Progress Update
Discovery & Research

ONO PHARMACEUTICAL CO.,LTD.

May 12, 2017

In-house pipeline

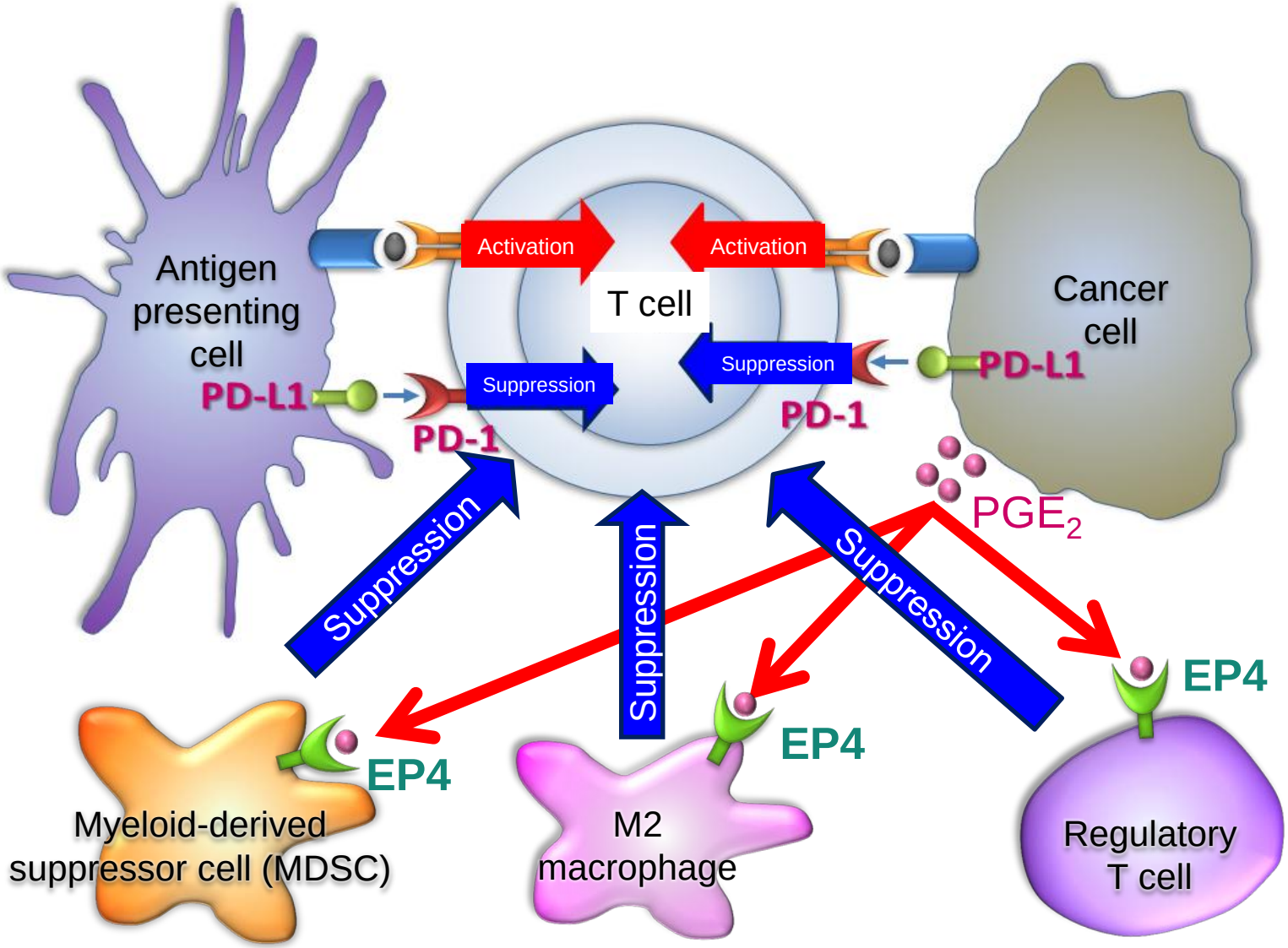
Development code (generic name)	Target indication/ pharmacological action	Development phase/ region	
ONO-4474	Osteoarthrosis / Trk inhibition	Ⅱ	EU
ONO-8577	Overactive bladder / relaxation of bladder smooth muscle	Ⅱ	JP
ONO-9054 (Sepetaprost)	Glaucoma, ocular hypertension / FP/EP3 agonistic activity	Ⅱ *1	US*1
ONO-4059 (Tirabrutinib)	B-cell lymphoma / Btk inhibition	Ⅱ *2	US/EU*2
		Ⅰ	JP
	Sjögren's syndrome / Btk inhibition	Ⅱ *2	US*2
ONO-8055	Underactive bladder / EP2/EP3 agonistic activity	Ⅰ	EU
ONO-2160/CD	Parkinson's disease / levodopa pro-drug	Ⅰ	JP
ONO-7475	Acute leukemia / Axl/Mer inhibition	Ⅰ	US
ONO-4578	Solid tumor / EP4 antagonistic activity	Ⅰ	JP
ONO-7579	Solid tumor / Trk inhibition	Ⅰ	US/EU

Red: Change from the announcement in May 2016 *1Conducted by Santen Pharmaceutical *2Conducted by Gilead Sciences

