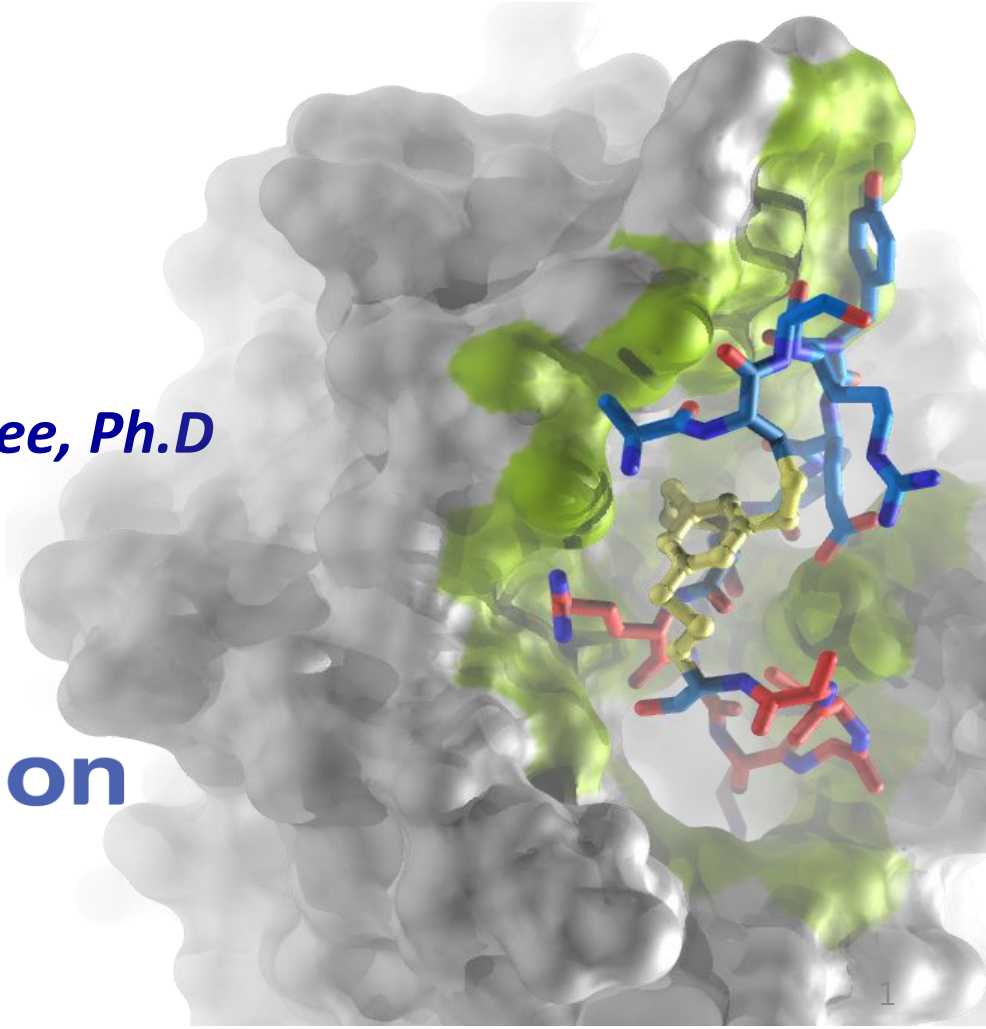
BioSynergy Antibody AC101 (1A12) in HER2+ Gastric Cancer

Jong-Seo Lee, Ph.D



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Your Hope We Keep

Antibody plants in Korea

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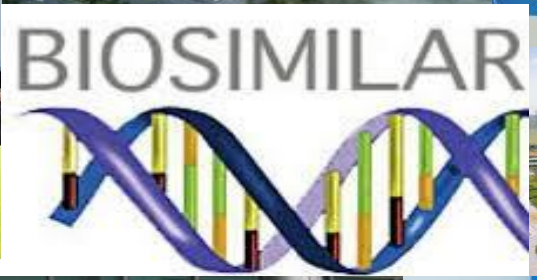
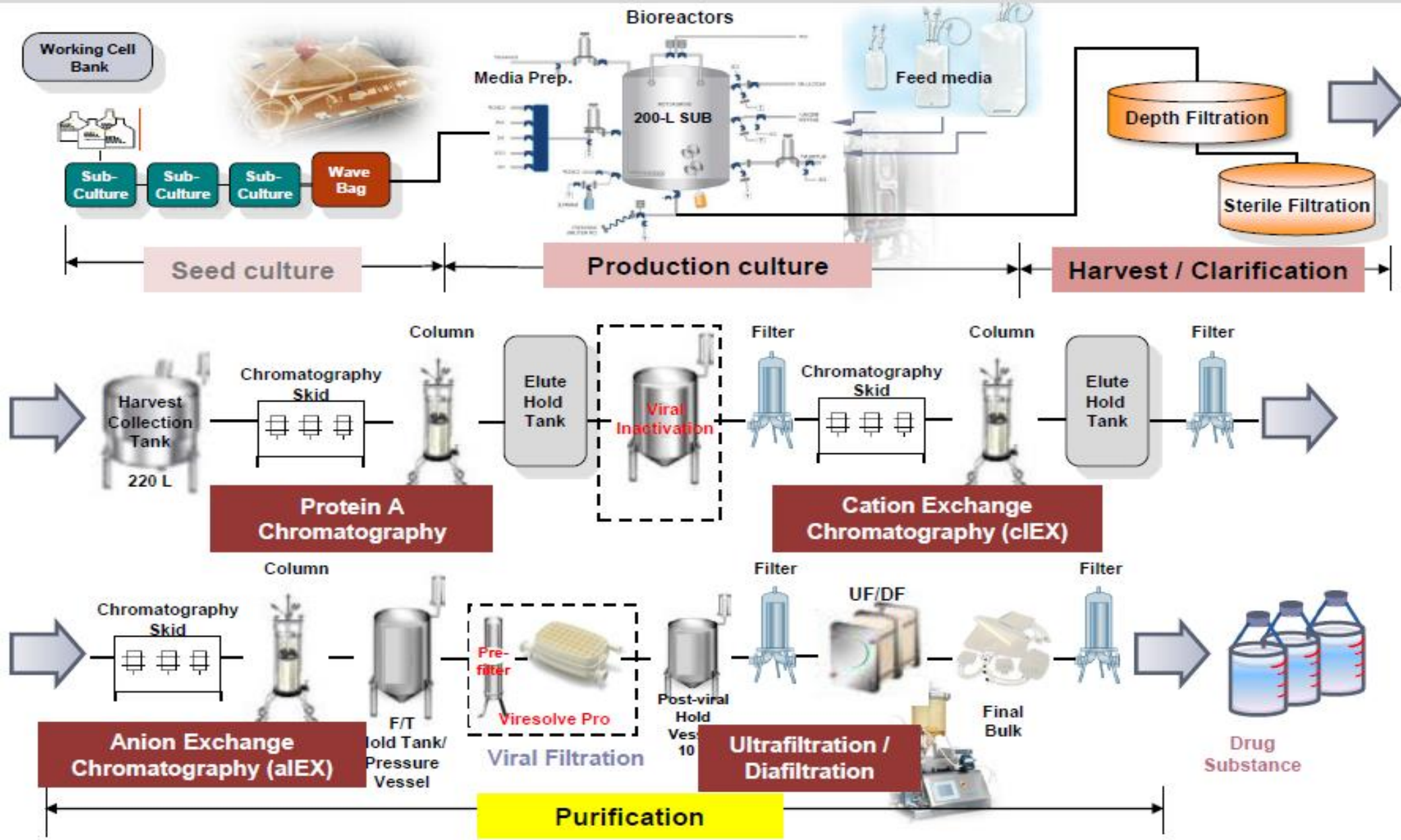
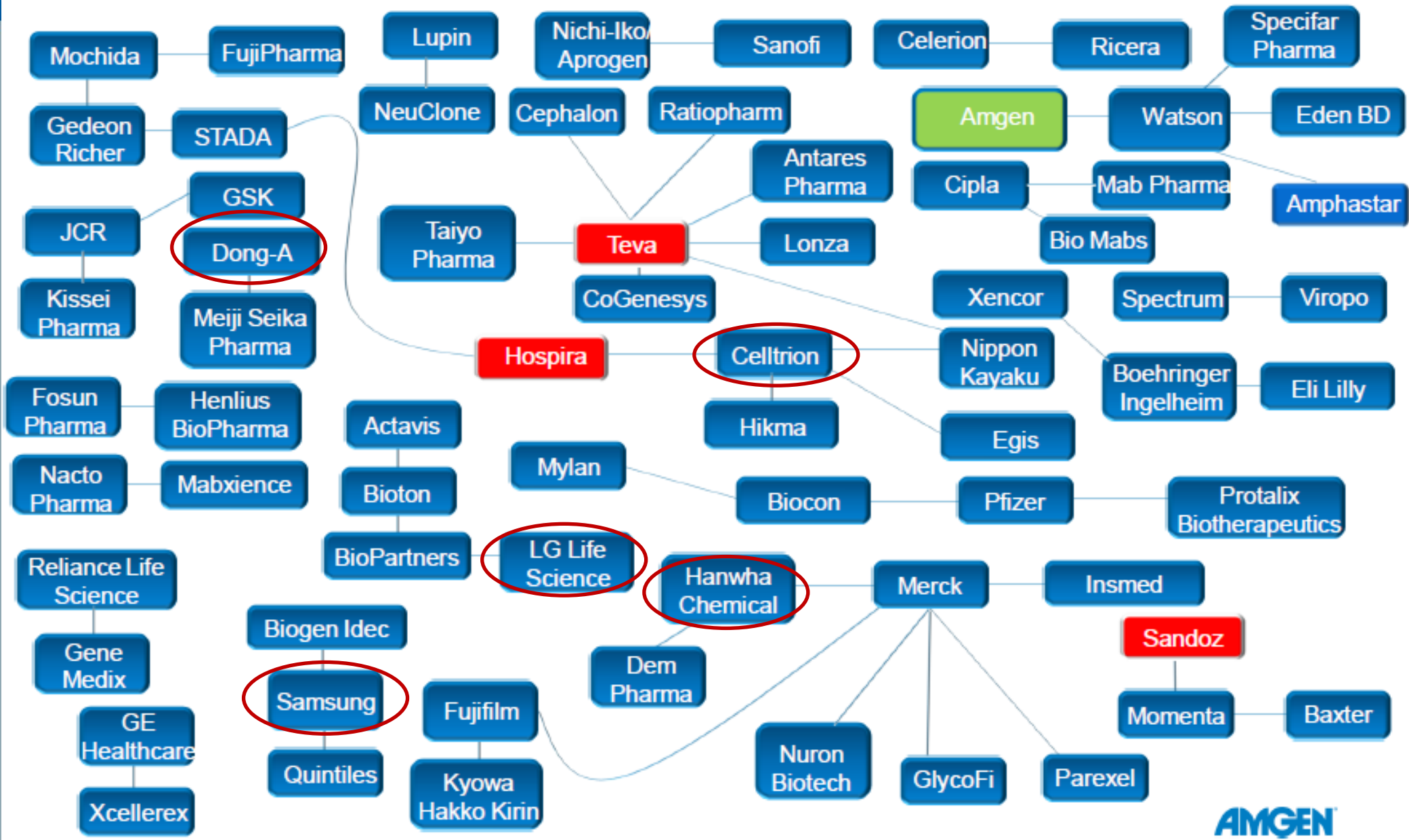
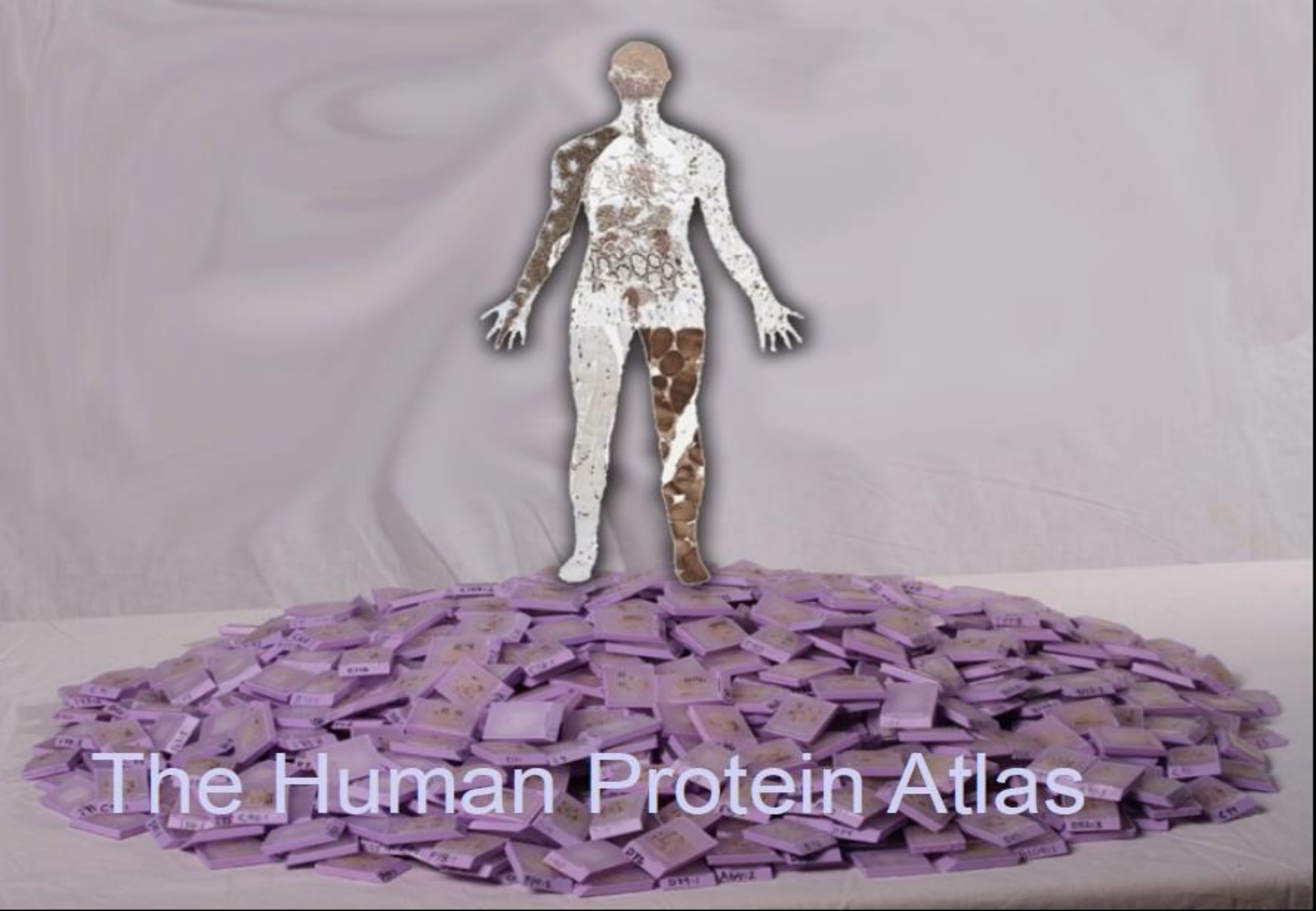


