Taming Asthma/ New Drugs affecting TH1/Th2 lymphocytes in Asthma

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Summary of Pathophysiology

- This should start looking familiar
- This is the language of the new medicine
- The mechanisms of actions are here
- When we use medications, When we test patients, When we look for underlying disease, we will look here.

- The primary article for this talk is

www.ncbi.nlm.nih.gov/pmc/articles/PMC2259400

Asthma

- Asthma is a conditions characterized by Airflow obstruction.
- Hyperresponsiveness and inflammation to viruses, Allergens cold and even exercise.
- Most of the time these events are temporary and reversible
- On occasion they can be chronic and irreversible with a buildup of basement membrane and inflammatory tissue.
- It is often associated with Eosinophilia, Atopy, and other allergies.

Current Treatment- Corticosteroids

- Steroid have profound effect in reduction of Mast cells, Macrophages, T Lymphocytes and Eosinophils.
- It reverses shedding of epithelial cells. Mucous Cell Hyperplasia and basement membrane Thickening
- The type of inflammation most responsive is eosinophilic inflammation.
- Difficult to control asthma seems to have eosinophilic independent inflammation
- Steroids decrease Cytokine levels and induce eosinophil apoptosis

Current Treatment- Corticosteroids

- **There is a complete absence of understanding of steroids and its effect on the TH1/TH2/Th17 System**

Current Treatment- Beta-Agonists

- Seem to have no direct anti-inflammatory effect
- Its primary effect is inducing smooth muscle relaxation and easing bronchoconstriction
- It use with steroids seems to augment the effectiveness of steroids
- The fear that is hides worsening inflammation has by and large not been seen

Current Treatment- Beta-Agonists

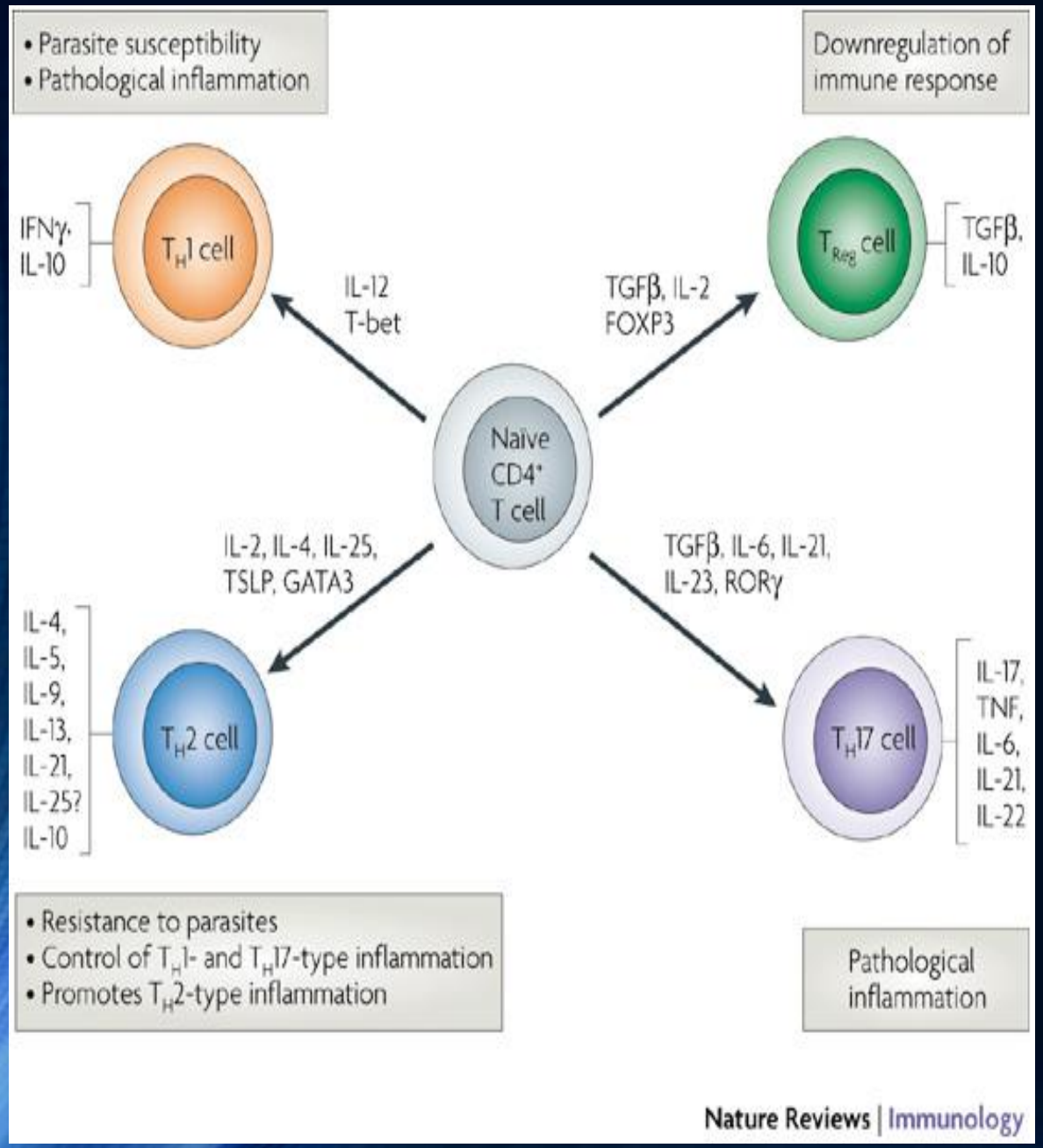
- It has been observed that there are decreasing IFN-Gamma decreasing IL12 and increasing IL-4, IL-5, IL-10
- There is some evidence that they selectively inhibit TH1 and favor TH2 cell developement

Current Treatment- Leukotriene Receptor antagonists

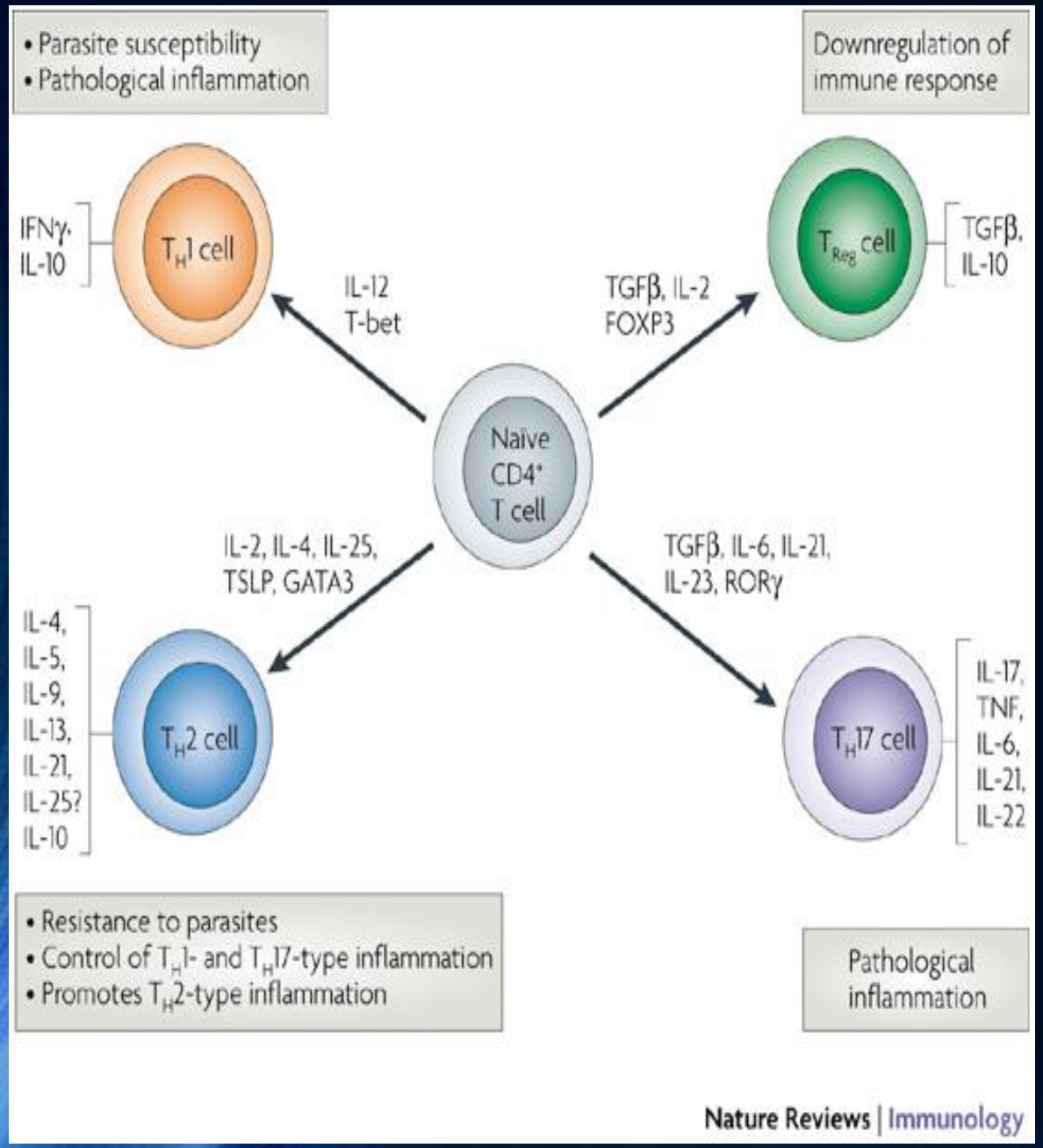
- Pranlukast- ONON
- Zafirlukast- ACCULATE
- Montelukast- SINGULAIR
- Zileuton - ZYFLO