ONO-4578

Pharmacological action	**Selective EP4 receptor antagonistic activity (enhancement of antitumour immunity)**
Dosage form	**Oral agent**
Target indication	**Solid tumor**
Expectation	**A drug to potentiate the antitumour effect in combination with anti-PD-1 antibody**
Current status	**Started Phase I study in Japan in January 2017 (Safety, tolerability, and PK after single administration are under evaluation)**

Effect of PGE2 in cancer microenvironment



Dedicated to Man's Fight against Disease and Pain

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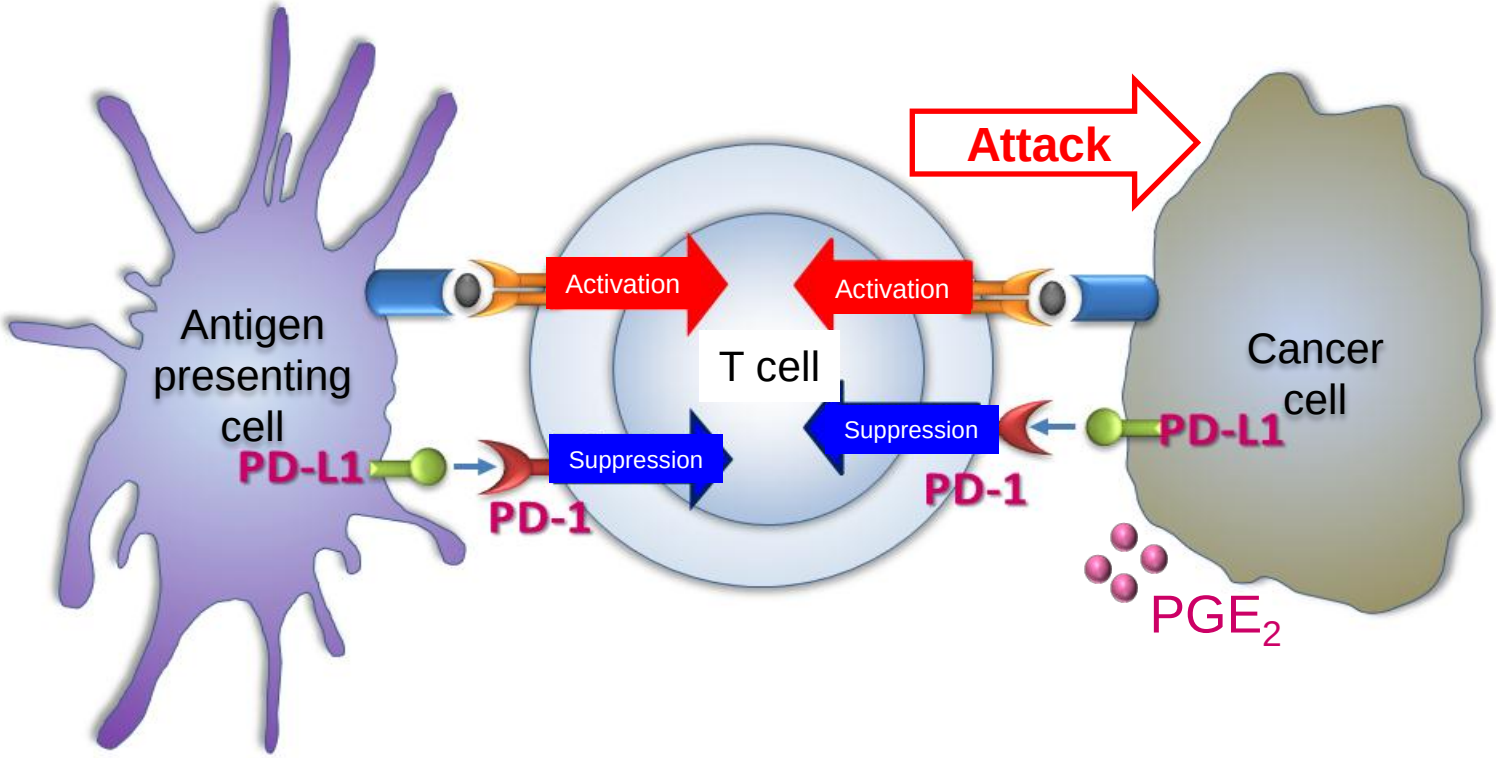
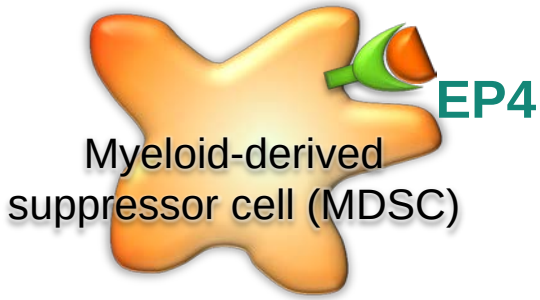
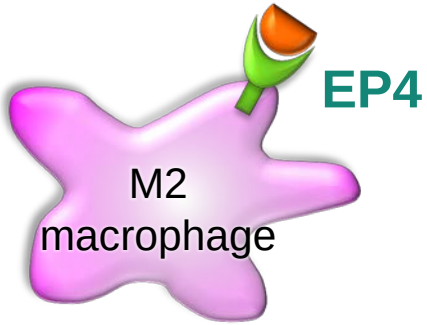
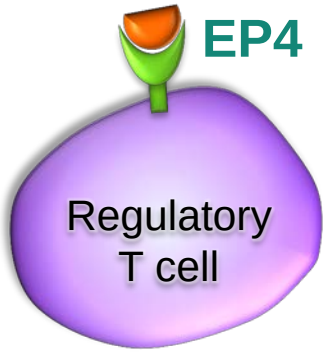
ONO-4578 releases suppressed tumor immunity



