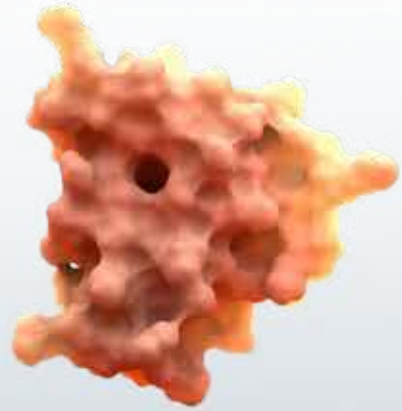
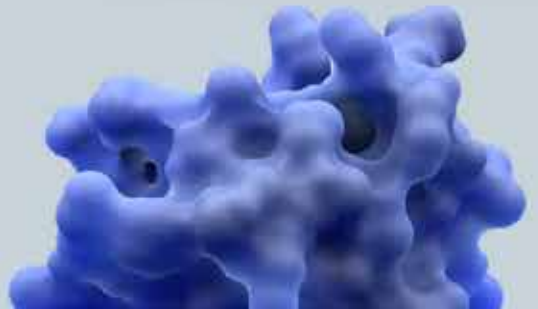


## SECTION 01

# THE BENEFITS OF UNDERSTANDING THE IMMUNOPATHOPHYSIOLOGY OF INFLAMMATORY SKIN DISEASES



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# The benefits of understanding disease pathology in chronic inflammatory skin disease[1-7]

An understanding of how dysregulated immune response pathways can cause disease

Development and use of therapies that selectively target the dysregulated immune response pathways

Allows for development of potentially more effective treatments with fewer safety concerns than traditional immunosuppressants

May allow the potential for long-term use and disease control

Potential for improved outcomes for patients, optimized management for you

1. Wakelin SH. Medicine 2017;45:P363-367; 2. Seegräber M et al. Expert Rev Clin Pharmacol. 2018;11:467-474; 3. Armstrong AW et al. PLoS One. 2019;14:e0210517; 4. Wu J & Guttman-Yassky E. Expert Opin Biol Ther. 2020;20:525-538; 5. Hajar T et al. An Bras Dermatol. 2018;93:104-107; 6. Holm JG et al. Dermatol Ther. 2020;33(2):e13222; 7. Lee JK & Simpson RS. J Allergy Clin Immunol Pract. 2019;7:1659-1661.e1651.

# The importance of long-term disease control for patients with chronic inflammatory skin disease

Chronic inflammatory skin diseases can have a detrimental, long-term impact on patients' lives[1,2]

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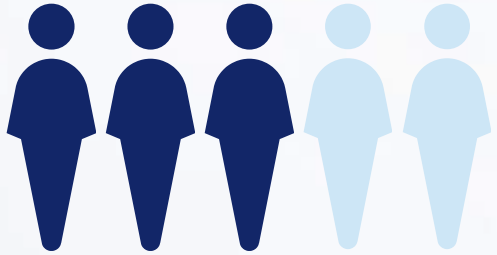
**E.g. Adults with moderate-to-severe atopic dermatitis**



Around

**3 in 5**

patients on systemic immunosuppressants or corticosteroids have inadequately controlled disease despite treatment[2]

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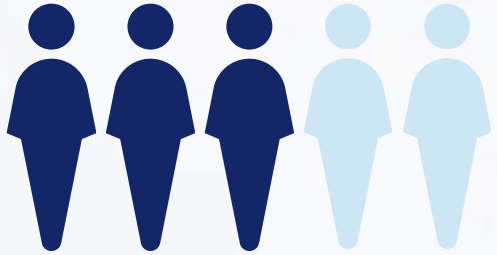

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**Negative impact on:[1,2]**

- **Sleep**
- **Mental health**
- **Quality of life**
- **Productivity** at work/school

Up to **75%**

of surveyed patients with atopic dermatitis/caregivers cite **effective disease control** as the most important contributor to their quality of life[1]

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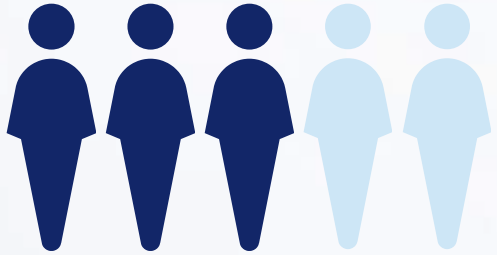

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**Treatments that provide long-term disease control improve the quality of life of patients[1,2]**

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# The benefits of targeted treatments for long-term disease control

## Targeted treatments

## Targeted treatments[1-5]

- Targeted treatments can be defined as those affecting a particular signaling molecule, cytokine, or receptor within a single pathway or a limited set of pathways, and having a demarcated, specific effect on disease
- May provide effective therapeutic outcomes with fewer off-target effects than non-targeted treatments, with the potential for fewer safety concerns
- A favorable benefit-risk profile can reduce the risk of treatment discontinuation due to safety concerns, allowing for long-term use and disease control

1. Simpson EL et al. J Am Acad Dermatol. 2017;77:623-633; 2. Yang N et al. BioDrugs. 2021;35(4):401-415; 3. Wakelin SH. Medicine 2017;45:P363-367; 4. Hajar T et al. An Bras Dermatol. 2018;93:104-107;
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### Non-targeted treatments

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## Broad-acting immunosuppressants[3-7]

- Broad-acting immunosuppressants can be defined as those affecting multiple components of the immune system, or a downstream signaling pathway active across more than one immune response
- The use of broad-acting immunosuppressants can lead to toxicities, due to off-target effects
- Can lead to safety and tolerability concerns for patients and clinicians, increasing the burden of monitoring and potentially limiting their use in long-term disease control

1. Simpson EL et al. J Am Acad Dermatol. 2017;77:623-633; 2. Yang N et al. BioDrugs. 2021;35(4):401-415; 3. Wakelin SH. Medicine 2017;45:P363-367; 4. Hajar T et al. An Bras Dermatol. 2018;93:104-107;
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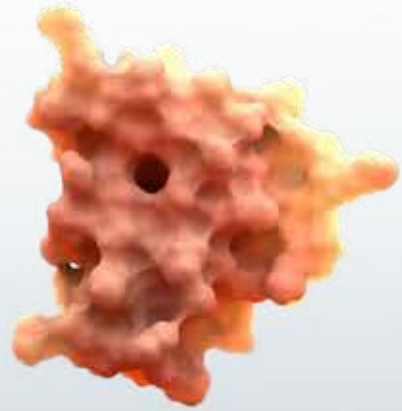
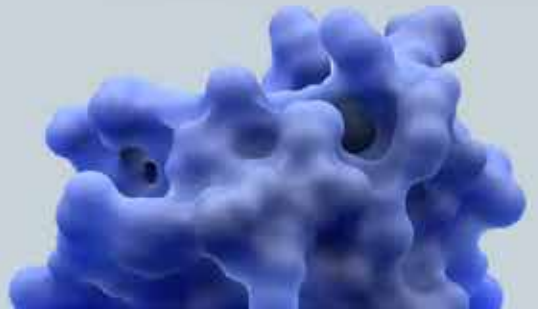


## SECTION 02

# THE CELL-MEDIATED IMMUNE RESPONSES UNDERLYING INFLAMMATORY SKIN DISEASES



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# The three major types of cell-mediated immune response*

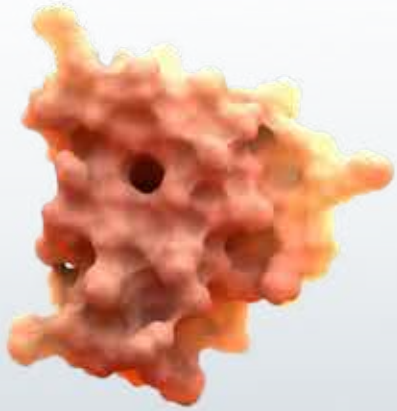
| | Type 1 | Type 2 | Type 3 |
|---|---|---|---|
| **Naturally protective role against:**[1-3] | Intracellular bacterial and viral infection, cancer cells | Parasitic worms | Extracellular bacterial and fungal infection |
| **Immune cells**[1] | Th1, ILC1, NK | Th2, Mast cell, ILC2, Eosinophil | Th17, ILC3, Tc17 |
| **Key cytokines**[1,4] | IFN-γ, IL-12, IL-2, TNF | IL-4, IL-13, IL-5, IL-31 | IL-17, IL-22, IL-23 |
| **Examples of broad-acting intracellular signaling pathways associated across immune responses**[5-8] | Calcineurin-NFAT ⟷ Calcineurin-NFAT ⟷ Calcineurin-NFAT (Calcineurin-NFAT signaling acts across **all three immune responses** and acts within T cells, including: Th1 Th2 and Th17) | | |
| | JAK-STAT ⟷ JAK-STAT ⟷ JAK-STAT (JAK-STAT signaling acts across all three immune responses and interacts with multiple cytokines) | | |

When immune response pathways are functioning normally they play a protective role, but when they become dysregulated they can contribute to disease[1]

*While the three types of cell-mediated immune responses are well recognized, the distinction is a simplification. The three responses may functionally overlap, interact, and change over time

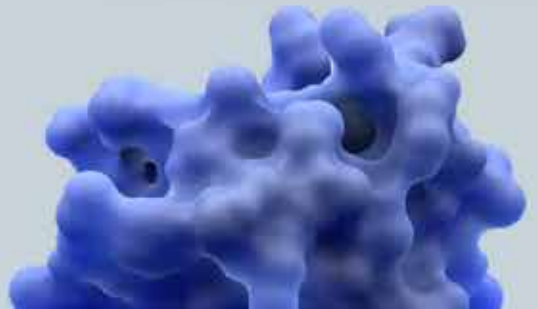
IL, interleukin; ILC, innate lymphoid cell; IFN-γ, interferon gamma; JAK, janus kinase; NFAT, nuclear factor of activated T cells; NK, natural killer; STAT, signal transducer and activator of transcription; Tc, cytotoxic T cell (CD8+); Th, T helper cell (CD4+); TNF, tumor necrosis factor.

1. Annunziato F et al. J Allergy Clin Immunol. 2015;135:626-635; 2. Gandhi NA et al. Nat Rev Drug Discov. 2016;15:35-50; 3. Kaiko GE et al. Immunology. 2008;123:326-338; 4. Weidinger S et al. Nat Rev Dis Primers.2018;4:1; 5. Yoshida H et al. Immunity 1998;8:115-124; 6. Park YJ et al. Front Immunol. 2020;11:195; 7. Morris R et al. Protein Sci. 2018;27:1984-2009. 8. Schindler C & Plumlee C. Semin Cell Dev Biol. 2008;19:311-318.



