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FOR EVOLUTIONARY BIOLOGY

Modulation of naive T cell repertoire diversity by individual MHC II in stickleback fish

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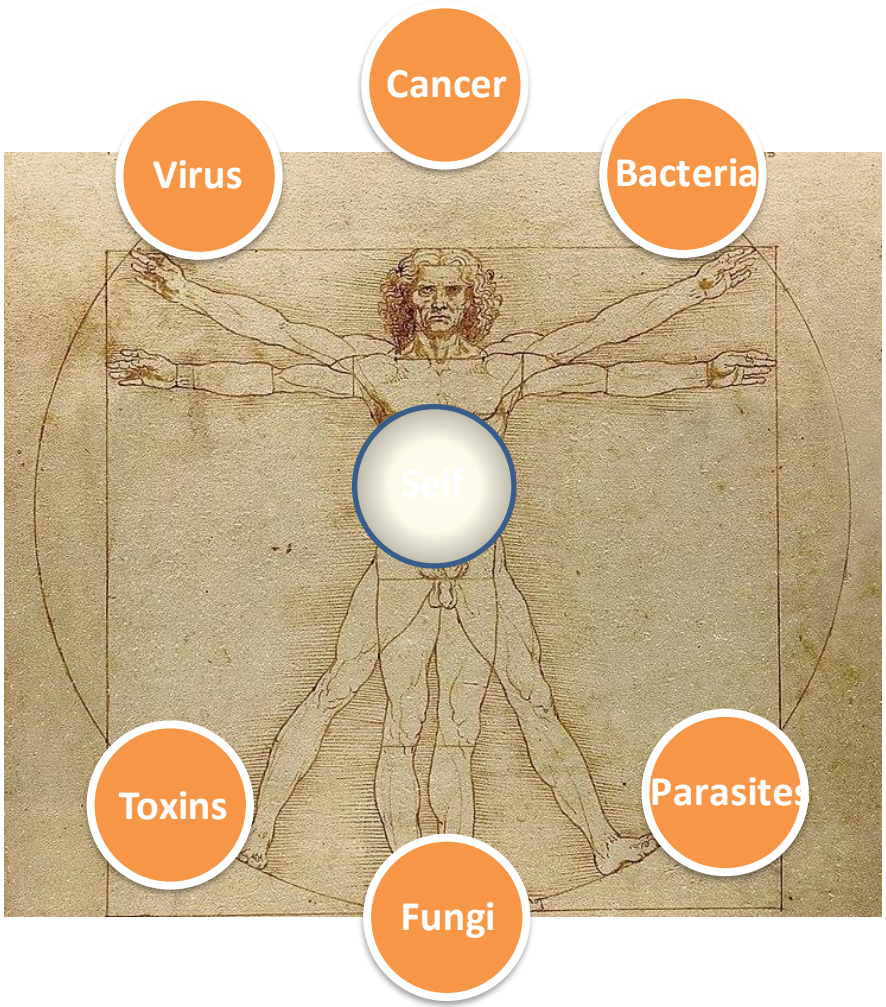
EVOLUTION: BALANCE IN IMMUNITY



