



Current status and outlook for Eisai's major R&D themes

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Eisai R&D management Company

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Eisai R&D Management Company

Our Policy of R&D

Major Themes

E2007 AMPA Receptor Antagonist

E5564 Endotoxin Antagonist

E2012 Gamma-Secretase Modulator

E7389 Microtubule Growth Suppressor

Establishing Oncology Franchise



Eisai R&D Management Company

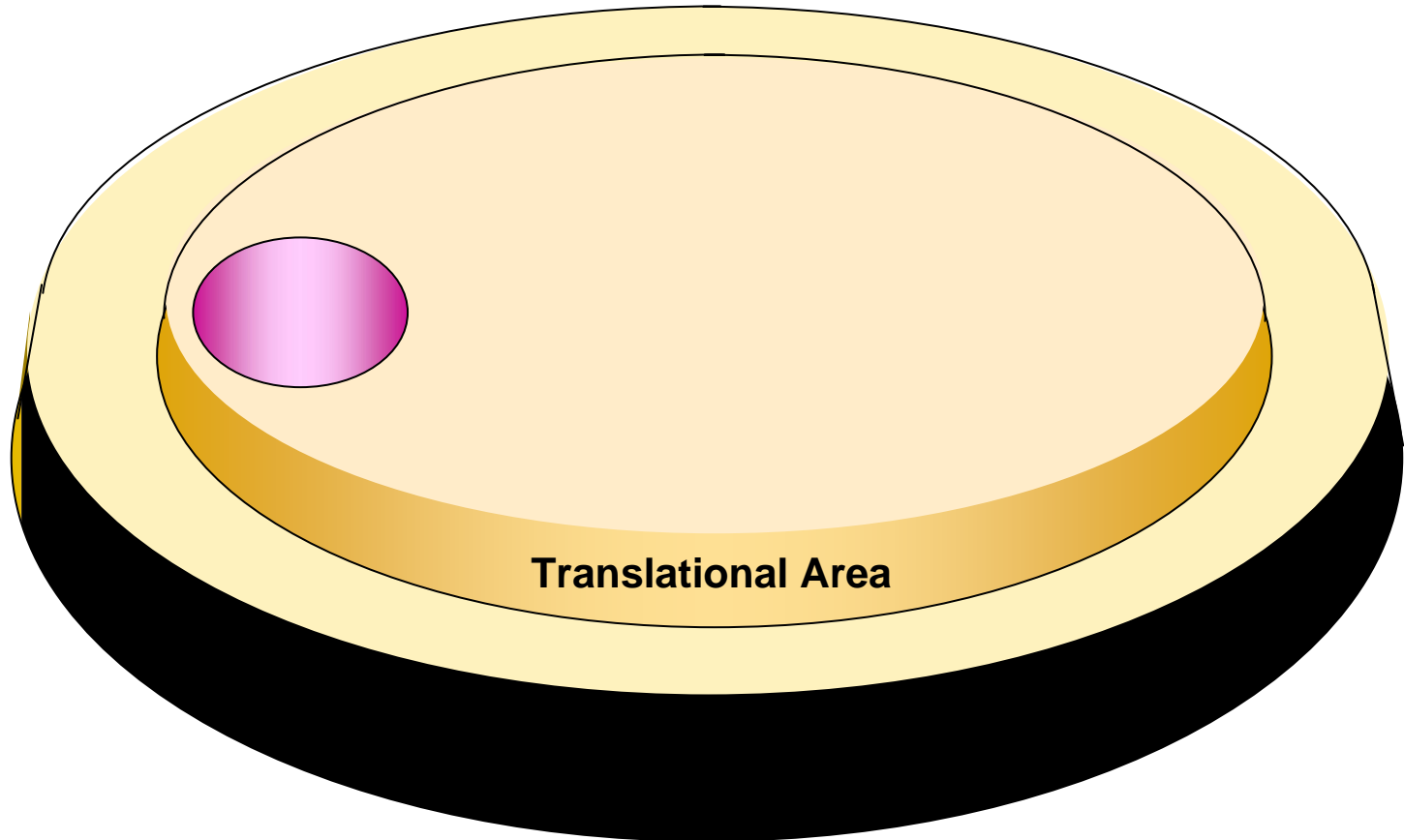


Eisai R&D Management Company

- Manage International Project Team for each project



The New Global R&D Framework



Applying -omics technology to every level
and sharing bioinformatics



Importance of Translational Research

***Prototype
Design or***

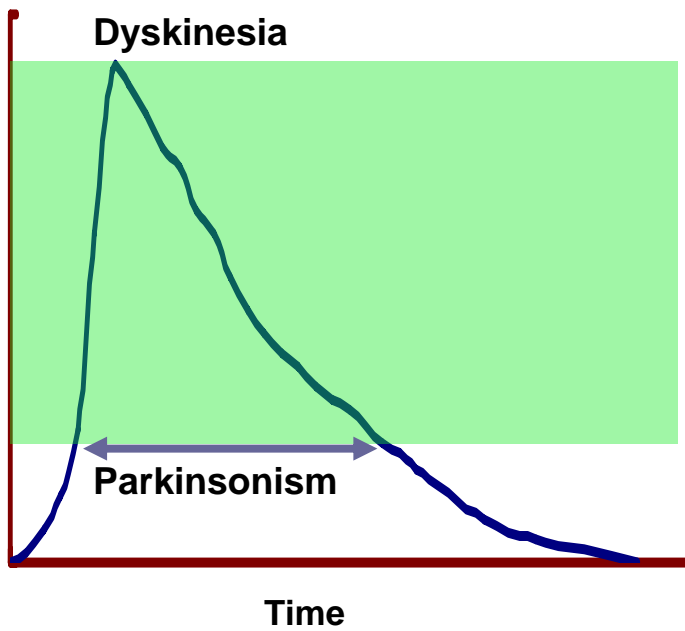


E2007