SECTION 03

# THE ROLE OF THE TYPE 2 IMMUNE RESPONSE IN INFLAMMATORY SKIN DISEASES



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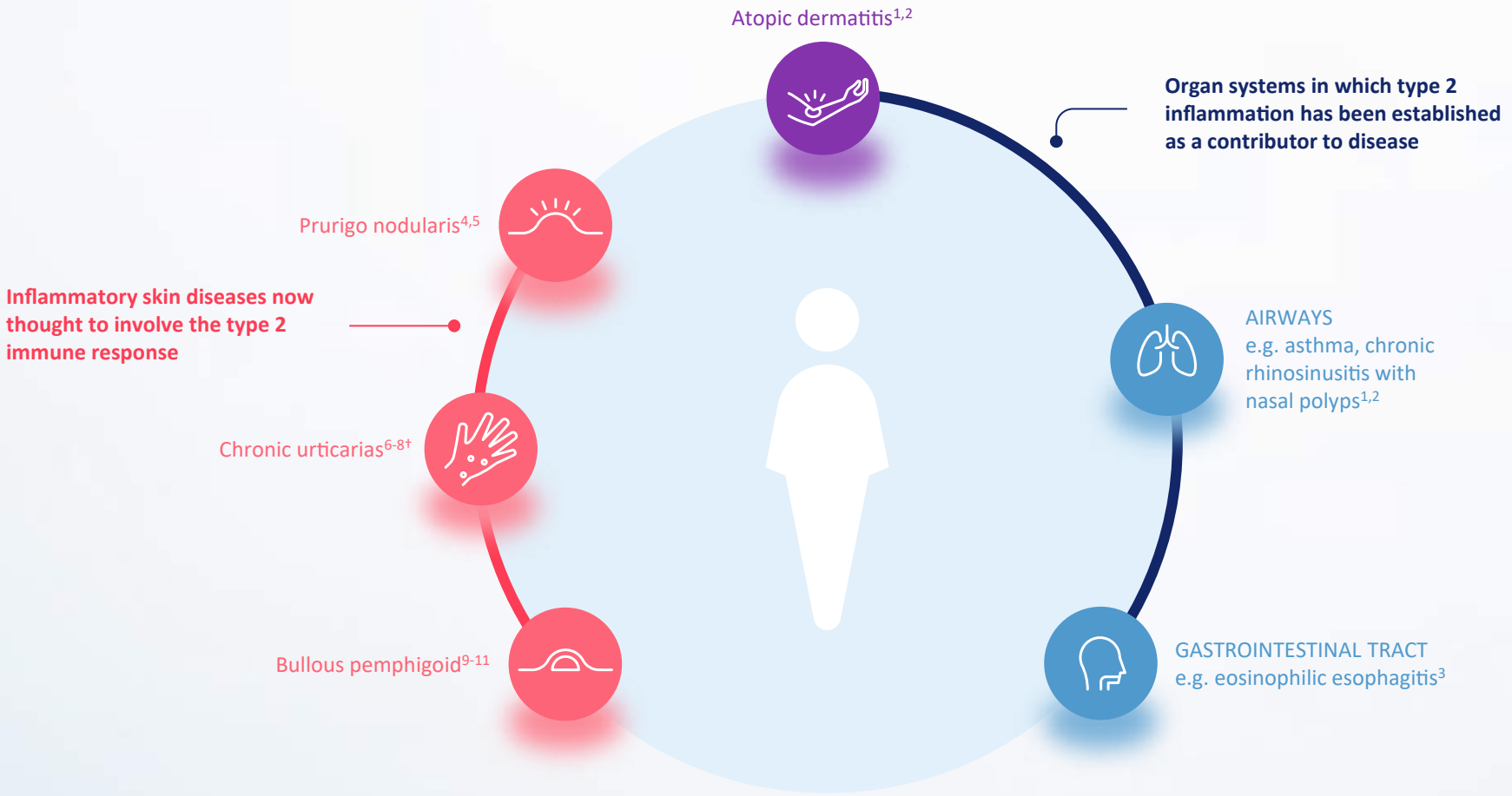
# Dysregulation of the type 2 immune response can result in type 2 inflammation and drive disease*

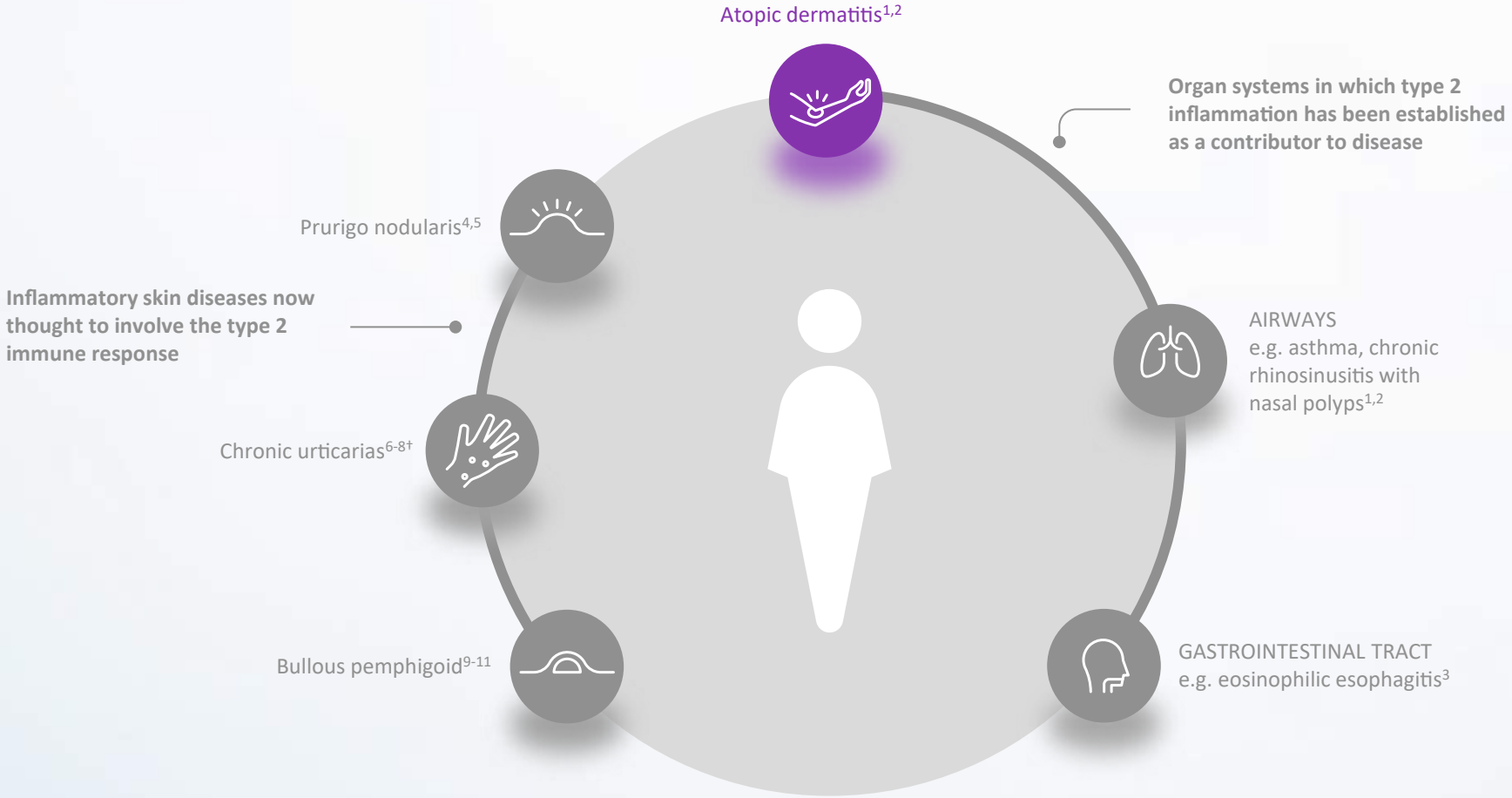



- Patients can experience individual or multiple type 2 inflammatory diseases[1,3,12,13]
- Type 2 inflammation occurs systemically and can affect multiple organ systems, including the:[1-3]
  - Skin (e.g. atopic dermatitis)
  - Airways (e.g. asthma)
  - Gastrointestinal tract (e.g. eosinophilic esophagitis)
- Type 2 inflammatory diseases may occur in genetically predisposed individuals and/or within certain environments[1,14]

*The visual shows examples of diseases now thought to involve type 2 inflammation or the type 2 immune response: it does not provide an exhaustive list
†Chronic spontaneous urticaria and chronic inducible urticaria

1. Gandhi NA et al. Nat Rev Drug Discov. 2016;15:35-50; 2. Hammad & Lambrecht BN. Immunity. 2015;43:29-40; 3. Hill DA & Spergel JM. Curr Allergy Asthma Rep. 2016;16:9; 4. Fukushi S et al. Br J Dermatol. 2011;165:990-996; 5. Fostini AC et al. J Dermatol Treat. 2013;24:458-462; 6. Kay AB et al. Br J Dermatol. 2015;172:1294-1302; 7. Caproni M et al. J Dermatol Sci. 2004;36:57-59; 8. Church MK et al. Immunol Rev. 2018;282:232-247; 9.Hashimoto T et al. J Am Acad Dermatol. 2020;83:53-62; 10. Teraki Y et al. J Invest Dermatol. 2001;117:1097-1102; 11. Gounni AS et al. Clin Immunol. 2006;120:220-231; 12. Zeidler C & Ständer S. Eur J Pain. 2016;20:37-40; 13. Zheng T et al. Allergy Asthma Immunol Res. 2011;3:67-73; 14. Weidinger S et al. Nat Rev Dis Primers. 2018;4:1.

# Exploring the driving role of type 2 inflammation in atopic dermatitis*

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# Type 2 inflammation drives atopic dermatitis

- Type 2 inflammation drives atopic dermatitis regardless of patient characteristics (e.g. age, ethnicity)[1]
- Multiple cytokines contribute to type 2 inflammation. Increased **IL-4** and **IL-13** signaling is a key and central driver of type 2 inflammation and contributes to clinical features of atopic dermatitis. **IL-31** is also a key cytokine contributing to itch[2-6]

IL, interleukin; ILC, innate lymphoid cell; IL-4Rα, IL-4 receptor α; IL-13Rα1, IL-13 receptor α1; IL-31Rα, IL-31 receptor α; Tc2, cytotoxic T cell 2; Th2, T helper type 2 cell.

