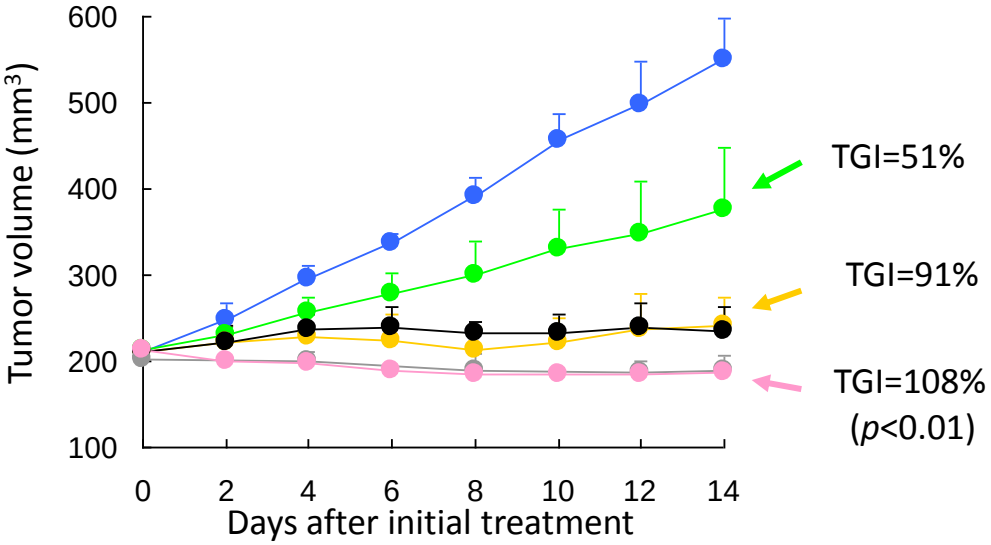
Chung, et al., Oncotarget (2012)

OTS167 in vivo: IV Administration

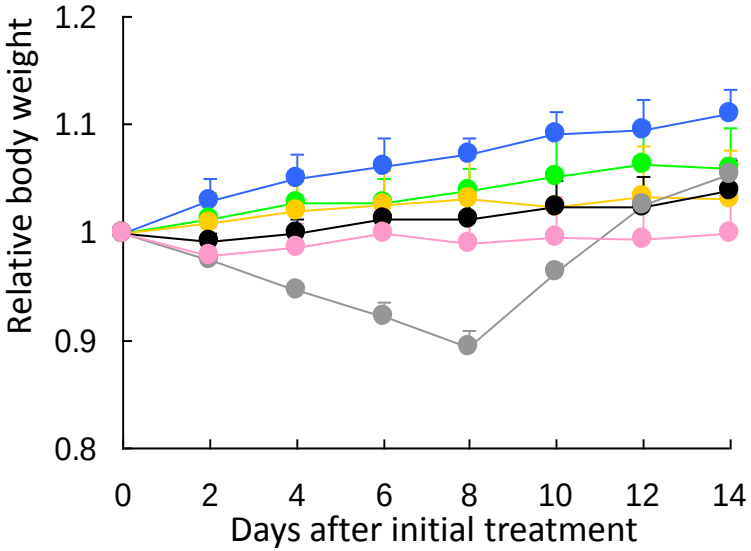
OTS167 has strong growth suppression with no severe adverse events, compare to Paclitaxel.

Intravenous administration: once daily (A549 xenograft model)

Tumor volume (n = 6)



