BILOGICS AND BEYOND
Biologics

A biologic drug is composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.

Biologic drugs include a wide variety of products derived from human, animal, or microorganisms by using biotechnology.

They are produced from living organisms or contain components of living organisms.
Immunology and the The Epithelium

Airway epithelial cells, gut epithelium, keratinocytes, and other epithelia are at the interface of the human body and the environment.

They form a complex physicochemical barrier and the first line of defense against environmental cues, such as viruses, bacteria, fungi, parasites, allergens, and inorganic particles.
Interleukins are the “communicators between the white blood cells.” as originally described in 1977.

Since the discovery of TH subsets, it was discovered that almost all immune cells display different functional subsets.

These include distinct surface receptors and cytokine profiles, such as CD4 and CD8 T cells, B cells, innate lymphoid cells (ILCs), natural killer (NK) cells, and dendritic cells (DCs)
Immunology and the Epithelium

There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules CD4 and CD8.

T lymphocytes expressing CD4 are also known as T Helper cells (TH‘x’), and these are regarded as being the most prolific cytokine producers.

This subset can be further subdivided into Th1 and Th2, and the cytokines they produce are known as Th1-type cytokines and Th2-type cytokines.
Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular parasites, bacterium and for perpetuating autoimmune responses.

Interferon gamma is the main Th1 cytokine.
Immunology and the The Epithelium

The Th2-type cytokines include interleukins 4, 5, and 13.

These are associated with the promotion of IgE and eosinophilic responses in atopy, and also interleukin-10, which has more of an anti-inflammatory response.

If Th1 is present in excess, Th2 responses will counteract the Th1 mediated microbicidal action.
Immunology and the Epithelium

After sensing of allergens, epithelial cells can produce IL-1α, IL-25, IL-33, TSLP, and GM-CSF. These cytokines start to orchestrate TH2 immunity.
Immunology and the The Epithelium

Epithelial cells regulate both innate and adaptive immunity, among others, through the production of various costimulatory molecules, chemokines, cytokines, and lipid mediators in response to environmental stimuli sensed by the rich panel of intracellular sensors, such as Toll-like receptors (TLRs), NOD-like receptors, melanoma differentiation-associated protein 5, and retinoic acid–inducible gene 1.
Some allergens have additional protease activity and/or are accompanied by microbial components, such as endotoxins or inorganic particles.

This can cause epithelial secretory responses that can lead to mixed TH2 and TH17 immunity or even TH1 responses.
Immunology IL-1

IL-1 was first described as a protein that induced fever and was called human leukocytic pyrogen.

It is derived from macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts, synovial lining cells.

Major functions include Induction of proinflammatory proteins; hematopoiesis; differentiation TH17 cells; development of IL-10–producing cells.
IL-2

IL-2 expands T cell proliferation, activates B cells and was initially called T cell growth factor.

It stimulates antibody synthesis, and promotes proliferation and differentiation of NK cells.
PSORIASIS
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Etanercept in Psoriasis (Phase 3 Study)

Patient 1661

Week 0

Week 12

Week 24

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<th>Week 24</th>
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<tr>
<td>PASI</td>
<td>22.7</td>
<td>6.3 (72.25%)*</td>
<td>3.8 (83.26%)*</td>
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<td>BSA</td>
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*Percent improvement (decrease) in PASI score vs baseline.
Identified in 1975, TNF was isolated from human serum as responsible for necrosis in different tumors in mice.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.

The biological activity of TNF is dependent upon binding to either cell surface receptor p75 or p55 sub units.

TNF isn't just in the skin, joints and gut. Depressed individuals have been found to have higher levels of pro-inflammatory cytokines, especially tumor necrosis factor-alpha (TNF-α) and interleukin-6.
Anti-TNF Monoclonal Antibodies

End in: “mab” Monoclonal AntiBody

“u” designates h“u”man

“i” designates Ch“i”meric (mouse)

Infliximab

Adalimumab

Certolizumab

Golimumab
Adalimumab

It is produced by recombinant DNA technology using a mammalian cell expression system.

binds with specificity to tumor necrosis factor-alpha (TNF-alpha) and inhibits its interaction with the p55 and p75 cell surface TNF receptors.
Adalimumab decreases levels of acute phase reactant proteins of inflammation (C reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6).

Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that lead to the tissue remodeling responsible for cartilage destruction were also found to be decreased.