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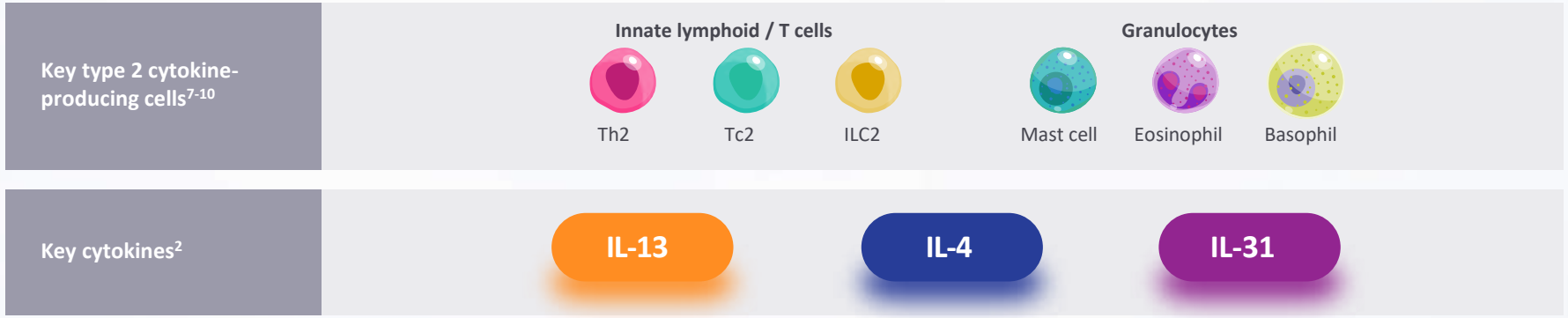


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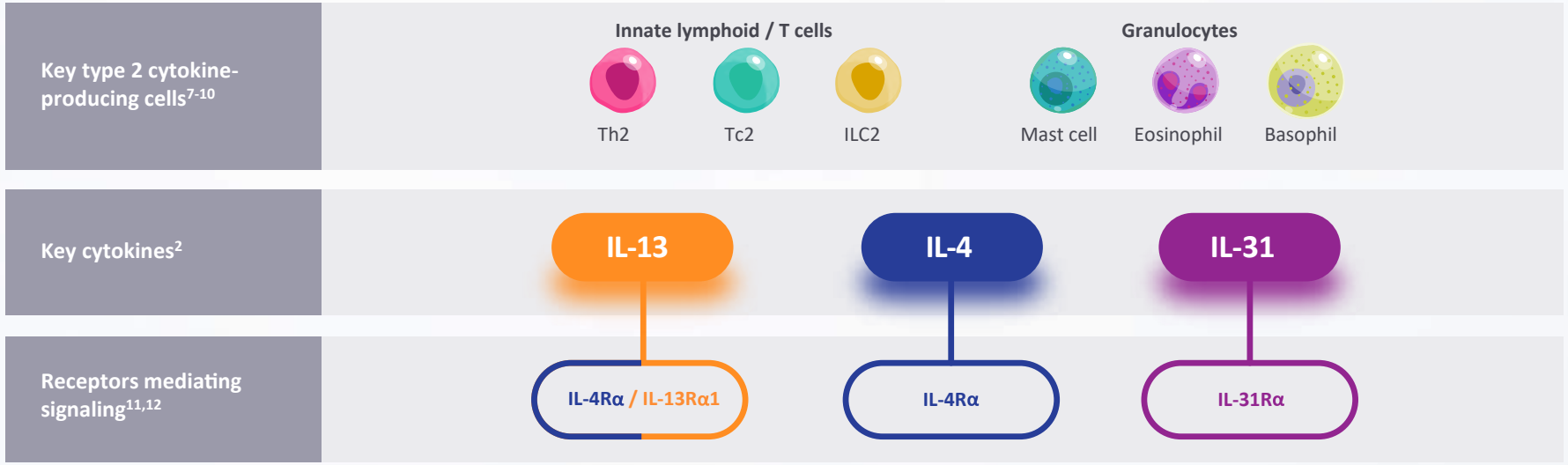


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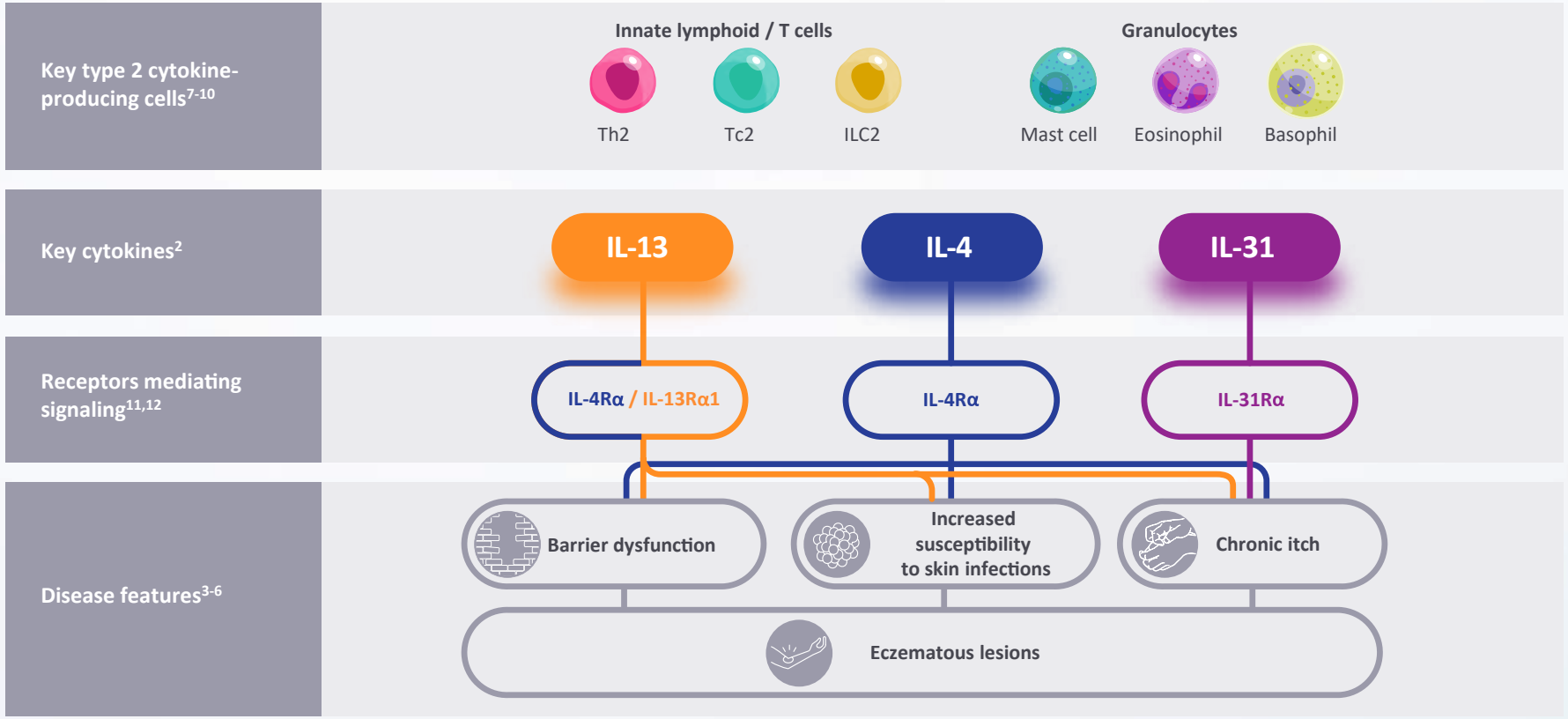


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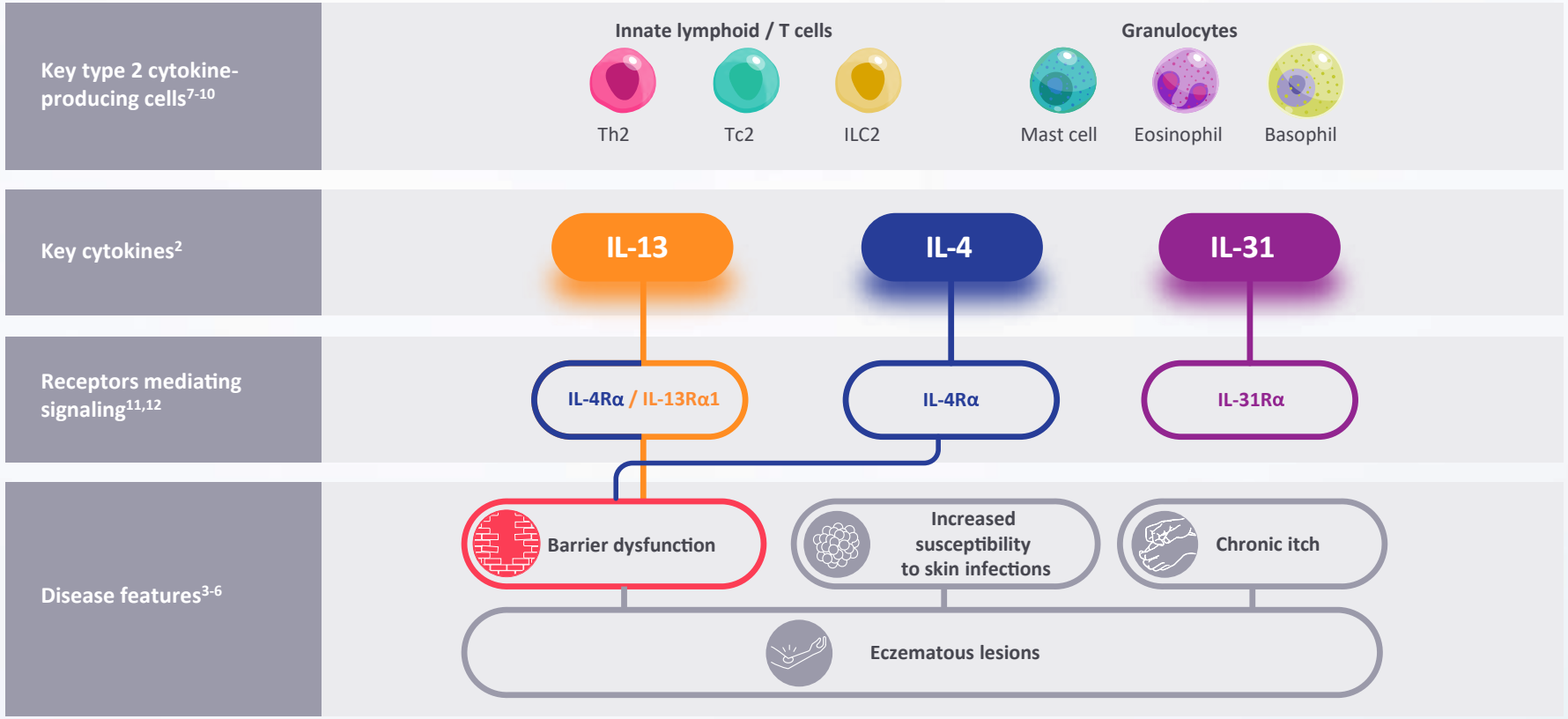