Current Treatment- Leukotriene Receptor antagonists

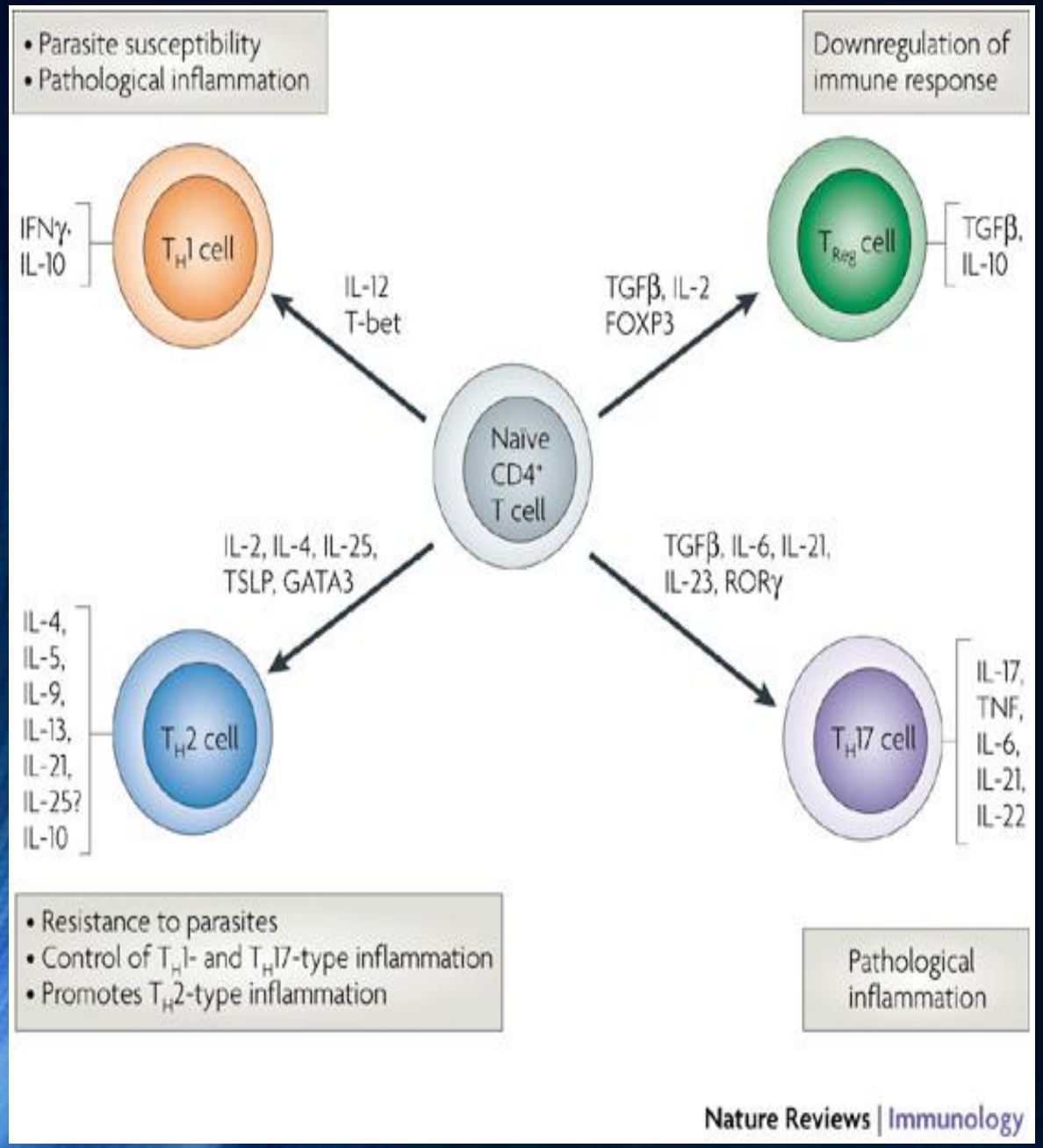
- These medication ns reduce the severity of bronchial hyperresponsiveness in asthma
- These medications inhibit release of Th2 Cytokines IL3, IL4, GM-CSF but not Th1 IL2
- This induced reduction in eosinophilia in sputum, peripheral blood, and induction of eosinophilia by allergen



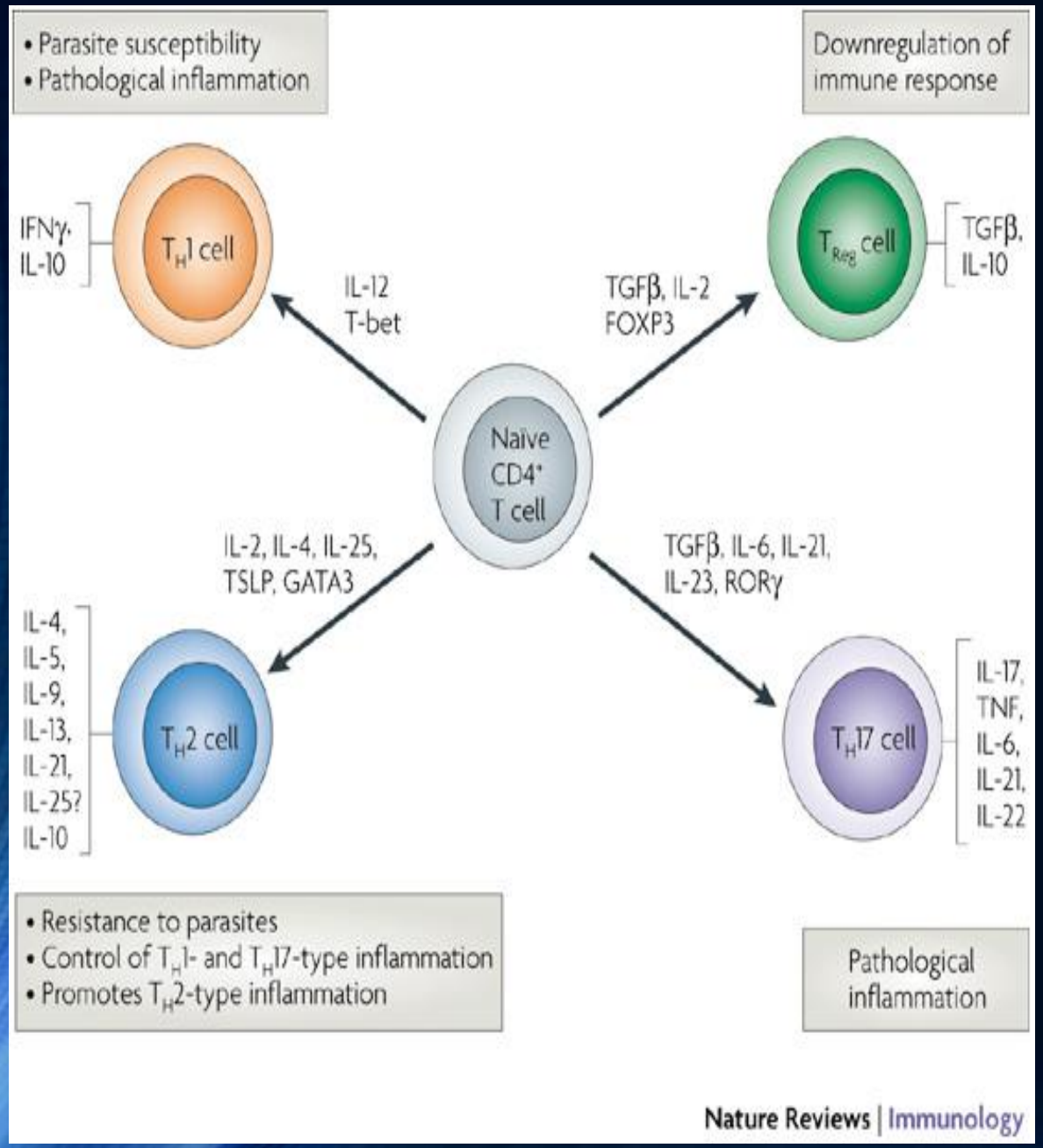
- TH1
- After antigen presentation to the Tho cell the cell then differentiates
- If it is a Virus and intracellular infection such was TB Then development Occurs along Th1
- This this triggers increase in phagocytes NK Cells to attack the infected cells demonstrating signs in intracellular disease



