ASP2713
NON-CONFIDENTIAL SUMMARY

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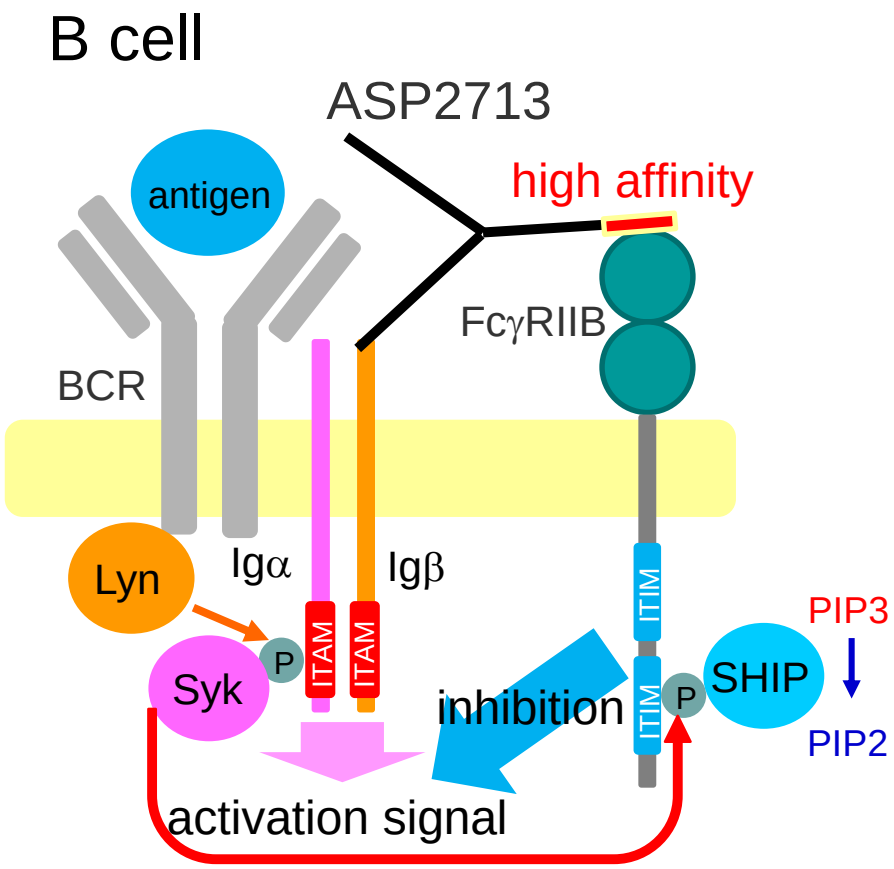
ASP2713 SUMMARY

Items	Note
Product name	ASP2713 (Fc engineered anti-human Igβ Ab with high affinity for FcγRIIB)
Mechanism of Action	Inhibition of B cell activation by Igβ and FcγRIIB cross-linking
Formulation	i.v.
Target Indication at Astellas	Autoimmune diseases (systemic lupus erythematosus)
Development Territory	Global
Latest development phase	CTA for P1

MECHANISM OF ACTION



Igβ

- Signal transduction component of the B cell antigen receptor(BCR).
- Expression on B cell and plasmablast
- Requirement for function of the BCR

