IMMUNOGENETICS AND PHARMACOGENOMICS OF ALLERGIC DISEASES

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Allergic Diseases and Associated phenotypes

are polygenic & multifactorial

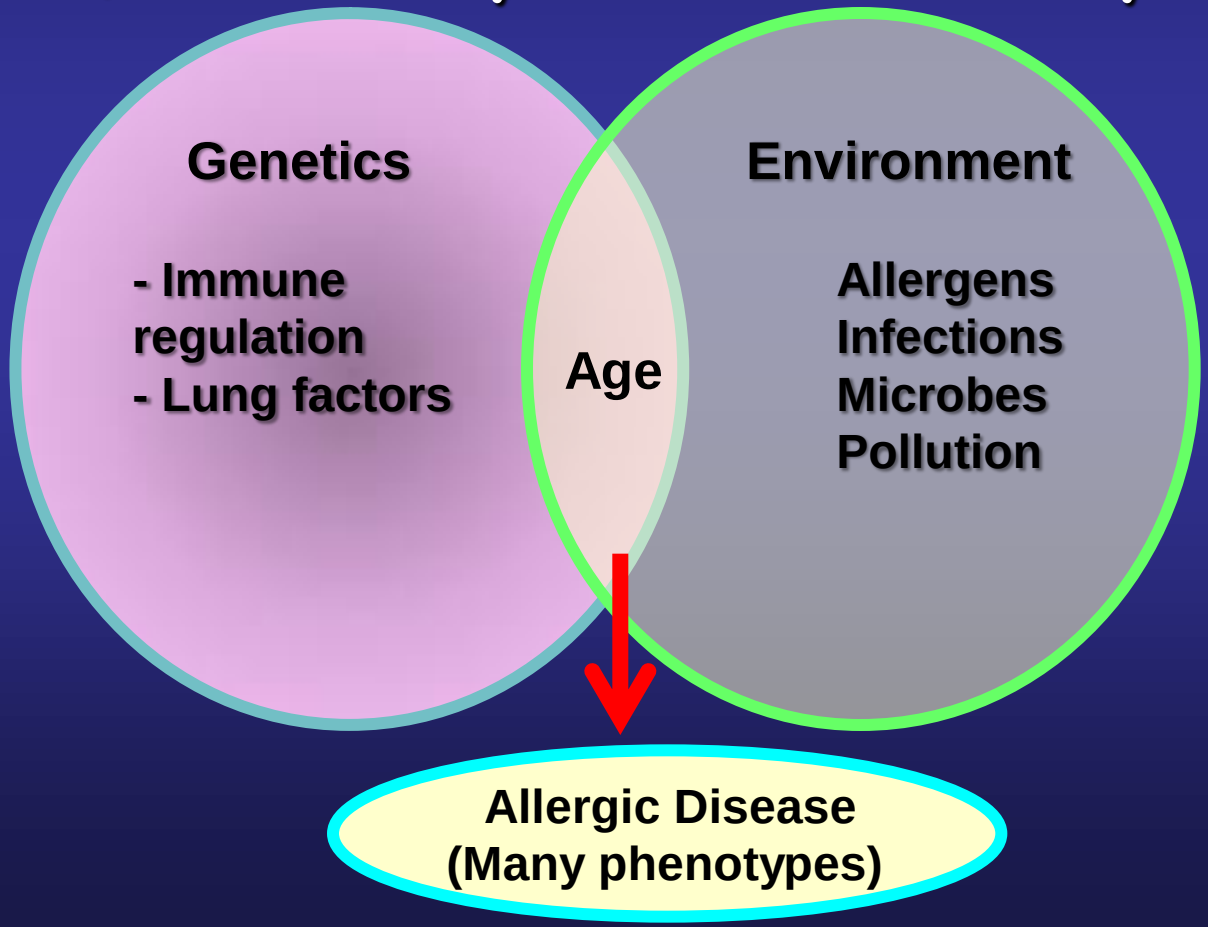
NOT EVERYTHING IS GENETICS!!

1. All features result of the interaction between environment and host genetics
2. The relationship patient-physician is relevantLa
3. More than diseases, there are patients, each of them with their own way of responding vs. The same unchaining agent

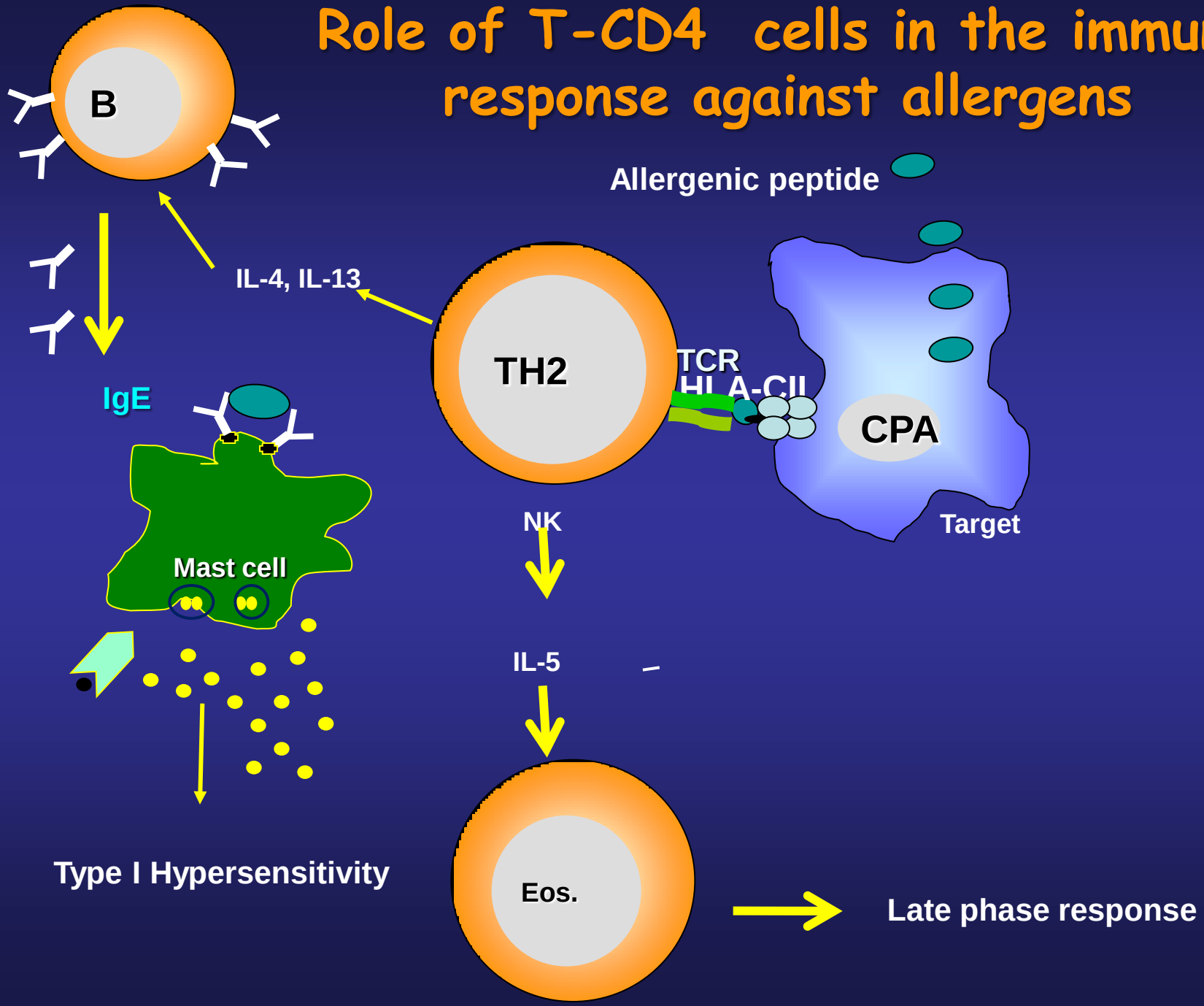
Genetic control of the immune response

The Development of Allergic Diseases

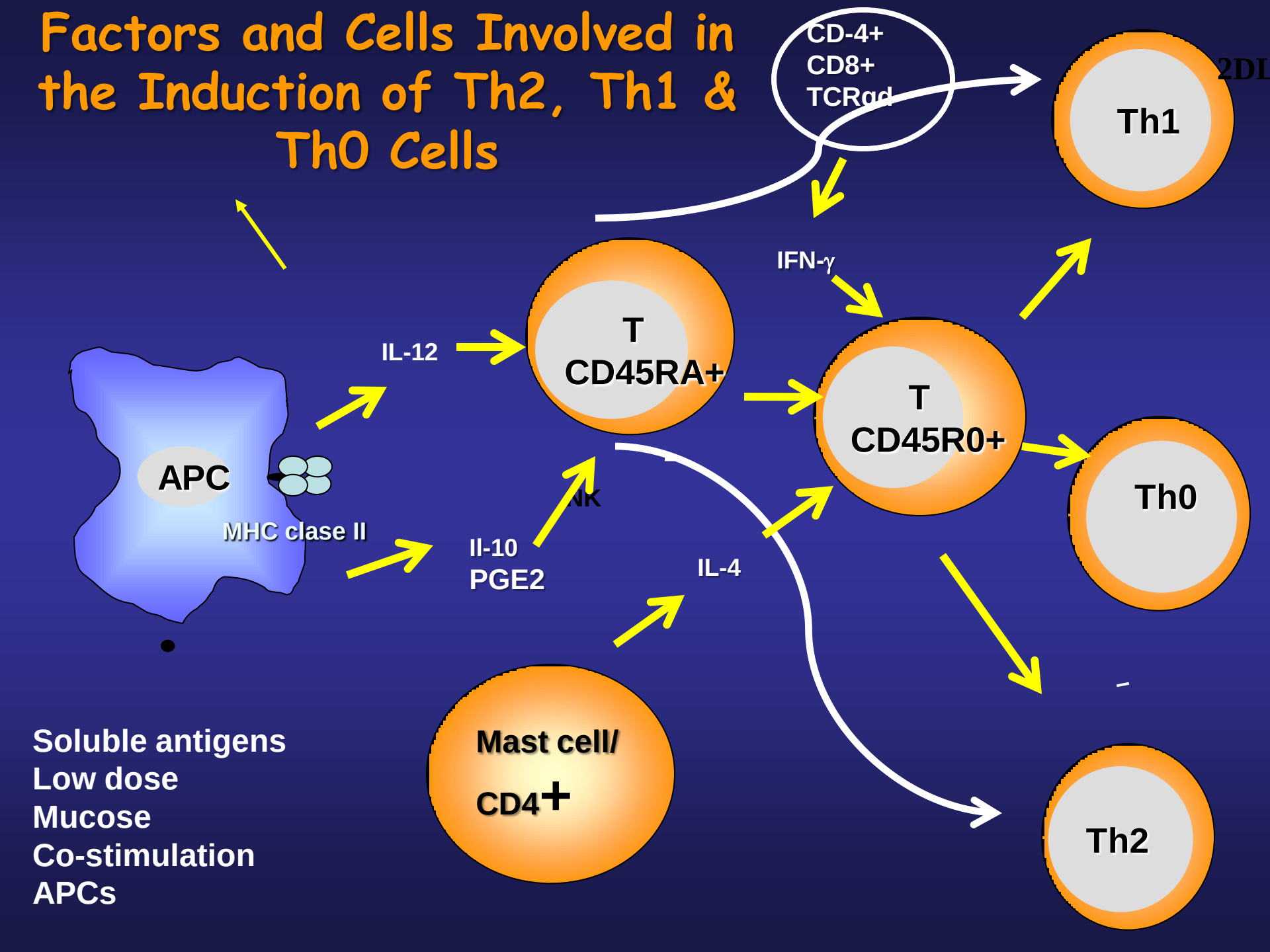
The development of these diseases represent an interaction between genetic and environmental processes, which may be influenced by age