Process development



The EU biosimilars landscape is growing fast



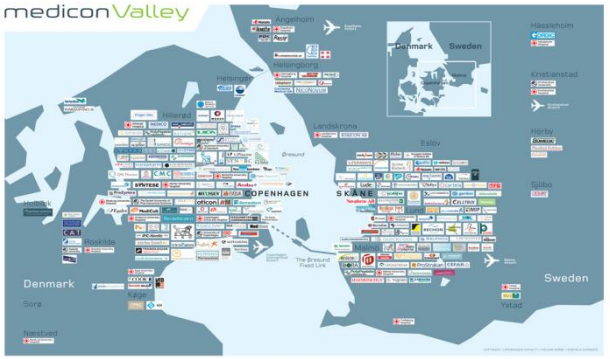

The Human Protein Atlas

AbClon Inc.

- Based in Seoul, KOREA
- 2010 founded by Korean & Swedish Scientists
  Mathias Uhlen, Carl Borrebaeck and Atlas Antibodies
- Jong-Seo Lee, CEO
- 40 employees
- 20 Million USD invested
- Under Listed Examination Standard in Seoul, KOSDAQ

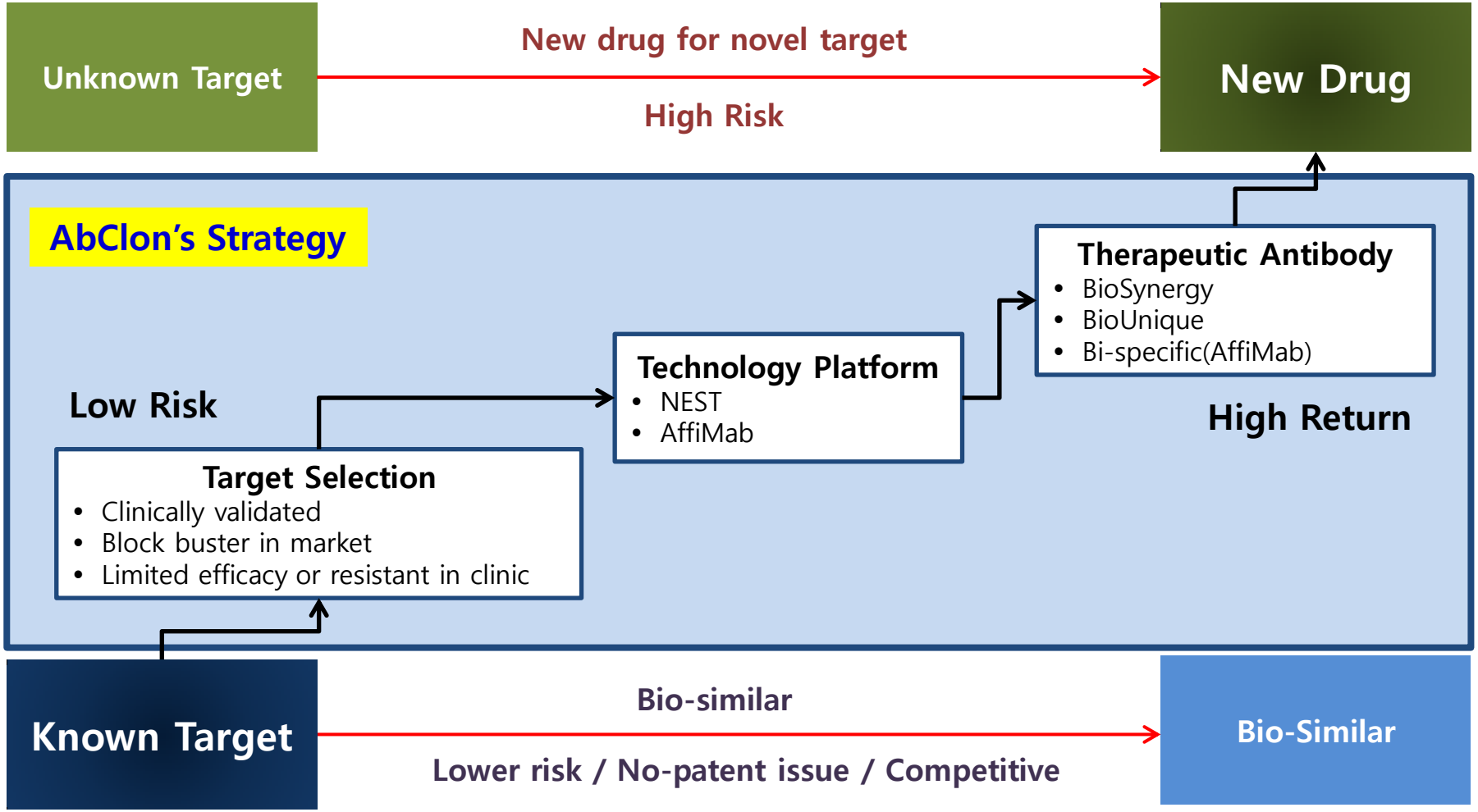
R&D programs, Business:

- Development of Biosynergic ACMab with Alligator Bioscience
- Development of AffiMab with Affibody
- Co-development of therapeutic Antibodies with partners
- Antibody services and reagents for research and development
- ADDs (Advanced Drug Discovery supports)



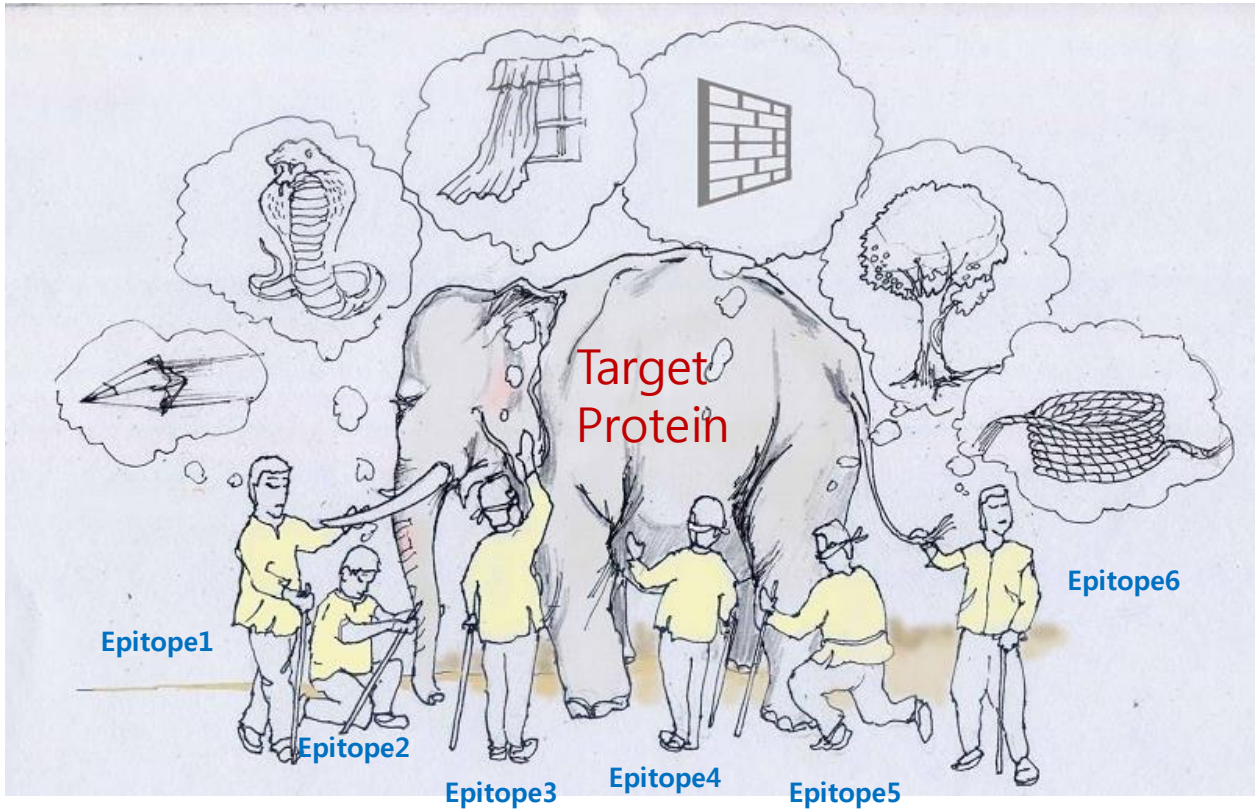
Strategy for drug development

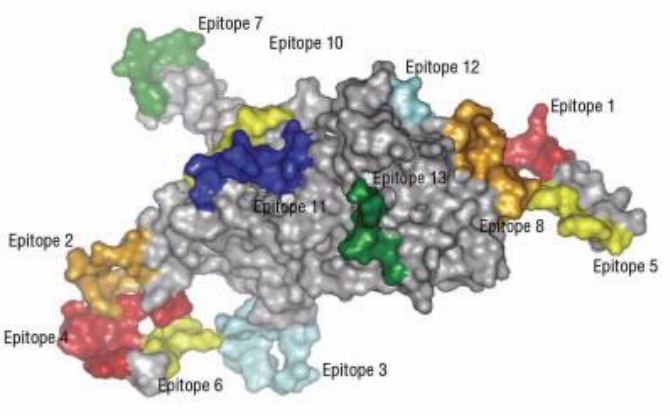
■ Strategy for Novel Therapeutic Antibodies: Novel Epitope Discovery from Clinically Validated Target