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THYMIC SELECTION OF T CELLS

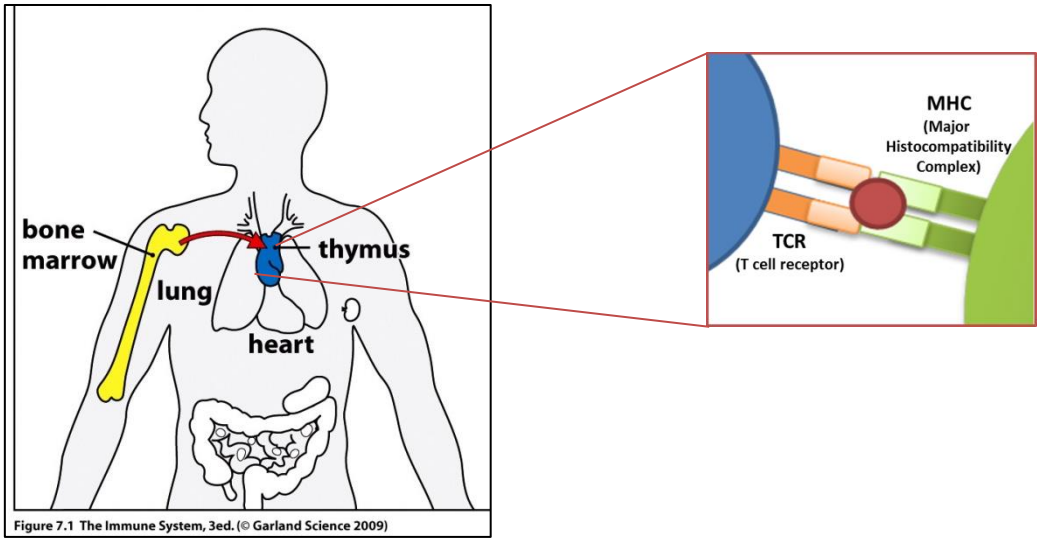
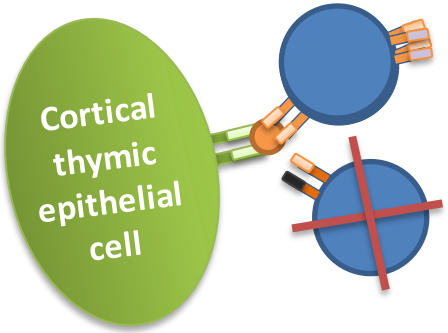


Figure 7.1 The Immune System, 3ed. (© Garland Science 2009)

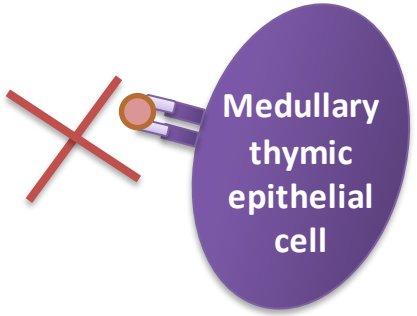
POSITIVE SELECTION

Deletion (death-by-neglect) of T cells which receptors does not interact with pMHC molecules



NEGATIVE SELECTION

Clonal deletion of T cells which receptors have high affinity with **self MHC peptides**



T CELLS IN THE PERIPHERY

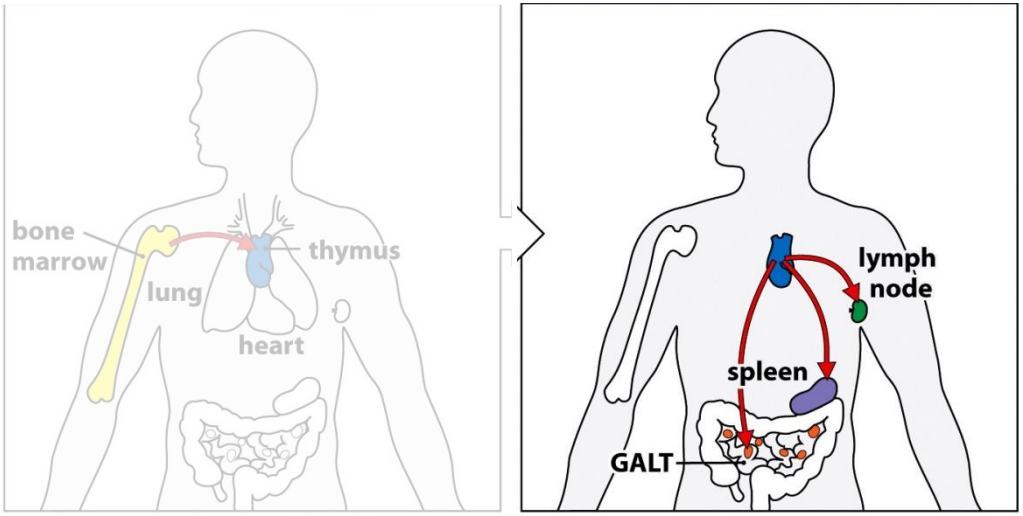
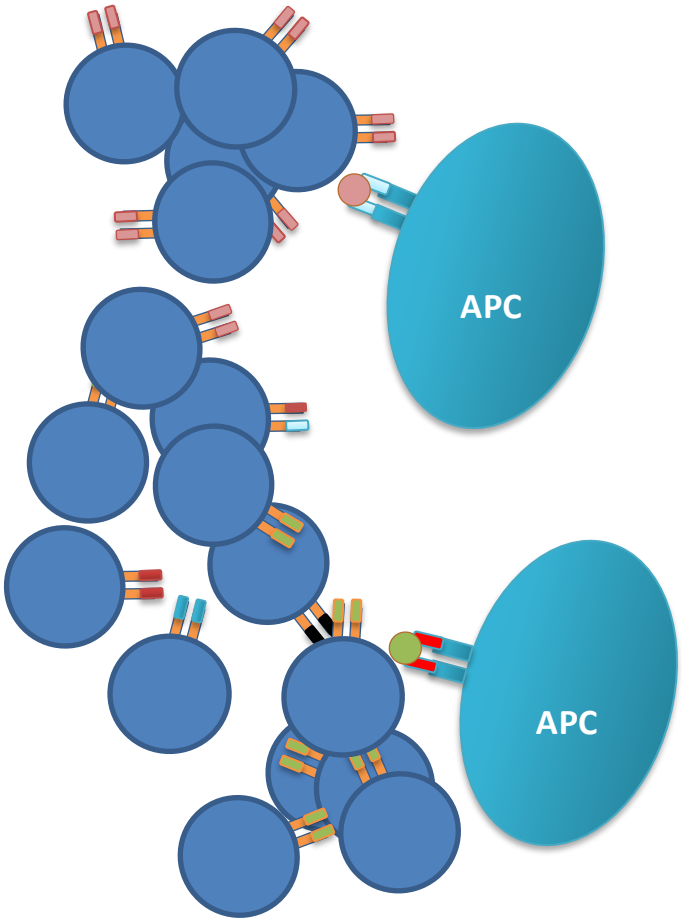