Role of T-CD4 cells in the immune response against allergens



Factors and Cells Involved in the Induction of Th2, Th1 & Th0 Cells



Approaches for Gene Discovery

Candidate gene association studies (1970s-present)

Advantages: Hypothesis-driven; easy to interpret; detects genes with modest effects

Disadvantages: Limited to what we know; Cannot discover novel genes or pathways; Requires LD between markers and causal agents

Genome-wide linkage studies (1980-1990s)

Advantages:Genome-wide; Can discover novel genes & pathways; Requires relatively few genetic markers; Does not rely on LD; Can detect genes harboring rare risk variants

Disadvantages: Requires families; Poor resolution; Low power to detect genes with modest effects

Genome-wide association studies (2007-present)

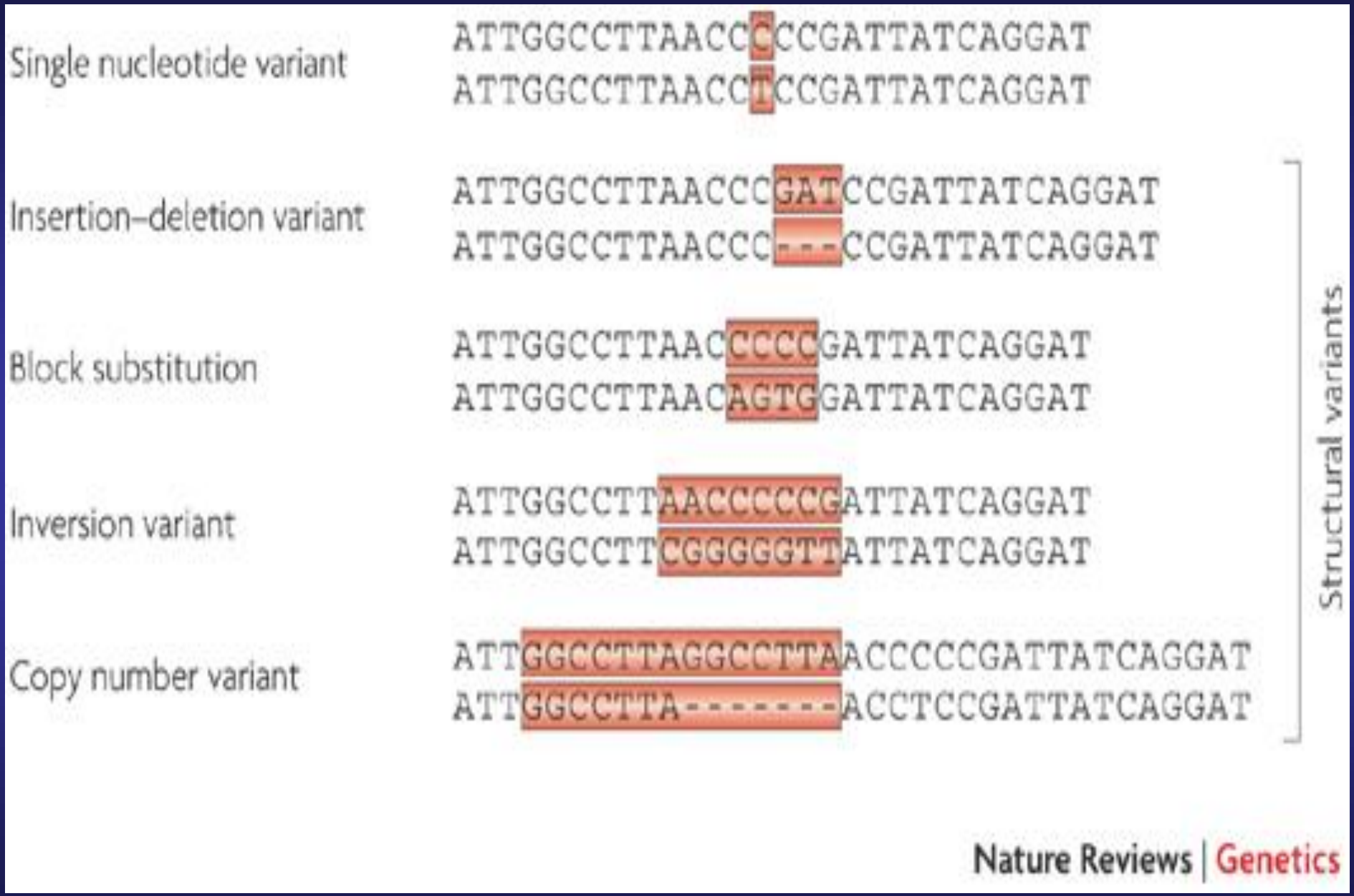
Advantages:Genome-wide; can discover novel genes & pathways; Excellent resolution; Can detect loci with modest effects

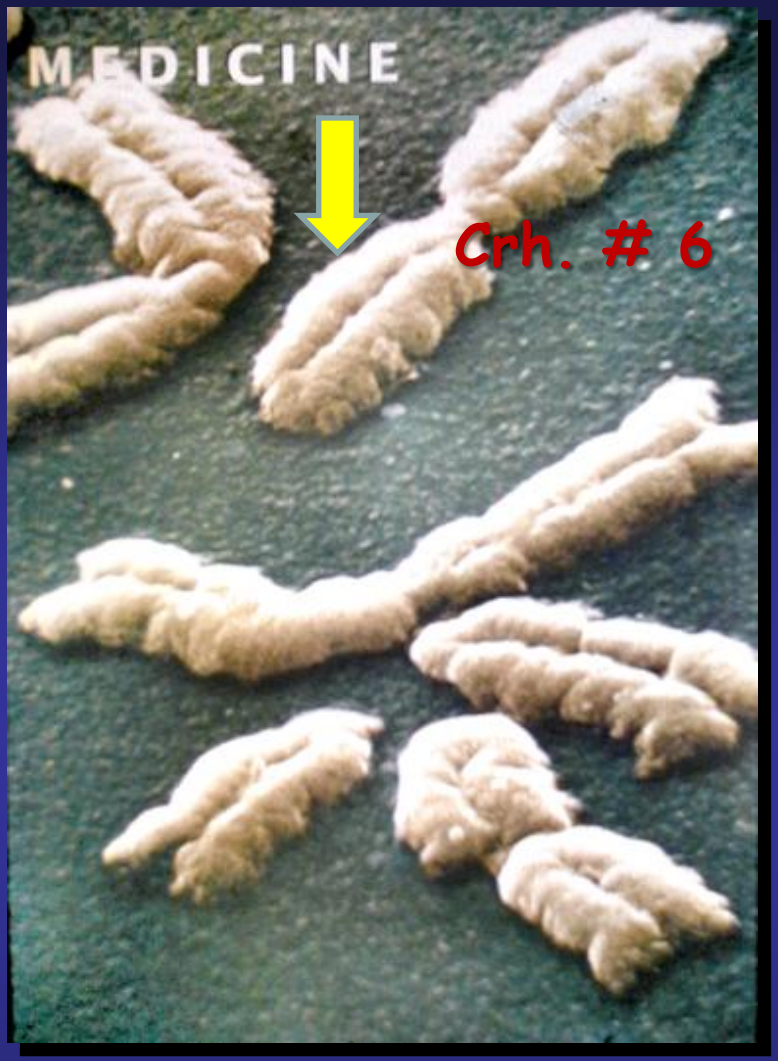
Disadvantages: Requires dense marker typing & large sample sizes; Requires LD; Limited to common variants

Re-sequencing in genes, exomes, or whole genomes (ongoing)

Advantages:Reveals all variations

Disadvantags: Costly; Large sample sizes; Computationally & analitically challenging; Difficult to interpret


Single nucleotide variant
ATTGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTAACCTCCGATTATCAGGAT
Insertion–deletion variant
ATTGGCCTTAACCCGATCCGATTATCAGGAT
ATTGGCCTTAACCC---CCGATTATCAGGAT
Block substitution
ATTGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTAACAGTGGATTATCAGGAT
Inversion variant
ATTGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTCGGGGGTTATTATCAGGAT
Copy number variant
ATTGGCCTTAGGCCTTAACCCCCGATTATCAGGAT
ATTGGCCTTA-------ACCTCCGATTATCAGGAT
Structural variants
Nature Reviews | Genetics