Body weight



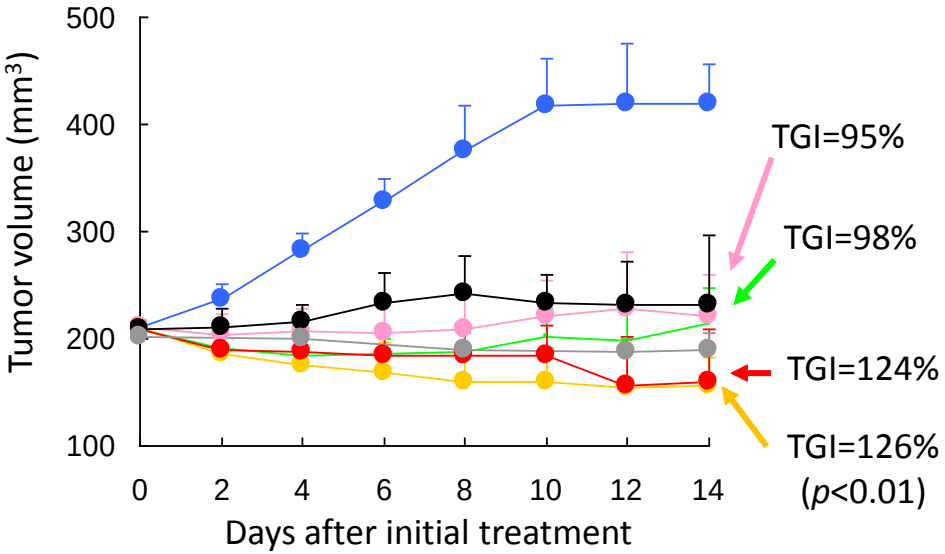
Vehicle q.d.
OTS167 1 mg/kg q.d.
OTS167 5 mg/kg q.d.
OTS167 10 mg/kg q.d.
Paclitaxel 24 mg/kg i.v. Day 0, 3, 7, 10
Paclitaxel 24 mg/kg i.v. Day 0, 1, 2, 3, 4

OTS167 in vivo: Oral Administration

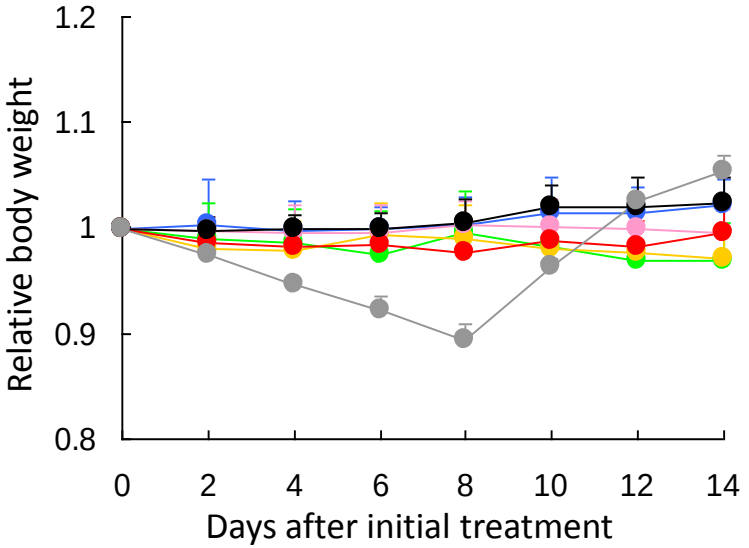
OTS167 is more effective for tumor growth suppression than Paclitaxel with no severe side effects such as loss of body weight.

Oral administration: once or twice daily (A549 xenograft model)

Tumor volume (n = 6)