Adalimumab alters biological responses that are induced/regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration during inflammation.
Infliximab disrupts the activation of pro-inflammatory cascade signalling. Infliximab has shown to reduce infiltration of inflammatory cells into sites of inflammation.

Attenuates the expression of molecules mediating cellular adhesion, vascular cell adhesion molecule-1, chemoattraction through IL-8 and monocyte chemotactic protein (MCP-1) and tissue degradation (MMP) 1 and 3
Infliximab

Binds to soluble and transmembrane forms of TNF-α with high affinity to disrupt the pro-inflammatory cascade signalling.

Binds to TNF-α

prevents TNF-α from interacting with its receptors.

leads to downregulation of local and systemic pro-inflammatory cytokines (i.e. IL-1, IL-6)
Anti TNF Fusion Proteins

Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules, thereby effectively removing them from circulation.

“r-cept” designates receptor protein

Etanercept
Etanercept

Etanercept binds specifically to tumor necrosis factor (TNF) and modulates biological processes that are induced or regulated by TNF including the level of adhesion molecules expressed, as well as serum levels of cytokines and matrix metalloproteinase-3.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules, thereby effectively removing them from circulation.

Half Life 102 +/- 30 hrs in individuals with rheumatoid arthritis and 68 hours in healthy adults.
Certolizumab

Certolizumab pegol is a recombinant Fab' antibody fragment against TNF

Monoclonal antibody (mAb) / Fusion proteins

PEGOL Polyethylene glycol helps to delay the metabolism and elimination of the drugs
Certolizumab

binds to free and membrane-bound human TNFα and neutralizes its activity.

Extent of neutralization is dose-dependent

inhibited the release of lipopolysaccharide-induced IL-1β from monocytes.

certolizumab is only a Fab' fragment and thus missing the Fc region, it does not fix complement or cause antibody-dependent cell-mediated cytotoxicity
TNF in Psoriasis

Psoriatic lesions demonstrate elevated levels of TNF in all layers of the epidermis, dermal blood vessels, and the synovial fluid of patients with psoriatic arthritis.

Psoriatic disease activity and severity correlates directly with circulating amounts of TNF.

Initial increases in TNF-α production may result from T cells.

Other leukocytes also have the ability to produce TNF.
Anti-TNF Biologics in Psoriasis Immunology

KC=Keratinocyte Cell
DC= Dendritic Cell

= ADALIMUMAB
Anti-TNF Side Effects

The main risk of anti-TNF therapy is reduced immunity to bacterial, fungal, viral and parasitic infections, including:

- Tuberculosis
- Histoplasmosis
- Coccidioidomycosis
- Blastomycosis
Anti-TNF’s Potential Side Effects

Anti-TNFs can lose their effect over time, possibly because of the induction of antibodies against them. Paradoxically, anti-TNFs can sometimes result in dermatological side effects, such as:

- Palmoplantar pustulosis
- Various forms of psoriasis
- Eczema
- Lupus erythematosus
- Morphea
- Alopecia areata
- Vitiligo
- Granuloma annulare
- Sarcoidosis
- Erythema multiforme
- Vasculitis
- Stevens Johnson syndrome — toxic epidermal necrolysis
- Drug-induced nummular dermatitis
IL-17’s

Ixekizumab

Secukinumab

Brodalumab

IL-17 causes induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment and activation of neutrophils.
IL-17’s

It is known that dysregulation of innate and adaptive immune responses plays part in the chronic inflammation associated with the Psoriasis.

IL-17 represents is a six-membered family (IL-17A to F) of pro-inflammatory cytokines, expression of which is found to be elevated in psoriatic skin.

These cytokines act on many different cell types and provide defense against different extracellular pathogens causing fungal or bacterial infections.
Ixekizumab

Ixekizumab is a *humanized* immunoglobulin G subclass 4 (IgG4) monoclonal antibody binding interleukin-17A (IL-17A) and prevents it from interacting with the IL-17A receptor.

Ixekizumab is produced by recombinant DNA technology in a recombinant mammalian cell line and purified using standard technology for bioprocessing.

Ixekizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Secukinumab

Secukinumab is a human monoclonal antibody that targets IL-17A cytokine to downregulate inflammation in psoriasis.

Secukinumab is designed for the treatment of uveitis, rheumatoid arthritis, ankylosing spondylitis, and psoriasis.

