December 7, 2012
Inflammatory Mediators in Allergic Asthma

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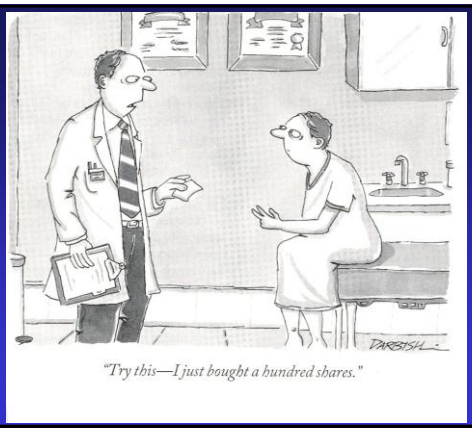


"Try this—I just bought a hundred shares."

Disclosure Statement
Lanny J. Rosenwasser, MD

- RESEARCH STUDIES
  Genentech, Novartis, National Institutes of Health
- CONSULTANT
  A-Z, Genentech, Novartis, Regeneron, Sanofi-Aventis
- SPEAKERS' BUREAU
  Alcon, A-Z, Genentech, Novartis

Learning Objectives

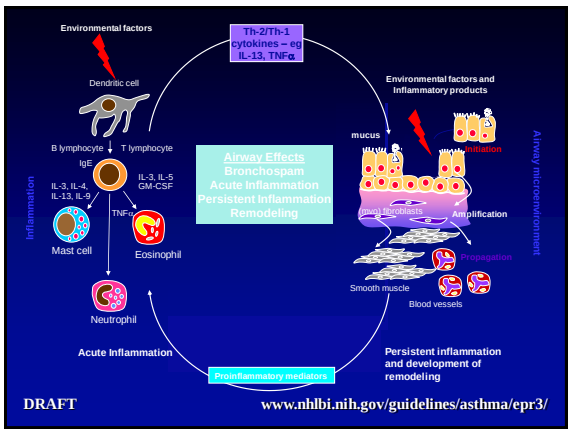
At the completion of this program, the participant will be able to…

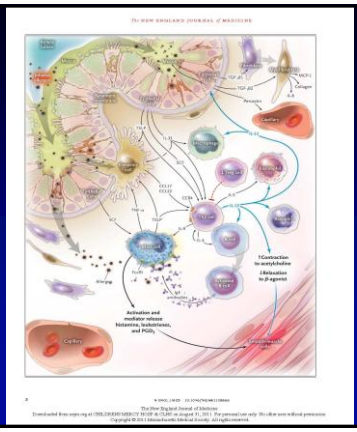
- *Understand the role of allergy and genetic mechanisms in asthma and allergy.*
- *Understand the role of IgE regulation in the genetics and pharmacogenetics of asthma.*

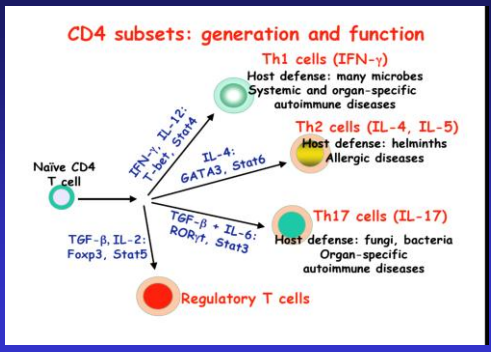
Characteristics of Asthma

- Narrowing of the airways
- Airway obstruction
- Airway inflammation
- Increased airway responsiveness

NHLBI, NAEPP, 1997.