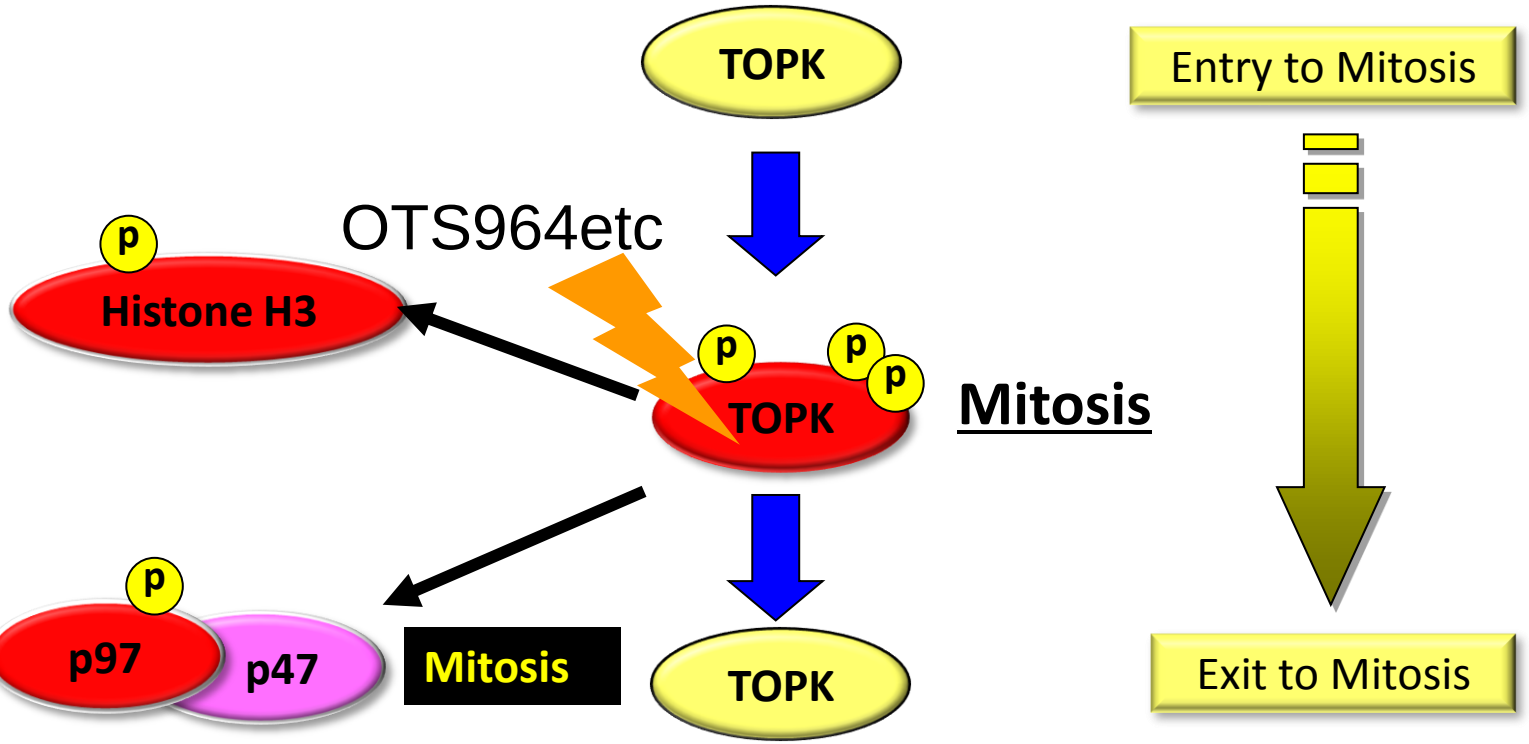
Body weight



- Vehicle q.d.
- OTS167 2.5 mg/kg b.i.d.
- OTS167 5 mg/kg b.i.d.
- OTS167 5 mg/kg q.d.
- OTS167 10 mg/kg q.d.
- Paclitaxel 24 mg/kg i.v. Day 0, 3, 7, 10
- Paclitaxel 24 mg/kg i.v. Day 0, 1, 2, 3, 4

New Anti-Cancer Drug Target: TOPK

TOPK is involved in cancer cell cytokinesis during mitosis



TOPK

- New Anti-cancer drug target.
- Several anti-cancer drugs which target mitosis are already approved, however they inhibit normal cells, too. Whereas inhibition of TOPK is expected to less adverse effect since its expression is limited to cancer.

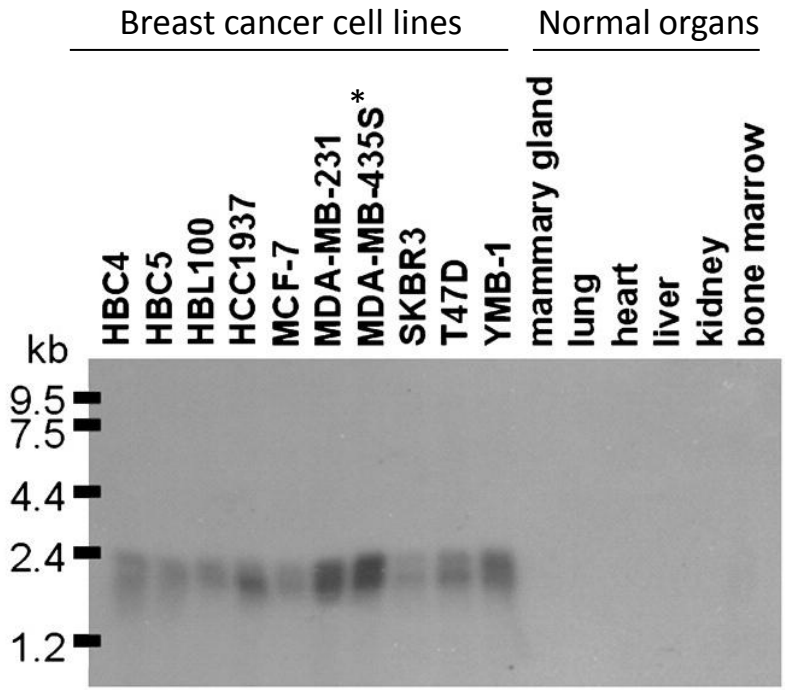
TOPK Highly Expressed in Various Human Cancers

