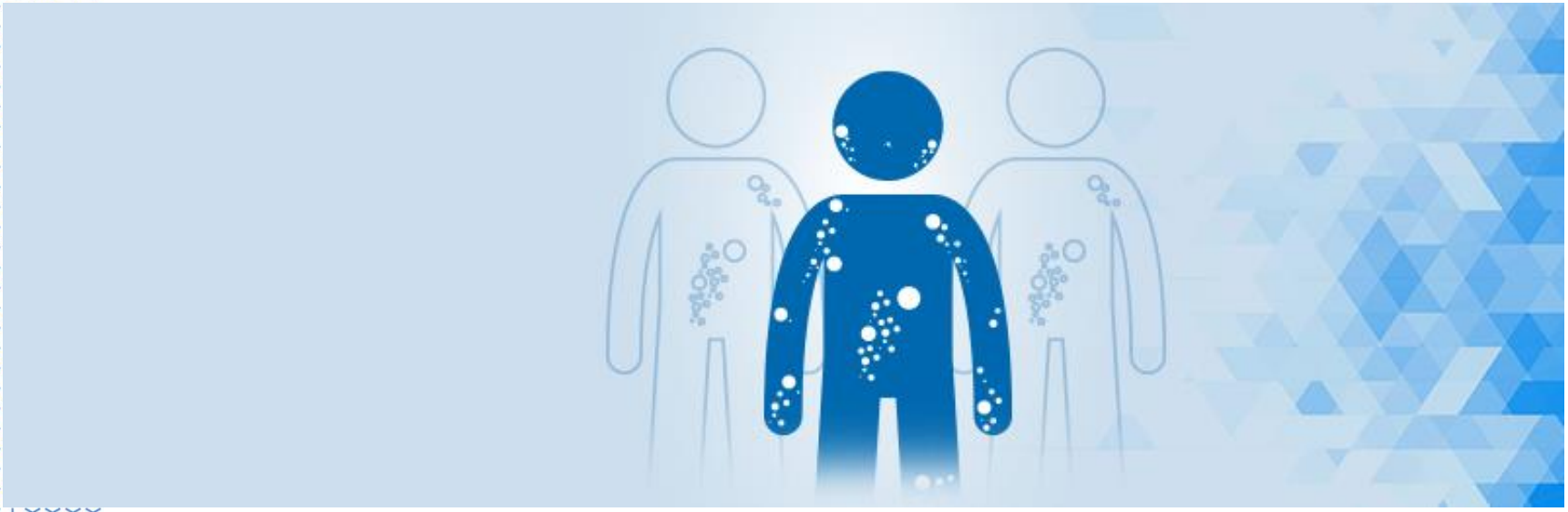

IgE inhibition in CSU: Not all anti-IgEs are born equal

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This meeting is sponsored by Novartis Pharma AG
Ligelizumab is an investigational drug in development for the treatment of CSU and has not received marketing authorization
Zinc number: GLDEIM/QGE031C/0030e

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Disclosures

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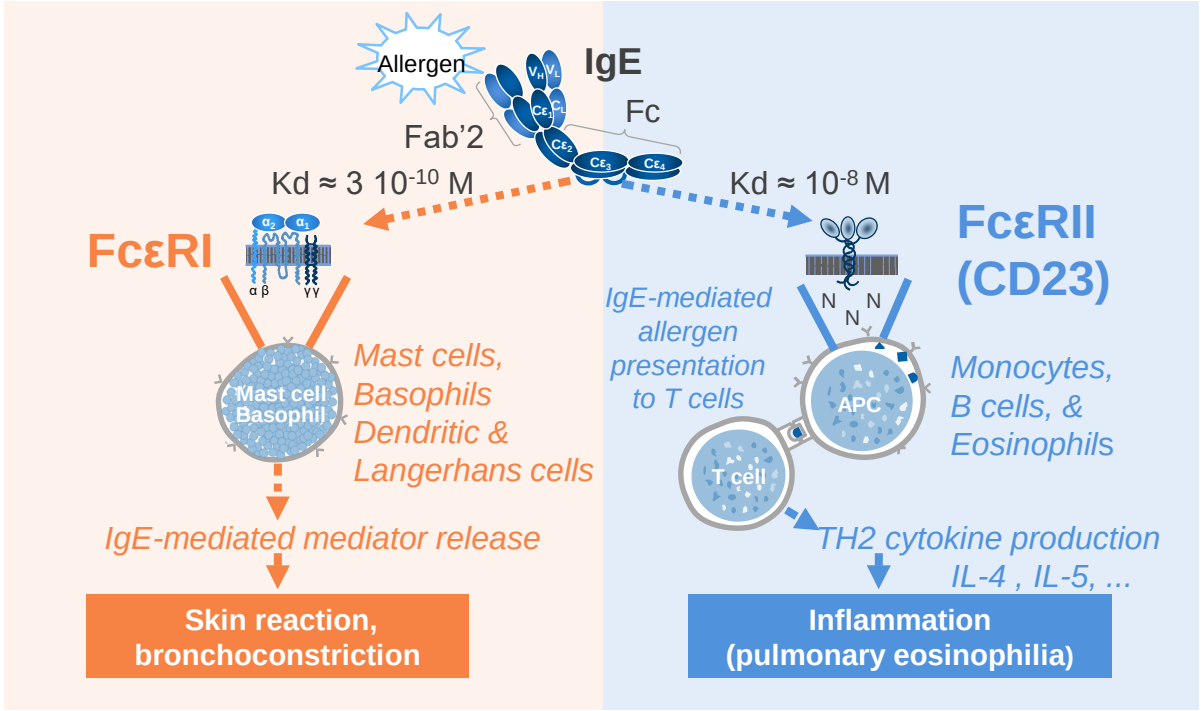
IgE targets two different IgE-receptors with varying contributions to disease