Regulatory T Lymphocytes

$CD4^+$, $CD25^+$ T lymphocytes

- Regulatory
- Express TGFβ, IL-10
- Suppressive to other T cells
- Express Foxp3 transcription factor
- IL-35 growth factor

IL-1 and Allergy/Asthma

- IL-1 in a critical co-factor for Th2 and Th17 T cell activation in vivo and in vitro for Humans and Mice
- Airway and tissue involvement n asthma and allergy

References
Adherent Cell Function in Murine T-Lymphocyte Antigen Recognition. IV. Enhancement of Murine T-Cell Antigen Recognition by Human Leukocitic Pyrogen. Rosenwasser, Lanny J. Dinarello, Charles A. Rosenthal Alan S. *The Journal of Experimental Medicine* – Vol. 150, 1979

Detection of Alveolar Macrophage-Derived IL-β in Asthma[1] Inhibition with Corticosteroids. Borish, Larry. Mascali James J. Dishuck, John. Beam, Martin , Richard J. Rosenwasser, Lanny J. *The American Association of Immunologists* Vol 149. 3076-3082; N0 9. November 1, 1992.

IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and Differentiation. Shlomo , Z. Sasson, Ben. Hu-Li, Jane. Quisl, Juan. Cauchetaux, Stephane. Ratner, Maya. Shapira, Hana. Dinarello, Charles A. Paul, William E.. *PNAS* April 28, 2009 Vol. 106 No. 17. 7119-7124

Cytokine . IL-1 acts on T cells to enhance the magnitude of in vivo immune Responses. S.Z. Sasson-Ben. Cauchetaux, Stephanie. Crank, Michelle. Jane, Hu-Li. Paul, William. *Elsevier Ltd.* 56 (2011) 122-125

Pathogen-induced human T_H17 cells produce IFN-γ or IL-10 and are regulated by IL-1β. Zielinski, Christina E. Mele , Federico. Aschenbrenner, Dominik, Jarrossay, David, Jarrossay, Francesca, Ronchi, Gattorno, Marco, Norticelli, Silvia, Lanzavecchia, Antonio, Sallusto, Frederica. *Nature* 2012

Extended IL-1 Family

(Caspase 3 Dependent)

- IL-18 – shared receptor and genetics (IL-18bp)
- IL-32 – TNF inducer
- IL-33 – Ligand for ST2 Induces TH2 Cytokines
- IL-37 – Downregulation of IL-1 family activities

IL-1 family members – Chr. 2q13

New Name	Other Name	Property
IL-1F1	IL-1α	Agonist
IL-1F2	IL-1β	Agonist
IL-1F3	IL-1Ra	Receptor antagonist
IL-1F4	IL-18	Agonist
IL-1F5	FIL1δ	Anti-inflammatory
IL-1F6	FIL-1ε	Agonist
IL-1F7	IL-37	Anti-inflammatory
IL-1F8	IL-1H2	Agonist
IL-1F9	IL-1ε	Agonist
IL-1F10	IL1HY2	Receptor antagonist
IL-1F11	IL-33	Agonist

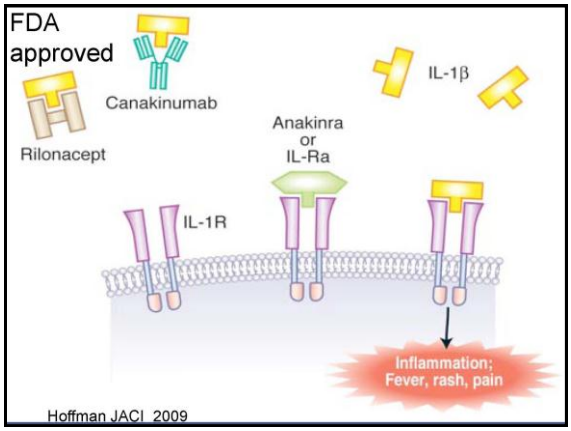
Gene	Cytokine
IL1F5	IL-36 Ra
IL-1F6	IL-36
1F8	IL-36
1F9	IL-36
IL-1F7	IL-37
IL-1F10	IL-38

Successful IL-1 targeted therapy

- Gout - acute and chronic
- Pseudogout
- Type 2 Diabetes
- Post MI remodeling
- Systemic onset juvenile idiopathic arthritis (Still's)
- Adult onset Still's disease
- Schnitzler's Disease

