Mechanism of disease:
The role of the epithelial cytokines in asthma

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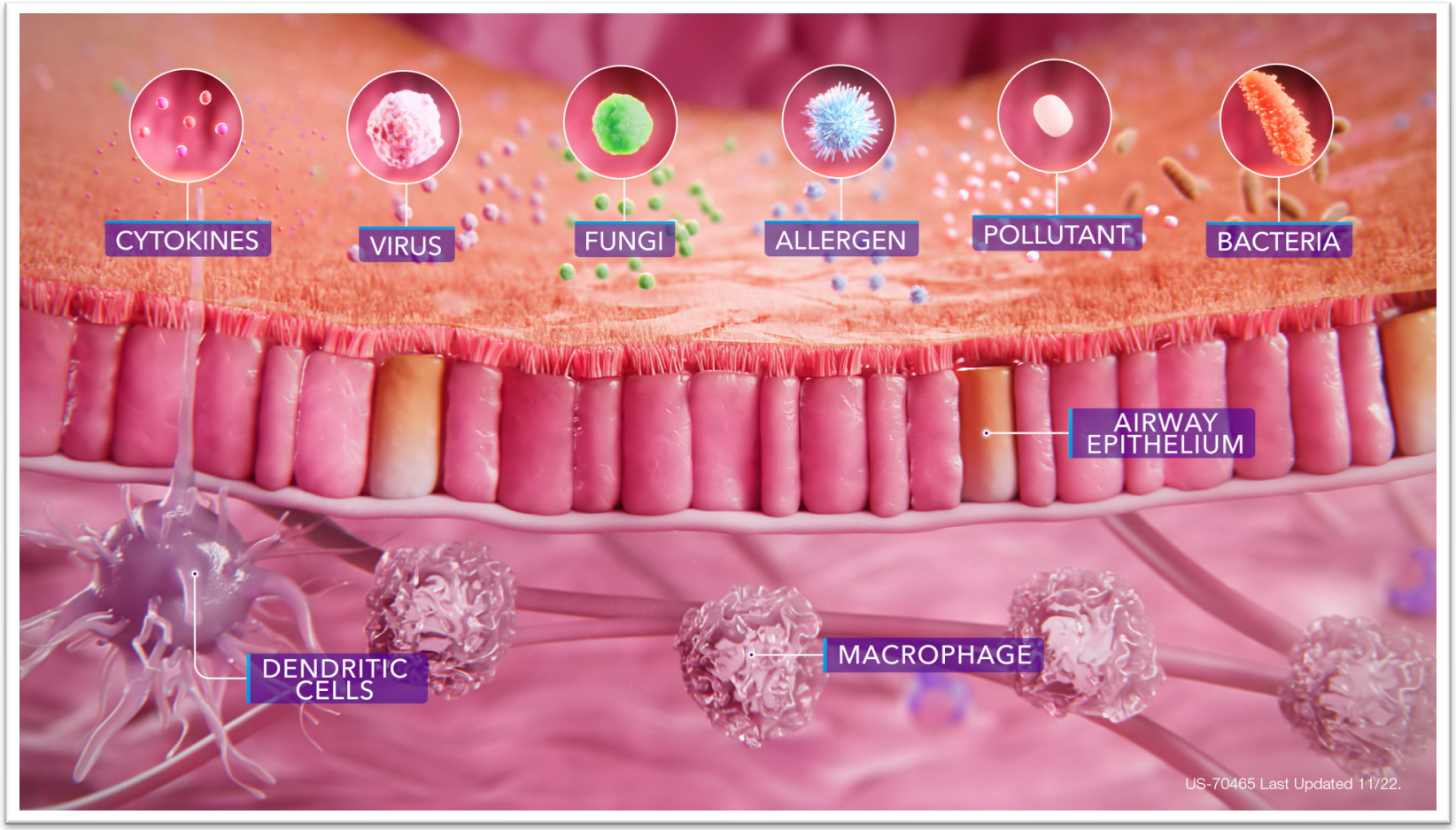
EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

US-70465 Last Updated 11/22.

The airways are exposed to environmental insults

The airways are constantly exposed to insults such as inhaled pathogens, pollutants and aeroallergens[1,2]