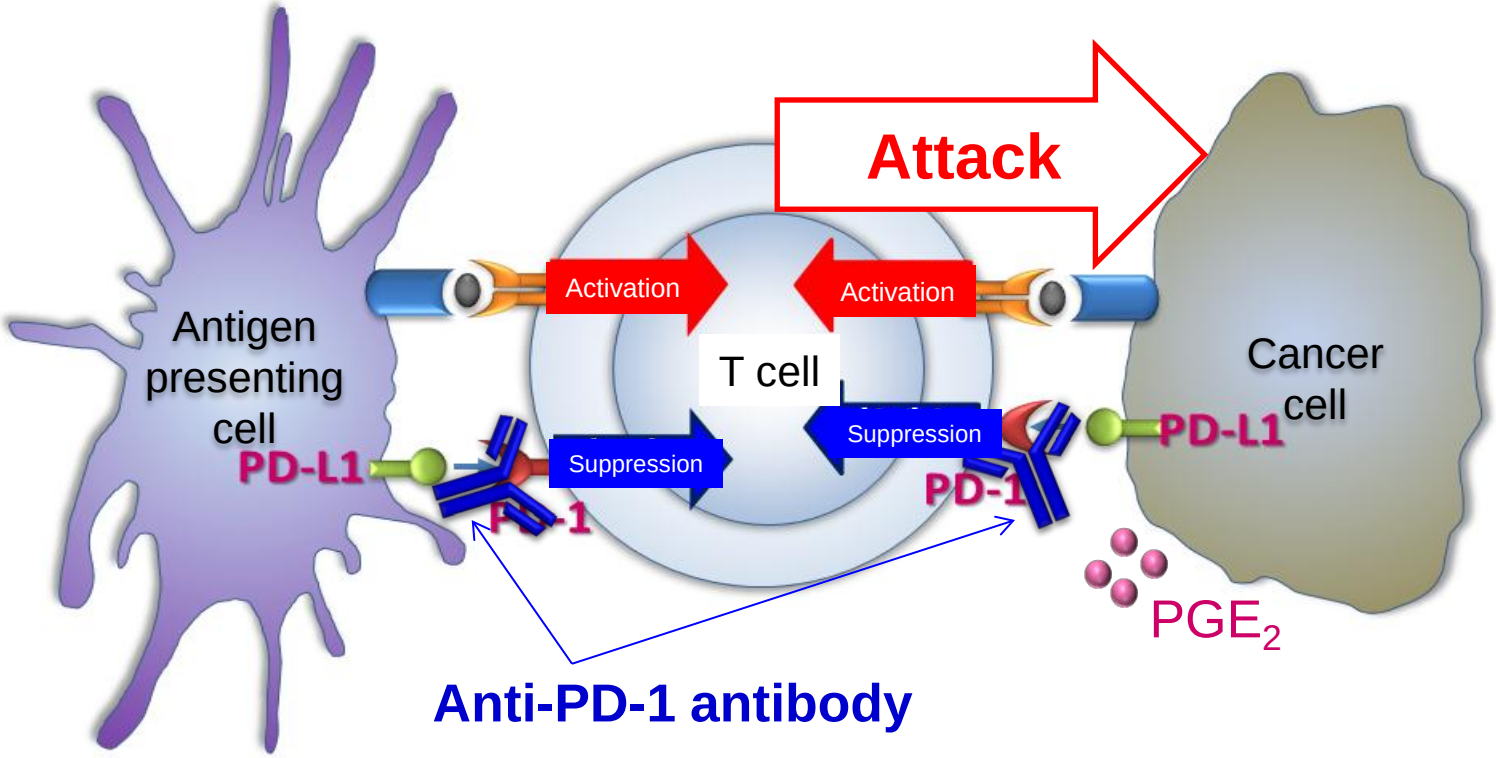
ONO-4578



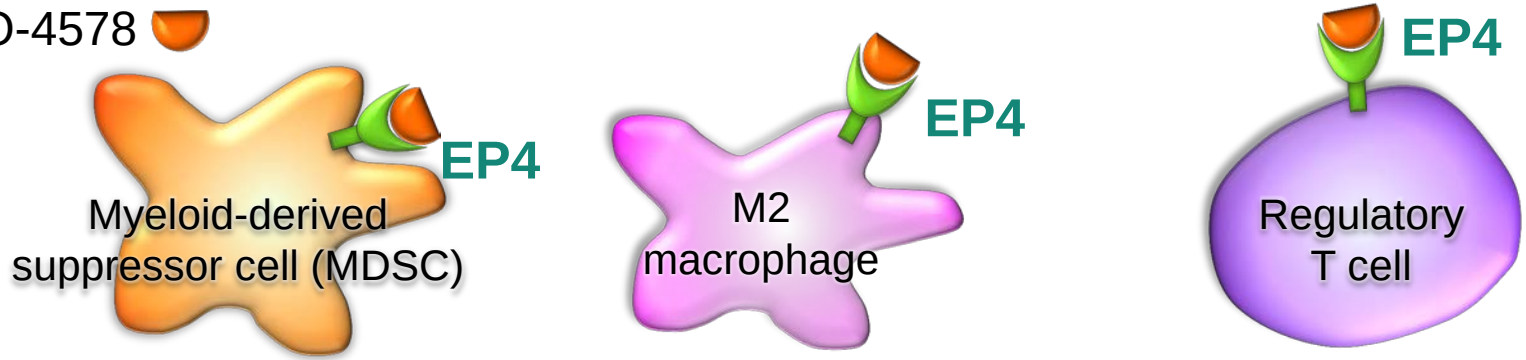




Potentiation of antitumour effect is expected through the combination effect with anti-PD-1 antibody



ONO-4578



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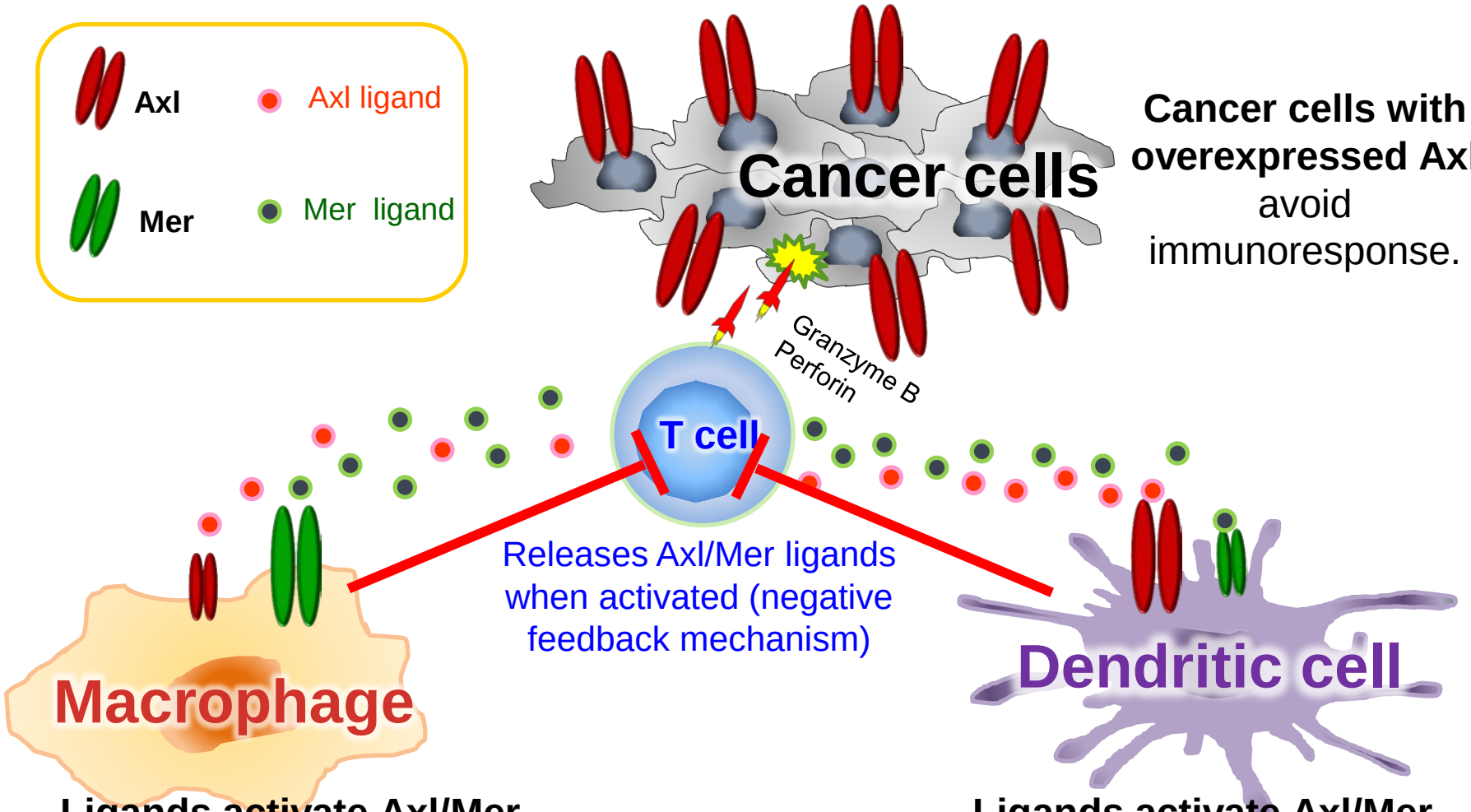
ONO-7475

Pharmacological action	**Axl/Mer dual inhibition**
Dosage form	**Oral agent**
Target indication	**Hematologic cancer**
Expectation	**A drug for the treatment of cancer in which Axl/Mer is responsible for tumor proliferation**
Current status	**Started Phase I study in the US in January 2017**

Further, potential as an immuno-oncology drug is expected.

Axl/Mer suppress tumor immunity



Cancer cells with overexpressed Axl avoid immunoresponse.

