Эволюционная иммунология
Лекция 8«Альтернативный адаптивный иммунитет Круглоротых»

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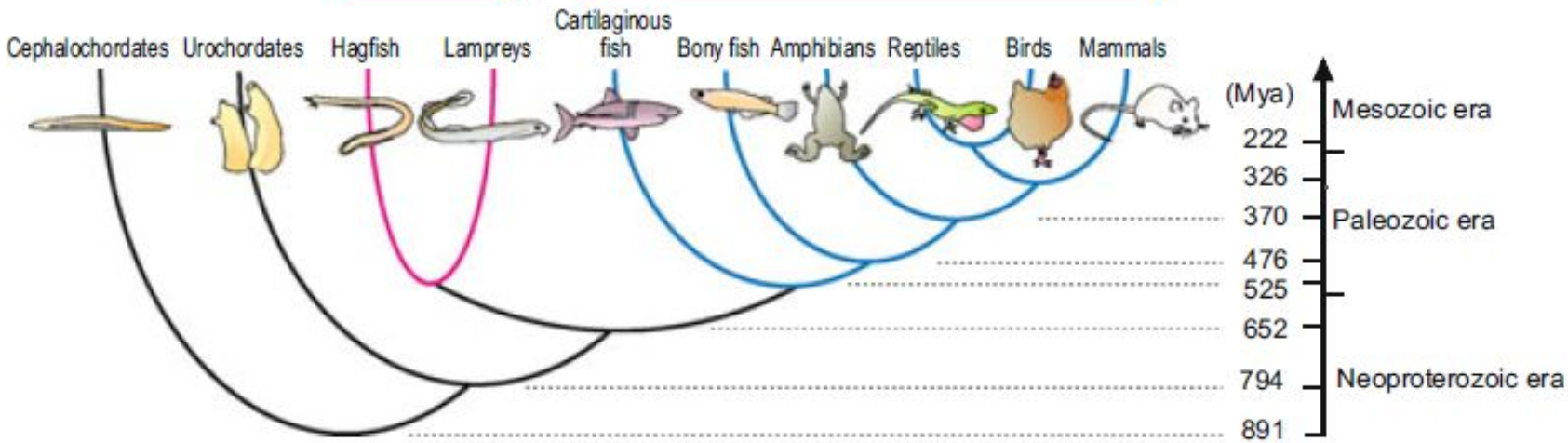
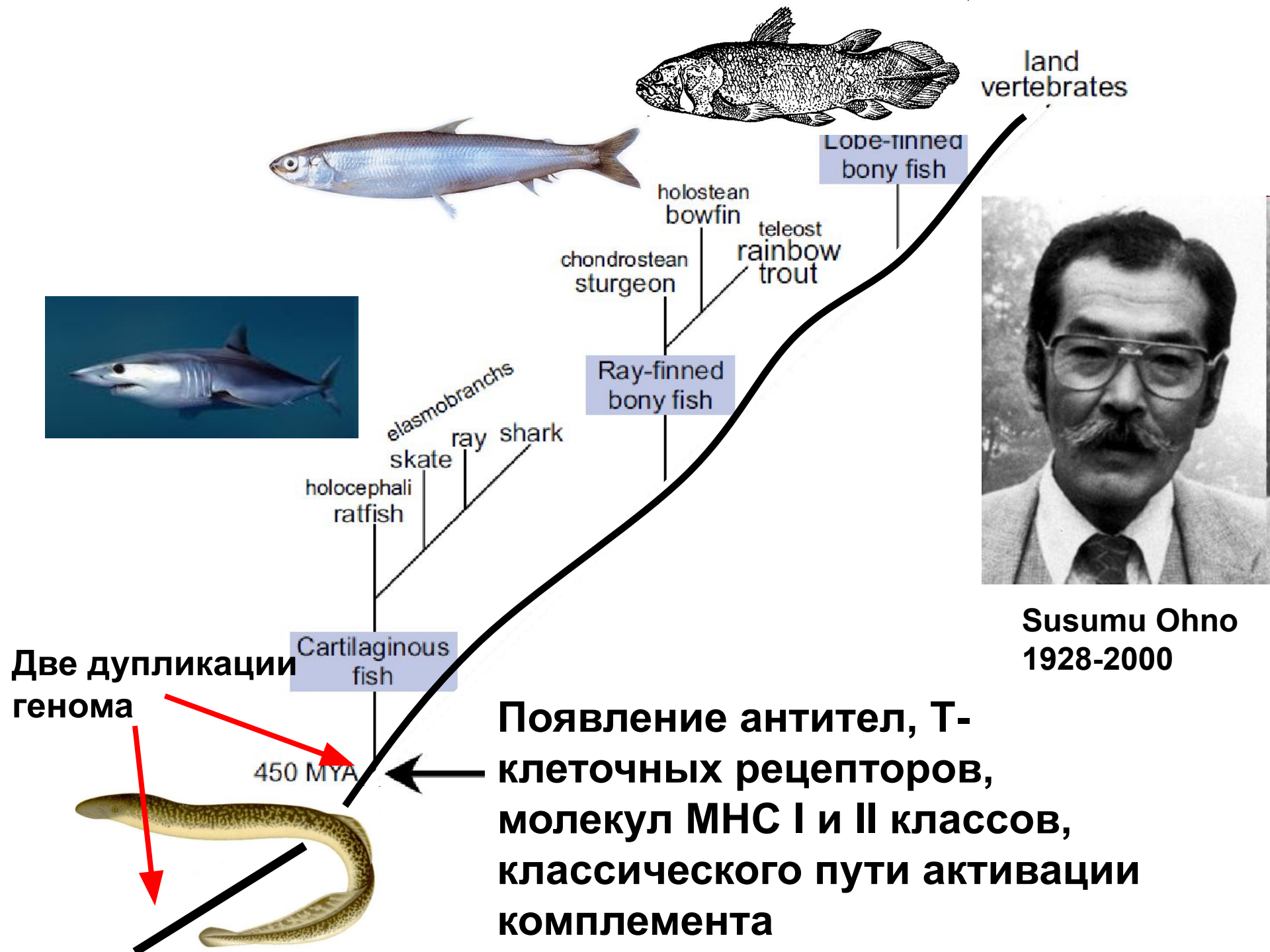
2 апреля 2018

