



Global Development: Japanese Efforts and Views

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- この発表は演者の個人的意見に基づくものであり、医薬品医療機器総合機構としての見解を示すものではありません

Disease which spreads across the border

Countries Reporting Avian Influenza during 2004



Hien, T. T. et al. N Engl J Med 2004;351:2363-2365

The New Era of Human Genome Project

Vol 437|27 October 2005|doi:10.1038/nature04226

nature

ARTICLES

A haplotype map of the human genome

The International HapMap Consortium*

Inherited genetic variation has a critical but as yet largely uncharacterized role in human disease. Here we report a public database of common variation in the human genome: more than one million single nucleotide polymorphisms (SNPs) for which accurate and complete genotypes have been obtained in 269 DNA samples from four populations, including ten 500-kilobase regions in which essentially all information about common DNA variation has been extracted. These data document the generality of recombination hotspots, a block-like structure of linkage disequilibrium and low haplotype diversity, leading to substantial correlations of SNPs with many of their neighbours. We show how the HapMap resource can guide the design and analysis of genetic association studies, shed light on structural variation and recombination, and identify loci that may have been subject to natural selection during human evolution.

Despite the ever-accelerating pace of biomedical research, the root causes of common human diseases remain largely unknown, preventative measures are generally inadequate, and available treatments are seldom curative. Family history is one of the strongest risk factors for nearly all diseases—including cardiovascular disease, cancer, diabetes, autoimmunity, psychiatric illnesses and many others—providing the tantalizing but elusive clue that inherited genetic variation has an important role in the pathogenesis of disease. Identifying the causal genes and variants would represent an important step in the path towards improved prevention, diagnosis and treatment of disease.

diabetes)⁶, *PTPN22* (rheumatoid arthritis and type 1 diabetes)^{7,8}, insulin (type 1 diabetes)⁹, *CTLA4* (autoimmune thyroid disease, type 1 diabetes)¹⁰, *NOD2* (inflammatory bowel disease)^{11,12}, complement factor H (age-related macular degeneration)^{13–15} and *RET* (Hirschsprung disease)^{16,17}, among many others.

Systematic studies of common genetic variants are facilitated by the fact that individuals who carry a particular SNP allele at one site often predictably carry specific alleles at other nearby variant sites. This correlation is known as linkage disequilibrium (LD); a particular combination of alleles along a chromosome is termed a haplotype.

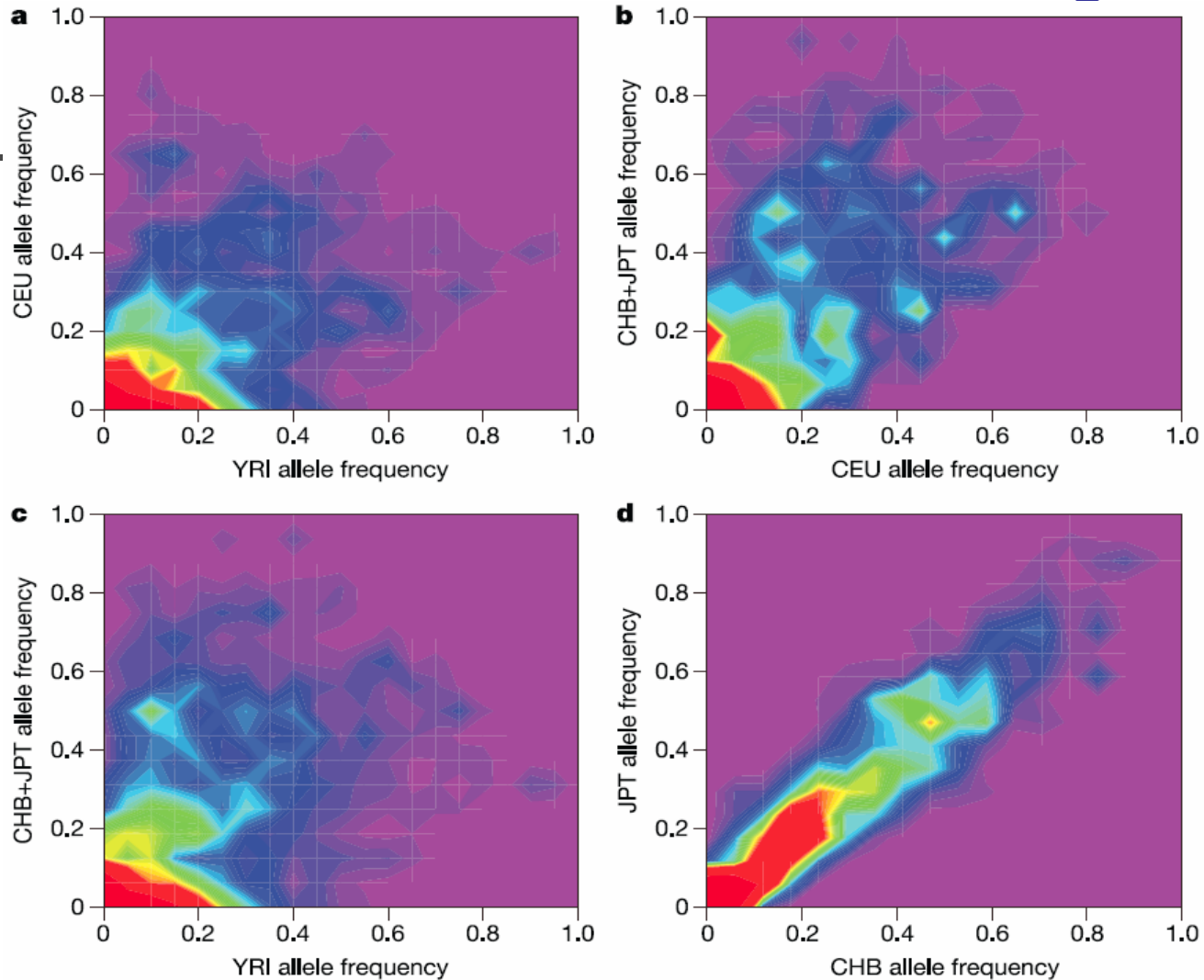
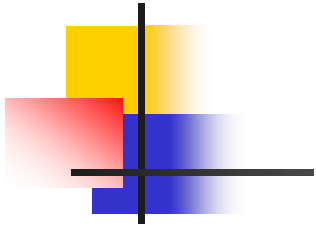
LD exists because of the shared ancestry of contemporary chromo-