Figure 7.1 The Immune System, 3ed. (© Garland Science 2009)

PERIPHERY

Clonal expansion of T cells which encounter and recognize MHC-peptides on surface of Antigen Presenting Cells (APC)

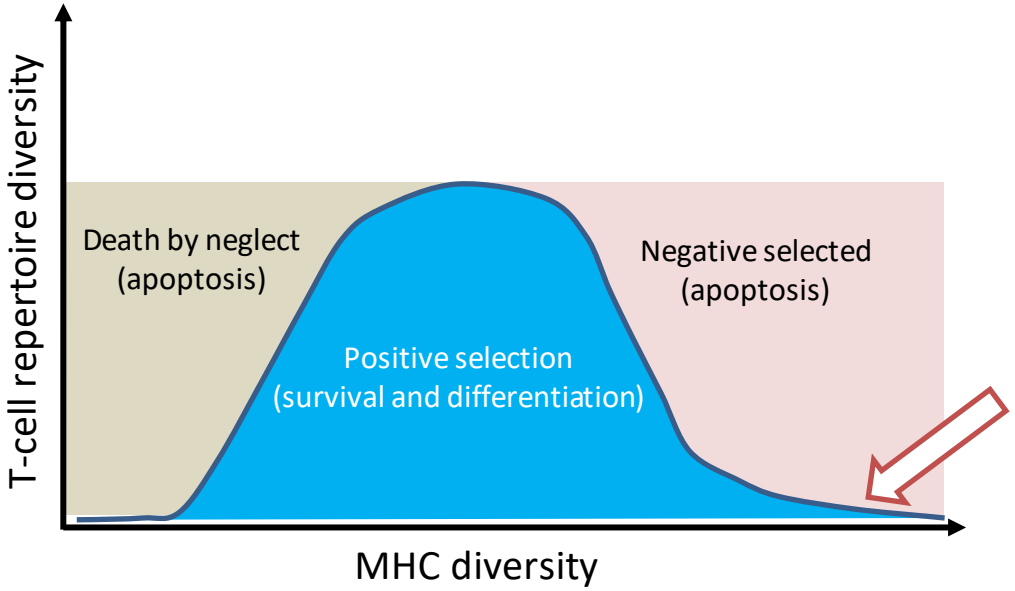


INDIVIDUAL MHC RESTRICTS T CELL REPERTOIRE DIVERSITY

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 10896–10899, November 1992

The optimal number of major histocompatibility complex molecules in an individual