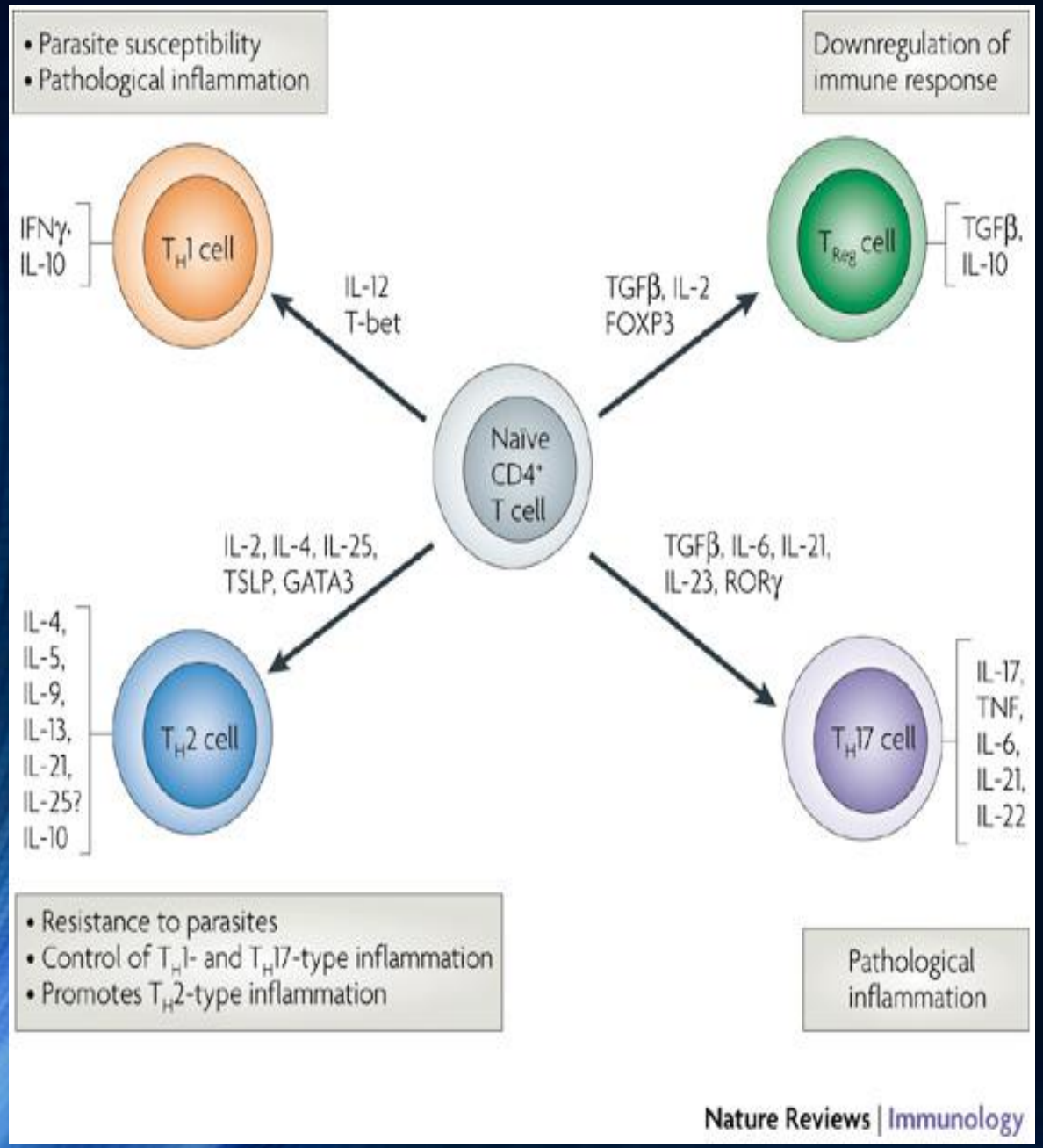
- TH2
- If the presentation of Antigen os of an extracellular pathogen suggestive of a parasite or fungus, then stimulation and development down the Th2 pathway occurs
- Along with that there is increase in Mucous barriers Eosinophils, and mast cells



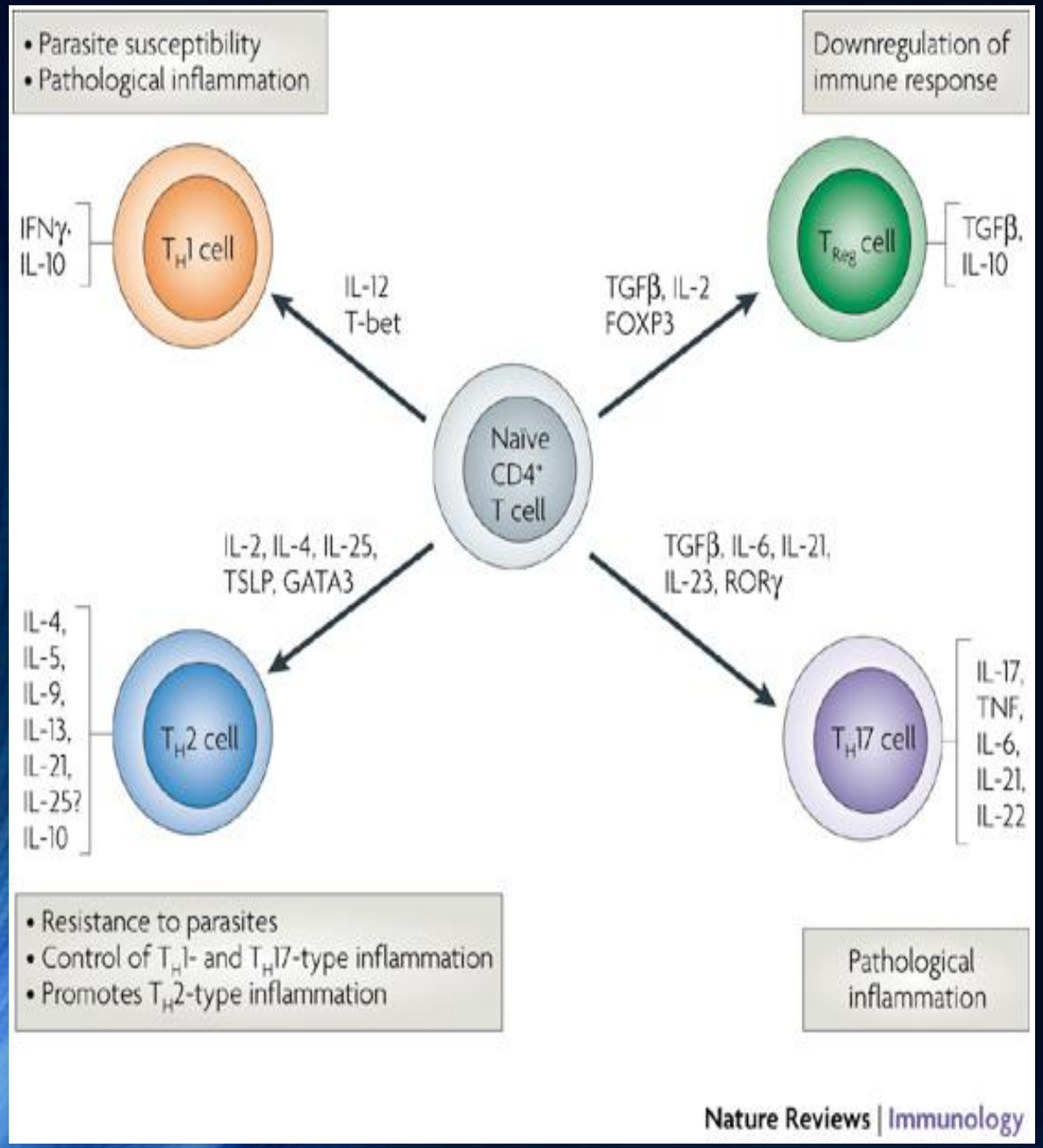
- **TH17**
- If the presentation of Antigen is of a an extracellular bacteria then the cell differentiates along the TH17 pathway
- Recruitment of Neutrophils then occurs



- **Treg**
- This Cells are triggered as a counterbalance to the other pathways They Dampen the immune response and help to enhance resolution to the inflammation and help to prevent Autoimmune disease