FcεRI (high-affinity receptor)

- *Present in high density on basophils and mast cells*
- *Mediates release of inflammatory mediators*

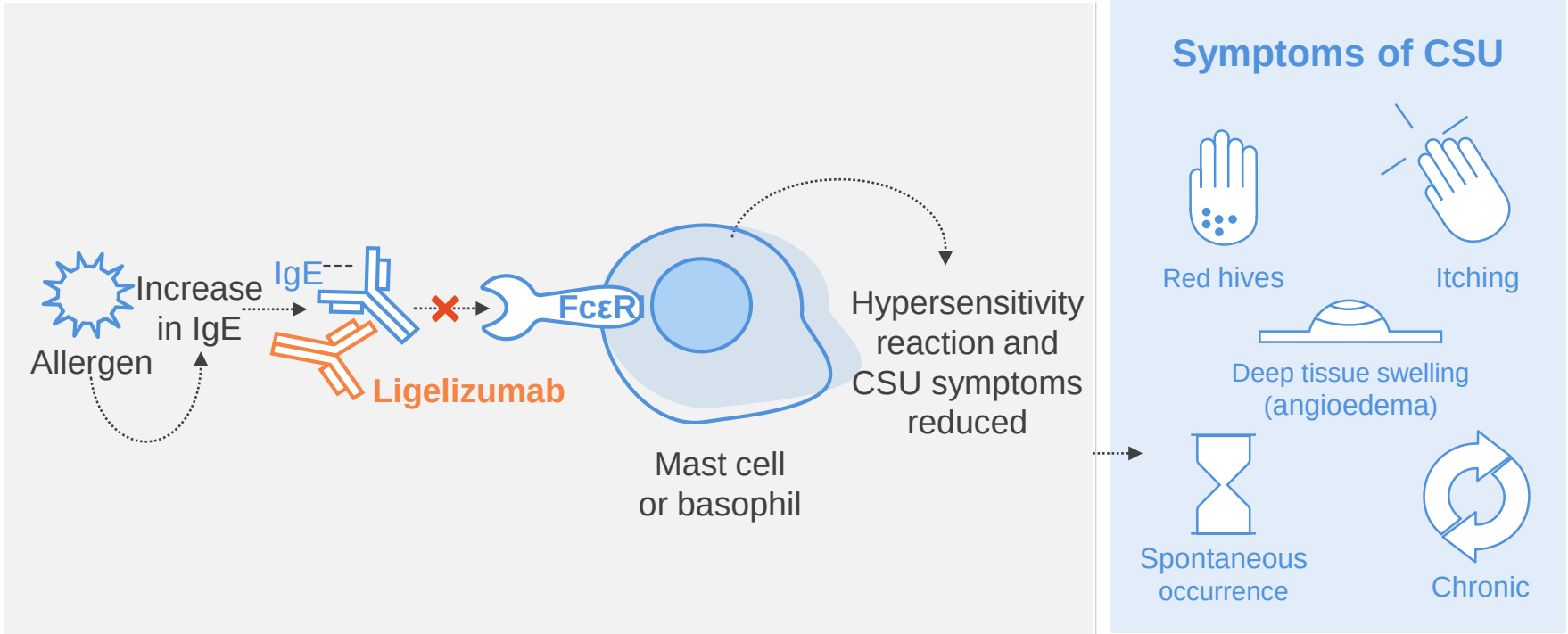
FcεRII / CD23 (low-affinity receptor)