MARTIN A. NOWAK*†, KRISTINA TARCZY-HORNOCH‡, AND JONATHAN M. AUSTYN†§



Individuals with too high MHC diversity must have a depleted TCR repertoire due to the deletion of T-cells that react with self-peptide–MHC combinations during development

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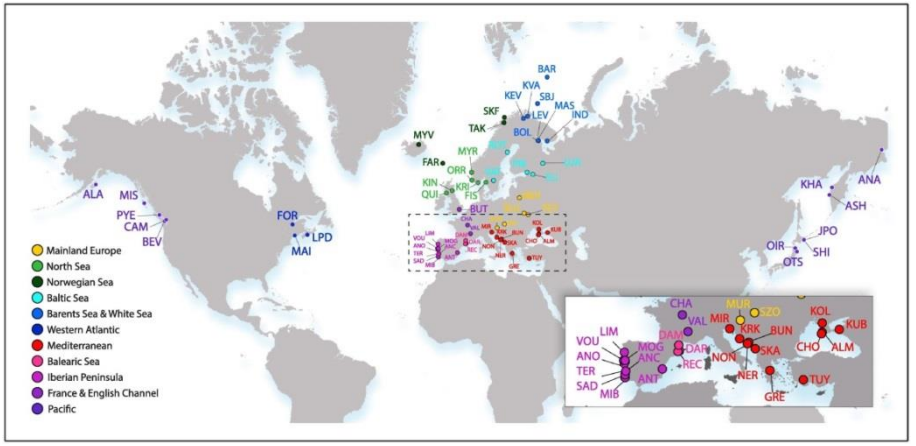
THREE-SPINED STICKLEBACK FISH

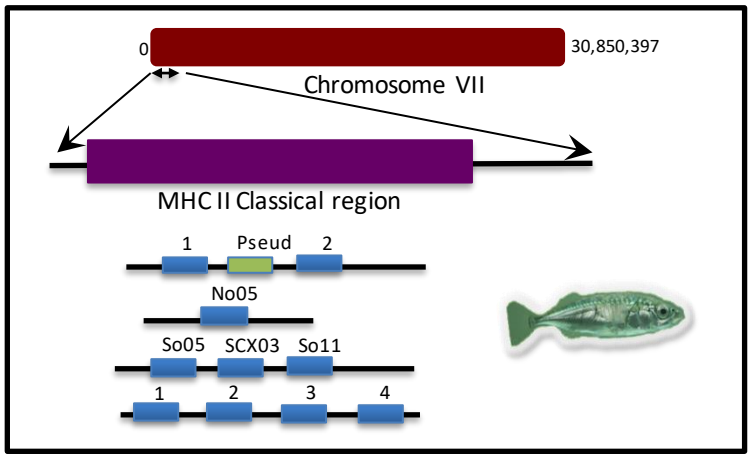
Small vertebrate that inhabits a wide variety of natural habitats



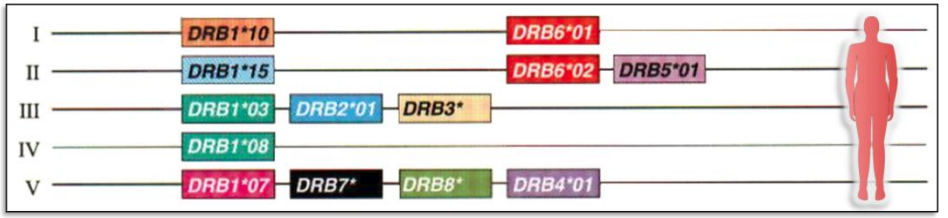
Fang et al., Mol. Phylogenetics Evol (2018)

Completely functional adaptive immune system with a natural level of MHC II diversity