AMPA Receptor Antagonist

AMPA receptor: - amino- 3- hydroxy- 5- methyl –
4- isoxazolepropionic acid receptor.
Neurotoxicity is induced by glutamate,
a neurotransmitter

Characteristics of E2007



Plan

- **Parkinson's disease**

- Plan to submission in FY2007
- Phase III study is ongoing

Completed End-of-Phase II meeting with US FDA, initiate Phase III study in the US

- **Migraine Prophylaxis**

- Phase II b is ongoing
- Plan to complete POC study within FY2006

- **Epilepsy**

- Phase II b is ongoing
- Plan to complete POC study within FY2006

- **Multiple sclerosis**

- Plan to initiate Phase II b study

- **Development in Japan**

- Phase I is ongoing



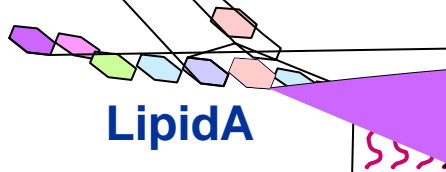
E5564

Endotoxin Antagonist

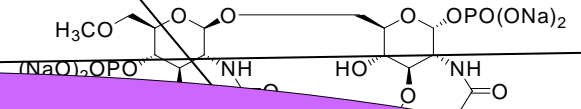
Mechanism of E5564 in TLR4 signal pathway