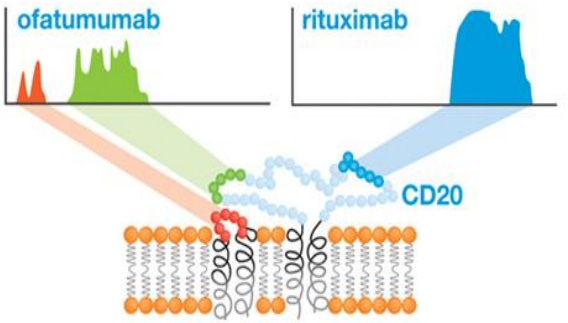


Development Strategy

■ **Different epitope ? → Different Effect !**

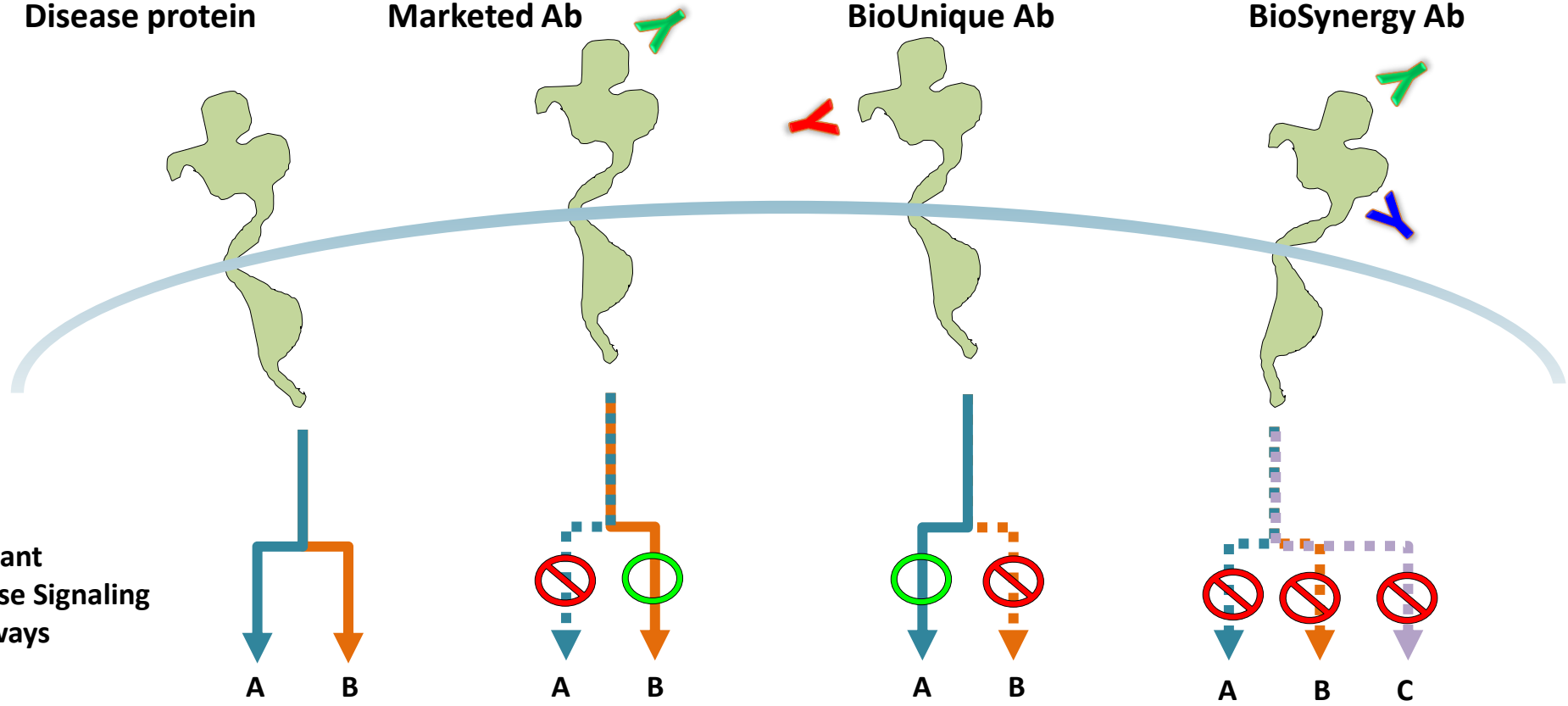




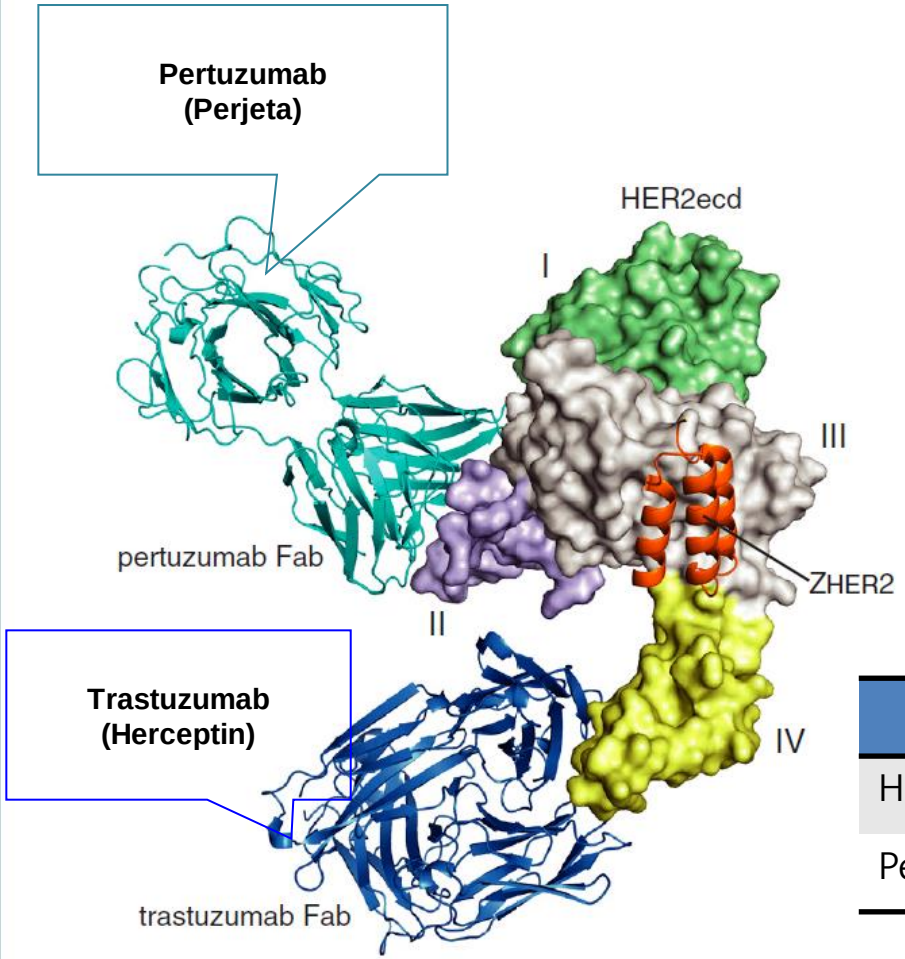


Concept of BioSynergy Ab

BioSynergy Ab can meet the unmet-medical needs



Different Epitope, Different Effect



(Eigenbrot C et al., Proc Natl Acad Sci U S A. (2010) 107(34):15039-44)

- **DEDE: Different Epitope Different Effect**
- **Therapeutic antibodies have frequently distinct mode-of-action according to their epitopes.**
- **Herceptin (trastuzumab) binding to domain-IV region of HER2, and its 2010 sales was 6 billion USD**
- **Perjeta (pertuzumab) binding to domain-II region of HER2, and its sales expected sales are 500 million ~ 2 billion US$.**

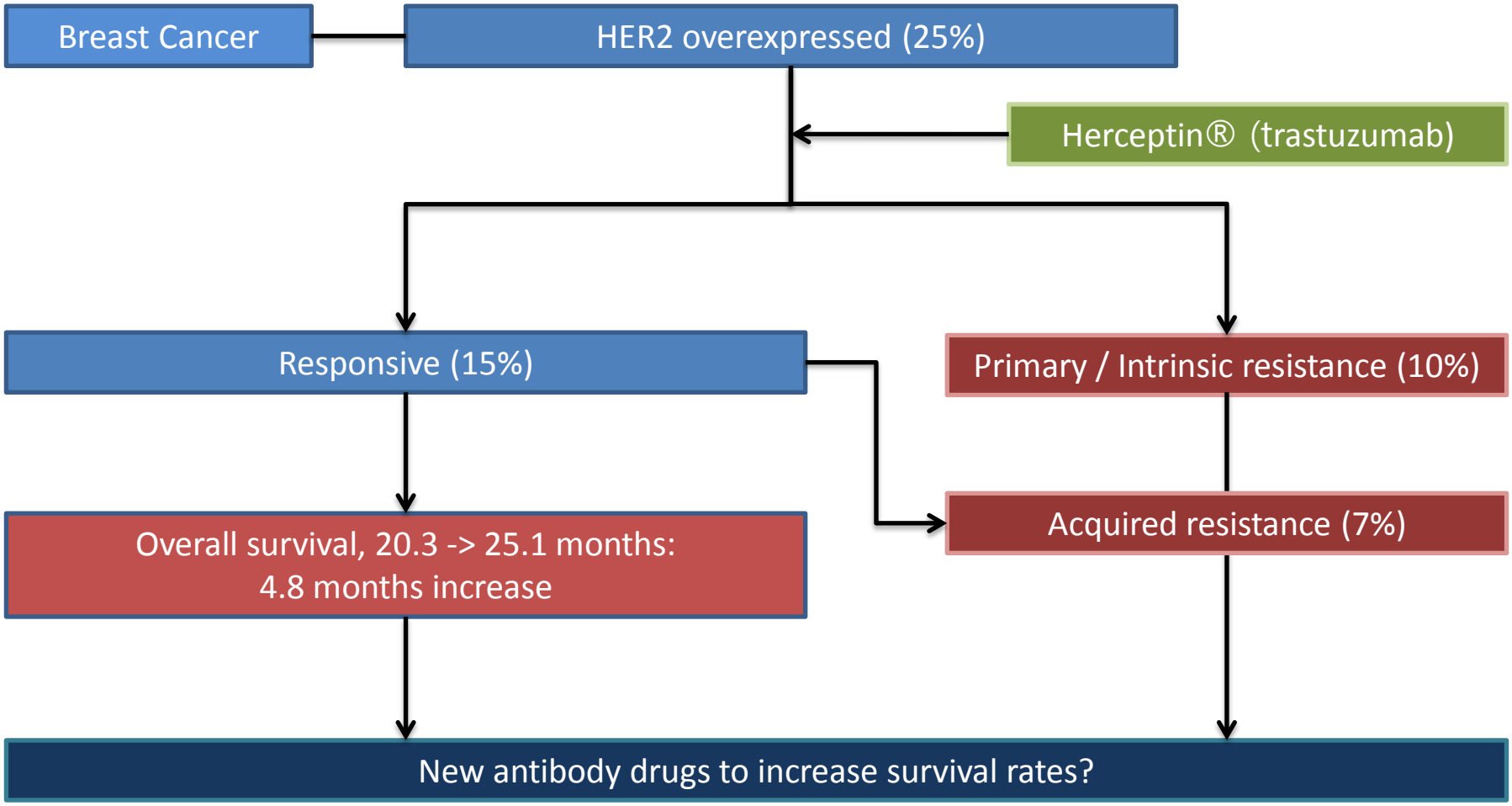
Consensus outlook for Herceptin and Perjeta ($m)

	2014	2015	2016	2017	2018	2019	2020
Herceptin	6939	6611	6104	5447	5306	4070	3476
Perjeta	816	1327	1851	2640	3363	4875	5532

www.firstwordpharma.com, source: Bloomberg

Existing HER2 therapy has limited efficacy in breast cancers

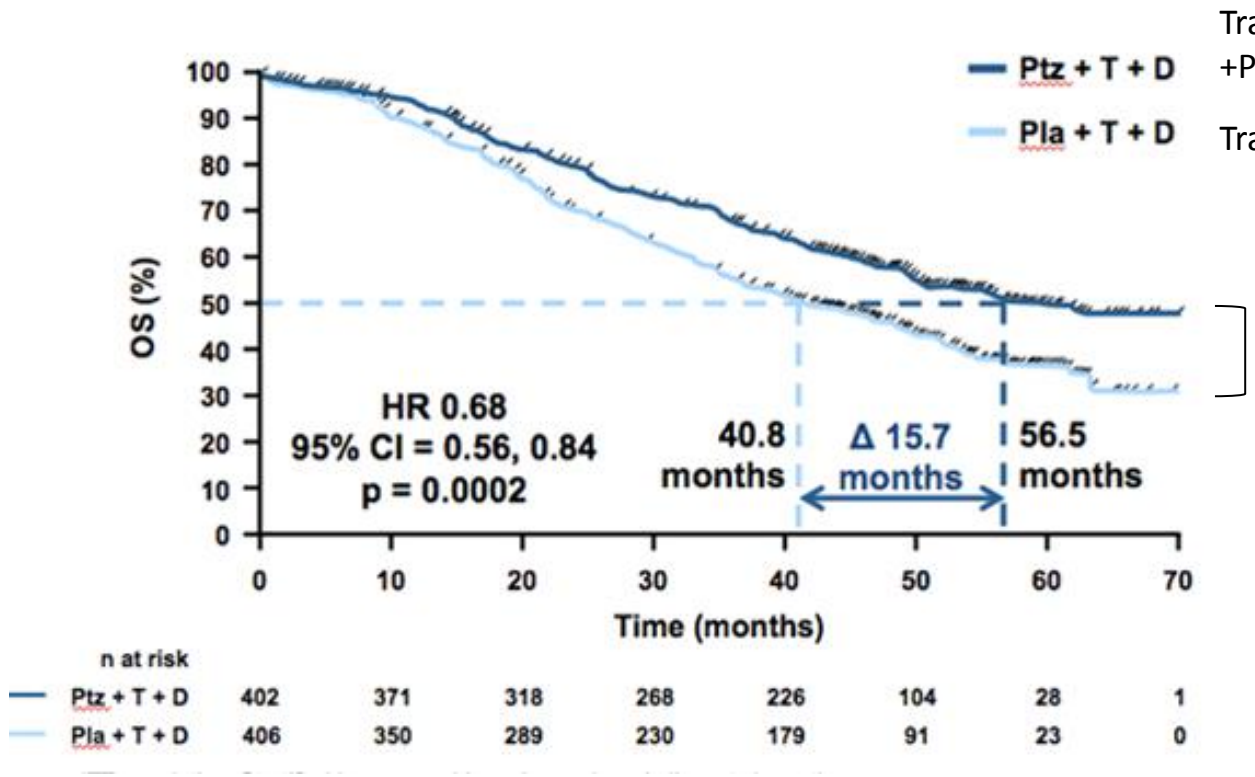
■ **Unmet medical needs: monotherapy of Herceptin against breast cancer**



