



JNI 15^{es} Journées
Nationales
d'Infectiologie

Bordeaux
et l'interrégion Aquitaine & Limousin



du mercredi 11 au vendredi 13 juin 2014
Palais des Congrès de Bordeaux

Polymorphisme génétique et infection

Jean-Paul Mira

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Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Mira/Jean-Paul

Titre : Intitulé de l'intervention

L'orateur ne souhaite pas répondre

- Consultant ou membre d'un conseil scientifique OUI NON
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents OUI NON
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations OUI NON
- Investigateur principal d'une recherche ou d'une étude clinique OUI NON



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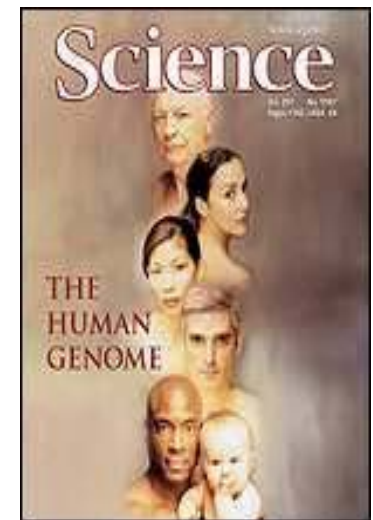


Déclaration d'intérêts de 2012 à 2014

- **Intérêts financiers : Aucun**
- **Liens durables ou permanents : MSD, Astellas, LFB, Eli Lilly, Thermofisher**
- **Interventions ponctuelles : Novartis, Gilead**
- **Intérêts indirects : Aucun**

Odyssey to Genome Project

- 1953** Watson & Crick: double helical structure of DNA
- 1960s** Role of RNA and Genetic Code
- 1970s** Recombinant DNA technology
- 1977** Sanger and Gilbert: DNA sequencing
- 1983** Mapping of disorders by linkage (Huntington disease)
- 1986** Polymerase Chain Reaction
- 1995** *Haemophilus influenzae* genome
- 2003** Human and mice genome sequences
SNPs Map



Odyssey to ENCODE Project

1953 Watson & Crick: double helical structure of DNA



2003 Human and mice genome sequences

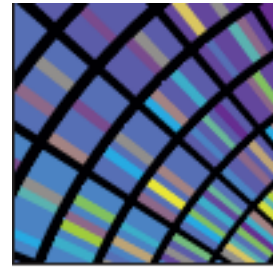
SNPs Map

2005 Haplotype Map

2006 Ins/del map

2008 1000 genome project

2012 ENCODE project



ENCODE
Encyclopedia of DNA Elements
nature.com/encode



An integrated encyclopedia of DNA elements in the human genome

The ENCODE Project Consortium*

The accessible chromatin landscape of the human genome

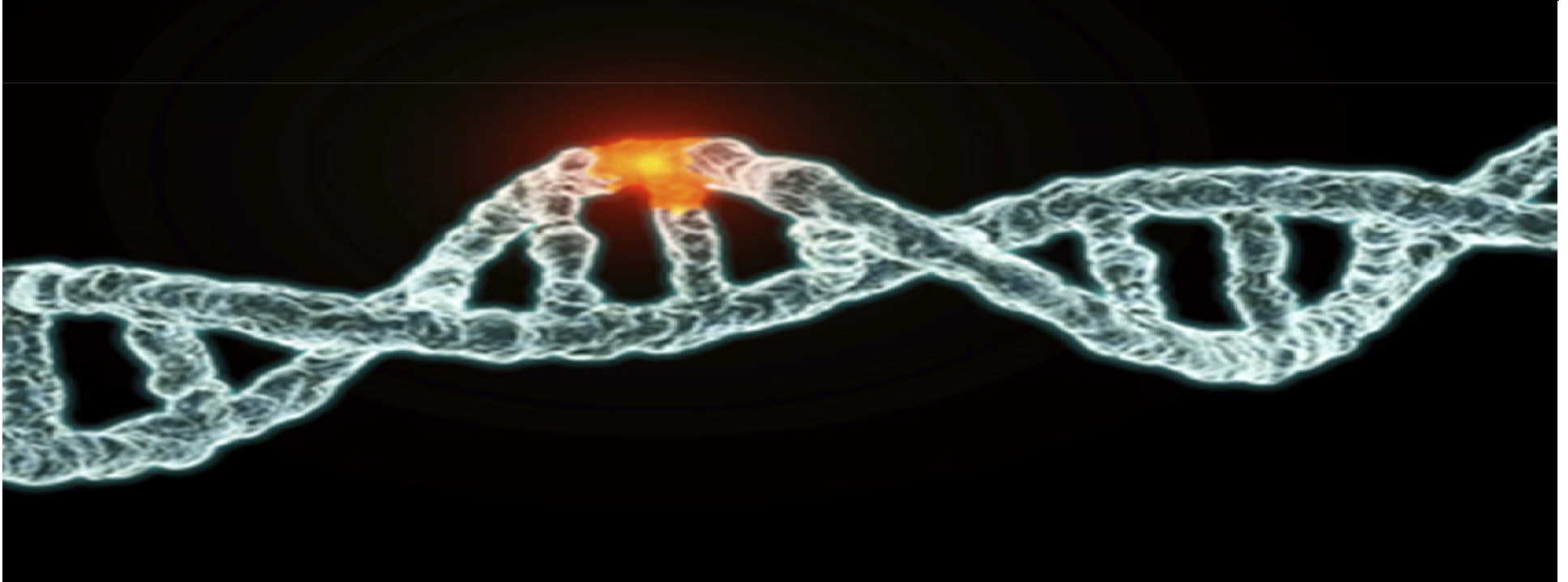
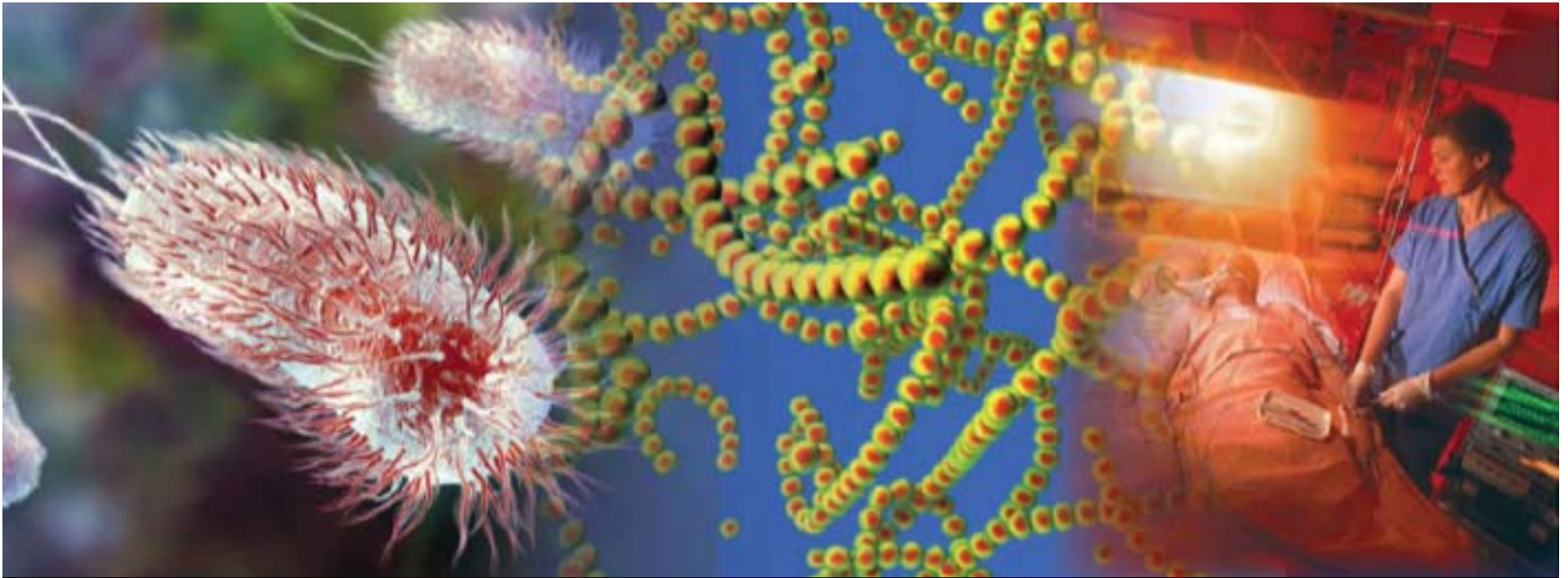
An expansive human regulatory lexicon encoded in transcription factor footprints

Shane Neph^{1*}, Jeff Vierstra^{1*}, Andrew B. Stergachis^{1*}, Alex P. Reynolds^{1*}, Eric Haugen¹, Benjamin Vernot¹, Robert E. Thurman¹,

Basic features of the Human genome

BASIC FEATURES OF THE HUMAN GENOME

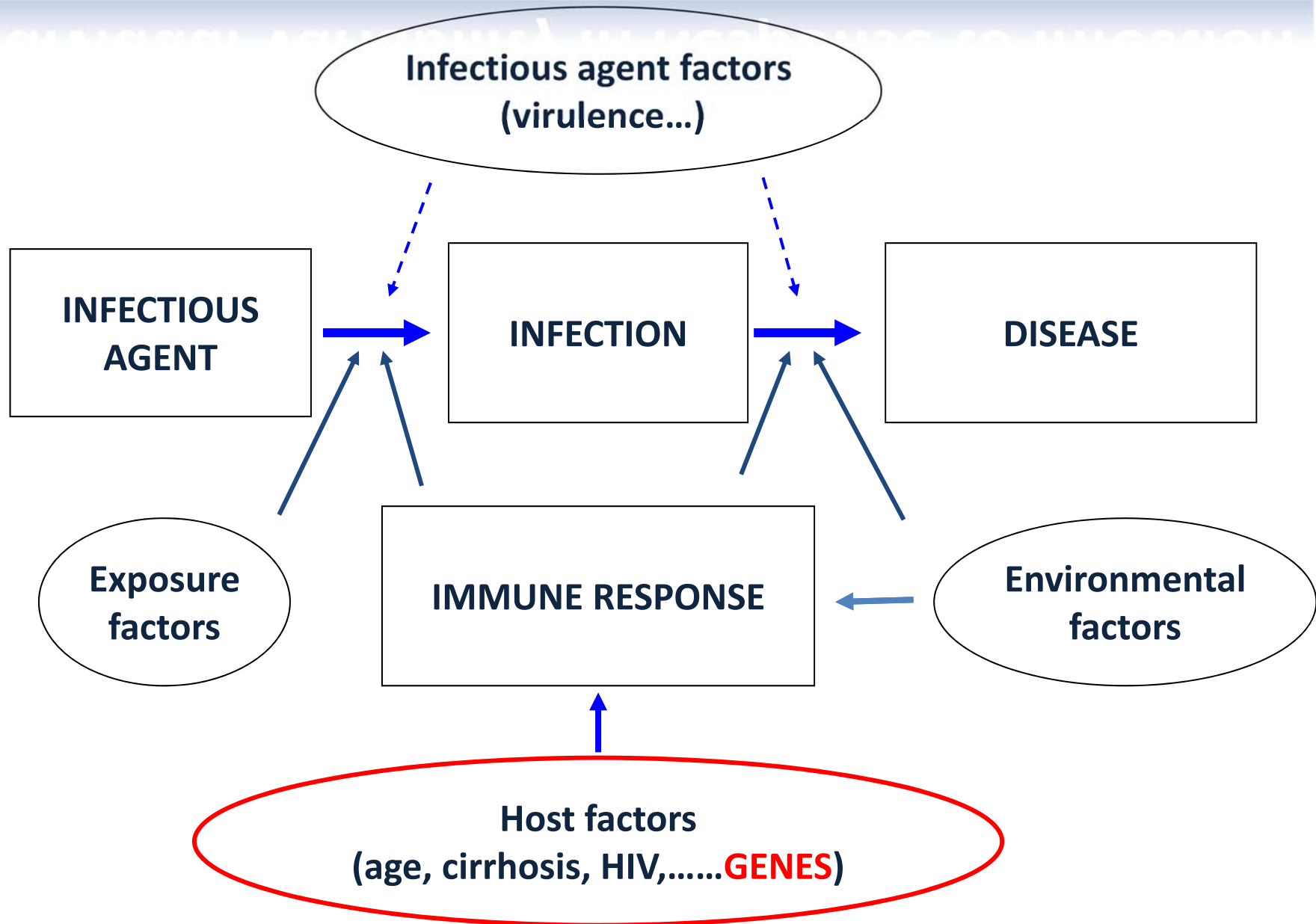
Nucleotides in the genome	3.2×10^9
Protein-coding genes in the genome	23,500
DSVs	4×10^6
SNPs	3.5×10^6
nsSNPs	10,000
SV/CNVs	10^3-10^5
Variants known to be associated with inherited diseases	50-100
De novo variants	30