The International HapMap Consortium. A haplotype map of the human genome. Nature 2005;437:1299-320

Oct. 13, 2006

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Correlation between 4 ethnic groups

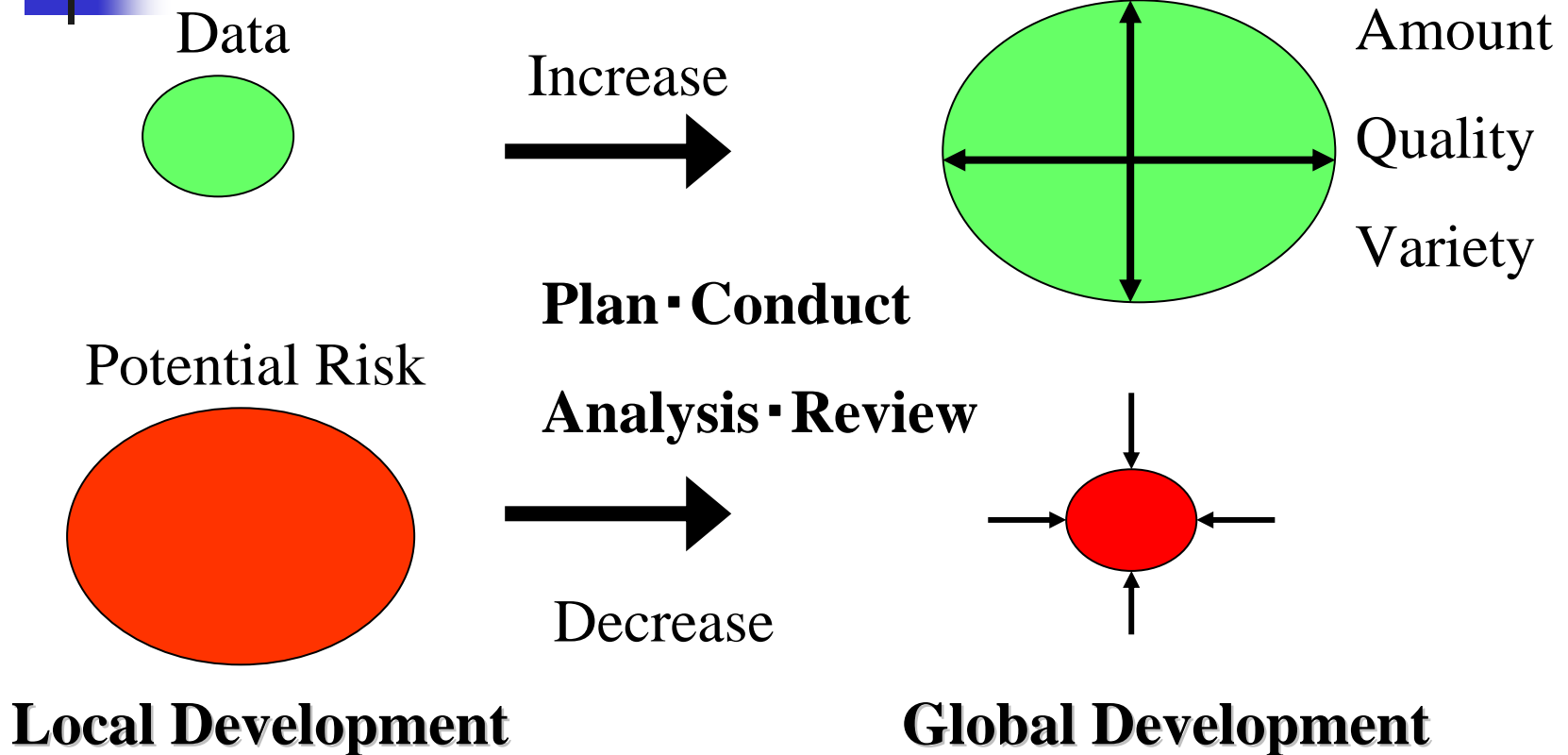


The International HapMap Consortium. A haplotype map of the human genome. Nature 2005;437:1299-320

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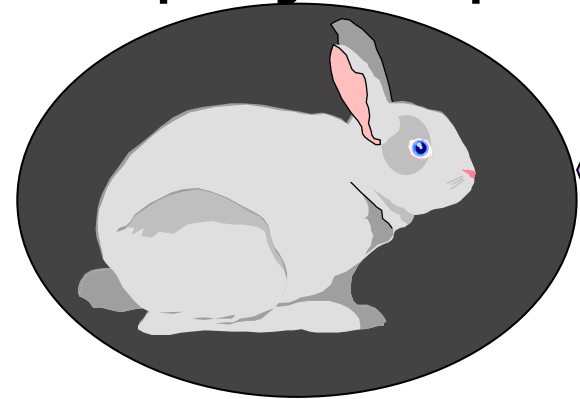
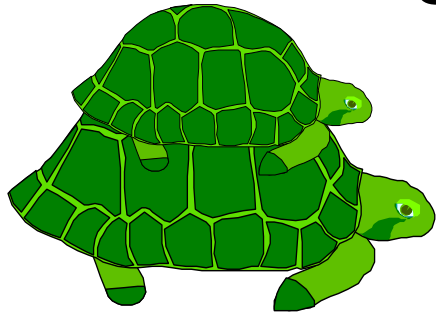
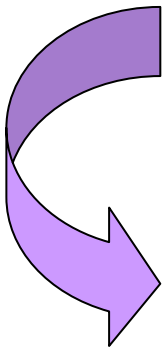
Paradigm for Global Development



Let's change the world!