Advance in treatment has combined two antibodies targeting different HER2 domains

■ CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab)

- **Both pertuzumab and trastuzumab target HER2, but different epitopes.**
- **Combination treatment of pertuzumab and trastuzumab increase survival rate of HER2 positive breast cancer patients.**



Trastuzumab+chemo +Pertuzumab

Trastuzumab+chemo

http://www.cancernetwork.com/conference-report/top-8-highlights-esmo-2014-congress

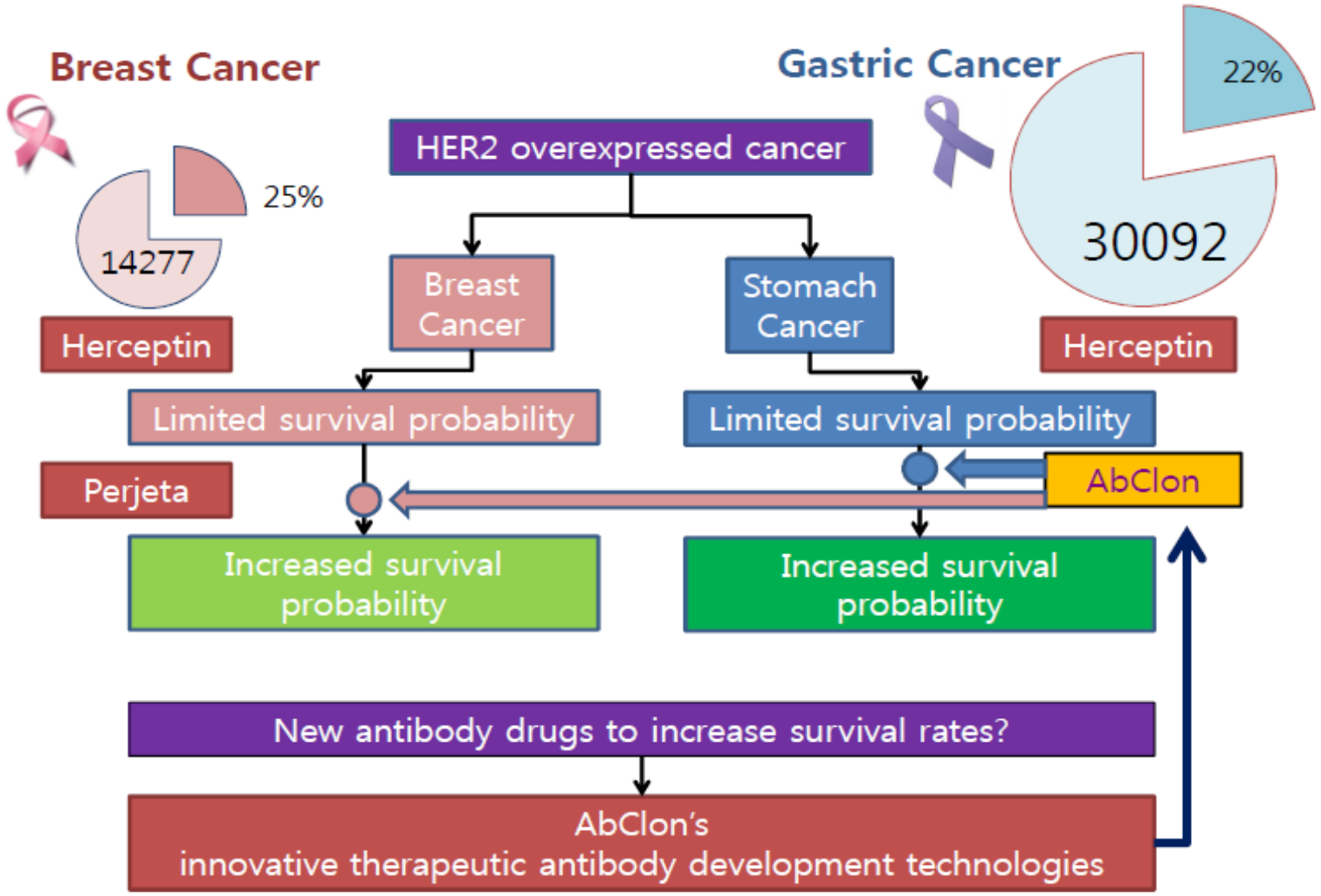
HER2 is over-expressed in gastric cancer

- Gastric cancer (GS) is a major global health problem.
  - 1 million new cases of gastroesophageal and gastric cancer are diagnosed annually.
  - The third leading cancer cause of death globally.
  - 1st or 2nd cancer incidence in Asia including Korea, Japan, China.

- HER2 positive rate in gastric cancer: 22% (n=3,667) FISH/IHC
  - ToGA trial
  - HER2 is associated with bad prognosis in gastric cancer.

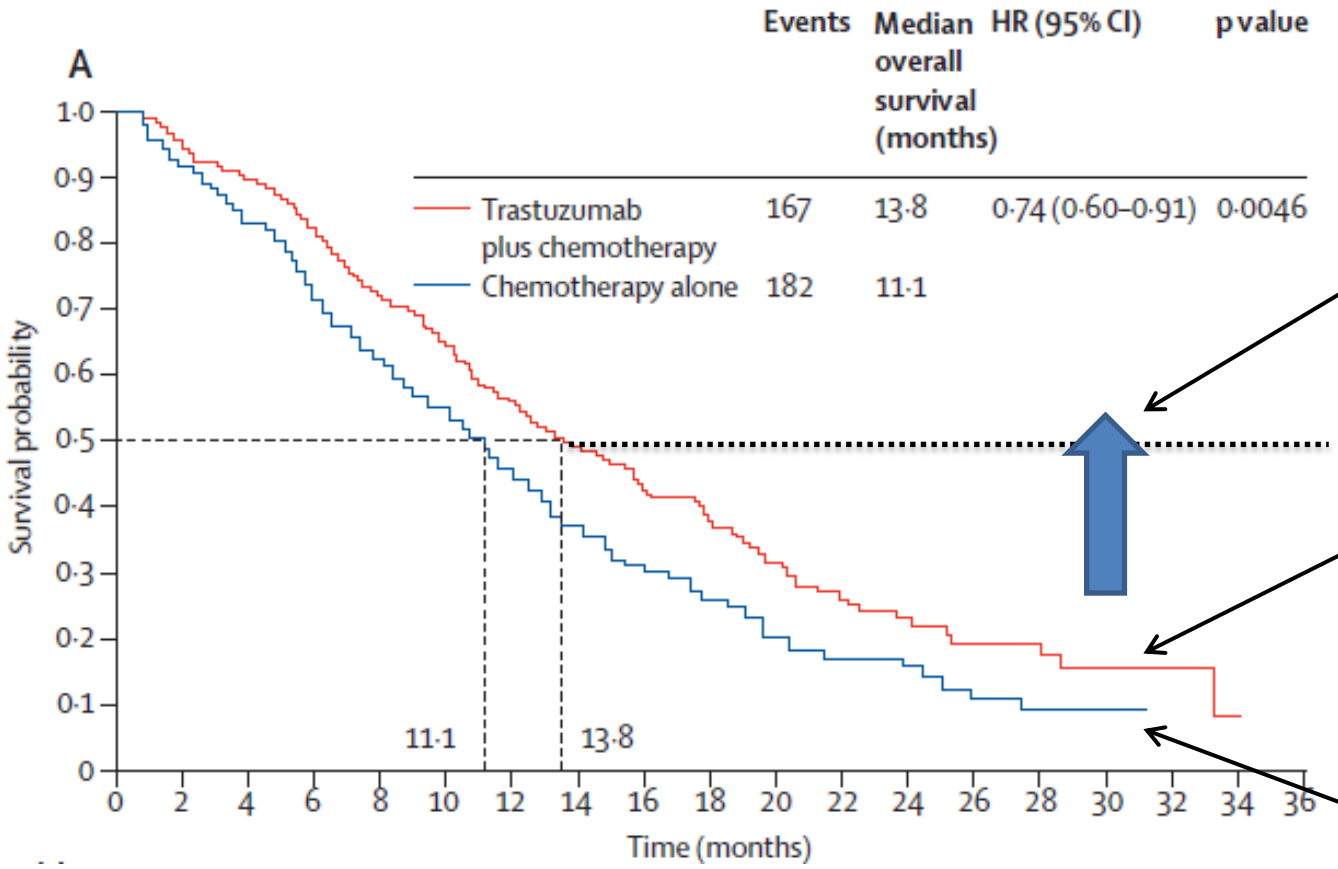
- FDA approves Herceptin for HER2-positive metastatic gastric cancer
  - Combination with chemotherapy (cisplatin or 5-fluorouracil [5-FU]) for HER2-positive metastatic cancer of the stomach or gastroesophageal junction.

HER2 Biosynergy Ab.



Targeting of HER2 in GC

■ **ToGA (trastuzumab with chemotherapy in HER2-positive advanced Gastric Cancer) initiate approval of Herceptin for GC whilst it has limitation.**



Chemo+ trastuzumab+ new antibody drug ?

Chemo+ trastuzumab

Chemo only

Bang YJ et al. (2010) Lancet. 376(9742):687-97

NEST Platform

Old: Select, group.

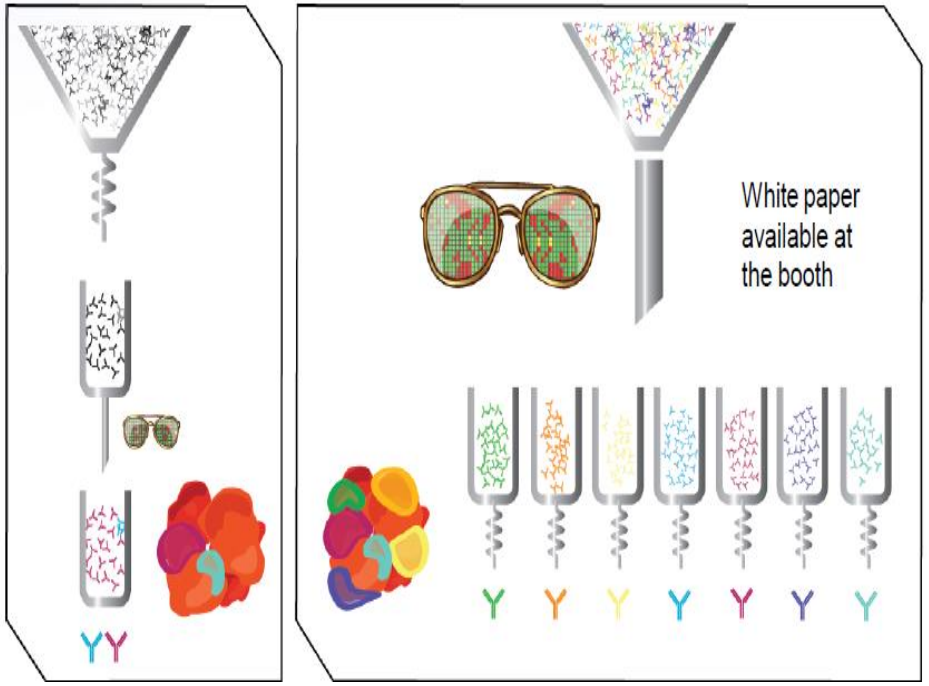
Epitope bias?

Functional epitope?

New: Group, select.

Maximize diversity.

Function correlates with epitope.