Potential disease targets for IL-1 directed therapy

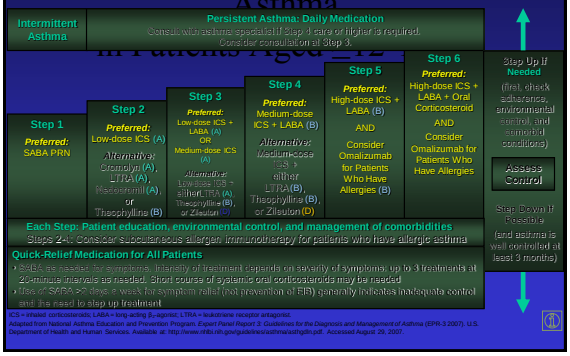
- **Neutrophilic urticaria**
  - Chronic urticaria
- **Neutrophilic lung disorders**
  - COPD
  - Neutrophilic asthma
  - Acute Chest syndrome
- **Neutrophilic CNS disease**
  - Acute Hemorrhagic Leukoencephalitis



Complexity of Asthma

- Several orders of magnitude more complex
- Microbiome, Proteome, Transcriptome, Genome
- Tissues, Organs, Whole Body, Brain
- Third and Fourth Dimensions

Stepwise Approach for Managing Asthma



Progression of Genetic Studies in Allergy

- •Candidate Genes
- •Linkage
- •Association
- •GWAS
- •Systems Biology
- •ENCODE

Other Critical Factors

- Epigenetics
- Microbiome

March, Slieman, Hakonarson, Genomics, In Press

Candidate Gene/Linkage

Table 1: Summary of well-replicated loci identified through candidate gene studies

Gene	Chromosomal Locus	Function
Immune Function		
IL10	1q31-q32	Cytokine – Immune Regulation
CTLA4	2q33	Control/Inhibition of T cell responses/Immune Regulation
IL13	5q31	Induces T_H2 effector functions
IL4	5q31.1	T_H2 differentiation
CD14	5q31.1	Microbe detection – recognizes Pathogen Associated Molecular Patterns
HAVCR1	5q33.2	T cell responses – Hepatitis A Virus receptor
LTC4S	5q35	Leukotriene synthase – inflammatory mediator
LTA	6p21.3	Inflammatory mediator
TNF	6p21.3	Inflammatory mediator
HLA-DRB1	6p21	Major Histocompatibility Complex Class II – Antigen Presentation
HLA-DPB1	6p21	
FCER1B	11q13	Receptor for IgE – Atopy
IL1R	11q22.2-q22.3	Inflammation
STAT6	12q13	IL-4 and IL-13 signaling
CMA1	14q11.2	Chymase – Mast cell expressed amine protease
IL4R	16p12.1-p12.2	Alpha chain of receptors for IL-4 and IL-13
Barrier Function/Innate Immunity		
FLG	1q21.3	Epithelial integrity and barrier function
SPINK5	5q32	Epithelial serine protease inhibitor
CCL8	11q23.3-q23.1	Potential immunoregulatory function – epithelial expression
NOS1	12q24.2-q24.31	Nitric oxide synthase – cellular communication
CCL11	17q21.1-q21.2	Eotaxin-1: eosinophil chemoattractant
CCL5	17q11.2-q12	RANTES: chemoattractant for T cells, eosinophils, basophils
Tissue Response		
GSTM1	1p13.3	Detoxification, removal of products of oxidative stress
ADRB2	5q31-q32	Smooth muscle relaxation
GPRA	7p14.3	Regulation of metalloprotease expression, neuronal effects
NAT2	8p22	Detoxification
GSTP1	11q13	Detoxification, removal of products of oxidative stress
ALOX	17p13.3	Regulation of inflammation
TBXA2R	19p13.3	Platelet aggregation
TGFB1	19q13.1	Influences cell growth, differentiation, proliferation, apoptosis
ADAM33	20p13	Cell-cell and cell-matrix interactions
GSTT1	22q11.23	Detoxification, removal of products of oxidative stress