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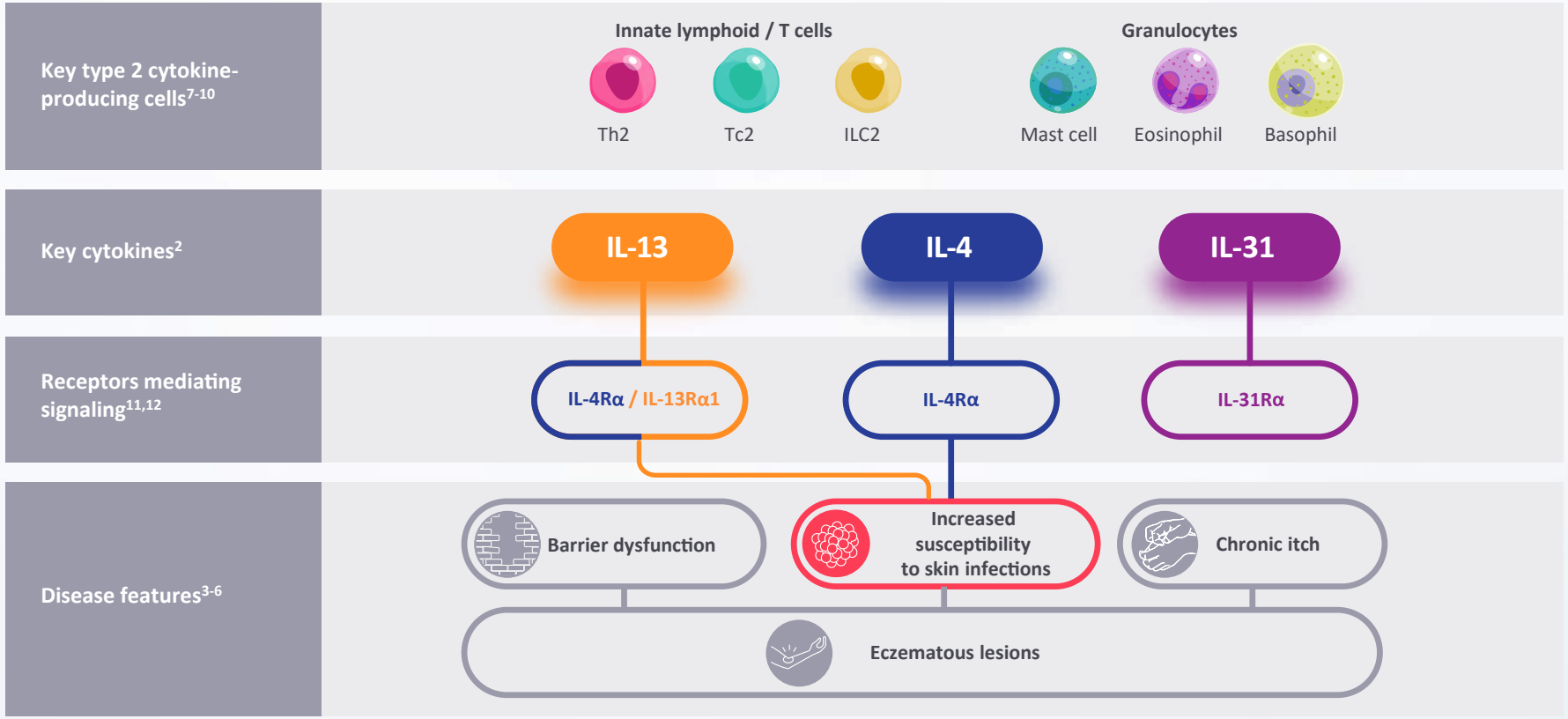


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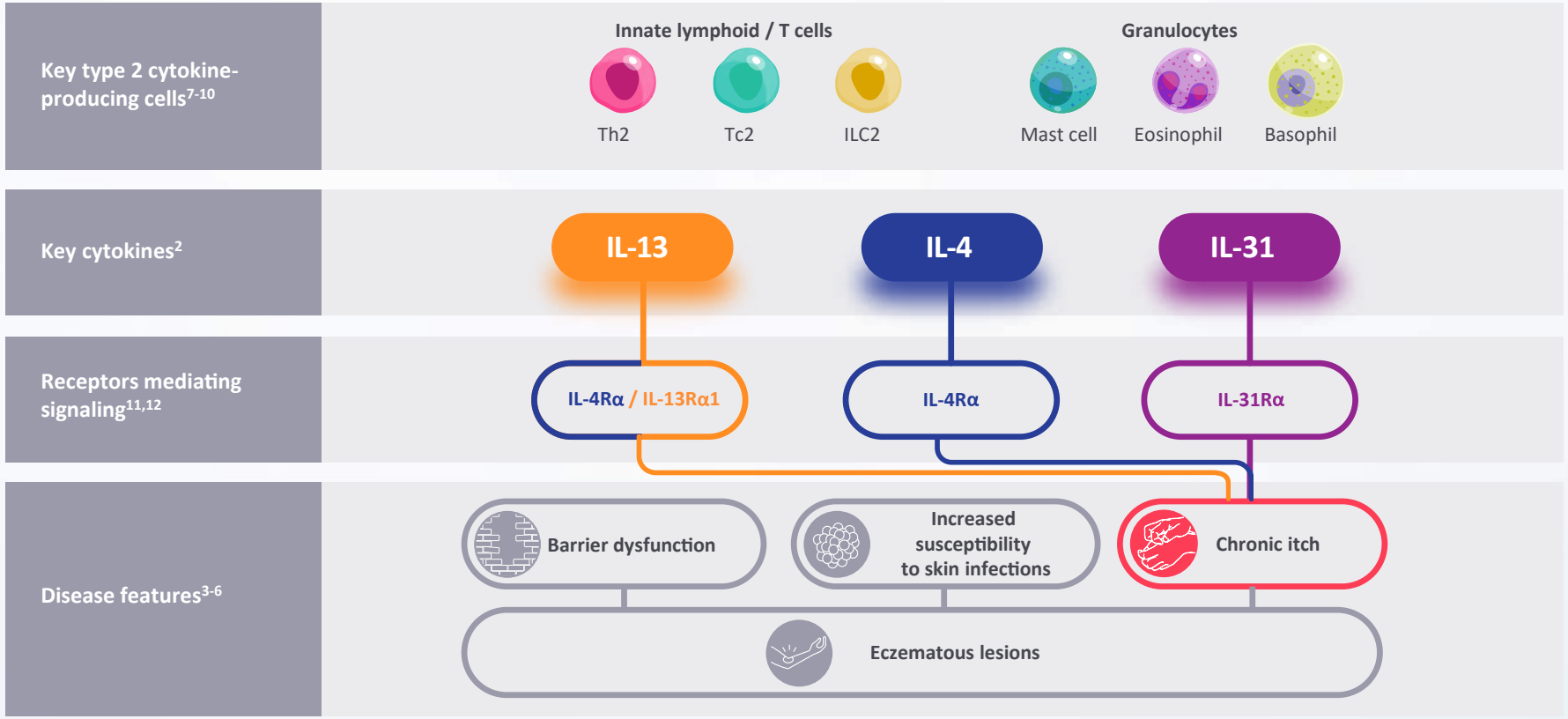
- Multiple cytokines contribute to type 2 inflammation. Increased **IL-4** and **IL-13** signaling is a key and central driver of type 2 inflammation and contributes to clinical features of atopic dermatitis. **IL-31** is also a key cytokine contributing to itch[2-6]




IL, interleukin; ILC, innate lymphoid cell; IL-4Rα, IL-4 receptor α; IL-13Rα1, IL-13 receptor α1; IL-31Rα, IL-31 receptor α; Tc2, cytotoxic T cell 2; Th2, T helper type 2 cell.

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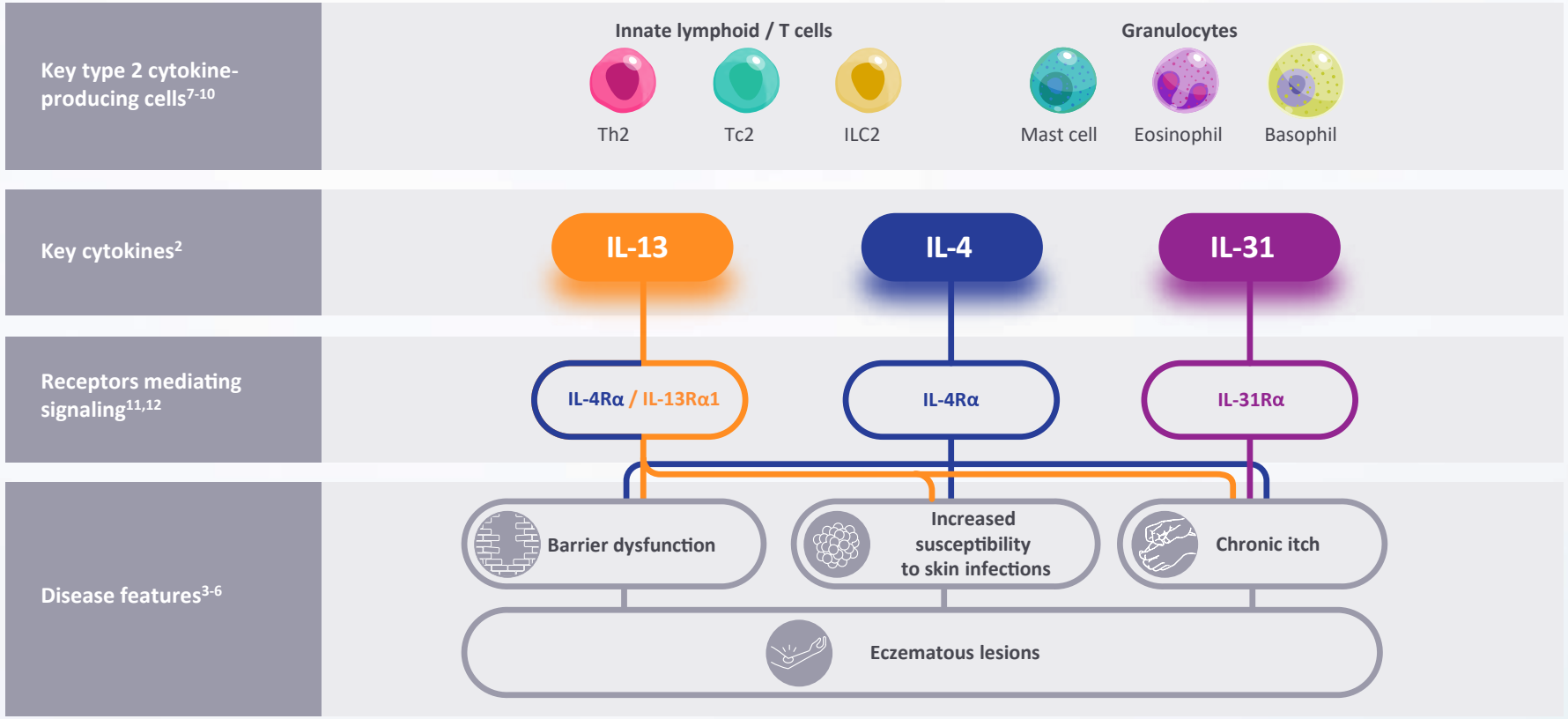