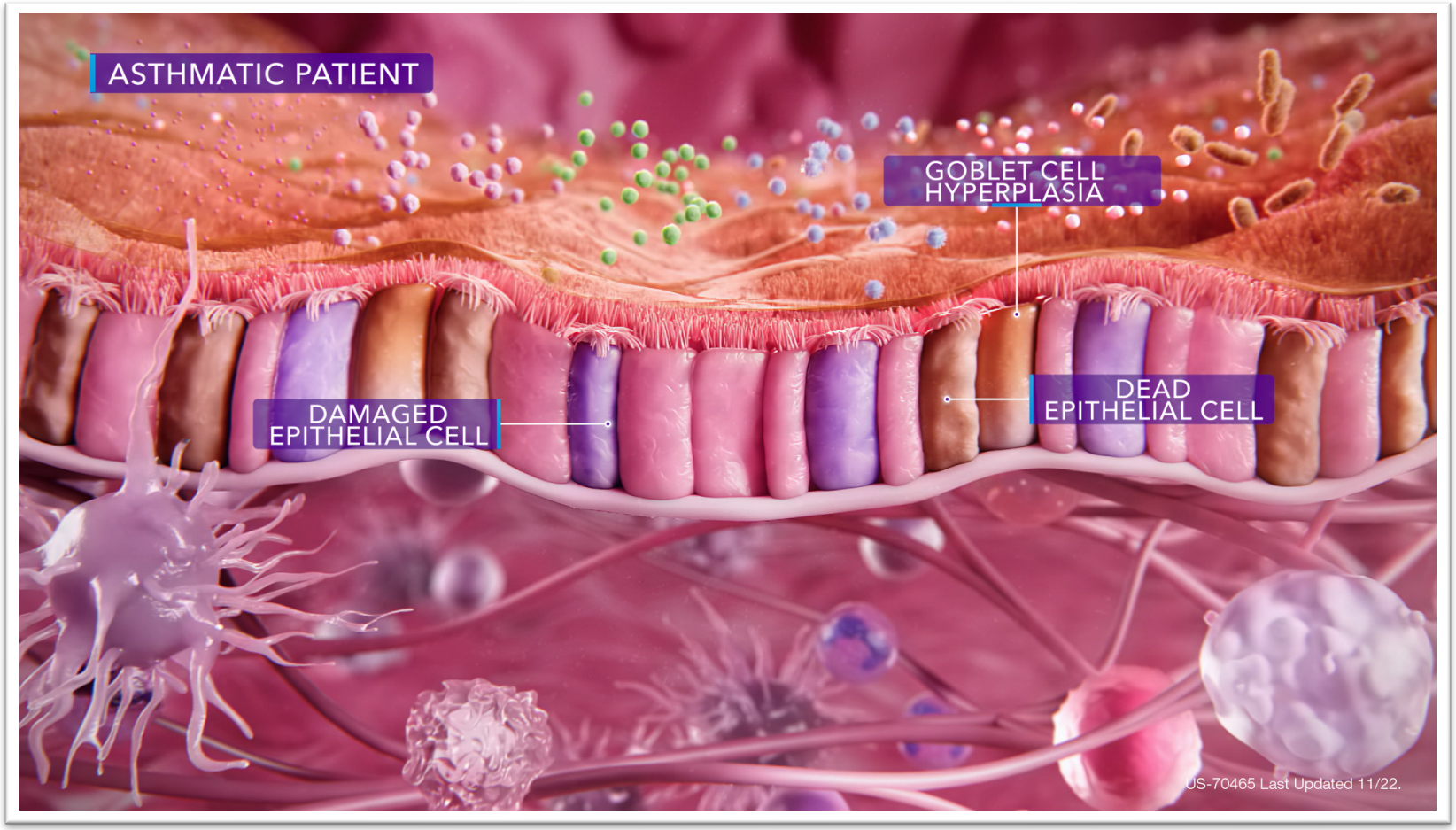
1. Tam A, et al. *Ther Adv Respir Dis.* 2011;5:255–273; 2. Heijink IH, et al. *Allergy.* 2020;75:1902–1917



The airway epithelium acts as a physical and immunological barrier

The airway epithelium is the first line of defense against insults such as allergens, pathogens and pollutants.[1,2] It provides an effective physical barrier comprising epithelial cells held together by cell-cell junctions, rendering the structure impermeable, and an immunological barrier that recognizes and controls pathogens[3,4]