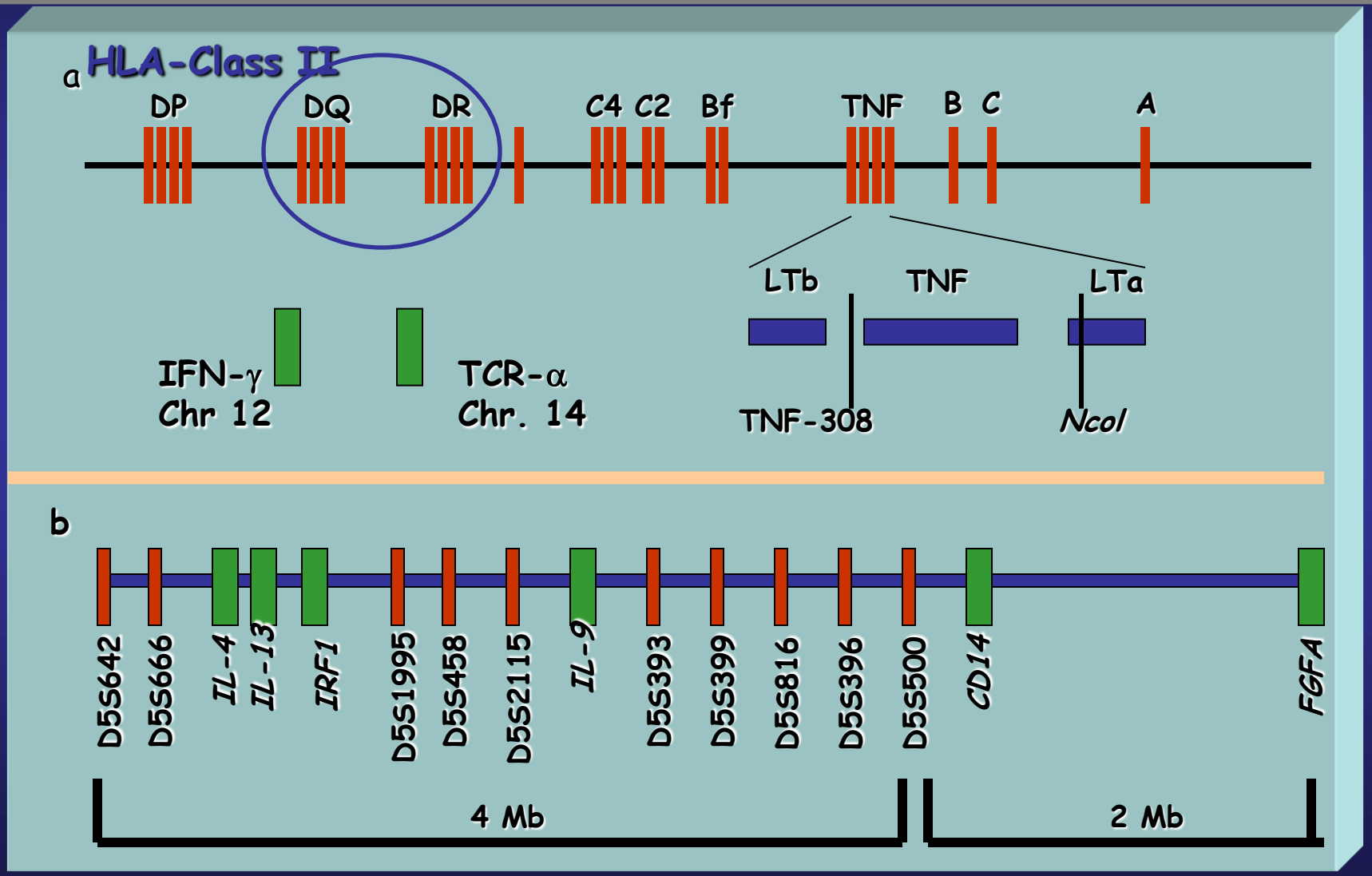


The Human MHC : HLA
July, 2011

Total alleles = 6403
Proteins= 4174

Prof. Jean Dausset †,
June 6, 2009

SOME GENES INVOLVED IN THE EXPRESSION OF ALLERGIC DISEASES



Willian Cookson, Nature 402: 88, 1999

Combined Results of Meta-Analyses of Asthma GWAS in European, African Caribbean & Latino Samples (EVE) & European Samples (Gabriel)

GENE/REGION	*RACE/ETHNIC GROUPS*
17q21(ORMDL3/GSDML	All
IL1RL1/IL18R1 (chr. 2)	All
TSLP (chr. 5)	All
IL33 (chr 9)	All
SMAD3 (chr. 15)	Euro, Euro-Am,
RORA (chr. 15)	Euro, Euro-Am
HLA-DQ (chr. 6)	All
PYHINI (chr 1)	Afr-Am/Afr.Caribb
IL2RB (chr. 22)	Euro
SLC22A5 (chr 5)	Euro
IL13 (chr 5)	Euro

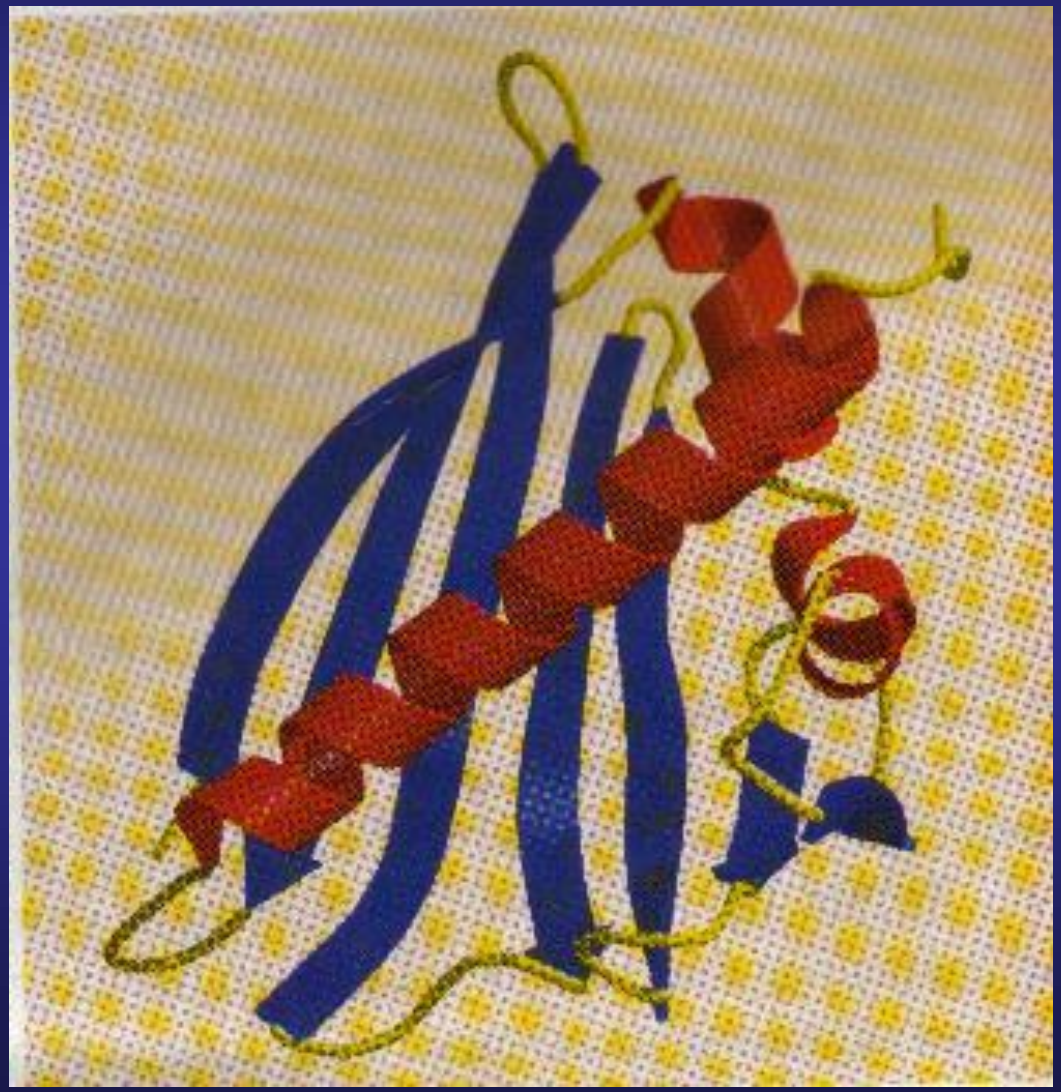
Ober & yao, 2011

EPITOPES OF DIFFERENT ALLERGENS

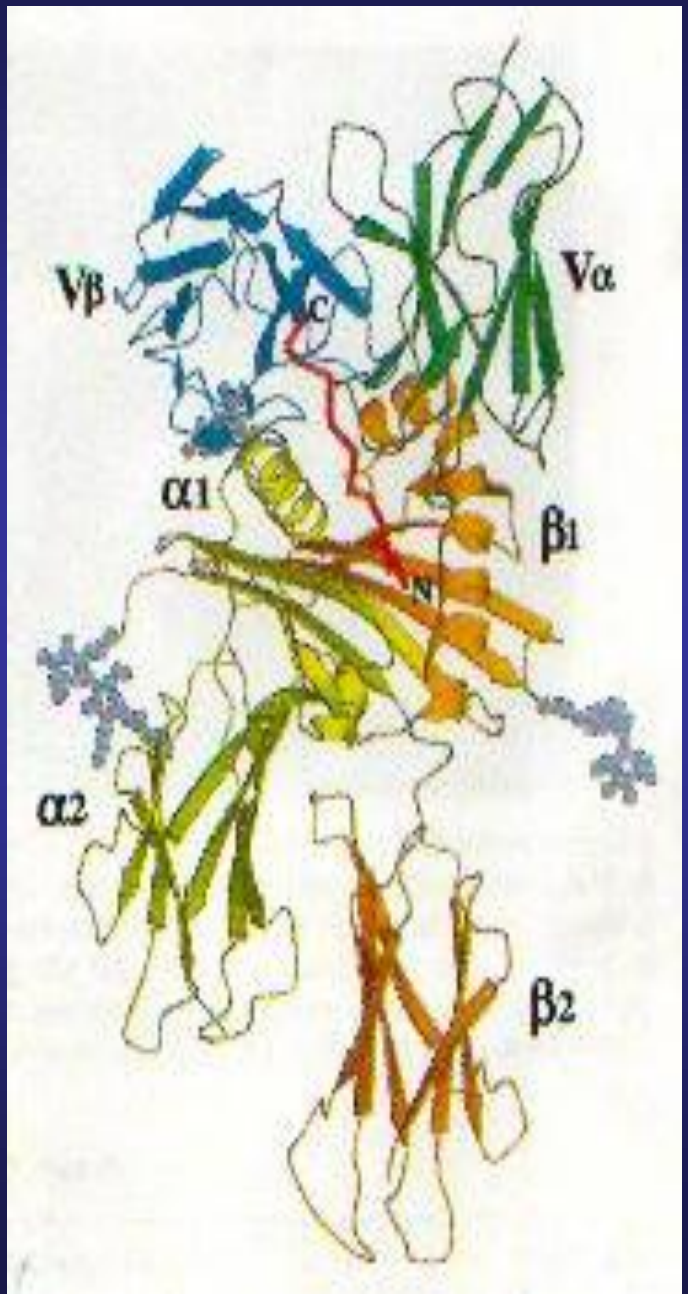
Antigens		Allergen	Size	T-cell Epitope
Dust				
Dermatophagoides pteronyssinus		Der p 1	24 kDa,222 aa	45-6794-104,117-143
		Der p 1		110-119, 110-131
		Der p 1		1-4,1-56,15-94,57-130
	(5 different)	Der p 2	15 kDa,129 aa	1-15,11-24,20-33,29-42
Felis domesticus		Fel d 1	17 kDa,	39-52,53-66
			70+92 aa	9-21,22-35,57-70
		Fel d 1	(dímero)	
Seasonal				
Betula verucosa	(4 different)	Bet vI	17 kDa, 159 aa	
Lolium perene	(4 different)	Lol p 1	34 kDa,240 aa	
Phleum partense		Phl p 1	34 kDa,240 aa	
Poa pratensis		rKBG60	28 kDa,268 aa	
Venoms (insects)				
Apis mellifera		Api m 1(PLA_2)	19 kDa,134 aa	
Bee		Api m 1(PLA_2)		
Food				
Chicken		Ovalbumin	43 kDa,385 aa	

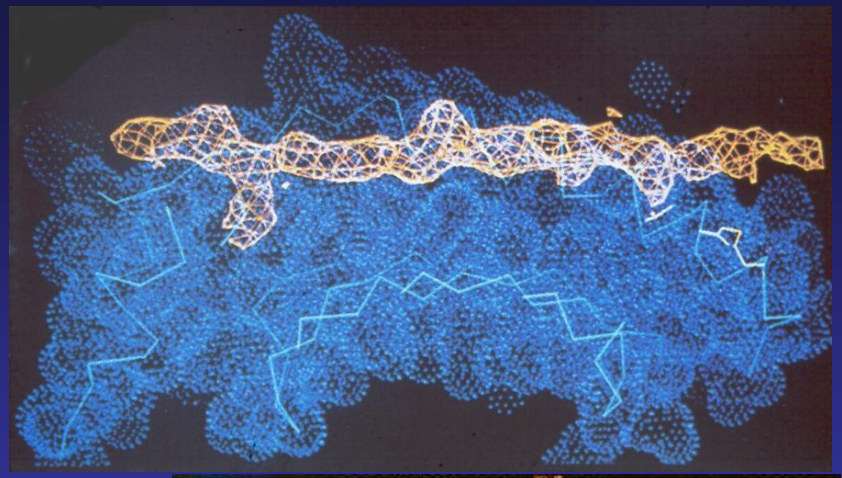
van Nerven y col, Trends Immunol; 2007

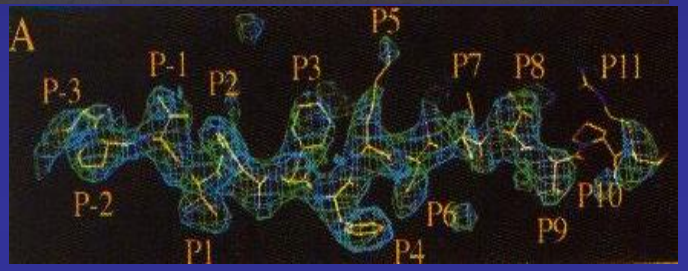
CHRISTALOGRAFHIC STRUCTURE OF BETUL BIRCH POLLEN