- **TOPK is highly expressed in various human cancers, including lung and breast cancers.**
- **TOPK is not expressed in human vital organs.**

Expression of TOPK (cDNA microarray)

Tumor type	Positive rate (%)
Bladder Cancer	100%
Cholangiocellular Carcinoma	100%
Lung Cancer	100%
Cervical Cancer	93%
Lymphoma	93%
Breast Cancer	91%
Prostate Cancer	86%
Colorectal Cancer	80%
Osteosarcoma	78%
CML	77%

Positive rate : % of cases where Tumor/Normal > 2
(Data from collaborator (U Tokyo))



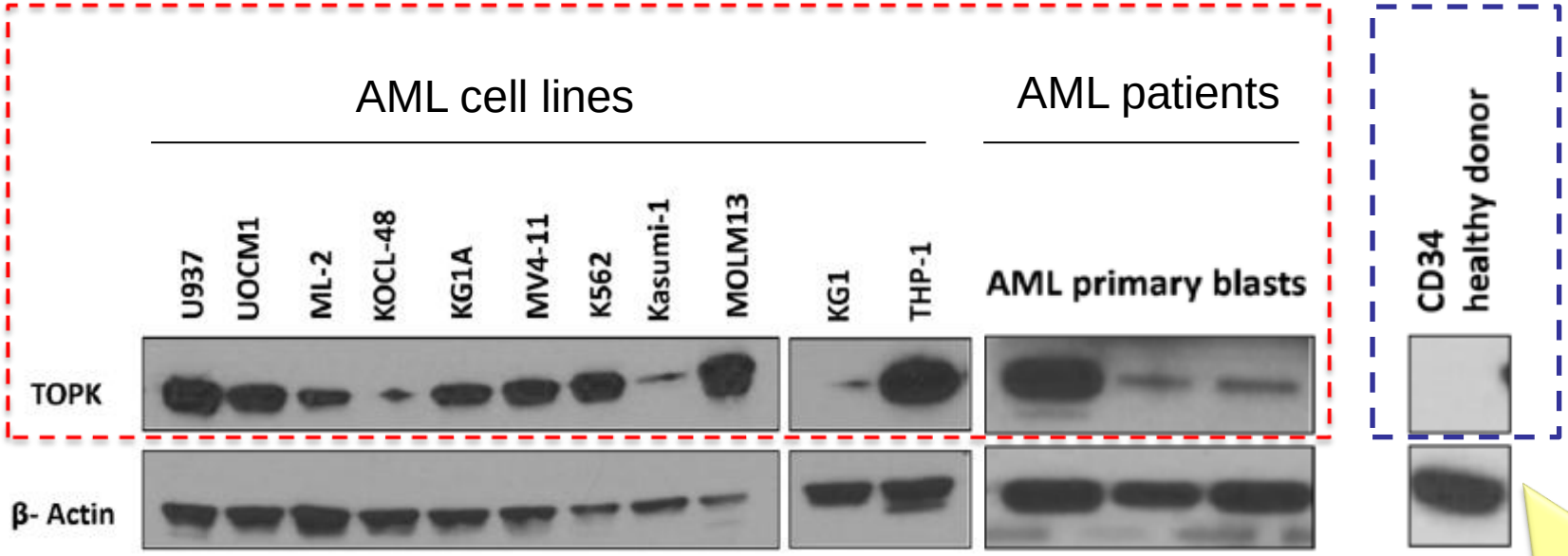
*MDA-MB-435 is reported to have been cross-contaminated with is the M14 melanoma line.

Northern blot analysis

Park, et al., Can Res (2006)

TOPK Expressed in AML as well.

TOPK is expressed in acute myeloid leukemia(AML) cell lines and AML patients samples.



TOPK is not expressed in health donor samples.