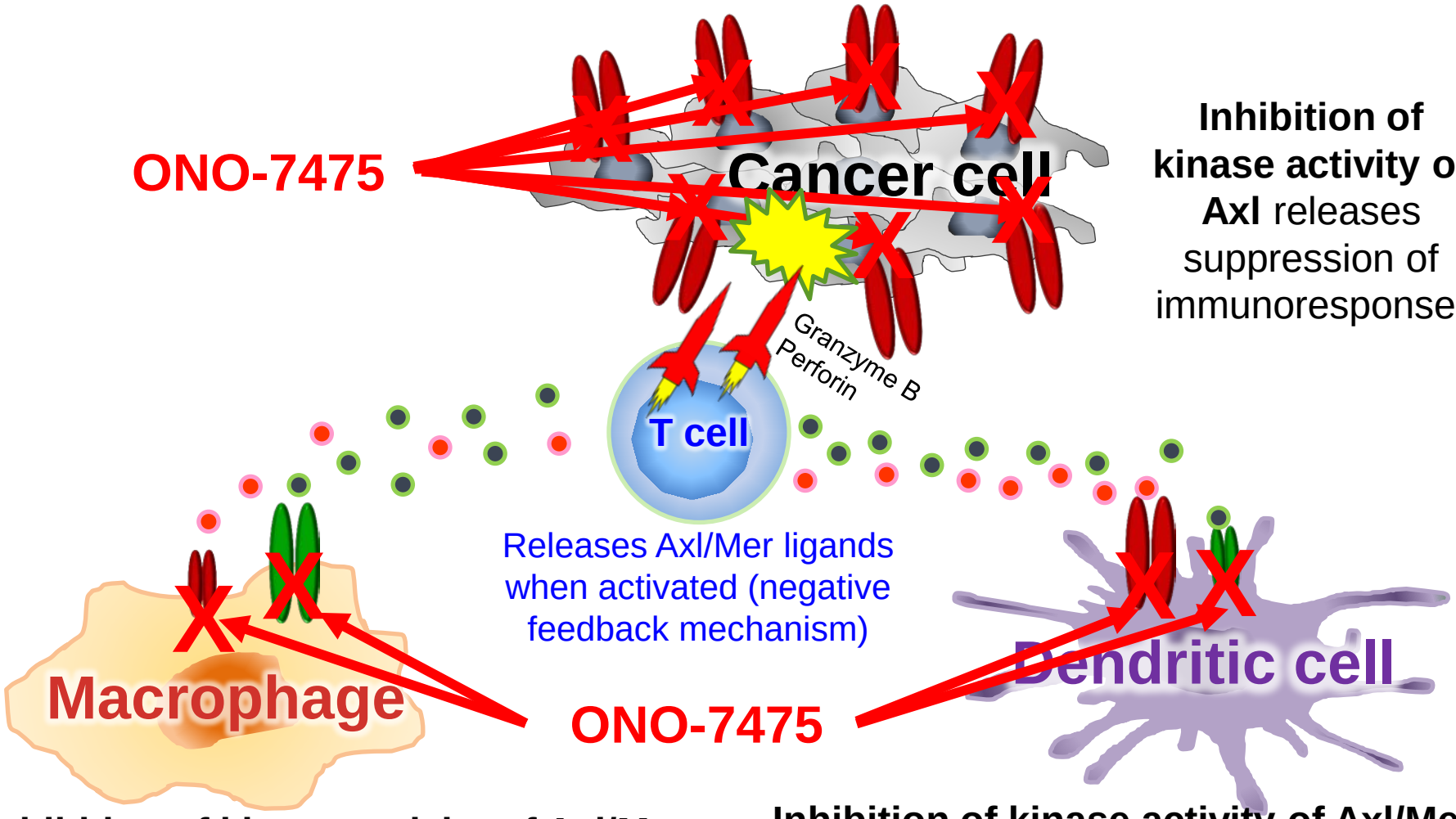
Ligands activate Axl/Mer

→Macrophages are differentiated into anti-inflammatory phenotype.

Ligands activate Axl/Mer

→ Dendritic cells deliver suppressive signal to T cells.