Copy-number variation at MHC genes: In Stickleback fish



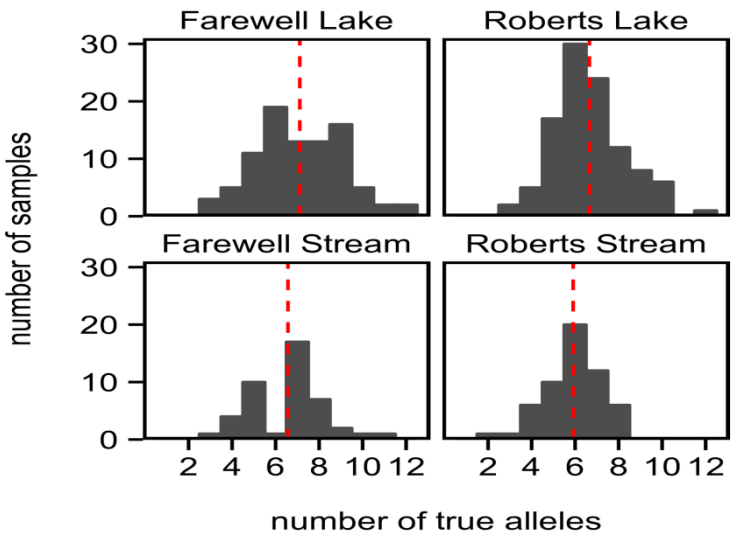
Copy-number variation at MHC genes: In humans



Bontrop *et al.* 1999; Horton *et al.* (2008)

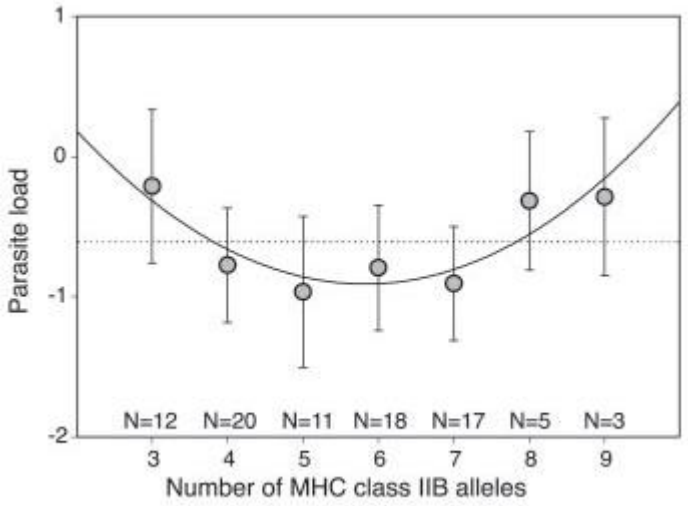
MHC IS UNDER SELECTION FOR DIVERSITY BY PARASITES

Frequency of MHCII alleles in the population



Stutz *et al.*, PlosOne (2014)

Parasite load varies with MHCII diversity



Wegner *et al.*, Science (2003)

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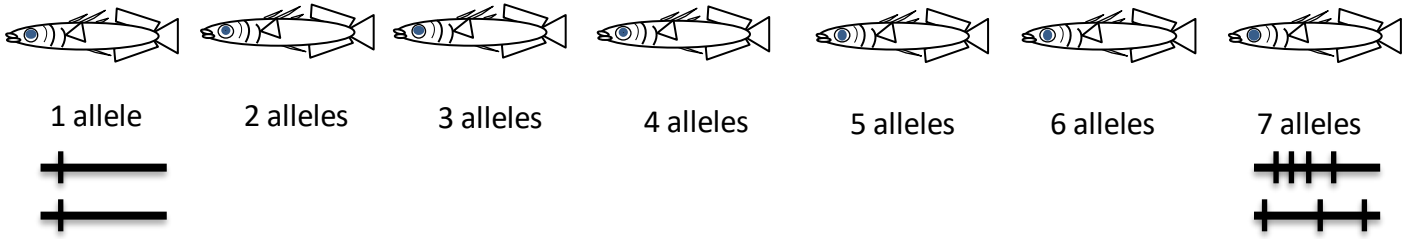
EVOLUTION OF INDIVIDUAL MHC DIVERSITY

MHC-restricted T-cell repertoire diversity: **Experimental test**

Number of individual MHCII alleles:



F2 generation (lab bred)

Sequencing and analysis of the TCR genes from the **whole body** of naive (2.5 month old) stickleback fish

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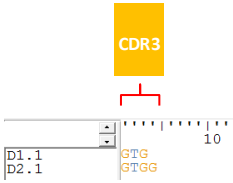
CHARACTERIZATION OF V D J GENES