Endotoxin



LipidA

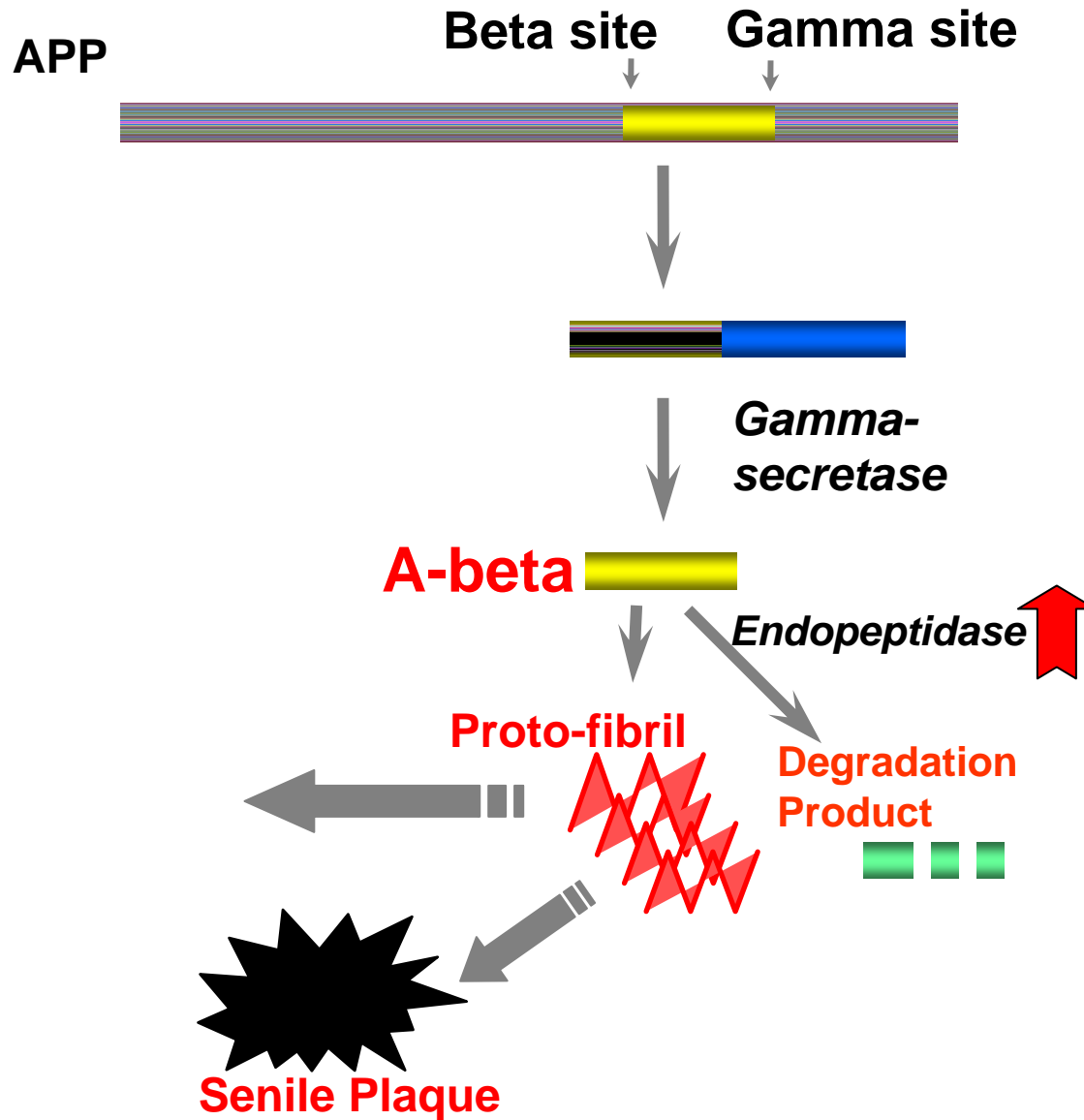


Plan

- E5564: Endotoxin Antagonist
(Plan to submission in FY2009)
 - Initiation of administration of US Phase III study for severe sepsis
 - Sites of the Phase III study are in the US, Europe, Japan, Asia, and Oceania, etc. – 250 sites in total will be opened
 - Plan to initiate Phase I study for Japanese population
 - Aim to submit NDA/MAA to the US, Europe and Japan simultaneously in FY2009