- **There are disease patterns associated with each pathway**



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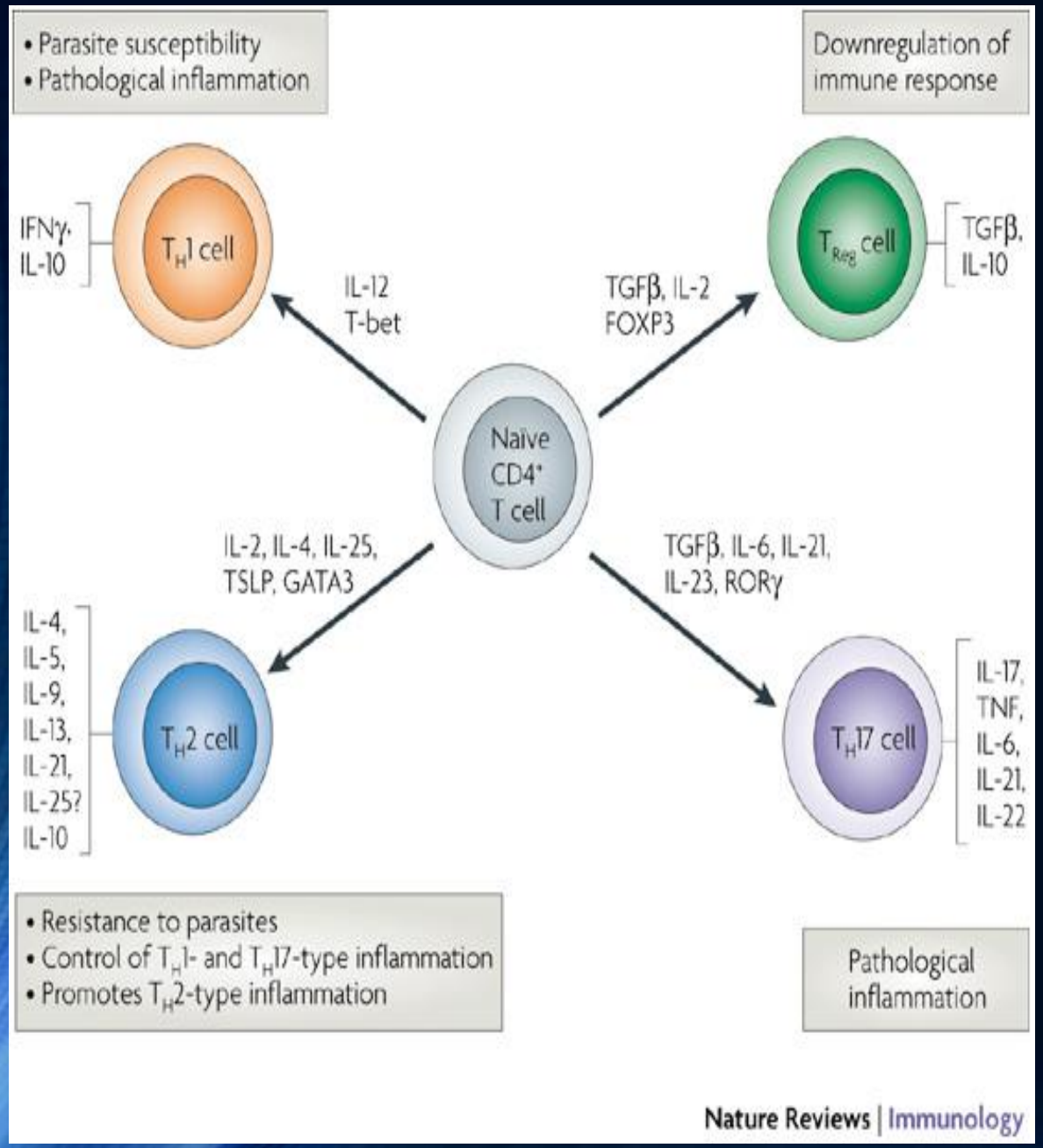
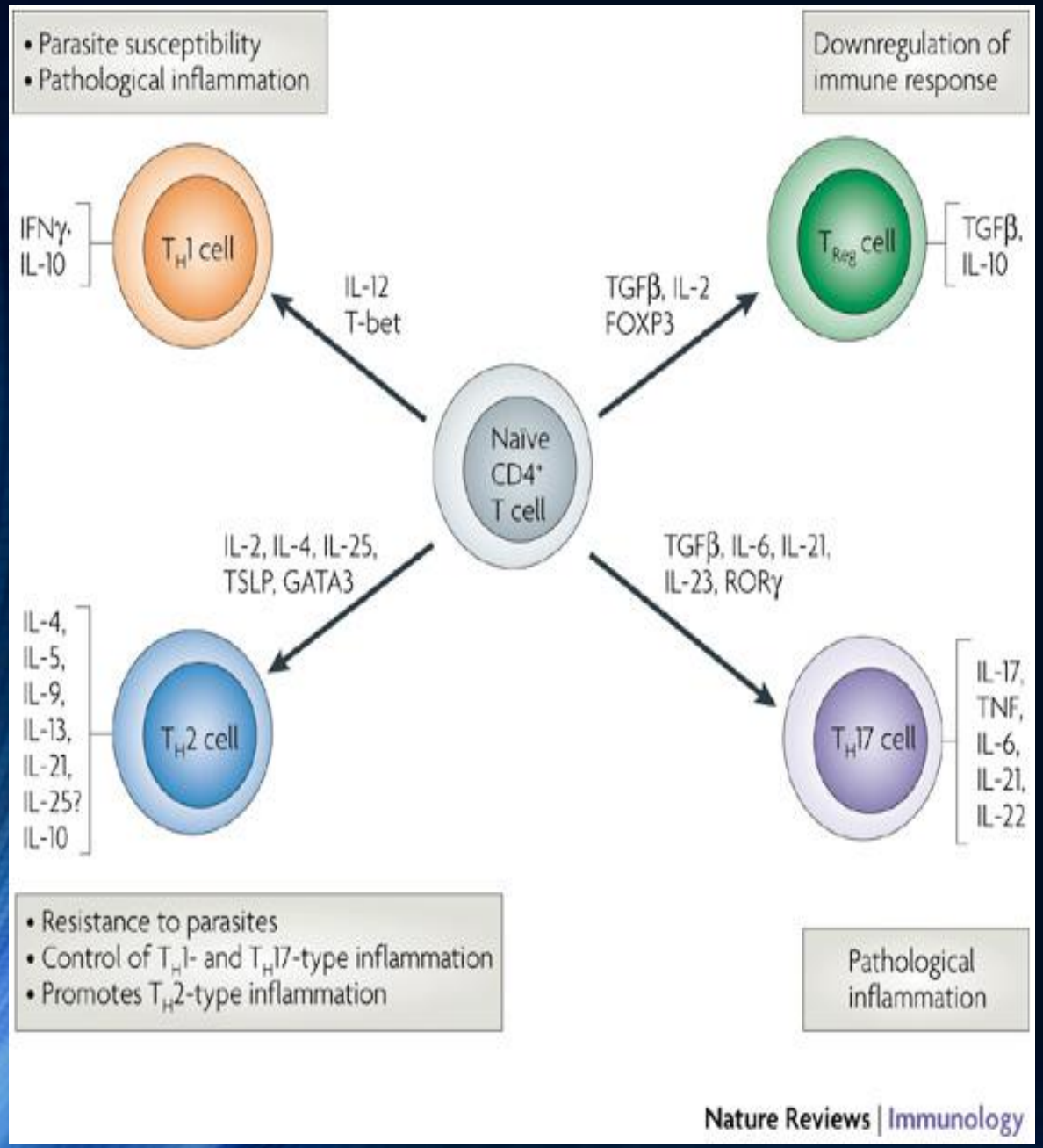
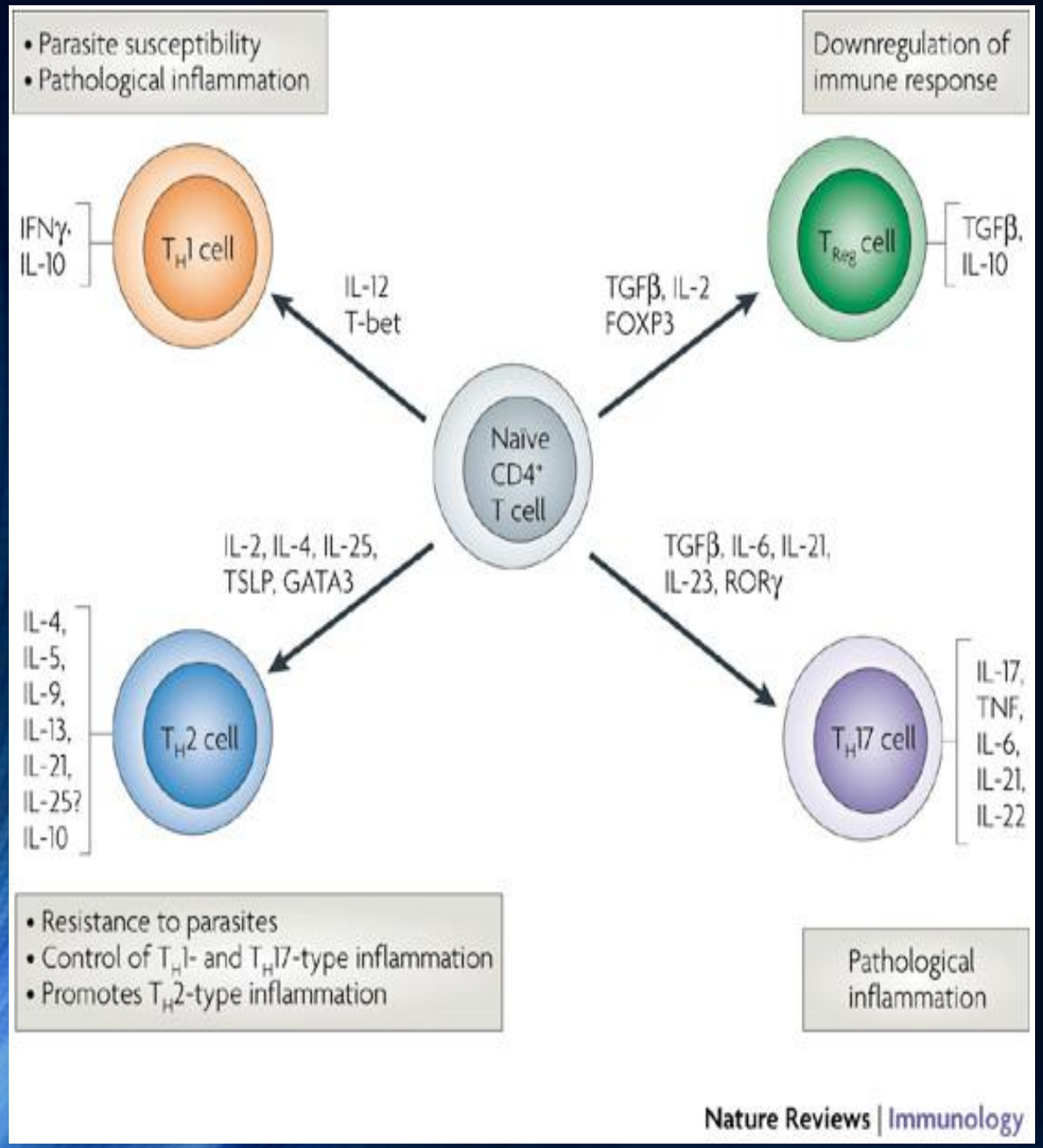