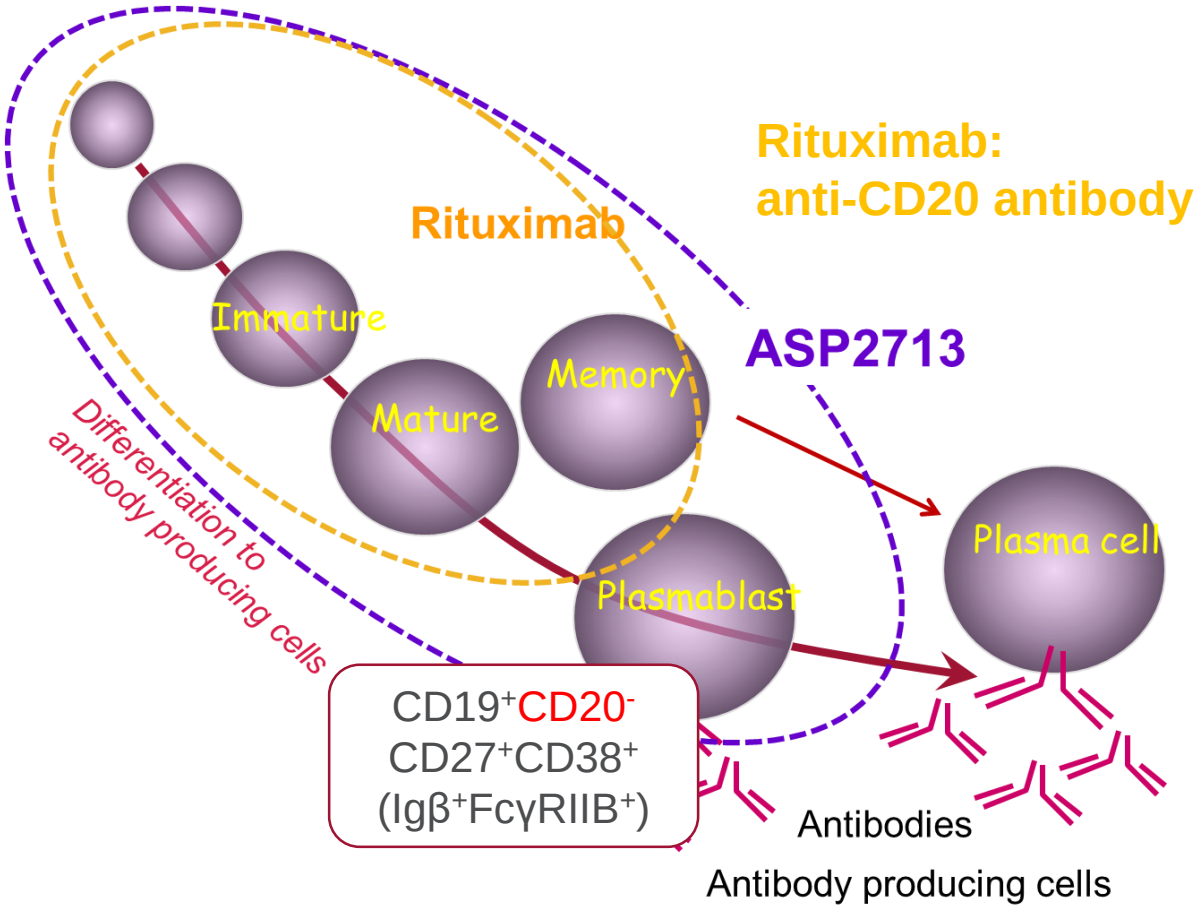
FcγRIIB

- Low affinity IgG receptor
- Expression on B cell, plasmablast, plasma cell, mast cell, Mϕ, dendritic Cell
- Having inhibitory ITIM motif in cytoplasmic region
- playing a role as negative feedback receptor