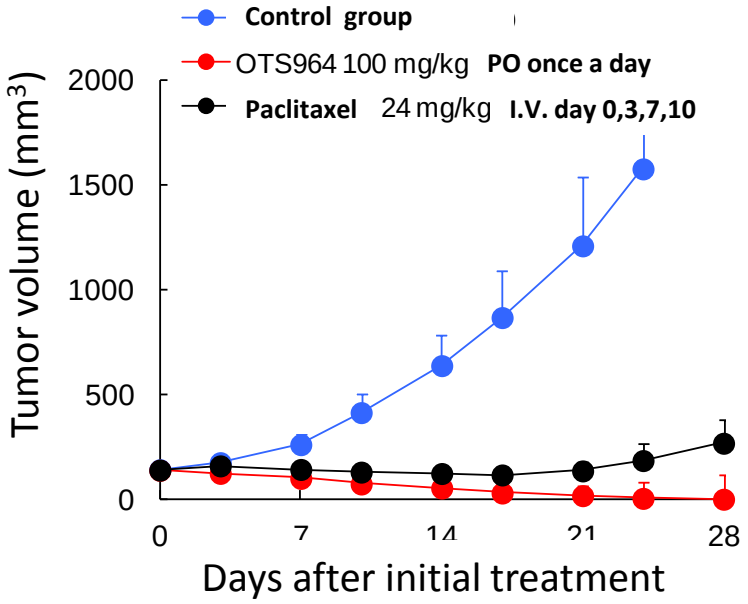
Modified form Alachkar, et al., Oncotarget (2015)

OTS964 in vivo : Oral Administration

OTS964 shows significant anti-tumor effect

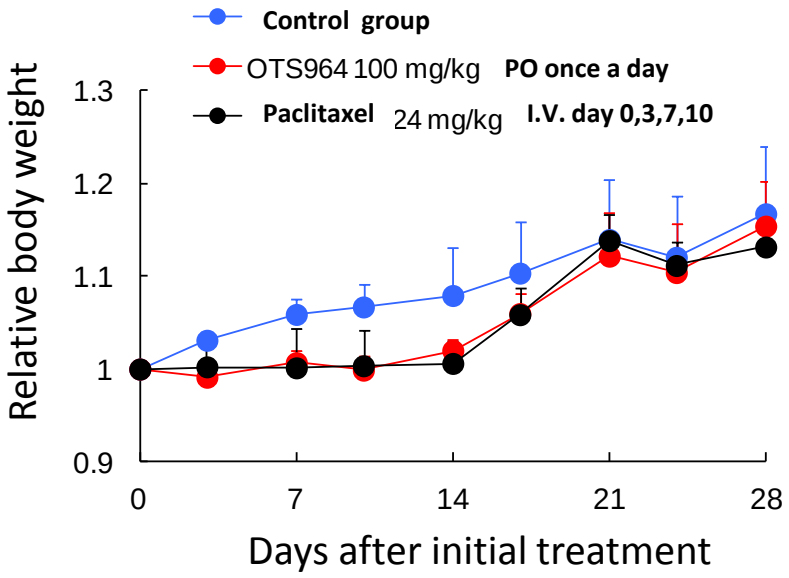
- ✓ **LU99（human lung cancer）xenograft model** (N=6)
- ✓ **Once a day, 14 days, PO (orally), OTS964 100mg/kg**

Tumor volume



Complete regression in all six mice.

Body weight



No severe side effects such as loss of body weight.

Source: Sci Transl Med, Matsuo et al, 2014 , OTS internal document

Actions for Cancer Precision Medicine

1) Cancer immunotherapy and genome

2) Launch of TCR analysis service

3) Novel immunotherapy based on genomic analysis; Precision Medicine

Cancer Immunotherapy and Genome

• It was reported about 20 years ago that the patients with hereditary colon cancer caused by mutation of DNA repair gene have better prognosis than those with common type of colon cancer.

⇒ From this relationship between cancer and gene mutation, we can propose a hypothesis of effective cancer therapy.