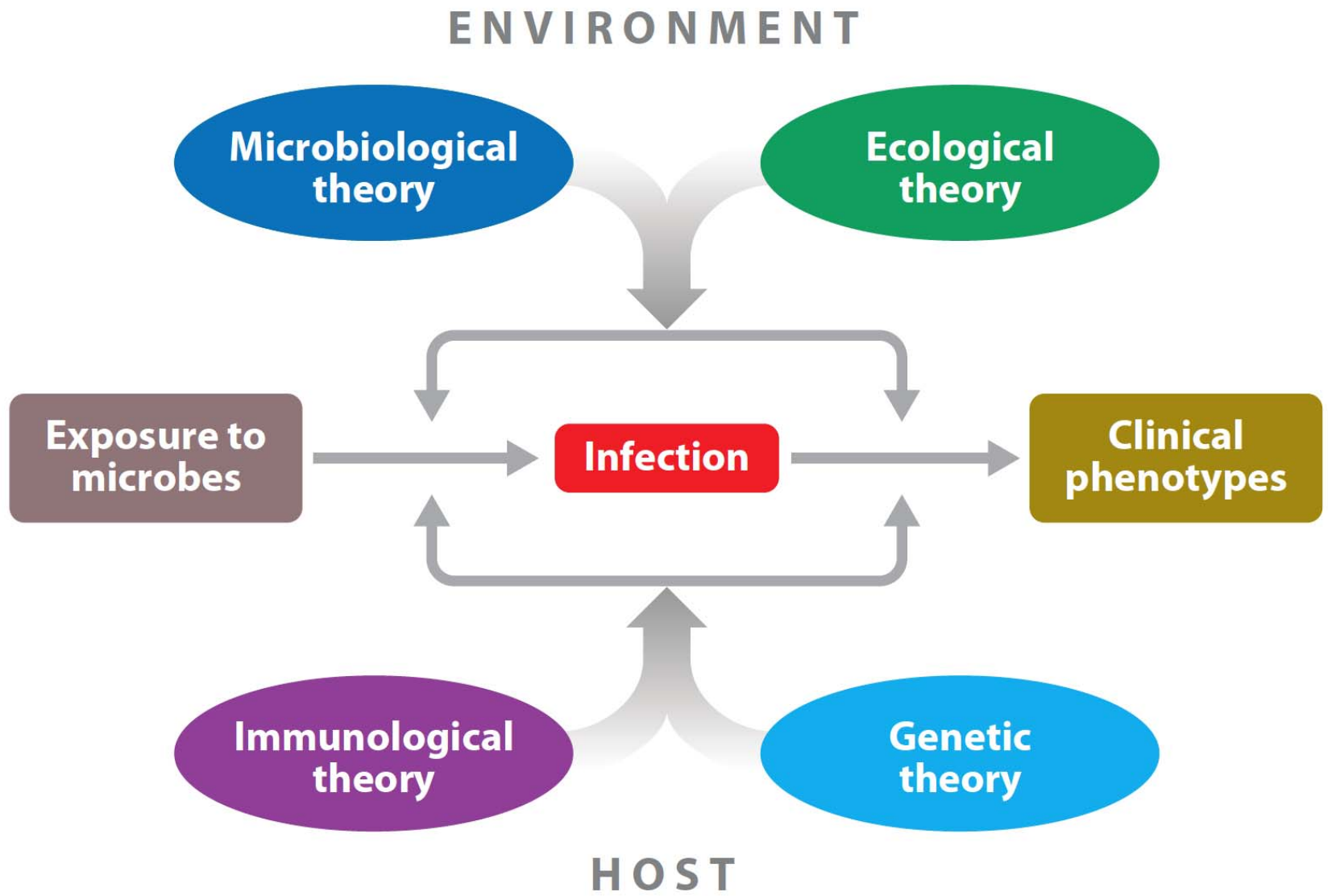


Host Genetics and Infectious Diseases

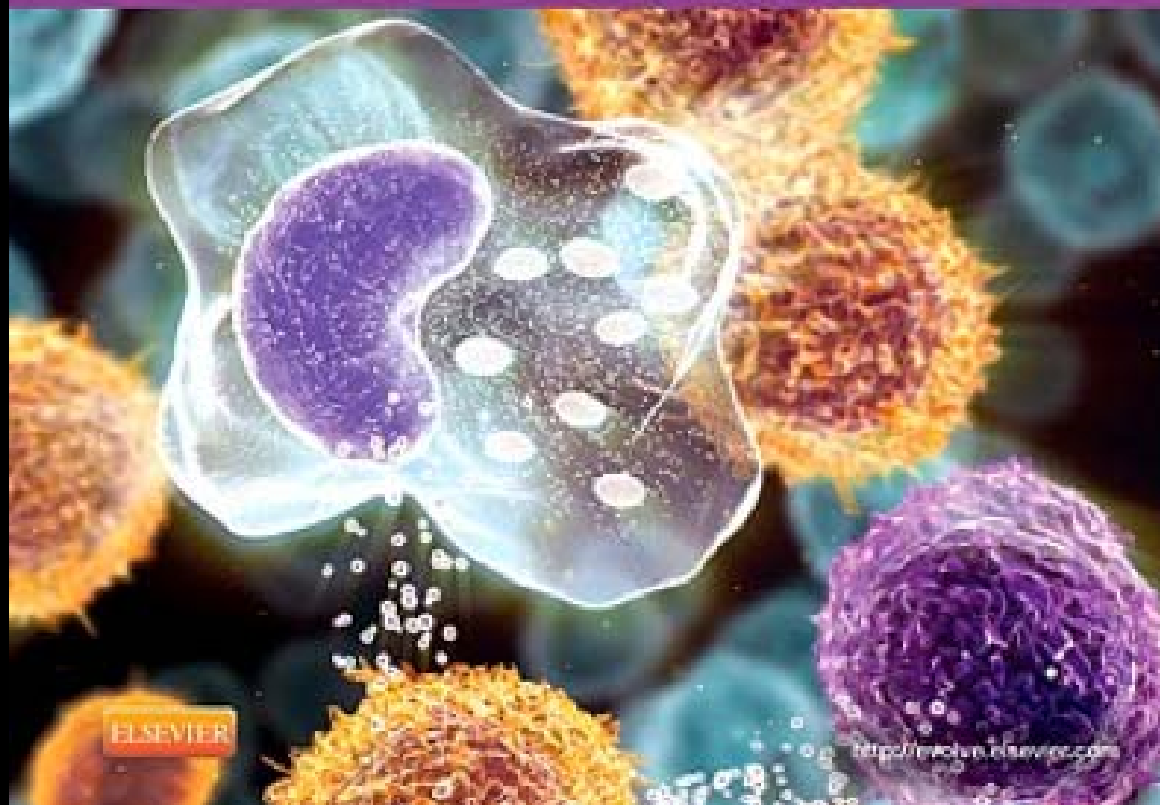
- **Infectious diseases are a major selective force in human evolution**
- **Host defense genes are more diverse than any other genes**
- **Human immune response genes more polymorphic than any other species**
- **Many exposed to infection; few develop disease**

Individual Variability in Response to Infection





Understanding Pathophysiology





Reverse Genetics

Select a gene

Generate a null mutant
of the gene

Forward Genetics

Identify gene(s)
causing the phenotype

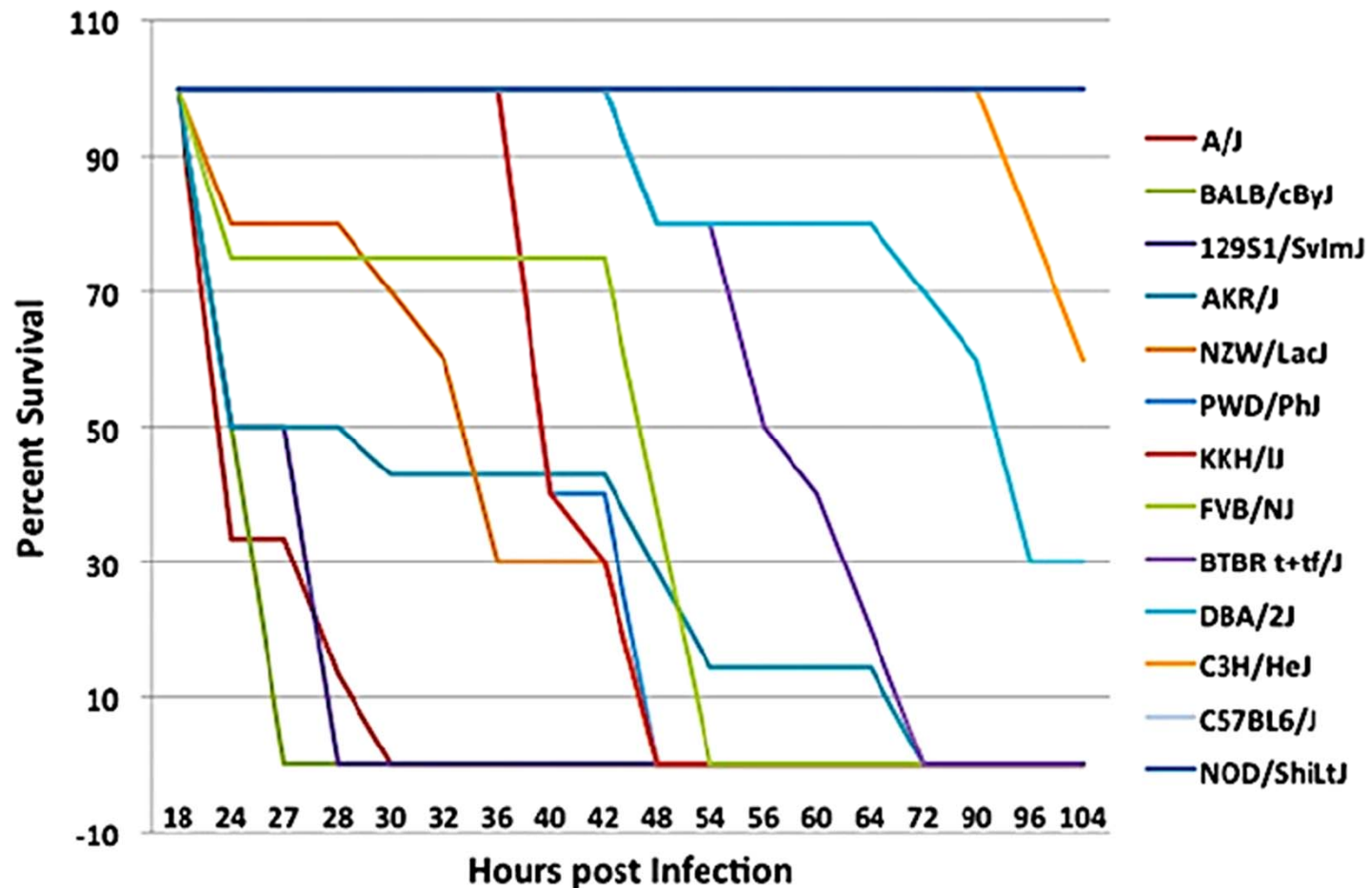
Screen a collection
of mutants

Phenotype



Haplotype Association Mapping Identifies a Candidate Gene Region in Mice Infected With *Staphylococcus aureus*

13 inbred strains intraperitoneally injected with 10^7 CFU/g of the Sanger 476 strain of *S. aureus* (332 mice)





Explore MGI

[All Search Tools](#)

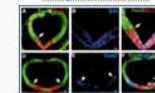
Genes



Phenotypes & Disease Models



Expression



Recombinases (cre)



Function



Pathways



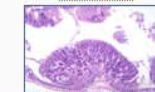
Strains / SNPs

Variation Type	JAX		IMSR (MGI)		Allele Summary (all strains)
	SNP	Indel	SNP	Indel	
SNP	G	G	A	A	A/G
SNP	C	C	T	T	C/T

Orthology



Tumors



Mouse Phenome Database

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Genotype >

Project data set: Perlegen2 (2005)