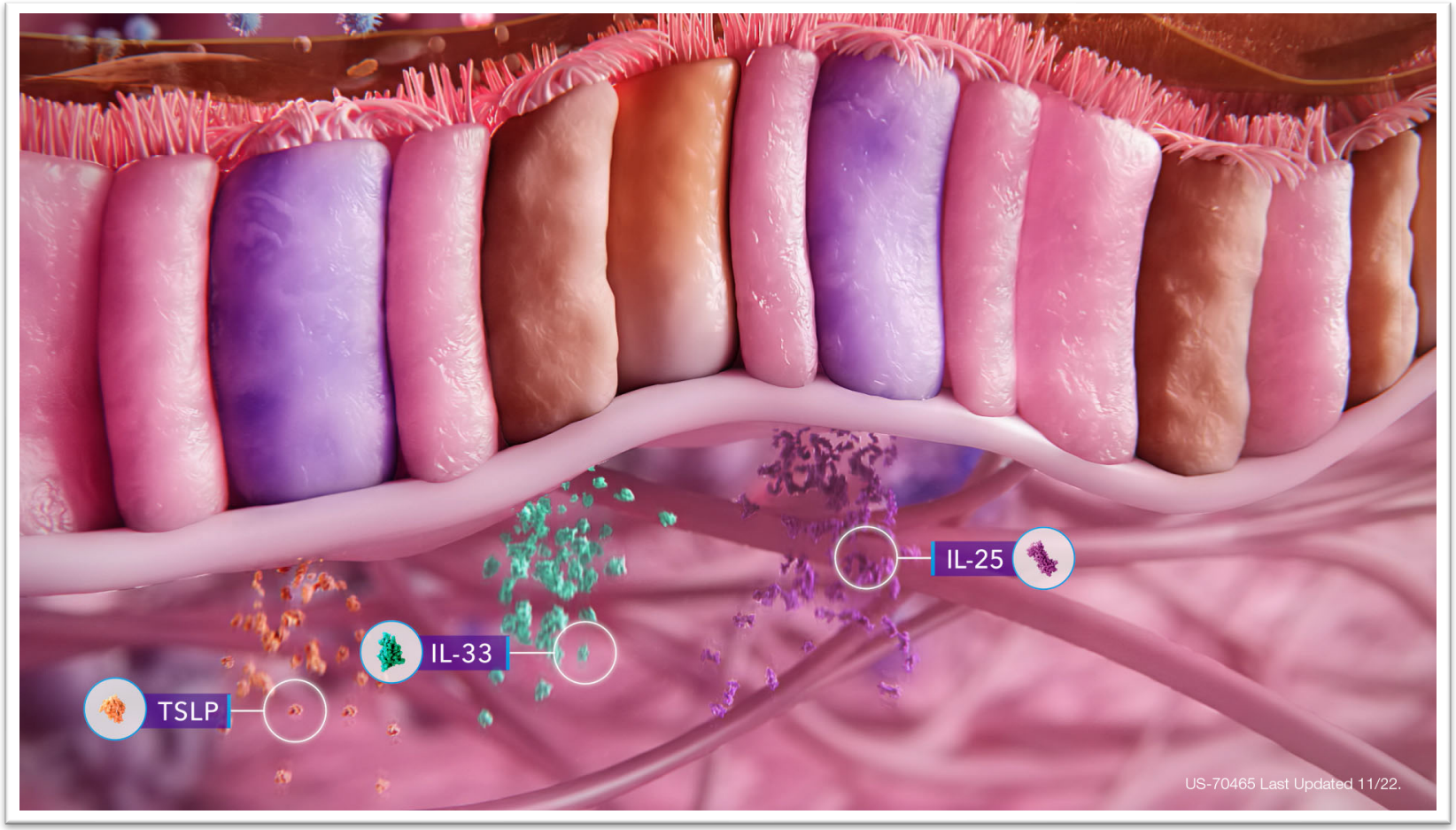
1. Tam A, et al. *Ther Adv Respir Dis.* 2011;5:255–273; 2. Heijink IH, et al. *Allergy.* 2020;75:1902–1917; 3. Vareille M, et al. *Clin Microbiol Rev.* 2011;24:210–229;
4. Bartemes KR, Kita H. *Clin Immunol.* 2012;143:222–235



Epithelial damage leads to physiological changes to the airways

In patients with asthma, the epithelial barrier is damaged: cell structure is compromised and there are gaps between cells.[1,2] These disruptions leave the cells vulnerable to environmental insults.[1,2] The resulting inflammation and structural changes can cause reversible airway obstruction and contribute to airway hyperresponsiveness[3,4]

1. Bartemes KR, Kita H. *Clin Immunol.* 2012;143:222–235; 2. Heijink IH, et al. *Allergy.* 2020;75:1902–1917; 3. Ward C, et al. *Thorax.* 2002;57:309–316; 4. Berend N, et al. *Respirology.* 2008;13:624–631

