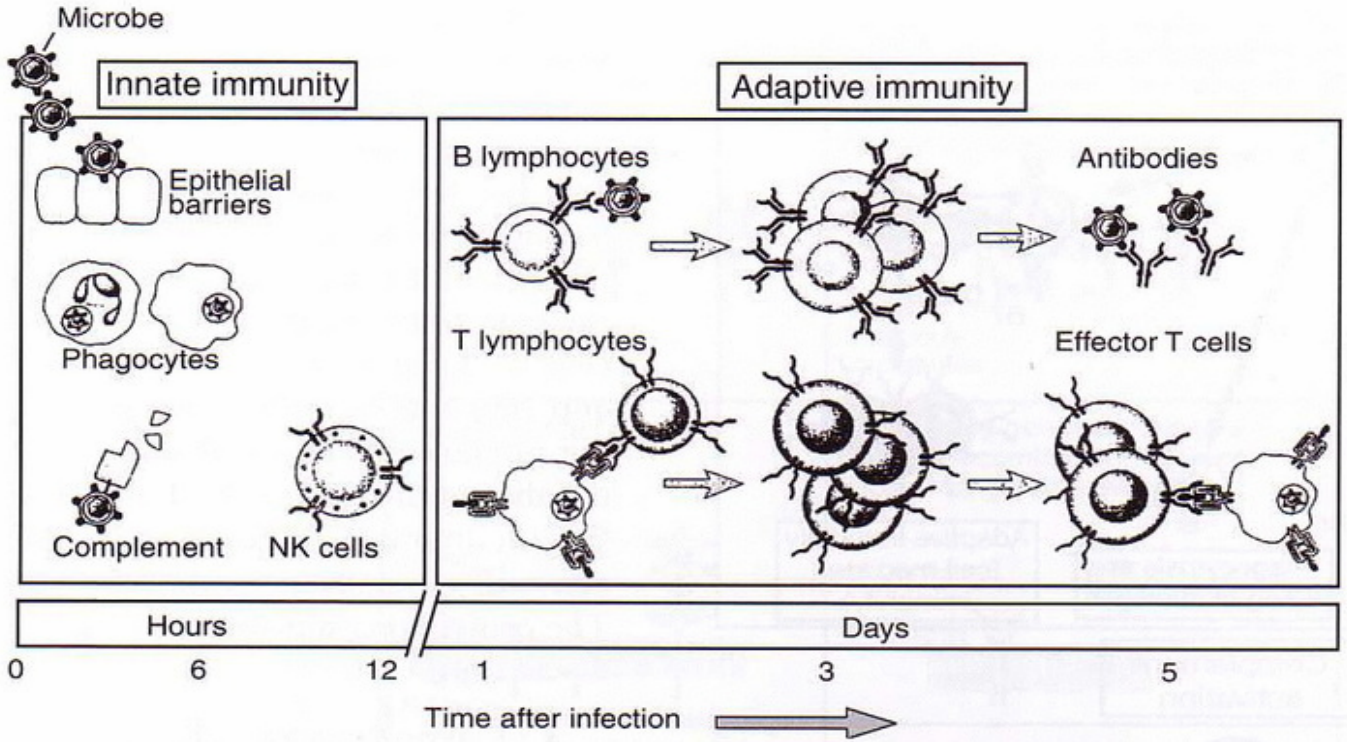
The Evolution of the Major Histocompatibility Complex (MHC)

What is MHC?

- the major histocompatibility complex
- a multigene family
- the most polymorphic genes known
- part of adaptive immune system
- wikipedia

The Adaptive Immune System:

- Pathogen and antigen specific response
- Lag time between exposure and maximal response
- Cells are called lymphocytes
- Exposure leads to immunological memory
- Present ONLY in vertebrates



http://personalpages.manchester.ac.uk/staff/j.gough/lectures/TIB/3imm_intro/page4.htm