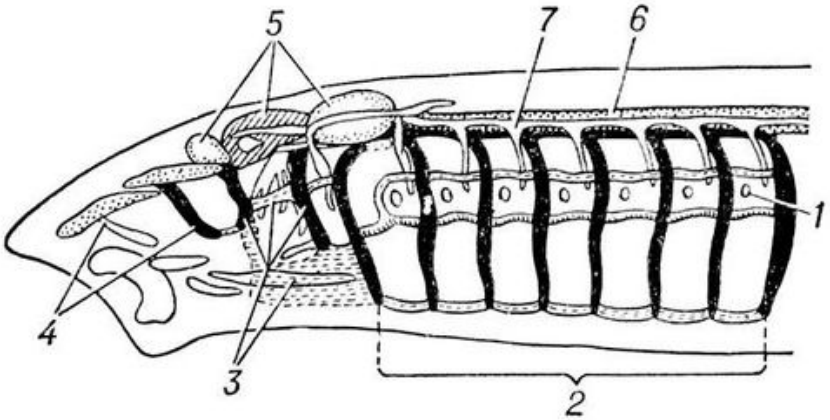
Эволюция хордовых и их адаптивный иммунитет

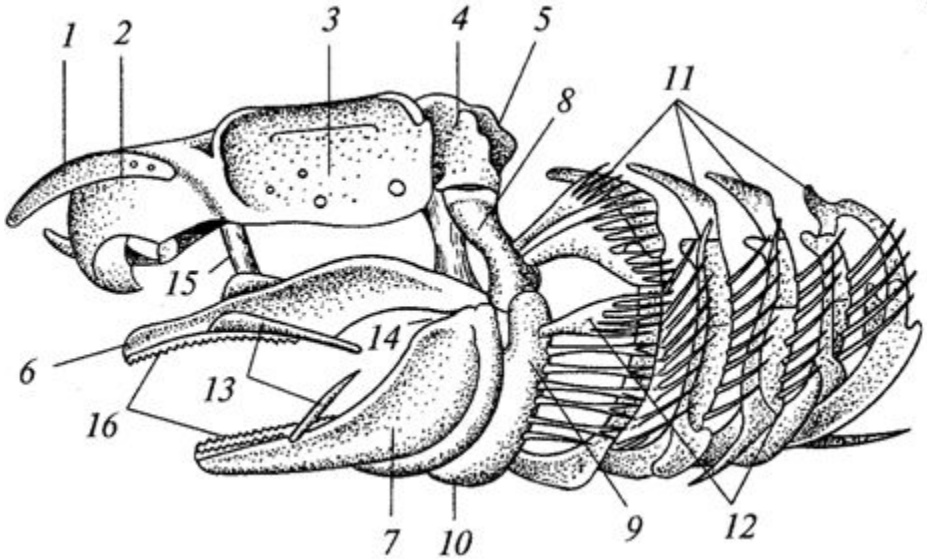
	Jawless vertebrates (Cyclostomes)	Jawed vertebrates
Antigen receptors	VLR	TCR/BCR
Antigen-presenting molecules	?	MHC
Enzymes involved in the generation of diversity	CDA1/CDA2	AID RAG1/RAG2