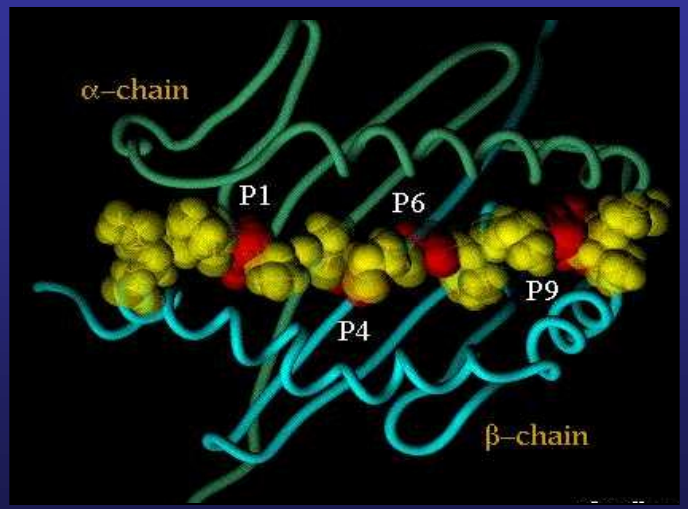


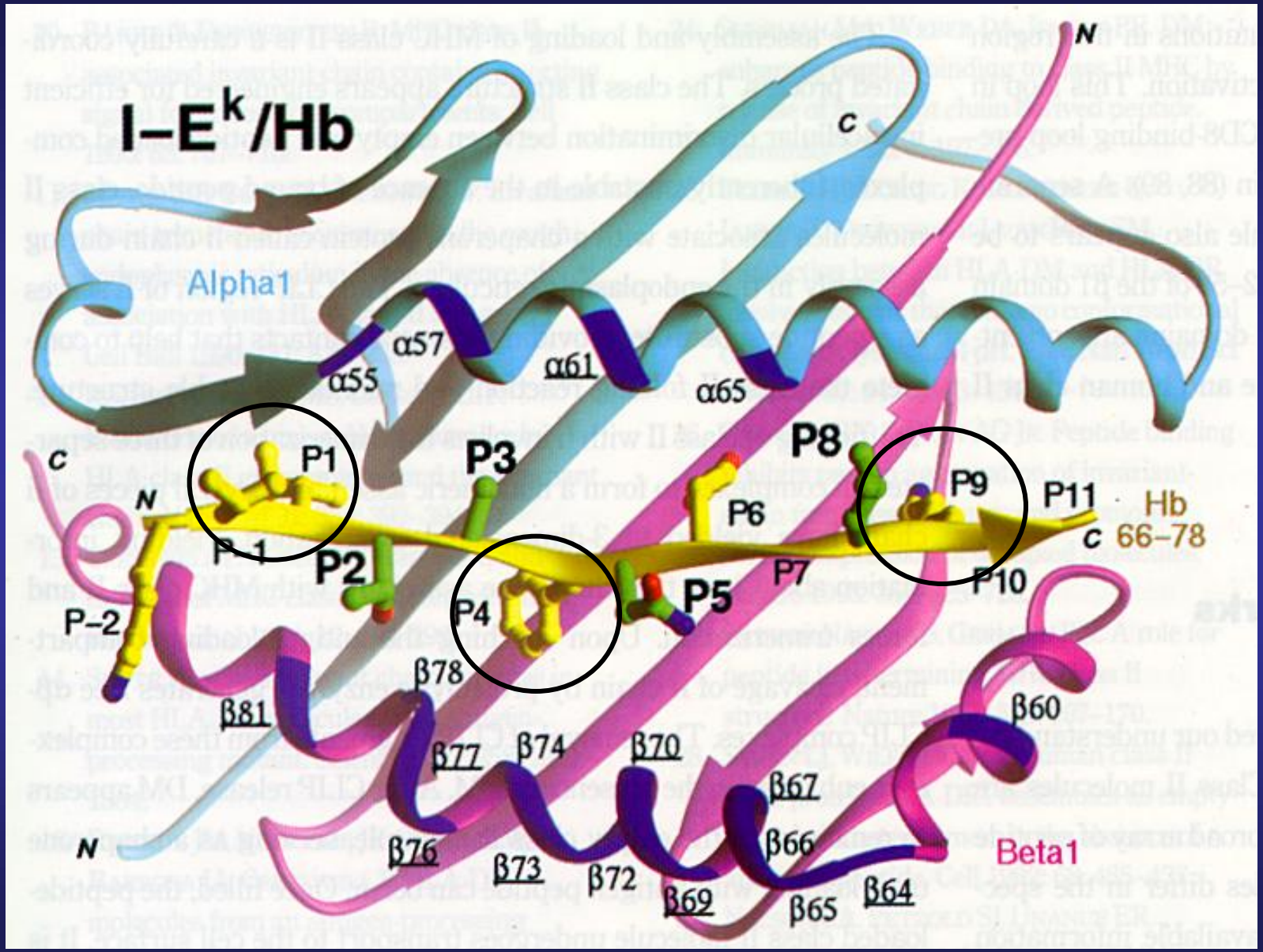
Class II Molecule










I–E^k/Hb
Alpha1
Beta1
Hb 66–78
N
C
α57
α55
α61
α65
P1
P3
P8
P9
P11
P6
P2
P4
P5
P7
P10
P-1
P-2
β78
β81
β77
β74
β70
β60
β67
β66
β76
β73
β72
β69
β65
β64

HLA Associated Genetic Control of the IgE Immune Response to Allergens

Allergen	Mol. Mass.	HLA	IgE+ (%)	OR
Amb a 5	5	DR2	100	65
Lol p 2	11	DR3	47	5.3
Lol p 3	11	DR3	43	3.5
Lol p 3	11	DR3	57	18
Amb a 6	11.5	DR5	85	35
Amb a 6	11.5	DR5	40	23
Alt a 1	14	DR4	26	1.9
Der p 2	15	DR3	19	>1
Bet v 1	17	DR52	62	2.5
Bet v 1	17	DRB3*0101	51	2.5
Fel d 1	17	DR1	16	2.0
Der p 1	24	DR3	16	<1
Lol p 1	34	DR3	36	7.3
Lol p 1	34	DR3	33	3.1

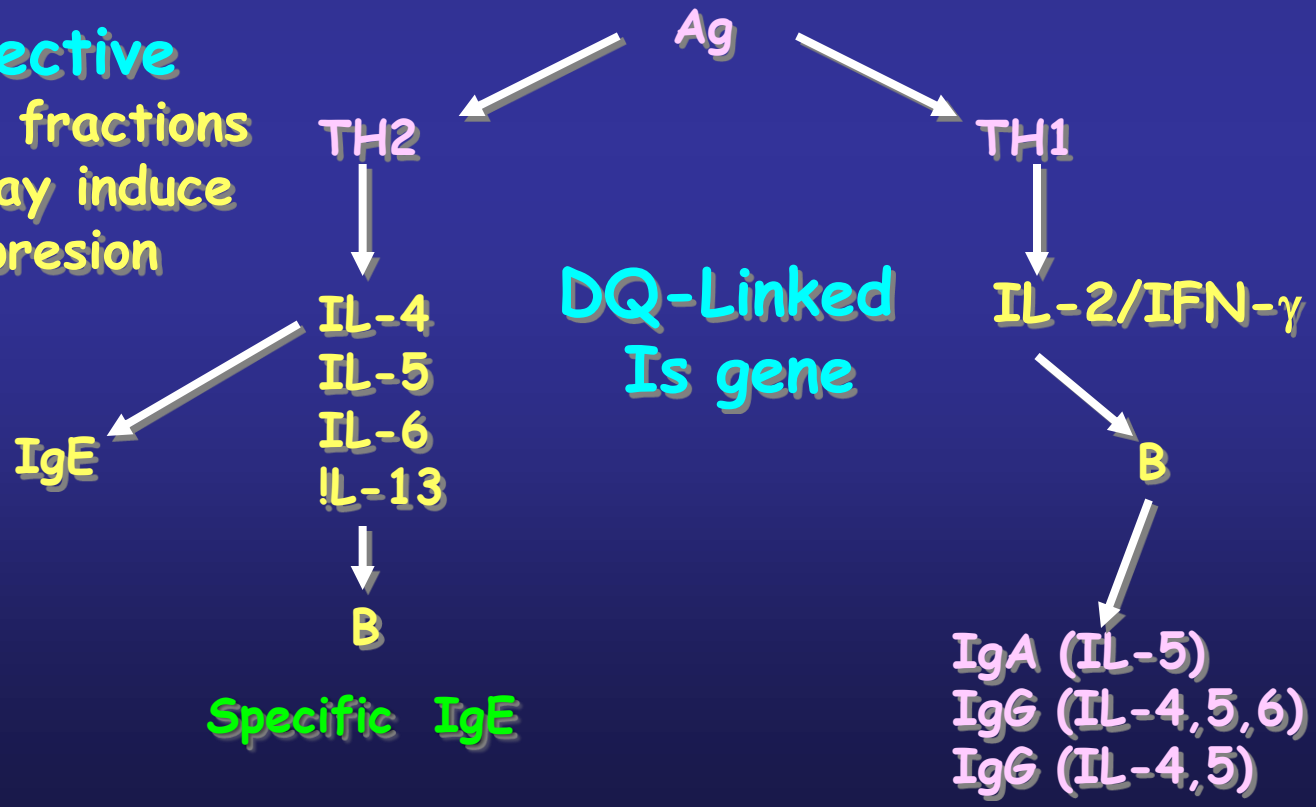
HLA Genes Associated With The Immune Response To Cedar Pollen In Japanese

- Susceptibility is linked to a recessive gen that has a high penetrance *(0.54)*

- Resistence is linked to a dominant HLA-DQ gene with a higher penetrance *(0.778)*