ONO-7475 releases suppressed tumor immunity

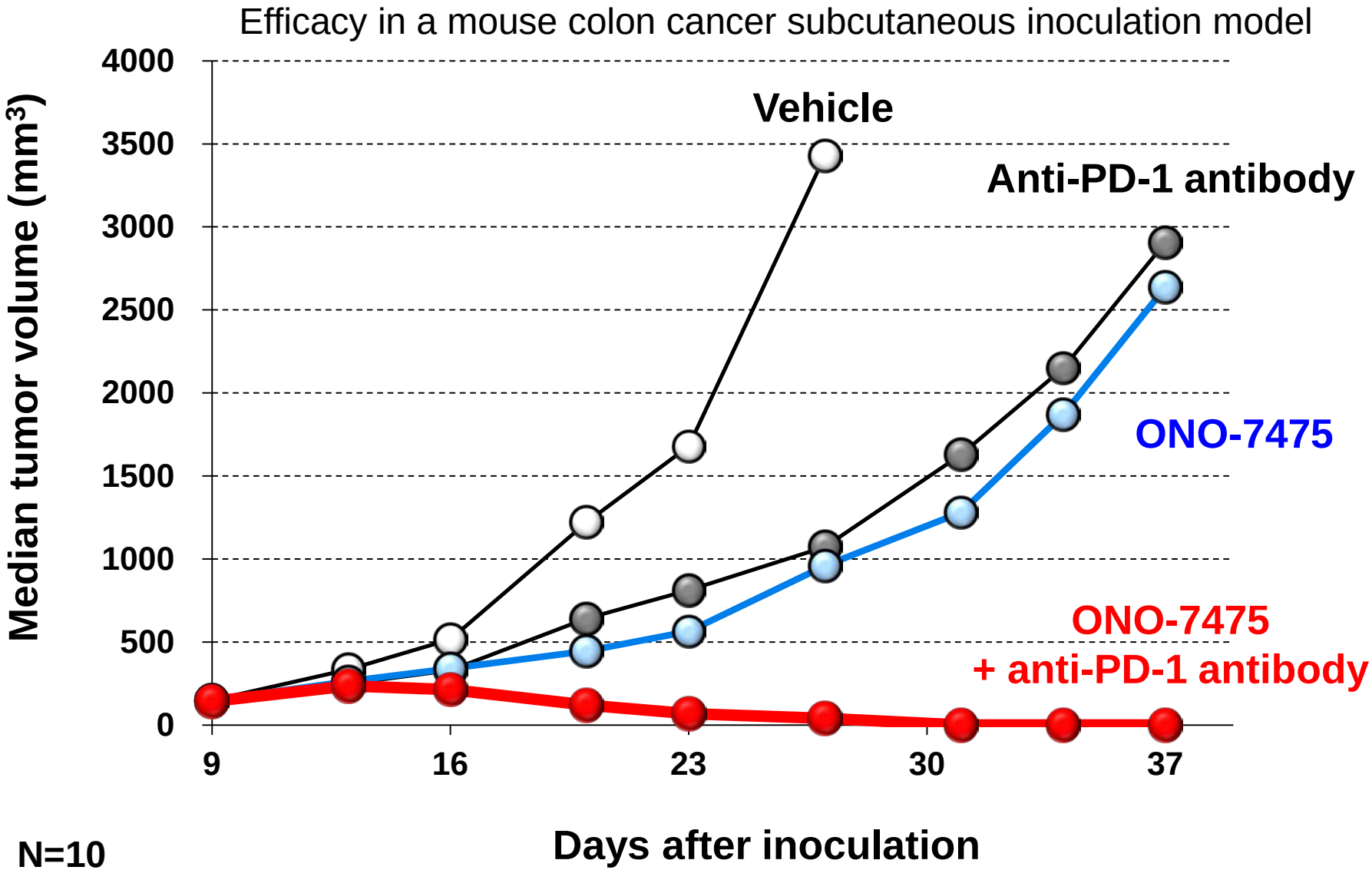


Inhibition of kinase activity of Axl releases suppression of immunoresponse.

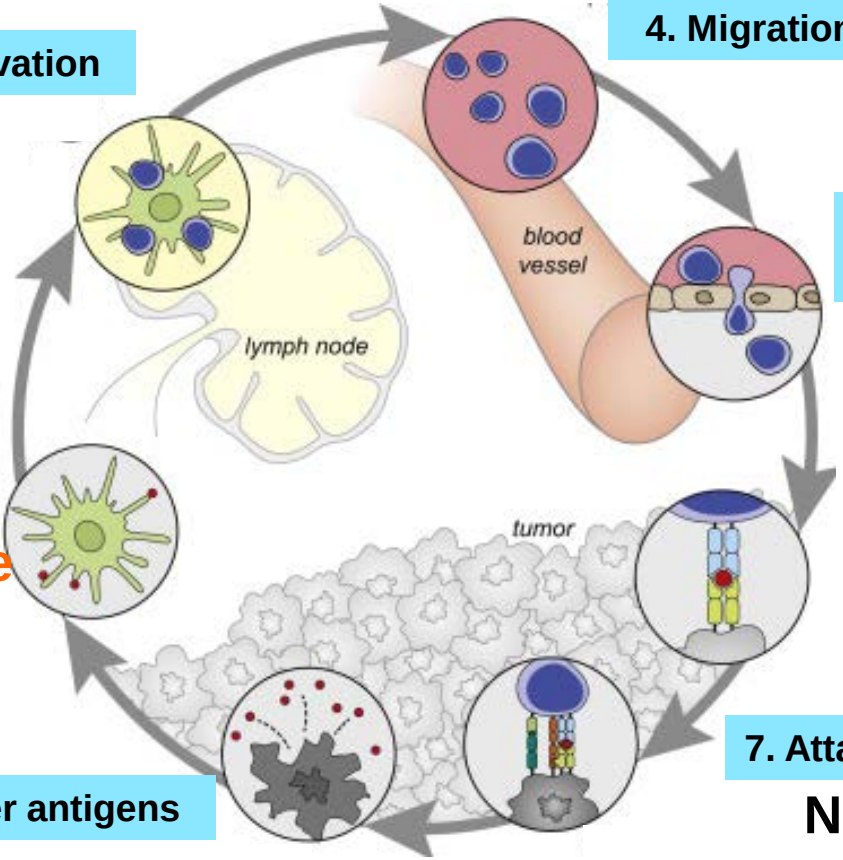
Inhibition of kinase activity of Axl/Mer suppresses anti-inflammatory macrophages.

