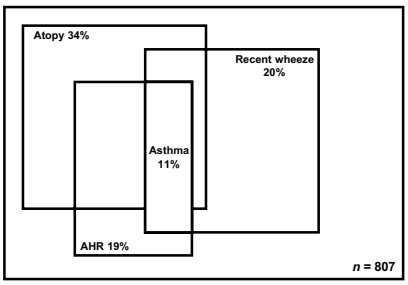
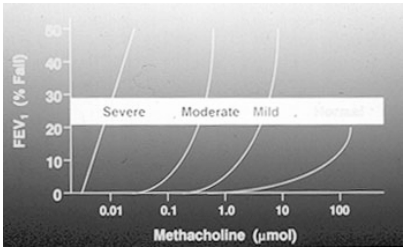
Defining Asthma: Clinical Criteria

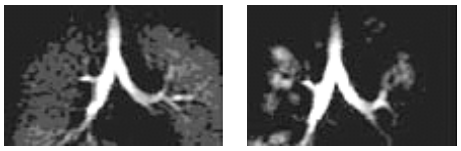


From: Woolcock, AJ. "Asthma" in *Textbook of Respiratory Medicine, 2nd ed.* Murray, Nadel, eds.(Saunders:Philadelphia) pp. 1288-1330, 1994

Defining Asthma: Bronchial Hyperresponsiveness



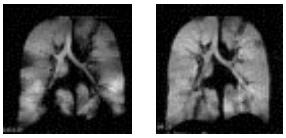
Impaired Ventilation in Asthma



Normal Asthmatic

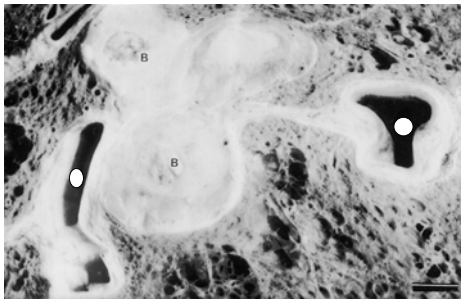
From: Klarreich, *Nature* 424:873, 2003

Dynamic Imaging of Asthma



Pre-treatment Post-treatment

Mucus Plugging is a Prominent Feature of Moderate to Severe Asthma



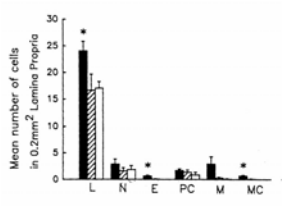
From: Bousquet et al., *Am. J. Respir. Crit. Care Med.*, 161:1720, 2000

Some Landmarks in the History of the Immunology of Asthma*

1989: Early genetic mapping assigns chromosome 5q to the "cytokine gene cluster"
Early 1990s: Asthma is an inflammatory disease
1990: Upregulation of ICAM-1 and LFA-1, adhesion molecules, in a primate model of asthma
1992: T_H2 bias of lymphocytes in asthma
1997: Experimental support grows for the "Hygiene hypothesis," first proposed in 1989
2000: Role of Tregs in regulation of asthma

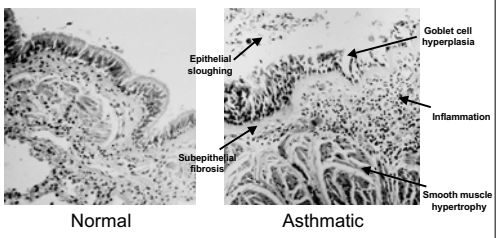
*Highly biased view; therefore, commit to memory

Nature of Inflammatory Cells in Biopsies From Airways of Asthmatics



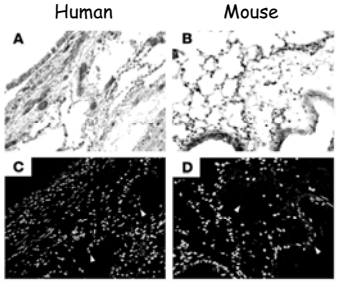
From: Ollerenshaw and Woolcock., *Am. Rev. Resp. Dis.* 145:922, 1992

Defining Asthma: Pathological Features



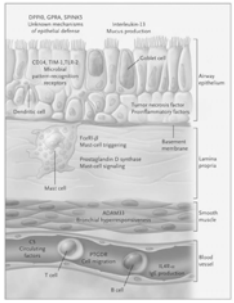
From: Bousquet et al., *Am. J. Respir. Crit. Care Med.*, 161:1720, 2000