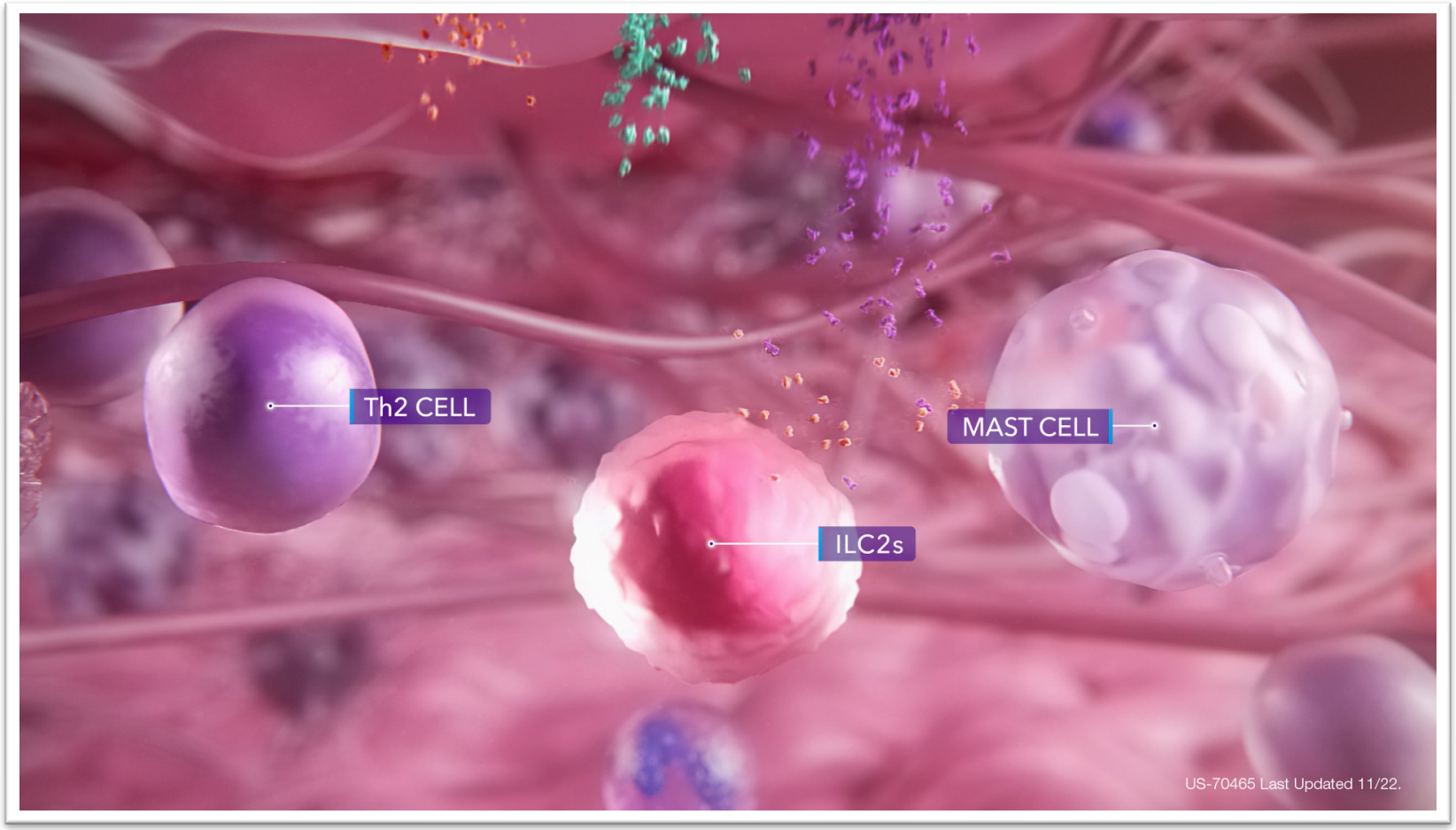


Epithelial damage results in the release of alarmins

Environmental insults and the subsequent epithelial damage trigger the release of epithelial cytokines, or alarmins, including IL-33, TSLP and IL-25