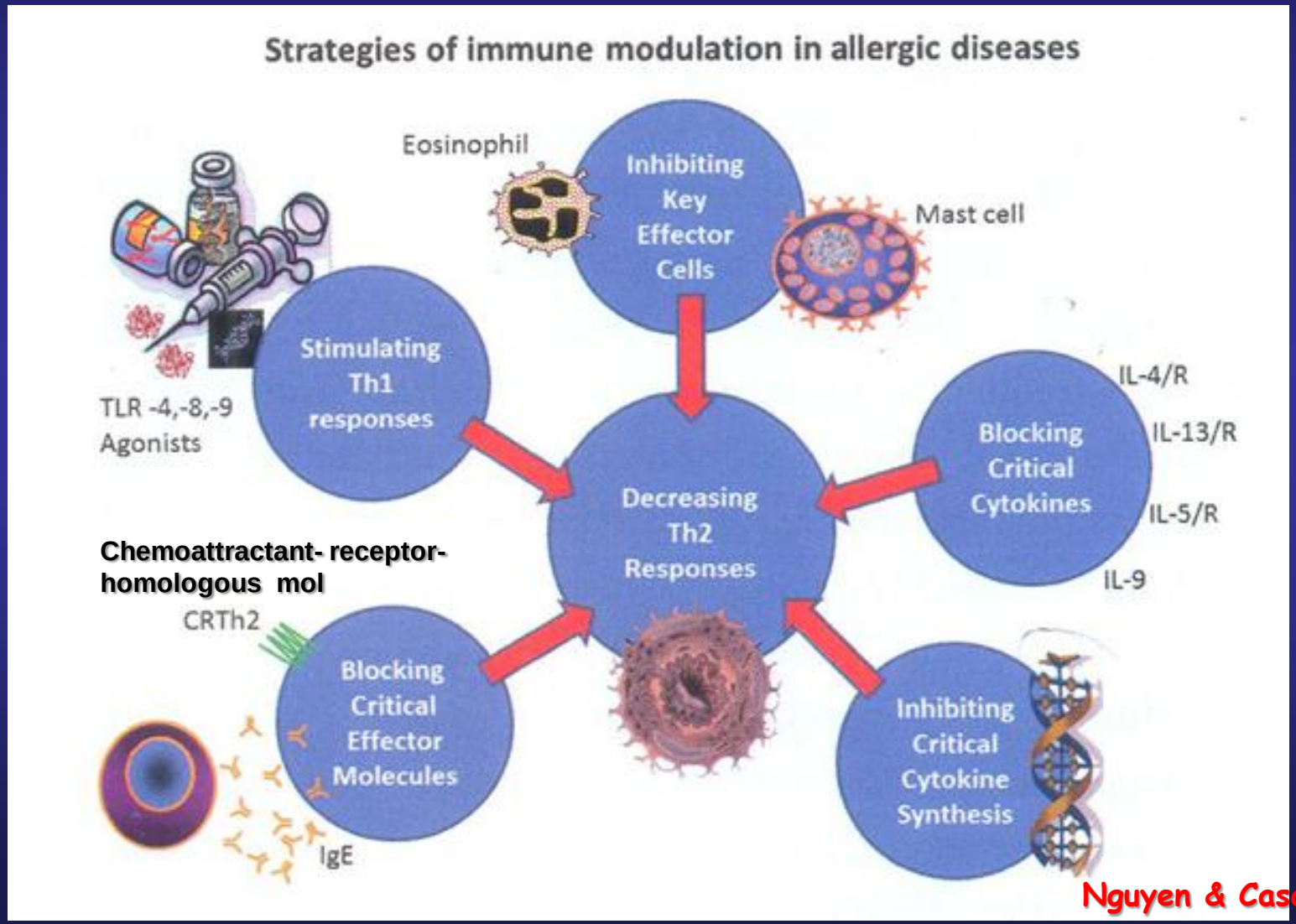
Therapy Perspective

Select the antigenic fractions of allergens that may induce IgE specific suppresion



Strategies of Immune Modulation in Allergy

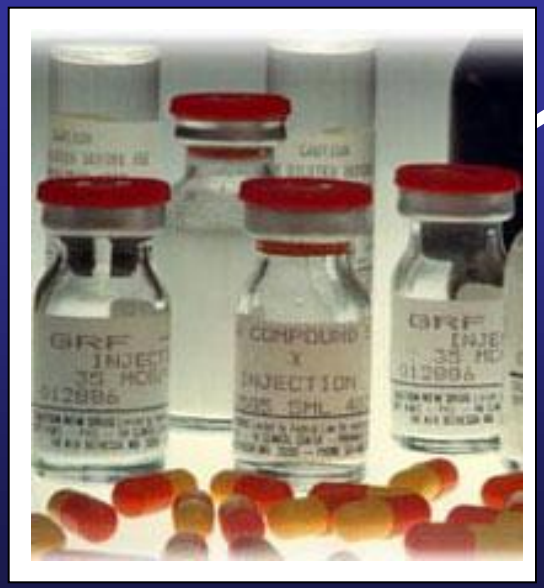
The common goal is to decrease Th2 responses that lead to allergic disease!



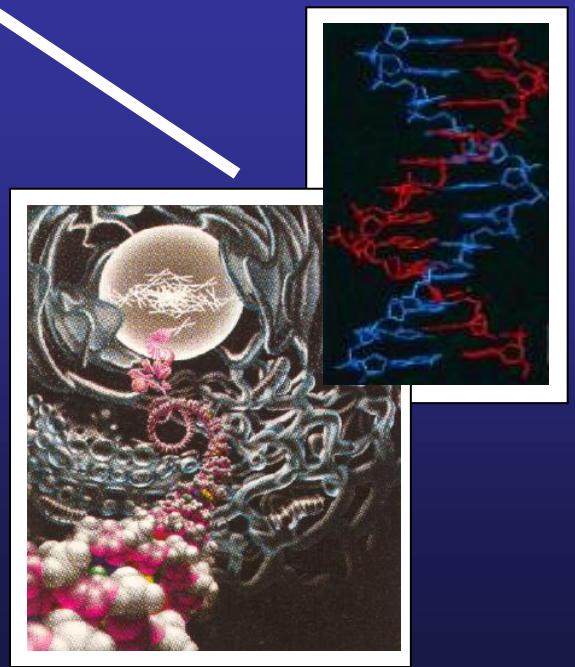
Nguyen & Casale, 2011

PHARMACOGENOMICS

PHARMACOLOGY



GENOMICS



¿DO ALL INDIVIDUALS RESPOND THE SAME WAY TO DRUG TREATMENTS ?

Rx + ☹ = ☺

Rx + ☹ = ☹

Rx + ☹ = ☠

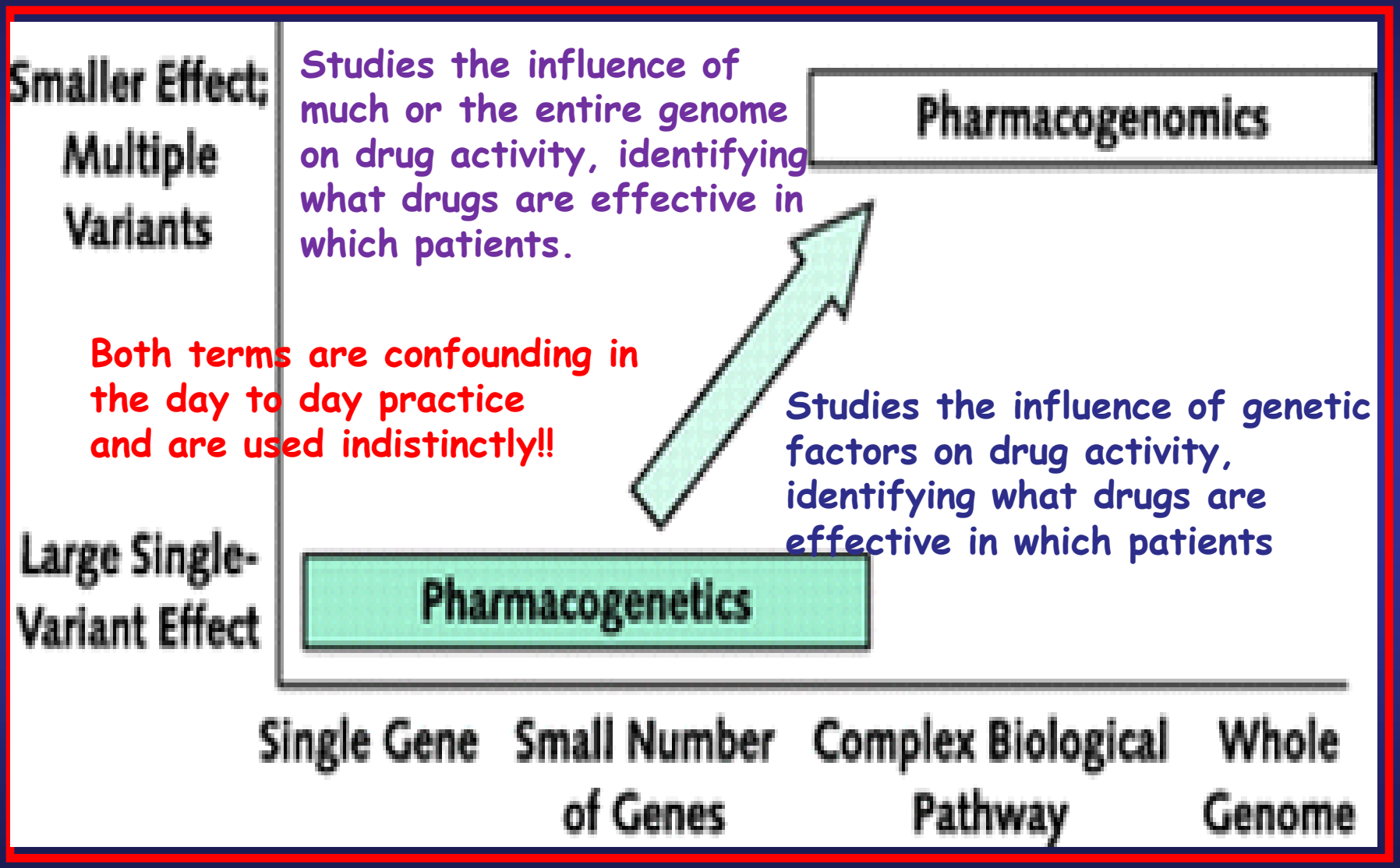
????

PHARMACOGENOMICS

Study and analysis of the individual genetic variability, related to:

- drug response
- drug design and development
- therapeutic design to achieve successful results in clinical assays
- more effective and less dangerous therapies for the patient

Pharmacogenetics Vs. Pharmacogenomics



Roden, D. M. et. al. Ann Intern Med 2006;145:749

Interaction of our Genes with the Environment

INDIVIDUAL RISK:

DRUG INEFFICACY/TOXICITY

GENES + ENVIRONMENTAL FACTORS INTERACTIONS

Gender, ethnicity, diet, nutrition, función organic function, drug interaction, tobacco, cofee & alcohol intake, concomitant diseases, disease severity

- GENETIC FACTORS

The most important are…….