March, Slieman, Hankonasson, Genomics, In Press

Positional Cloning

Gene	Chromosomal Locus	Reference
CYFIP2	5q33.3	Noguchi *et al*, 2005[64]
DPP10	2q14.1	Allen *et al*, 2003[65]
HLAG	6p21.33	Nicolae *et al*, 2005[66]
PHF11	13q14.3	Zhang *et al*, 2003[67]
GPRA	7p14.3	Laitinen *et al*, 2003[68]
ADAM33	20p13	Van Eerdewegh *et al*, 2002[69]

GWAS Results

- March, Slieman, Hakonarson, Genomics, in press

Reported Gene	Locus	Top SNP	Endpoint Analyzed	Reference
RAD50	5q31.1	rs2244012	Asthma	Li *et al*, 2010[69]
HLA-DR/DQ	6p21.32	rs3998159		
DENND1B	1q31.3	rs2786098	Asthma	Sleiman *et al*, 2010[70]
TLE4	9q21.31	rs2378383	Asthma	Hancock *et al*, 2009[71]
PDE4D	5q12.1	rs2548659	Asthma	Himes *et al*, 2009[58]
ORMDL3	17q12	rs7216389	Asthma	Moffatt *et al*, 2007[59]
PDE11A	2q31.2	rs11684634	Asthma	DeWan *et al*, 2010[72]
CHI3L1	1q32.1	rs4950928	Asthma/YKL-40 Serum Levels	Ober *et al*, 2008[38]
IL18R1	2q12.1	rs1420101	Blood Eosinophil Count/Asthma	Gudbjartsson *et al*, 2009[61]
IKZF2	2q31.1	rs12619285		
GATA2	3q21.3	rs4857855		
IL5	5q12.1	rs4143832		
SH2B3	12q24.12	rs3184504		
CHRNA 3/5	15q24	rs8034191	COPD	Pillai *et al*, 2009[74]
HHIP	4q31.22	rs13147785	FEV_1/FVC	Wilk *et al* 2009[60]
TNS1	2q35	rs2571445	FEV_1	Repapi *et al*, 2010[60]
GSTCD	4q24	rs10516526	FEV_1	
HTR4	5q33.1	rs3995090	FEV_1	
AGER	6p21.32	rs2070600	FEV_1/FVC	
TNS3	15q23	rs1389918	FEV_1/FVC	
GPR126	6p24.1	rs3817928	FEV_1/FVC	Hancock *et al*, 2010[71]
ADAM19	5q33	rs2277027	FEV_1/FVC	
AGER/PPT2	6p21.3	rs2070600	FEV_1/FVC	
FAM13A	4q22.1	rs2869967	FEV_1/FVC	
PTCH1	9q22.32	rs16909898	FEV_1/FVC	
PID1	2q36.3	rs1435867	FEV_1/FVC	
HTR4	5q33.1	rs7731584	FEV_1/FVC	
INTS12/GSTCD/NPNT	4q24	rs17331332	FEV_1	
IL18R1/IL18R1	2q12.1	rs3771166	Asthma	Moffatt *et al*, 2010[61]
HLA-DQ	6p21.32	rs9273349		
IL33	9p24.1	rs1342326		
SMAD3	15q22.33	rs744910		
IL2RB	22q12.3	rs2284033		
ORMDL3/GSDMB	17q12	rs2305480	Childhood Onset Asthma	
IL6R	1q21.3	rs4129267	Asthma	Ferreira MA *et al* 2011[48]
C21orf30/LRRC32	11q13.5	rs7130588		
PRKG1	10q21.1	rs7922491		
RPL32P28/OR7E156P	13q21.31	rs3119939		
ORMDL3	17q12	rs6503525	Asthma	Ferreira MA *et al* 2011[48]