IL, interleukin; TSLP, thymic stromal lymphopoietin

Roan F, et al. *J Clin Invest.* 2019;129:1441–1451

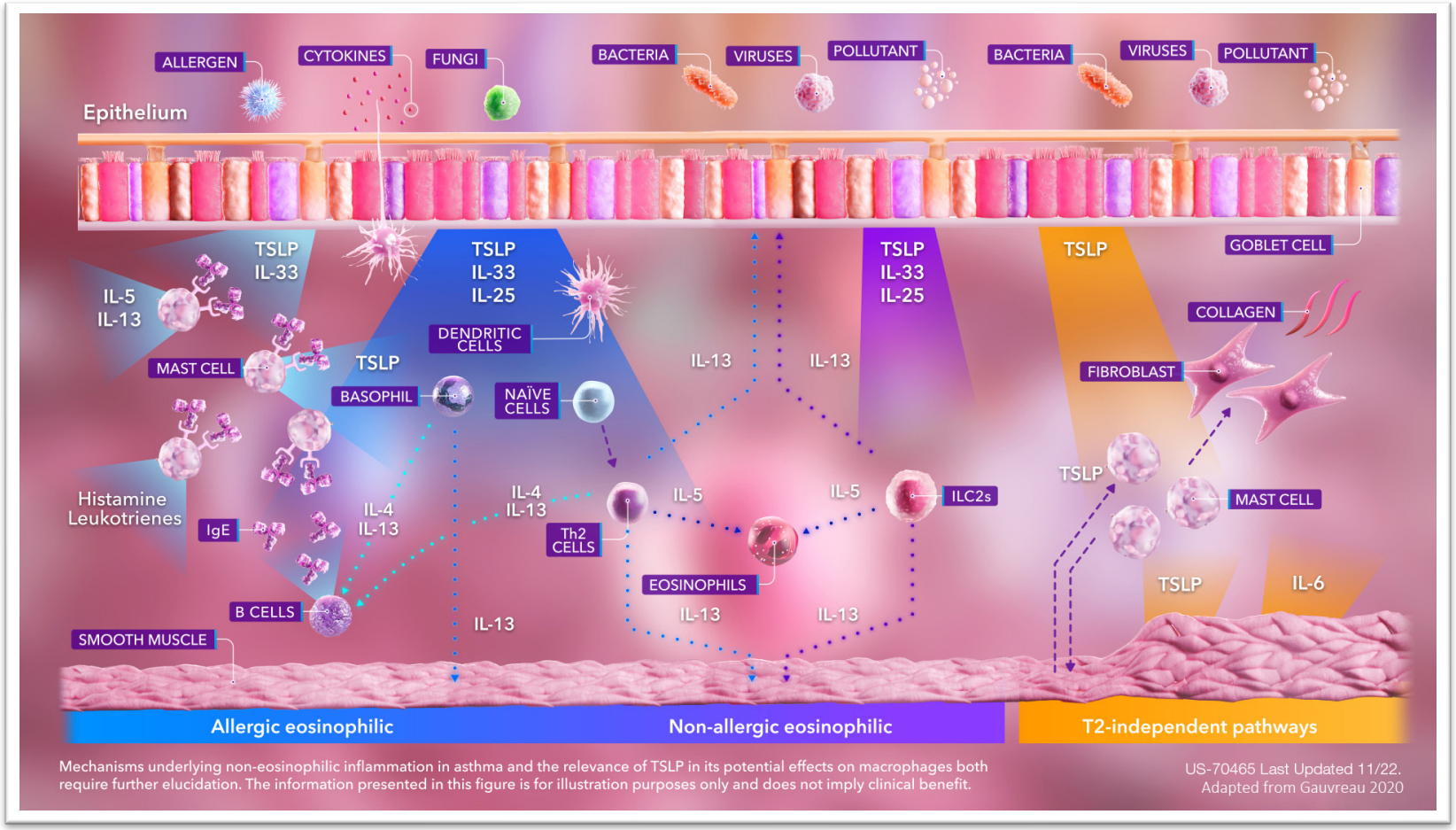


Alarmins drive airway inflammation

Alarmins such as IL-33, TSLP and IL-25 drive innate and adaptive inflammatory responses and act across the spectrum of asthma inflammation in overlapping but distinct ways. Their targets include Th2 cells, ILC2s and mast cells

IL, interleukin; ILC2, type 2 innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin

Roan F, et al. *J Clin Invest.* 2019;129:1441–1451

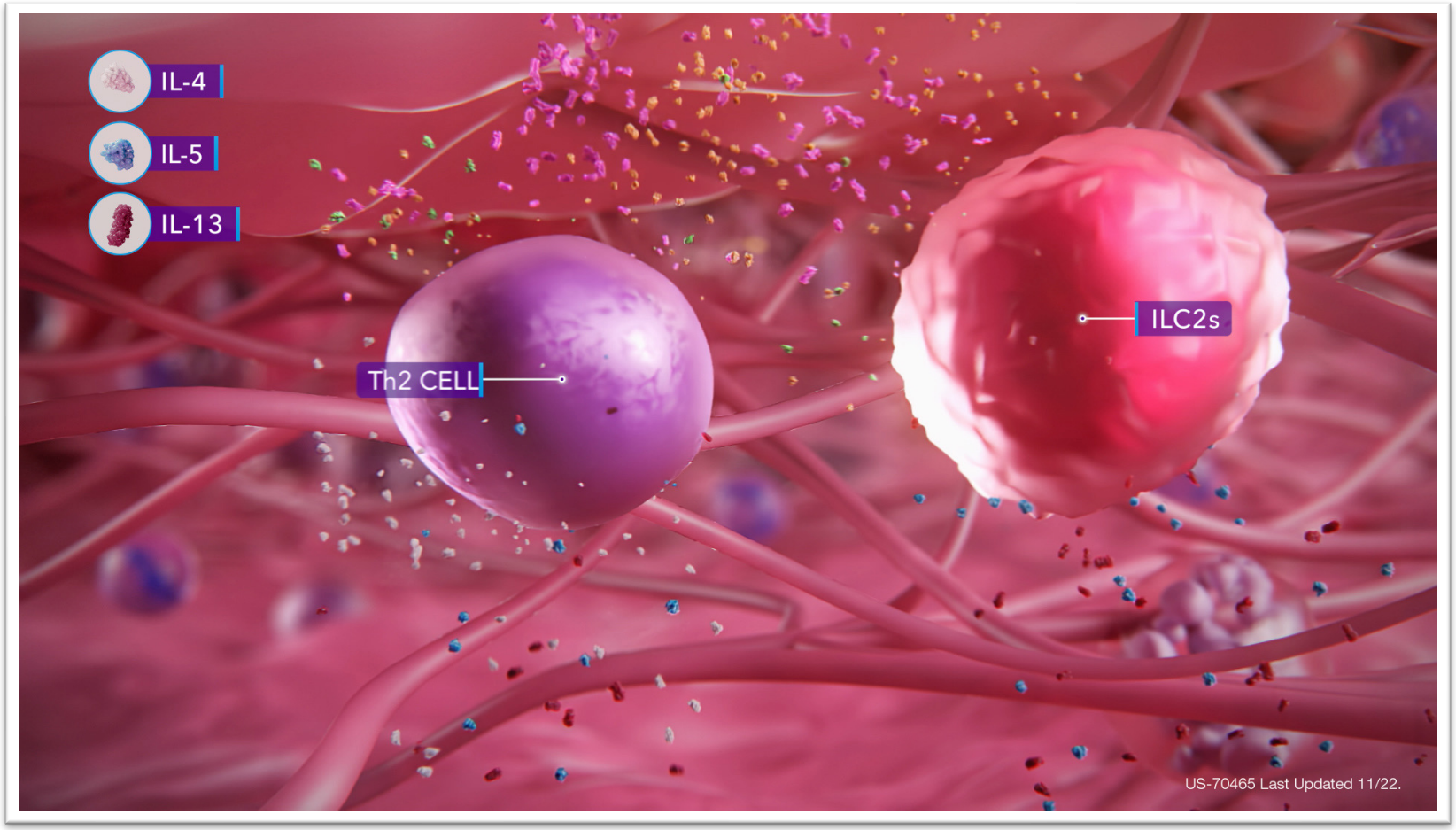


Alarmins drive inflammation from the top of the cascade

IL-33, TSLP and IL-25 can all drive allergic and non-allergic eosinophilic inflammation via effects on dendritic cells, basophils, mast cells and ILC2s.[1,2] Beyond T2 inflammation, TSLP can regulate the interaction between mast cells and airway smooth muscle cells.[3,4] TSLP has also been reported to stimulate the synthesis of collagen by lung fibroblasts, promoting airway remodeling.[4] Ultimately, these T2-independent effects can contribute to airway hyperresponsiveness[4,5]

IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; T2, type 2; Th, T helper; TSLP, thymic stromal lymphopoietin

1. Menzies-Gow A, et al. Respir Res. 2020;21:268; 2. Roan F, et al. J Clin Invest. 2019;129:1441–1451; 3. Kaur D, et al. *Chest.* 2012;142:76–85;
4. Gauvreau GM, et al. *Expert Opin Ther Targets.* 2020;24:777–792; 5. Ishmael FT. *J Am Osteopath Assoc.* 2011;111:S11–S17

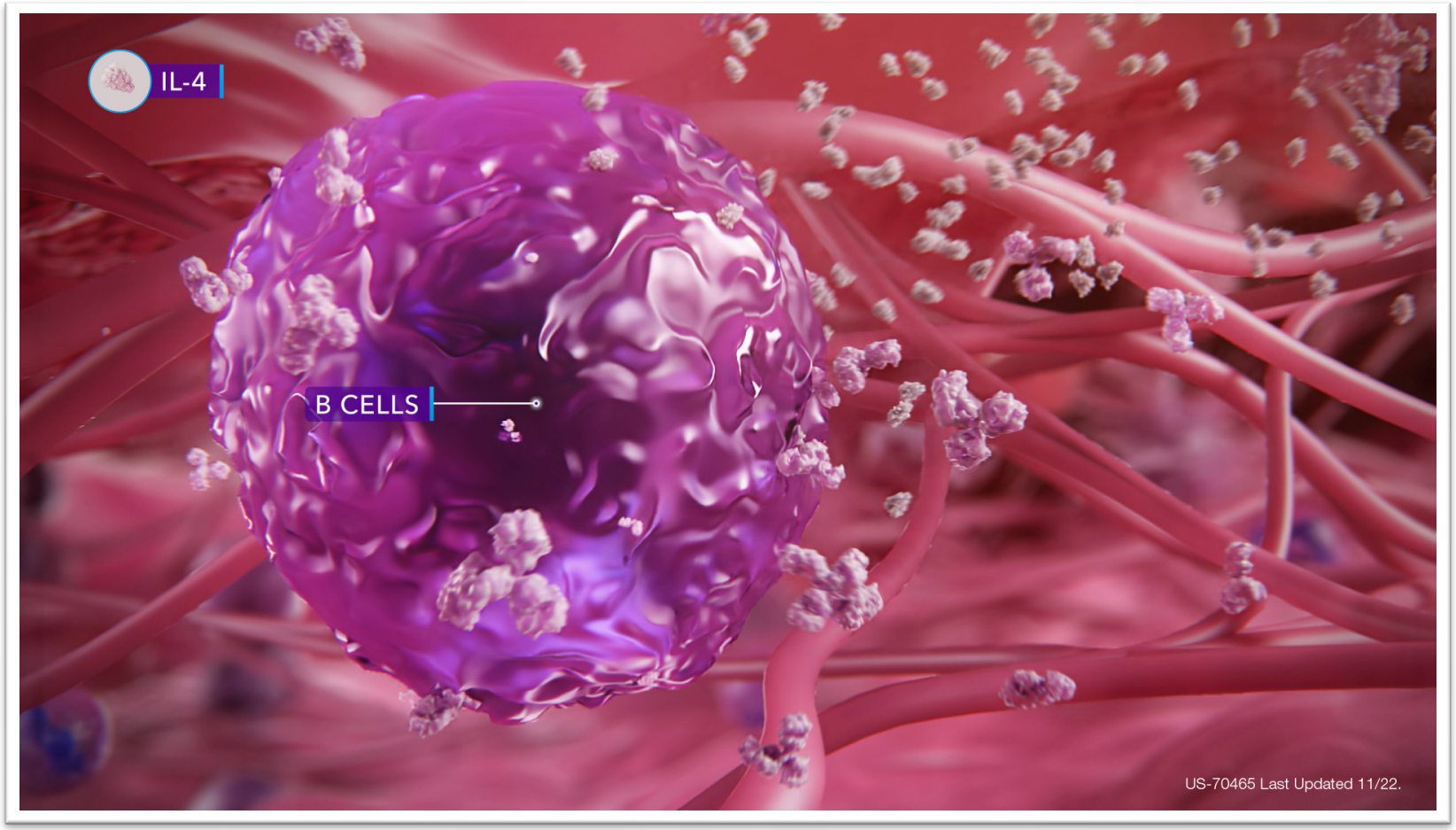


Th2 cells and ILC2s act downstream of the epithelial cytokines

In response to stimulation by epithelial cytokines TSLP, IL-33 and IL-25, Th2 cells and ILC2s release downstream cytokines including IL-4, IL-5 and IL-13[1–3]

IL, interleukin; ILC2, type 2 innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin

1. Menzies-Gow A, et al. *Respir Res.* 2020;21:268; 2. Roan F, et al. *J Clin Invest.* 2019;129:1441–1451; 3. Gauvreau GM, et al. *Expert Opin Ther Targets.* 2020;24:777–792