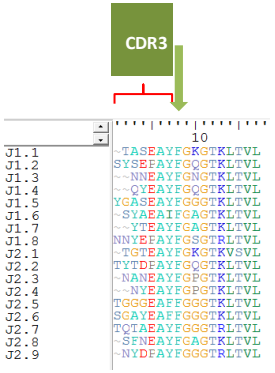
Based on the IMGT (international ImMunoGeneTics information system)

V GENES

D GENES



J GENES

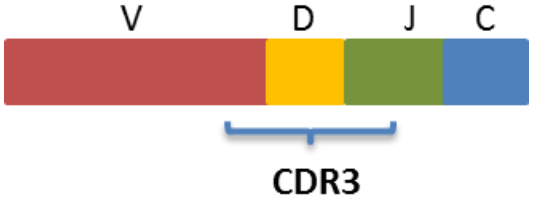


TRβ1:

- 19 V segments (2 are pseudogenes)
- 1 D segment
- 8 J segments

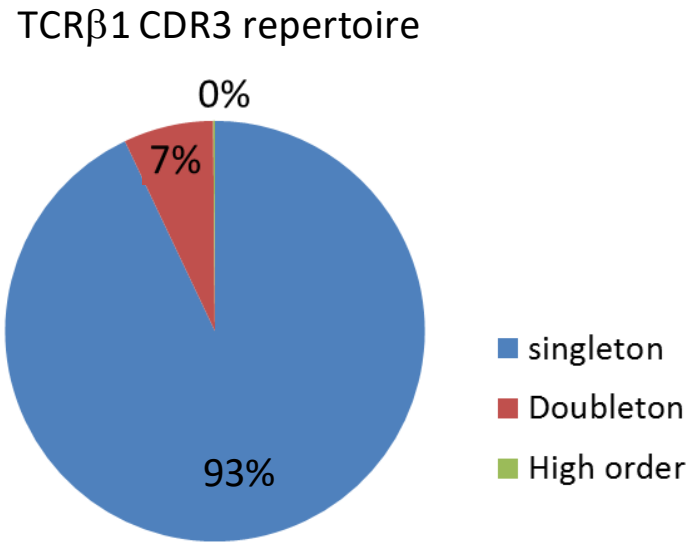
TRβ2:

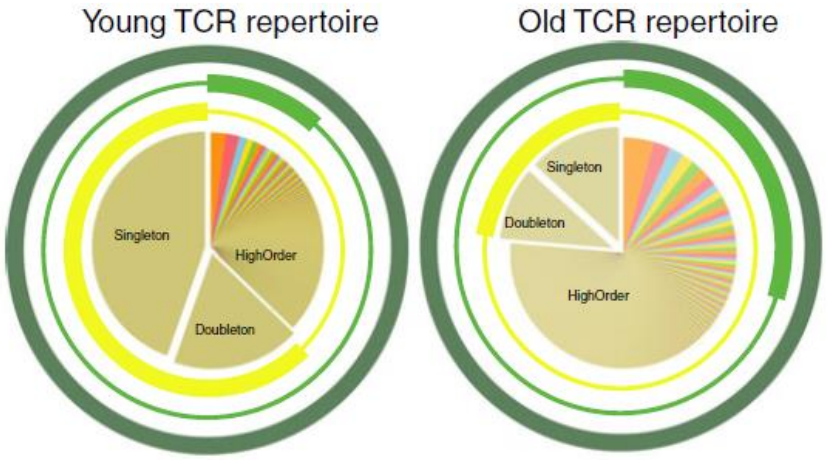
- 13 V segments
- 1 D segment
- 9 J genes



MAJORITY OF T CELLS DETECTED SEEM TO BE NAÏVE

- YOUNG FISH -





Izraelson et al., Immunology (2017)