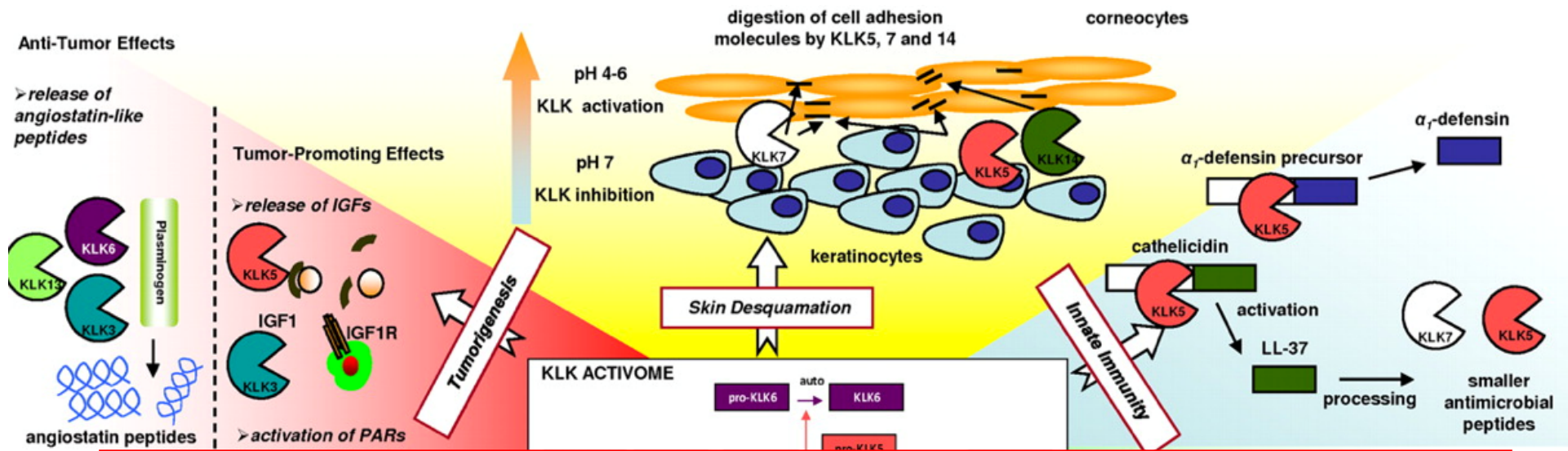
Project

SNP data, 8.2+ million locations for 16 inbred strains of mice

Haplotype Association Mapping Identifies a Candidate Gene Region in Mice Infected With *Staphylococcus aureus*

Chromosome 7 block: candidate genes

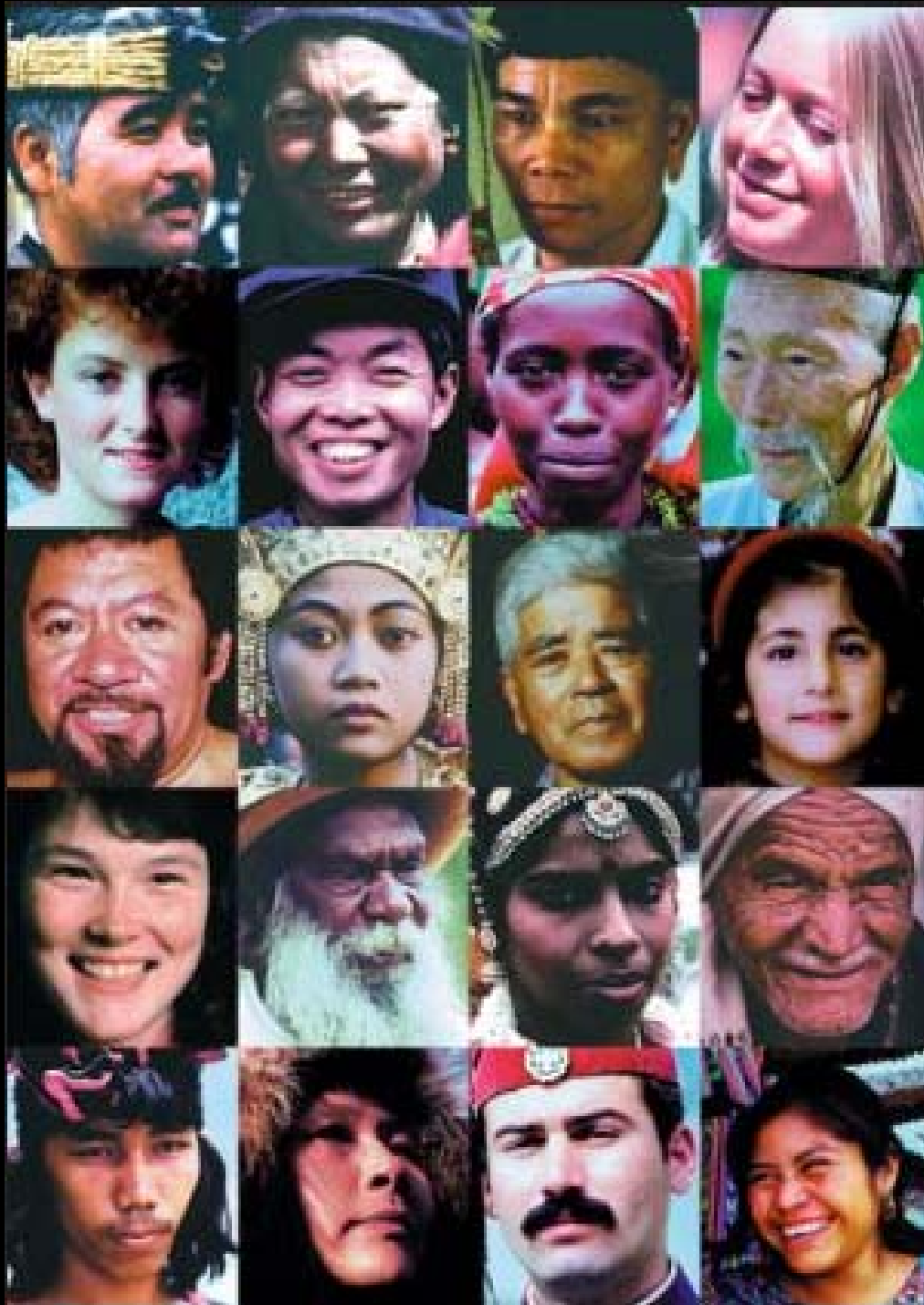
Genomic Location (bp)	Gene Symbol	Gene Name	Differentially Expressed	
50945788	50950906	Klk14	Kallikrein related-peptidase 14	
50967937	50982128	Klk13	Kallikrein related-peptidase 13	
51024267	51028946	Klk12	Kallikrein related-peptidase 12	
51029987	51034628	Klk11	Kallikrein related-peptidase 11	Downregulated
51036424	51040780	Klk10	Kallikrein related-peptidase 10	
51047261	51052126	Klk9	Kallikrein related-peptidase 9	
51052947	51059192	Klk8	Kallikrein related-peptidase 8	
51066814	51071729	Klk7	Kallikrein related-peptidase 7	
51079869	51087172	Klk6	Kallikrein related-peptidase 6	
51097639	51106551	Klk5	Kallikrein related-peptidase 5	
51136542	51141174	Klk4	Kallikrein related-peptidase 4	Upregulated
51189141	51194960	Klk15	Kallikrein related-peptidase 15	
51206034	51210311	Klk1b8	Kallikrein 1-related peptidase b8	Downregulated
51222138	51226686	Klk1b1	Kallikrein 1-related peptidase b1	Downregulated
51231431	51235746	Klk1b9	Kallikrein 1-related peptidase b9	
51251247	51255245	Klk1b11	Kallikrein 1-related peptidase b11	Downregulated
51268048	51272335	Klk1b26	Kallikrein 1-related peptidase b26	
51307660	51312075	Klk1b27	Kallikrein 1-related peptidase b27	
51357662	51361944	Klk1b21	Kallikrein 1-related peptidase b21	
51368043	51372292	Klk1b22	Kallikrein 1-related peptidase b22	
51392137	51396977	Klk1b16	Kallikrein 1-related peptidase b16	
51443606	51447822	Klk1b24	Kallikrein 1-related peptidase b24	Downregulated
51453561	51457721	Klk1b3	Kallikrein 1-related peptidase b3	
51462805	51467124	Klk1b4	Kallikrein 1-related peptidase b4	
51471844	51476073	Klk1b5	Kallikrein 1-related peptidase b5	
51480807	51484987	Klk1	Kallikrein 1	Downregulated



Targeting the kallikrein-related peptidases for drug development

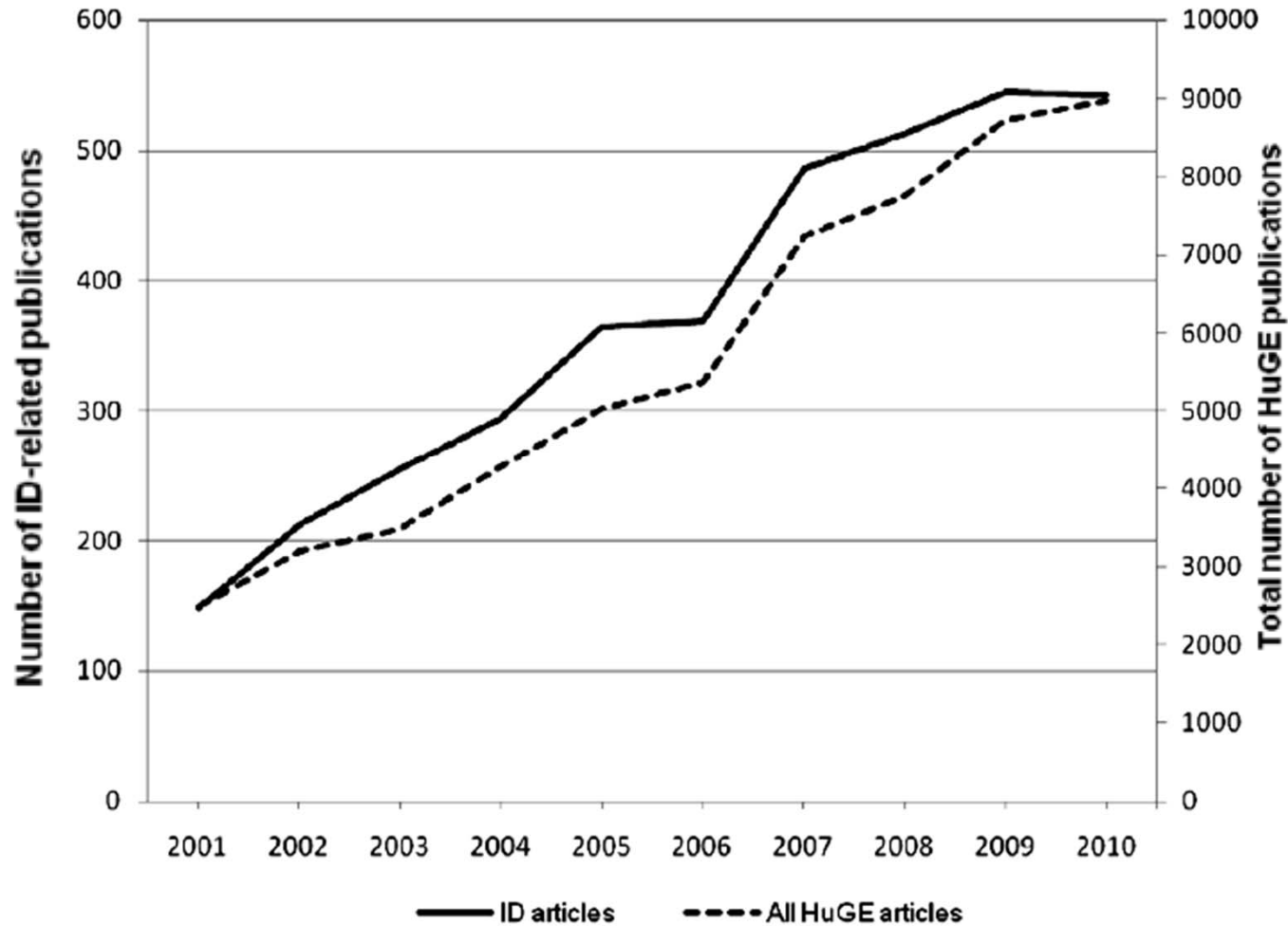
Georgia Sotiropoulou and Georgios Pampalakis

Kallikrein proteins (KLK) have well-established roles in the generation of antimicrobial peptides, and the regulation of immune responses, particularly inflammation



Trends in Population-Based Studies of Human Genetics in Infectious Diseases

Publication of infection-related articles in human genome epidemiology



http://www.hugenavigator.net



HuGE Navigator (version 2.0)

An integrated, searchable knowledge base of genetic associations and human genome epidemiology.

[Home](#) | [Download Center](#) | [Open Source Projects](#) | [Contact](#)

Curator's recommended HuGE article for this week:

The utility of molecular diagnostics to predict recurrence of head and neck carcinoma.