MHC, Receptor, Transport & other genes & drug metabolizing enzymes (DMEs)

(15 a 30%-95%)

INTER-INDIVIDUAL VARIATION TO DRUG RESPONSES

* Non efficacy of Treatment: 25-80%
  Efficacy 51.5%

Spear et al;2001.Trends Mol Med 7:201

- Adverse Drug Reactions (ADR) USA (1994)

6.7% hospitalization (2,216,000 patients)
0.32% Fatal reactions (106,000 patients)
4-6 Deaths

Lazarou et al. 1998; JAMA 279:1200

Examples of Associations between Drug Response and Genetic Variants

Table 2. **Examples of Associations between Drug Response and Genetic Variants***

Drug	Variable Clinical Effect	Genes with Associated Variants	Possible Mechanism
Azathioprine and mercaptopurine	Bone marrow aplasia Reduced therapeutic effect at standard doses	*TPMT*	Hypofunctional alleles Wild-type alleles
Some antidepressants and β-blockers	Increased side effect risk Decreased efficacy	*CYP2D6*	Hypofunctional alleles Gene duplication
Omeprazole	*Helicobacter pylori* cure rate	*CYP2C19*	Hypofunctional alleles
Irinotecan	Neutropenia	*UGT1A1*	Decreased expression due to regulatory polymorphism
HIV protease inhibitors	Central nervous system levels	*MDR1*	Altered P-glycoprotein function
β-blockers	Blood pressure lowering and heart rate slowing	*ADRB1*	Altered receptor function or number
Inhaled β_2-agonists	Bronchodilation	*ADRB2*	Altered receptor function or number
Diuretics	Blood pressure lowering	*ADD1*	Altered cytoskeletal function by adducin variants
Warfarin	Anticoagulation	*VKORC1*	Variant haplotypes in regulatory regions leading to variable expression
		CYP2C9	Coding region variants causing reduced S-warfarin clearance
Abacavir	Immunologic reactions	HLA variants	Altered immunologic responses
QT-prolonging antiarrhythmics	Drug-induced arrhythmia	Ion-channel genes	Exposure of subclinical reduction in repolarizing currents by drugs
General anesthetics	Malignant hyperthermia	*RYR1*	Anesthetic-induced increased release of sarcoplasmic reticulum calcium by mutant channels
Inhaled steroids	Bronchodilation	*CRHR1*	Unknown
HMG-CoA reductase inhibitors (statins)	Low-density lipoprotein cholesterol lowering	*HMGCR*	Altered HMG-CoA reductase activity

* *ADD1* = the gene encoding α-adducin; *ADRB1* = the gene encoding the β_1-adrenergic receptor; *ADRB2* = the gene encoding the β_2-adrenergic receptor; *CRHR1* = the gene encoding corticotrophin-releasing hormone receptor-1; *CYP2C19* = the gene encoding the 2C19 cytochrome P450 isoform; *CYP2C9* = the gene encoding the 2C9 cytochrome P450 isoform; *CYP2D6* = the gene encoding the 2D6 cytochrome P450 isoform; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; *HMGCR* = the gene encoding HMG-CoA reductase; *MDR1* = the gene encoding P-glycoprotein; *RYR1* = the gene encoding the skeletal muscle calcium-release channel; *TPMT* = the gene encoding thiopurine methyltransferase; *UGT1A1* = the gene encoding uridine diphosphate glycosyltransferase 1 family, polypeptide A1; *VKORC1* = the gene encoding vitamin K epoxide reductase complex, subunit 1.

Roden, D. M. et. al. Ann Intern Med 2006;145:749

Annals of Internal Medicine

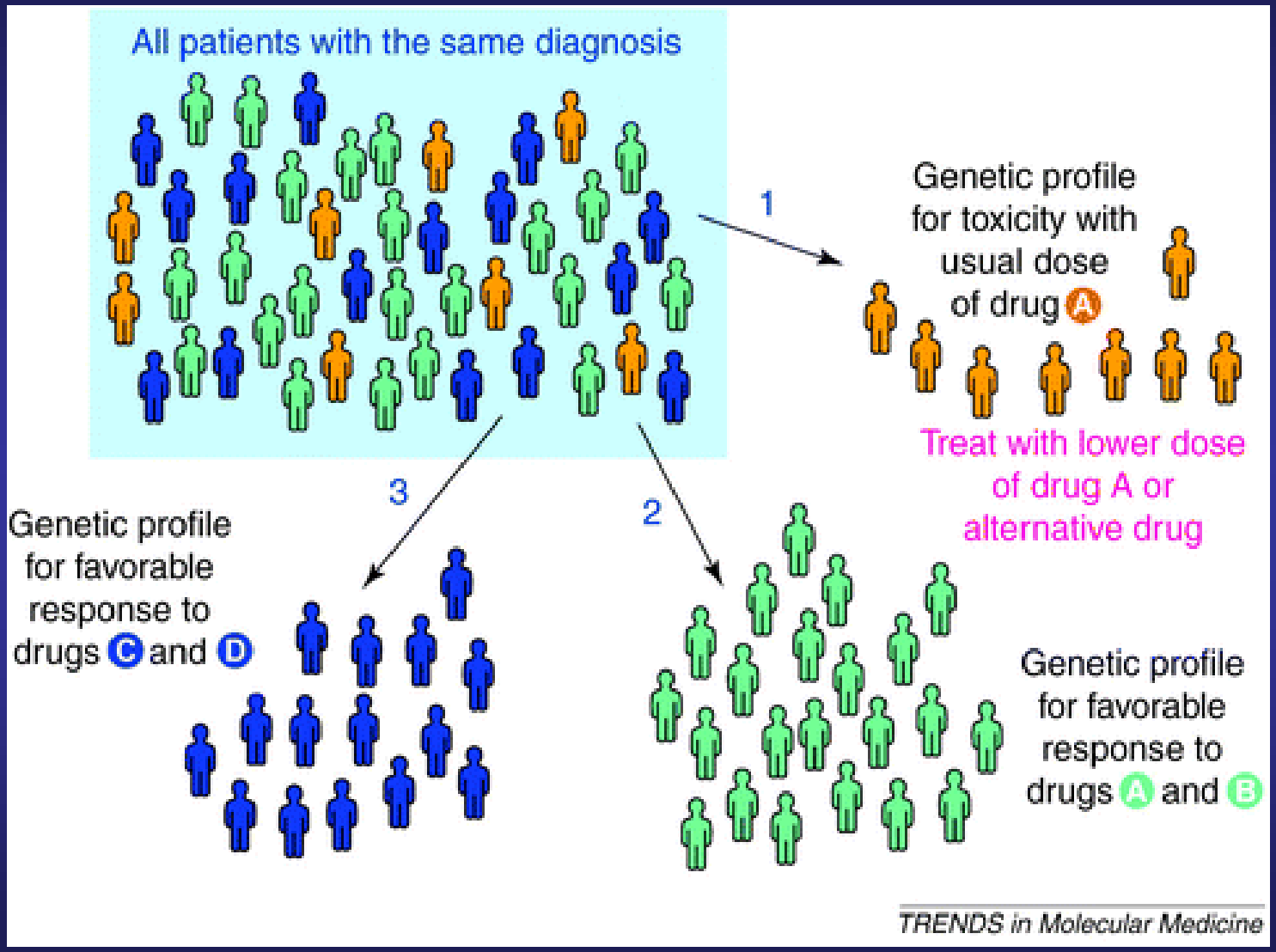
Table 1. US FDA or EMEA drug pharmacogenomic labeling: constitutive genetic variants.

Drug	Gene target	Information	Outcome
Thioridazine	*CYP2D6*	ADRs: W&P Test not required	QT prolongation, torsades de pointes
Codeine	*CYP2D6*	ADRs: W&P Test not required	Apnea among children from breastfeeding mothers
Atomoxetine	*CYP2D6*	ADRs: W&P Test not required	Dose reduction for PMs
Tamoxifene	*CYP2D6–CYP2C19*	Lower response rate: W&P Test not required	Loss of efficiency among PMs and with CYP2D6 inhibitors
Voriconazole	*CYP2C19*	ADRs: W&P Test not required	Hepatotoxicity
Warfarin	*CYP2C9*	ADRs: W&P Individualized dosing: W&P Test not required	Risk of bleeding
Warfarin	*VKORC1*	ADRs: W&P Individualized dosing: W&P Test not required	Risk of bleeding
Irinotecan	*UGT1A1*	ADRs: W&P Individualized dosing Test not required	Diarrhea, neutropenia
Azathioprine and 6-mercaptopurine	*TPMT*	ADRs: W&P Individualized dosing Test not required	Neutropenia
Capecitabine	*DPD*	ADRs: contraindication Test not required	Orodigestive – neutropenia
Maraviroc	*CCR5*	Nonresponse Test required	For CCR5-negative patients
Rasburicase	*G6PD*	ADRs: contraindication Test not required	Hemolysis in G6PD-deficient patients
Carbamazepine	*HLA-B*1502*	ADRs: W&P Test not required	Severe immunoallergic cutaneous
Abacavir	*HLA-B*5701*	ADRs: W&P Test not required	Hypersensitivity reactions

W&P section of the summarized product characteristics [104,105].
ADR: Adverse drug reaction; EMEA: European Medicines Agency; PM: Poor metabolizer; W&P: Warnings and precautions.

Becquemont L.Pharmacogenomics of adeverse drug reactions: practical applications and perspectives

PHARMACOGENOMICS



Johnson JA, Evans WE. (2002) *Trends in Molecular Medicine 8*:300

HLA typing: clinical significance Pharmacogenomics

Severe allergic or hypersensitivity reaction to drugs are common and preclude necessary treatment.

Association between allergy or hypersensitivity to a medication and HLA type.

HLA typing allows risk stratification of the patients.

Drugs associated to SJS and TEN

Antiepileptic agents: Carbamazepine
Phenytoin; Phenobarbital; Lamotrigine
Allopurinol; Nevirapine

Anti-inflammatories of oxicam family
Sulfonamides

SJS: Stevens Johnson Syndrome
TEN: toxic epidermal necrolysis

HLA and Drug adverse reactions

HLA-B*5701	hypersensitivity to Abacavir
HLA-B*1502	carbamazepine induced SJS or TEN
HLA-B*5801	allopurinol induced SJS or TEN
HLA-DRB1*01	nevirapine
HLA-DRB1*07	ximelagatran
HLA-A29,B12,DR7	sulfonamides
HLA-A2,B12	oxicam
HLA-DQA1*0102	Lumiracoxib

SJS: Stevens Johnson Syndrome
TEN: toxic epidermal necrolysis

HIV infection treatment

HAART highly active antiretorviral therapy

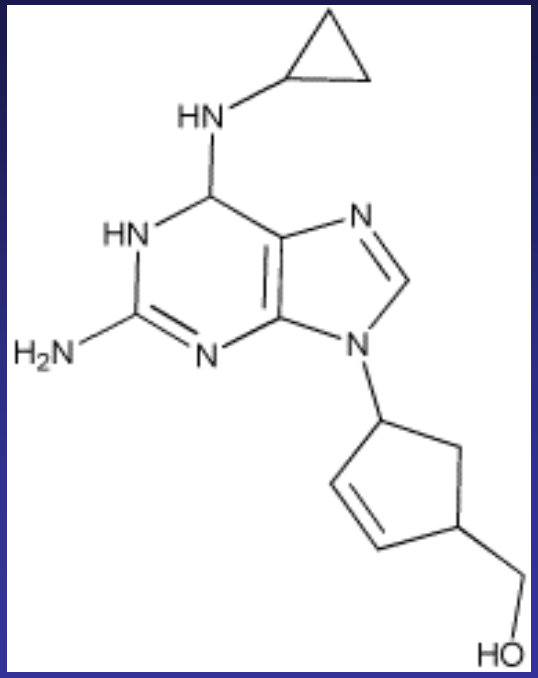
- NRTI Nucleoside analogue Reverse Transcriptase Inhibitor

+

- NNRTI Non Nucleoside analogue RTI

or

- HIV Protease Inhibitors



Ziagen, Abacavir Sulfate: (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)

Ziagen, an oral medication taken twice daily, is a nucleoside analogue reverse transcriptase inhibitor (NRTI) and is taken in combination with other anti-HIV medications.