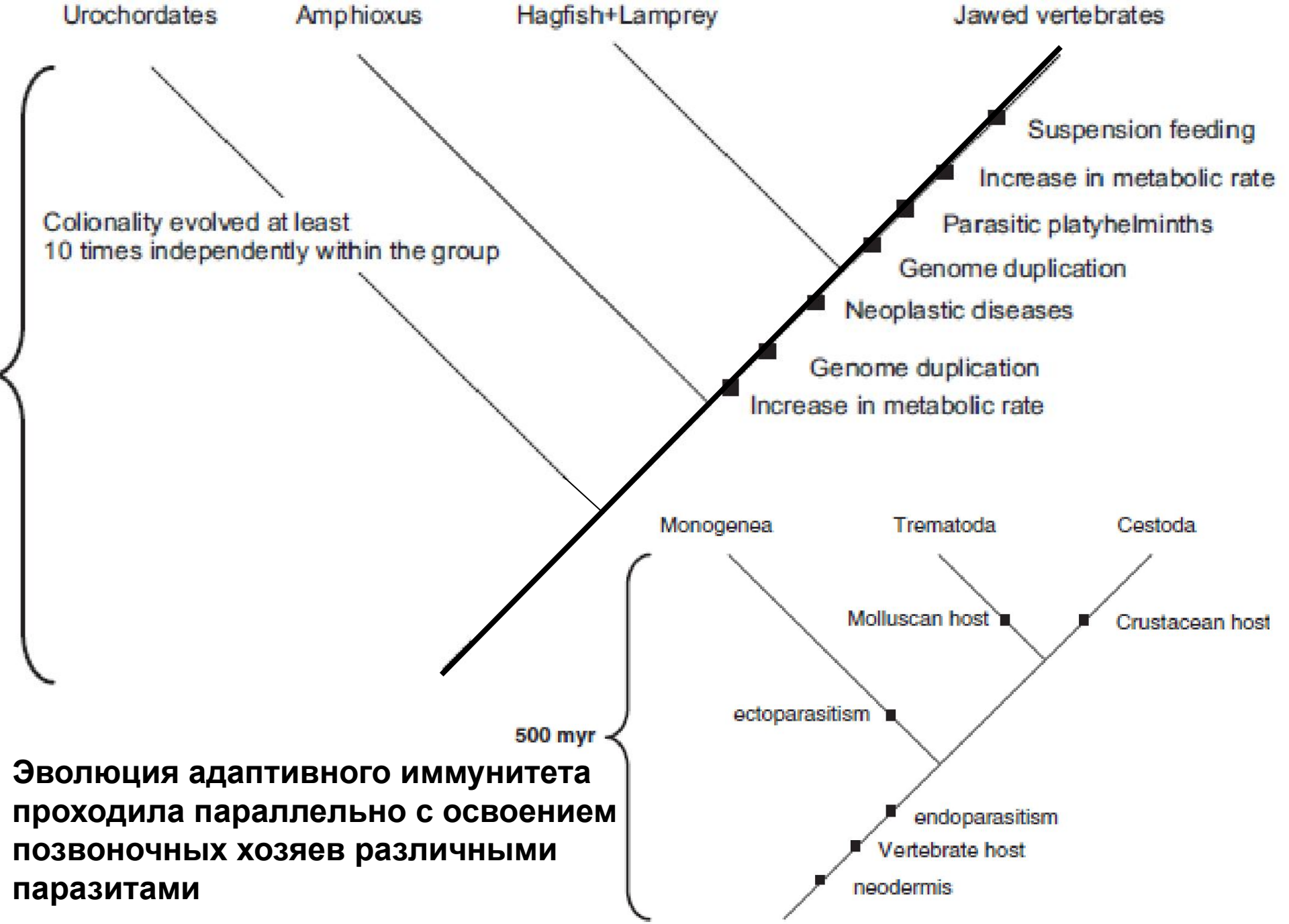

land vertebrates
Lobe-finned bony fish
holostean bowfin
teleost rainbow trout
chondrostean sturgeon
Ray-finned bony fish
elasmobranchs
ray
shark
skate
holocephali ratfish
Cartilaginous fish
450 MYA
Susumu Ohno
1928-2000
Две дупликации генома
Появление антител, Т-клеточных рецепторов, молекул МНС I и II классов, классического пути активации комплемента

Возникновение челюстноротых





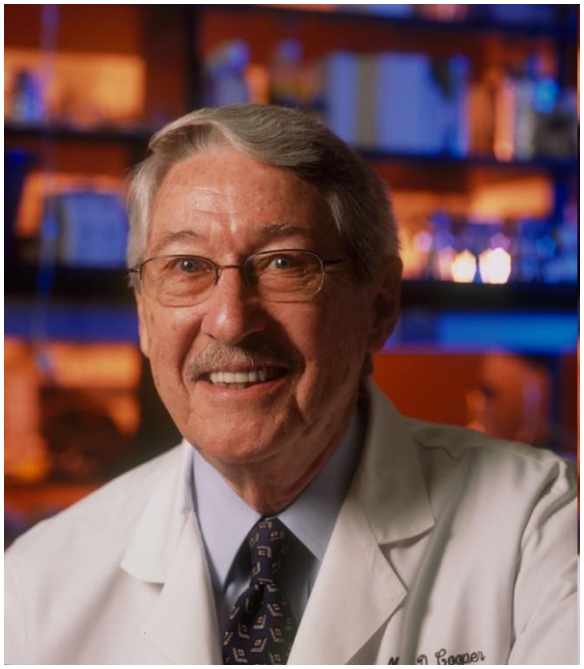
С возникновением челюстей на основе первой жаберной дуги наши предки получили возможность стать наиболее эффективными хищниками ордовика и занять верхние трофические уровни. Чем, видимо, не преминули воспользоваться разнообразные паразиты. Следует также помнить, что у первых челюстноротых (панцирных рыб) не было плавательного пузыря, и они перемещались по мутному дну, шагая на плавниках, что облегчало заражение рыб патогенами.