- From

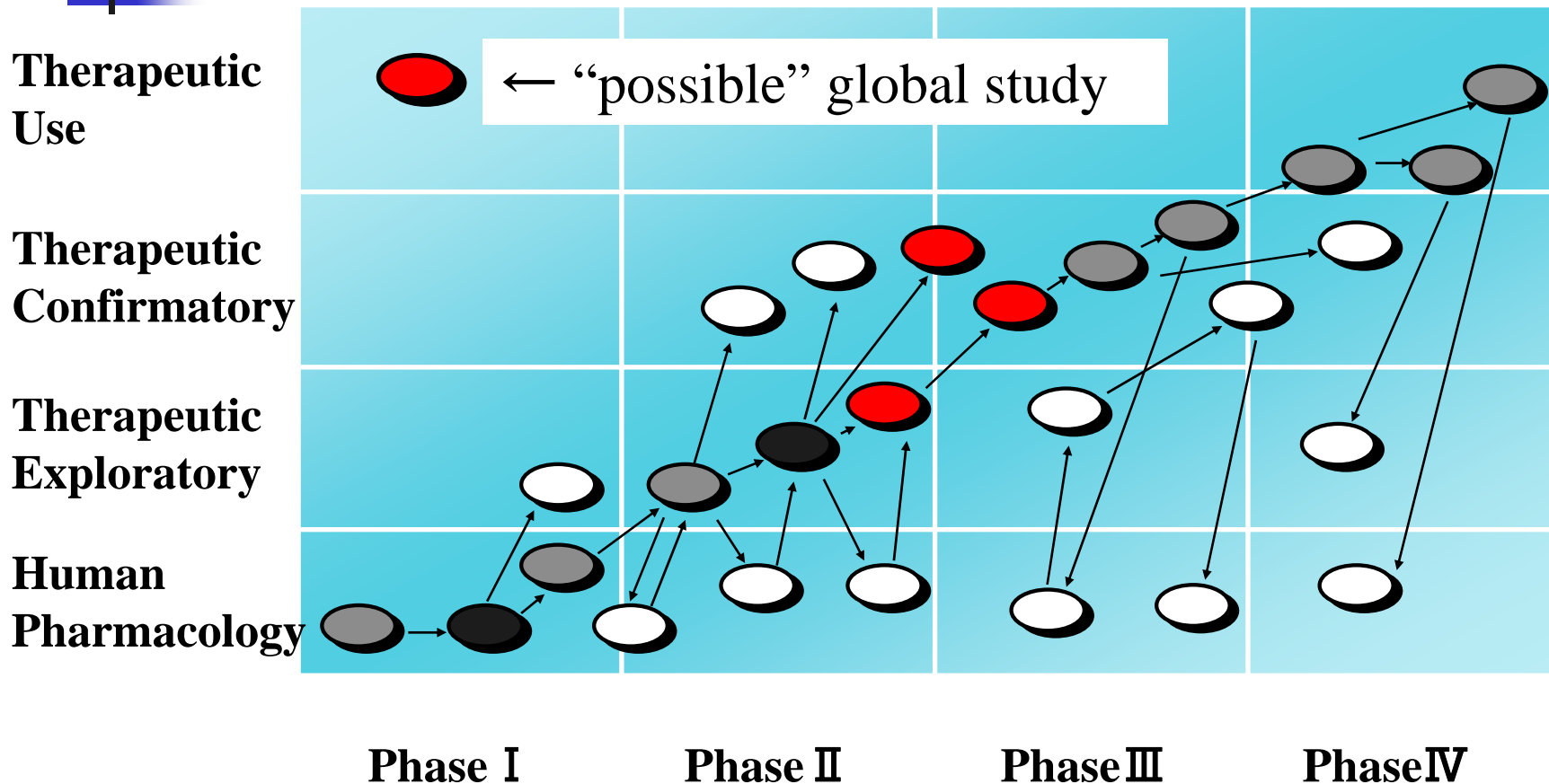
Bridging Strategy (Step by Step)