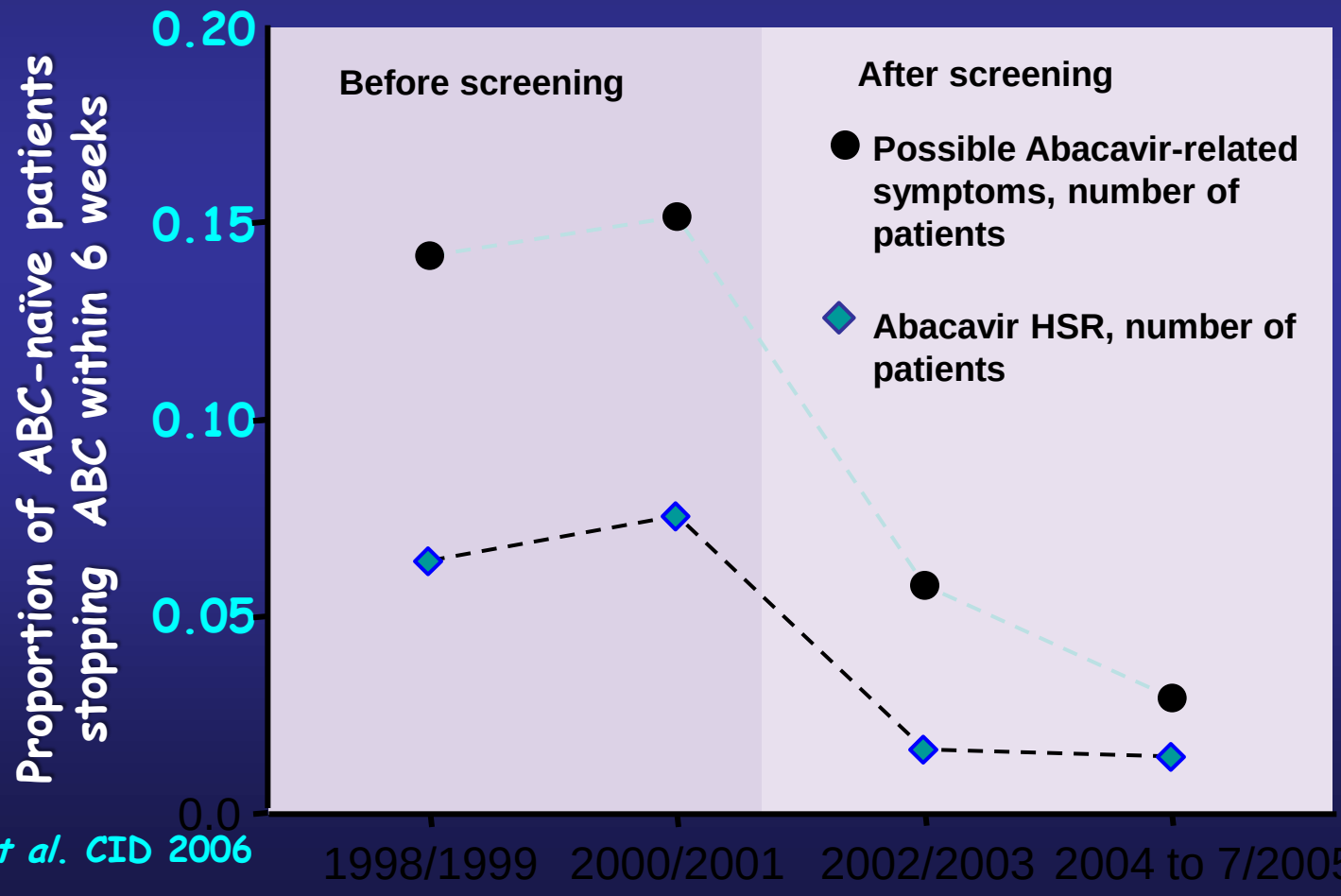
The combination helps to lower the amount of HIV found in the blood.

Allergic reaction to Abacavir

The allergy, frequently referred to as an abacavir hypersensitivity reaction (AHR), is a serious side effect that occurs in up to 8 percent of those taking the drug.

Symptoms, including fever, rash and shortness of breath, often worsen with continued use of the drug. These symptoms can be fatal, especially if the drug is stopped and then restarted.

Proportion of patients stopping ABC therapy in the first 6 weeks Before/after introduction of prospective HLA-B*5701 typing



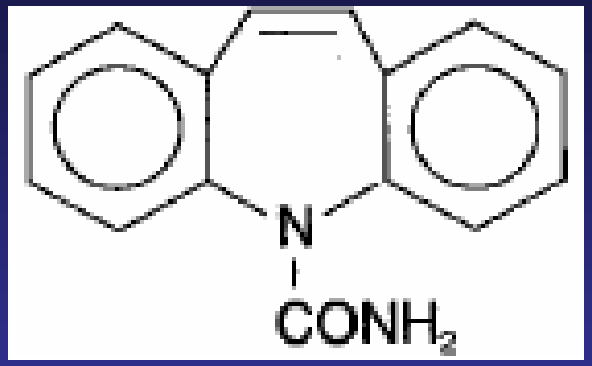
Rauch *et al.* CID 2006

DHHS Treatment guidelines for HIV-1 infection in Adults and Adolescents (12/01/2007 update):

HLA-B*5701 Testing - The Panel recommends HLA-B*5701 testing prior to initiating abacavir therapy to reduce the risk of hypersensitivity reaction (AI).

HLA-B*5701 + patients should not be prescribed abacavir (AI), and the positive status should be recorded as an abacavir allergy in the patient's medical record (AII).

When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of abacavir-associated hypersensitivity reaction (CIII).



Tegretol, carbamazepine
USP: 5H-dibenz[b,f]azepine-5-carboxamide

Carbamazepine has both antiepileptic and psychotropic properties.

Indications: Epilepsy

Pain syndromes: Trigeminal neuralgia and glossopharyngeal neuralgia.

Manic depressive illness unresponsive to lithium.

FDA alert 12/12/2007

recommends HLA-B*1502 typing before prescribing Carbamazepine to patients of Asian origin

SJS/TEN and HLA-B*1502 Allele

Retrospective case-control studies have found that in Chinese patients there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of HLA-B*1502.

The occurrence of higher rates of these reactions in countries with high freq. of B*1502 suggests that the risk may be increased in allele+ individuals of any ethnicity.

Chung et al. Nature 428, 486, 2004

WARNING

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK

Variation in the prevalence of HLA-B*1502

ASIA.-

>15% of the population is pos. in Hong Kong, Thailand, Malaysia, and parts of the Philippines

About 10% in Taiwan & 4% in North China.

South Asians, including Indians, have intermediate prevalence of HLA-B*1502, 2-4%

B*1502 is in <1% in Japan & Korea

B*1502 is absent/low in non Asians (e.g., Caucasians, African-Americans, Hispanics, Mexicans and Amerindians).

Prior to initiating Tegretol therapy, testing for HLA-B*1502 should be performed in patients of populations in which HLA-B*1502 may be present.

In deciding which patients to screen, the given prevalence of B*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry.

Tegretol should NOT be used in B*1502 patients, unless the benefits clearly outweigh the risks.
B*1502 - patients, are thought to have a low risk of SJS/TEN

B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management.

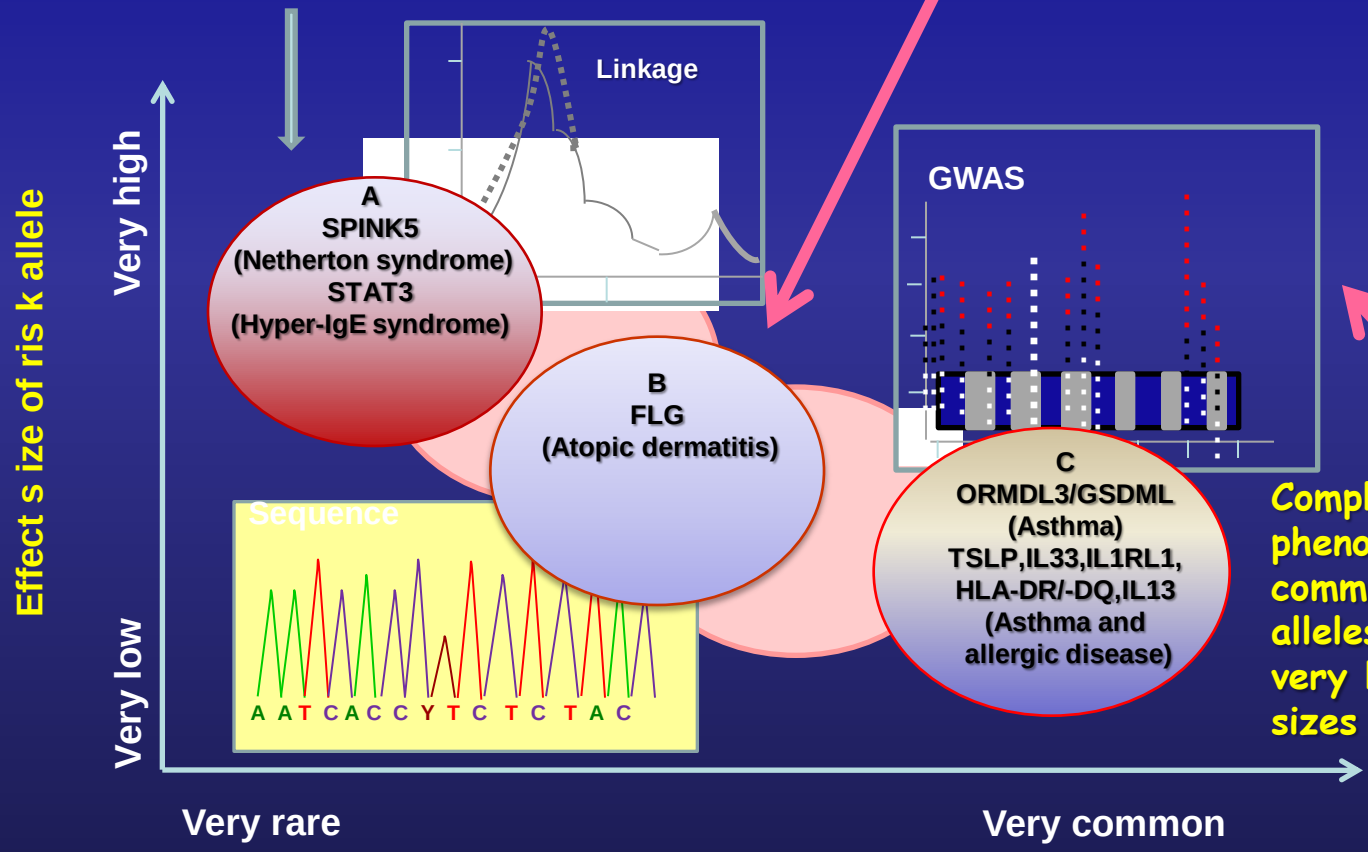
Many *1502+ Asian patients treated with Tegretol will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502- patients of any ethnicity.

www.fda.gov/Cder/drug/infopage/carbamazepine/default.htm

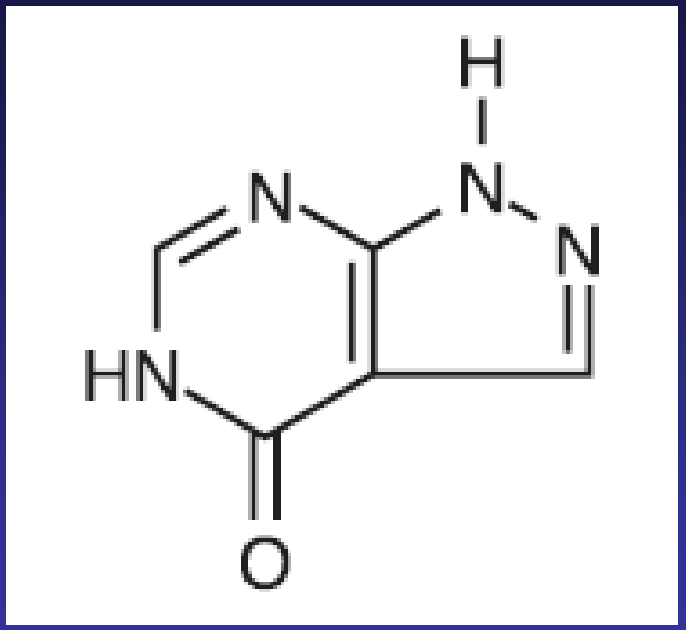
Genetic Architecture of Asthma and Allergic Diseases

A. Monogenic.- Caused by highly penetrant <1% rare mutations

B. Complex diseases or phenotypes w/low freq. (1-5%) risk alleles w/ intermediate effect sizes



Complex diseases & phenotypes with common disease risk alleles (>5%), w/ very low effect sizes & penetrance



ZYLOPRIM (allopurinol) : 1,5-dihydro-4H-pyrazolo [3,4-d]pyrimidin-4-one

Allopurinol is a xanthine oxidase inhibitor which reduces serum and urinary uric acid concentrations.