- *Downregulatory signal for IgE synthesis*
- *Present on APCs*
- *Induces T-cell activation in the presence of specific allergen and IgE, leading to inflammation*

APC, antigen presenting cell; FcεRI, high-affinity IgE receptor; FcεRII/CD23, low-affinity IgE receptor; IgE, immunoglobulin-E; Kd, dissociation constant; IL, interleukin

Sutton BJ and Davies AM. Immunol Rev 2015;268(1):222–35

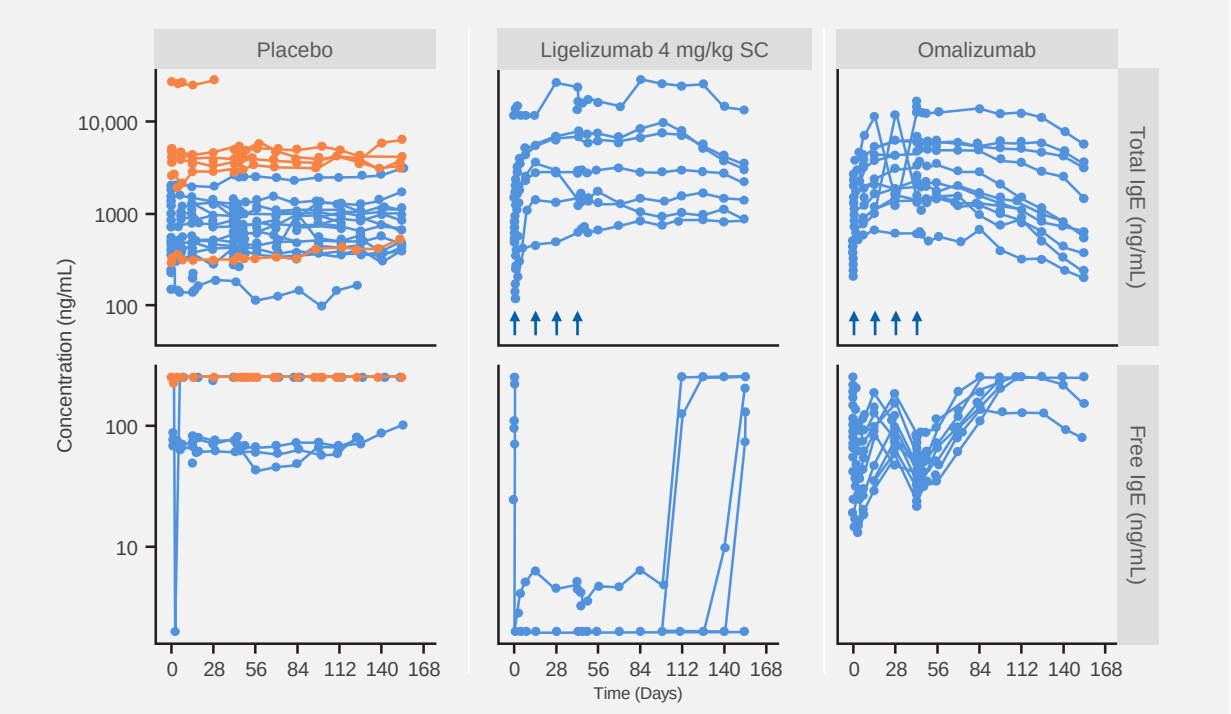
The IgE/FcεRI axis plays a central role in allergen and auto-antigen-driven inflammation in CSU



CSU, chronic spontaneous urticarial;
FcεRI, high-affinity IgE receptor; IgE, immunoglobulin-E

Gasser P, et al. Nat Commun 2020;11(1):165

Ligelizumab dose dependently reduced the circulating free IgE and the basophil cell surface bound IgE



IgE, immunoglobulin E; IV, intravenous; SC, subcutaneous.

Arm JP, et al. Clin Exp Allergy 2014;44(11):1371–1385.