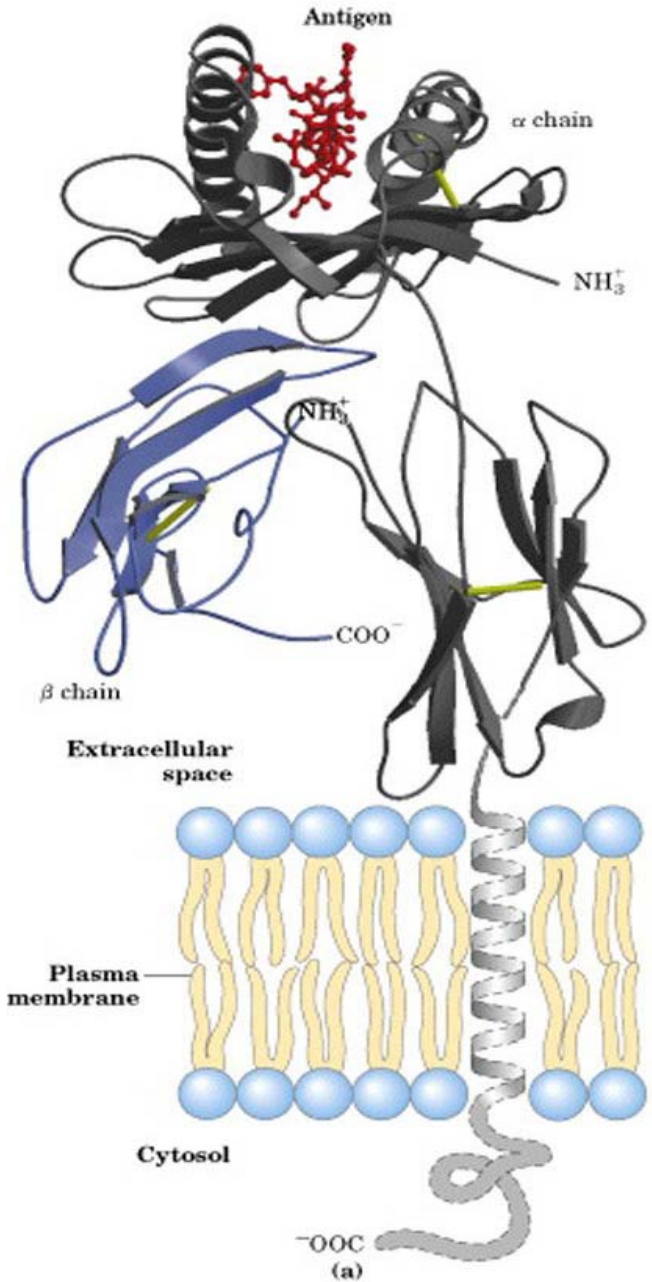
MHC

- name: "major" because
  a. it failed to pass the test for corporal
  b. it's really important
  c. it's located on a major chromosomal area
  d. it has reached the legal drinking age

- name: "histocompatibility" because
  a. it's really long and important sounding
  b. for it's role in graft rejection
  c. not just friends, not just lovers, but TRUE compatibility at the tissue level*

     *just $39.95 for one month subscription

  d. face it, molecular biologists just aren't that good naming things



MHC

- Codes for cell surface proteins that bind and present antigen fragments to T-cells (link)
- Peptide binding region
  - site of most variation

http://courses.cm.utexas.edu/archive/Spring2002/CH339K/Robertus/overheads-1.htm

MHC

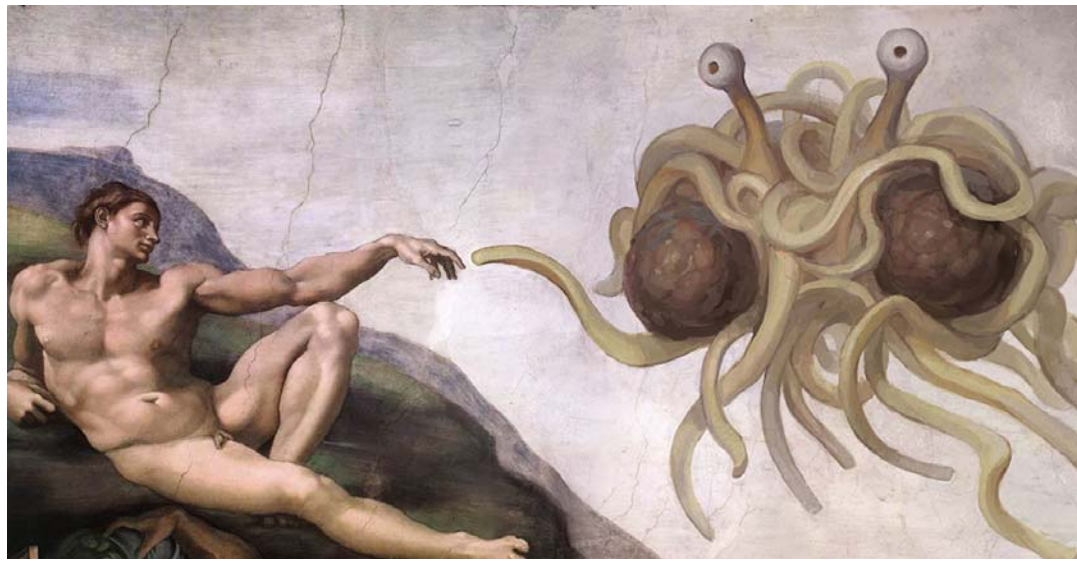
Class I

1. expressed surface of nearly all nucleated cells
2. present endogenously derived peptides
3. associated with defense against intracellular pathogens--VIRUSES
4. contains classical and non-classical genes

Class II

1. expressed on antigen-presenting cells
2. present exogenous antigens
3. associated with defense against extracellular pathogens—BACTERIA...
4. just one type

Levels of MHC Evolution



- origin of MHC
- evolution of multigene families
- theories to explain MHC polymorphism
- selection on MHC

Introduction: The major histocompatibility complex is a set of genes that are an integral part of the vertebrate adaptive immune system. MHC genes code for proteins that recognize and bind peptides. These peptides are displayed on the cell surface to T-cells which initiate an immune response if the peptides are not recognized as self. (link)

Phenomenon: The MHC has three paralogous regions in the human and other genomes. What and when is their origin?

Hypothesis: The MHC and adaptive immune system emerged as a result of large scale, possibly genome wide, duplication that occured during chordate evolution, before the jawed vertebrate radiation.

Theory: Susumu Ohno first suggested that large scale genome duplications occured early in chordate evolution, resulting in the vertebrate's larger genome size, and that such duplications played an important role in evolution. The existence of 3 MHC paralogous regions suggests that duplication of a "proto MHC" region relaxed functional constraints on one of the four regions, allowing it to evolve into the modern MHC. This "proto-MHC" should be present in all vertebrates (link), and in closely related non-vertebrates.

Tests: Reconstruct a minimal proto-MHC region based MHC paralogous genes and the MHC-like chromosome of cephalochordates. Then compare the proto-MHC with the genomes of extant species (Danchin and Pondtarotti, TREE 20(12) 587-591).

Results: see following slides. Evidence for two large scale duplications that included a proto-MHC region which existed prior to the origin of vertebrates.