Secukinumab binds to and neutralizes interleukin (IL)-17A.
Brodalumab

Brodalumab, a human monoclonal IgG2-antibody, acts as a potent antagonist at the interleukin-17 receptor A.

Brodalumab increases the level of circulating IL-17 due to blocking of its receptors.

It is approved for the treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma.

Brodalumab binds with high affinity to interleukin (IL)-17 receptor A, thereby inhibiting several pro-inflammatory cytokines from the IL-17 family.
Brodalumab Safety

**SIX** completed suicides in the clinical trial.

Completed Suicide: Five of 6 were males, 4 were psoriasis patients.

All had risk factors, 2 with depression and 4 with significant social stressors.

Received a Black Box Warning by FDA.
59/Male 210 mg 100  329 days after first dose of brodalumab  
History of financial stressors (lost disability due to brodalumab response and unable to find work)

39/Male 210 mg 73  140 days after first dose of brodalumab 
Informed investigator he had legal difficulties and was likely to be incarcerated  
Family reported he killed himself, means unknown

56/Male 210 mg 100  845 days after first dose of brodalumab  
Ongoing treatment for depression and anxiety.

Described recent stress and isolation due to relocation  
Indeterminate case
56/Male 210 mg 100  History of depression; on antidepressant and benzodiazepine  97 days after first dose of brodalumab

Toxic levels of mixed opiates compatible with ingestion of poppy seed tea and methadone; therapeutic level of citalopram, elevated alprazolam, and alcohol

HADS baseline depression and anxiety score decreased from 15 to 2 and 14 to 6, respectively, 2 weeks before the event

Ruled indeterminate by C-CASA adjudication
Psoriasis Immunology

KC=Keratinocyte Cell
Secukinumab, Brodalumab

DC= Dendritic Cell

Triggers

Genetics (HLA-C*06)

KC
LL-37

DC

IL-12

TNFα, INFγ

IL-8, LL-37

TNFα, IL-17

CXCL20

Th1

Th22

Th17

IL-16, TNFα

IL-17A, IL-22, IL-17F, TNFα

IL-17F

IL-23

IL-23

IL-20, IL-21

Innate immune cells (neutrophils, mast cells...)

= Ixekizumab,
IL23

Tildrakizumab

Guselkumab

IL 23 causes stimulation of production of proinflammatory IL-17; enhancement of T-cell proliferation and promotion of memory T cells; activation of NK cells; regulation of antibody production
Tildrakizumab

Tildrakizumab is a high-affinity, humanized, IgG1 κ antibody selectively binds interleukin (IL)-23 p19 subunit of cytokine IL-23 and neutralizes its function. IL-23 regulates Th17 cells and is a powerful activator of keratinocyte proliferation.

Downregulation of Th17 and Th22 cell responses occur

Approximately 6.5% of subjects treated with ILUMYA 100 mg developed antibodies to tildrakizumab. Of the subjects who developed antibodies to tildrakizumab, approximately 40% (2.5% of all patients receiving ILUMYA) had antibodies that were considered neutralizing.
Guselkumab

Guselkumab is a human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that selectively blocks interleukin-23.

Guselkumab targets the p19 alpha subunit of IL-23 in dendritic cells and keratinocytes and blocks its interaction with IL-23 receptor, which further prevents the release of other pro-inflammatory cytokines and chemokines via stimulation of immune cells such as Th17 cells.
Guselkumab

While IL-23 promotes the normal inflammatory and immune responses, the p19 and p40 subunits of IL-23 are found to be over-expressed in the condition of psoriasis and other autoimmune inflammatory skin diseases.
IL-23’s in Psoriasis Immunology

KC = Keratinocyte Cell and Guselkumab

DC = Dendritic Cell

= Tildrakizumab
Ustekinumab is a human IgG1-kappa monoclonal antibody.

Ustekinumab blocks interleukin IL-12 and IL-23 by binding with high affinity and specificity to the p40 subunit of IL-12 and IL-23, therefore disrupting the proinflammatory pathway.