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Ligelizumab binds to IgE with higher affinity compared with omalizumab

- 88.2-fold higher IgE-binding affinity of ligelizumab, compared with omalizumab, is due to slower dissociation rate, i.e. more stable IgE/ligelizumab complexes

Affinities of anti-IgE antibodies

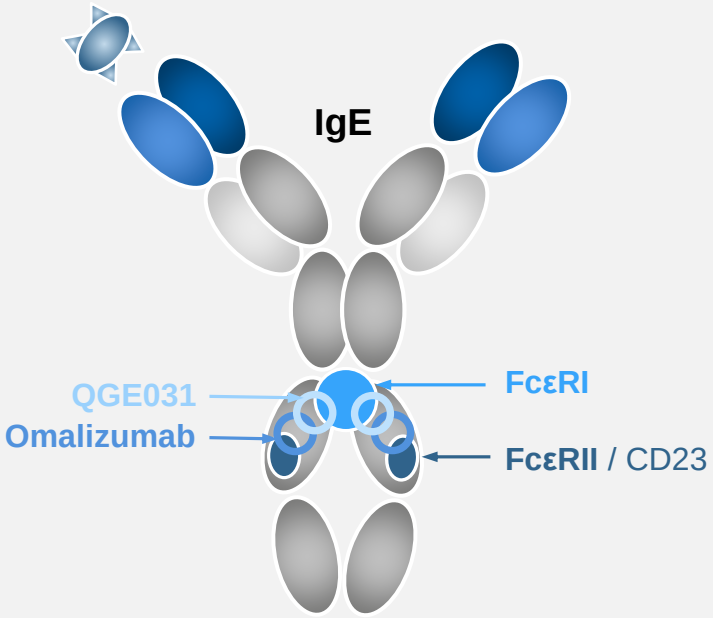
	Ka (M-1 s-1)	Kd (s-1)	K_D (pM)
Ligelizumab IgG	1.8×10^{6}	33×10^{-6}	**18**
Omalizumab IgG	0.91×10^{6}	$2{,}400 \times 10^{-6}$	**2,659**
Ligelizumab Fab	9.2×10^{6}	320×10^{-6}	**35**
Omalizumab Fab	1.5×10^{6}	$4{,}600 \times 10^{-6}$	**3,090**

A lower K_D value indicates that lesser drug is required to occupy 50% of receptors
Ka is a measure of the affinity of the drug for the receptor; Kd is a measure of drug dissociation from the receptor

IgE/G, immunoglobulin-E/G; IC_{50}, concentration for 50% inhibition; Ka, association rate; K_D, equilibrium dissociation constant, Kd, dissociation rate

Gasser P, et al. Nat Commun 2020;11(1):165

Ligelizumab binds to a different epitope compared with omalizumab



1 **Ligelizumab**

- Recognizes a **different IgE epitope** than omalizumab
- Important **overlap** in IgE binding **with** that of **FcεRI** (only minor overlap with CD23)
- Binds IgE distant from CD23 binding site and **sterically similar** to FcεRI
- Interacts with **open IgE conformation** similar to FcεRI