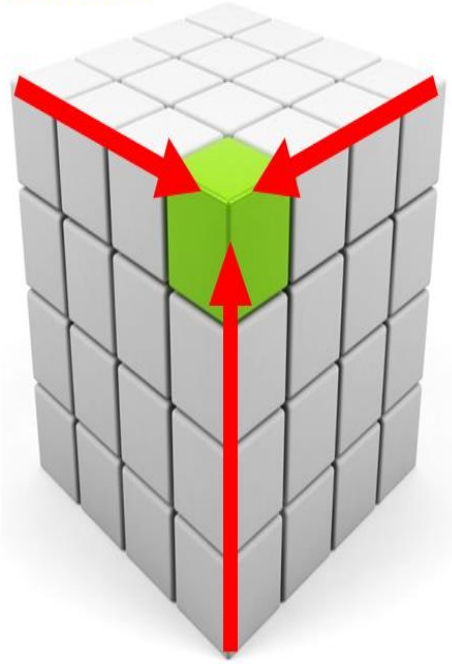
Y_{PLUS}:

Priority to Patents

Unique to Pharmaceutics

Efficacy
(Pharmacological window)

- Single/combination treatment
- Cell line profiling (sensitive & resistant)
- Matrix



Interaction
(Biochemical window)

- Affinity ranking
- Specificity
- Simultaneous binding
- Epitope binning
- Epitope mapping

Mode-of-Action
(Biological window)

- Neutralization
- Cell signaling
- Apoptosis
- Cell cycle arrest
- ADCC/CDC

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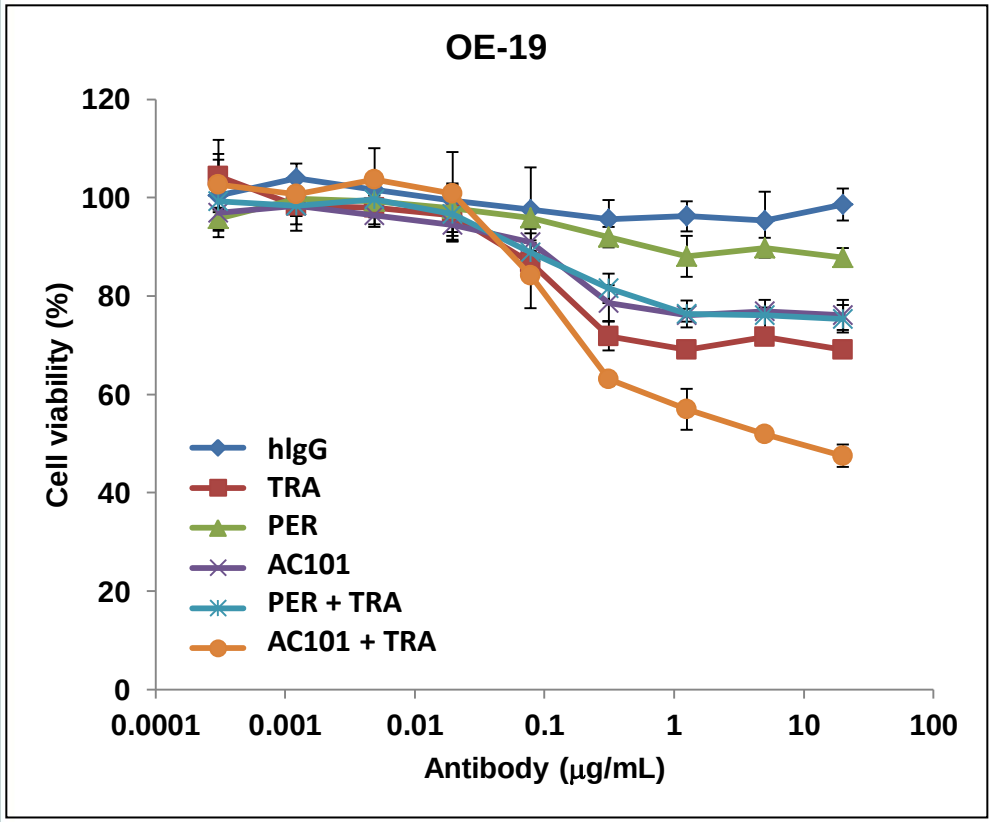
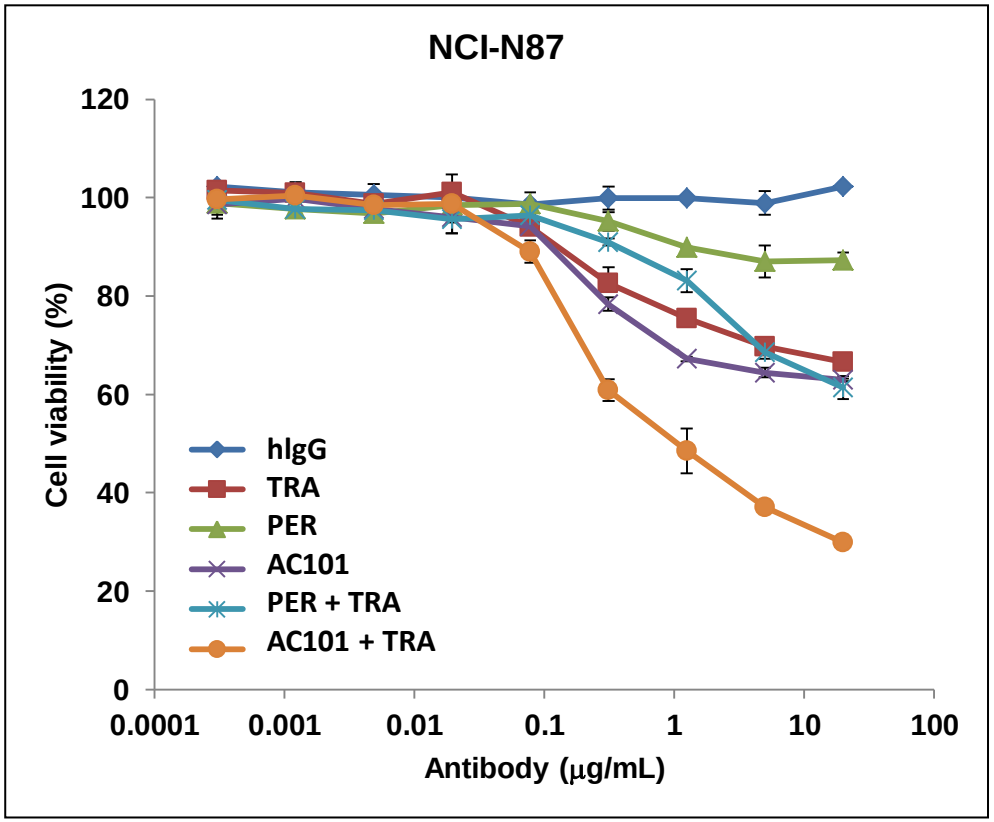
AC101(1A12) to Her2 positive

In vitro efficacy in gastric cancer cells

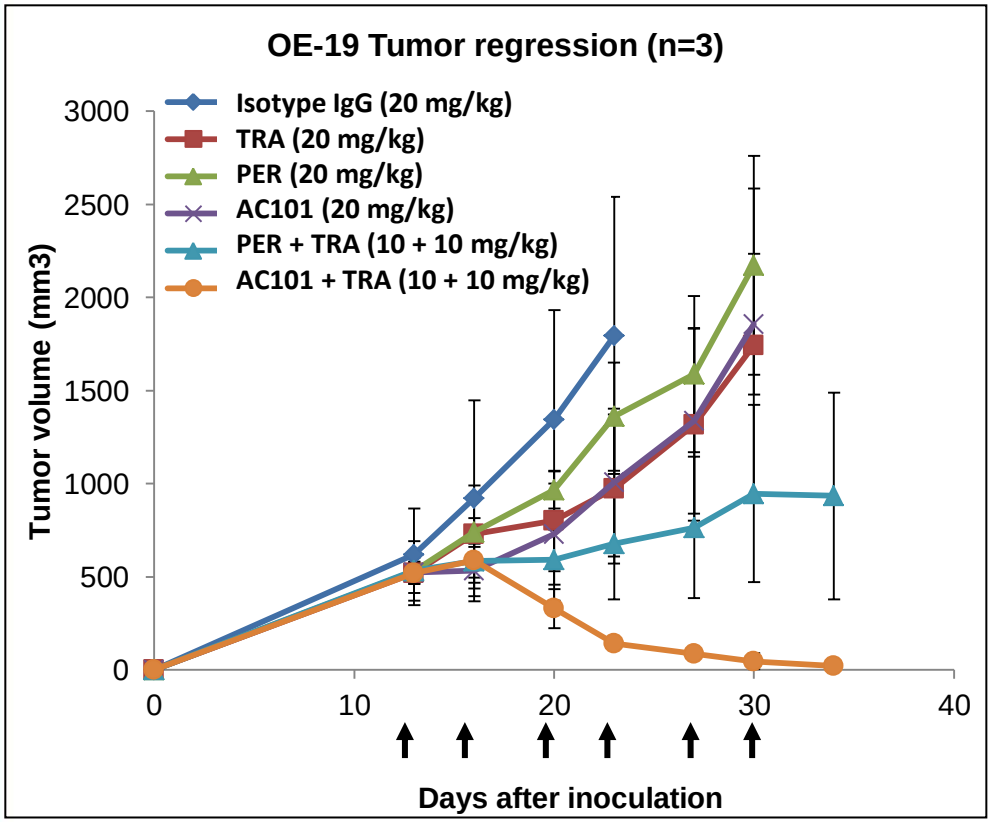
- Antitumor activity of AC101 in HER2-overexpressing gastric cancers
- Cell viability assay in OE-19 and NCI-N87

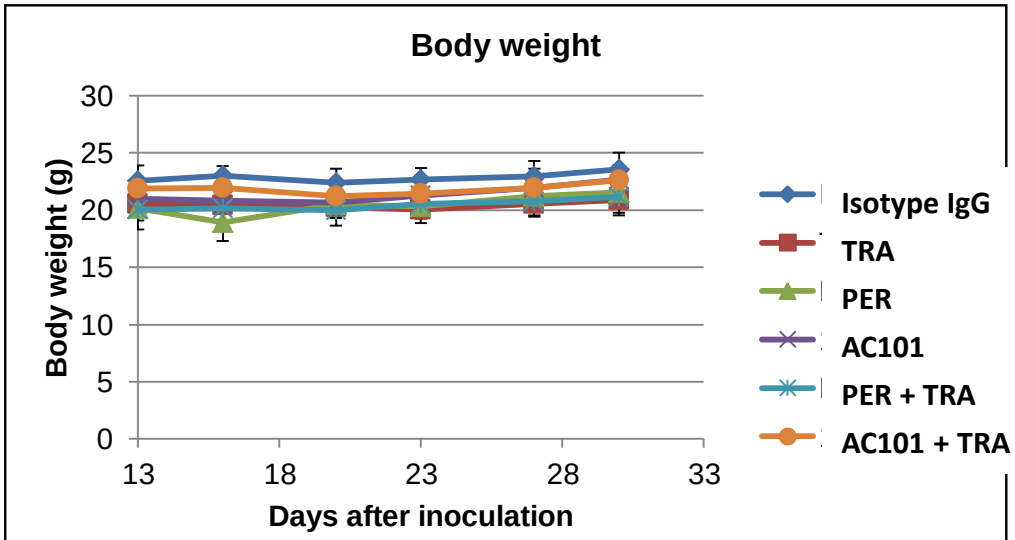




In vivo efficacy: OE-19

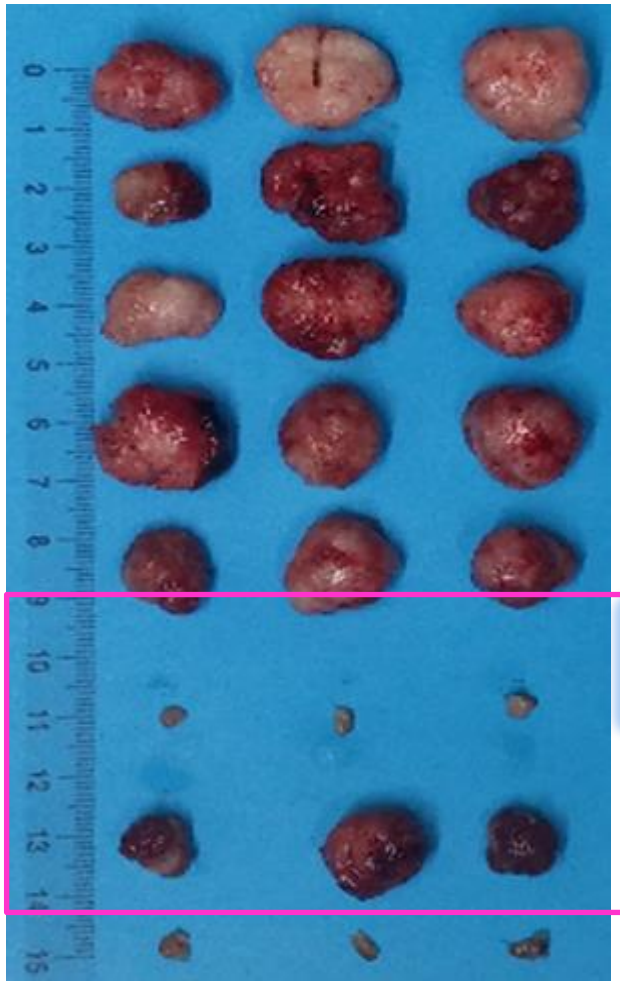
- Antitumor activity of AC101 in OE-19 xenograft model (i.p, two times a week for 3 weeks)
- Monitoring of tumor growth and body weight





Tumor Growth Inhibition(%)				
TRA	PER	AC101	PER + TRA	AC101 + TRA
61.6 %	29.4 %	59.0 %	87.7 %	132.2 %