Ustekinumab also interferes with the expression of monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), interferon-inducible protein-10 (IP-10), and interleukin IL-8.
IL-12/IL-23 in Psoriasis Immunology

KC=Keratinocyte Cell
DC= Dendritic Cell

= Ustekinumab
Apremilast

cAMP, cyclic adenosine monophosphate; CReB, cAMP responsive element-binding protein; IFN, interferon; IL, interleukin; NF-κB, nuclear factor-kappa B; PDe, phosphodiesterases; PKA, protein kinase A; TNF-α, tumor necrosis factor-alpha.
PDE4 Inhibitors

roflumilast

apremilast

crisaborole

Phosphodiesterase-type 4 (PDE4), mainly present in immune cells, epithelial cells, and brain cells, manifests as an intracellular non-receptor enzyme that modulates inflammation and epithelial integrity. Inhibition of PDE4 is predicted to have diverse effects via the elevation of the level of cyclic adenosine monophosphate (cAMP) and the subsequent regulation of a wide array of genes and proteins.
Apremilast

Apremilast is a small molecule selective inhibitor of phosphodiesterase 4 (PDE4).

Inhibition of PDE4 impacts cellular cyclic AMP production and thus reduces TNF-α production and secondarily reduces IL17 and IL23 while increasing IL10.

Developed and FDA approved as an oral agent specifically for use in psoriasis and psoriatic arthritis, this agent has been utilized in small case series of patients with HS with some efficacy.
Atopic Dermatitis
PDE-4 Inhibitor: Crisaborole

Crisaborole is a topical broad-spectrum anti-inflammatory with activity targeting phosphodiesterase 4 (PDE4) expressed in keratinocytes and immune cells in Atopic Dermatitis.

Crisaborole mediates an anti-inflammatory effect on almost all inflammatory cells.

Its structure contains a boron atom, which facilitates skin penetration and binding to the bimetal center of the phosphodiesterase 4 enzyme.
Interleukin 4 (IL-4)

Receptors:
IL-4R type I, IL-4R type II

Cell Sources:
TH2 cells, basophils, eosinophils, mast cells, NKT cells and g/d T cells T and B cells Induction of TH2 differentiation;

Cellular Targets:
Triggers IgE class-switching;
upregulation of class II MHC expression on B cells;
upregulation of CD23 and IL-4R; survival factor for B and T cells;
role in tissue adhesion and inflammation
Interleukin 13 (IL-13)

**Receptor:**
IL-13R1α1 and IL-13R1α2

**Cell Sources:**
T, NKT, and mast cells; basophils and eosinophils; and ILCs

**Cellular Targets:**
B cells, mast cells, epithelial cells, eosinophils, smooth muscle cells, and macrophage
Dupilumab

a human monoclonal IgG4 antibody receptor blocker

Consistent with receptor blockade, serum levels of IL-4 and IL-13 were increased following dupilumab treatment. The relationship between the pharmacodynamic activity and the mechanism(s) by which dupilumab exerts its clinical effects is unknown.
Dupilumab

Indications.

**Atopic Dermatitis**: treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

**Asthma**: indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.
PDE-4 Inhibitor

Crisaborole

Inhibition of PDE4 by crisaborole leads to elevated levels of cyclic adenosine monophosphate (cAMP).

Increased intracellular levels of cAMP inhibit the NF-κB pathway and suppress the release of pro-inflammatory mediators such as TNF-alfa and various interleukins.

Suppression of downstream effects in different cell types may explain the therapeutic role of crisaborole in immune-mediated skin diseases.
PDE-4 Inhibitor

Crisaborole

Reduces the local inflammation in the skin and prevents further exacerbation of the disease.

Its structure contains a boron atom, which facilitates skin penetration and binding to the bimetal center of the phosphodiesterase 4 enzyme.

It is currently under development as topical treatment of psoriasis.
JAK Inhibitors

A mixture of animal model studies and human case studies have reported the use of baricitinib (JAK 1/2), ruxolitinib (JAK 1/2), and tofacitinib (JAK 1/3) for the management of Alopecia Areata.
Jak-Stat with Respective Interleukins

- IL-10, IL-6, IL-11, OSM, LIF, CNTF, IL-22
- EPO, TPO, IL-3, IL-5, Leptin, GM-CSF, Prolactin, GH
- IFN-α/β
- IL-12, IL-23

JAK1, JAK2, JAK3, TYK2
Interleukin
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Abbreviations: AML, acute myeloid leukemia; ET, essential thrombocytosis; JIA, juvenile idiopathic arthritis; PV, polycythemia vera; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
Immune modulating vs Immune suppression

Immunomodulating:

Correcting the overactive or upregulated or the hypo-active or suppressed immune response to a normal eupathic state.

Immune Suppression:

Decreasing an upregulated or the normal immune response to a hypo-active or suppressed state.