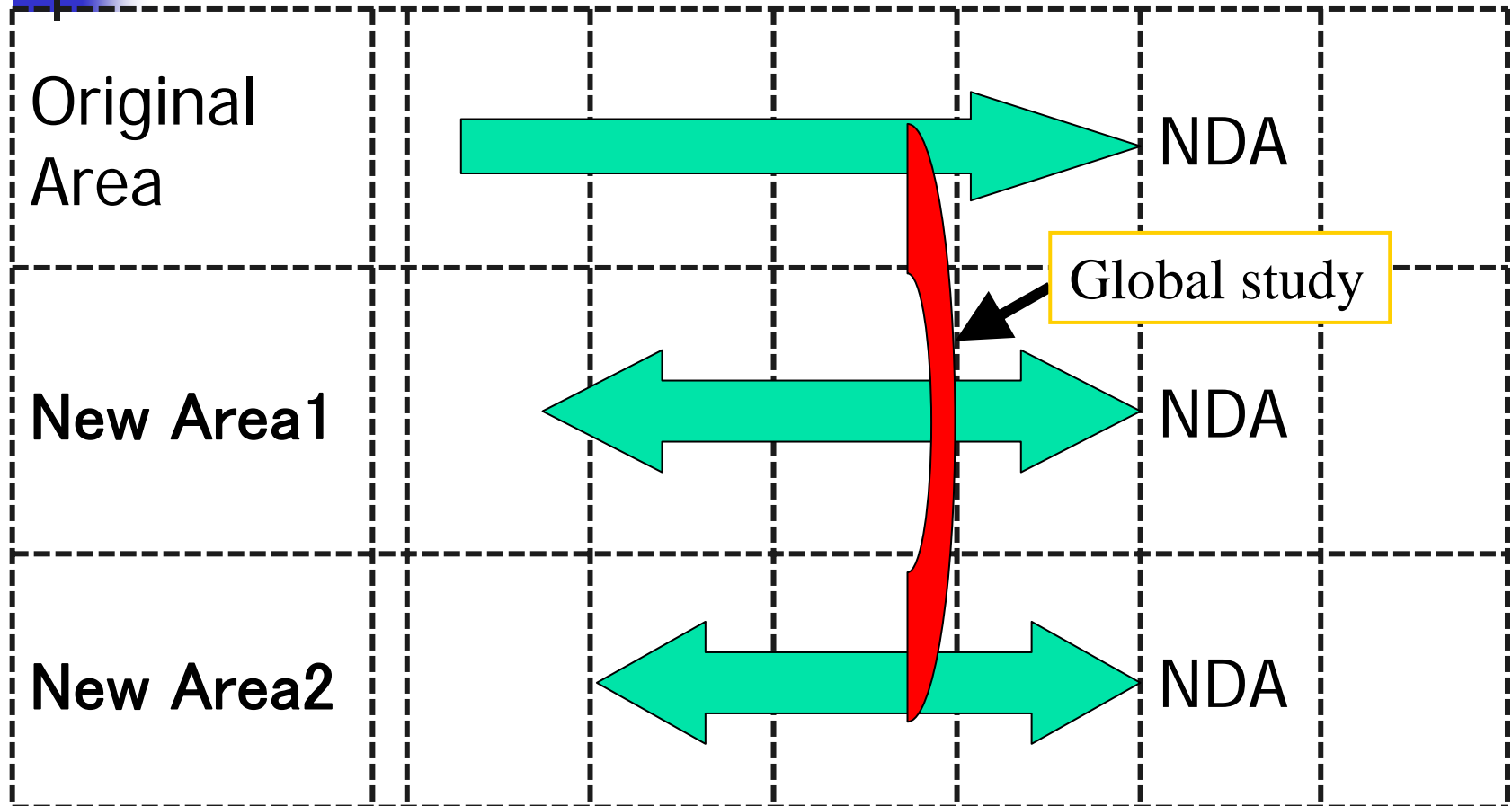
- To

Global Development/Study
(Simultaneous)

Simultaneous global development



Simultaneous global development





PtC for designing global study

- Meet Global standards (High standard of Science)
 - **Ex.** ICH-GCP compatibility, universal eligible criteria
- Sample size estimation
 - 1-global study **VS.** studies for every country/area
- Proportion of specific population
 - **Ex.** Minimum number of Japanese patient
- How to analyze consistency of data
 - **Similarity or Difference** between ethnic groups