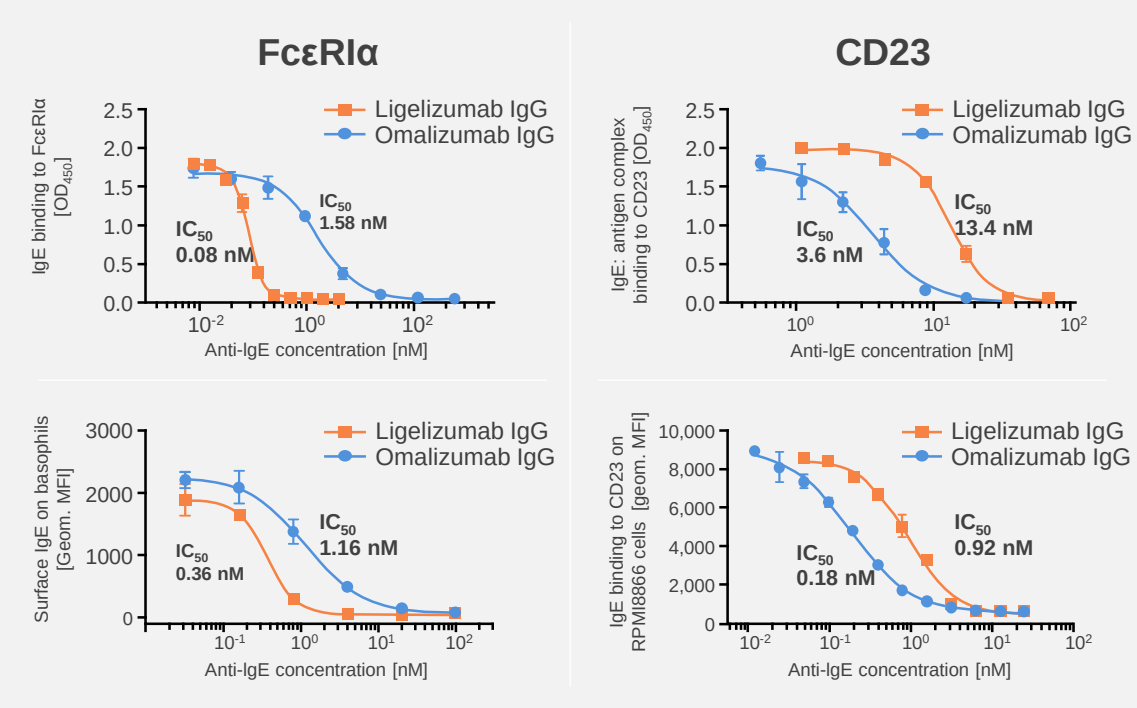
2 **Omalizumab**

- Directly **competes with CD23** for IgE binding with physical steric overlap
- Binds farther from the FcεRI site
- Inhibits IgE-FcεRI interaction by steric hindrance

IgE, immunoglobulin-E; FcεRI, high-affinity IgE receptor; FcεRII/CD23, low-affinity IgE receptor

Gasser P, et al. Nat Commun 2020;11(1):165

Ligelizumab inhibits IgE binding to FcεRI more potently than to CD23



IgE inhibition profiles

Ligelizumab

FcεRI > CD23

Mast cells/basophil activation

Omalizumab

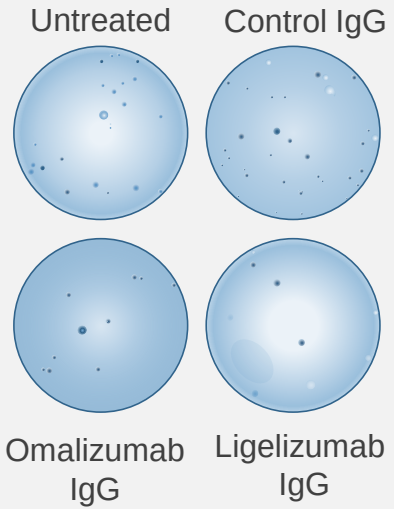
CD23 > FcεRI

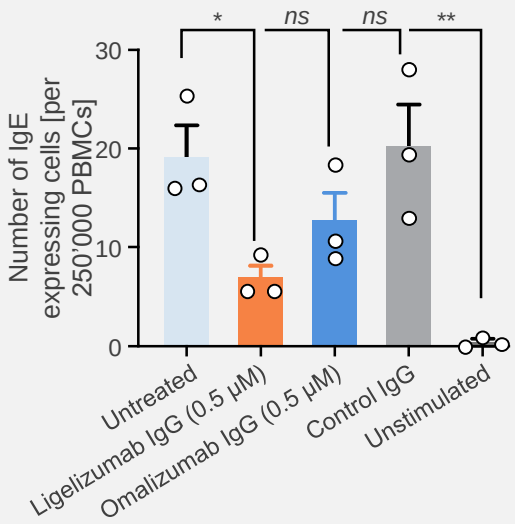
AP and transport across epithelial barriers

AP, antigen presentation; FcεRI, high-affinity IgE receptor; CD23, low-affinity IgE receptor; IgE, immunoglobulin-E; IC_{50}, concentration for 50% inhibition

Gasser P, et al. Nat Commun 2020;11(1):165

Ligelizumab downregulates IgE production in human PBMCs stronger than omalizumab





- Human PBMC were stimulated with anti-CD40 + IL-4 in presence of anti-IgE antibodies
- Numbers of IgE producing B cells were measured
- Ligelizumab, but not omalizumab, has the ability to recognize CD23-bound IgE on B cells which may contribute to the observed reduction of IgE production in PBMC cultures

IgE/G, immunoglobulin-E/G; IL, interleukin; ns, not significant; PBMC, peripheral blood mononuclear cells