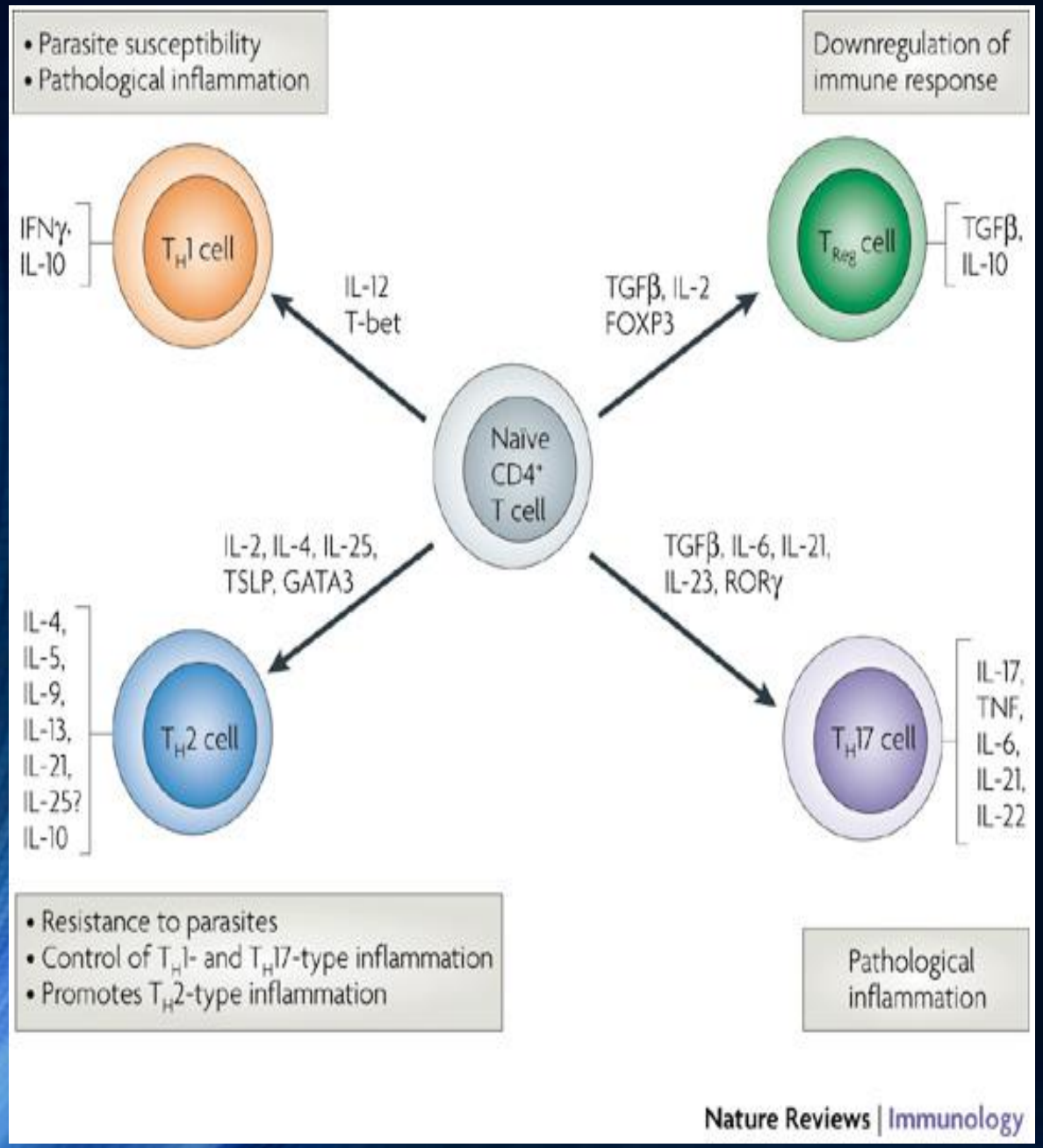
- TH1
- Viral infection
- Intracellular infection Mycobacteria, Mycoplasma
- Autoimmune disease MS, Crohns Disease, Atherosclerosis, RA



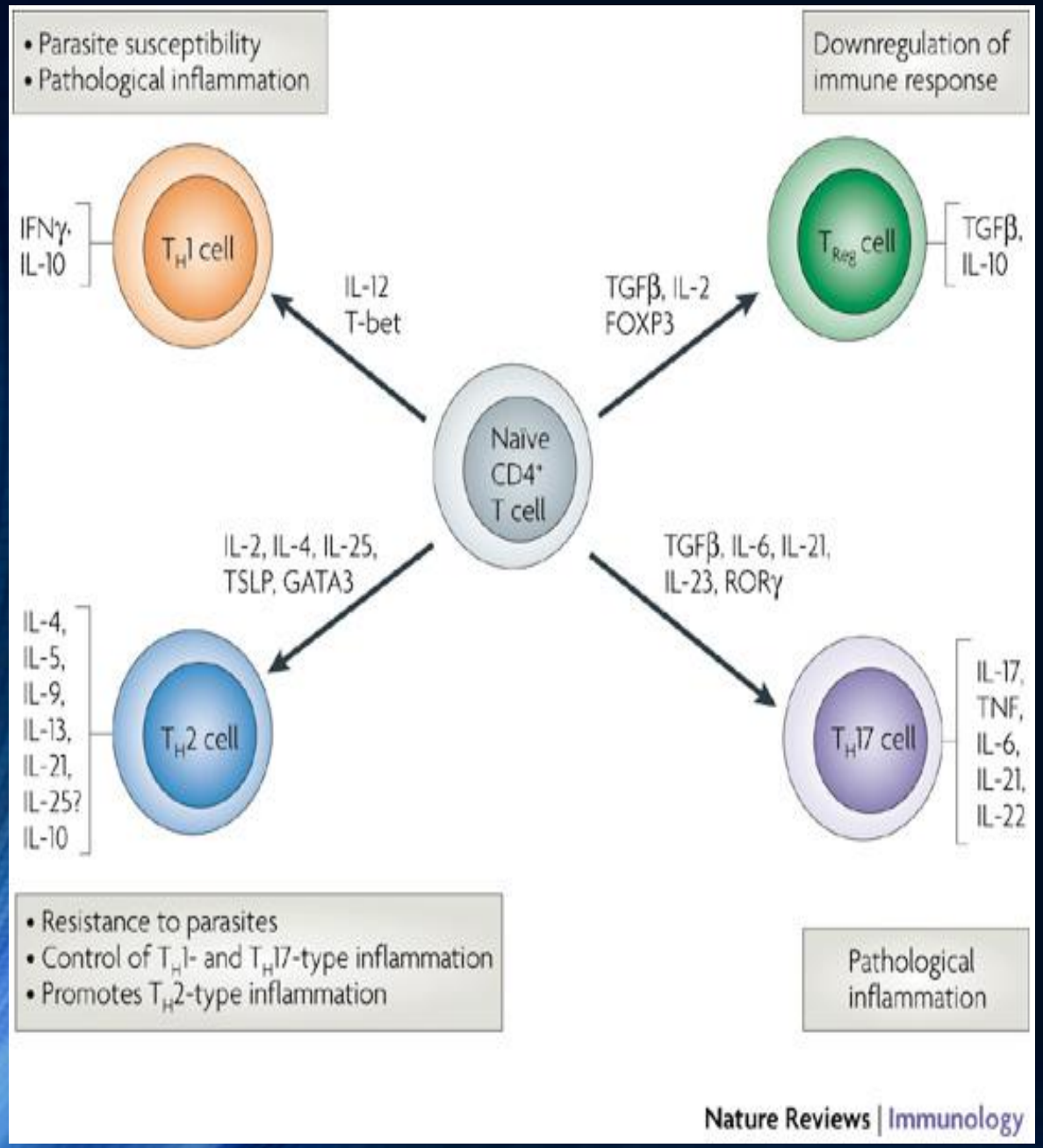
- TH2
- Diseases associated with this pathway
- Allergy, Asthma, Parasite clearance, Atopic Dermatitis, Contact dermatitis, Allergic reactions



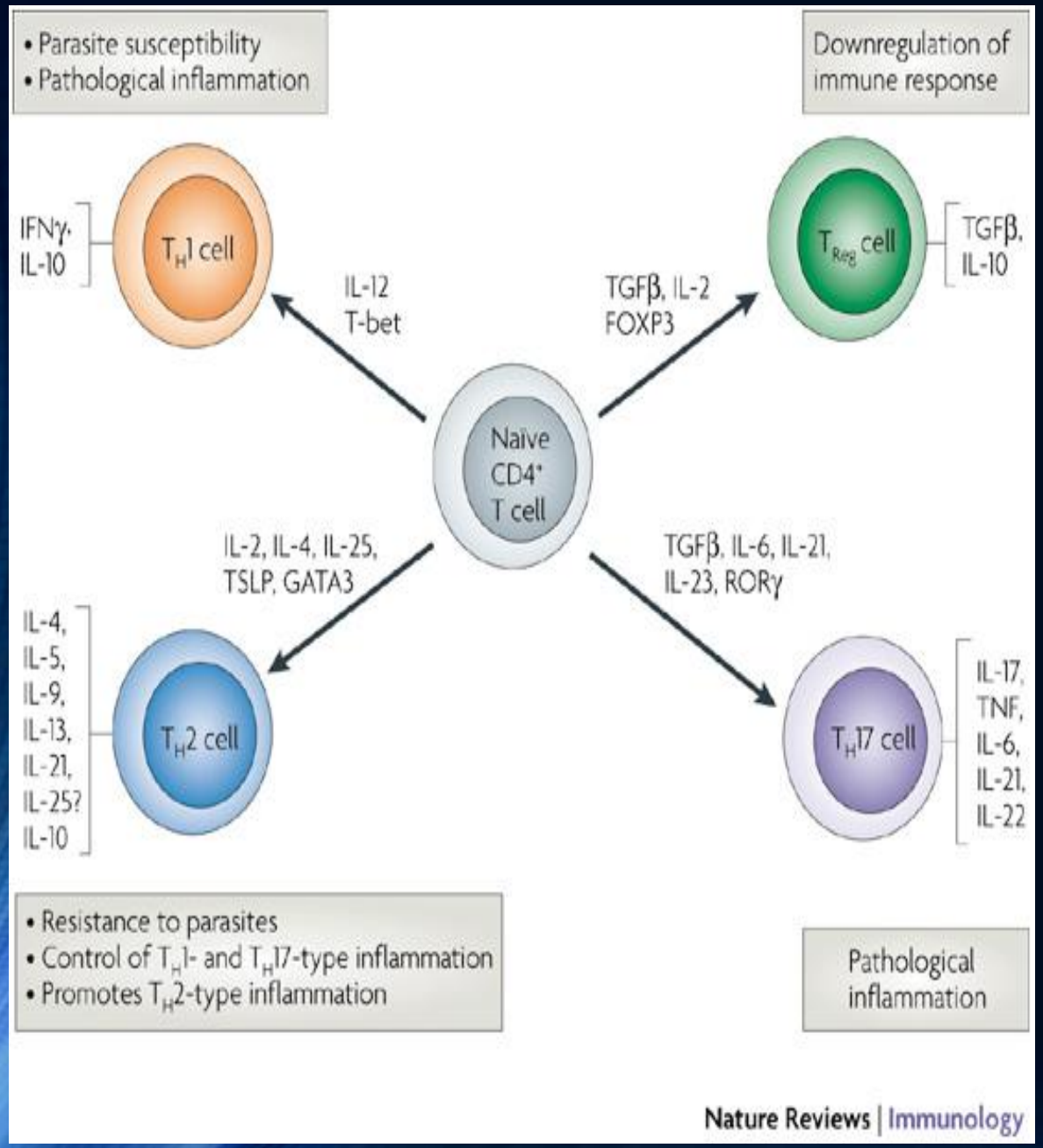
- TH17
- Their role in pathophysiology and disease is it extends the pathologic response to infection and immune response especially to extracellular bacteria
- Overstimulation plays also plays a role in the development of autoimmune disease