Treatment of primary or secondary gout

Patients with leukemia, lymphoma and other malignancies who are receiving cancer therapy which causes elevations of uric acid levels.

ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE AN ALLERGIC REACTION

In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, and purpuric lesions, as well as Stevens-Johnson syndrome (erythema multiforme exudativum), and/or generalized vasculitis, irreversible hepato-toxicity, and, on rare occasions, death.

HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol.

Hung et al. Proc Natl Acad Sci U S A. 2005 Mar 15;102(11):4134-9.

Study: 51 patients with allopurinol-SCAR and 228 controls:

135 allopurinol-tolerant subjects and 93 healthy subjects were genotyped for 823 SNPs in genes related to drug metabolism and immune response.

The initial screen revealed strong association between allopurinol-SCAR and SNPs in the MHC region, including BAT3 (encoding HLA-B associated transcript 3), MSH5 (mutS homolog 5), and MICB (MHC class I polypeptide-related sequence B) ($P < 10^{-7}$.

HLA -A, B, C, DRB1 typing was performed.

HLA-B*5801 was present in 100%/ 51 patients with allopurinol-SCAR but only in 20 (15%) of 135 tolerant patients

RR=580.3 ; p= 4.7×10^{-24}

and in 19 (20%) of 93 of healthy subjects

RR= 393.51 p= 8.1×10^{-18}

HLA -A*3303, Cw*0302, DRB1*0301 were in Δ with HLA-B*5801

HLA Alleles Is Associated With Lumiracoxib In Patients With Inflammatory Diseases

A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury

4378 SUBJECTS FROM 25 COUNTRIES WERE TYPED FOR DQA1*0102:

Caucasians (N=3557), Blacks (N=78), Hispanics (N=675) & others (N=68)

Results from follow-up of the genome-wide analysis of 67 SNPs to search for additional markers that associate with risk of liver enzyme elevations (peak ALT/AST > 3x U), showed strong DQA1*0102 carrier status.

Singer, Lewitsky et al, Nature Genetics, 2010:38. 632

HLA Alleles Is Associated With Lumiracoxib In Patients With Inflammatory Diseases

Liver Injury:	% Carriers	% Non-Carriers
Hepatocellular	76.5	45.9
Mixed	20.6	48.6
Cholestatic	2.9	5.4

p=0.01

OR for >3x U =5.8; >5x U=11.1; >8x U= 21.6;>10x U=24.1

DQA1*0102 patients freq by race:

Caucasian	35.4%;	Hispanic	21.2%;
Black	57.7%;	Other	38.7%

HLA Alleles Is Associated With Lumiracoxib In Patients With Inflammatory Diseases

A logistic regression model was applied with an indicator of liver enzyme levels as a dependent variable, variable number of copies of HLA as an independent variable, and sex, age, study as co-variants

DRB1*1501 yielded the most significant result among Hispanics (p=0.0007; OR=6), similar to that obtained from the whole analysis (OR=5).

This association with the increase in liver enzymes was stronger than the one of DQA1*0102, however, all DRB1*1501 carriers were also DQA1*0102,

..which one is the primary susceptibility allele?

HLA Alleles Is Associated With Lumiracoxib In Patients With Inflammatory Diseases

It is important to emphasize, that results were compred with HLA DQA1* typed patients taking Naproxen and Ibuprofen, with no HLA association at all

More studies are needed in patients from ethnic specific populations, taking Lumiracoxib for inflammatory diseases such as rheumatic diseases

The FDA will soon provide an alert for HLA typing in patients, before taking Lumiracoxib

HLA typing and Pharmacogenomics: It is already here!!

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

FDA alert 12/12/2007 recommends HLA-B*1502 typing before prescribing Carbamazepine to patients of Asian origin.

DHHS Treatment guidelines for HIV-1 infection in Adults and Adolescents (12/01/2007 update) recommends HLA-B*5701 typing before prescribing Abacavir.

It is already here

From NEJM, Feb. 2008, 358

HLA-B*5701 Screening for Hypersensitivity to Abacavir. Mallal et al.

Pharmacogenomic Biomarkers for Prediction of Severe Adverse Reactions. M. Ingelman-Sundberg, 2009

(7 listed, 3 HLA alleles).

HLA AND PERSONALIZED MEDICINE

pharmacogenomics
disease diagnostics
immunotherapy
infectious disease vaccines
tumor vaccines

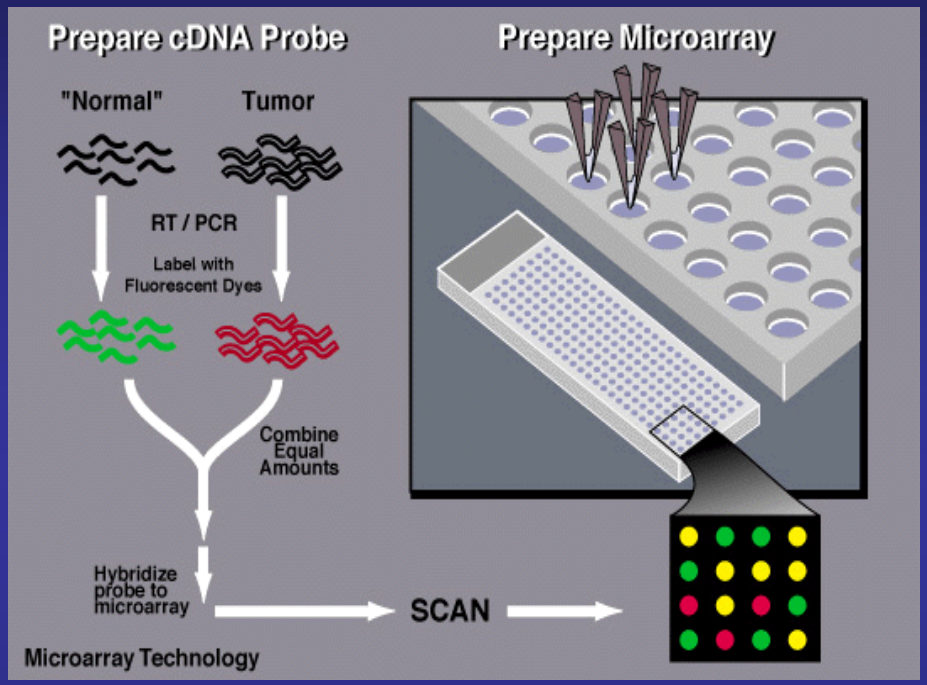
http://www.pharmgkb.org
PharmGKB (Pharmacogen Base)

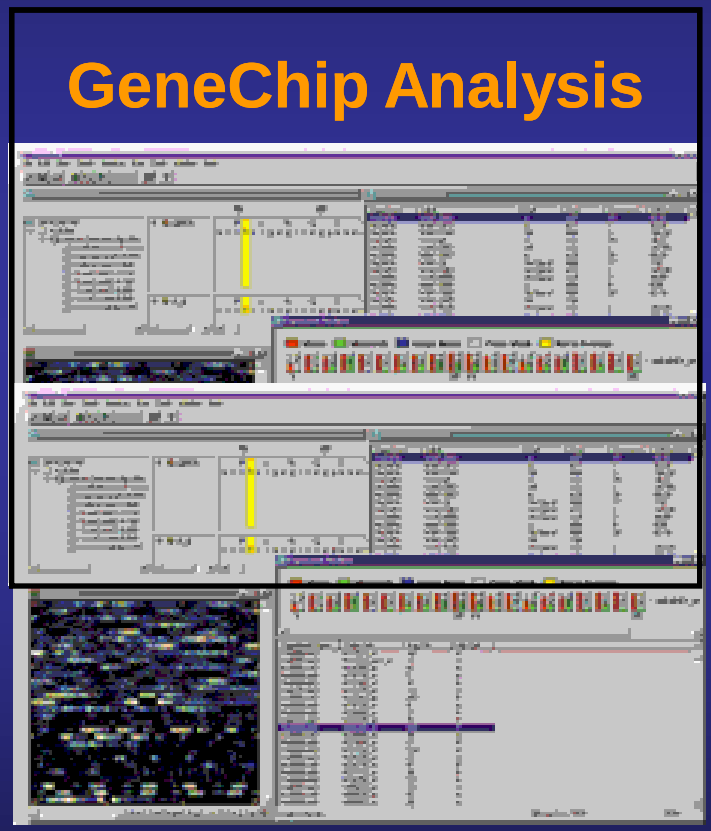
GOALS OF PHARMACOGENOMICS

* To identify the functional genes or polymorphisms associated with the individual response to drugs
* To obtain personalized drugs
* To improve de efficacy of disease therapeutics
* To avoid adverse drug reactions
* To select patients for clinical trials of new drugs and for better terapheutic strategies
* To design new drugs

Personalized Medicine

PERSONALIZED MEDICINE:THE FUTURE





16th INTERNATIONAL HISTOCOMPATIBILITY WORKSHOP

COMPONENT: PHARMACOGENOMICS

CO-CHAIRS: CLARA GORODEZKY & SUSIE LEFFELL

clarag@servidor.unam.mx; msl@jhmi.edu

Serious adverse reactions to drugs in association with certain HLA alleles have been confirmed in some ethnic groups, but have not been investigated in other populations. It is also likely that additional associations may be established for other drugs with increasing awareness of possible immunogenetic predisposition.

AIM: The aim of this study is to establish an ongoing registry for compilation of data on the incidence of the association of HLA alleles and/or other immunogenetic factors with adverse drug reactions in various populations.

PHRMACOGENOMICS AND CLINICAL PRACTICE

Sir William Osler
1849-1919

http://www.pharmgkb.org

PharmGKB (Pharmacogen Base)

"If it was not, because of the enormous variability among individuals, Medicine would be a science and not an art"