MHC ‘Big Bang’

- MHC and adaptive immune system emerged abruptly
- emerged as a result of large-scale en bloc or chromosomal duplication
- large number of genes exist in four paralogous regions, supporting hypothesis that there were two large scale duplication events early in verterbrate evolution
- 3 MHC-like paralogous regions ID’d in humans
- distribution of MHC orthologs in phylogeny supports the existence of a common ancestor

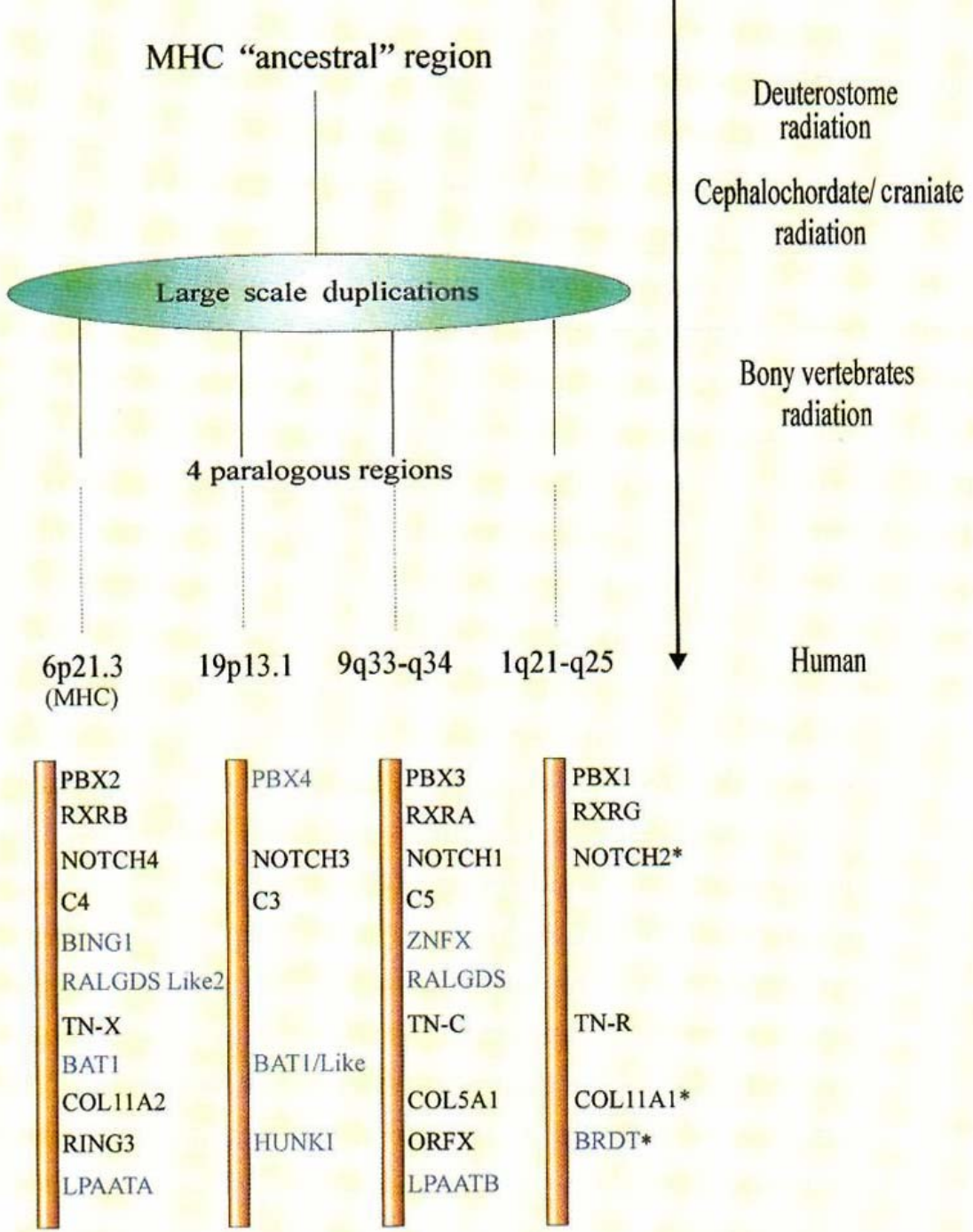


Fig. 2. Large scale duplication of the ancestral MHC region, and description of the four paralogous regions. Only genes that have occurred via block duplication are indicated. Genes in black print were described in earlier work (15) and those in blue are described in the present study. *COLL11A2*, *BRDT* and *NOTCH2* map respectively to chromosome 1p21, 1p21-p22 and 1p13-p11.