1. Mutations occur in DNA repair gene.

2. The number of gene mutation increases in cancer cells.

3. Tumor-specific antigens increase.

4. Cytotoxic T lymphocytes against tumor-specific antigens are activated.

5. Better clinical efficacy of immune checkpoint antibody therapy is shown because of the increased number of lymphocytes that can attack tumor cells.

http://yusukenakamura.hatenablog.com/entry/2015/02/15/131903

Actions for Cancer Precision Medicine

2) Launch of TCR analysis service

- After the first half of this fiscal year of preparation, we posted revenues since this September.
- We promoted public awareness through conference presentation and BioJapan luncheon seminar.
- We received orders from the researchers in the fields of oncology as the first step.
- We will expand our business to the research in the other fields and pharmaceutical companies.

3) Novel immunotherapy based on genome analysis data; Precision Medicine

TCR analysis: solving issues of cancer immunotherapy

- Immunomonitoring

  Establishment of "**diagnostic marker (TCR analysis)**" that reflects the change of immune state effected by therapy.

  ➡**Rapid and quantitative** evaluation of therapy contributes accurate judgment of continuation/cessation of treatment.

- Patient selection

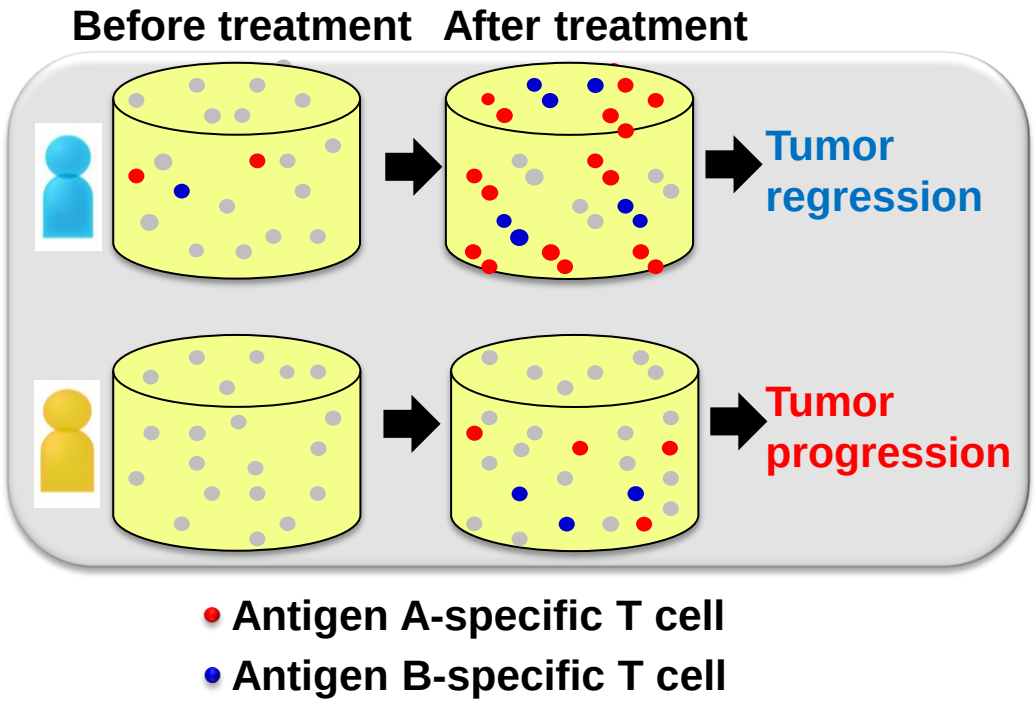
  Prediction of clinical efficacy

  - Detecting T cells in the tumor before treatment

  → Start cancer immunotherapy