Pena Murillo C, Huang X, Hills A, et al. Br J Cancer. 2012 Aug 23.

[PubMed Link](#)

HuGE Navigator is a continuously updated knowledge base in human genome epidemiology, including population prevalence of genetic variants, genetic associations... [more](#)

Join us on Facebook  and follow us on Twitter 

Last database update: **30 Oct 2012**

Site citation: W Yu, M Gwinn, M Clyne, A Yesupriya & M J Khoury. [A Navigator for Human Genome Epidemiology](#). *Nat Genet* 2008 Feb;40(2): 124-5.



Phenopedia: Look up genetic associations and human genome epidemiology summaries by disease. [?](#)



Genopedia: Look up genetic associations and human genome epidemiology summaries by gene. [?](#)



HuGE Literature Finder: Find published articles in genetic associations and human genome epidemiology. [?](#)



Gene Prospector: A gateway for evaluating genes in relation to disease and risk factors. [?](#)



GWAS Integrator: Explore published GWAS and relevant information. [?](#)



Cancer GAMadb: Database of cancer genetic associations from meta analyses and GWAS. [?](#)



HuGE Watch: Track the evolution of published literature in human genome epidemiology. [?](#)



Variant Name Mapper: Map common names and rs numbers of genetic variants. [?](#)



HuGE Investigator Browser: Find investigators in a particular field of human genome epidemiology. [?](#)



Genotype Prevalence Catalog: Present genotype prevalence estimates in US population. [?](#)



Download Center: Download complete datasets from different databases/applications. [?](#)



GAPscreeener: Screening tool for published literature on human genetic associations. [?](#)



HuGE Risk Translator: Calculate the predictive value of genetic markers for disease risk. [?](#)



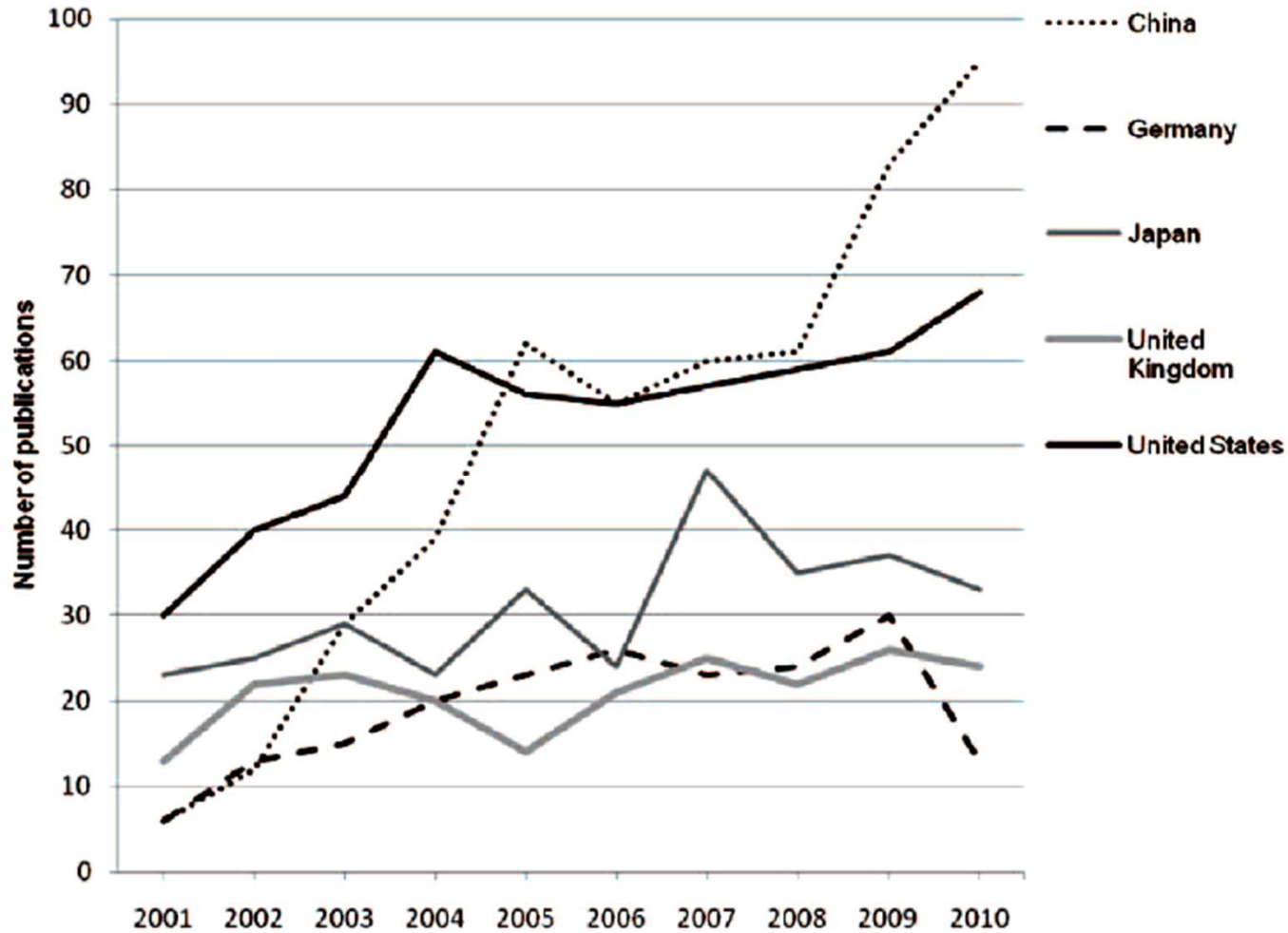
Open Source: Infrastructure for managing knowledge and information from PubMed. [?](#)



HuGE Track : A custom track built for HuGE data in the UCSC Genome Browser. [?](#)

Trends in Population-Based Studies of Human Genetics in Infectious Diseases

Countries with the largest numbers of infectious disease-related publications in HUGE



Trends in Population-Based Studies of Human Genetics in Infectious Diseases

Gene-disease associations, 2001-2010

Gene category	HBV	HCV	HIV	H. pylori	Malaria	Sepsis	TB	Other	Total
Cytokine receptor genes	162	156	110	291	55	119	115	772	1780
Chemokine receptor and ligand genes	44	50	397	34	3	16	15	150	709
HLA Class II genes	68	75	72	43	19	8	46	292	623
TNF and related genes	39	47	29	63	30	62	26	212	508
Toll-like receptor genes	19	16	27	39	23	67	36	222	449
HLA Class I genes	24	53	159	11	11	12	15	162	447
Killer immunoglobulin-like receptor genes	23	48	27	0	3	2	0	160	263
Complement genes	13	13	23	3	5	31	14	117	219
Immunoglobulin Fc and related receptor genes	3	2	12	0	16	13	2	70	118
Red blood cell genes	0	2	7	0	53	7	1	7	77
Metal transport genes	1	1	3	0	0	0	41	25	71
Genes not categorized	910	463	846	319	141	168	194	1514	4555
Total	1306	926	1712	803	359	505	505	3703	9819

Meeting report

The PIRO concept: P is for predisposition

Derek C Angus¹, David Burgner², Richard Wunderink³, Jean-Paul Mira⁴, Herwig Gerlach⁵,
Christian J Wiedermann⁶ and Jean-Louis Vincent⁷

Critical Care 2003, 7:248-251 (DOI 10.1186/cc2193)

Susceptibility

Severity

Drug
response



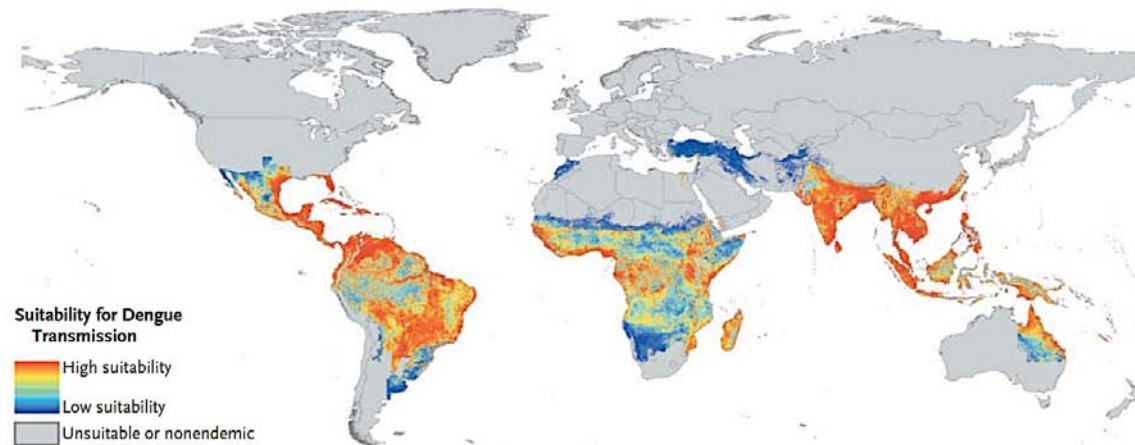
Genome-wide association study identifies susceptibility loci for dengue shock syndrome at *MICB* and *PLCE1*

Dengue: 100 million infections / year

Dengue → Hypovolemic shock (DSS: Dengue shock syndrome)

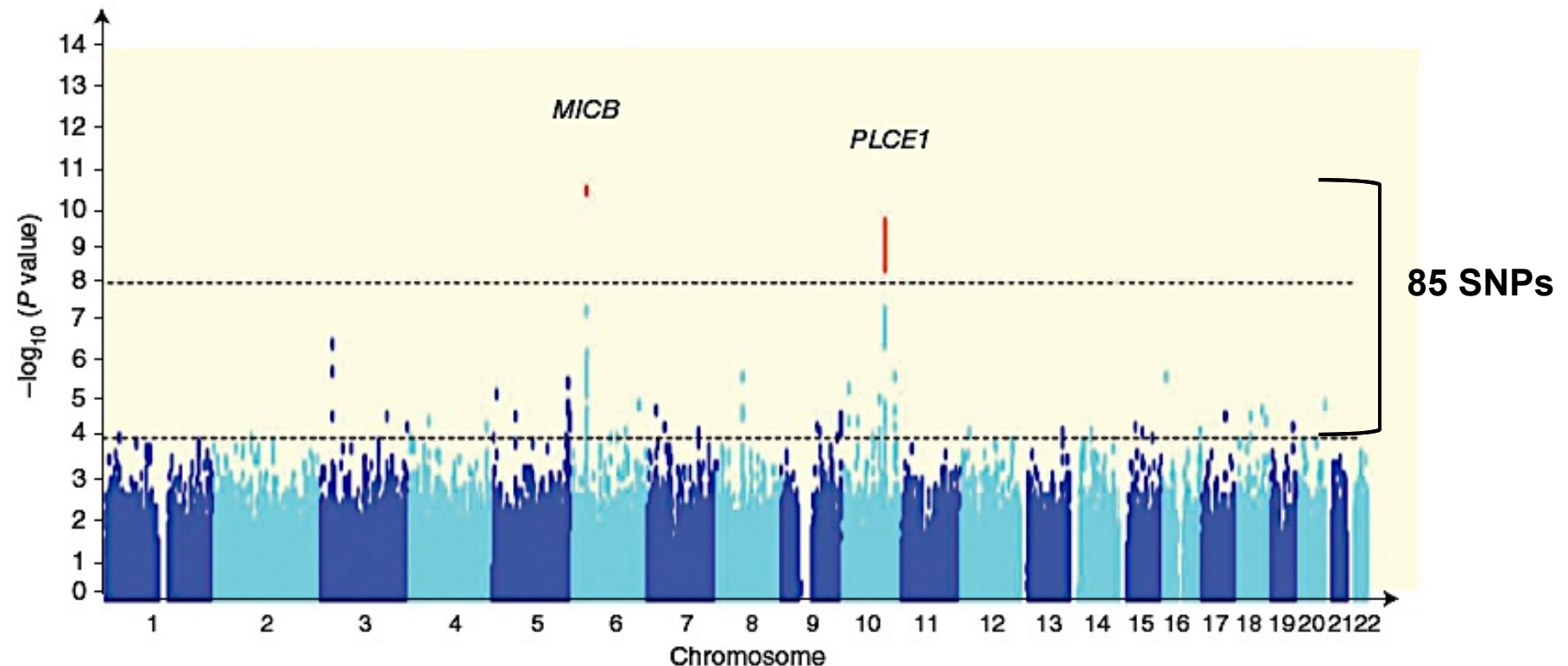
First GWA study 2,008 cases and 2,018 controls from Vietnam (Illumina 660W)