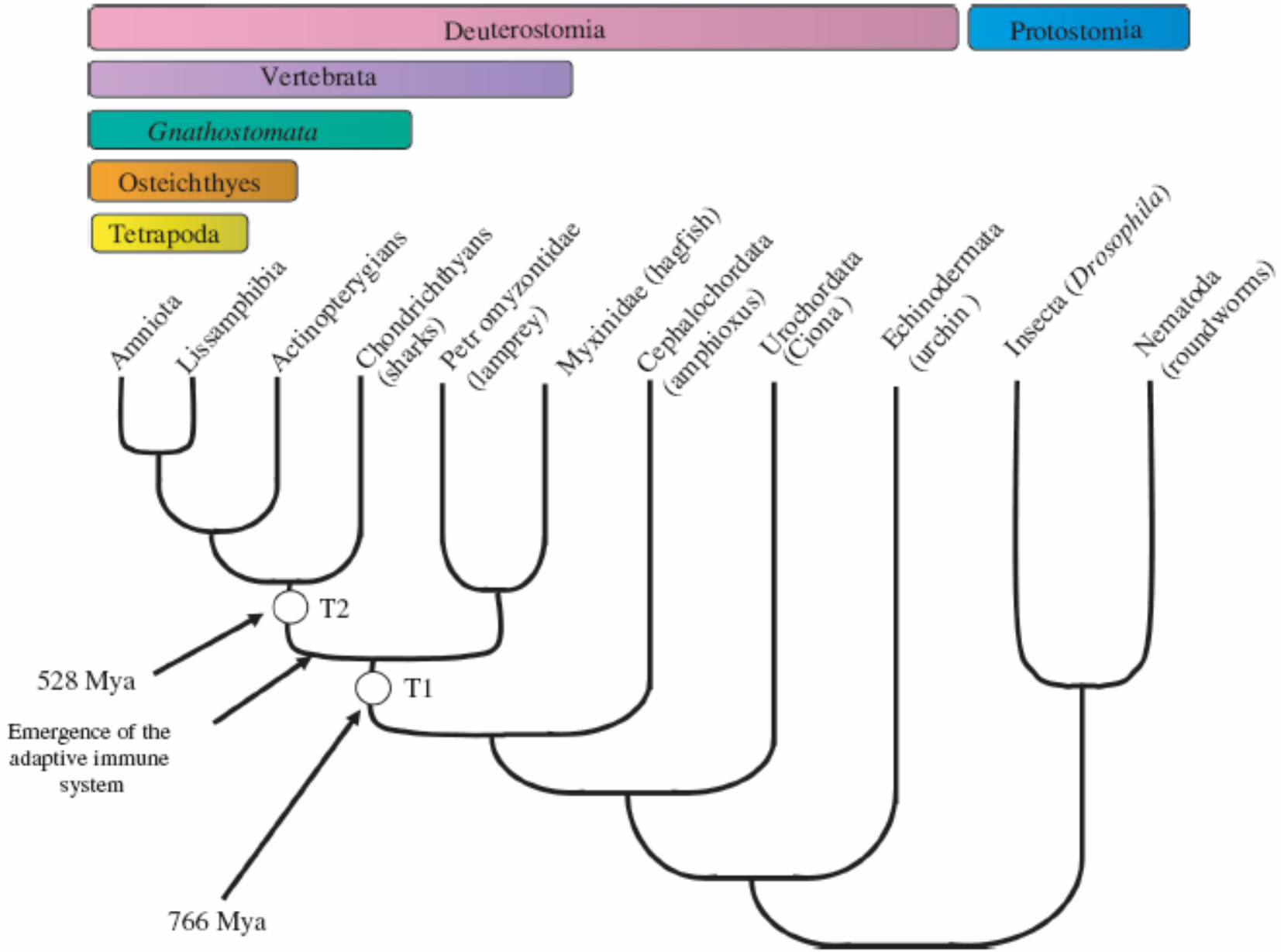


Fig. 1. Metazoan phylogeny. A simplified general metazoan phylogeny is shown. The arrows indicate en bloc duplication events (labeled T1 and T2) in the proto-major histocompatibility complex (MHC) and the emergence of the adaptive immune system, including the MHC.