Gasser P, et al. Nat Commun 2020;11(1):165

Key characteristics of ligelizumab vs omalizumab

	Ligelizumab	Omalizumab
Affinity to IgE	17.8 x 10^{-12} pM	~ 10^{-9} M
Specificity (domain)	Anti-IgE (Cε3)	Anti-IgE (Cε3)
Preferential IgE-Fc conformation	Open	No
IgE receptor inhibition profile	FcεRI > CD23	CD23 > FcεRI
IgE to FcεRI inhibition	+++ Competitive + steric	++ Steric hindrance
IgE to CD23 inhibition	++ Steric + conformational lock	+++ Competitive
IgE dissociation from FcεRI	No	Yes
Inhibition of IgE production	+++	++

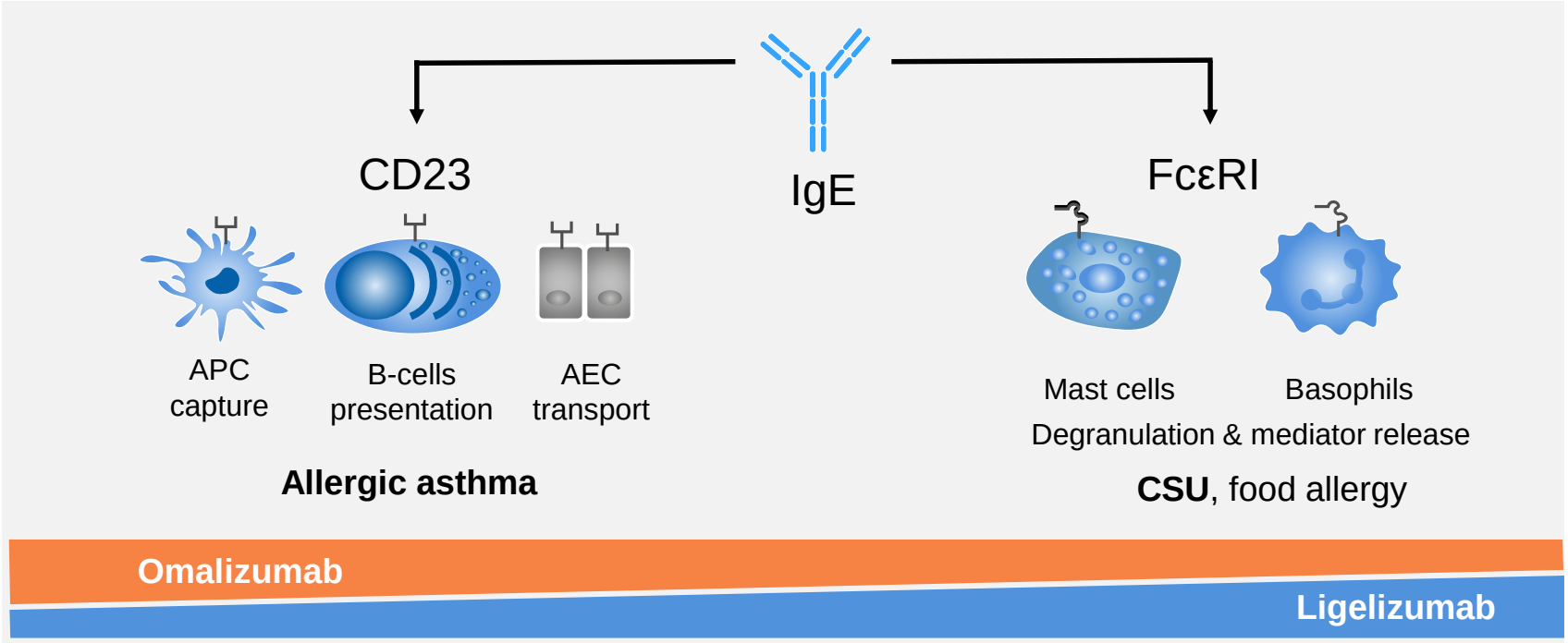
Ligelizumab vs omalizumab shows…

- Stronger neutralization of free IgE
- Higher efficacy in the FcεRI-driven pathophysiologies (e.g. CSU, anaphylaxis)
- Possibly greater disease modification

IgE, immunoglobulin-E; IC_{50}, concentration for 50% inhibition;
Ka, association rate; K_D, equilibrium dissociation constant, Kd, dissociation rate

Gasser P, et al. Nat Commun 2020;11(1):165

In conclusion…



AEC, airway epithelial cell; APC, antigen presenting cell;
CSU, chronic spontaneous urticaria; IgE, immunoglobulin E