Second replicative Vietnamese study : 1,737 cases and 2934 controls (Sequenom Mass-Array Platform)



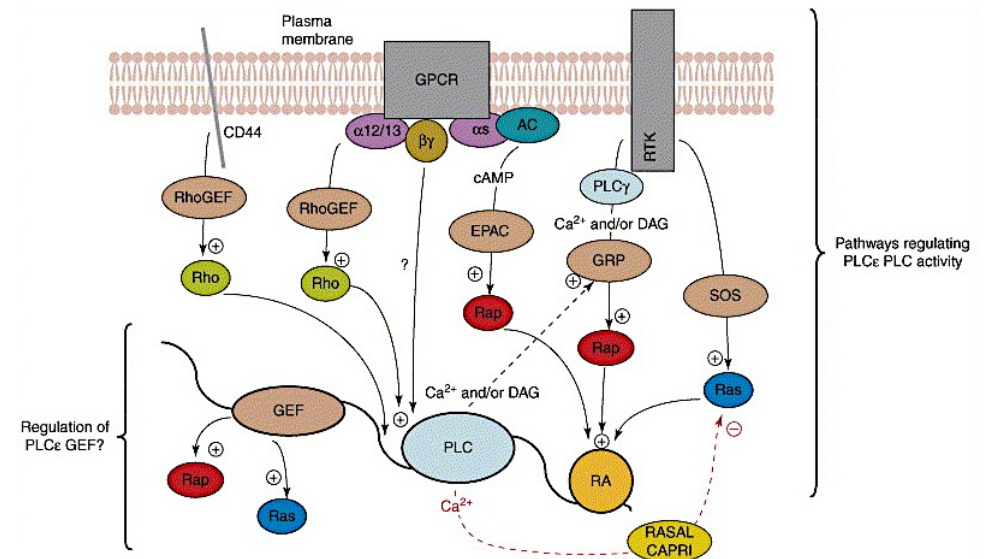
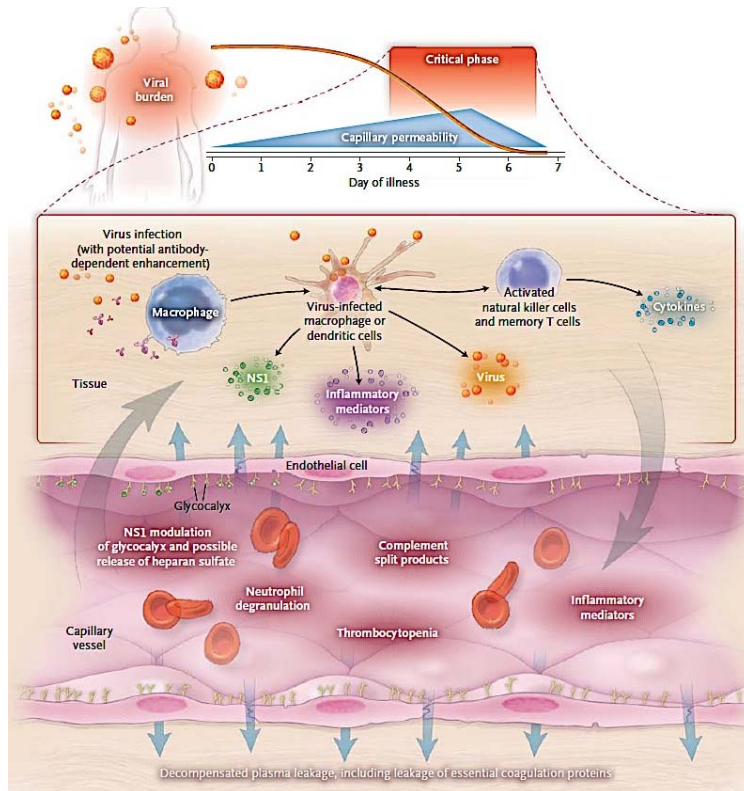
Genome-wide association study identifies susceptibility loci for dengue shock syndrome at *MICB* and *PLCE1*

First GWA study 2,008 cases and 2,018 controls from Vietnam



Genome-wide association study identifies susceptibility loci for dengue shock syndrome at *MICB* and *PLCE1*

- ✓ ***MICB*** encodes an inducible activating ligand for the NKG2D type II receptor on NK and CD8+ T cells.
- ✓ Mutations within ***PLCE1*** are associated with nephrotic syndrome suggesting a key role for ***PLCE1*** in maintaining normal vascular endothelial cell barrier function





Recurrent Purpura Fulminans

2002/01: 15 yo girl admitted in ICU

- Temperature 40° C; HR 125; BP 74/45; RR 38
- Meningitis with purpura fulminans
- MOF (Shock, ARDS, ARF, DIC, Lactic acidosis)
- Meningococcus type N in the skin biopsy
- Survival with multiple finger amputations and skin grafting
- 6 month hospitalization

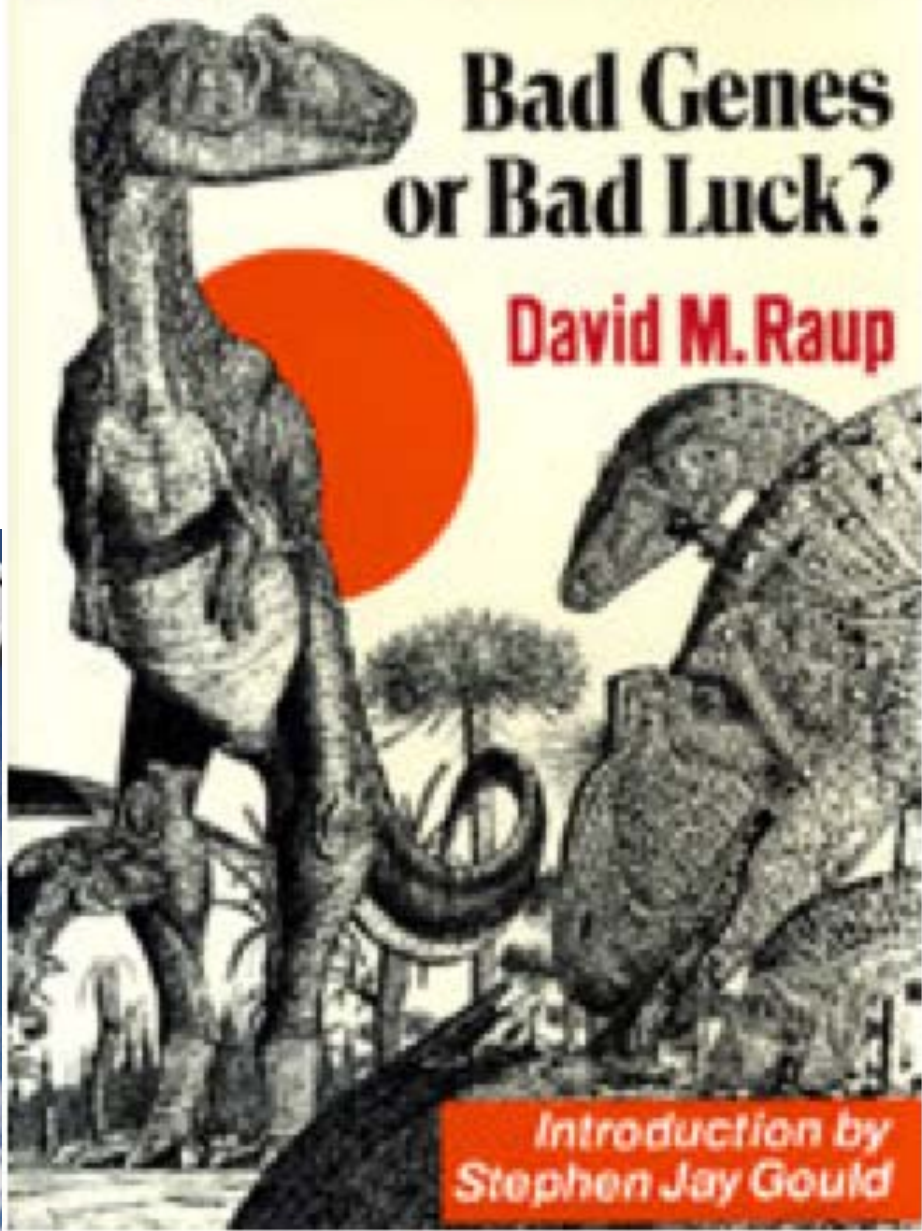
2003/02:

- Temperature 39° C; HR 125; BP 83/48; RR: 33
- Meningitis with purpura fulminans
- Lumbar puncture → meningococcus type Y
- Shock and DIC
- Survival with new skin grafting
- 3 month hospitalization

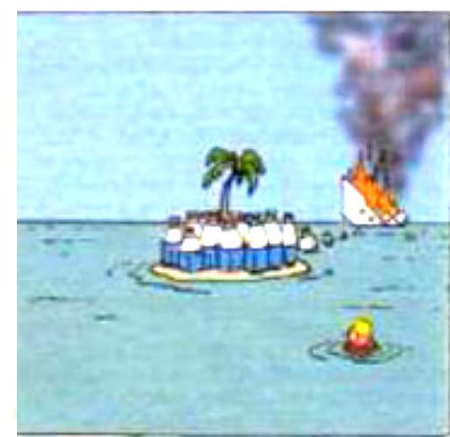
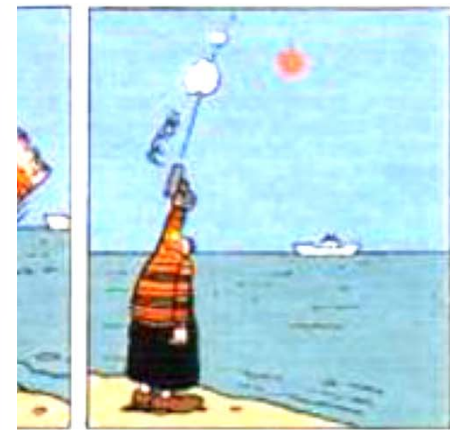
EXTINCTION

Bad Genes or Bad Luck?

David M. Raup



Introduction by
Stephen Jay Gould





Severe *Plasmodium malariae* Malaria in a Patient With Multiple Susceptibility Genes

Anne-Pauline Bellanger, PharmD,* Fabrice Bruneel, MD,† Olivier Barbot, MD,‡
Jean-Paul Mira, MD PhD,§ Laurence Millon, PharmD, PhD,* Pascal Houzé, PharmD,||
Jean-François Faucher, MD PhD,¶ and Sandrine Houzé, PharmD#

BMC Infectious Diseases



Open Access

Case report

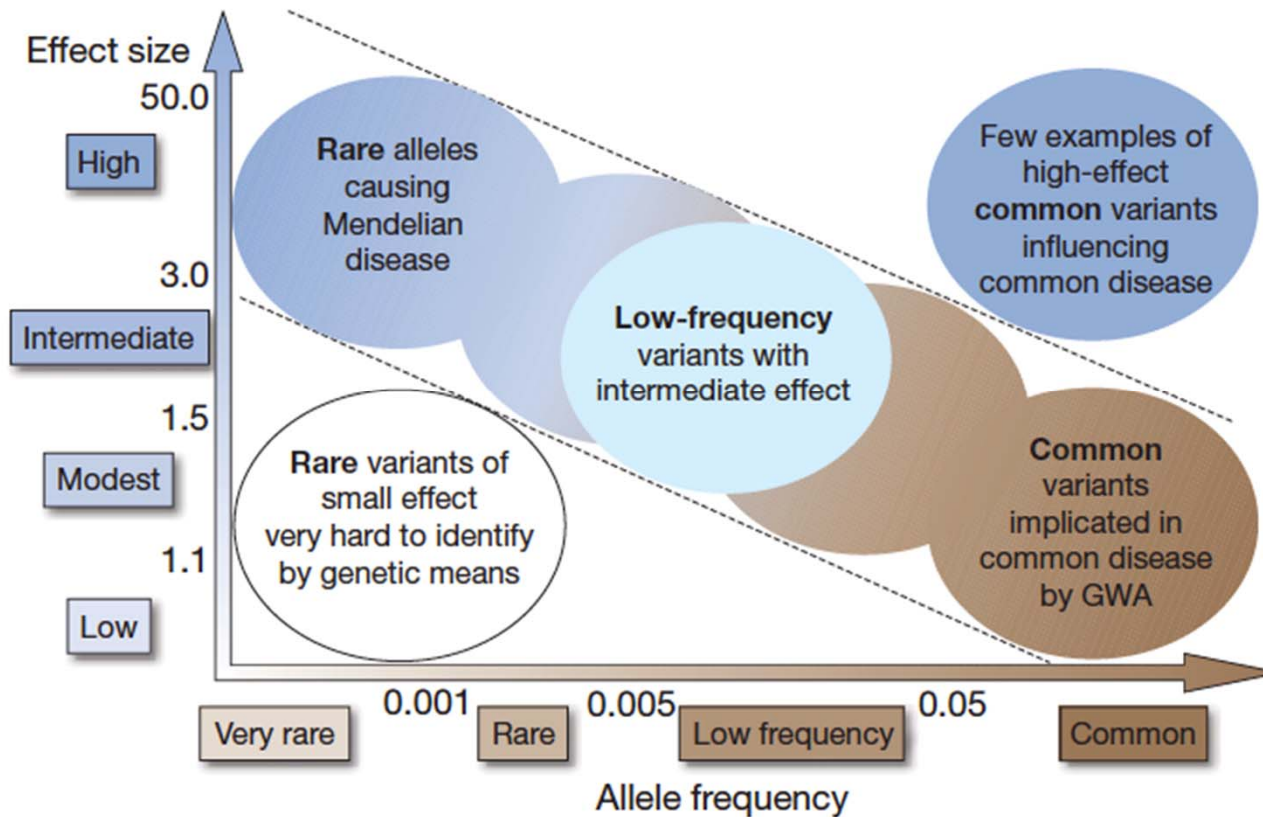
Lemierre's syndrome and genetic polymorphisms: a case report