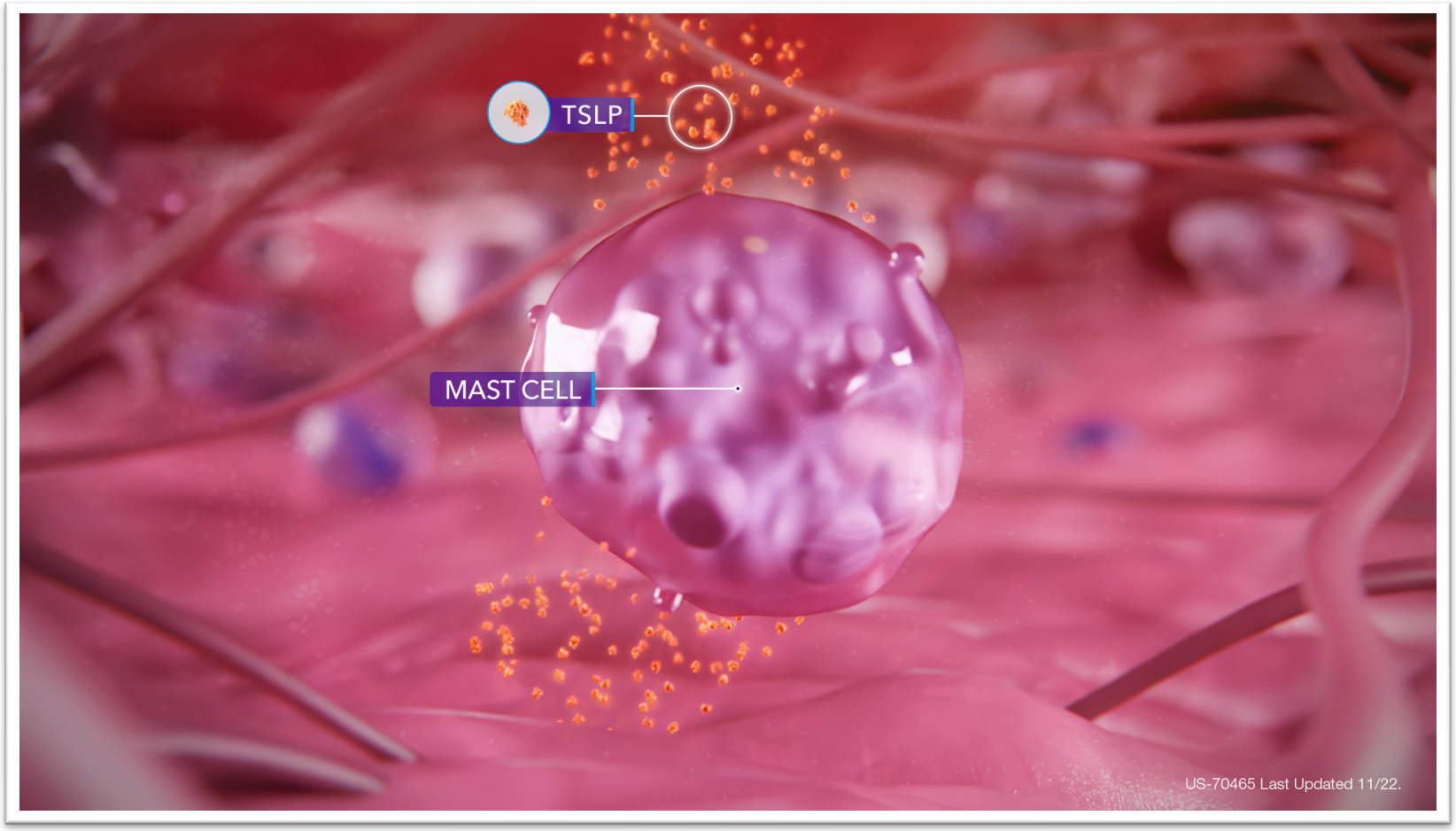


B-cell synthesis of IgE is upregulated in response to inflammatory signaling

IL-4, released by Th2 cells in response to stimulation by epithelial cytokines, triggers immunoglobulin class switching and the production of IgE by B cells[1–3]

IgE, immunoglobulin E; IL, interleukin; Th, T helper

1. Menzies-Gow A, et al. *Respir Res.* 2020;21:268; 2. Roan F, et al. *J Clin Invest.* 2019;129:1441–1451; 3. Gauvreau GM, et al. *Expert Opin Ther Targets.* 2020;24:777–792