ITIM: Immunoreceptor tyrosine-based inhibitory motif

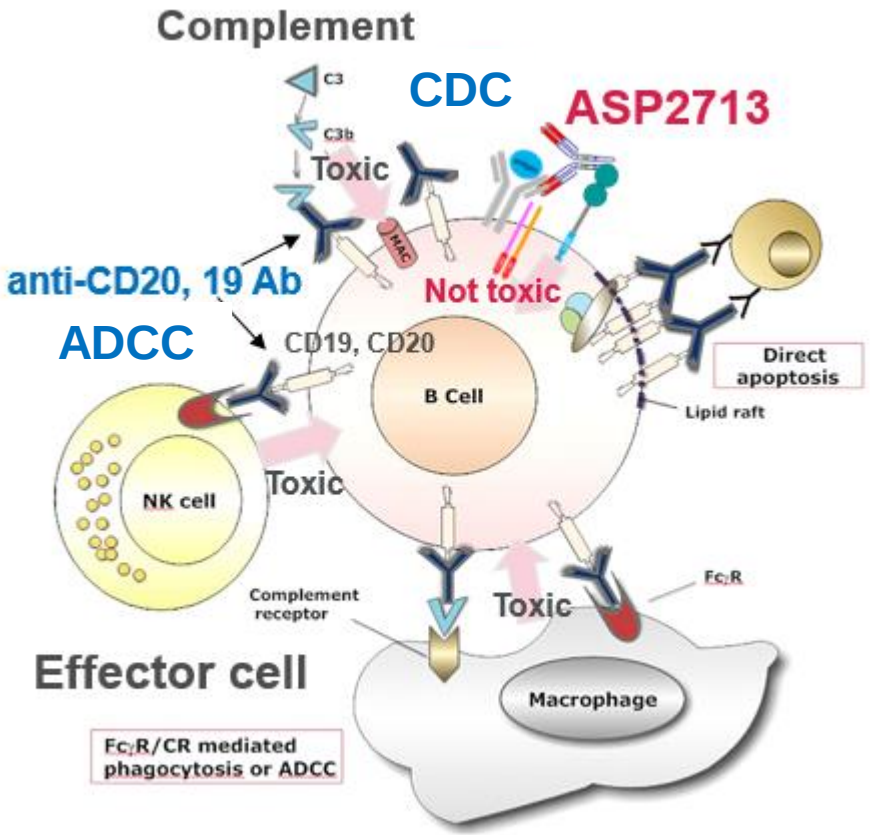
- ASP2713 is a Fc engineered anti-Igβ with high affinity for FcγRIIB.
- Through the cross-linking of Igβ and FcγRIIb, ASP2713 can inhibit B cells in BCR signal dependent manner without destroying these important immune cells.

TARGET CELLS OF ASP2713



- The targets cells of ASP2713 are not only B cells but also plasmablasts, CD20$^-$ antibody producing cells, therefore ASP2713 can broadly show suppressive effects compared to rituximab.

UNIQUENESS OF MOA OF ASP2713 IN COMPARISON TO EXISTING B CELL INHIBITORS



Blood 2010 116:3705-3714 modified

CDC: Complement-Dependent Cytotoxicity
ADCC: Antibody-Dependent Cell-mediated Cytotoxicity

anti-CD20, anti-CD19 Ab

ADCC and CDC

(requirement for effector cells and complement help)