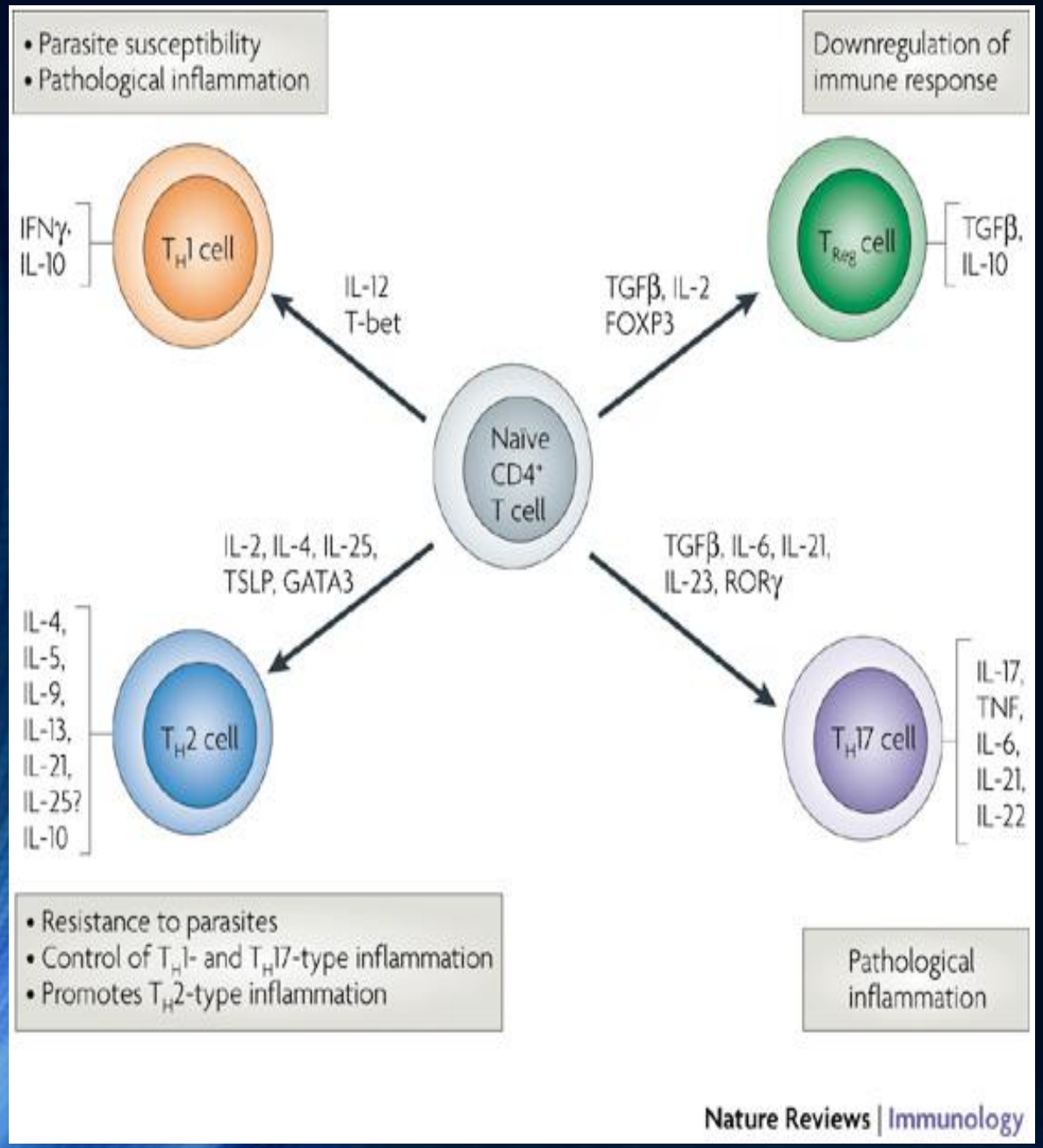
- Treg
- The counterregulatory function of Treg or the lack of proper function of Treg leads to the Escalating inflammation Which we might see in anaphylaxis or Cytokine storm from Covid pneumonia
- Or the development of Autoimmune disease Such as MS, Lupus, Crohn's disease or Diabetes.



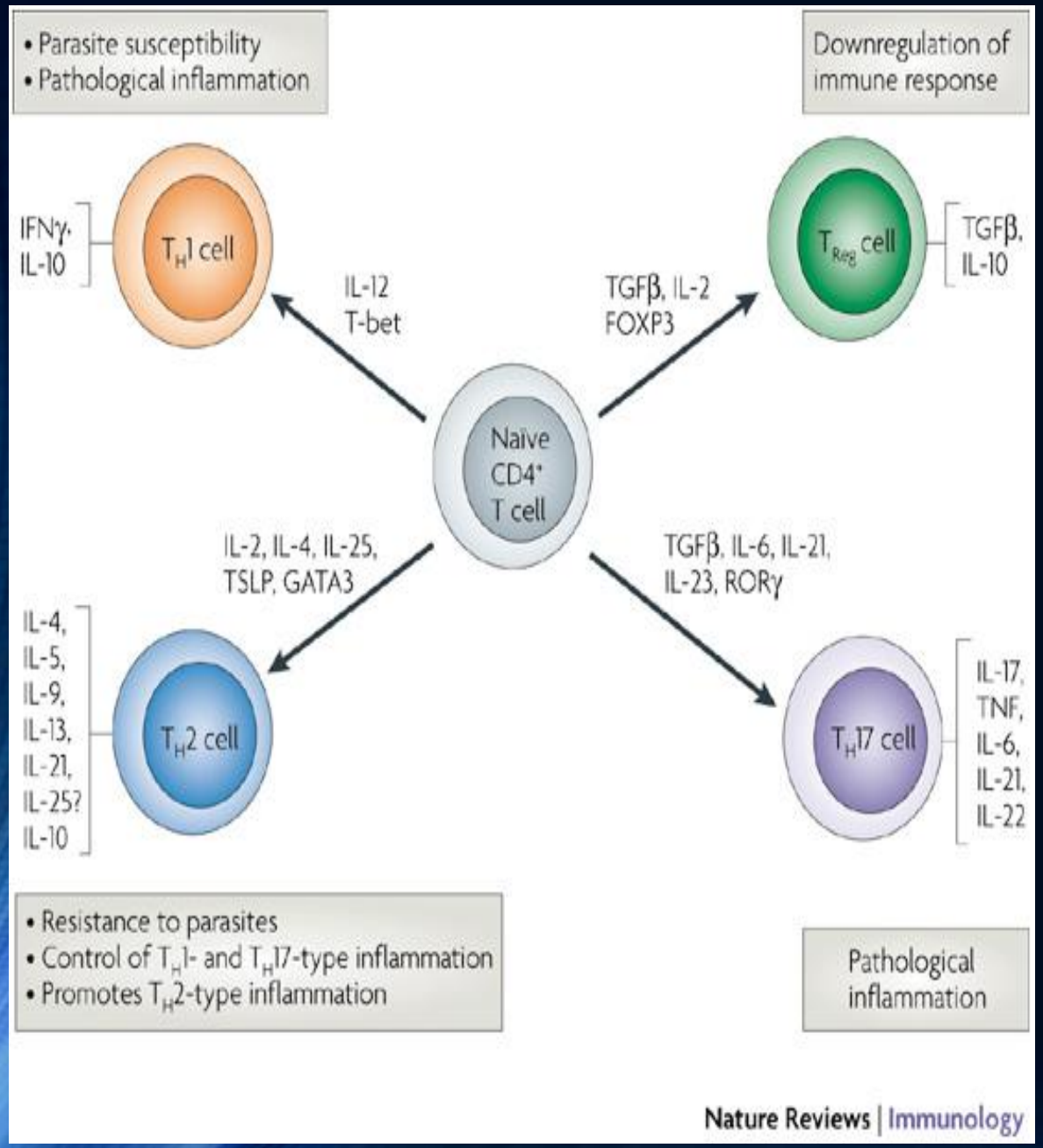
- Th1 vs Th2
- Current understanding centers around Th1 and Th2
- While both pathways can be stimulated both pathways counter regulate each other.
- Each pathway is associated with in own set of Cytokines
- Each Cytokine have receptors
- Each pathway when stimulated will tend to inhibit the other pathway