E2012

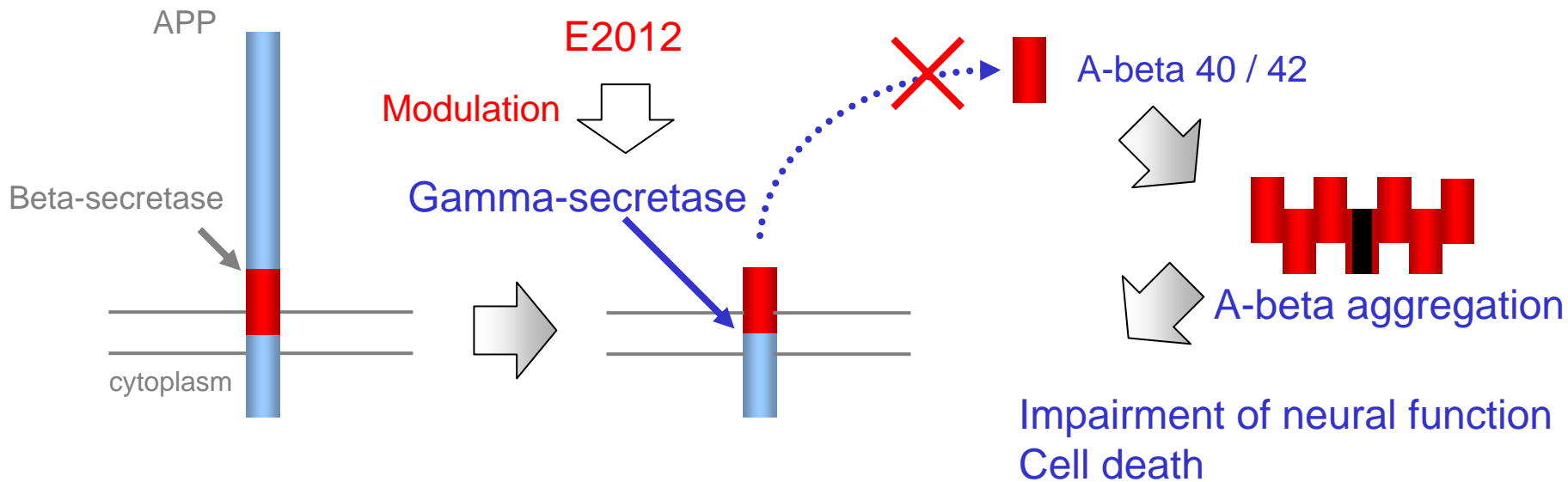
Approaches for AD Disease Modifier



E2012: Novel Gamma-secretase Modulator



Modulate gamma-secretase, enzyme to produce A-beta 40 and 42 in Alzheimer's Disease