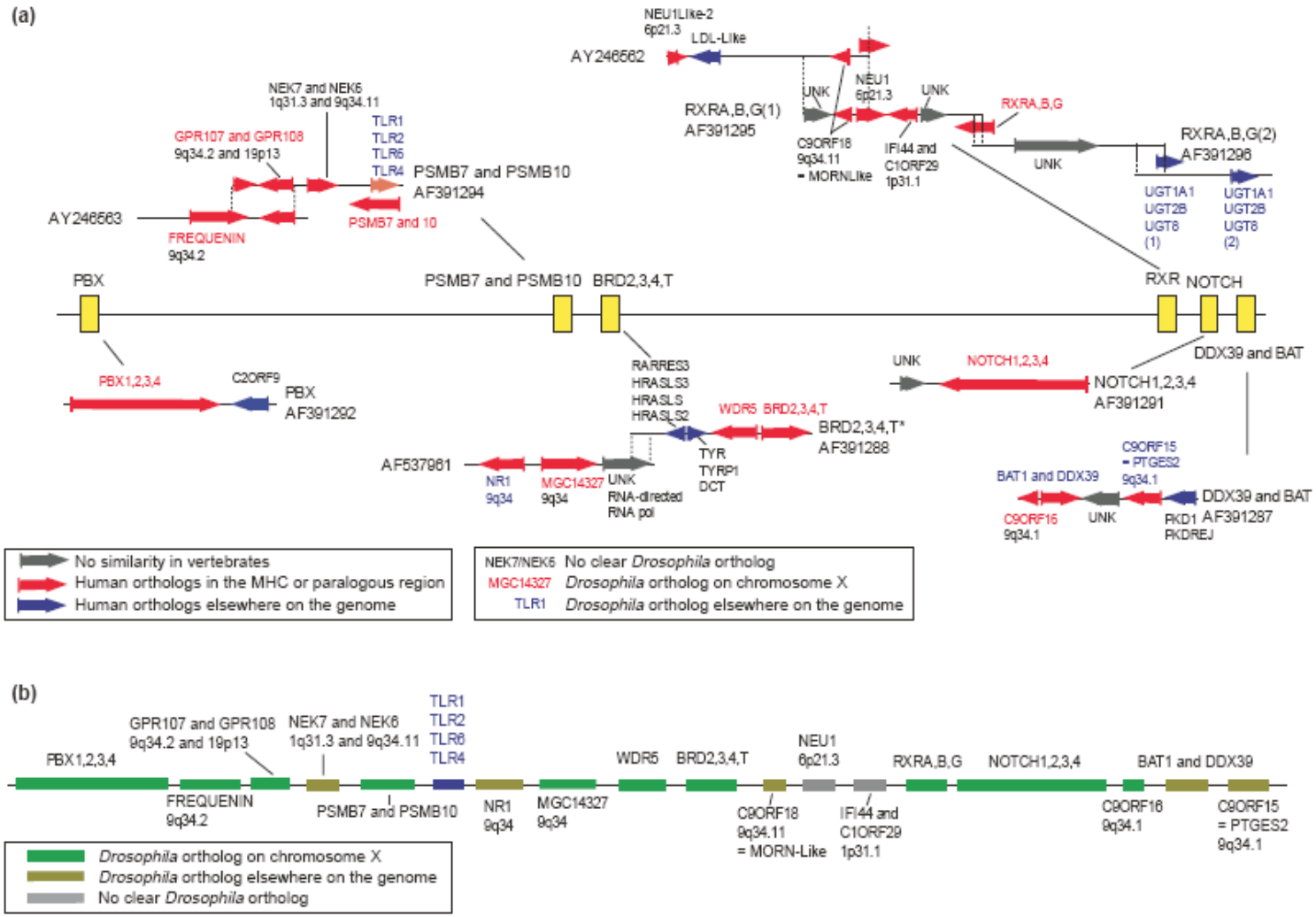


Figure 1. Amphioxus major histocompatibility complex (MHC)-cosmids organization and Ureuchordata proto-MHC region. (a) Minimal gene content of the cephalochordates MHC-like region. The relative positions of the amphioxus MHC-like cosmids are given according to fluorescent in situ hybridization (FISH) experiments performed by Castro et al. [4]. Yellow boxes indicate FISH-anchoring points of the cosmids along the amphioxus chromosome. Because the relative orientation of these cosmids is unknown, the gene order shown here is arbitrary along the chromosome but correct within the contig. Gene names are given relative to their corresponding human orthologs (their position on the MHC and paralogous regions is indicated). Genes in black and represented by 'UNK' have not been confirmed in anyother species and thereforemight be false predictions. (b) Reconstruction of the Ureuchordata proto-MHC region deduced from genes that are conserved in the MHC-like regions of vertebrates and cephalochordates. This region represents a minimal evaluation of the gene content of the euchordates ancestor (Ureuchordata) proto-MHC region. The gene order is given according to cephalochordates MHC-like region (Figure 2a) but is not thought to represent the actual ancestral-gene order, which is difficult to infer as a result of extensive intra-chromosomal rearrangements and poor gene-order conservation compared with gene content. Gene names are given according to their human counterparts. Trends in Genetics. 2004. 20(12): 587-591.

Just how old is the MHC region?

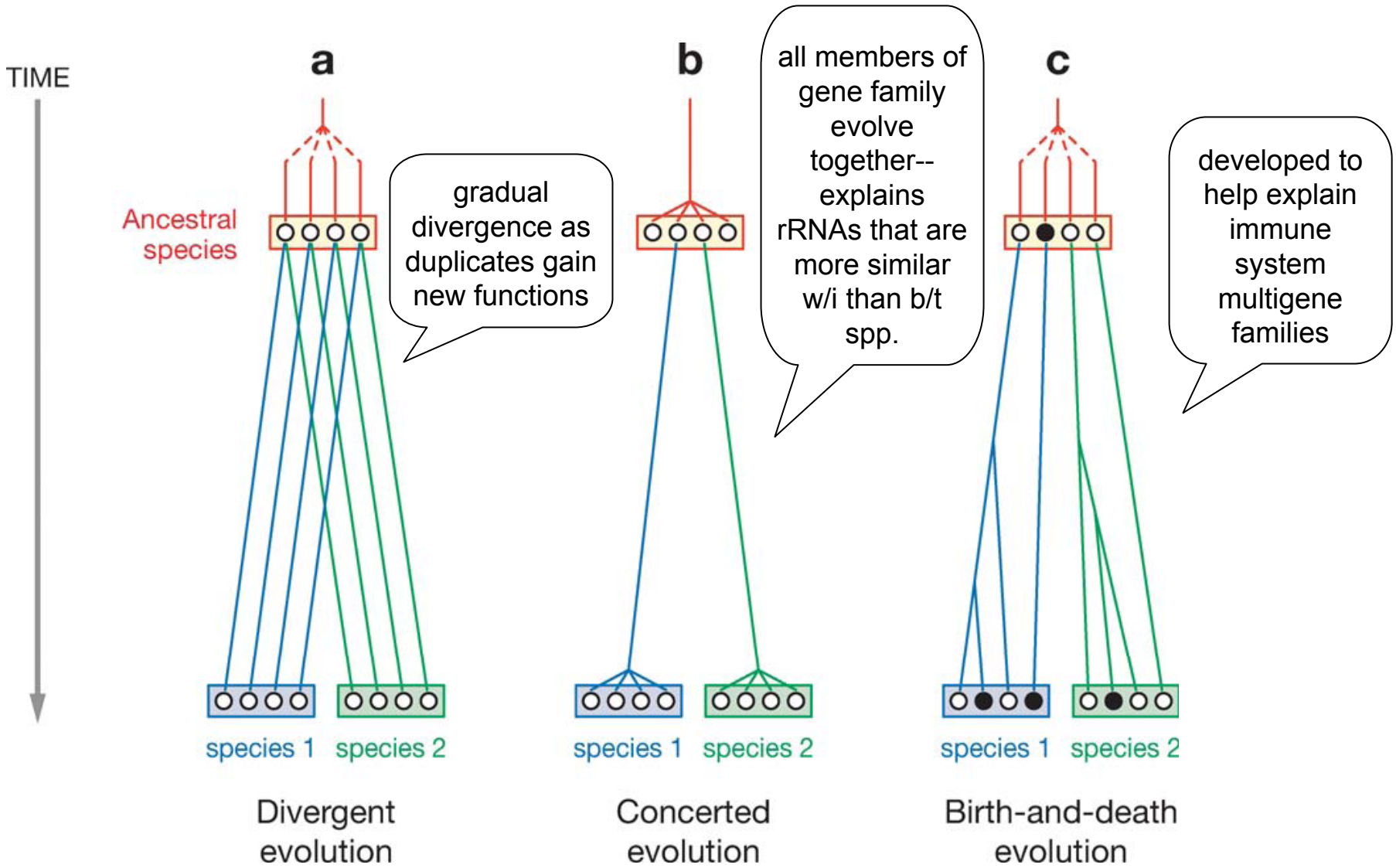
Gene content of a proto MHC region could by inferred by comparing MHC like regions of amphioxus with the MHC region of vertebrates and retaining genes present in both. However, gene order could not be inferred; conservation of gene order is too low.