Fibrin Deposition in the Airways of Asthmatics

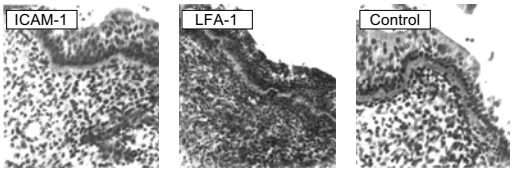


From: Wagers et al. *J. Clin. Invest.* **114**:104-111, 2004

Tissue "Compartments" in Asthma



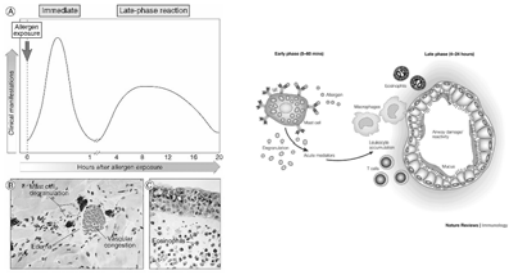
Adhesion Molecules ICAM-1 and LFA-1 in Experimental Asthma



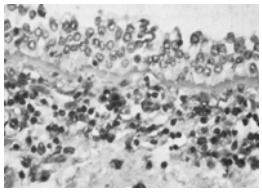
From: Wegner et al., *Science* 247:456, 1990

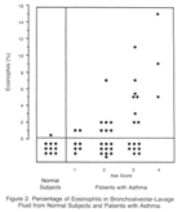
Asthma and the Immune Response

Early- and Late-phase Allergic Reactions



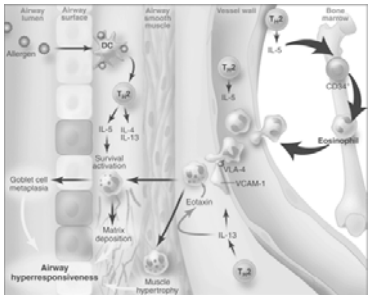
Presence of Degranulated Eosinophils in Asthmatic Airways





From: Bousquet et al., *N. Engl. J. Med.* 323:1033, 1990

Eosinophils and Asthma



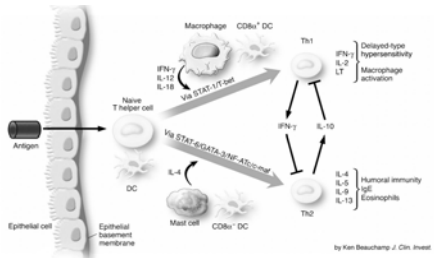
From: Wills-Karp and Karp, Science 305:1726-1729, 2004

Asthma as a T_H2-dominated Disease

First Recognition of a T_H2 Bias in Lymphocytes Obtained by BAL in Asthmatics

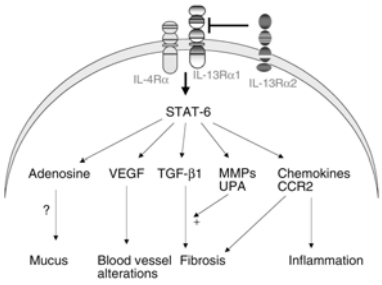
From: Robinson et al., *New Engl. J. Med.* 326:298,1992

Emergence of T_H1 and T_H2 Cells from Naïve Precursors



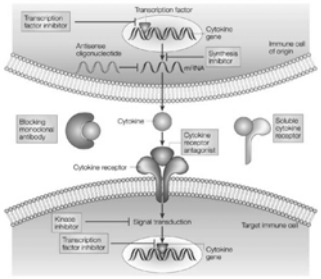
From: Elias et al., *J. Clin. Invest.* 111:291, 2003

STAT-6 Signaling Pathways Leading to the Asthmatic Phenotype



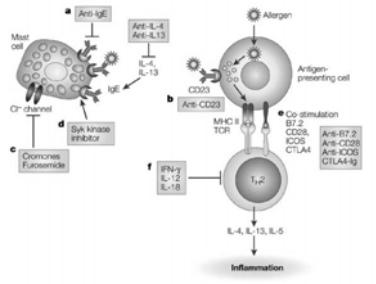
From: Elias et al., *J. Clin. Invest.* 111:291, 2003

Potential Drug Targets in Asthma



From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

Understanding the Immunology of Asthma Leads to Insights Into Novel Therapeutics



From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

Who Gets Asthma?