**As type 2 inflammation occurs systemically, it can impact lesional and non-lesional skin**[11,15,16]

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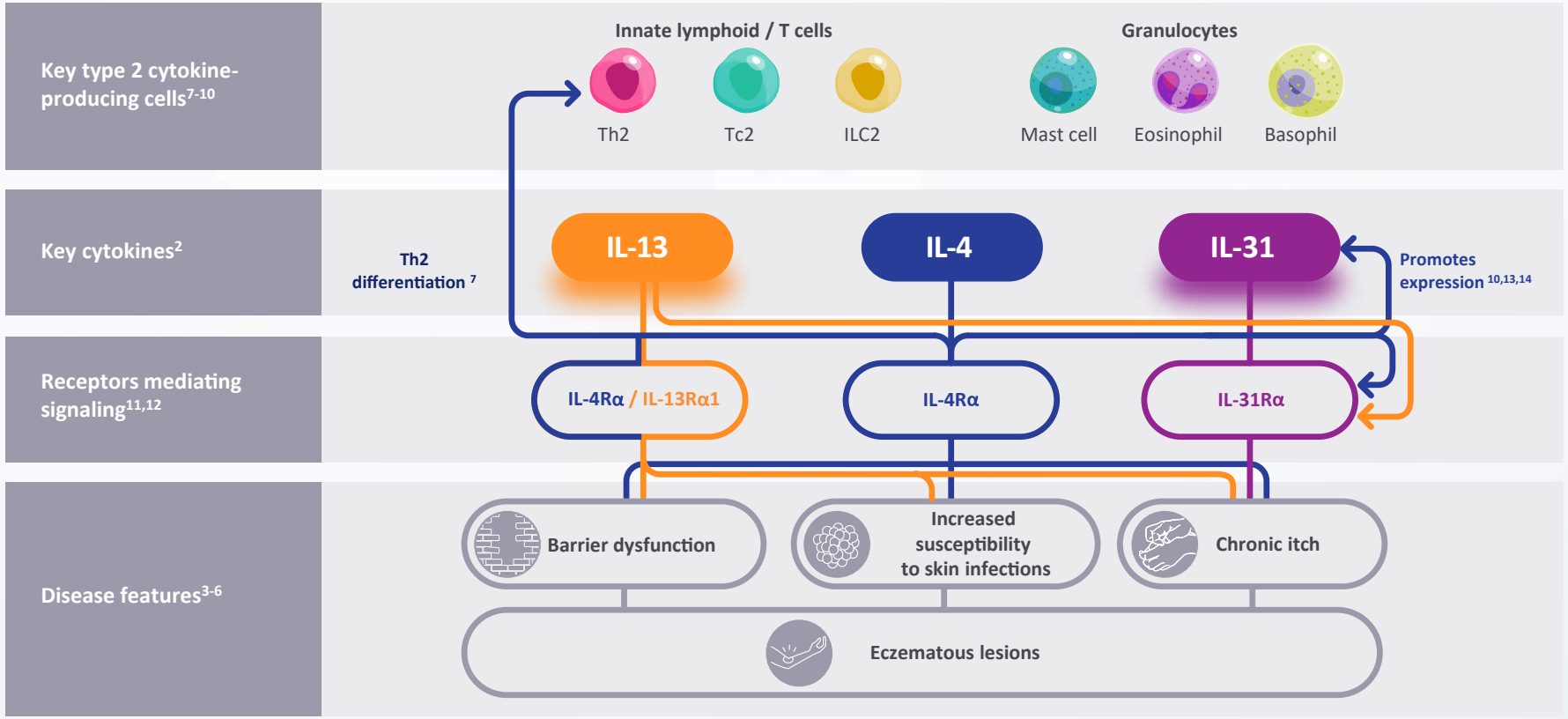


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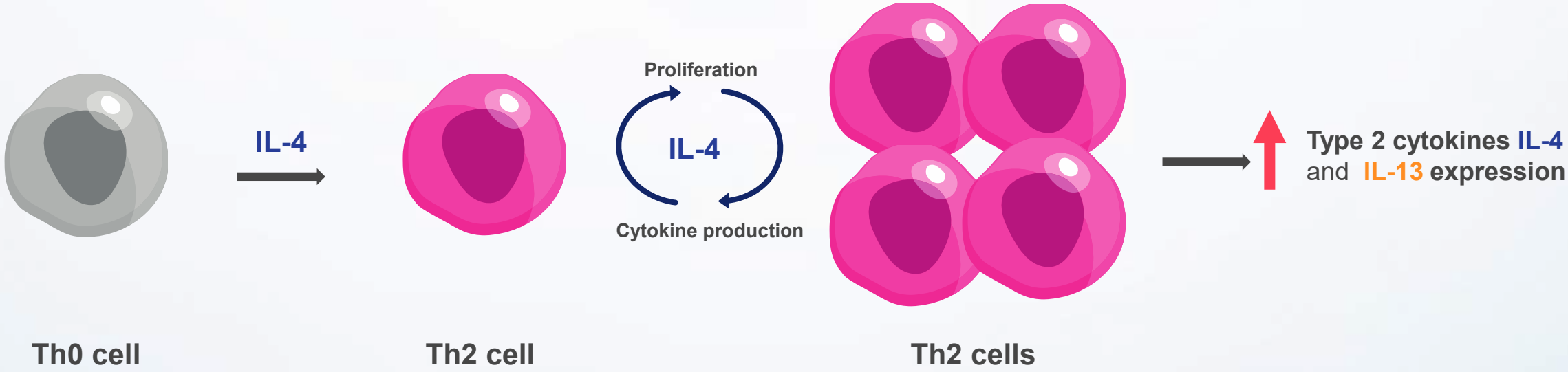
# IL-4 and IL-13 signaling via IL-4Rα is key and central to perpetuation of type 2 inflammation: Role in Th2 cells

## Th2 cells, the classic type 2 immune cell

**IL-4,** mediated by IL-4Rα, promotes the differentiation of Th0 cells into Th2 cells. These Th2 cells then proliferate in response to **IL-4** and produce more **IL-4,** and other type 2 cytokines, in a positive feedback loop[1]




IL, interleukin; Th0, naïve T cell; Th2, T helper type 2 cell.

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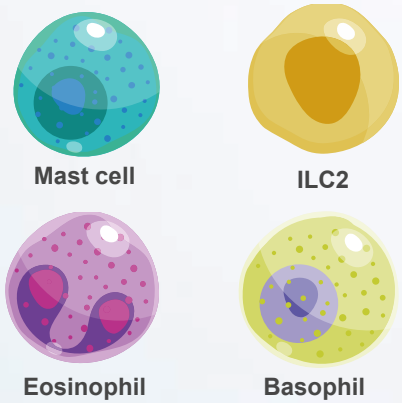


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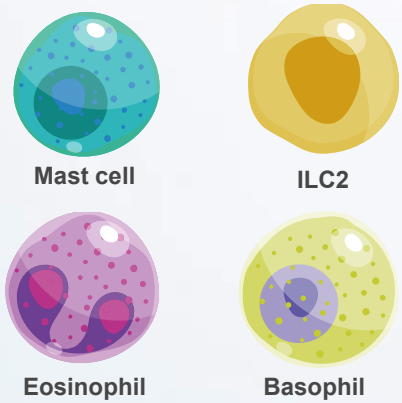
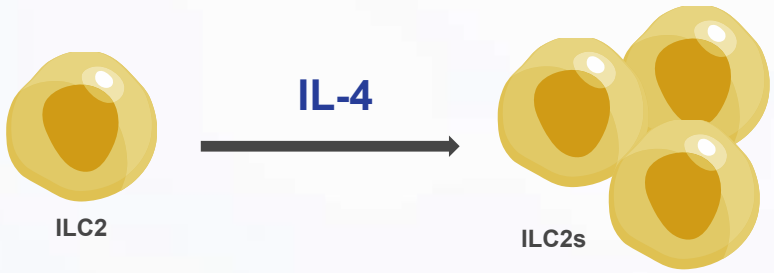



**IL-4** signaling promotes ILC2 proliferation[5]

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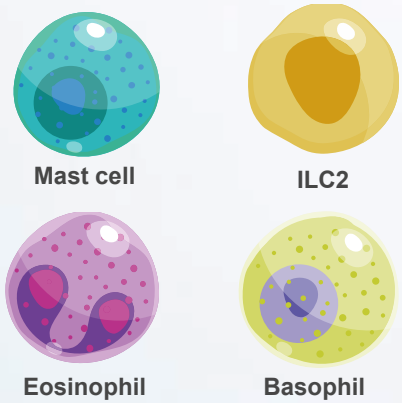


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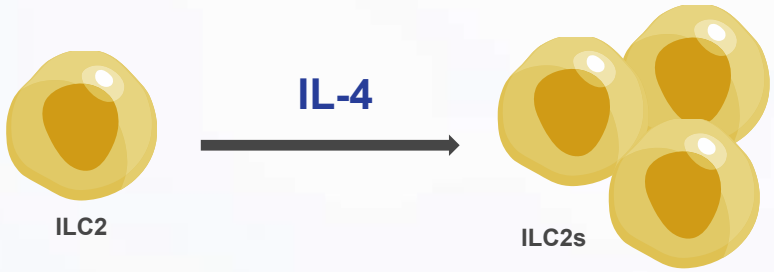
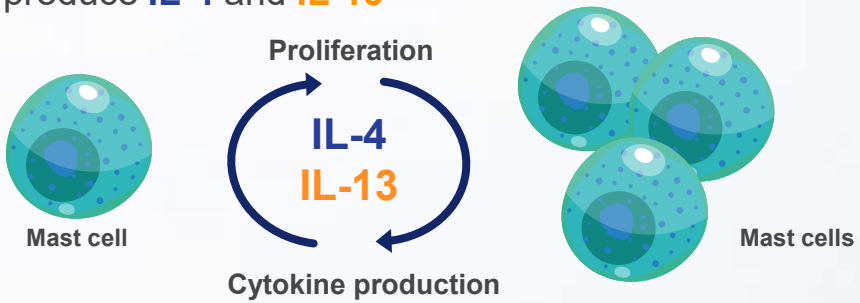



**IL-4** and **IL-13** signaling promotes mast cell proliferation.[6,7] Mast cells (and other type 2 cells) produce **IL-4** and **IL-13** [1,2,4,8,9]

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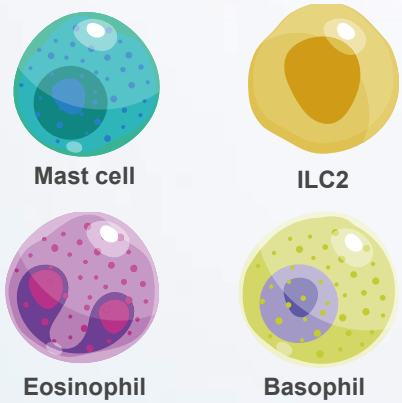


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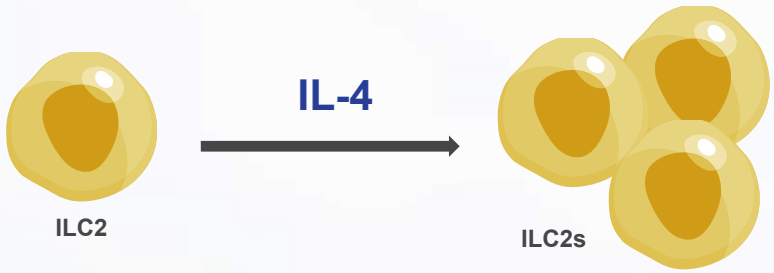