Jean-Michel Constantin*¹, Jean-Paul Mira², Renaud Guerin¹, Sophie Cayot-Constantin¹, Olivier Lesens³, Florence Gourdon³, Jean-Pierre Romaszko⁴, Philippe Linval⁵, Henri Laurichesse³ and Jean-Etienne Bazin¹

Pachymeningitis after meningococcal infection

Julie Toubiana, Claire Heilbronner, Cyril Gitiaux, Mehdi Oualha, Muhamed-Kheir Taha, Christophe Rousseau, Capucine Picard, Jean-Paul Mira,

Finding the missing heritability of complex diseases



Research strategies:

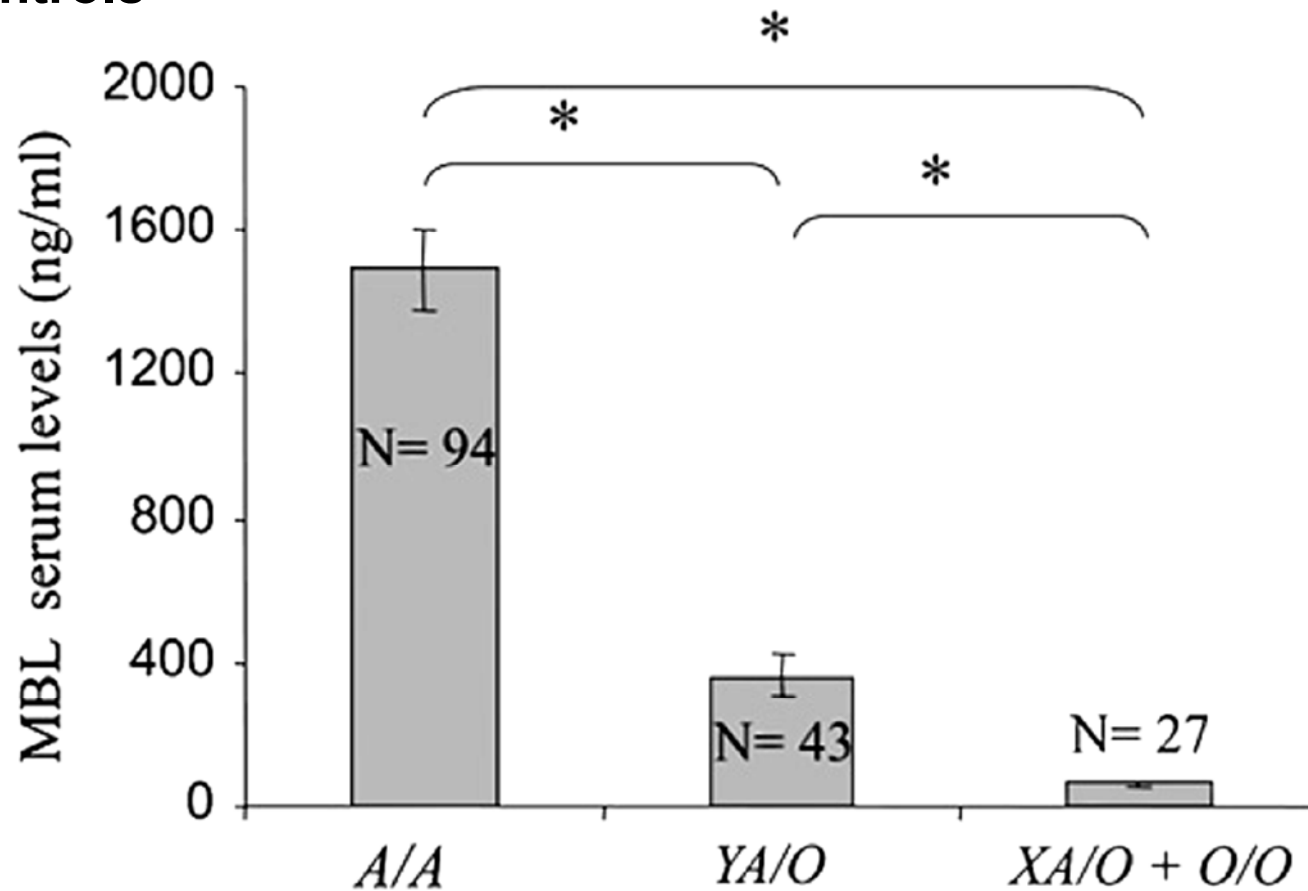
- **SNPs**
- **GWAs**
- **Sequencing studies**

Biomarker



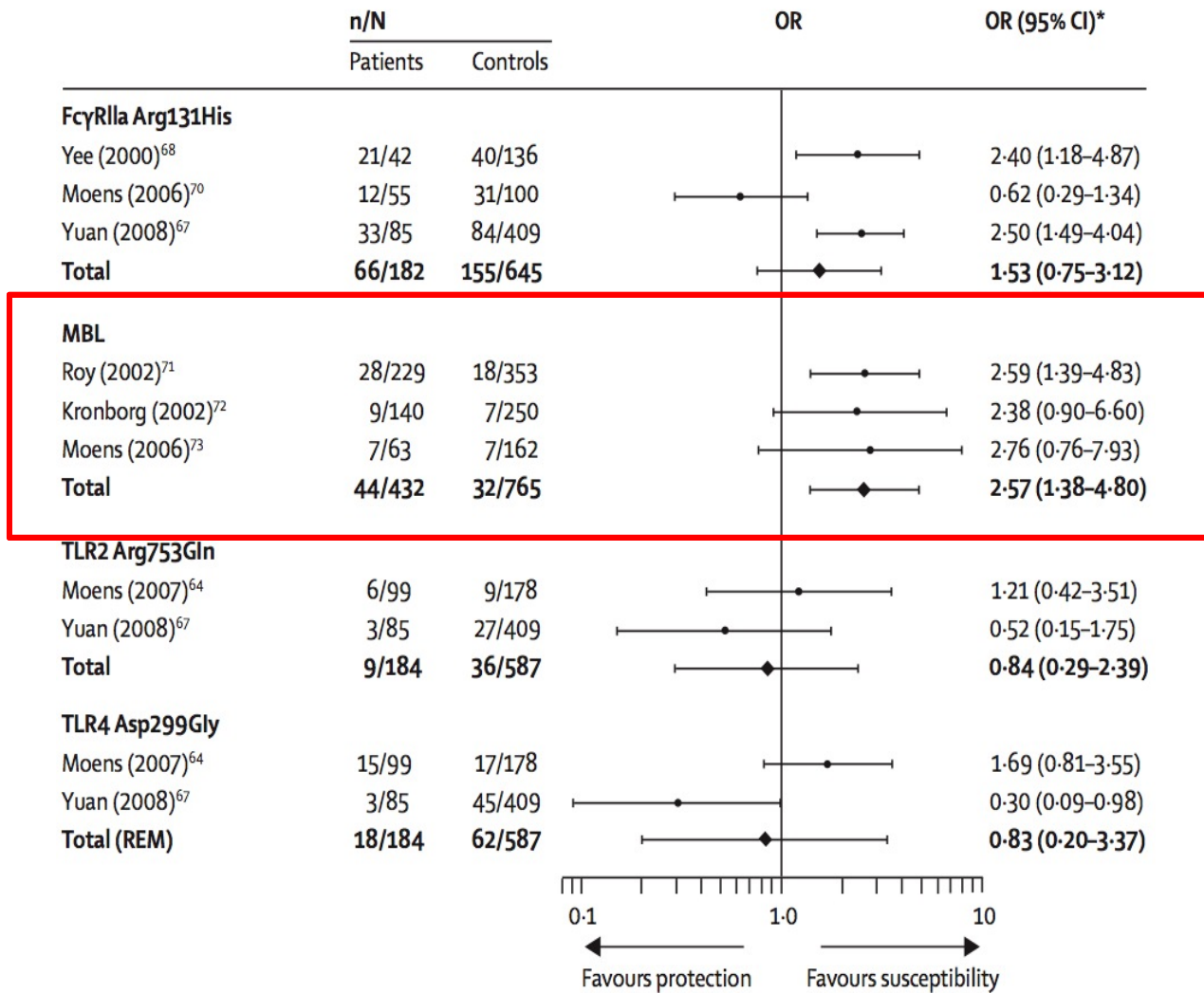
MBL genotypes and protein levels

164 controls



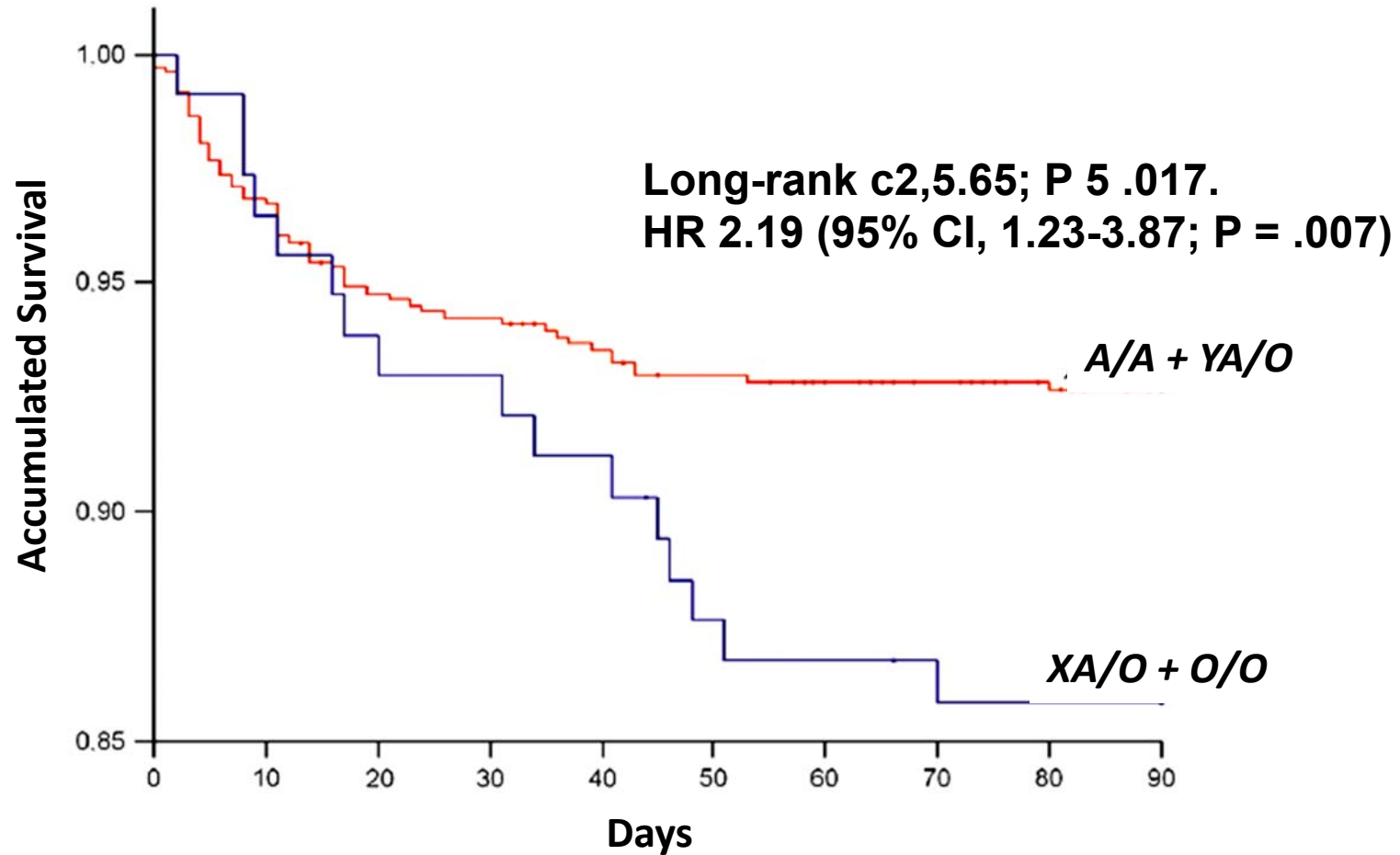
Host genetic susceptibility to pneumococcal and meningococcal disease: a systematic review and meta-analysis