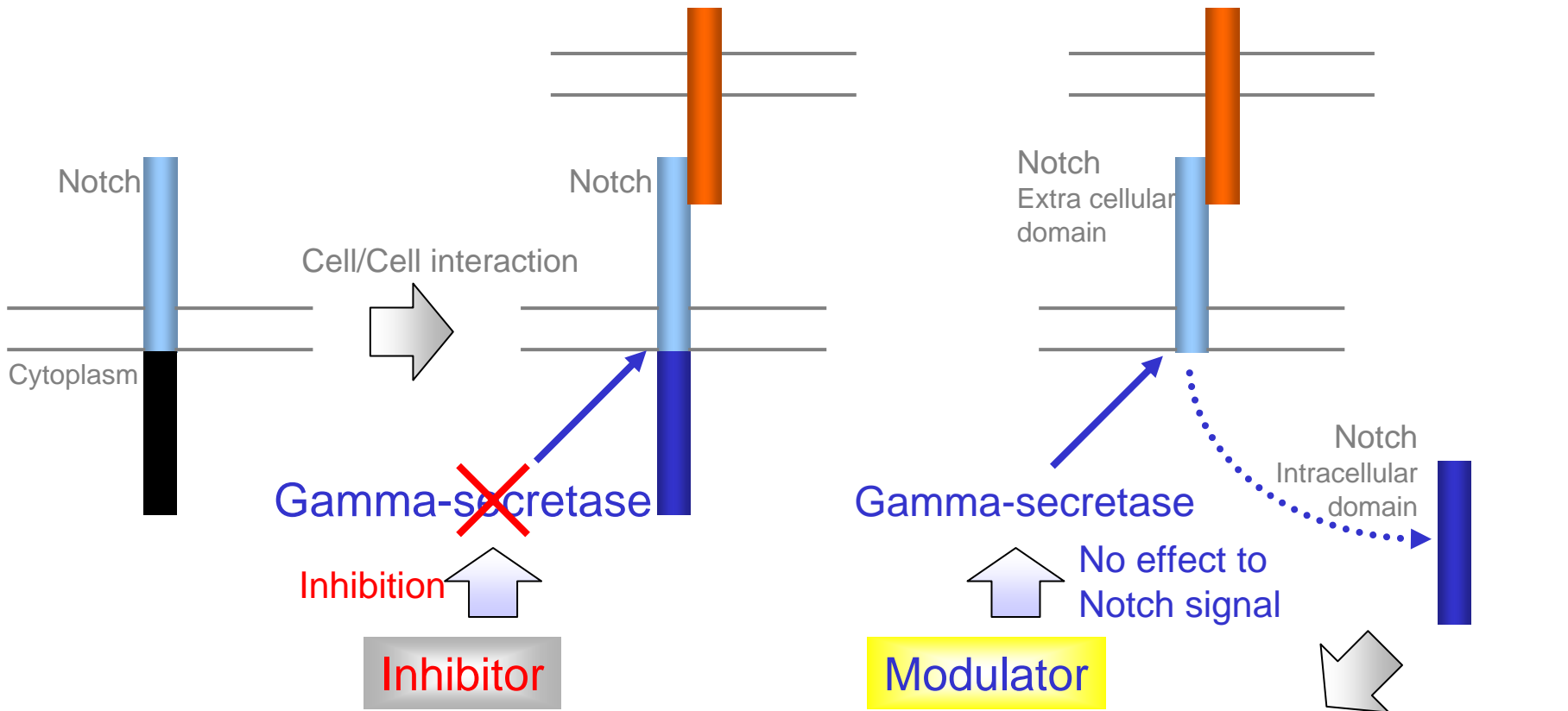


- E2012 was discovered from Eisai's original compound library
- Inhibition of A-beta 40/42 production in in-vivo model

Difference between "Modulator" and "Inhibitor"

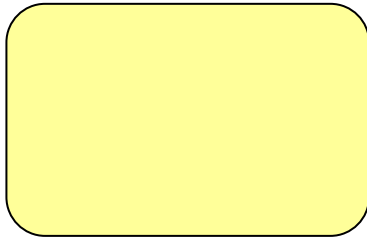
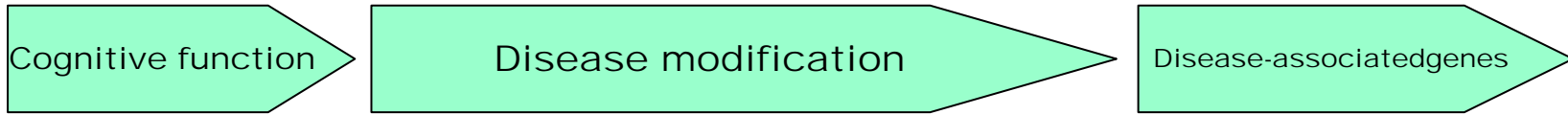
Modulator does not affect Notch processing



- No effect on normal cell differentiation -



Normal cell differentiation

Eisai's Approaches to AD



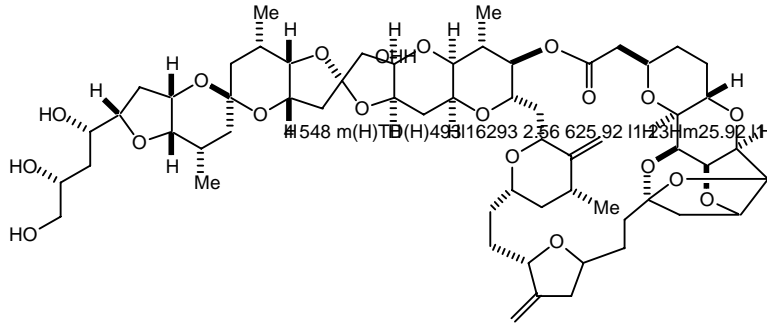


E7389

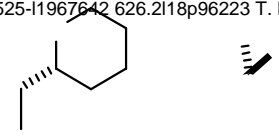
Microtubule Growth Suppressor



E7389: Microtubule Growth Suppressor



#548 m(H)T (H)49316293 2.56 625.92 111231m25.92 1177 286 u7 6223 Td(Me)Tj0Tc 625.92/74.5205. 1192.5.921174.525-11967642 626.2118p96223 T. 117.9 633.96 05967-2383293 2.56 625