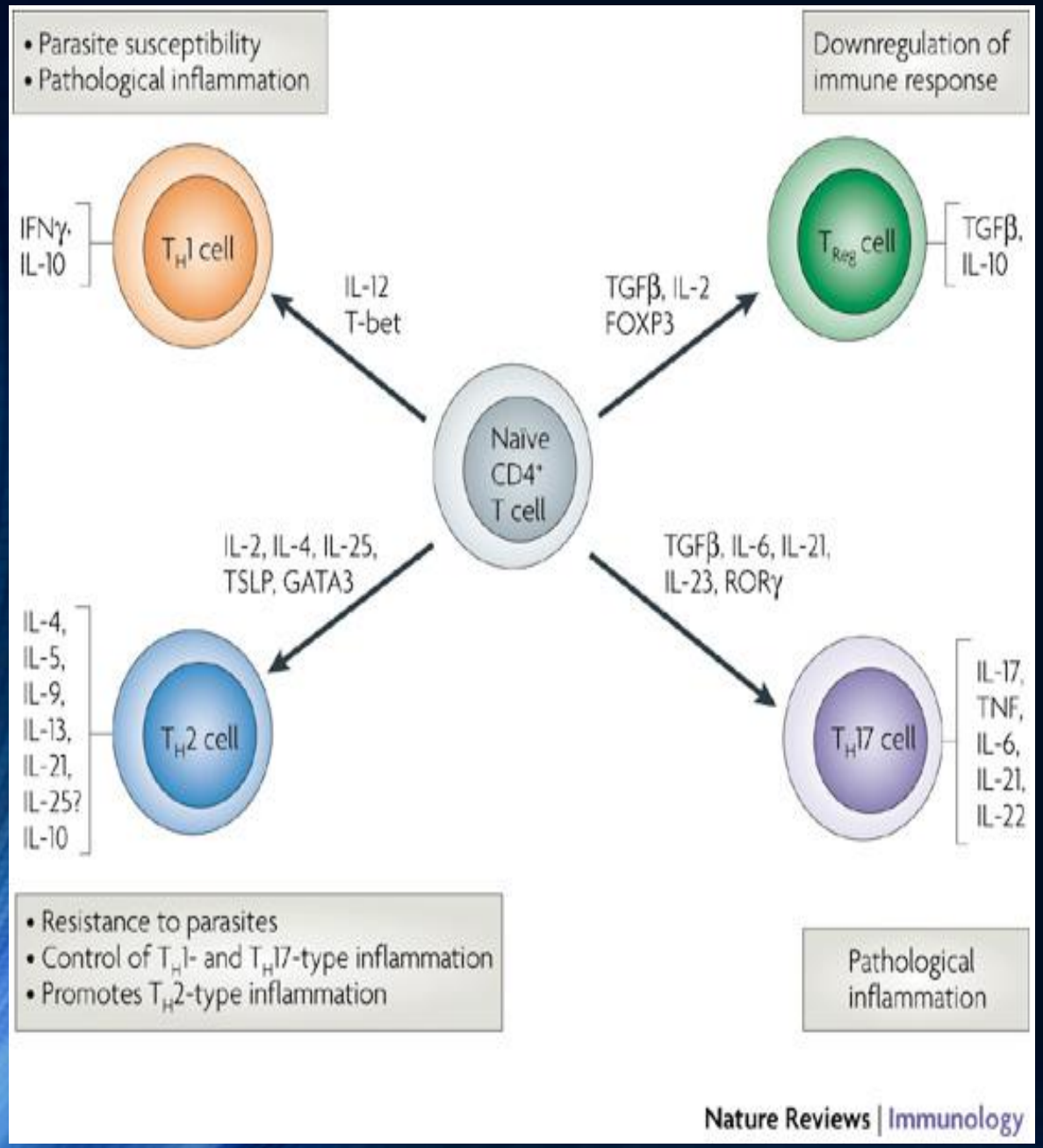
- Th1 vs Th2
- With the easy development of Monoclonal antibodies against the Cytokines, or the receptor for the cytokines or the development of analog copies of these stimulatory Cytokines we have a plethora of new potential drugs and influence into this matrix.



- Th1 vs Th2
- Remember also the counter regulatory influence Th1 and Th2 pathways.
- Stimulating Th1 inhibits Th2
- And the opposite is also true



- Returning to Asthma
- Asthma is a Th2 predominant process.
- Thus IL-2, IL-4,IL-25, Stimulation of Transcriptase GATA-3 (explain later) will induce the Naïve T Cell to mature down TH2 pathway
- Similarly IL-12, and stimulation of transcriptase T-bet will induce the T cell to mature down the Th1 pathway.



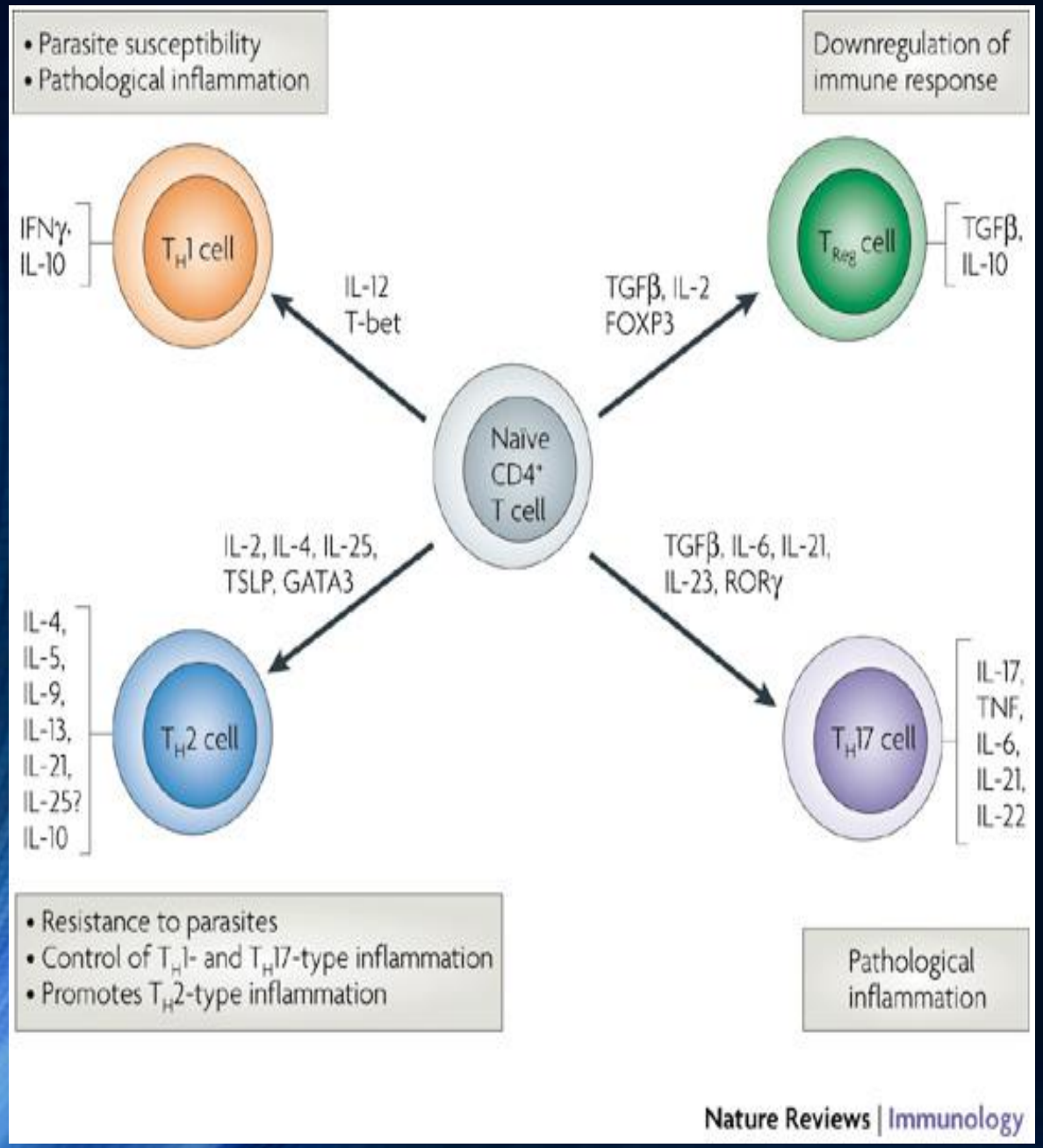
Once the T cell is matures it then secreats its own family of Cytokines.