ASP2713

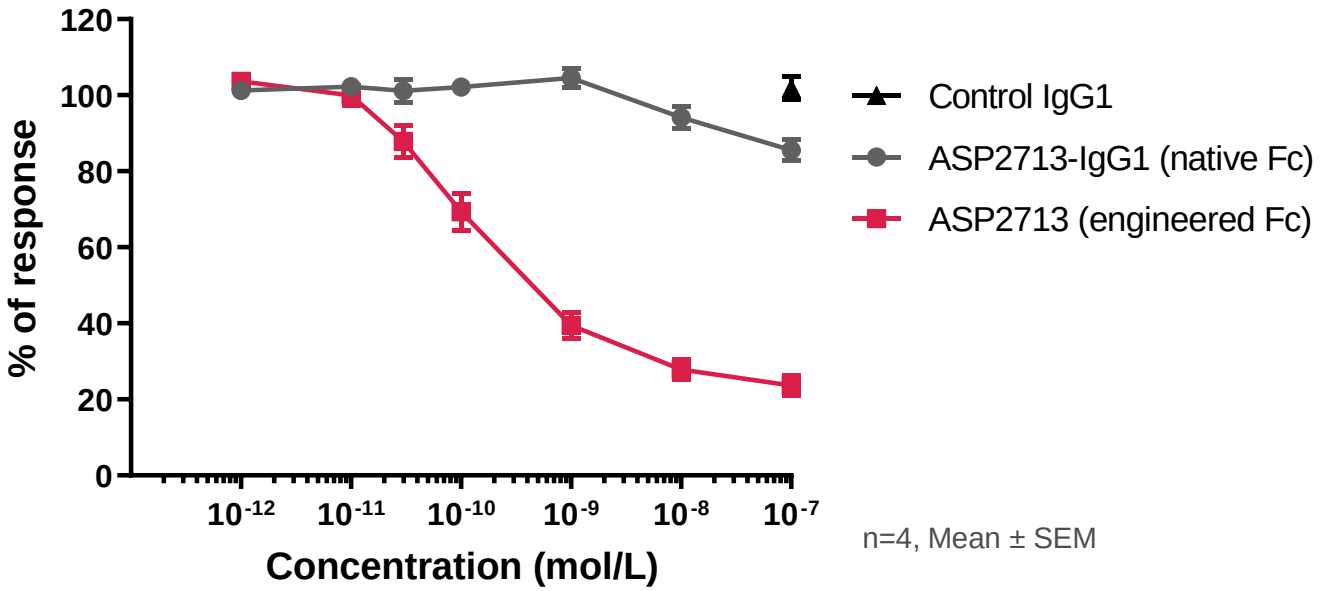
Non-cytotoxic activity and Direct inhibition

(no requirement for effector cells and complement)

PHARMACOLOGY
INHIBITORY EFFECT ON HUMAN B CELL PROLIFERATION

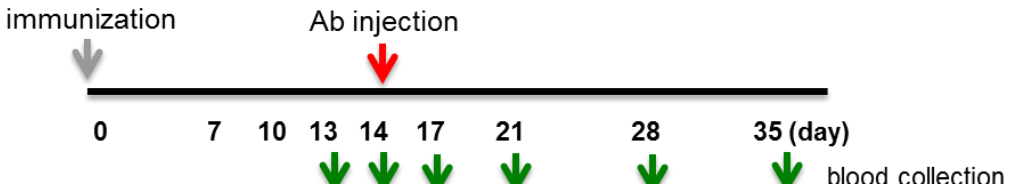
- **Healthy human primary B cells were treated with anti-IgM Ab in the presence of ASP2713.**
- **B cell proliferation was measured by ATP quantification.**

anti-IgM stimulated
human primary B cell proliferation



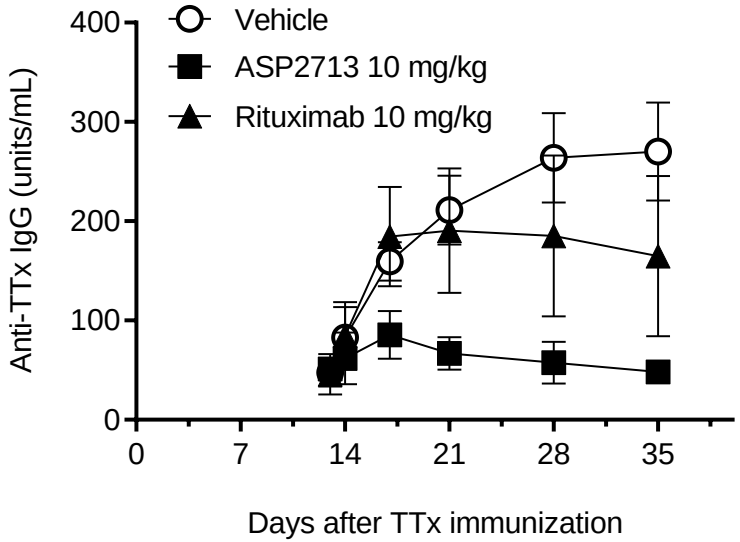
- ASP2713 directly inhibited BCR-stimulated human B cell proliferation and did not require effector cells and complement.