In vivo Efficacy: OE-19

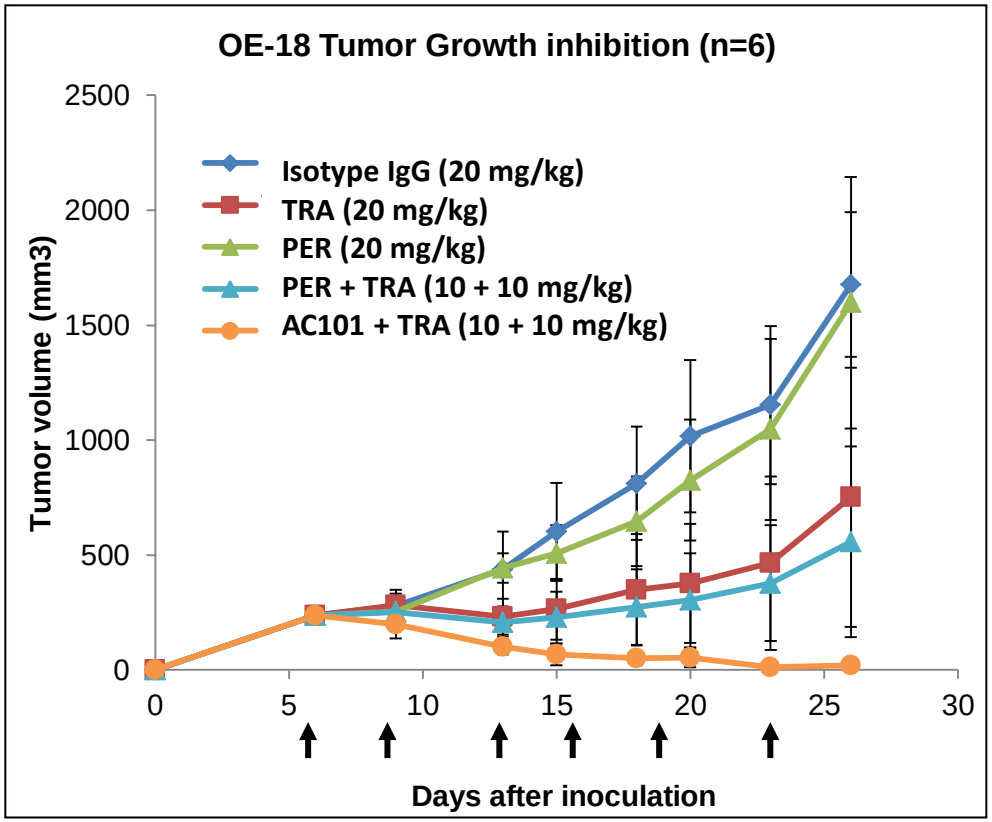


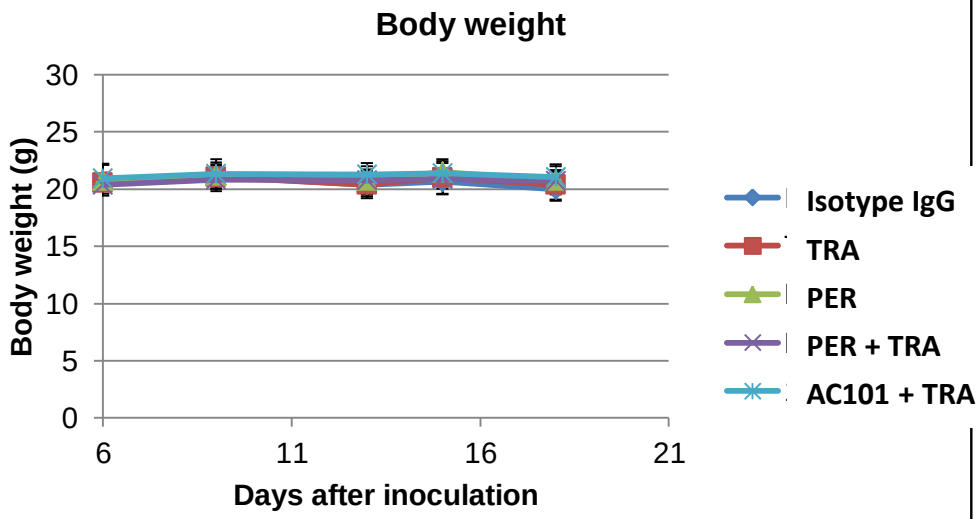
- Tumor mass: OE-19, HER2 positive gastric cancer cells.
- Injection point: 500 mm^3.
- Combination of Herceptin and AC101 reduce tumor mass in 21 days.
- Combination of Herceptin and AC101 is superior to Herceptin, Perjeta and the combination of these two antibodies.

* 1F11: another affinity-matured clone

In vivo Efficacy: OE-19

- Antitumor activity of AC101 in OE-19 xenograft model (i.p, two times a week for 3 weeks)
- Monitoring of tumor growth and body weight



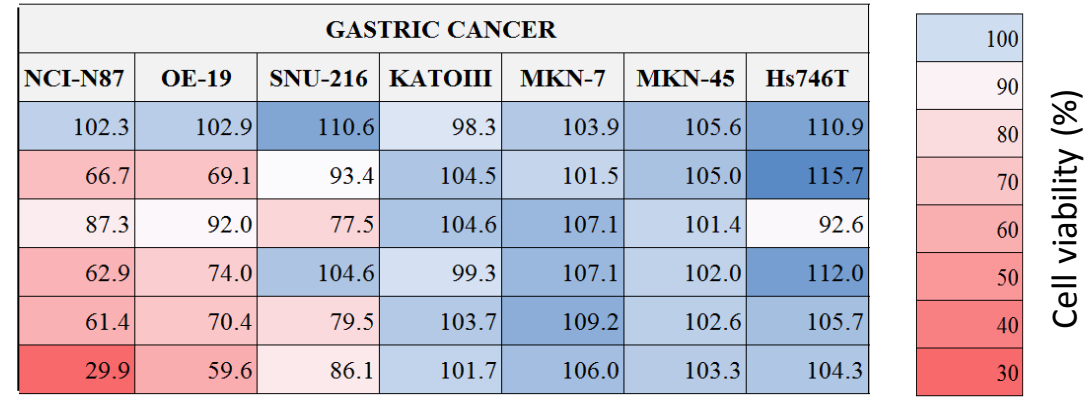


TGI (%)				
TRA	PER	AC101	PER + TRA	AC101 + TRA
64.3 %	5.5 %	N.A.	77.9 %	115.1 %

In vitro efficacy profile: gastric cancer cells

- Established human gastric cancer cell panel
- Cell viability assay & ErbB expression

	GASTRIC CANCER						
	NCI-N87	OE-19	SNU-216	KATOIII	MKN-7	MKN-45	Hs746T
hIgG	102.3	102.9	110.6	98.3	103.9	105.6	110.9
TRA	66.7	69.1	93.4	104.5	101.5	105.0	115.7
PER	87.3	92.0	77.5	104.6	107.1	101.4	92.6
AC101	62.9	74.0	104.6	99.3	107.1	102.0	112.0
PER + TRA	61.4	70.4	79.5	103.7	109.2	102.6	105.7
AC101 + TRA	29.9	59.6	86.1	101.7	106.0	103.3	104.3



Efficacy:
Combination with chemotherapy

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In vitro efficacy

Unpublished data

- Combination with chemotherapy

Efficacy against breast cancer

In vitro profile: Breast Cancer Cells

Unpublished data

- **AC101 could overcome the trastuzumab-resistance in HCC-202**

Efficacy against breast cancer

In vitro efficacy: breast cancer

Unpublished data

- Anti-proliferative activity of AC101 in TRA-resistant breast cancers

Mode-of-action: Affinity

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■ **AC101 has the highest affinity (lowest Kd) among HER2 binders.**

Clone	Ka (1/Ms)	Kd (1/s)	KD (M)
TRA (trastuzumab)	4.90E+04	1.50E-04	3.00E-09
PER (pertuzumab)	3.80E+04	1.20E-04	3.30E-09
hz1E11	3.60E+04	8.30E-04	2.30E-08
AC101	**6.40E+04**	**9.90E-05**	**1.50E-09**

Mode-of-action: Specificity

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Epitope

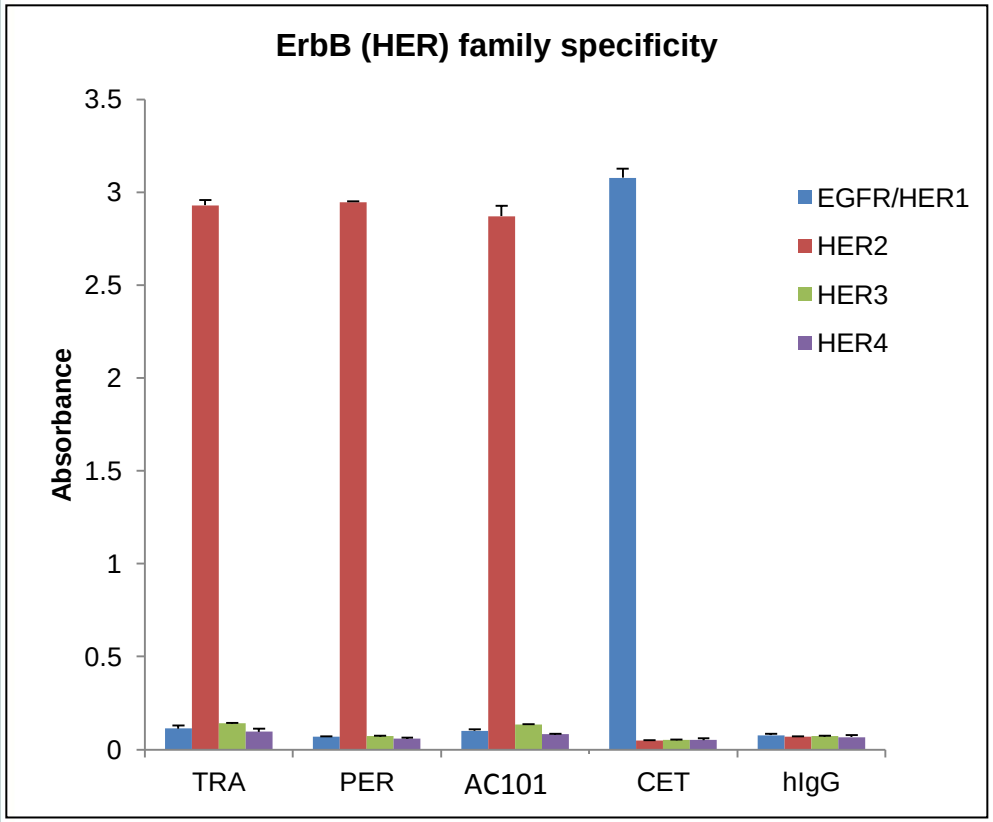
Unpublished data

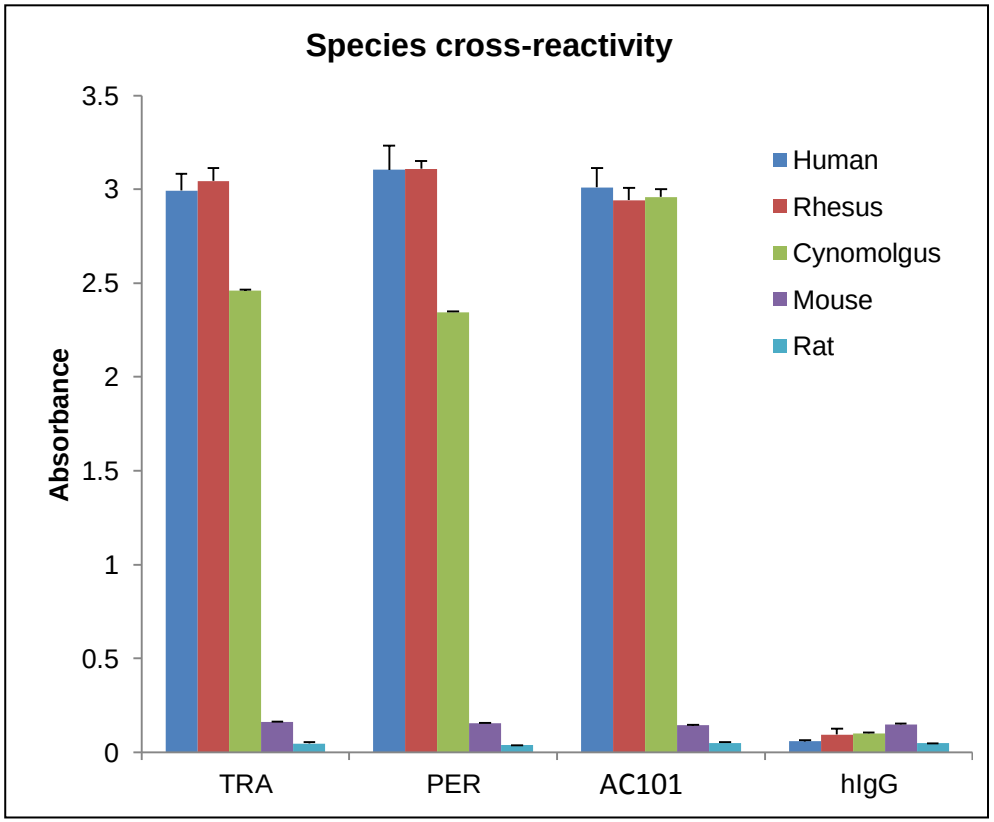
- Sub-domain IV, simultaneous binding with trastuzumab, conformational epitope

MoA: Specificity

HER family and Species cross-reactivity

- **Specificity: HER2-specific binding in ErbB family**
- **Species cross-reactivity: cross-reactive with monkey but not with rodent HER2s**