Conservation of these proto-MHC genes was examined in the urochordates *Ciona savignyi* and *intestinalis*. There is some evidence for the existence of a proto-MHC region in *C. intestinalis* (Immunogenetics. 2003. 55:570-581). However, since the geneome of these organisms has not been fully assembled, this evidence does not extend beyond the existence of a few small clusters of conserved genes on multiple scaffolds in both *Ciona* speices. However, there is enough evidence to indicate that the genes of the MHC region pre-date the common anscestor of vertebrates.

There is further evidence for the existence of MHC-like genes prior to the origin of vertebrates. Comparisons of *Drosophila melanogaster* chromosome X to the reconstructed proto-MHC identified several drosophila orthologs that were confirmed phylogenetically. This strongy suggests an evolutionary link between these two regions. This further suggests that the MHC region may be more ancient than previously thought, even predating the separation of protostomes and deuterostomes. (Trends in Genetics. 2004. 20(12): 587-591)

However, others argue that the MHC has more recent origins. Azumi and collegues examined the *Ciona* gneome for MHC genes and found none. However, their methods for looking for MHC genes was much less sensitive that that of Danchin and Pontarotti (above), using Blast searches and a pattern discovery based method. Nevertheless, their efforts with MHC and other adaptive immune genes highlights the fact that MHC based antigen processing and presentation is absent in non-vertebrates. (Immunogenetics. 2003. 55:570-581)

Evolution of Multigene Families



Annu. Rev. Genet. 2005.39:121-152.

MHC Polymorphism: Concerted Evolution

- 1970s and 1980s: unequal crossover or gene conversion
  - doesn't explain why gene conversion starts
  - trouble explaining different levels of polymorphism between Ia and Ib genes
  - if g.c., the shouldn't have monophyletic clades for each MHC locus (but do)

gene conversion

during meiotic division, DNA sequence information is transferred from one DNA helix (unchanged) to another DNA helix, whose sequence in altered.

unequal crossover

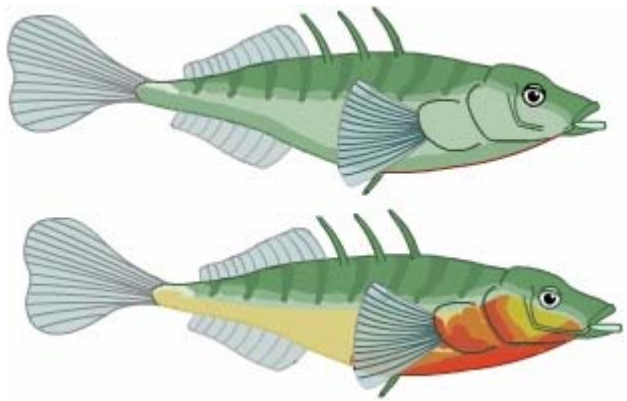
in recombination, where chromosomes break at different loci, resulting (sometimes) in duplication of genes on one chromosome and deletion from the other

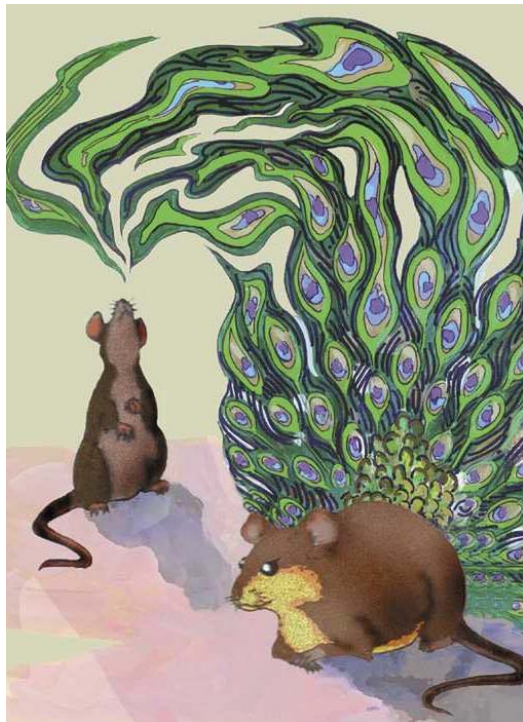
MHC Polymorphism

- late 1980s: overdominant selection (Hughes and Nei)
  - MHC polymorphism is primarily caused by it
  - maintains long term polymorphism
  - phylogeny of MHC class I and II shows different orders/families don't have truly orthologous genes
    - some genes generated by duplication, some lost after divergence of mammals
  - BUT, doesn't necesarily explain high polymorphism
    - mathematical model (Borghans, Beltman, and De Boer Immunogenetics (2004) 55:732–739)

Evidence for Overdominance

- Very little—most studies fail to detect it
- Sticklebacks count MHC alleles (Nature 2001. 414:.300-3)
  - gravid females preferred males with more MHC class IIB alleles
- Mice heterozygote advantage in coinfections (Infection and Immunity. 2003. 71: 2079–2086)





MHC Polymorpism

- 1990s: Birth and Death Evolution
  - genes generated by duplication, other mechanisms; genes lost through loss of function or deletion
  - MHC polymorphism primarily generated by nucleotide substitution and selection
  - supported by:
    - lage number of pseudogenes
    - non-classical loci that diverged evolutionarily and developed new functions
    - phylogeny of MHC genes