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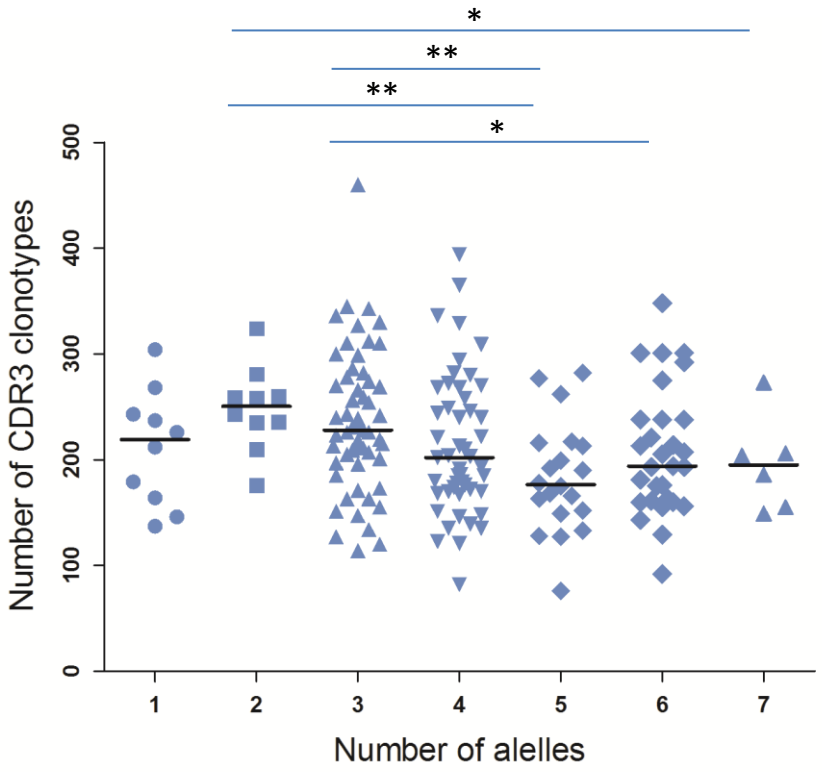
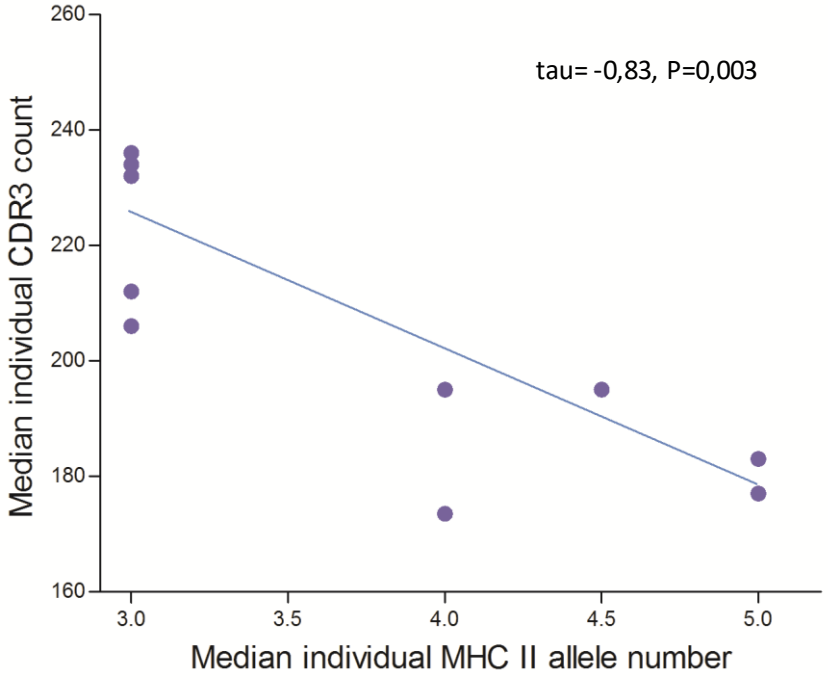
CDR3 DIVERSITY IS SIGNIFICANTLY HIGHER IN INDIVIDUALS WITH LOW-INTERMEDIATE NUMBER OF MHC ALLELES