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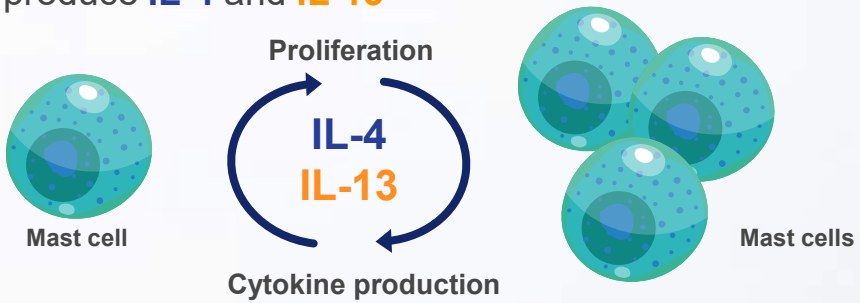
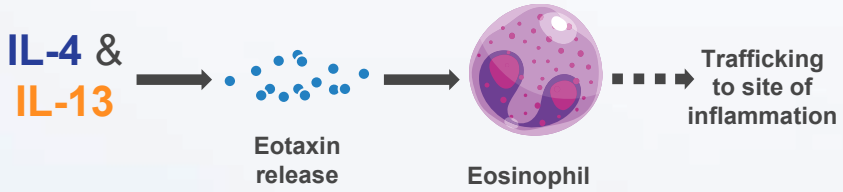



**IL-4** and **IL-13** signaling can affect molecules that control eosinophil trafficking to areas of inflammation[8]

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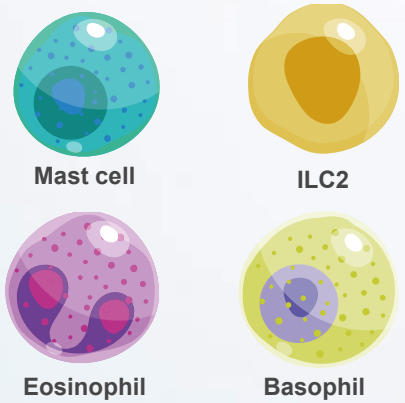


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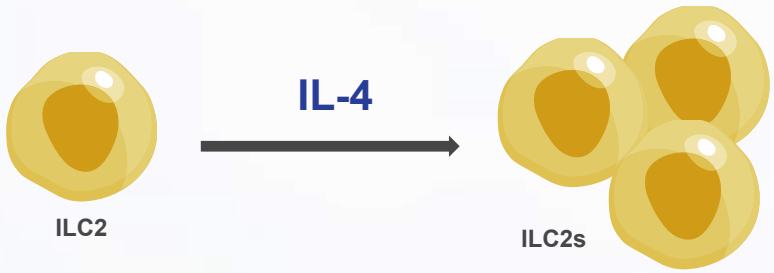


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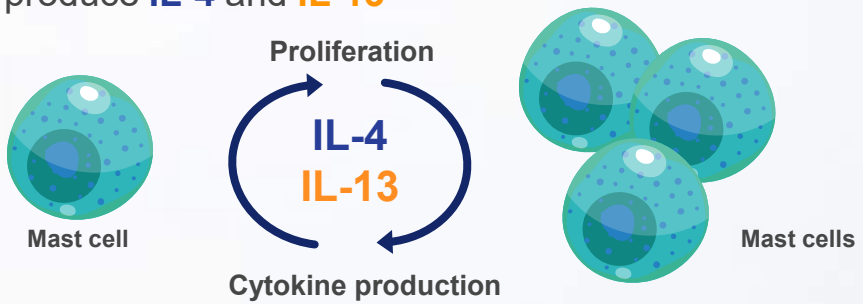


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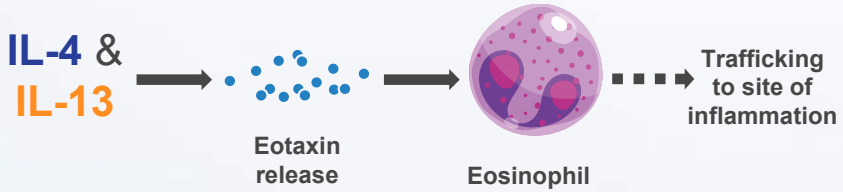
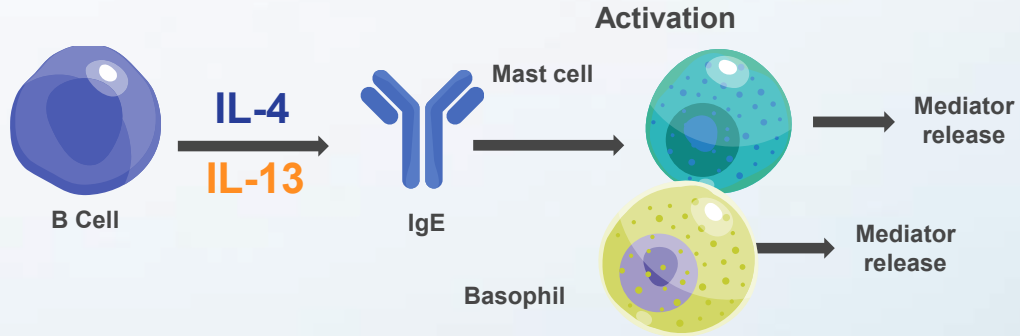



## IL-4 and IL-13 signaling promote IgE production via B cells,[8] inducing the IgE-dependent activation of mast cells and basophils, and release of type 2 cytokines and other inflammatory mediators[10,11]

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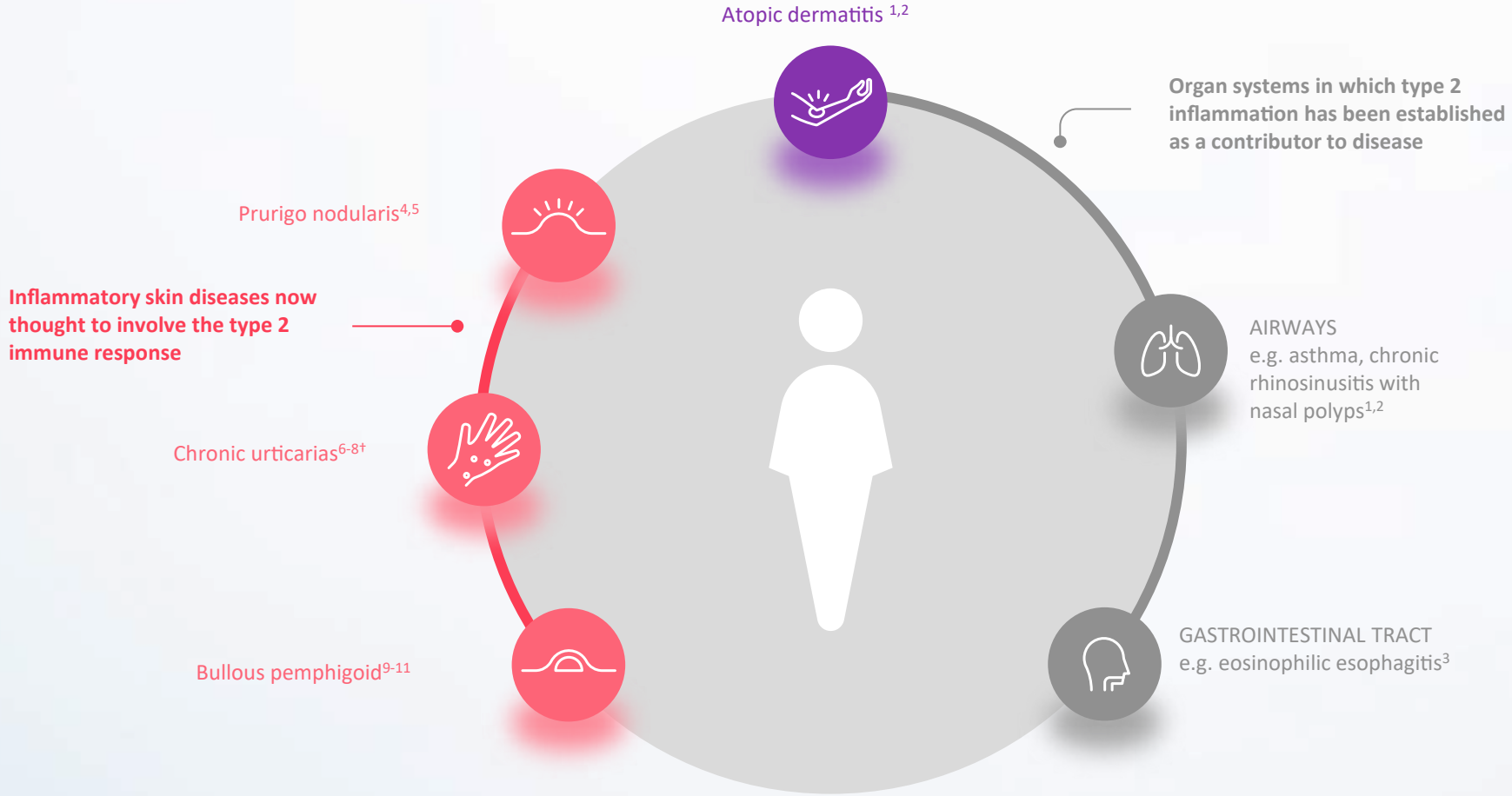
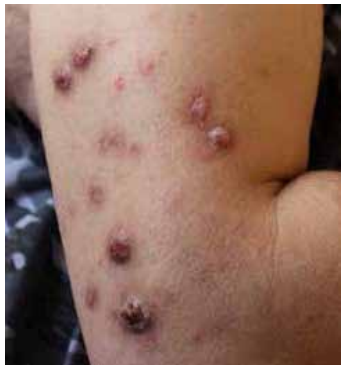
# Introducing the other inflammatory skin diseases now thought to involve the type 2 immune response




*The visual shows examples of diseases now thought to involve type 2 inflammation or the type 2 immune response: it does not provide an exhaustive list
†Chronic spontaneous urticaria and chronic inducible urticaria

1. Gandhi NA et al. Nat Rev Drug Discov. 2016;15:35-50; 2. Hammad & Lambrecht BN. Immunity. 2015;43:29-40; 3. Hill DA & Spergel JM. Curr Allergy Asthma Rep. 2016;16:9; 4. Fukushi S et al. Br J Dermatol. 2011;165:990-996; 5. Fostini AC et al. J Dermatol Treat. 2013;24:458-462; 6. Kay AB et al. Br J Dermatol. 2015;172:1294-1302; 7. Caproni M et al. J Dermatol Sci. 2004;36:57-59; 8. Church MK et al. Immunol Rev. 2018;282:232-247; 9.Hashimoto T et al. J Am Acad Dermatol. 2020;83:53-62.; 10. Teraki Y et al. J Invest Dermatol. 2001;117:1097-1102; 11. Gounni AS et al. Clin Immunol. 2006;120:220-231.

# Prurigo nodularis



## 1. WHAT IS IT?

- A neuroimmune-mediated inflammatory skin disease characterized by intense itch and the development of nodular lesions[1,2]
- Typically affects people in their 50s and 60s, but can occur at other ages[3,4]
- There are no approved therapies for prurigo nodularis[5]

## 2. WHAT CAUSES IT?

- Pathophysiology is not well understood but is thought to depend on an interplay of signals between the skin, and immune and nervous systems[2,6,7]
- Prurigo nodularis is seen with a range of comorbidities (e.g. atopic dermatitis or chronic kidney failure),[8] but may also appear in isolation without comorbidities[1]

## 3. ROLE OF THE TYPE 2 IMMUNE RESPONSE

Type 2 cytokines and signaling proteins have been shown to be elevated in the lesional skin of patients with prurigo nodularis[9,10] and have been suggested to play a role in the disease features/mechanisms, e.g.