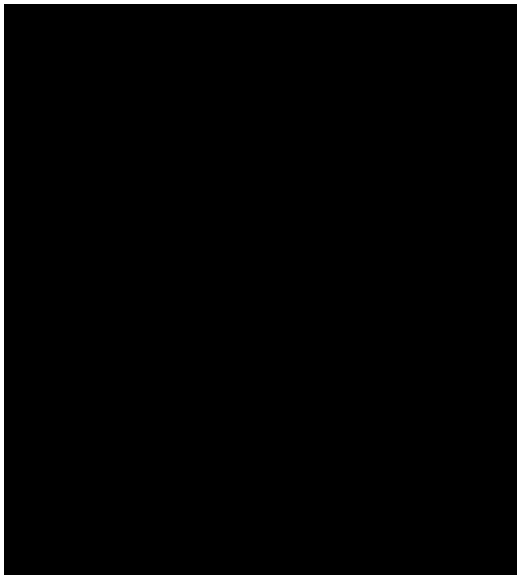




Taxol and E7389 have opposing effects on spindle microtubule dynamics

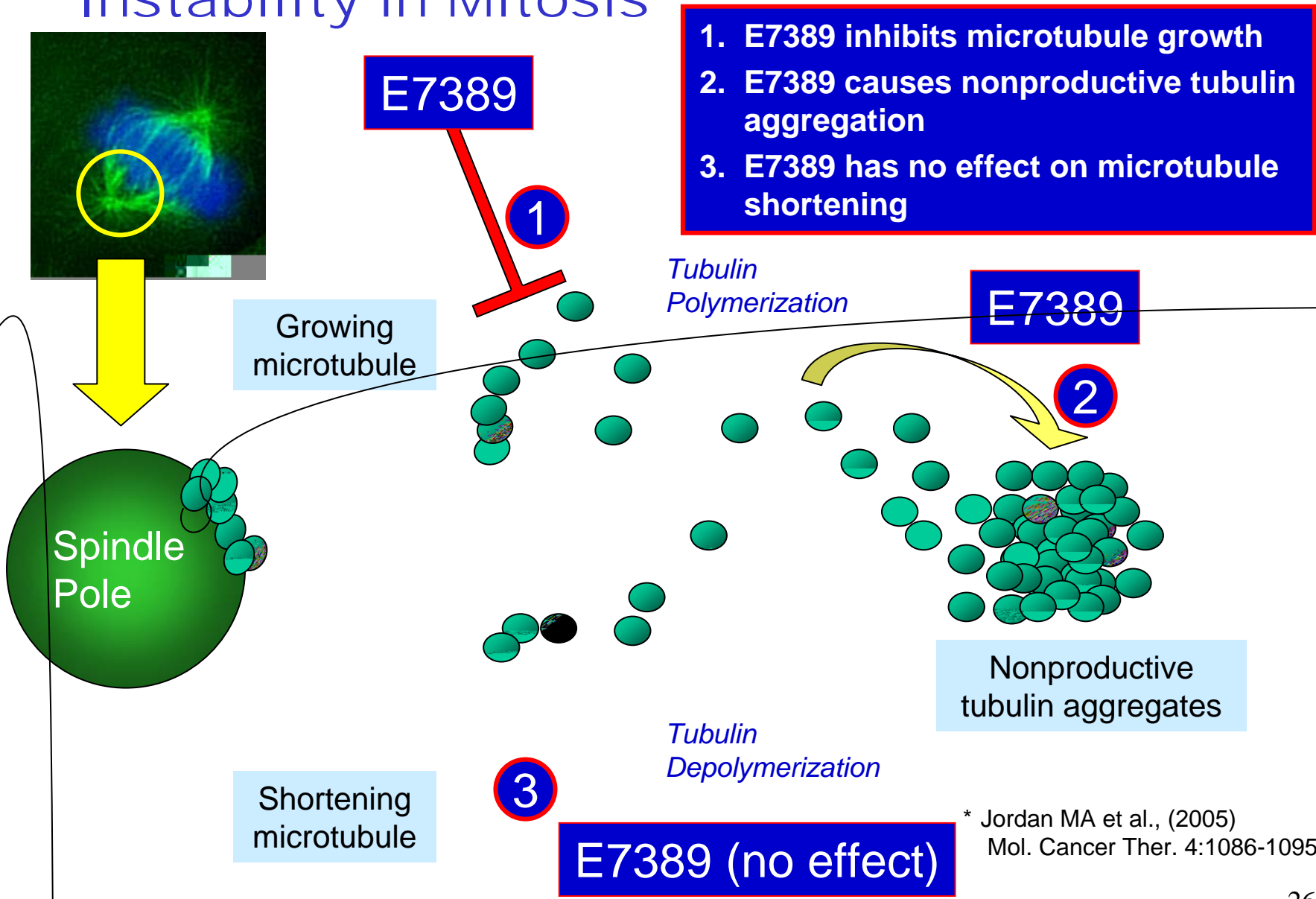
Taxol enhances spindle-microtubule polymerization.

E7389 induces spindle-microtubule shortening.



Green : microtubule
Blue : chromosome

E7389 Effects on Microtubule Dynamic Instability in Mitosis*





Establishing Oncology Franchise



Aiming to enter into oncology area

Examination in a project (1986)

After a research group starts, the policy is reexamined. (1987)

Aim to create candidates at the following three points.