  - Not detecting T cells in the tumor before treatment

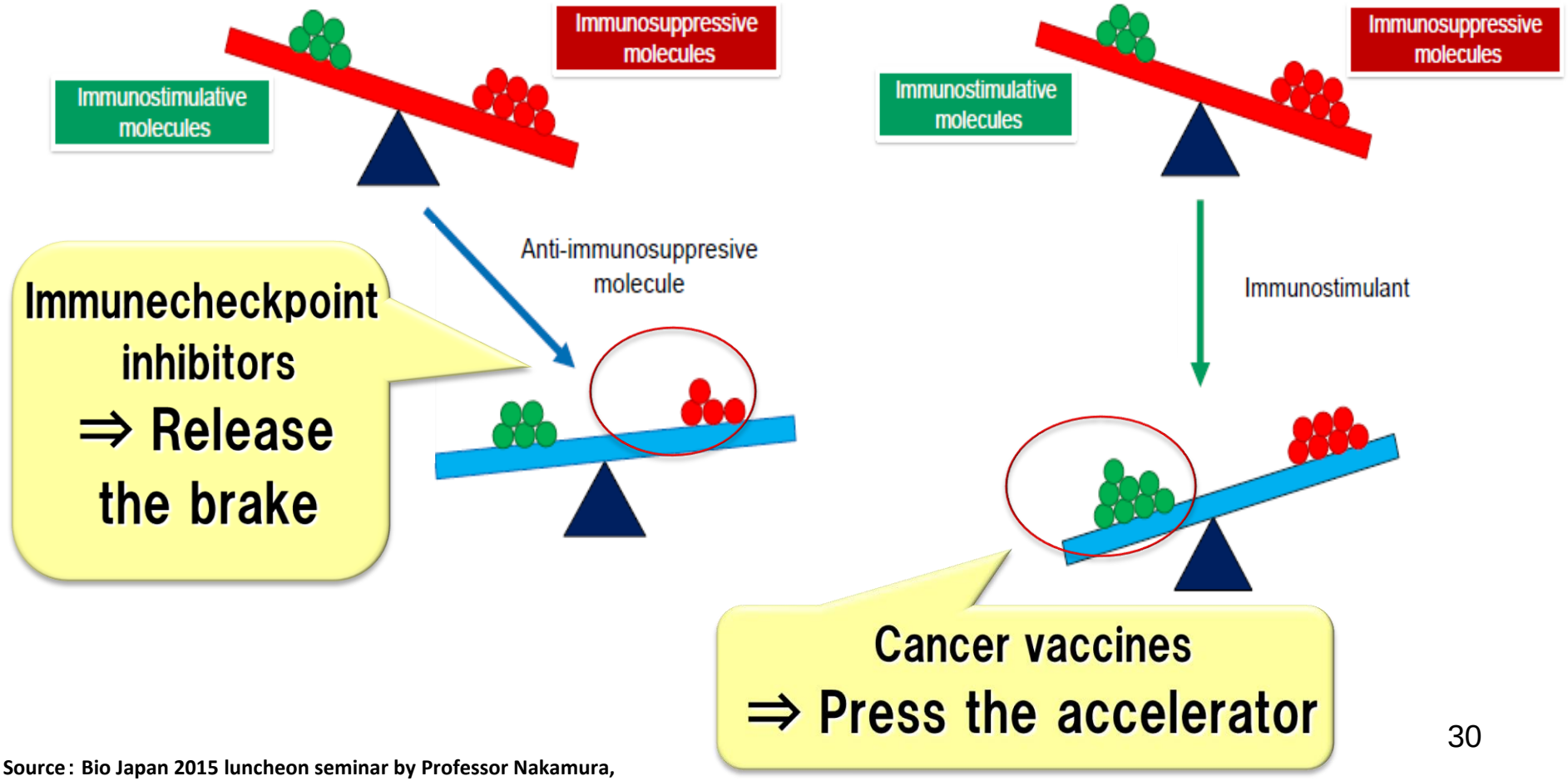
  → Avoid cancer immunotherapy



➡ **Increase of response rate**
Decision of the start of treatment

Novel Therapy based on Immunopharmacogenomics

Immunecheckpoint inhibitors are now under developing, and hereafter, therapy of activating immune system and enhancing the attack against tumor will become important.



Source : Bio Japan 2015 luncheon seminar by Professor Nakamura, University of Chicago

Clinical Development Status of OTSA101

- On-going phase I clinical trial for synovial sarcoma, in France
  - ✓ Under the direction of Professor Jean-Yves BLAY (former President of European Organization for Research and Treatment of Cancer; EORTC) who is global key opinion leader in sarcoma treatment.
  - ✓ Financially supported by Cancéropôle Lyon Auvergne Rhône-Alpes=CLAR
- Designated as orphan drug for treatment of soft tissue sarcoma by EMA(EU) and FDA(US)
- Seeking approval for synovial sarcoma in EU and US
  - ✓ Based on phase I study result, design the next phase clinical trial, consulting with EMA/FDA（designation of orphan drug）
  - ✓ Consider next clinical trial as the pivotal study to evaluate the effectiveness of OTSA101 and plan to application of NDA after the study
- Develop companion diagnostics and seek expansion of application to another cancer type

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