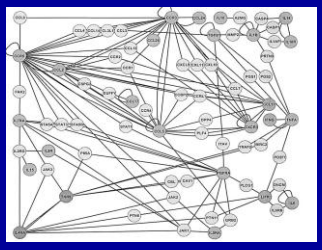
NOTCH4	6p21.32	rs404860	Asthma	Hirota T *et al* 2011[85]
TSLP	5q22.1	rs1837253		
PBX2	6p21.32	rs204993		
LOC338591	10p14	rs10508372		
C6orf10	6p21.32	rs3129943		
HLA-DQB1	6p21.32	rs7775228		
IKZF4	12q13.2	rs1701704		
HLA-DRA	6p21.32	rs3129890		
LOC729675	4q31.21	rs7686660		
HLA-DQA2	6p21.32	rs9275698		
BTNL2	6p21.32	rs3117098		
CDK2	12q13.2	rs2069408		
HLA-DOA	6p21.32	rs9500927		
GAB1	4q31.21	rs3805236		
GSDMB	17q12	rs11078927	Asthma in 3 ethnically diverse North American populations	Torgerson DG *et al* 2011[87]
IL1RL1	2q12.1	rs3771180		
TSLP	5q22.1	rs1837253		
IL33	9p24.1	rs2381416		
PYHIN1	1q23.1	rs1101999		
C11orf71	11q23.2	rs11214966		
CRCT1	1q21.3	rs4845783		

Network analysis of single nucleotide polymorphisms in asthma

Jutta Renkonen[1,2]
Sakari Joenvaara[1,2]
Ville Parviainen[1,2]
Pirkko Mattila[1,2]

Journal of Asthma and Allergy 2010:3 177-186

Network analysis of SNPs in asthma



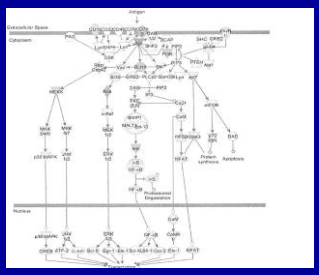
Journal of Asthma and Allergy 2010:3

Pathways Activated during Human Asthma Exacerbation as Revealed by Gene Expression Patterns in Blood

Unnur S, Bjornsdottir[1], Stephen T. Holgate[2], Padmalatha S. Reddy[3], Andrew A. Hill[4], Charlotte M. McKee[4], Cristina I. Csimma[4], Amy A. Weaver[3], Holly M. Legault[4], Clayton G. Small[4], Renee C. Ramsey[3], Debra K. Ellis[4], Conor M. Burke[5], Phillip J. Thompson[6], Peter H. Howarth [2], Andrew J. Wardlaw[7], Phillip G. Bardin[8], David I. Bernstein[9], Louis B. Irving[10], Geoffrey L. Chupp[11], George W. Bensch[12], Jon E. Stahlman[13], Monroe Karetzky[14], James W. Baker[15], Rachel L. Miller[16], Brad H. Goodman[17], Donald G. Raible[3], Samuel J. Goldman[3], Douglas K. Miller[3], John L. Ryan[4], Andrew J. Dorner[4], Frederick W. Immermann[3], Margot O'Toole[3]

Plos One, July 2011, Volume 6, Issue 7

Asthma Exacerbation Pathways



Plos One July 2011 Vol. 6 Issue 7

Systematic Localization of Common Disease-Associated Variation in Regulatory DNA

Matthew T. Maurano[1], Richard Humbert1, Eric Rynes[1], Robert E. Thurman[1], Eric Haugen[1], Hao Wang[1], Alex P. Reynolds[1], Richard Sandstrom[1], Honghu Qu[1], Jennifer Brody[3], Anthony Shafer[1], Fidencio Neri[1], Kristen Lee[1], Tanya Kutyavin[1], Sandra Stehling-Sun[1], Audra K. Johnson[1], Theresa K. Canfield[1], Erika Giste[1], Morgan Dieget[1], Daniel Bates[1], R. Scott Hansen[4], Shane Neph[1], Peter J. Sabo[1], Shelly Heimfeld[5], Anthony Raubitschek[6], Steven Ziegler[6], Chros Cotsapas[7,8], Nona Sotoodehnia[3,9], Ian Glass[10], Shamil R. Sunyaev[11], Rajinder Kaul[4], John A. Stamatoyannopoulos[1,12]