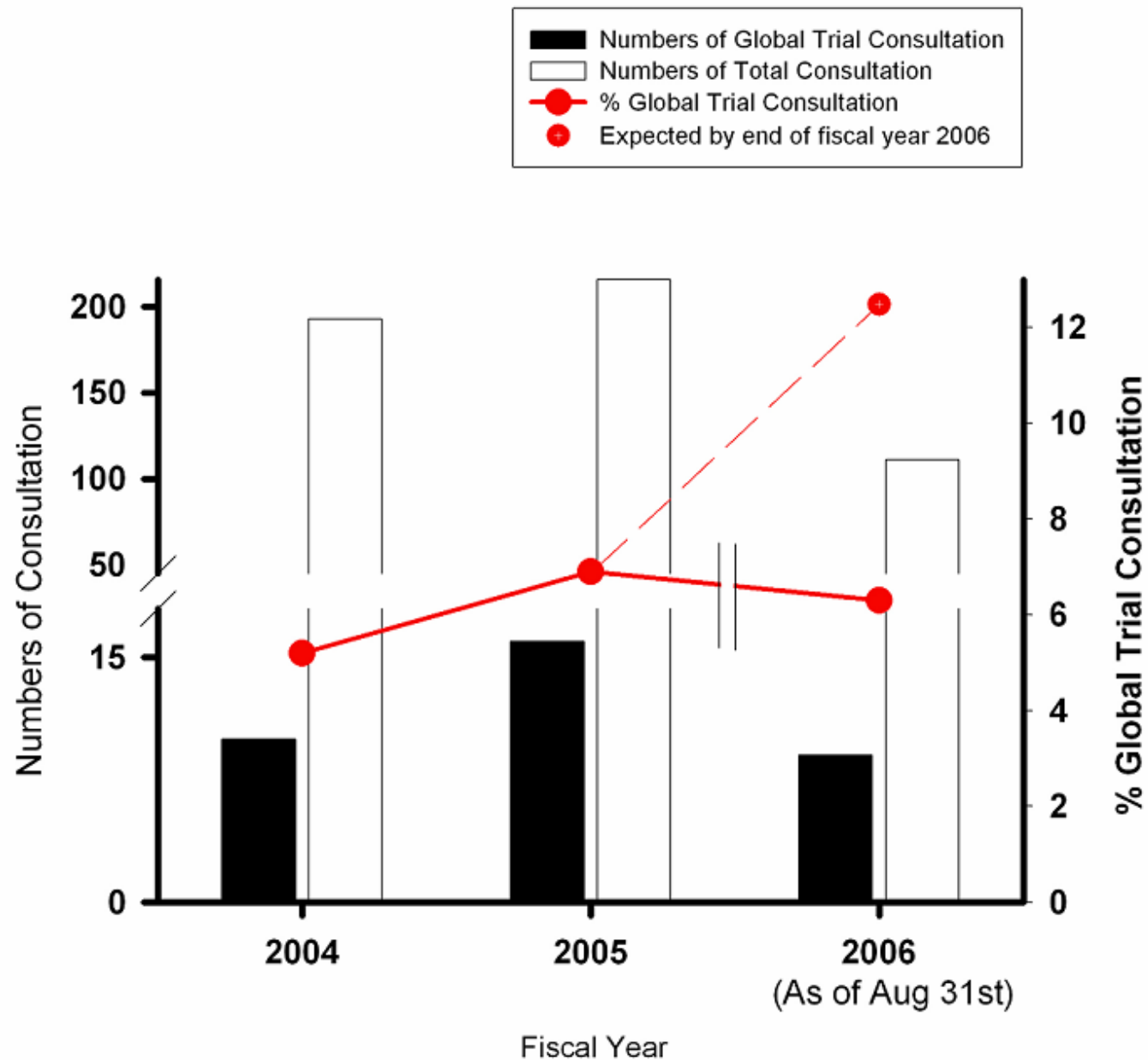


PMDA consultation about Multinational clinical trial

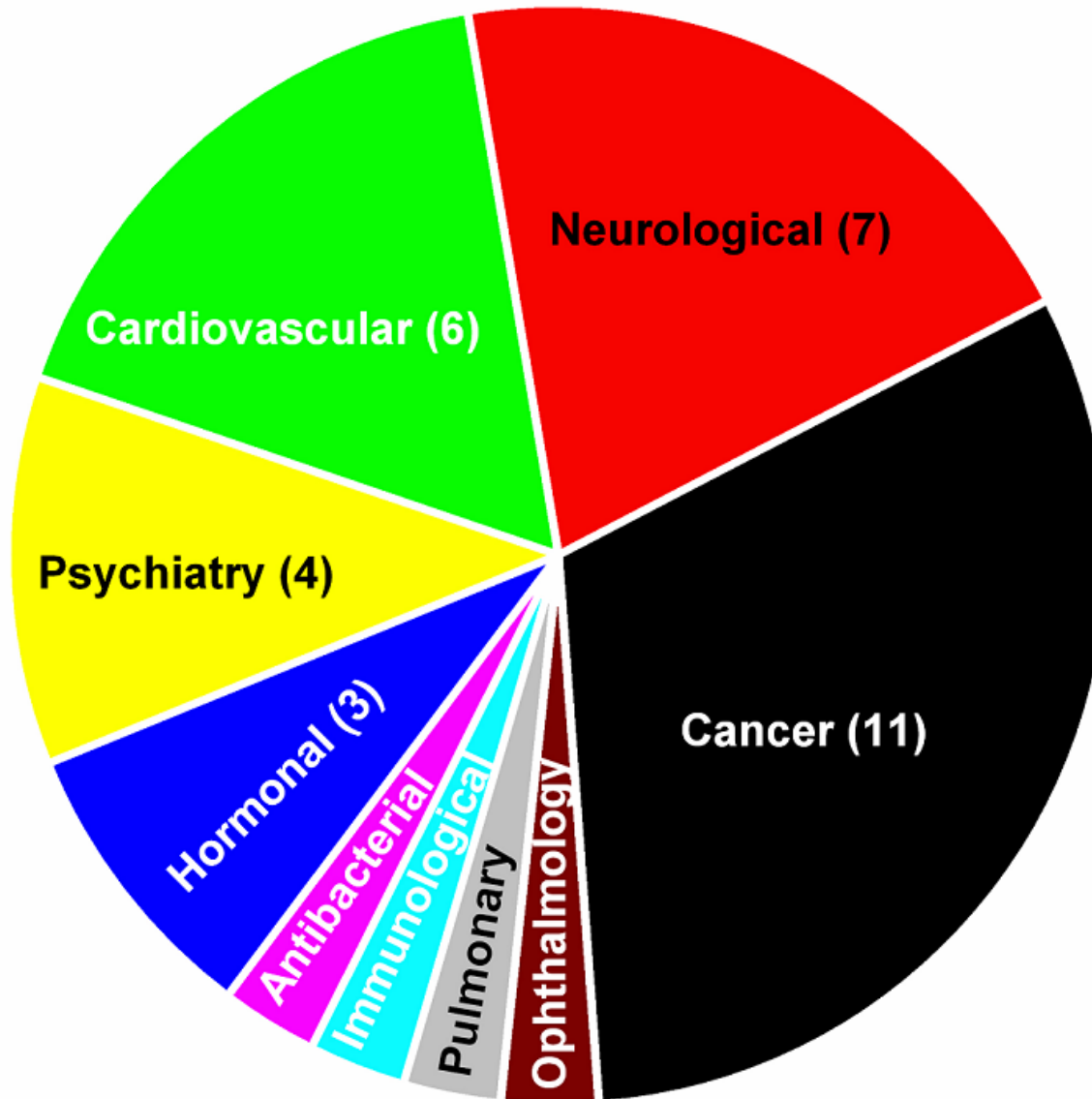
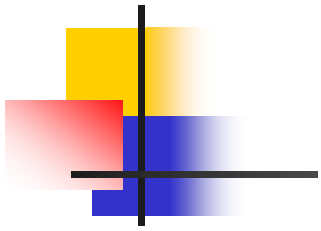
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Changes of Global Trial Consultation in PMDA between 2004-2006