Matthijs C Brouwer, Jan de Gans, Sebastiaan G B Heckenberg, Aeilko H Zwinderman, Tom van der Poll, Diederik van de Beek



MBL haplotypes and 90 days mortality

848 CAP





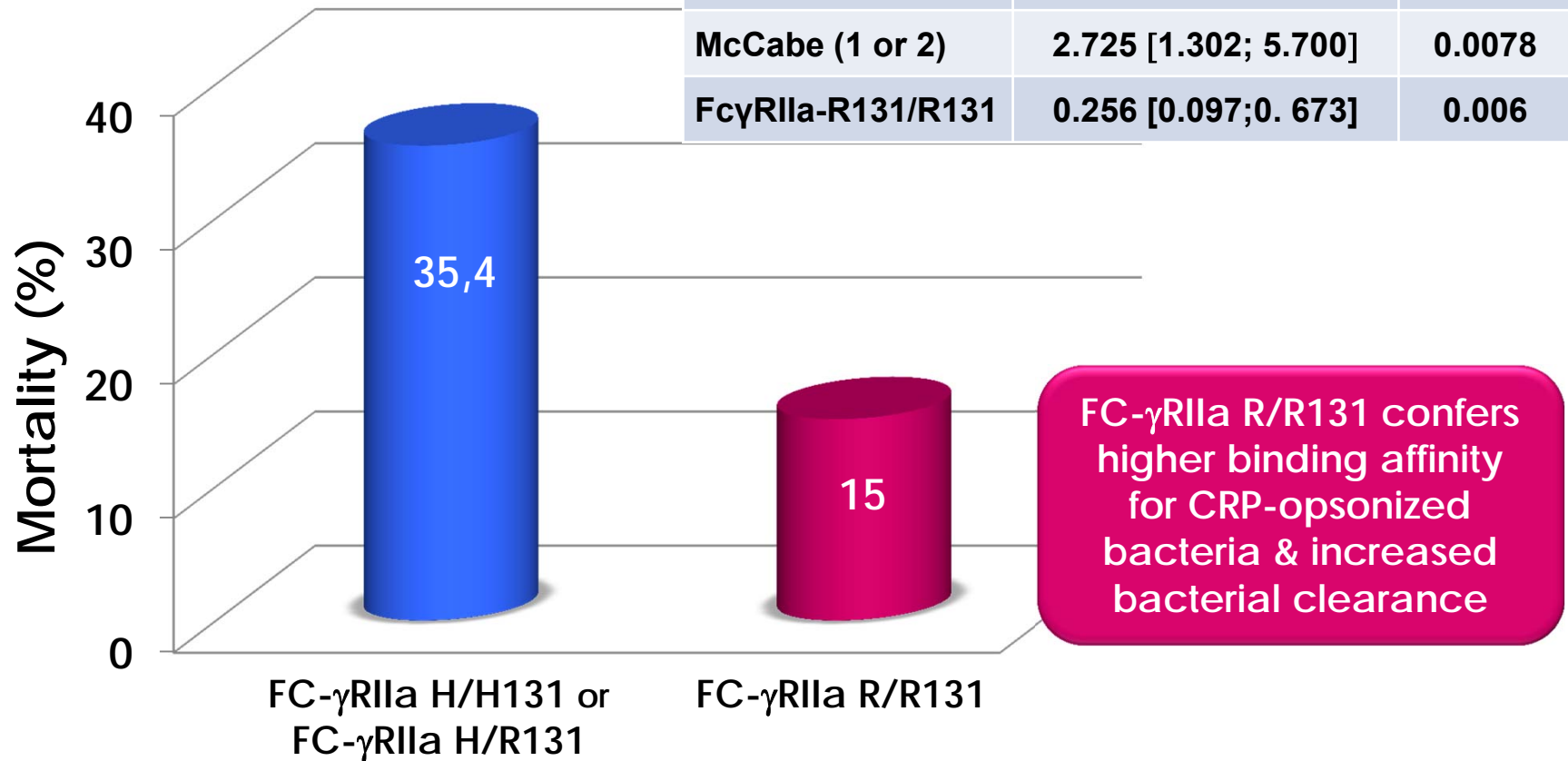
Protective Effects of *FCGR2A* Polymorphism in Invasive Pneumococcal Diseases

Adrien Bouglé, MD; Adeline Max, MD; Nicolas Mongardon, MD; David Grimaldi, MD; Frédéric Pène, MD, PhD; Christophe Rousseau, MSc; Jean-Daniel Chiche, MD, PhD; Jean-Pierre Bedos, MD; Eric Vicaut, MD, PhD; and Jean-Paul Mira, MD, PhD



- 243 caucasian pts with proven IPD & no comorbidity

	Adjusted OR [95% CI]	P
SAPS II	1.068 [1.044; 1.091]	<0.0001
McCabe (1 or 2)	2.725 [1.302; 5.700]	0.0078
FcγRIIa-R131/R131	0.256 [0.097; 0.673]	0.006



PREVENTION AVE

← THIS WAY



Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation

Hypothesis : polymorphisms in *TLR* genes from the donor and the recipient may influence

susceptibility to invasive aspergillosis in stem cell transplantation

Discovery study: DNA from 336 patients and their unrelated donors (1995 – 2003)

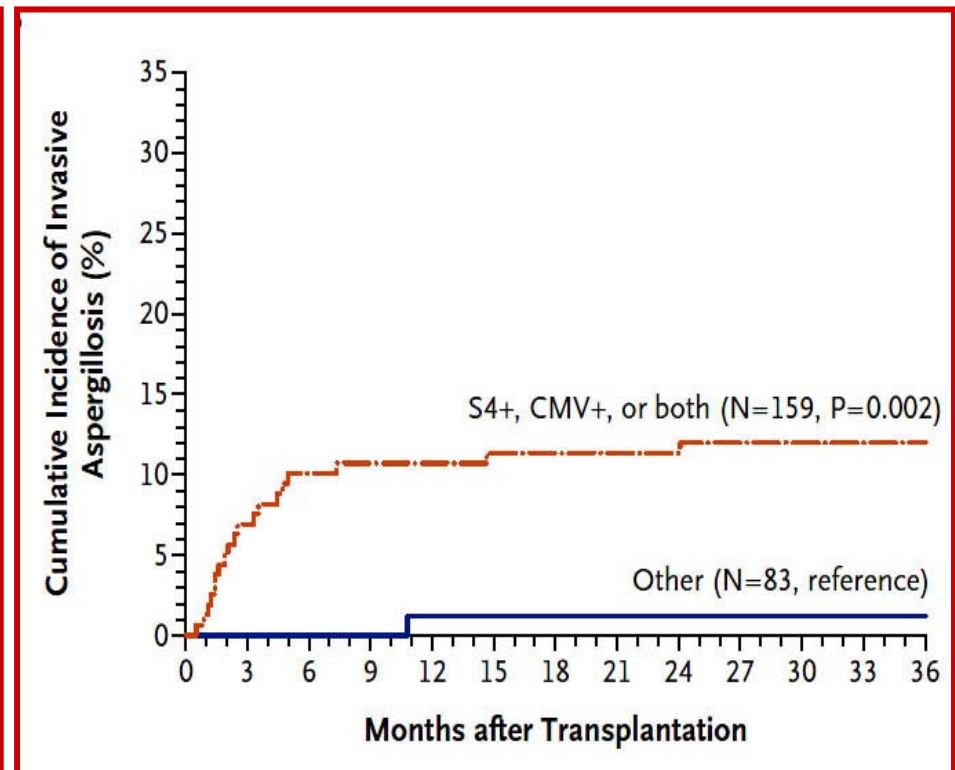
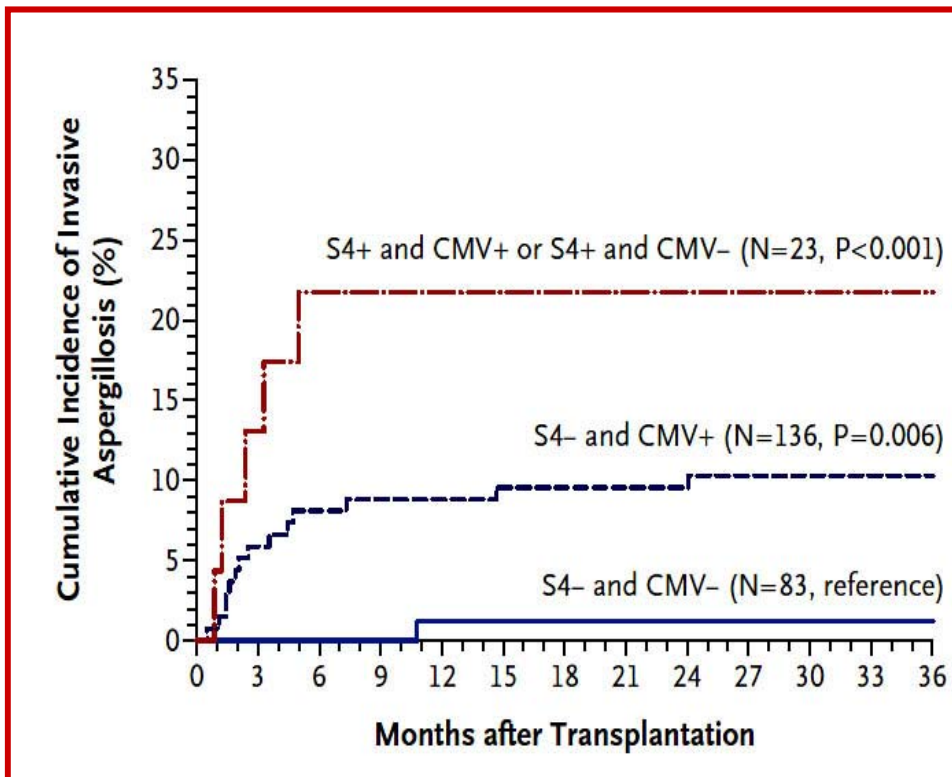
33 cases of aspergillosis

Validation study: matched case-control study with recipients of donors

103 patients with invasive aspergillosis and 263 recipients without aspergillosis.