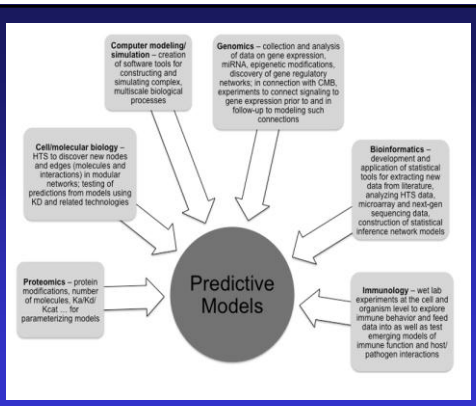
Science, September 2012, Vol .337

Definitions

Systems Biology – Integrated basis for functionality of an Organism

Immune Responses – Symphonies of Molecular and Cellular Mechanisms with each component generating a coordinated effective response

Analogies - Multiple



Modeling and Simulation at Molecular Scale

- Informatics – Software driven
- Modeling of Signaling and Receptor Activity
- Modeling of Cellular Behavior and Interactions

Large Scale Data Acquisition Technologies

- Cell and Molecular Biology
- Proteomics, Genomics
- Immunology Wet Lab

Molecular Biological Tools

- Gene and MiRNA Expression
- Transcript Profiling
- Next Generation Sequencing
- RNA; Screening
- Assay Design
- Applications

Interactional Measures

- Network Models
- 2 Hybrid Screens
- Mass Spec
- Proteomics
- Array Protein Assays
- Flow Cytometry

Allergy - 2030

- Systems Biology Approach to Allergic Cascades
- Biotherapeutics
- Pharmacogenetic Profiling
- Early Intervention

Systems Medicine

- Predictive
- Preventive
- Pharmacologically Effective
- Personalized

Challenges for the Future in Complex Genetic Disease Translational Research

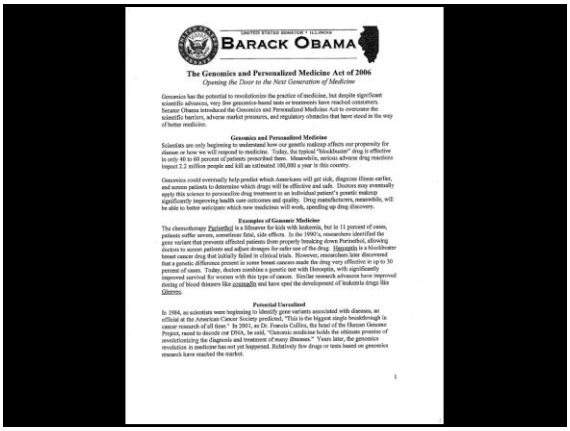
- Robust Biomarkers
- Phenotype Analysis
  Phenotype/Genotype Association
- Diagnostic/Pathologic Visualization
  (Nanomedicine)
- Informatics Modeling

References

Ronald N. Germain et al. Systems Biology in Immunology – A Computational Modeling Perspective. Annu Rev Immunol. 2011 29: 537-585

David J. Weatherall . Systems Biology and Red Cells, N ENGL J MED. 2011 364; 375-77.

Sydney Brenner. Sequence and consequences. Phil. Trans. R. Soc. B 2010 365,207-212.



BARACK OBAMA

The Genomics and Personalized Medicine Act of 2006

Opening the Door to the Next Generation of Medicine

Genomics has the potential to revolutionize the practice of medicine, but despite significant scientific advances, very few genomics-based tests or treatments have reached consumers. Senator Obama introduced the Genomics and Personalized Medicine Act to overcome the scientific barriers, adverse market pressures, and regulatory obstacles that have stood in the way of better medicine.