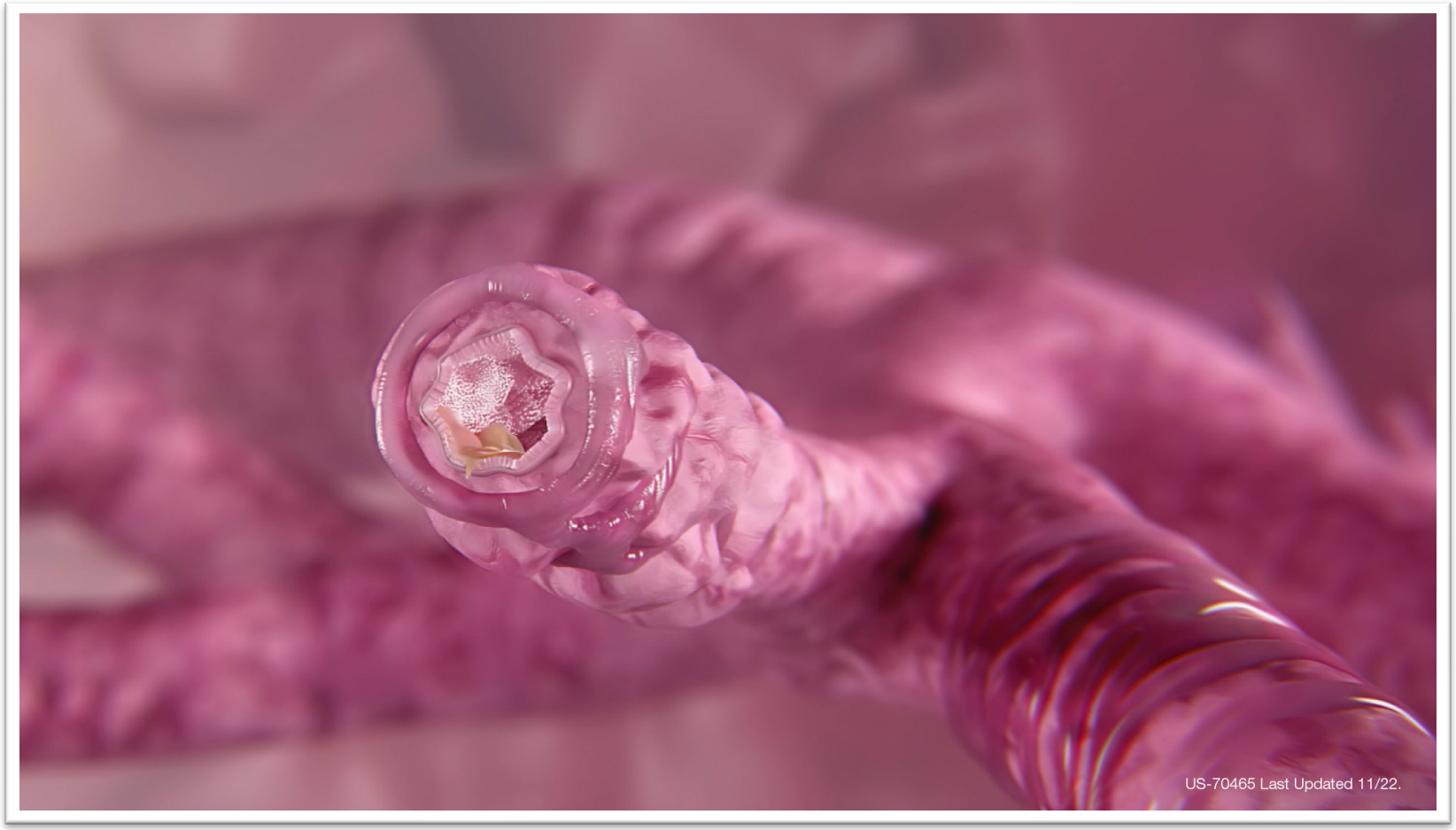


TSLP can influence mast cells, contributing to airway hyperresponsiveness

As part of its T2-independent effects, TSLP can regulate the crosstalk between mast cells and airway smooth muscle by stimulating the release of signaling molecules.[1] In doing so, TSLP-mediated mast cell-airway smooth muscle crosstalk can contribute to airway hyperresponsiveness[2] – a cardinal feature of asthma[3]

T2, type 2; TSLP, thymic stromal lymphopoietin

1. Kaur D, et al. *Chest.* 2012;142:76–85; 2. Gauvreau GM, et al. *Expert Opin Ther Targets.* 2020;24:777–792; 3. Chapman DG, Irvin CG. *Clin Exp Allergy.* 2015;45:706–719



Epithelial cytokines drive pathophysiological changes to the airways in patients with asthma

As a result of inflammatory signaling downstream of the epithelial cytokines TSLP, IL-33 and IL-25, airway inflammation can ultimately lead to edema, mucus hypersecretion, airway hyperresponsiveness and bronchoconstriction[1–5]

IL, interleukin; TSLP, thymic stromal lymphopoietin

1. Bartemes KR, Kita H. *Clin Immunol.* 2012;143:222–235; 2. Marone G, et al. *Front Pharmacol.* 2019;10:1387; 3. Gauvreau GM, et al. *Expert Opin Ther Targets.* 2020;24:777–792;
4. Sumi Y, Hamid Q. *Allergol Int.* 2007;56:341–348; 5. Porsbjerg CM, et al. *Eur Respir J.* 2020;56:2000260

Clinical features of asthma are associated with the downstream effects of epithelial cytokines

Pathophysiological changes occurring in the airways, as a result of epithelial cytokine-mediated inflammatory signaling, can drive clinical features of asthma including cough, wheeze, shortness of breath and increased risk of severe asthma exacerbations[1,2]

1. Porsbjerg CM, et al. *Eur Respir J.* 2020;56:2000260; 2. Heijink IH, et al. *Allergy.* 2020;75:1902–1917