Inhibition of kinase activity of Axl/Mer inhibits suppressive signal to T cells.

ONO-7475/anti-PD-1 antibody combination therapy offers hope



To be a front runner in the immuno-oncology area



1. Release of cancer antigens

2. Antigen presentation

Peptide vaccine

3. Priming and activation

Nivolumab, Ipilimumab, anti-CD137 antibody

4. Migration of T cells into cancer tissue

5. Infiltration of T cells into cancer tissue

6. Recognition of tumor cells by T cells/NK cells

CAR-T (NKG2D)

7. Attack of T cells/NK cells on tumor cells

Nivolumab, anti-TIGIT antibody, anti-KIR antibody, anti-LAG-3 antibody

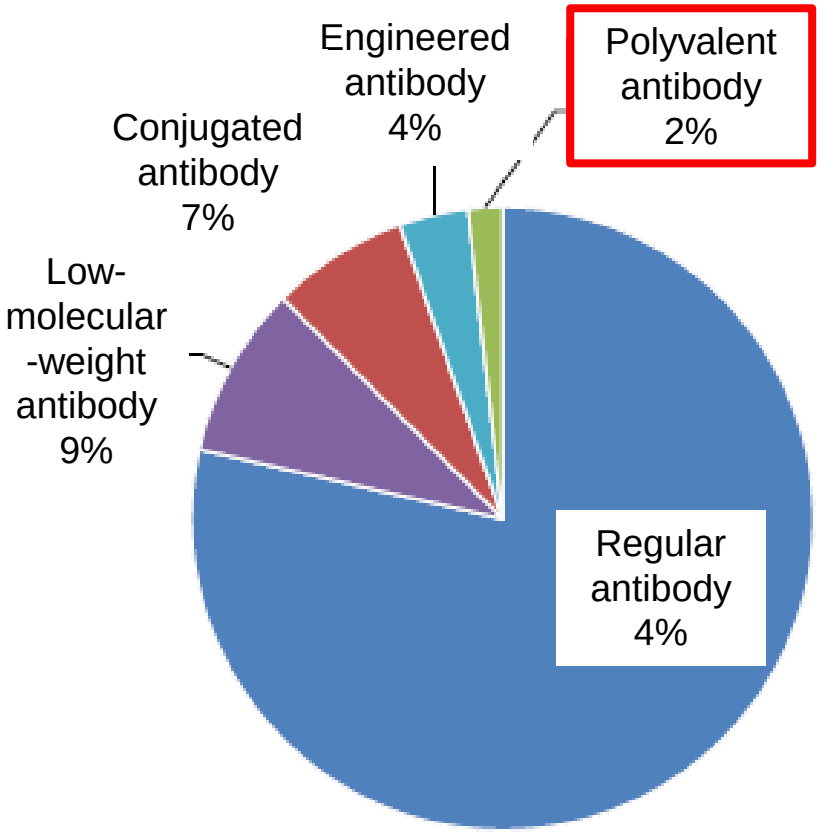
Regulation of cancer microenvironment

ONO-4578, ONO-7475, anti-CD4 antibody, anti-CSF-1R antibody, IDO1 inhibitor, anti-CCR4 antibody

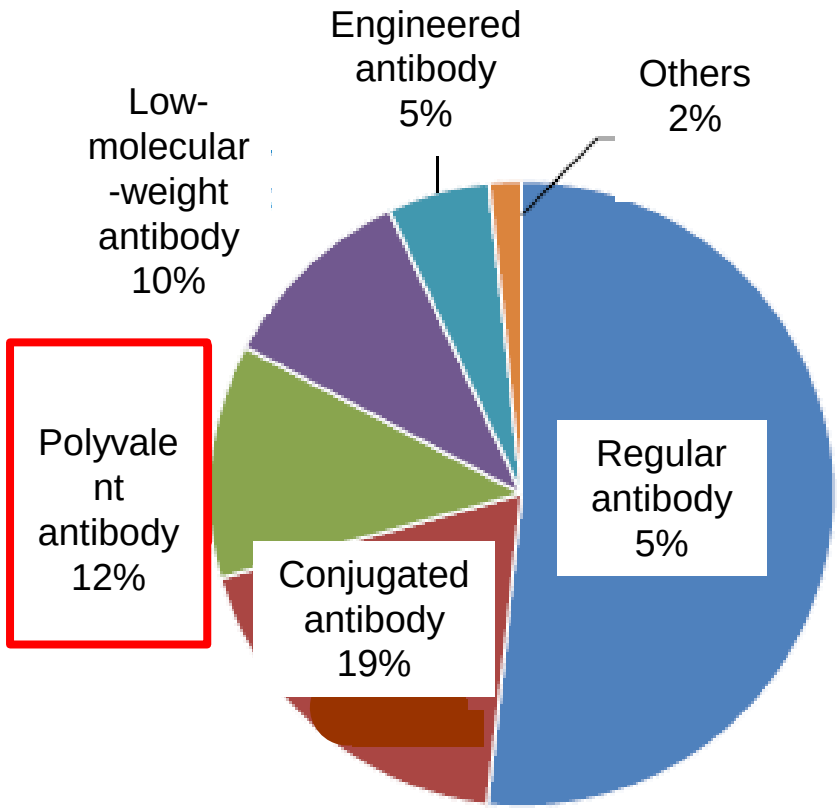
Immunity. 2013 Jul 25;39(1):1-10. (modified)