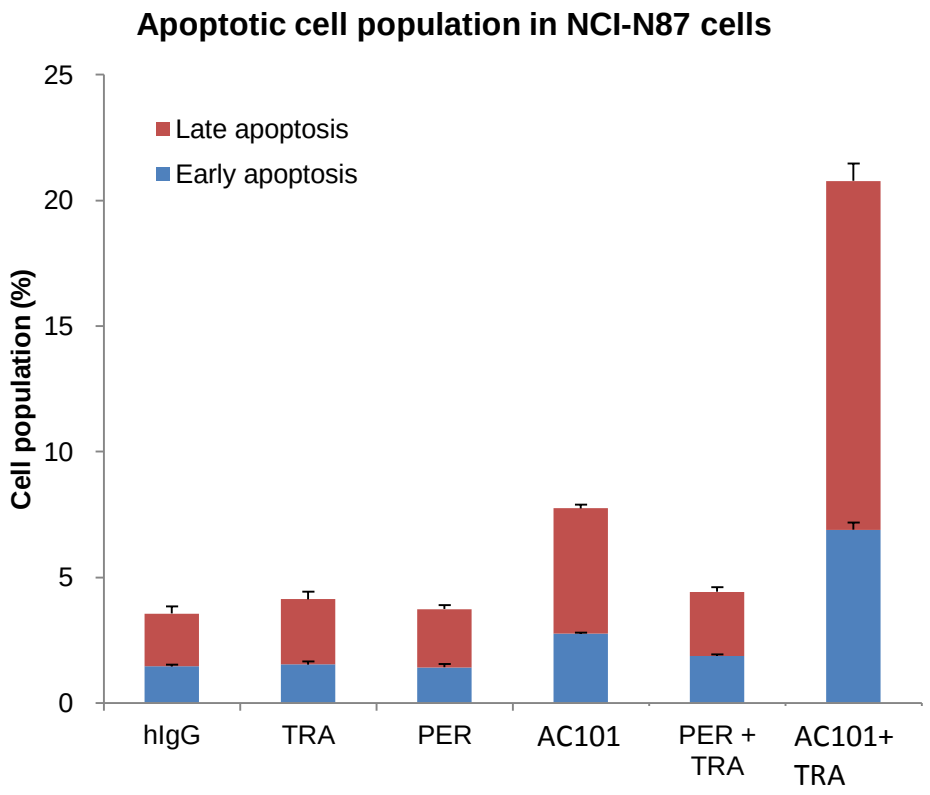


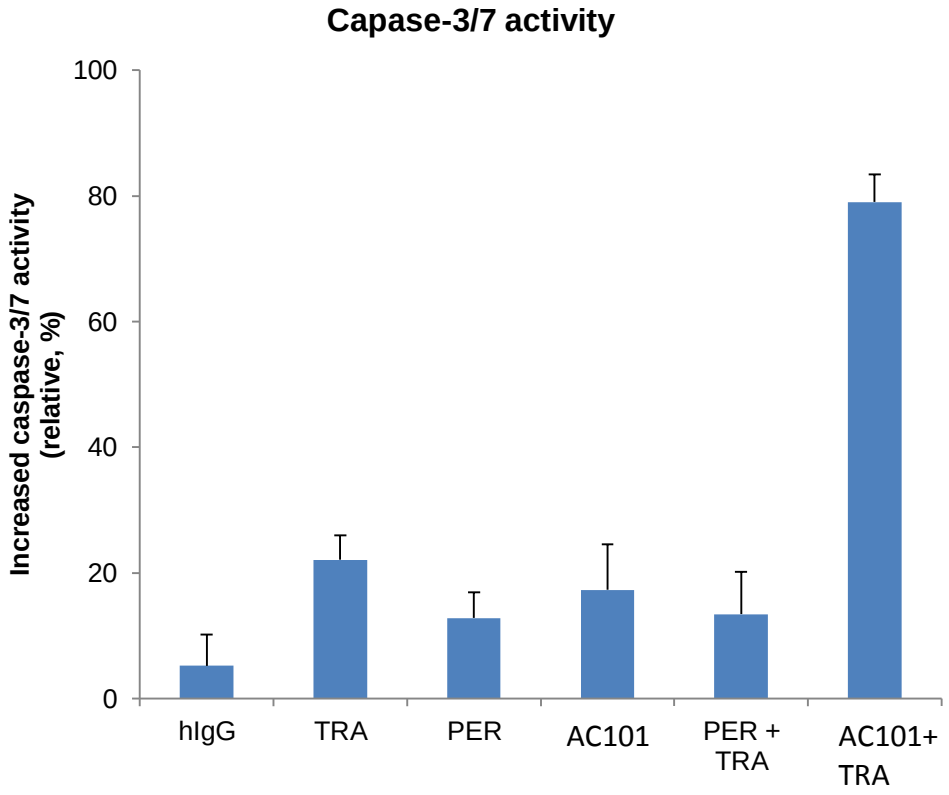


MoA: Apoptosis

Apoptosis (in vitro)

- AC101 induces apoptosis in HER2-positive NCI-N87 gastric cancer
- Flow cytometry analysis (PI & Annexin-V staining) & Caspase-3/7 activity

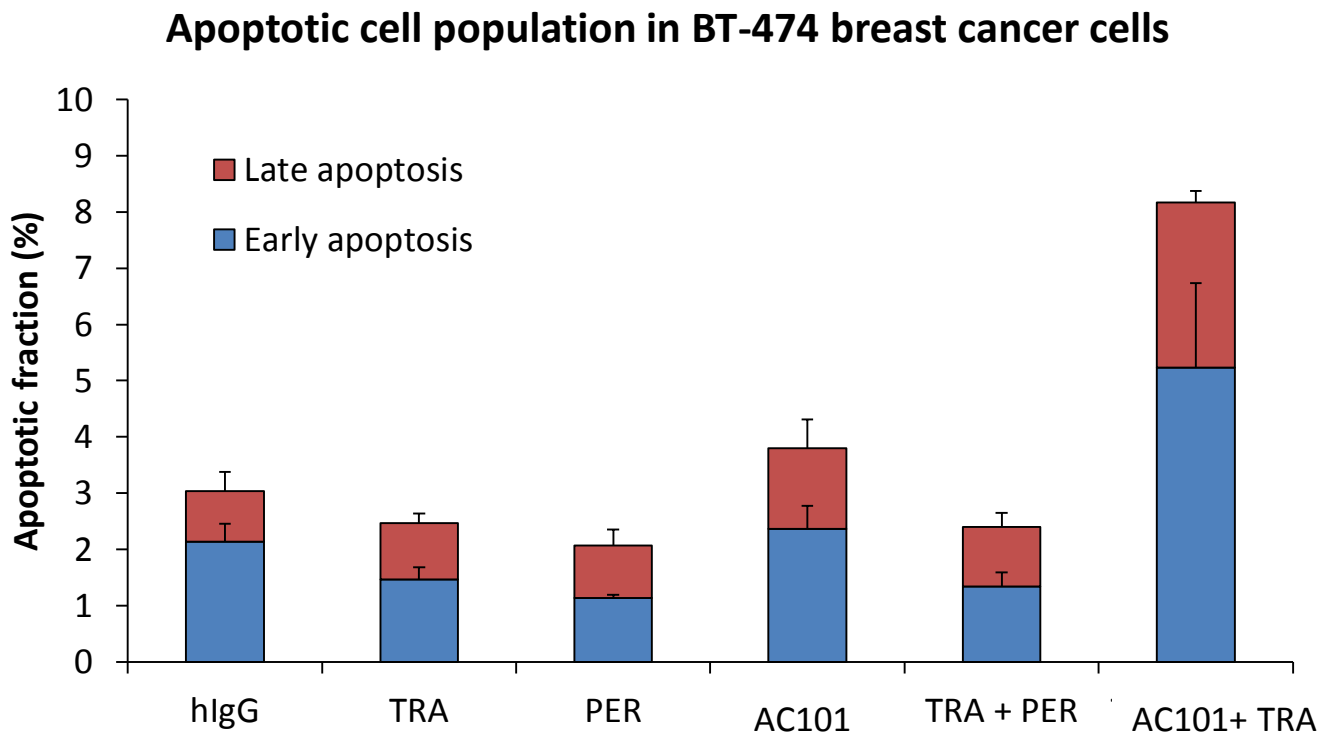




MoA: Apoptosis

Apoptosis (in vitro)

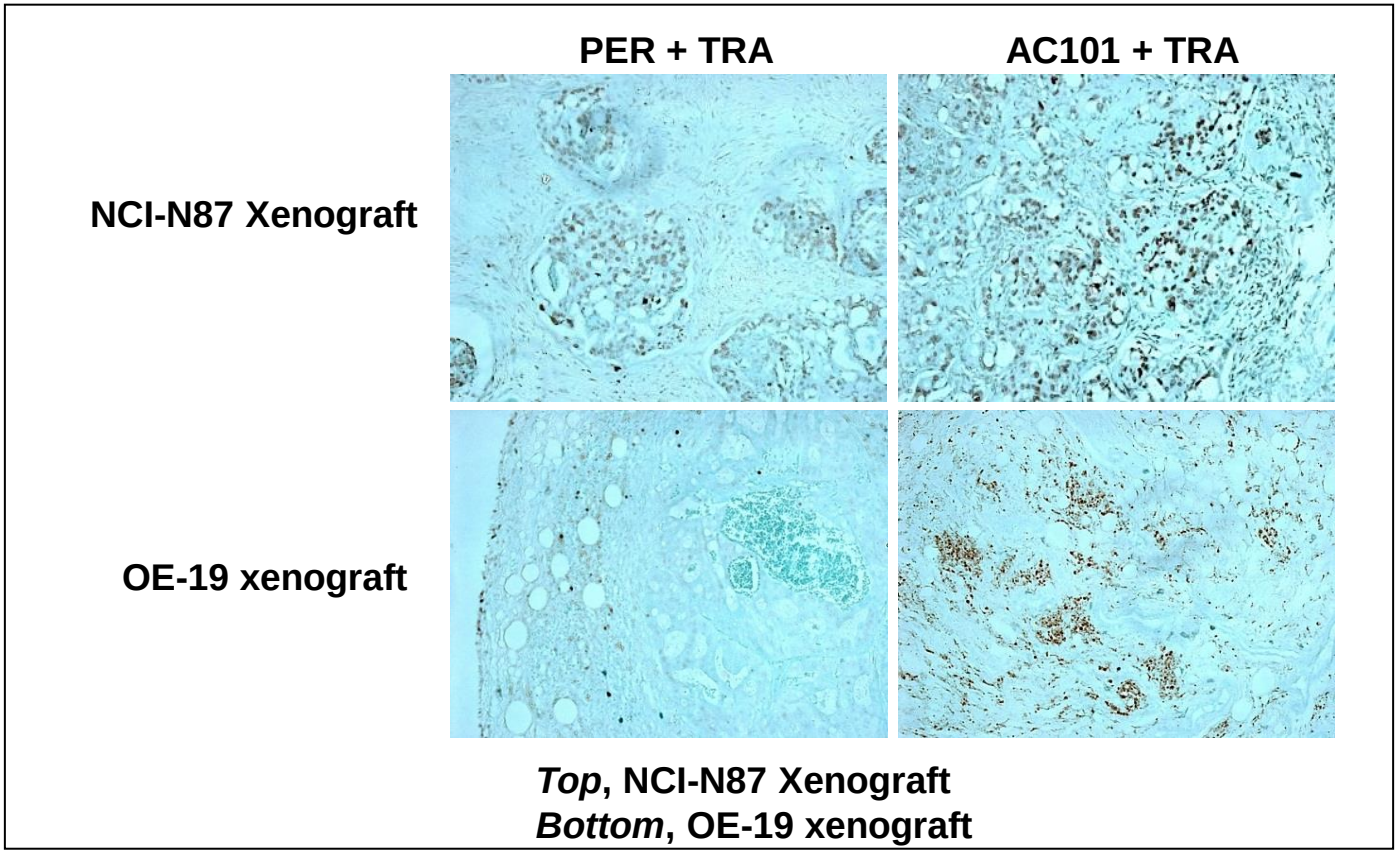
- AC101 induces apoptosis in HER2-positive BT-474 breast cancer
- Flow cytometry analysis (PI & Annexin-V staining)



MoA: Apoptosis

Apoptosis (in vivo)

- Combination treatment of AC101 and trastuzumab increases apoptotic cell population in xenograft models
- TUNEL assay