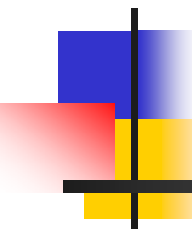


Global Trial Consultation by disease area



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Approved example of Multinational Clinical Trial

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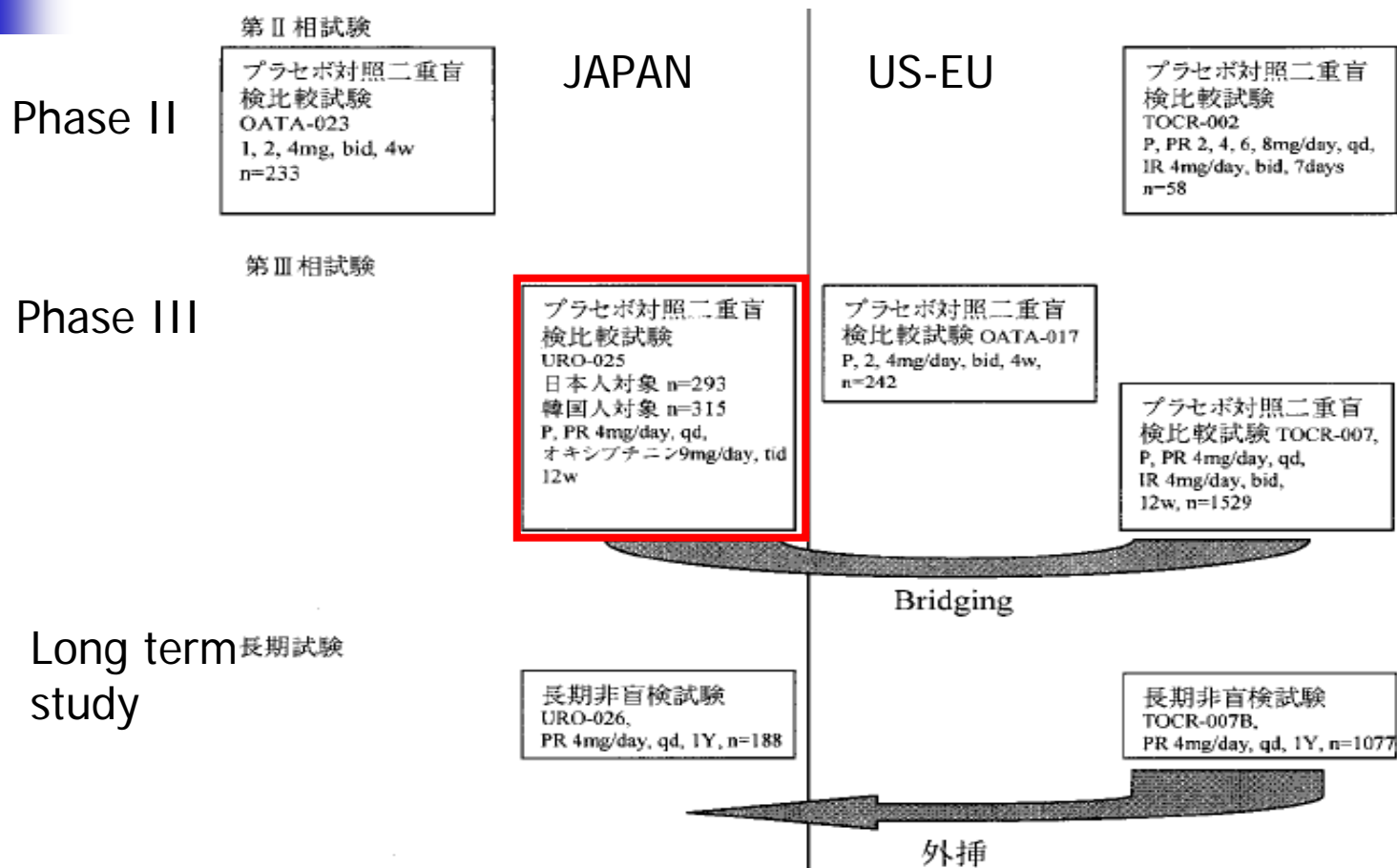
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Example from approved NDA

- 2 products approved on Apr. 20th 2006
- Detrusitol Cap 2mg/4mg (Pfizer)
 - Korea-Japan study for bridging (n≐600)
 - Tolterodine tartrate
 - OAB
- NU-LOTAN 25/50 (BANYU)
 - RENAAL study as global study (n≐1500)
 - Losartan potassium
 - Nephropathy in Type 2 Diabetic Patients