The Inverse Association Between Tuberculin Responses and Atopic Disorder

Taro Shirakawa, Tadao Enomoto, Shin-ichiro Shimazu, Julian M. Hopkin*

From: Shirakawa et al., *Science* 275:77, 1997

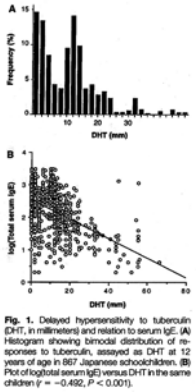


Fig. 1. Delayed hypersensitivity to tuberculin (DHT, in millimeters) and relation to serum IgE. **(A)** Histogram showing bimodal distribution of responses to tuberculin, assayed as DHT at 12 years of age in 867 Japanese schoolchildren. **(B)** Plot of log(total serum IgE) versus DHT in the same children ($r = -0.492$, $P < 0.001$).

Table 1. History of infectious diseases, atopic symptoms, IgE levels, and cytokine profiles in subjects grouped by tuberculin reactivity. ASE, allergen-specific IgE; UD, undetectable.

Measurement	Group 1 (n = 290)	Group 2 (n = 289)	Group 3 (n = 213)	Group 4 (n = 75)	Total (n = 867)
Tuberculin response					
At 6 years	−	−	+	+	
At 12 years	−	+	+	−	
Positive antiviral immunity (%)					
Measles (history + vaccine)	83.4	87.2	84.5	81.3	84.3
Chicken pox (history + vaccine)	86.9	82.3	82.2	82.7	83.9
Mumps (history + vaccine)	62.8	60.9	60.1	57.3	61.0
Number with IgE to *Ascaris*	2	2	2	1	7
Symptoms (%)					
Atopy (past + present)	46.8	33.9‡‡	25.8‡‡	38.7	36.6
Atopy (present)	32.1	7.9‡‡‡	9.8‡‡‡	30.7	18.5
Asthma (past + present)	13.4	4.1‡‡	3.7‡‡	6.8	7.4
Rhinitis (past + present)	16.2	4.8‡‡	8.6‡	14.6	10.4
Eczema (past + present)	22.7	12.8‡‡	12.2‡‡	16.0	16.2
Geometric mean IgE (IU/ml)	208	149**	98***	178	154
Positive ASE (%)	55.8	43.9‡‡	41.8‡‡	53.3	48.2
Atopic (high IgE or positive ASE) (%)	65.5	54.0‡‡	49.2‡‡	61.3	57.3
Median cytokine level (pg/ml)					
IL-4	1.88	0.96†	0.92†	1.66	1.22 (10.2-UD)§
IL-13	18.3	10.2†††	7.8†††	19.1	14.2 (45.6-UD)
IL-10	5.9	3.1††	2.9††	5.9	3.9 (10.2-UD)
IL-12	UD	UD	UD	UD	UD
IFN-γ	7.8	11.0††	13.2††	6.4	10.5 (23.2-UD)
Positive family history within three generations (%)	54.1	49.8	49.8	48.0	51.0
Mean BMI	21.1	22.0	21.9	21.2	21.6

$^{**}P < 0.01$, $^{***}P < 0.001$ on the basis of Student's test. †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ on the basis of a median test. ‡$P < 0.05$, ‡‡$P < 0.01$, ‡‡‡$P < 0.001$ on the basis of χ^2 against group 1, respectively. §Maximum-minimum values.

From: Shirakawa et al., *Science* 275:77, 1997

Table 2. Odds ratios for atopy and for occurrence and remission of atopic symptoms in positive versus negative tuberculin responders by age. Multiple logistic analysis was conducted with the SPSSX package, version 2.2. In all models, allowance was made for dichotomized variables including sex, life-style, nutritional status, environmental factors, and family history. Only significant values are shown.

Tuberculin response	Odds ratio		
	Atopy	Atopic symptoms	
		Occurrence	Remission
Conversion to positive up to 6 years of age	0.50 (0.29 to 0.83)*	Asthma: 0.31 (0.22 to 0.45)* Eczema: 0.50 (0.33 to 0.91)*	Asthma: 8.2 (6.0 to 9.8)** Eczema: 1.6 (1.0 to 2.2)*
Conversion to positive between 6 and 12 years of age	0.43 (0.25 to 0.83)**	Asthma: 0.42 (0.24 to 0.56)*	Asthma: 6.0 (2.8 to 10.3)*** Eczema: 6.7 (4.8 to 11.4)*** Rhinitis: 9.0 (6.2 to 14.2)***

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$.