**Itch**:[11,12]
**IL-4, IL-13, and IL-31**

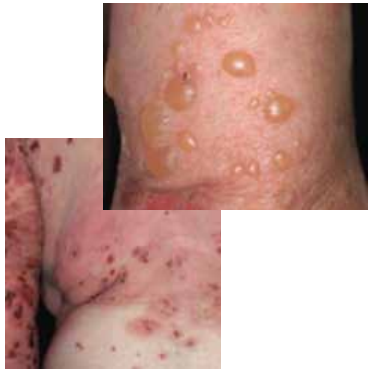
**Barrier dysfunction**:[9]
**IL-4 and IL-13**

**After a number of case series and early clinical trials, treatments for prurigo nodularis targeting mediators of the type 2 immune response are undergoing clinical investigation**[13-17]

IL, interleukin.

1. Elmariah S et al. J Am Acad Dermatol. 2021;84(3):747-760; 2. Zeidler C et al. Dermatol Clin. 2018;36(3):189-197; 3. Hughes JDM et al. Medicines (Basel). 2020;7:4; 4. Pereira MP et al. J Eur Acad Dermatol Venereol. 2020;34:2373-2383; 5. Ständer HF et al. J Am Acad Dermatol. 2020;82:460-468; 6. Mack MR, Kim BS. Trends Immunol. 2018;39(12):980-991; 7. Kwatra SG. N Engl J Med. 2020;382(8):757-758; 8. Huang AH et al. J Invest Dermatol. 2020;140(2):480-483.e484; 9. Fukushi S et al. Br J Dermatol. 2011;165:990-996; 10. Park K et al. Eur J Dermatol. 2011;21:135-6; 11. Oetjen LK et al. Cell. 2017;171:217-228; 12. Mack MR & Kim BS. Trends Immunol. 2018;39:980-991; 13. Holm JG et al. Dermatol Ther. 2020;33:e13222; 7; 14. NCT04183335. Available at https://clinicaltrials.gov/ct2/show/NCT04183335; 15. NCT04202679. Available at https://clinicaltrials.gov/ct2/show/NCT04202679; 16. Ständer S et al. N Engl J Med. 2020;382:706-716; 17. NCT04204616. Available at https://clinicaltrials.gov/ct2/show/NCT04204616.

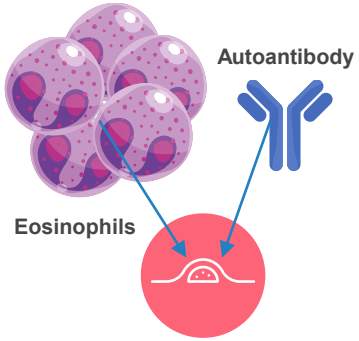
# Bullous pemphigoid



## 1. WHAT IS IT?

- Chronic-relapsing, blistering autoimmune disease, often associated with itch[1-3]
- Predominantly affects the elderly (>late 60s)[4]
- No approved therapies and ~10–40% mortality in the first year[5-7]

Images reproduced from Kayani & Aslam, 2017[6] with permission from BMJ Publishing Group Ltd




## 2. WHAT CAUSES IT?

- It may begin as urticarial or eczematous lesions[3]
- Exact pathogenesis is not well understood but central concepts include the formation of autoantibodies against proteins involved in dermal-epidermal adhesion and subsequent eosinophil infiltration[3,8]
- The type 1, type 2, and type 3 immune responses have been suggested to play a role[1,8-14]

## 3. ROLE OF THE TYPE 2 IMMUNE RESPONSE

Type 2 cytokines have been found to be elevated in the blood and/or lesional skin of patients with bullous pemphigoid,[1,9, 10,14] and, alongside Th2 cells, have been suggested to contribute to disease mechanisms, e.g.

**Itch**:[1,15]
**IL-4**, **IL-13**, and **IL-31**


**Eosinophilia**:[12,16]
**IL-4**, **IL5**, and **IL-13**

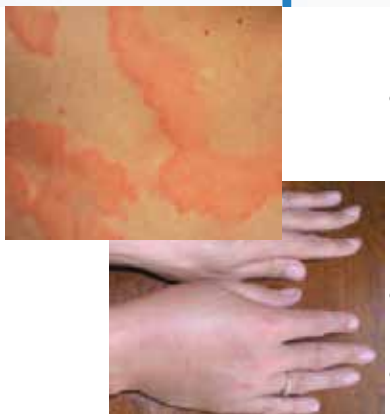
**Autoantibody production**:[11,13,14,17]
**Th2 cells**, **IL-4**, and **IL-13**

**After a number of case series and early clinical trials, treatments for bullous pemphigoid targeting mediators of the type 2 immune response are under ongoing clinical investigation**[18-22]

IL, interleukin; Th, T helper cell (CD4+).

1. Hashimoto T et al. J Am Acad Dermatol. 2020;83:53-62; 2. Wang Y et al. Ann Med 2018;50:234-239; 3. Amber KT et al. Front Med. 2018;5:201; 4. Liu YD et al., Arch Dermatol Res. 2017;309:335–347; 5. Kridin K et al., Acta Derm Venereol. 2019;99:72-77; 6. Abdat R et al. J Am Acad Dermatol. 2020. doi: 10.1016/j.jaad.2020.01.089; 7. Kayani M & Aslam AM. BMJ. 2017;357:j2169; 8. Giomi B et al. J Dermatol Sci. 2002;30(2):116-128; 9. D'Auria L et al. Arch Dermatol Res. 1998;290:25-27; 10. Gounni AS et al. Clin Immunol. 2006;120:220-231; 11. Bowszyc-Dmochowska M & Dmochowski M. J Med. 2002;33:189-198; 12. Gandhi NA et al. Nat Rev Drug Discov. 2016;15:35-50; 13. Hertl M et al. J. Clin Invest. 2006;116:1159-1166; 14. Teraki Y et al. J Invest Dermatol. 2001;117:1097-1102; 15. Oetjen LK et al. Cell. 2017;171:217-228; 16. Kayani M & Aslam AM. BMJ. 2017;357;j2169; 17. Schiavo AL et al. Clin Dermatol. 2013;31:391-399; 18. Abdat R et al. J Am Acad Dermatol. 2020. doi: 10.1016/j.jaad.2020.01.089; 19. Kaye A et al. JAMA Dermatol. 2018;154:1225-1226; 20. NCT04206553. Available at https://clinicaltrials.gov/ct2/show/NCT04206553; 21. Kremer N et al. Am J Clin Dermatol. 2019;20:209-216; 22. Izumi K et al. Frontiers in immunology. 2019;10:978-978..

# Chronic spontaneous urticaria



Images sourced from DermNet NZ

## 1. WHAT IS IT?

- Chronic, immune-mediated disease with no specific, identified, inducing factor[1,2]
  - Characterized by the spontaneous appearance of wheals (hives) and/or angioedema persisting for more than 6 weeks, often associated with intense itch[1,2]
- Typically affects adults aged 20–40 years old and is nearly twice as common in women than men[3]
- Despite available treatment options, many patients remain inadequately controlled[3-5]

## 2. WHAT CAUSES IT?

- Complex and not fully characterized pathophysiology, involving:[1,6,7]
  - Activation and degranulation of key effector cells, primarily mast cells and basophils

Mast cell Basophil

  - Release of inflammatory mediators, including those related to the type 2 immune response (e.g. IgE, IL-4, IL-13)


For example:

- An autoimmune process involving IgE (anti-self) or IgG (anti-IgE or anti-FcεRI) antibodies is thought to contribute to the pathogenic activity of mast cells and basophils[6,8]
- Type 2 cytokines IL-4 and IL-13 promote IgE and IgG1 production;[9,10] and IL-4 also contributes to mast cell proliferation and may increase FcεRI expression[10,11]

## 3. ROLE OF THE TYPE 2 IMMUNE RESPONSE

Type 2 cytokines have been found to be elevated in the blood and/or lesional skin of patients with chronic spontaneous urticaria,[12-15] and, alongside Th2 cells, have been suggested to contribute to disease mechanisms, e.g.

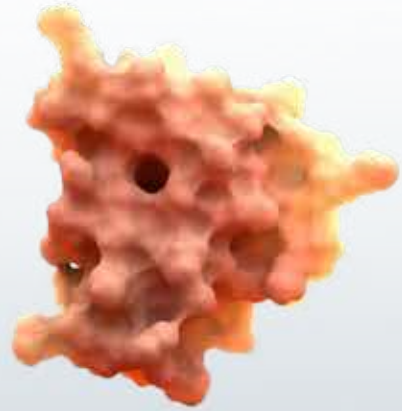
**Itch**:[15,16]
**IL-4**, **IL-13**, and **IL-31**

**Wheal development**:[14]
**IL-4**, and **IL-13**

**After promising case series, treatments for CSU targeting the type 2 cytokines are under ongoing clinical investigation[13-17]**

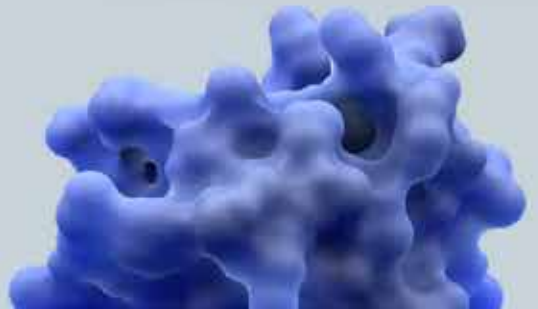
FcεRI, Fc epsilon receptor 1 (high-affinity IgE receptor); IgE, Immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; IFN-γ, interferon gamma.

1. Ying S et al. J Allergy Clin Immunol. 2002;109:694-700; 2. Bae Y et al. Allergy Asthma Immunol Res. 2016;8:457-460; 3. Lin W et al. Sci Rep. 2017;7:17797; 4. Caproni M et al. J Dermatol Sci. 2004;36:57-59; 5. Cevikbas F et al. J Allergy Clin Immunol. 2014;133:448-460; 6. Feld M et al. J Allergy Clin Immunol. 2016;138:500-508; 7. Oetjen LK et al. Cell. 2017;171:217-228; 8. Yang TLB & Kim BS. J Allergy Clin Immunol. 2019;144:353-360; 9. Gandhi NA et al. Nat Rev Drug Discov. 2016;15:35-50; 10. Mak TW & Saunders ME. 2006. 'Cytokines and cytokine receptors' in The Immune Response. pp. 463-516; 11. McLeod JJA et al. Cytokine 2015;75:57-61; 12. Gibbs BF et al. Front Immunol. 2019;10:1383; 13. Kolkhir P et al. Ann Allergy Asthma Immunol. 2020;124:2-12; 14. Magerl M et al. J Dtsch Dermatol Ges. 2018;16:477-478; 15. Maurer M et al. J Eur Acad Dermatol Venereol 2018;32:e86-e121; 16. NCT03749135. Available at https://clinicaltrials.gov/ct2/show/NCT03749135; 17. NCT03183024. Available at: https://clinicaltrials.gov/ct2/show/NCT03183024.