Th1-- INF gamma, IL-10

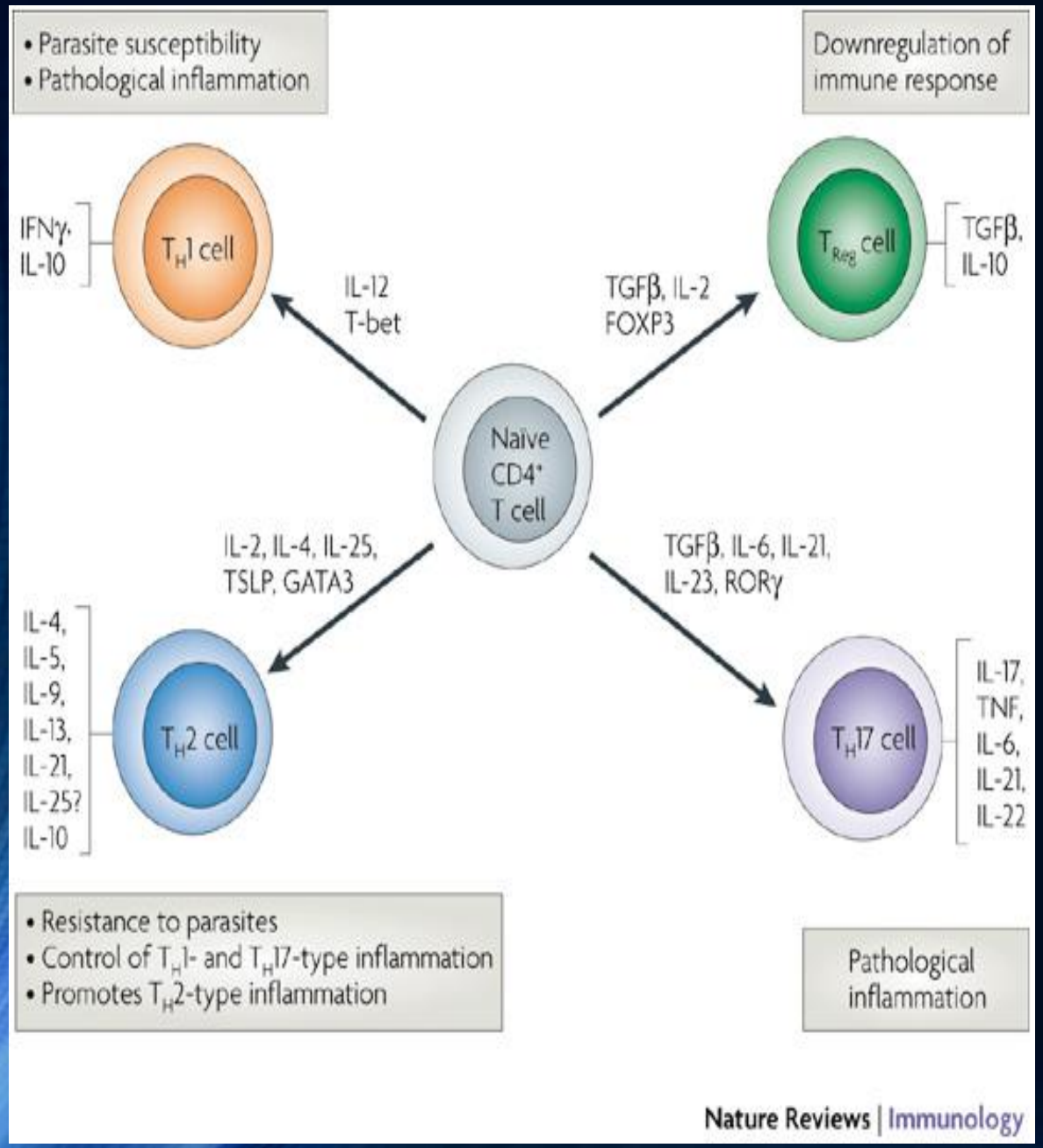
Th2-- Il4,IL5,IL9, IL13,IL21, IL25

Th17– IL17, TNF, IL6,IL21,IL22

Treg– TGFB, IL10



- Understanding Slide
- The implications of the understanding of this slide leads to greater understanding of interlacing pathophysiology.
- MS can be overactivation of the Th1 pathway but it may be a result of chronic viral infection by EB virus or CMV virus which is known to occur in some patients.



- Understanding Slide
- The over stimulation of the Th2 pathway and the development of Atopic Dermatitis, Asthma, psoriasis can now be potentially associated with an infestation of fungus, or parasites.

New Treatment for Asthma-XOLAIR

- Omalizumab-XOLAIR
- Monoclonal Antibody to IGE
- Useful in allergic Asthma
- Maybe useful in some non-allergic asthma
- Also useful in Spontaneous urticaria and Angioedema
- Useful in Bullous Pemphigoig
- Useful in some with Interstitial Cystitis

New Treatment for Asthma-XOLAIR

- **There are No Studies Measuring the Effects on TH1/Th2 Balance**

New Treatment for Asthma--Anti-TNF Alpha

- Adalimumab- TALZ
- Certolizumab- CIMIZIA
- Etanercept- EMBRIL
- Golimumab- SUMPONI, ARIA
- Infliximab- XELJANZ

New Treatment for Asthma--Anti-TNF Alpha

- These medication aren't as specific regarding TH1/Th2 they are immune suppressing. There are cases of improvements with these drug in certain individuals.
- They are approved for use in RA Plaques Psoriasis, Psoriatic Arthirtis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis
- Taking these drugs one needs to be aware of Activation of TB, Valley fever and those should patients should not receive live viruses.

New Treatment for Asthma--Anti-TNF Alpha

- So now that we have a deeper understanding of the Th1/Th2 immune system, lets reflect on TB, and Valley Fever.
- Valley Fever is caused by a fungus Coccidioidiomycosis
- Both TB and Valley Fever can be controlled with stimulation and proper functioning of the Th2 System
- However Stimulation of the Th1 System can lead to activation or reactivation of these 2 diseases
- This gives us once again some insight to the reason why some individuals have chronic active TB and others do not.

New Treatment for Asthma- Cytokines

- Proinflammatory Cytokines IL4,IL5, IL13
- Anti-inflammatory Cytokines IL10, IL12, IL18, IL21, IL23, IL27
- Remember with monoclonal antibodies we can bind the inflammatory Cytokines or we can block their receptor
- Or we can create analogs of the anti-inflammatory Cytokins.

New Treatment for Asthma- Cytokines

Proinflammatory Cytokines Blockers for IL 4, IL 5 IL 13

IL4 blocker Duplimumab- DUPIXENT ** it is indicated for Atopic Dermatitis Severe Eosinophilic Asthma and Chronic Rhinosinusitis. Do not use if you have a helmith infection

IL5 blocker- Mepolizumab- NUCALA** it plays a role in esosinophil maturation, is injected once a month reduced eosinophilia and Airway Hyperresponsiveness but no significant effect on early or late response to allergen stimulation.

IL13 blocker- prevents asthma in animal models and is in phase 2 trials.

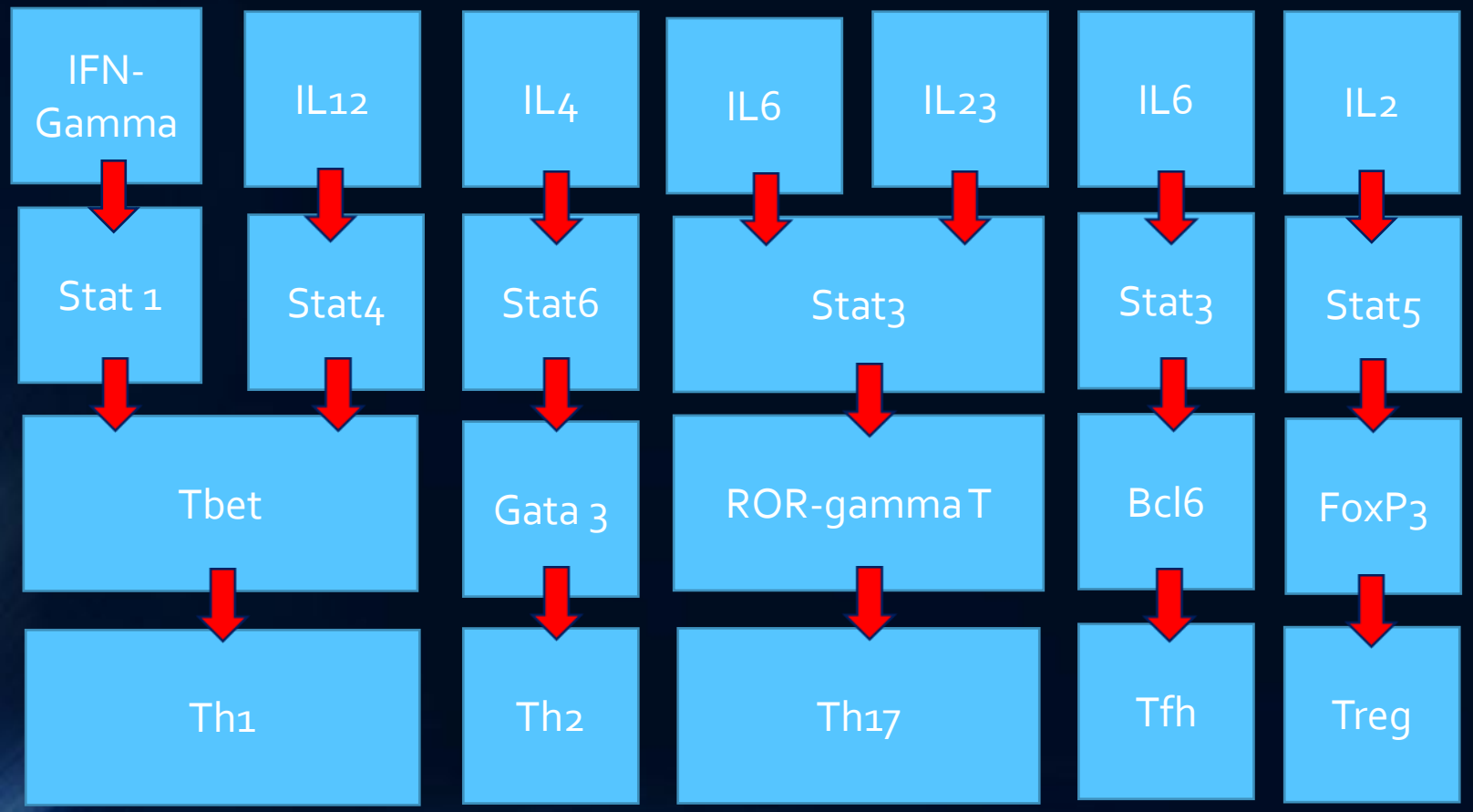
New Treatment for Asthma- Cytokines

- Anti-inflammatory Cytokines IL10, IL12, IL18, IL21, IL23, IL27
- IL10 analog has been licensed for Crohn's disease, has some effect on severe asthma, has side effect of anemia and thrombocytopenia
- IL12 is essential for Th1 response. Trials were terminated because of a death
- IL 19 is in the IL10 family. Has some effect of apoptosis of monocytes its role needs to be explored.

New Treatment for Asthma- Cytokines

- Anti-inflammatory Cytokines IL10, IL12, IL18, IL21, IL23, IL27
- IL 21 is produced by both TH1 and Th2 cells. And tends to encourage along Th1. It may help to keep IGE levels down. It is also being developed as a possible antitumor drug.
- IL23 this promotes Th1 Cells and TH17 cells and needs to be explored.

Transcription Factor Modulators



Tanscrition Factor Modulators.

- Stat 1 Modulators Seem to have an effect of hyperresponsiveness but it also seems to increase susceptibility to bacterial infecitons
- Stat 6 Modulators seem to have some effect on Goblet cell herperplasia
- PPAR (Peroxide Proliferator Activated Receptors) modulators they are activated by Fatty acids Oxidized fatty acids, phospholipids and important modulators of infection. They are present in eosinophils, T lymphocytes, Alveolar Macrophages, Epithelial Cells and Smooth Muscles– Selective stimulation can reduce inflammation. Research is underway

Closing Statements

- The progress and ease by which we can make new drugs with monoclonal anti-bodies and Analogs of signaling proteins is creating hundred of new potential useful drugs.
- Understanding of the Immune system is giving us insight into acute and chronic disease
- Very soon we will be drawing labs to assess that status of the immune system and then we ask very different kinds of questions Such was what is driving the Th1 or the Th2 response. Is there a chronic fungal infection or an underlying parasite infection.

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