From: Shirakawa et al., *Science* 275:77, 1997

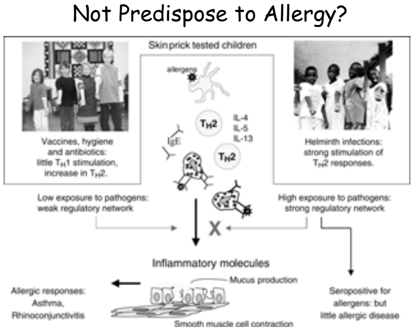
Environmental Influences and Asthma: The Hygiene Hypothesis

Asthma, rhinitis, other respiratory diseases

Hay fever and asthma in relation to markers of infection in the United States

Paolo Maria Matricardi, MD, Francesco Rosmini, DSc, Valentina Panetta, DSc, Luigina Ferrigno, BSc, and Sergio Bonini, MD Rome, Italy

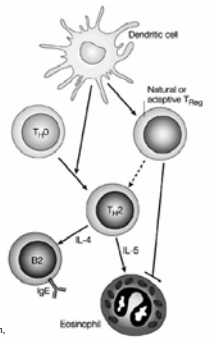
Paradox: Why Does Chronic Infection with Helminths Not Predispose to Allergy?



From: Yazdanbakhsh et al., *Science* 296:490, 2002

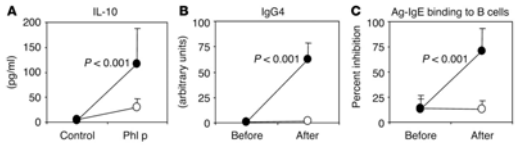
An Alternative to the Hygiene Hypothesis: Regulatory T-cells

The Role of Regulatory T-cells in Modifying T_H2 Immunity



Modified from: Maizels & Yazdanbakhsh, *Nature Rev. Immunol.* 3:733, 2003

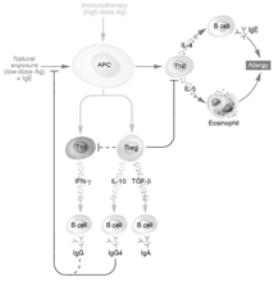
Immunotherapy of Atopic Diseases: a Role for Tregs?



Following 2-year grass pollen immunotherapy (closed circles), there were significant increases in (**A**) allergen-stimulated PBMC production of IL-10; (**B**) serum concentrations of grass pollen allergen-specific IgG4; and (**C**) serum inhibitory activity for allergen-IgE binding to B cells compared with controls (open circles). These changes were accompanied by a reduction in symptoms and inhibition allergen-induced late cutaneous response.

From: Robinson et al., *J. Clin. Invest* 114:1389, 2004

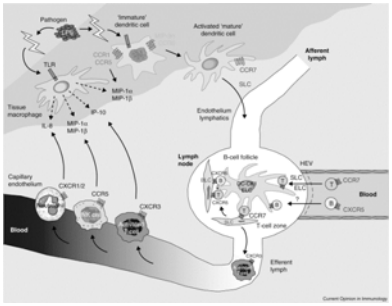
Regulatory T-cells (Tregs) in Asthma



From: Robinson et al., *J. Clin. Invest* 114:1389, 2004

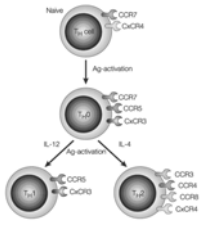
Chemokines: the Gatekeepers of Inflammation

Chemokines Direct Traffic

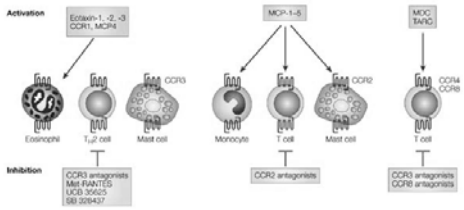


From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Chemokine Receptor Specificity in T_h2 Cells and Eosinophils



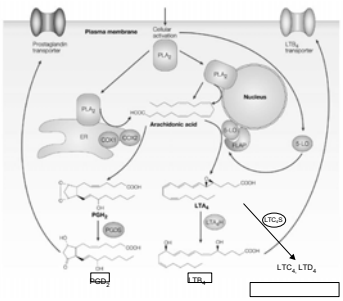
Potential Drug Targets in Asthma: Chemokines and their Receptors



From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

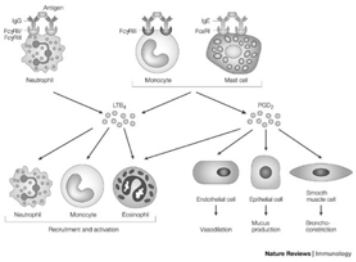
Inflammatory Mediators as Novel Drug Targets