Top, NCI-N87 Xenograft
Bottom, OE-19 xenograft

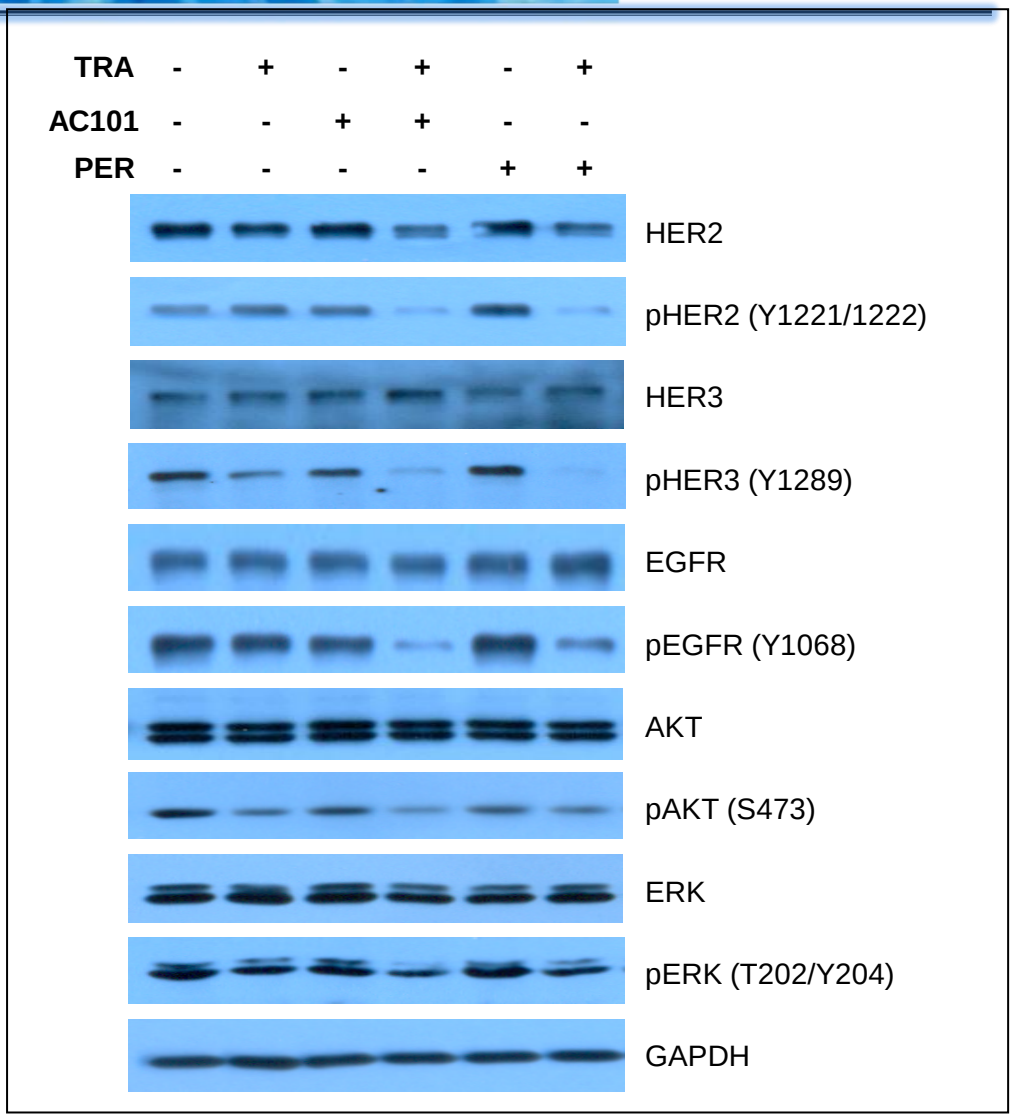
Mode-of-action:
Inhibition of Survival Signalings

HER2 downstream signaling

- Inhibition of ErbB signaling :

  Combination of AC101 and trastuzumab inhibits phosphorylation of Her2, Her3 and EGFR

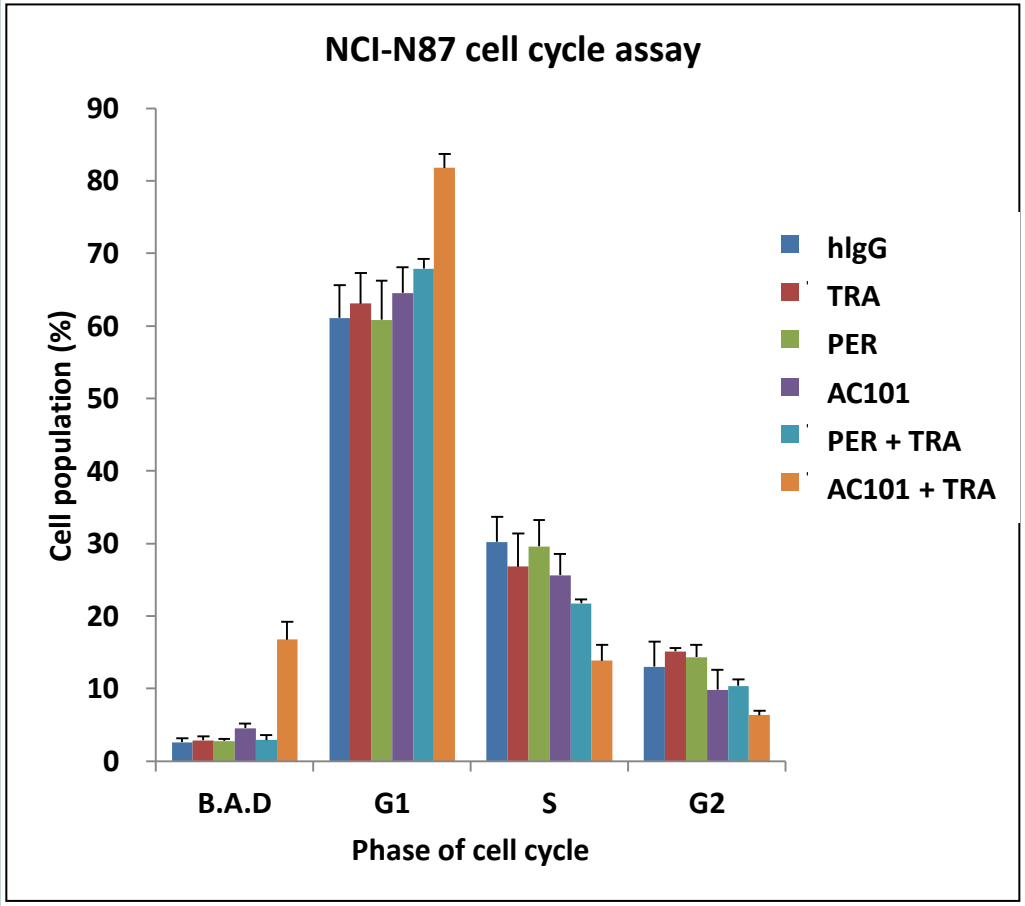
- Regulation of Survival signaling molecules includingPI3K/Akt and ERK pathways is weakly inhibited but not clear

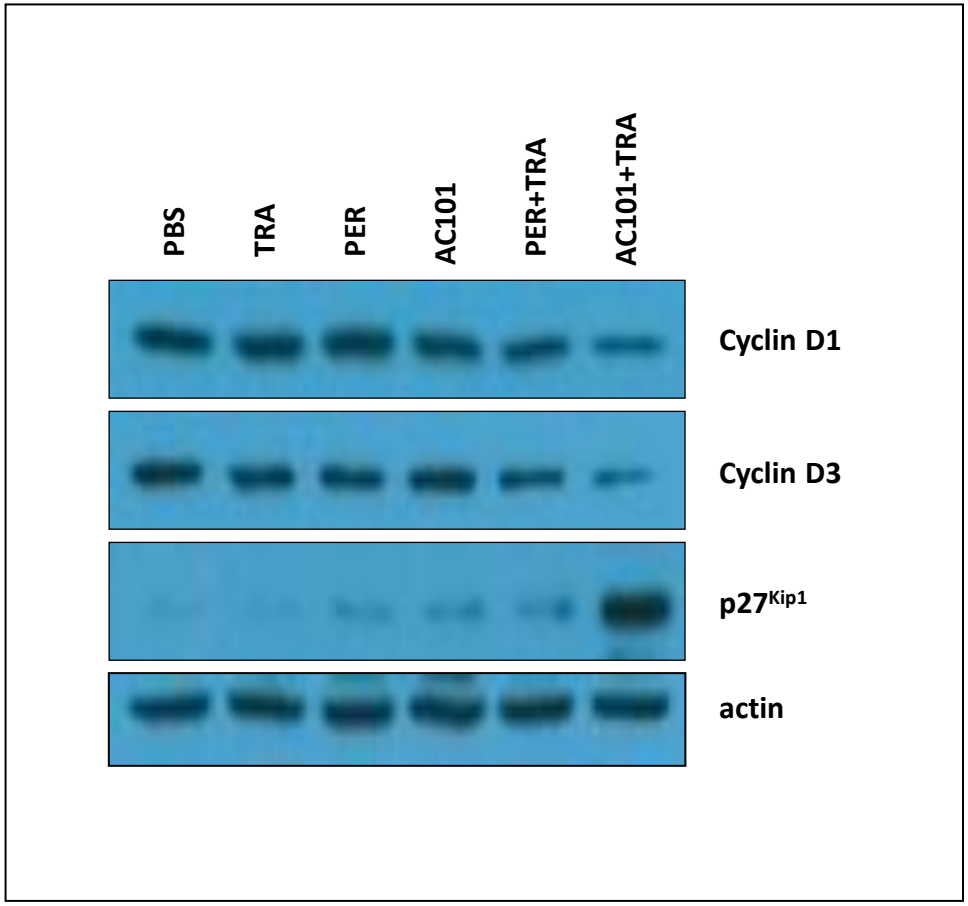


Mode-of-action: Cell Cycle Arrest

Cell Cycle Arrest

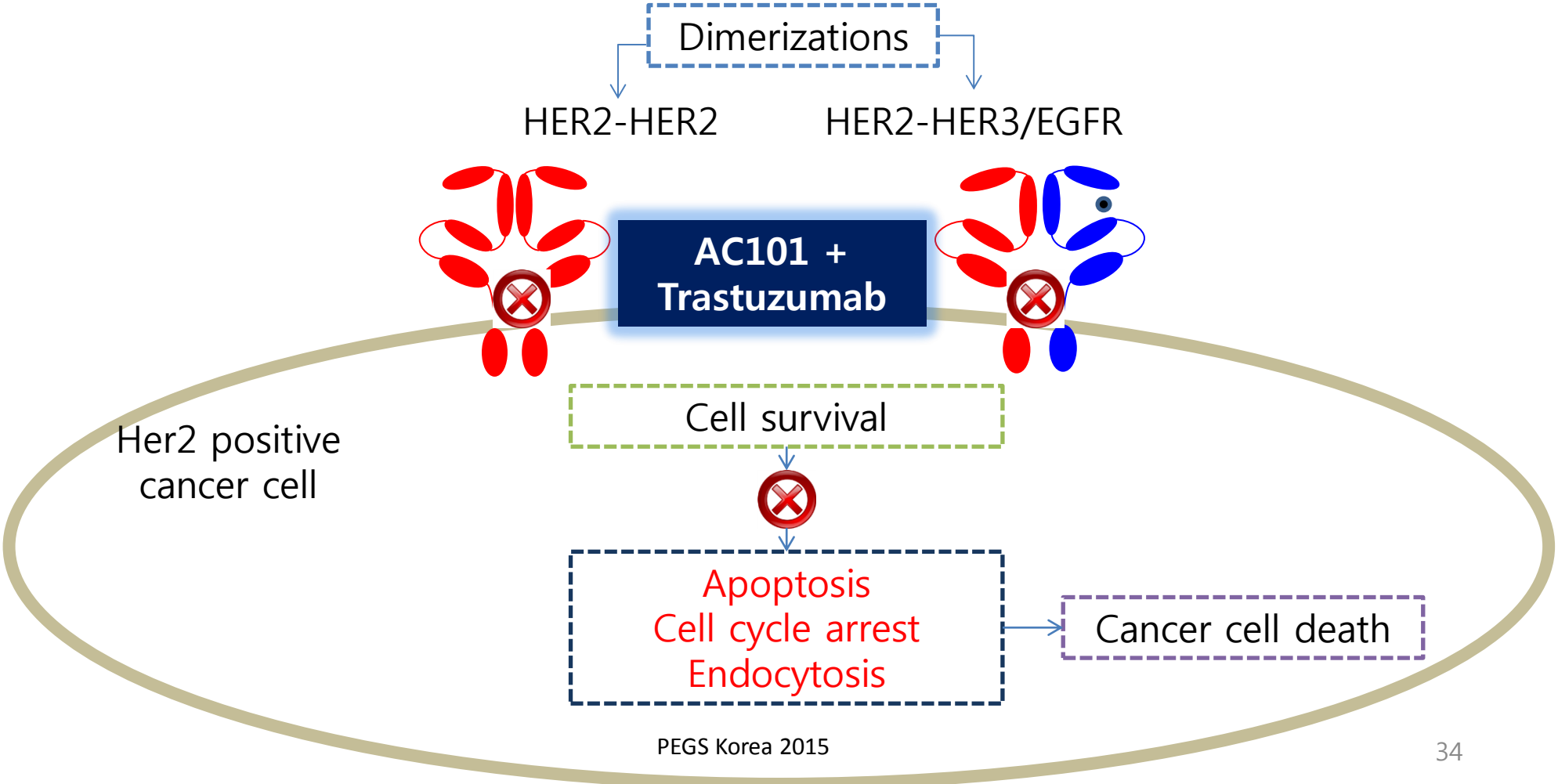
- Cell cycle arrest activity of AC101 in NCI-N87 : flow cytometry & WB analysis
- Flow cytometry data is analyzed with Multicycle in FCS Express (De Novo Software)





Proposed Mode of Action

■ **Combination of AC101 and trastuzumab inhibit both dimerization pathways and induce increased apoptosis and cell-cycle arrest**



Manufacturability

Stability

Unpublished data

- The solubility of AC101 is higher than 12.8 mg/mL in PBS buffer condition.
- AC101 has good physical/structural stability.

Summary

- AC101 is novel HER2 targeting therapeutic antibody.
- AC101 is synergistically efficacious against HER2 positive gastric cancer when it is combined with trastuzumab (TRA).
- AC101 is binding to distinct HER2 epitope from TRA or PER.
- Combination of AC101 and TRA induces increased apoptosis, cell-cycle arrest and endocytosis.
- AC101 is possible treatment to Herceptin resistant cancers even which have high level of Her2 and Her3 proteins.

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