Detrusitol Clinical data package

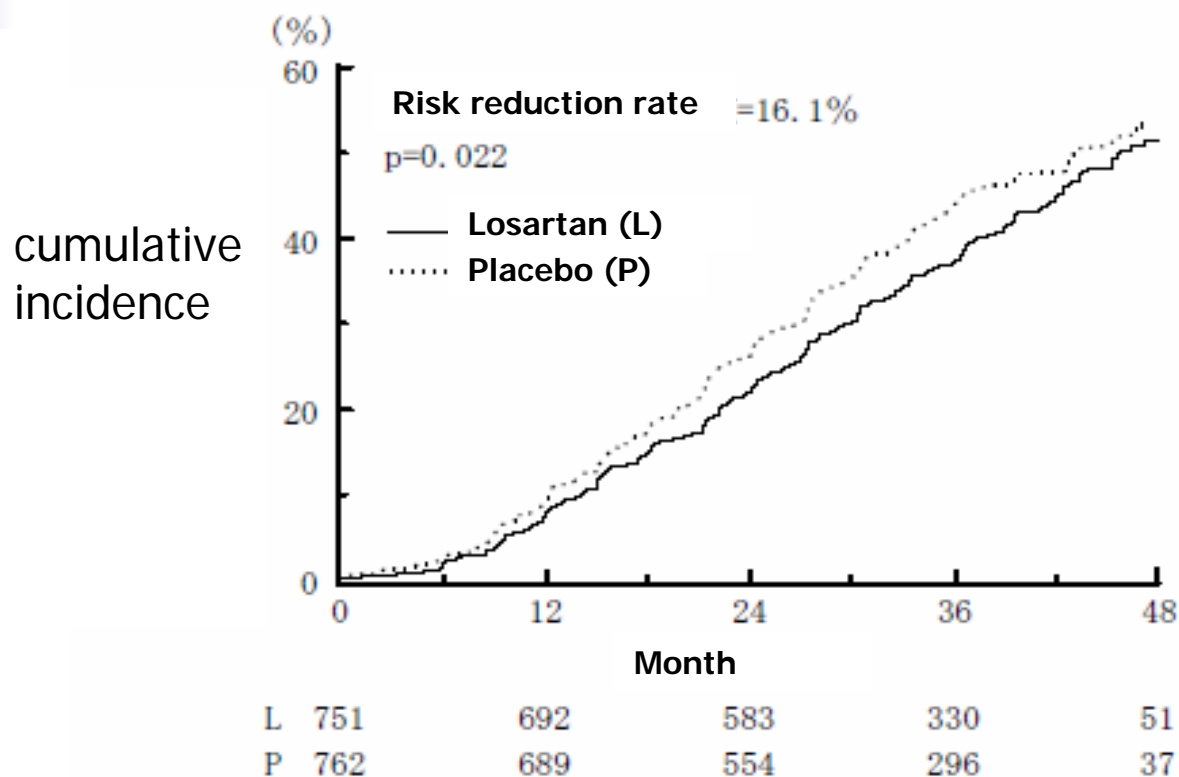




Example from PMDA review report

- Clinical efficacy and safety
 - Japanese + South Korean \doteq Caucasians
 - Successful Bridging
- Dose setting in Japanese patients is not made about PR capsule
 - Dose setting about IR capsule have failed
- Long term western clinical data have extrapolated in Japanese patients

Example from PMDA review report



Kaplan-Meier curve of cumulative incidence of primary composite end-point (doubling of CCr + ESRD + Death)



Example from PMDA review report

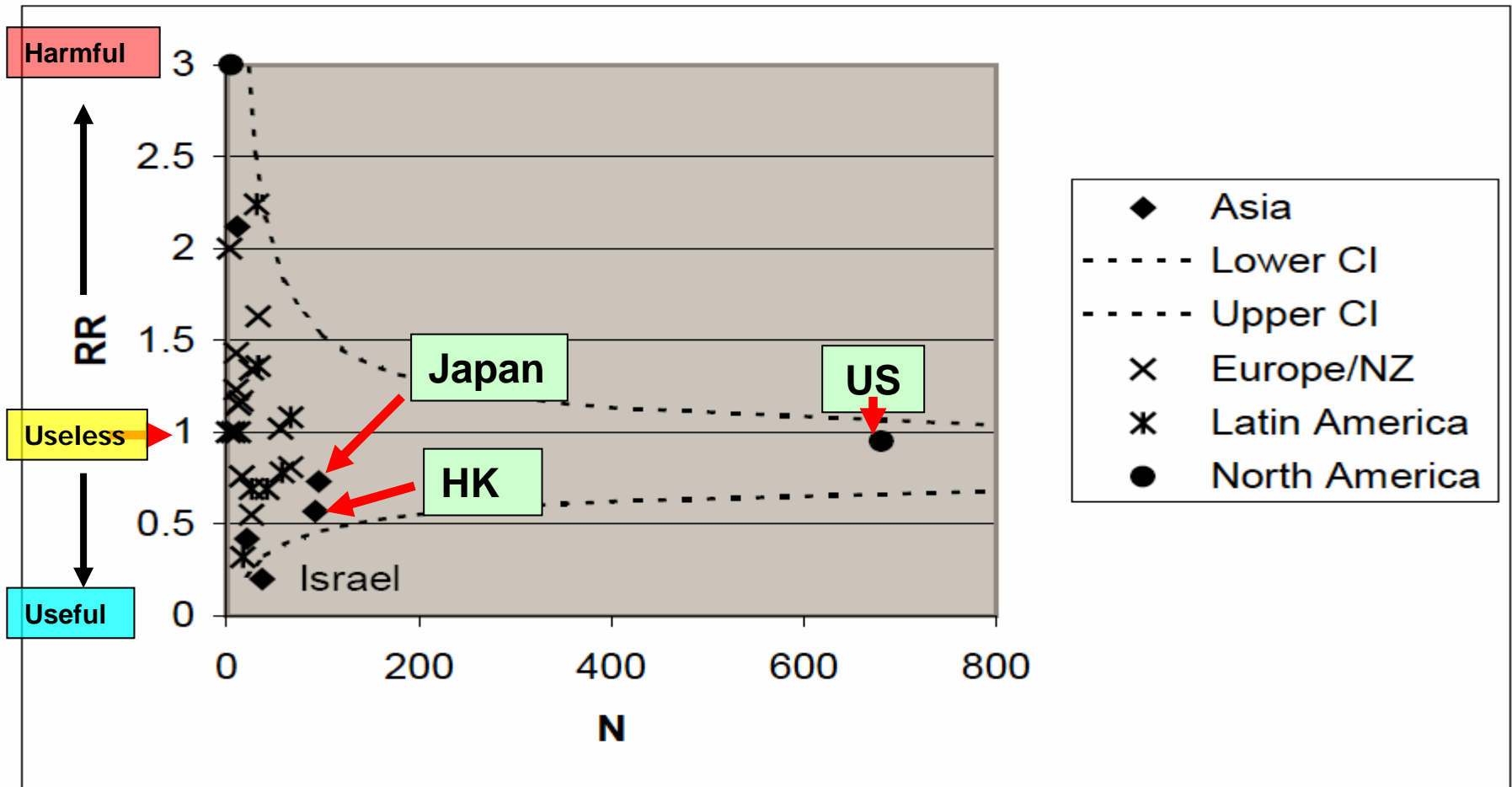
Adjusted Hazard Ratio using protein in urine data