PHARMACOLOGY
COMPARISON WITH RITUXIMAB IN MONKEY TETANUS TOXOID (TTX) AB PRODUCTION MODEL



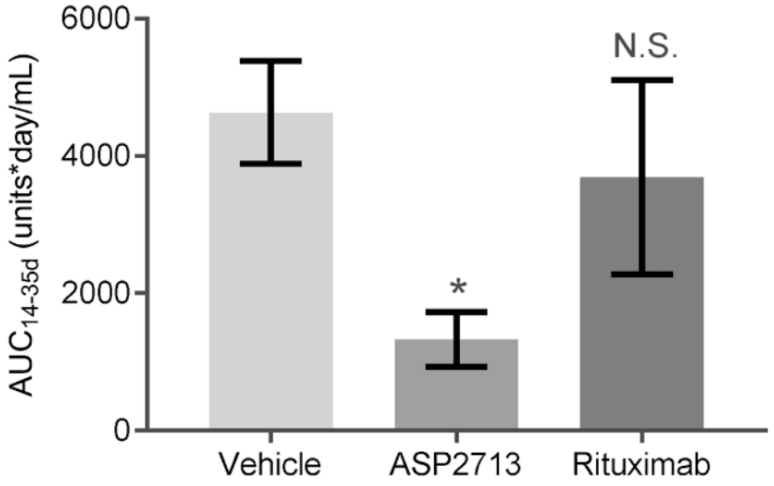
【Group】
Vehicle: Citrate buffer, IV, one-shot, n=3
Rituximab: 10 mg/kg, IV, one-shot, n=3
ASP2713: 10 mg/kg, IV, one-shot, n=3

Anti-TTx IgG titer



Mean ± SEM

Mean $AUC_{14\text{-}35d}$ of anti-TTx IgG



Mean ± SEM
*p<0.05 vs. vehicle group (unpaired t-test)

ASP2713 showed superior suppressive effect on antibody production to rituximab.