- Novel action mechanism
- Novel chemical structure
- Strong effect for tumors *in vivo*



Our policy for oncology R&D

1. We do not research analogs of existing classes for which competitors accumulate lots of knowledge.
2. We aim what we can demonstrate unique advantages of our own research.
3. We setup a goal of improving survival rate and survival time when we start research programs.
4. We setup endpoints and efficacy criteria in animal models corresponding to the feature and the objectives of the theme.



Anti-cancer drug pipeline

1. E7010: Sulfonamide tubulin polymerization inhibitor (1987)
2. Topoisomerase II inhibitor (1991)
3. Farnesyl transferase inhibitor for ras, an oncogene product (1991)
4. E7070: Sulfonamide G1 phase targeting agent (1992)
5. E7820: Antiangiogenesis (1992)
6. E7389: Halichondrin-type microtubule growth suppressor (1992)
7. E6020: Vaccine adjuvant (1997)
8. E7974: Hemiasterlin-type microtubule polymerization inhibitor (1998)
9. E7080: Multi-kinase inhibitor, antiangiogenesis (1999)
10. E7107: Pladienolide, fermented derivative (2000)
11. Exxxx: Specific molecule targeting agent (2002)
12. Exxxx: Specific molecule targeting agent (2003)



E7070

targeting agent

- Different antitumor spectrum from epidermal growth factor receptor tyrosine kinase inhibitors, ca



7820

Oral Anti-angiogenesis

- Inhibits tube formation and proliferation of endothelial cells
- Tube formation inhibition is due to integrin alfa 2 expression inhibition
- Inhibits angiogenesis due to either VEGF or FGF
- Anti-proliferation activity in human pancreatic, breast, colorectal, and renal cancer cell xenograft model
- Anti-metastatic activity in human breast cancer xenograft model
- Synergic effect with anti-VEGF antibody and EGFR Kinase inhibitor

- Current status: Phase I ongoing in the US; long-term Stable Disease cases
- Future plan: Phase Ib combination study in preparation

E7080

Oral Anti-angiogenesis

- Inhibition of all VEGF receptor family (VEGFR1:Flt-1, VEGFR3:Flt-4), not only VEGFR2:KDR
- Inhibition of other angiogenesis-related molecules such as FGFR1 and PDGFRb, in addition to VEGFR family
- Inhibition of c-Kit, inhibition of proliferation of SCF-dependent small cell lung cancer
- Anti-proliferation activity against human colorectal, pancreatic, non-small cell lung, breast, ovarian, prostate and small cell lung cancers xenograft models; tumor regression in some models
- Current status: Phase I, Japan, US and Europe; investigation of biomarkers relevant to angiogenesis ongoing
- Future plan: Phase II monotherapy and Phase Ib combination studies in preparation



E7974

Hemiasterlin-type tubulin polymerization inhibitor

- Synthetic derivative of Hemiasterlin (marine natural product)
- Binds both alpha and beta subunits of tubulin – different from existing tubulin polymerization inhibitors
- Also effective against Multi-drug resistant tumors
- Current status: Phase I ongoing in the US
- Future plan: Phase II monotherapy and Phase Ib combination studies in preparation



Cell Cycle Related Proteins and Sensitivity



cell lines	pRB	p16	cyclinE	cyclinD1	T/C%	
BSY-1	■	+++	+++	+++	0	
MDA-MB468		++	+++	++	0	
LC-6-JCK		+++	+++	+	0	
OVCAR3		+++	+++	++	0	
NCI-H146		±	+++	+++	±	1
NCI-H69		++	+++	±	±	1
NCI-H526		+++	+++	±	±	1
PC-3	++		++	+++	2	
FaDu			±	+++	3	
WiDr			+++	+++	4	
HBC4	*			++	5	
Lu99	+++		±	±	8	
NCI-H510	■	+++		±	10	
NCI-H596	■	+++	+++		18	
KPL-4				+++	23	
SK-OV-3	+++		++	+++	27	
DU145	■		+++	++	28	
MDA-MB435	+++	++	++	+++	28	
HT-29				±	28	
SW620	+++			++	28	
NCI-H460	+++			±	33	
KM12	++			++	34	
NCI-H522			+++	+++	42	
DLD-1	++			+++	47	
Calu-1			++	++	55	





Approach for establishing oncology franchise

- Steady progression of clinical development of our pipeline
- Product acquisition of launched products
- In-license of antibodies
- Development of infrastructure of antibody research
- Establishment of Oncology Business Unit