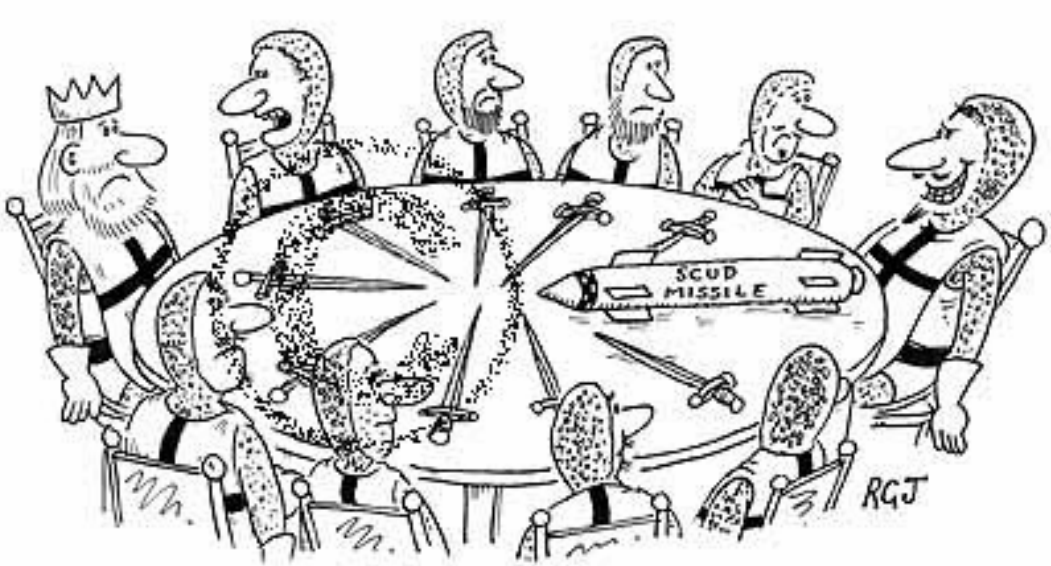
Annu. Rev. Genet. 2005.39:121-152.

Genes denoted with a (b) diverged from Ia loci and now have new functions. These genes are more closely related to genes in other species with a similar function that to other MHC genes within the species, suggesting that at least some MHC genes divereged in function prior to speciation

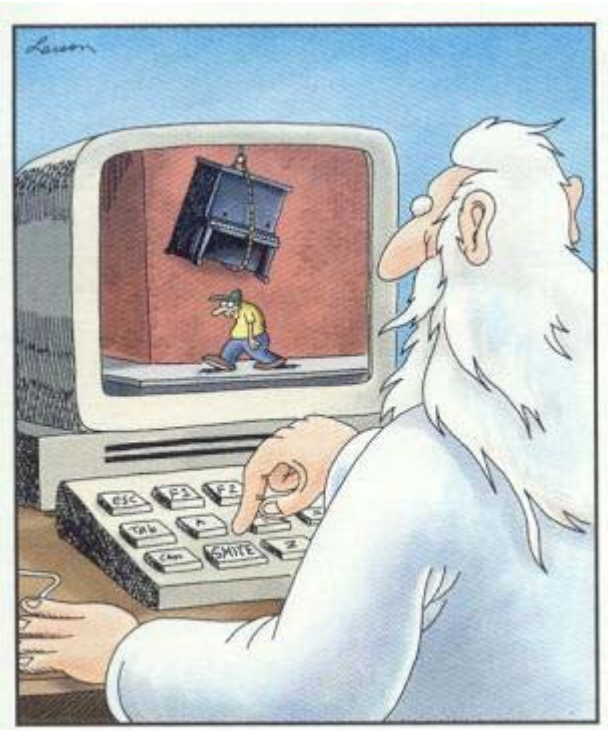
(*a*) Phylogenetic tree of MHC class I genes from vertebrates. Annu. Rev. Genet. 2005.39:121-152.

Genetic Mechanisms

- host-pathogen arms race
- sexual selection
- divine tinkering
- see also The Nature of Selection on the MHC. Critical Reviews in Immunology 1997. 17:179-224.



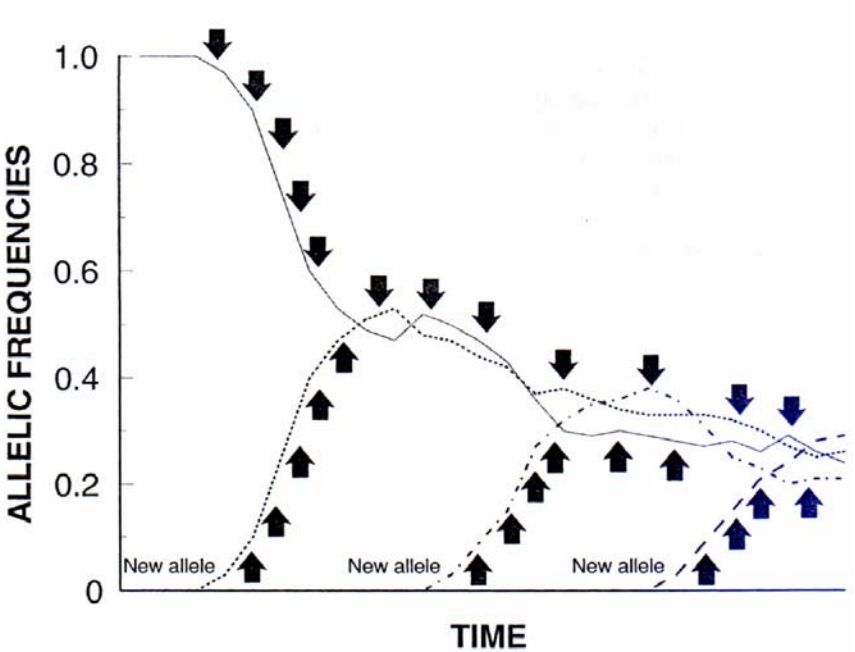
"Looks like Lancelot's starting an arms race."