Genomics and Personalized Medicine

Scientists are only beginning to understand how our genetic makeup affects our propensity for disease or how we will respond to medicine. Today, the typical "blockbuster" drug is effective in only 40 to 60 percent of patients prescribed them. Meanwhile, serious adverse drug reactions impact 2.2 million people and kill an estimated 100,000 a year in this country.

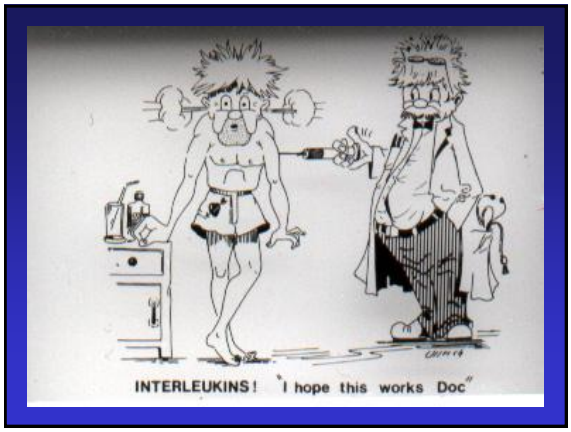
Genomics could eventually help predict which Americans will get sick, diagnose illness earlier, and screen patients to determine which drugs will be effective and safe. Doctors may eventually apply this science to personalize drug treatment to an individual patient's genetic makeup significantly improving health care outcomes and quality. Drug manufacturers, meanwhile, will be able to better anticipate which new medicines will work, speeding up drug discovery.

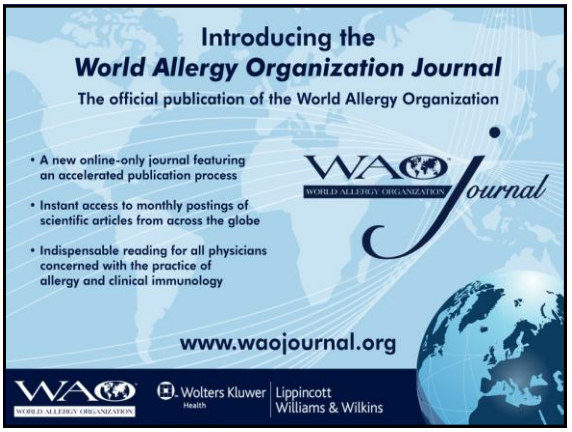
Examples of Genomic Medicine

The chemotherapy Purinethol is a lifesaver for kids with leukemia, but in 11 percent of cases, patients suffer severe, sometimes fatal, side effects. In the 1960's, researchers identified the gene variant that prevents affected patients from properly breaking down Purinethol, allowing doctors to screen patients and adjust dosages for safer use of the drug. Herceptin is a blockbuster breast cancer drug that initially failed in clinical trials. However, researchers later discovered that a genetic difference present in some breast cancers made the drug very effective in up to 30 percent of cases. Today, doctors combine a genetic test with Herceptin, with significantly improved survival for women with this type of cancer. Similar research advances have improved dosing of blood thinners like coumadin and have sped the development of leukemia drugs like Gleevec.

Potential Unrealized

In 1964, as scientists were beginning to identify gene variants associated with diseases, an official at the American Cancer Society predicted, "This is the biggest single breakthrough in cancer research of all time." In 2001, as Dr. Francis Collins, the head of the Human Genome Project, raced to decode our DNA, he said, "Genomic medicine holds the ultimate promise of revolutionizing the diagnosis and treatment of many illnesses." Years later, the genomics revolution in medicine has not yet happened. Relatively few drugs or tests based on genomics research have reached the market.


INTERLEUKINS! "I hope this works Doc"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