Utilization of the next-generation antibody technology in drug development

Development status of therapeutic antibodies by characteristics



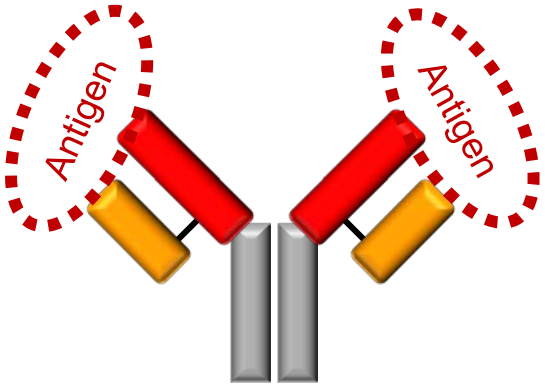
On market
(as of April 2016, total 56 products)



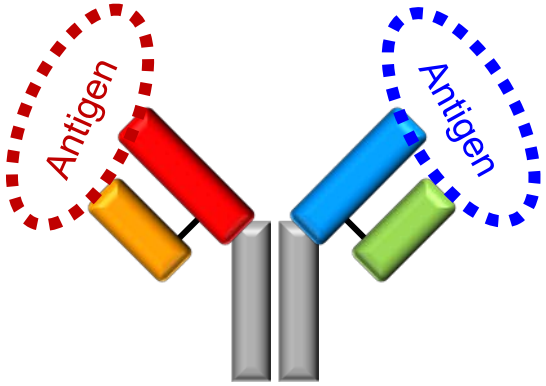
Under development
(as of April 2016, total 603 products)

[Development Trend and Future Prospect of Therapeutic Antibodies (2016 Edition)].
Permitted by BB-Bridge, Inc. Japanese

Development of bispecific antibody



Regular antibody
(monospecific antibody)



Bispecific antibody

Characteristic:

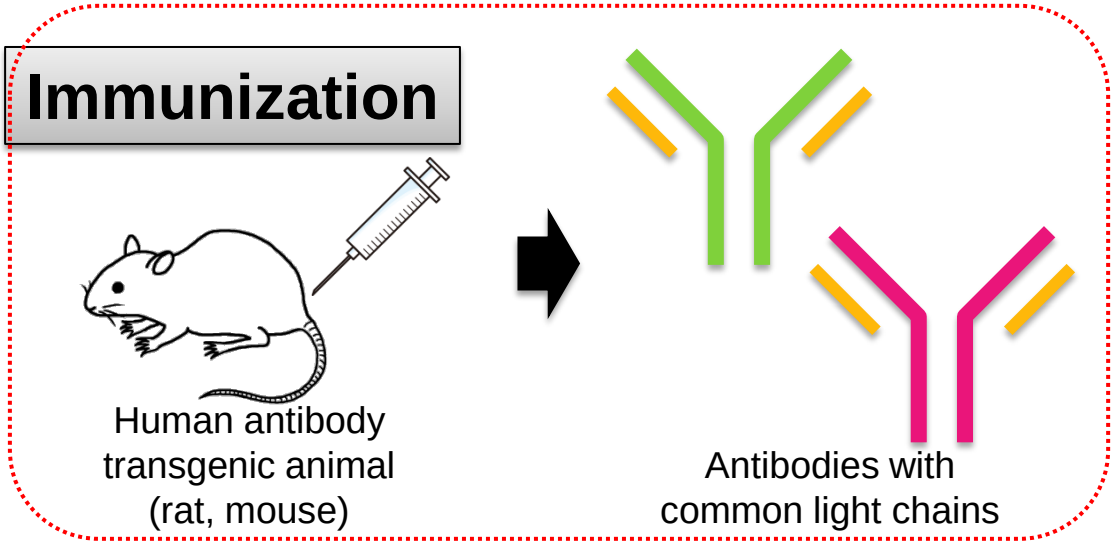
- Binds to different kinds of proteins

Application examples:

- Migration of T cells into tumor tissue
- Dually neutralizing antibody
- Anchorage of a blood coagulation factor

Partnership since	Partner	Purpose
April 2014	Merus (NL)	Production of a pipeline of drug candidates in autoimmune disease area
December 2016	Ligand (US)	Acquisition of a license to produce a fully human mono- or bispecific antibody
March 2017	Numab (CH)	Production of a pipeline of drug candidates in immuno-oncology area

Ligand's technology



Characteristics of Ligand's OmniAb® technology

- **Mice as well as rats can be used**
  - **Antibody against mouse antigen is available**
  - **Concept verification is expected to be accelerated**
- **Human antibody can be acquired**
- **Material antibody that is crucial for production of bispecific antibody can be produced**

Numab's technology

Immunization

Multispecific partial antibody or fully antibody-like substance

Characteristics of Numab's technology

- **Rabbits are used**
- **Technology to humanize rabbit-derived antibody**
- **Technology to stabilize the protein**
  - ✓ **Produced protein is as stable as that of regular antibodies**
- **Standardized manufacturing method is highly likely to be applied**

Eyes focused on the post-Opdivo era

Discovery of first-in-class drugs to fulfill unmet medical needs