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PHARMACOLOGY
CYTOTOXIC ACTIVITY FOR HUMAN B CELLS

CDC activity

Test articles + human serum Alamarblue → Measurement of living cells

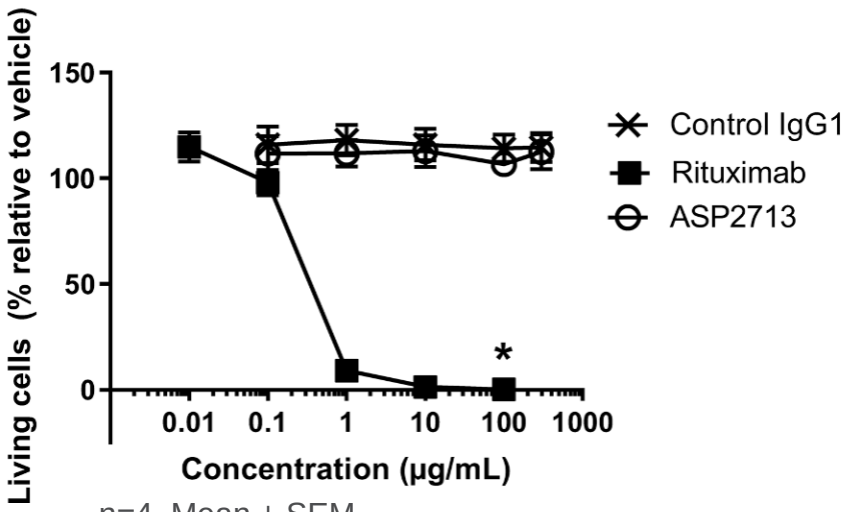
Daudi (B cell line) — 24hr

ADCC activity

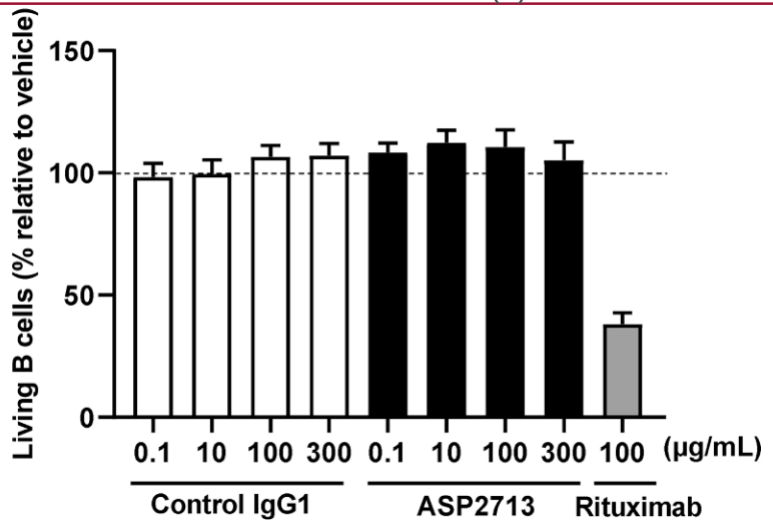
Test articles → Flow cytometry analysis
Living CD19⁺ cells: Annexin V(-), 7-AAD(-)

human PBMC 3 days

Annexin V(+): apoptotic cell marker
7-AAD(+): dead cell marker



n=4, Mean ± SEM
*p<0.05 vs. control IgG1 at 100 μg/mL (unpaired t-test)



n=4, Mean ± SEM

ASP2713 did not show cytotoxic activity for B cells in vitro, although rituximab showed.

CDC: complement-dependent cytotoxicity, ADCC: Antibody-dependent cell-mediated cytotoxicity

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TOXICOLOGY STUDY LIST

Type of Study		Species	Route	Dose (mg/kg)	GLP
Single-dose toxicity		Cynomolgus monkey	iv	0, 3, 10, 100	No
Repeat-dose toxicity	4-week dosing with 6-week recovery	Cynomolgus monkey	iv	0, 0.3, 1, 3, 30 (weekly)	Yes
	26-week dosing with 13-week recovery	Cynomolgus monkey	iv	0, 1, 3, 30 (weekly)	Yes
Others	Local irritation	Cynomolgus monkey	sc	0, 3, 100	Yes
	Tissue cross- reactivity	Human	in vitro	2, 10 µg/mL	Yes
		Cynomolgus monkey		0.5, 5 µg/mL	Yes
	Cytokine release assay	Human	in vitro (aqueous)	0, 1, 10, 100, 1000 µg/mL	No
			in vitro (solid)	0, 1, 10, 100, 1000 µg/mL	No

- Safety studies have been performed in single species (cynomolgus monkeys) as ASP2713 did not cross-react either with the rat or mouse Igβ and cynomolgus monkeys are pharmacologically relevant species to ASP2713.
- No stand-alone safety pharmacology study was conducted, but relevant information was obtained during the 4-week repeated intravenous dose toxicity study in cynomolgus monkeys.

ASP2713 CHARACTERIZATION SUMMARY

- A novel B cell-targeting antibody (anti-Igβ & FcγRIIB cross-linking mAb)
- Superior suppressive effect on antibody production to rituximab in a monkey model
- No ADCC/CDC activity in vitro
- No critical issues identified for further development

Patent covering ASP2713

- Substance Patent Family: WO2016/021621 (filed on Aug. 5, 2015)
  - Granted: Australia, China, European Patent (Austria, Belgium, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Portuga, Spain, Sweden, Switzerland, Turkey, United Kingdom), Hong Kong, Indonesia, Japan, Malaysia, Mexico, Philippines, Russian, Singapore, South Africa, Taiwan, Ukraine, USA
  - Pending: Argentina, Brazil, Canada, GCC, India, Israel, Korea, Thailand, Vietnam