TCRβ1





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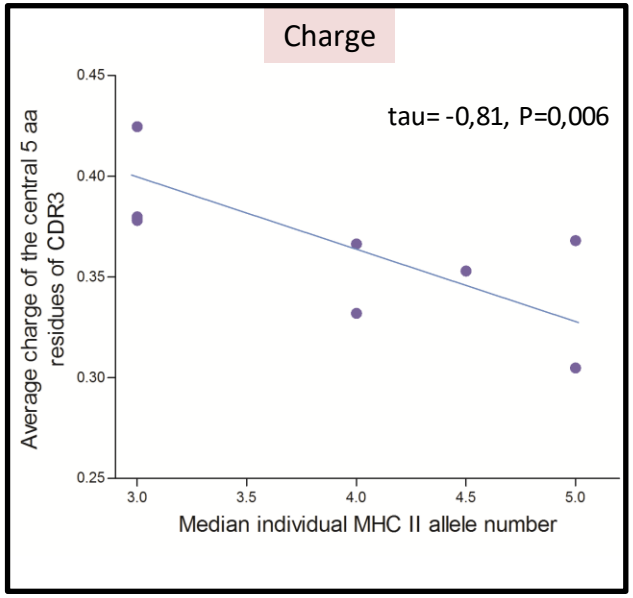
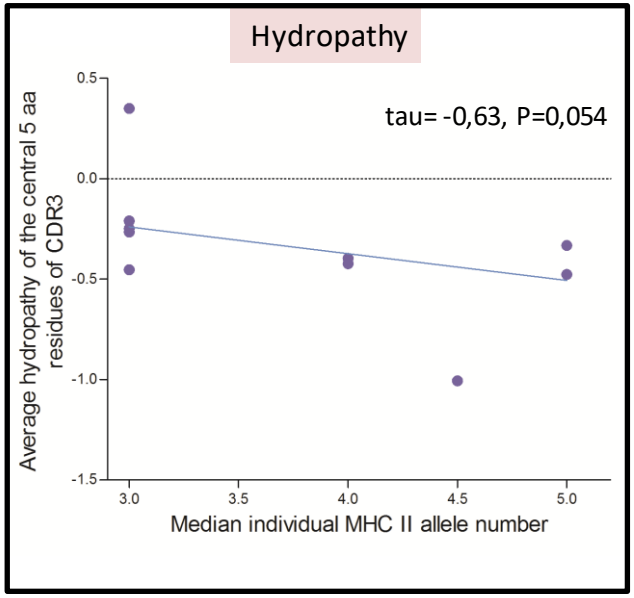
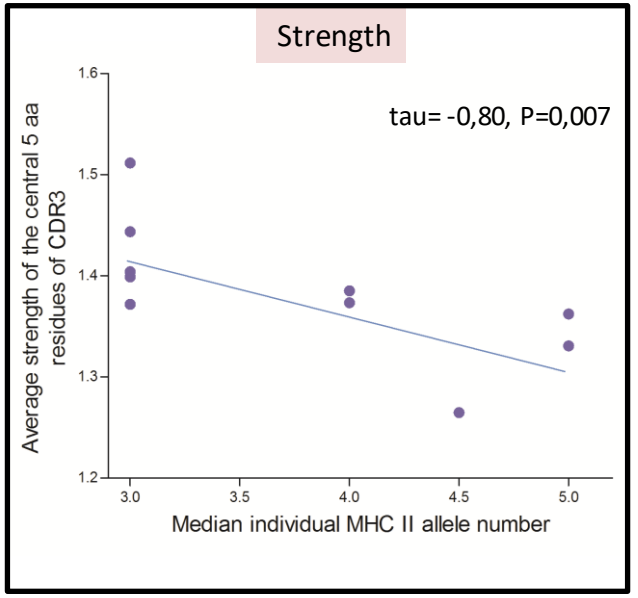
CHARGE, HYDROPATHY AND STRENGTH OF THE CENTRAL CDR3 AMINO ACIDS IS HIGHER IN INDIVIDUALS WITH LOW-INTERMEDIATE NUMBER OF MHC ALLELES

TCRβ1







Regulatory mechanisms mediated by MHC during selection of T cells

SUMMARY

Most of the T cells seem to be naïve in young fish (2.5 month old)

TCR diversity is significantly higher in individuals with lower/intermediate number of MHC alleles

Number/diversity of MHC alleles influences the CDR3 amino acid properties

MHC-TCR CO-EVOLUTION:

IT IS AN OPTIMIZED (NOT MAXIMIZED) NUMBER OF MHC MOLECULES IN AN INDIVIDUAL THAT FAVORS AN OPTIMAL DIVERSITY OF T CELLS

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