Lipid Mediators in Asthma: LTB_4, PGD_2, LTC_4



From: Luster and Tager Nature Reviews Immunol. 4:711, 2004

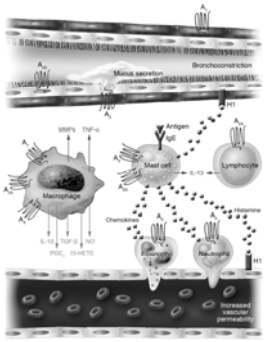
Biological Activities of LTB_4 and PGD_2



From: Tilley and Boucher J. Clin. Invest. **115**:13-16 (2005)

Adenosine Receptors as Drug Targets in Asthma

Pro- and Anti-inflammatory Activities of Adenosine in Asthma



From: Tilley and Boucher
J. Clin. Invest. **115**:13-16 (2005)

Summary of Genes Associated With Atopy

Gene	Chromosome	Phenotype	Genetic variation	Association	Reference
IL10	1q31	Total IgE, eosinophils	Haplotypes	Yes	[33]
CHRM3	1q41	Atopy (cockroach)	Haplotype	Yes	[34]
IL1A	2q14	Atopy	-889/C/T	Yes	[35]
CTLA4	2q33	Asthma severity	-318C/T	Yes	[37]
		Atopic asthma	-1147C/T	Yes	[37]
IL4	5q31	AD	-590C/T	Yes	[38]
IL13	5q31	Atopy	Haplotype	Yes	[39]
IL13		Atopy	Arg130Gln	Yes	[30]
		AD	Arg130Gln	Yes	[31]
CD14	5q31	Atopy, asthma, BHR, IgE, AD, Allergic Rhinitis	-159C/T	No	[32]
GGNP1	5q31-34	Asthma	+1122G/A	Yes	[33]
SCAR	5q33-34		Arg16His	Yes	[34]
LTC4	5q35	Asthma	-444 (A/C)	No	[35]
		FEV1/fc		Yes	
IL13R	5q33-34	Asthma severity	+4479/no	Yes	[36]
		AD	1184A/C	Yes	[37]
MHC	6p21	Asthma, total IgE	DRB1	Yes	[38]
		Atopy	DRB1, DQ	Yes	[39]
		Total, specific IgE	DRB1	Yes	[40]
		Atopy, specific IgE	DRB1	Yes	[41]
		Allergic asthma	DRB1	Yes	[42]
		Asthma	DRB1	Yes	[43]
TNF	6p21	Allergic asthma	-308G/A	No	[42]
		Allergic asthma	-308G/A	Yes	[43]
		Allergic asthma	-308G/A	No	[44]
		Childhood asthma	-308G/A	No	[45]
		Asthma	-857C/T	Yes	[46]
TCRQ	7p14	Asthma, IgE		No	[47]
Eotaxin 2	7q11.23	Asthma	1395A/G	Yes	[48]
NOS3	7q36	Asthma	27b(intron 4)	Yes	[49]
		Total IgE			
NAT2	8p22	Allergic asthma	Slow acetylating allele	Yes	[50]
CC16	11q13	BHR	38A/G	Yes	[51]
		Asthma	38A/G	No	[52]
		BHR			
FCER1B	11q13	Asthma	Rsa/ex7	Yes	[53]
		Atopy			
GSTP1	11q13	PVC, FEV,	Ile105Val	Yes	[54]
SART-1	11q12-13	Atopy	774C/T	Yes	[55]
			Gly489Ala		
STAT6	12q13	Allergy	2964C/A	No	[56]
			(CA)n intron 1	Yes	
			haplotype	Yes	
IFNG	12q21	Total IgE	(CA)n intron 1	Yes	[57]
PHF11	13q14	Total IgE	Haplotype	Yes	[58]
IL4RA	16p12	Allergic asthma	Ile50Val	Yes	[59]
IL31R		Total IgE		Yes	[59]
CARD15	16q12	Allergic rhinitis	2104C/T	Yes	[60]
		Allergic rhinitis, AD	3722G/C	Yes	
		Atopy, total IgE	3020insC	Yes	
RANTES	17q21	Asthma (late onset)	-28C/G	Yes	[61]
		Asthma severity	-28C/G	Yes	[62]
Eotaxin-1	17q21	Total IgE	+927C/T	Yes	[63]
		Total IgE in AD	+927C/T	Yes	[63]
ADAM 33	20p13	Asthma	Haplotype	Yes	[64]

BHR, bronchial hyperresponsiveness; AD, atopic dermatitis; PVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

From: Halapi and Hakonarson, *Curr. Opin. Pulm. Med.* 10:22, 2003