	country	Losartan			Placebo			尿蛋白層別レベルで調整した解析	尿蛋白対数値を連続変数として調整した解析
		N	k	%	N	k	%	HR (95% C.I.)	HR (95% C.I.)
Total	全体	751	327	43.5	762	359	47.1	0.84 (0.72~0.98)	0.81 (0.70~0.94)
Japan	日本	44	22	50.00	52	34	65.38	0.80 (0.47~1.36)	0.64 (0.37~1.10)
HK	香港	46	19	41.30	46	27	58.70	0.50 (0.27~0.90)	0.41 (0.22~0.75)
US	米国	338	142	42.01	348	149	42.82	0.95 (0.76~1.20)	0.93 (0.74~1.18)

N : 解析対象例数、k : エンドポイントを発現した症例数、HR : Hazard Ratio

Example from FDA NDA review report

Relative Risk of Primary Composite Endpoint by Country.





Usefulness of Global Clinical Data

- **Points to consider before planning**
 - The study should be Planned & conducted in keeping with ICH-GCP
 - Necessary to accept on-site inspection
 - Sub-group analysis among region and ethnic group should be available
 - Give a detailed description of the background of the study



Pros & Cons of Asian studies

- **Low cost/High performance clinical development (except in Japan)**
- **Rapid improvement in GCP compliance**
- **Genetic similarity**
- **Difference in**
 - Medical practices, insurance system
 - Physician & Patient behavior, mentality

Risk in the front line

- First in Human Trial-



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Health news

The Times March 16, 2006

As killer cells ravage victims, relatives pray for a miracle

BY NIGEL HAWKES

Trials were meant to find new way to tackle leukaemia by boosting the body's immune system

THE drug involved in the trial that resulted in six volunteers becoming critically ill is designed to activate the killer cells of the immune system. TGN1412 appears to have done so in this case to spectacularly damaging effect.

It belongs to a class of biological agents known as monoclonal antibodies (MABs), which were discovered at Cambridge



Marian Rauford, who said her

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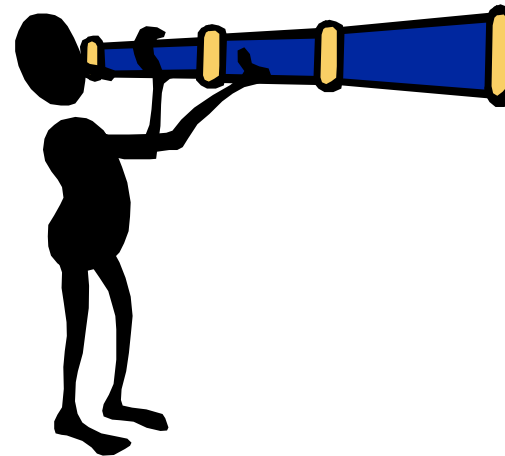
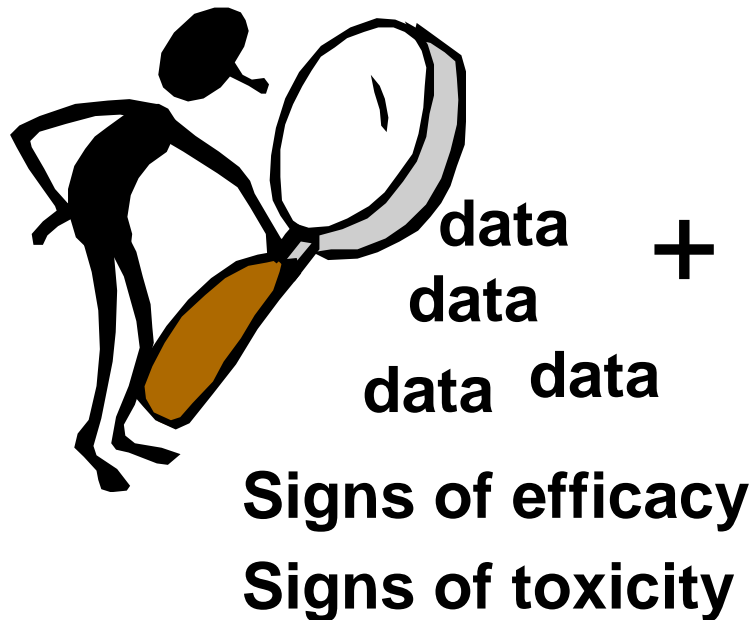
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Coexistence of a future view and bear scrutiny



Unmet medical needs

innovations

research

development

NDA review

Post-marketing

“for the welfare of patient!”

Very near future style of Global Study (Asia + US + EU)

- Asian Study is important for the global people of Asian decent
- Positive dialog about Asian Clinical Trial Network
- Let's try for a win-win situation

Thank you for your attention.