God at His computer

Host-Pathogen Arms Race

- heterozygote advantage
  - again, coinfected mice, not much other
- frequency dependent selection
  - selection may favor rare alleles as pathogens

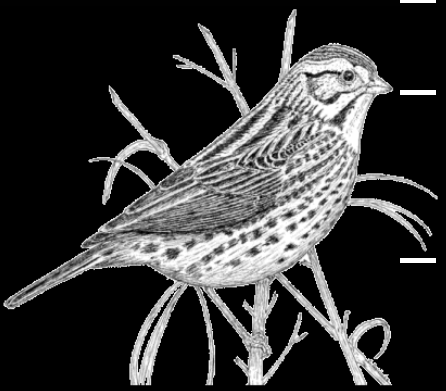


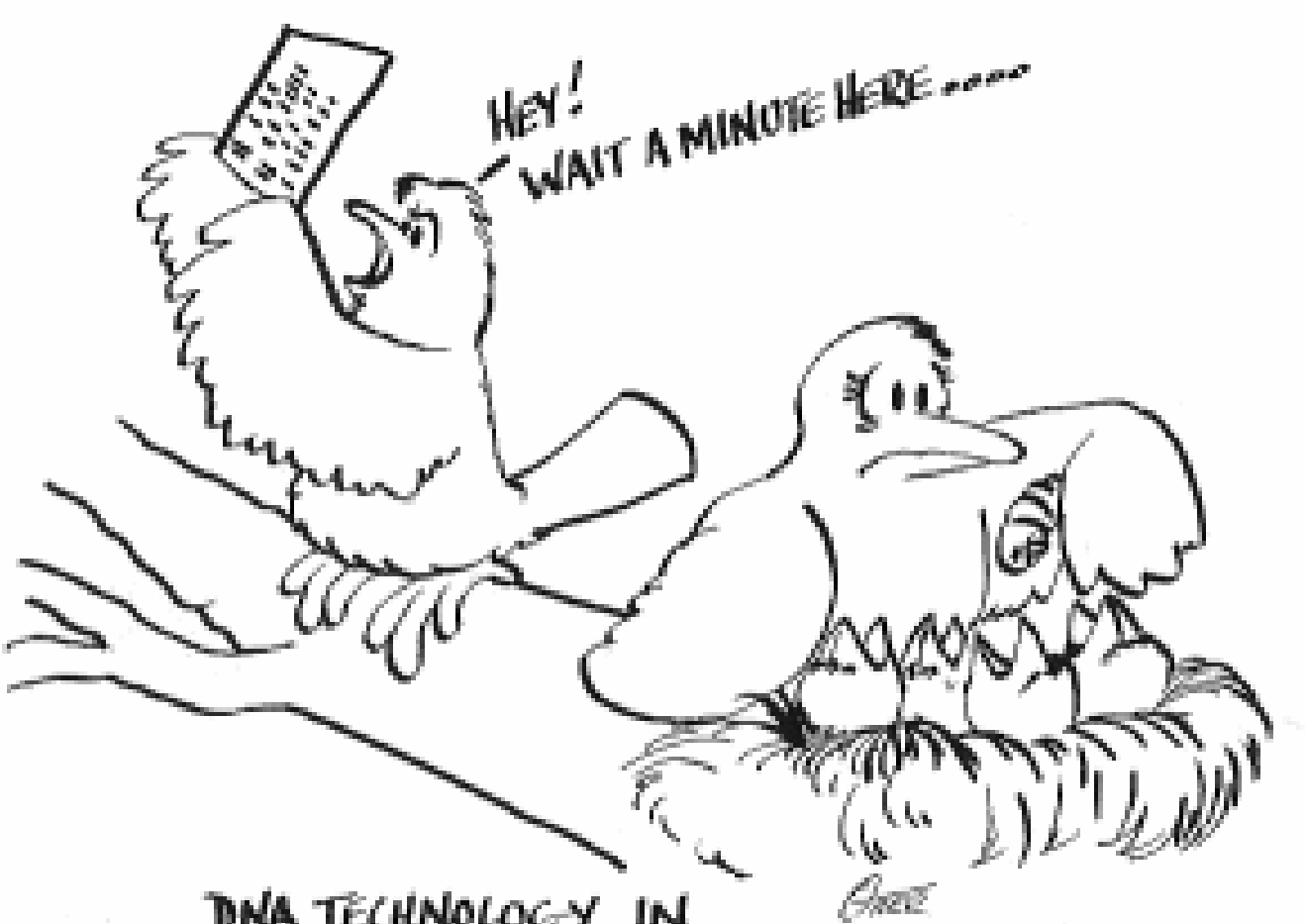
The Nature of Selection on the MHC. Critical Reviews in Immunology. 1997. 17:179-224.

Sexual Selection

- Pheasant (Von Schantz and colleagues, Hereditas. 19997. 127:133-140)
  - Females prefer males with long spurs
  - Particular MHC genotypes were significantly associated with spur length and viability
  - The preferred genotypes changed each year

- Savannah Sparrow (Freeman-Gallant and colleagues, Molecular Ecology. 2003. 12:3077-3083)
  - Estimated MHC sequence similarity b/t individuals
  - Female yearlings avoided mating with MHC similar males
  - EPP correlated with similarity to mate
    - Pairs more similar in nests with EPP than in nests with no EPP





DNA TECHNOLOGY IN
THE WRONG HANDS