Genes: 20 SNPs in *TLR2*, *TLR3*, *TLR4* and *TLR9*

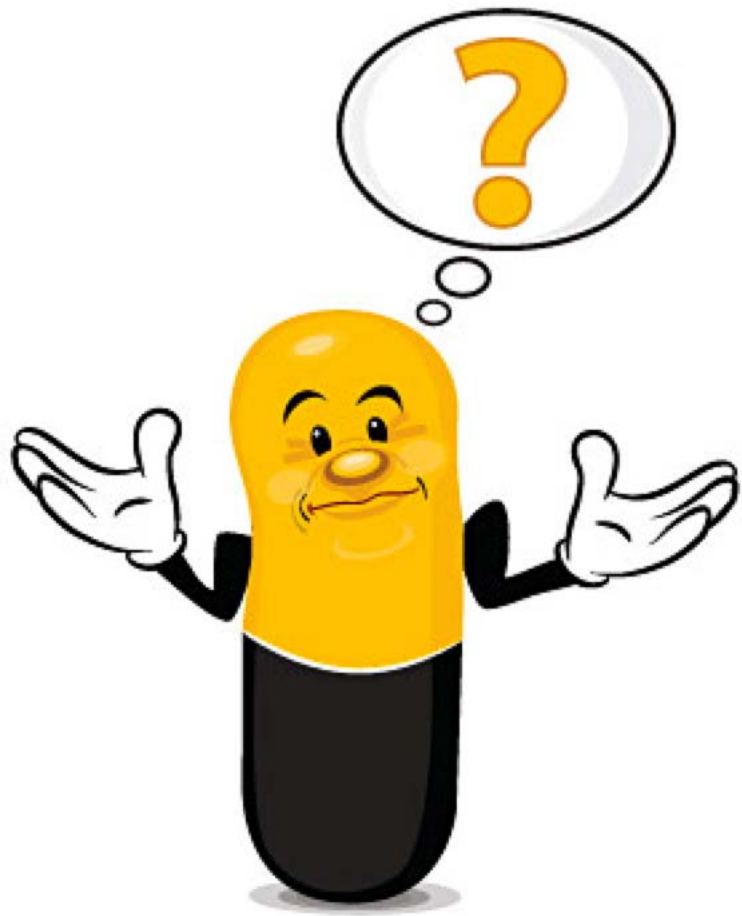
Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation



ORIGINAL ARTICLE

Genetic PTX3 Deficiency and Aspergillosis in Stem-Cell Transplantation

Cristina Cunha, Ph.D., Franco Aversa, M.D., João F. Lacerda, M.D., Ph.D.,

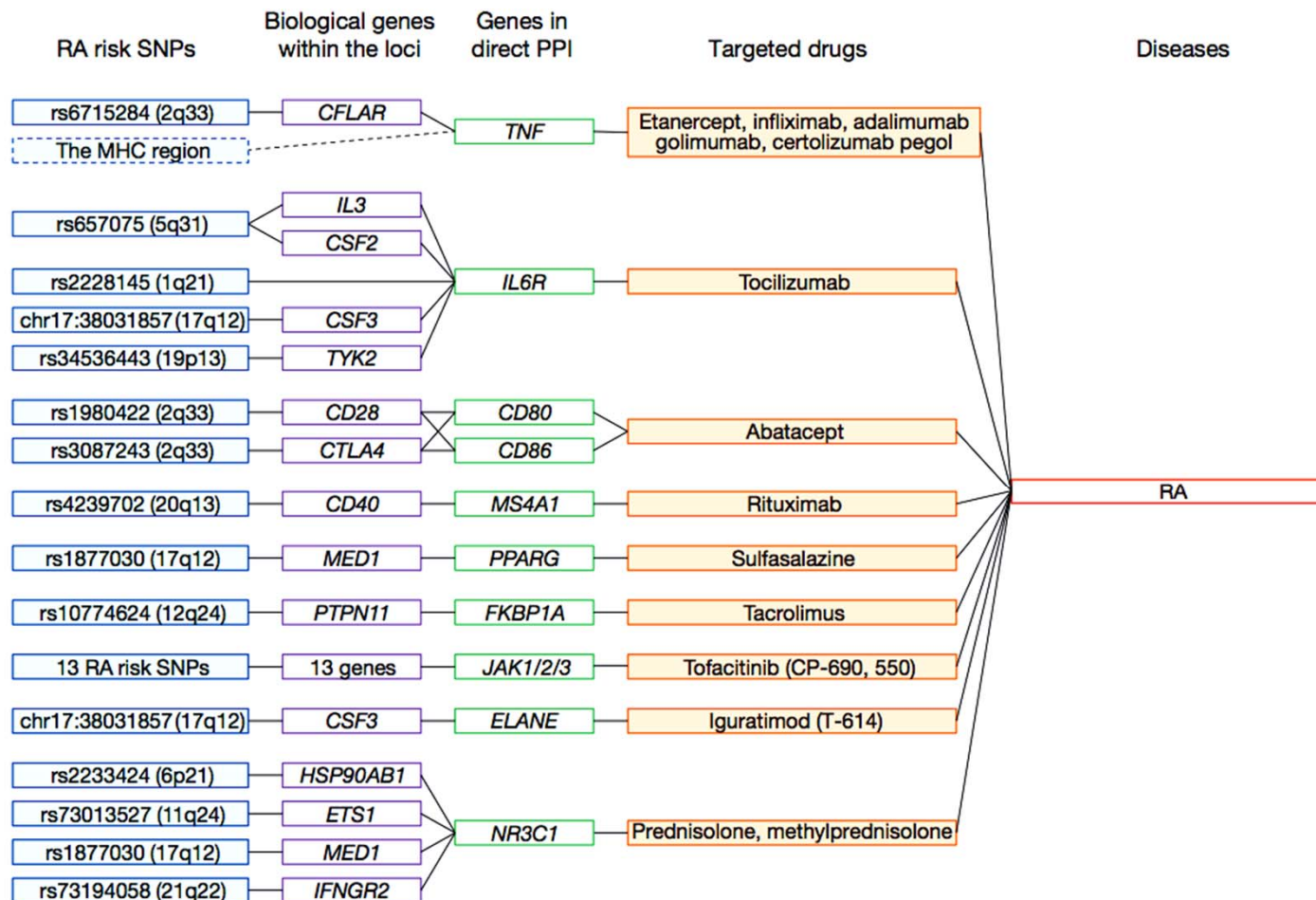


ORIGINAL ARTICLE

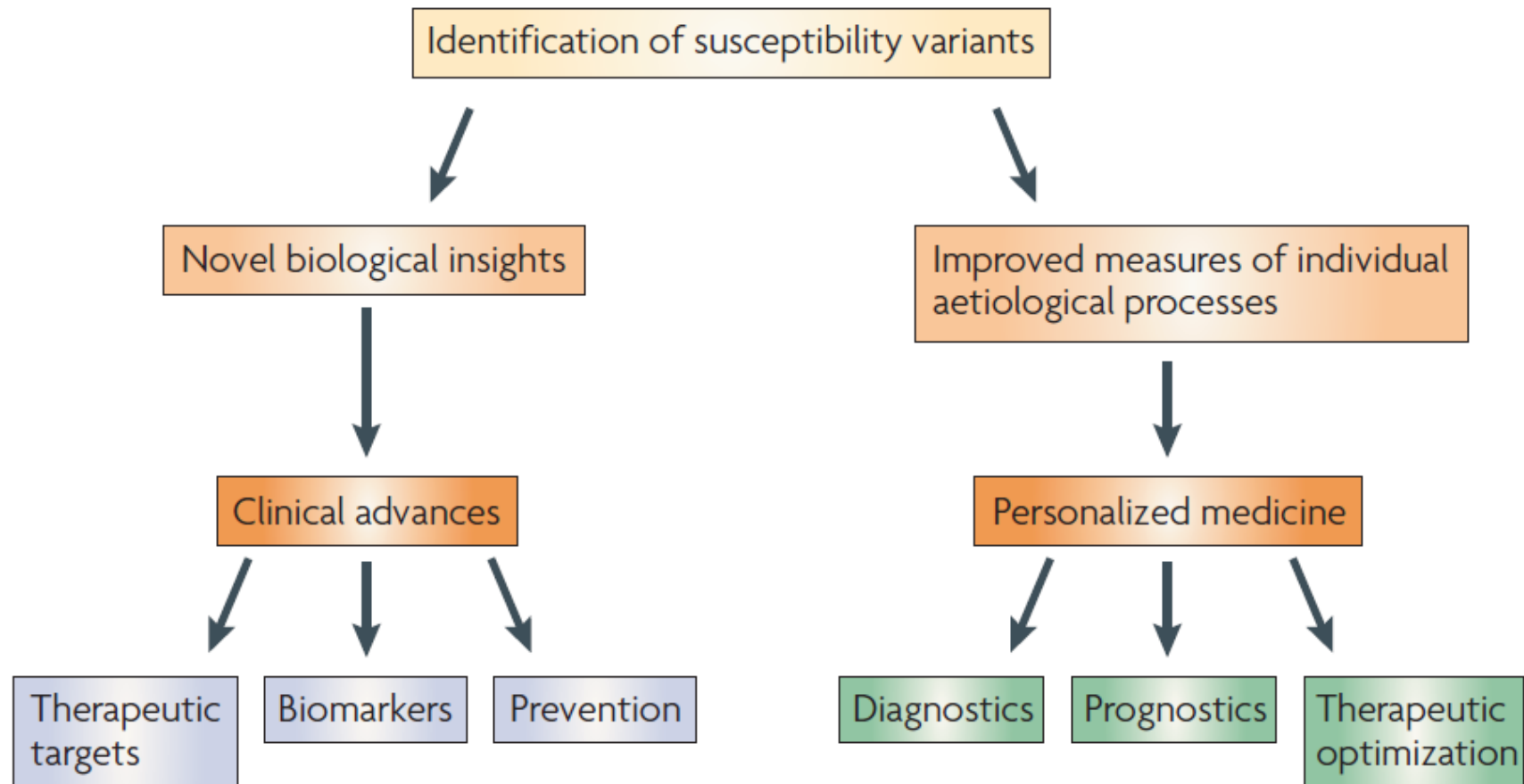
HLA-B*5701 Screening for Hypersensitivity to Abacavir

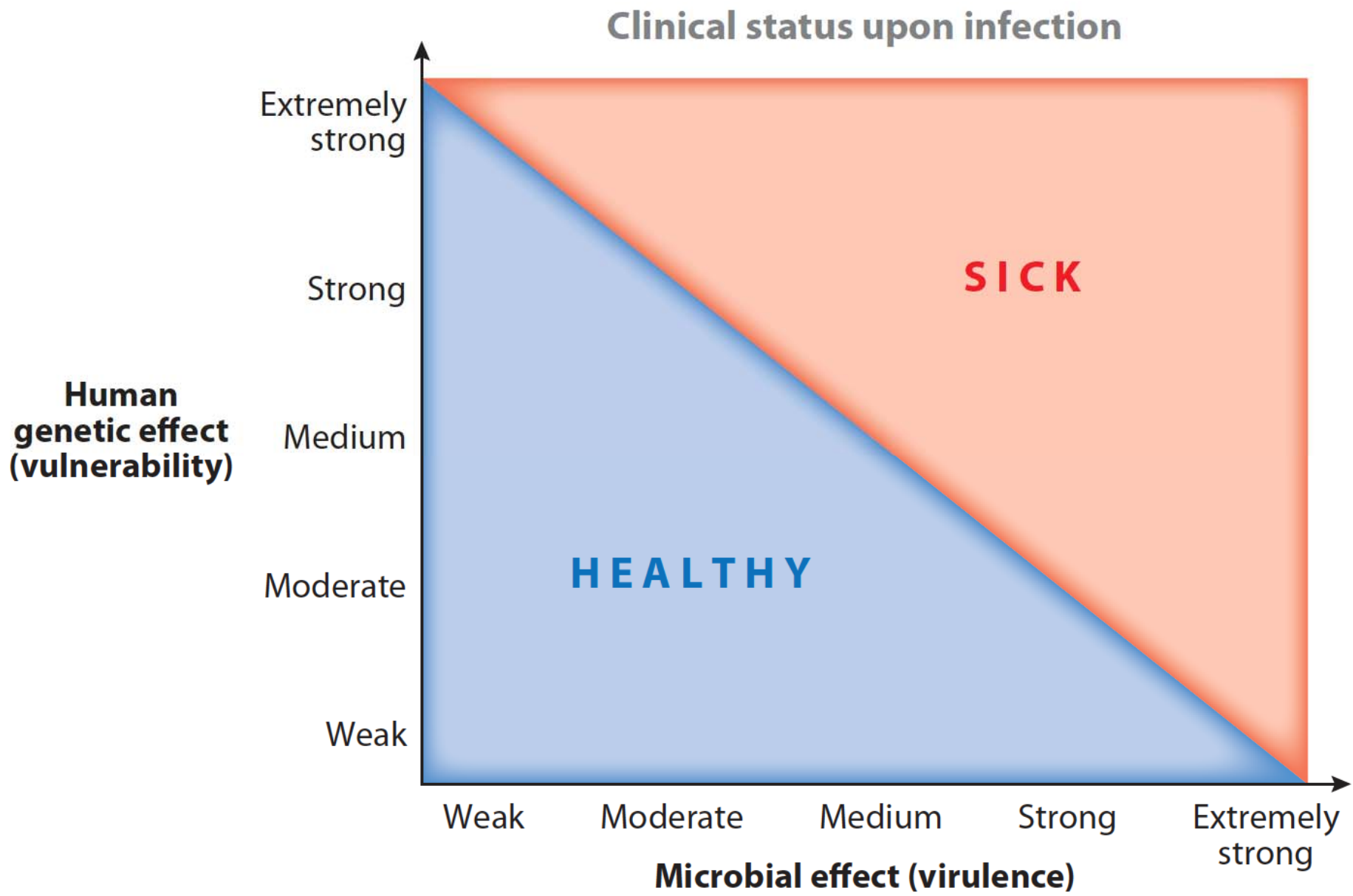
Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D.,

Genetics of rheumatoid arthritis contributes to biology and drug discovery



Clinical Translation of Immunogenetics





謝謝您
MERCi!
THANK YOU!