## SECTION 04

# THE ADVANTAGES OF TREATMENTS SELECTIVELY TARGETING MEDIATORS OF TYPE 2 INFLAMMATION



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# The advantages of treatments targeting mediators of type 2 inflammation in atopic dermatitis

## Targeting key receptors and cytokines within the type 2 inflammation pathway has demonstrated clinical benefits in atopic dermatitis[1-5]

| Treatment target | Cytokine signaling impacted | Evidence supporting efficacy and tolerability | Status |
|---|---|---|---|
| **IL-4** Receptor alpha | **IL-4** & **IL-13** | Clinical trials and real-world experience[1,6-9] | Approved in moderate-to-severe atopic dermatitis (patients aged ≥6 years)[10] |
| **IL-13** cytokine | **IL-13** | Phase II and Phase III trial data[2,3,11] | One treatment approved in the EU for use in adults with moderate-to-severe atopic dermatitis[12]<br>One treatment has an ongoing Phase III trial[13] |
| **IL-31** Receptor alpha | **IL-31** | Phase III trial data[14] | Phase III trial ongoing[15] |

**Treatments selectively targeting mediators of type 2 inflammation in atopic dermatitis have demonstrated improvements in:[1-3,16,17]**

**Itch**

**Lesions**

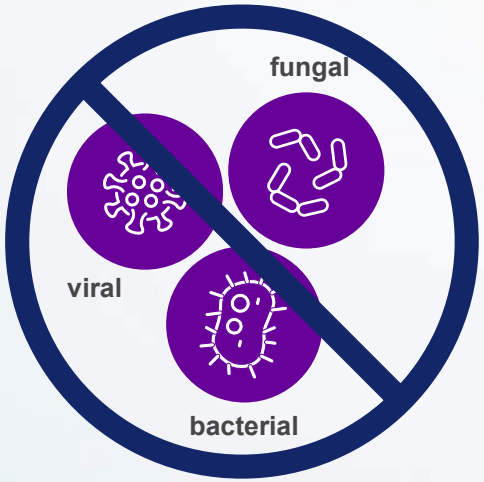
**Quality of life**

**Sleep**

IL, interleukin.

1. Simpson EL et al. N Engl J Med. 2016;375:2335-2348; 2. Guttman-Yassky E et al. JAMA Dermatol. 2020;156:411-420; 3. Wollenberg A et al. J Allergy Clin Immunol 2019;143:135-141; 4. Ruzicka T et al. N Eng J Med. 2017;376:826-835; 5. Cosmi L et al. Eur J Immunol. 2019;49:1334-1343; 6. Halling AS et al. J Am Acad Dermatol. 2021;84:139-147; 7. Hansel K et al. Clin Exp Dermatol. 2021. Online ahead of print; 8. Abraham S et al. Br J Dermatol. 2020;183:382-384; 9. Spekhorst LS et al. Allergy. 2020;75:2376-2379; 10. DUPIXENT SmPC. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. Updated Jan 2021. Last accessed July 2021; 11. Wollenberg A et al. Br J Dermatol. 2021;184:437-449; 12. ADTRALZA SmPC. https://www.ema.europa.eu/en/documents/product-information/adtralza-epar-product-information_en.pdf. Updated June 2021. Last accessed July 2021; 13. NCT04250350. Available at https://clinicaltrials.gov/ct2/show/NCT04250350; 14. Kabashima K et al. N Engl J Med. 2020;383:141-150; 15. NCT03989206. Available at https://clinicaltrials.gov/ct2/show/NCT03989206; 16. Kabashima K et al. J Allergy Clin Immunol. 2018;142:1121-1130; 17. Simpson EL et al. J Am Acad Dermatol. 2018;78:863-871.

# Safety profile for treatments targeting mediators of type 2 inflammation




Targeted immunomodulators tend to be associated with fewer side effects than treatments with broad immunosuppressive activity[1,2]

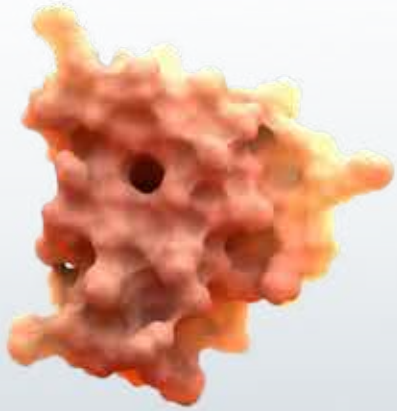
Treatments selectively targeting type 2 inflammation have not been associated with increased risk of infection compared with placebo in clinical trials[3-6]

Treatments modulating the type 1 immune response (e.g. for psoriasis) are associated with increased risk for bacterial/viral infection[7,8]

The divergent safety concerns reflect differences in both disease-driving and protective roles of the immune responses[10,11]

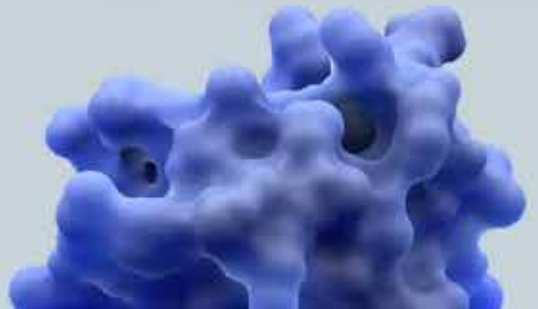
**Selective modulation of the dysregulated immune response can result in an effective therapy with fewer safety concerns than other treatments.[1,9] This may reduce the risk of treatment discontinuation, offering potential for long-term use and long-term control of chronic diseases.[1,9]**

1. Wakelin SH. Medicine. 2017;45:P363-367; 2. Simpson EL et al. J Am Acad Dermatol. 2017;77:623-633; 3. Wollenberg A, et al. Br J Dermatol. 2021;184:437-449; 4.Kabashima K, et al. N Engl J Med. 2020;383:141-150; 5. Simpson EL et al. N Engl J Med. 2016;375:2335-2348; 6. Ständer S, et al. New Engl J Med. 2020;382:706-716; 7. Mease P. Ther Clin Risk Manag. 2006;2:389-400; 8. Campanati A, et al. Expert Opin Biol Ther. 2017;17:387-394; 9. Hajar T et al. An Bras Dermatol. 2018;93:104-107; 10. Annunziato F et al. J Allergy Clin Immunol. 2015;135:626-635; 11. Kaiko GE et al. Immunology 2008;123:326-338.



## SECTION 05

# SUMMARY



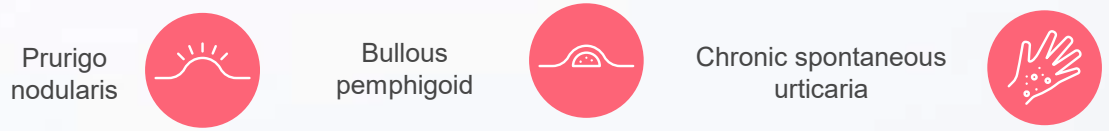
# Summary

- The type 2 immune response helps defend against invasive threats such as parasitic worms[1,2]

- Dysregulation of this response can lead to systemic type 2 inflammation and drive diseases in multiple organ systems[2-5]


- Key type 2 cytokines **IL-4** and **IL-13** contribute to the disease features of atopic dermatitis and perpetuate systemic type 2 inflammation; **IL-31** also plays a role in itch[3,6-11]

- Growing evidence supports the role of the type 2 immune response in other inflammatory skin diseases[12-15]

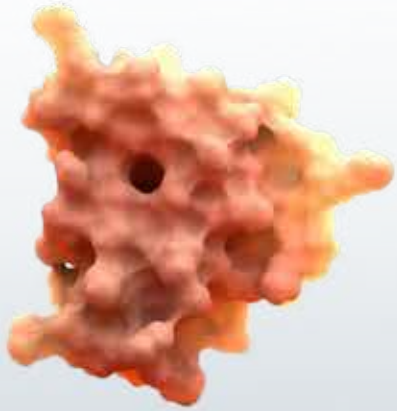



- Selective targeting of the type 2 inflammation pathway has shown clinical benefits in atopic dermatitis, including a distinct safety profile[16-23]
  - This benefit-risk profile offers potential for long-term use and long-term control of chronic diseases[24,25]

**Targeting type 2 inflammation across relevant diseases may help to improve long-term outcomes for patients and optimize clinical management for you[24,25]**

IL, interleukin; Th2, T helper type 2 cell.

1. Annunziato F et al. J Allergy Clin Immunol. 2015;135:626-635; 2. Gandhi NA et al. Nat Rev Drug Discov. 2016;15(1):35-50; 3. Hammad H & Lambrecht BN. Immunity. 2015;43:29-40; 4. Lloyd CM & Snelgrove RJ. Sci Immunol. 2018;3:eaat1604; 5. Hill DA & Spergel JM. Curr Allergy Asthma Rep. 2016;16:9; 6. Silverberg JI Kantor R. Dermatol Clin. 2017;35(3):327-334; 7. Erickson S et al. Dermatol Clin. 2018;36(3):325-334; 8. Rerknimitr P et al. Inflamm Regen. 2017;37:14; 9. Noda S et al. J Allergy Clin Immunol. 2015;135:324-336; 10. Wynn TA. Nat Rev Immunol. 2015;15:271-282. 11. Le Floc'h et al. Allergy. 2020;75:1188-1204; 12. Teraki Y et al. J Invest Dermatol. 2001;117:1097-1102; 13. Fukushi S et al. Br J Dermatol. 2011;165:990-996; 14. Kay AB et al. Br J Dermatol. 2015;172:1294-1302; 15. Fostini AC et al. J Dermatol Treat. 2013;24:458-462; 16. Simpson EL et al. N Engl J Med. 2016;375:2335-2348; 17. Guttman-Yassky E et al. JAMA Dermatol. 2020;156:411-420; 18. Wollenberg A et al. J Allergy Clin Immunol 2019;143:135-141; 19. Ruzicka T et al. N Engl J Med. 2017;376:826-835; 20. Cosmi L et al. Eur J Immunol. 2019;49:1334-1343; 21. Halling AS et al. J Am Acad Dermatol. 2021;84:139-147; 22. Abraham S et al. Br J Dermatol. 2020;183:382-384; 23. Spekhorst LS et al. Allergy. 2020;75:2376-2379; 24. Wakelin SH. Medicine. 2017;45:P363-367; 25. Hajar T et al. An Bras Dermatol. 2018;93:104-107.



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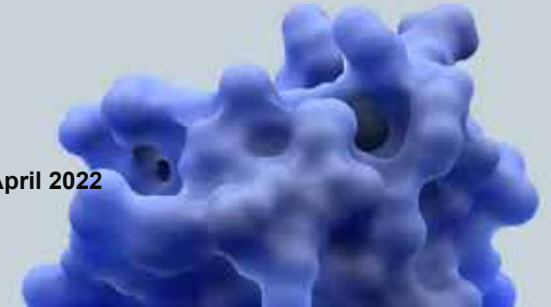

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