Эволюция адаптивного иммунитета проходила параллельно с освоением позвоночных хозяев различными паразитами

Открытие VLR в 2004

Zeev Pancer
1957-2014

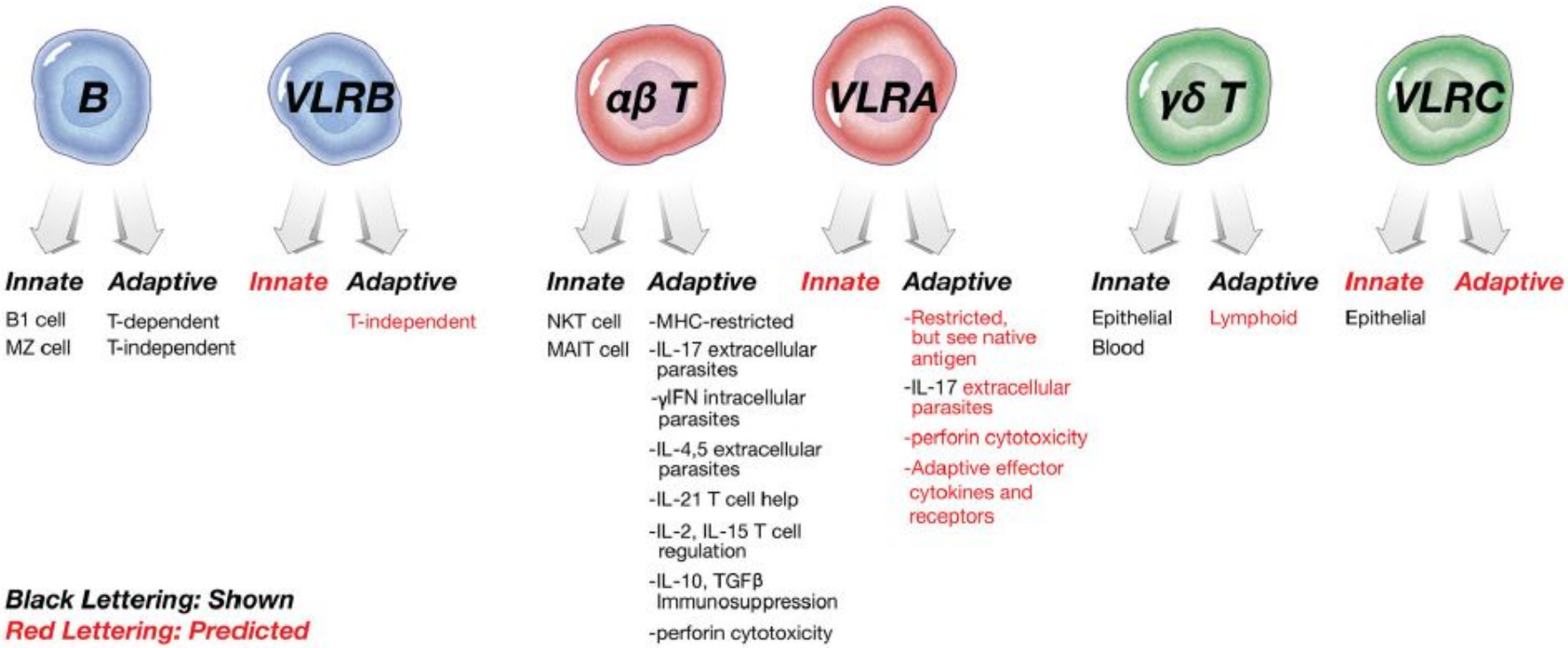


Max Cooper

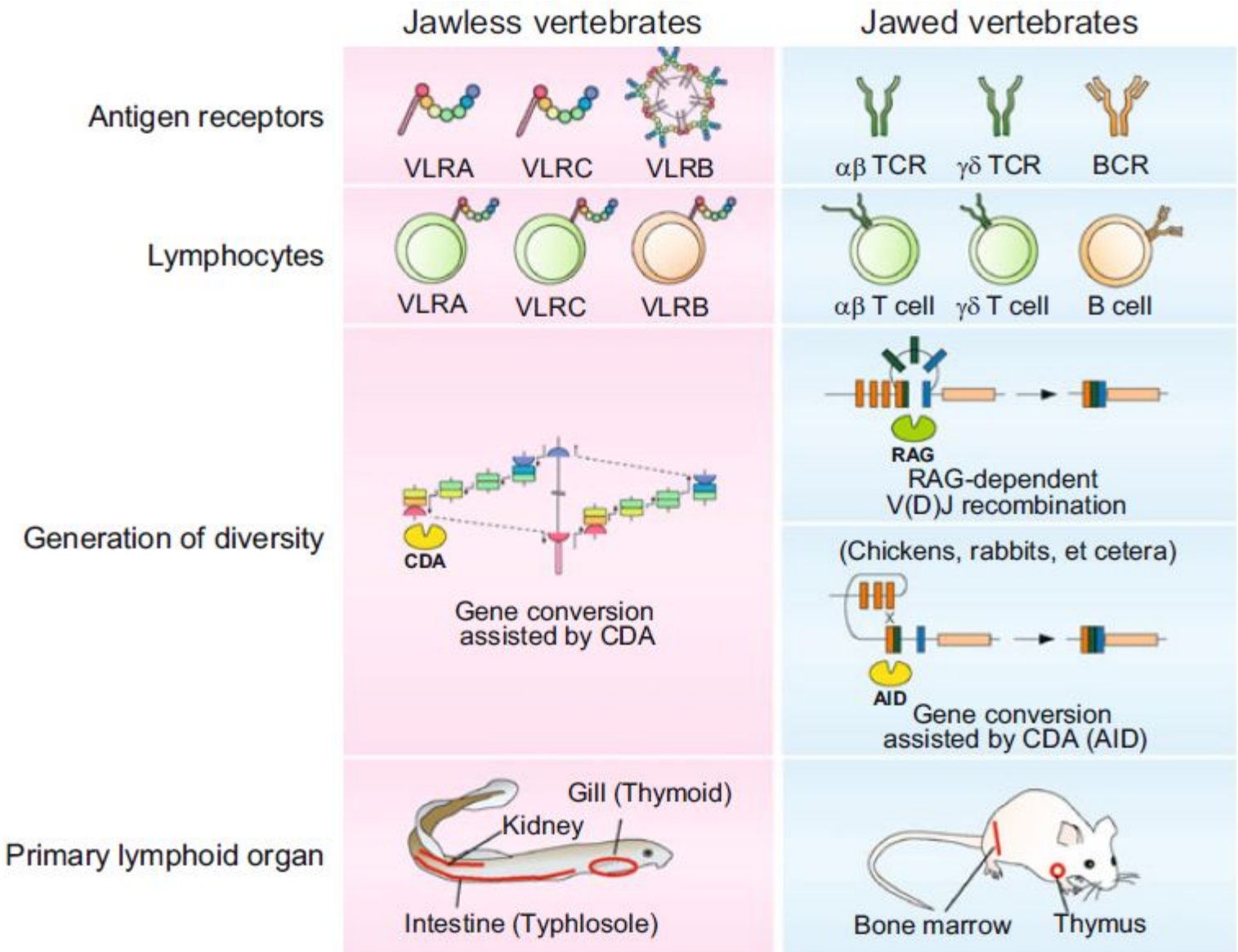
Somatic diversification of variable lymphocyte receptors in the agnathan sea lamprey

Zeev Pancer[1,2], Chris T. Amemiya[6], Götz R. A. Ehrhardt[1,5], Jill Ceitlin[7], G. Larry Gartland[1,4] & Max D. Cooper[1,2,3,4,5]

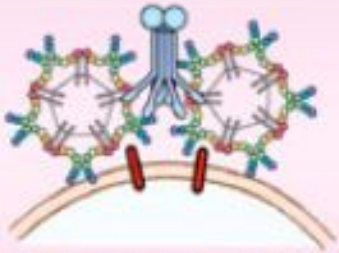
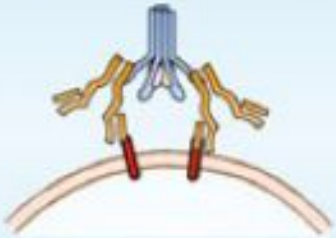
Типы лимфоцитов круглоротых



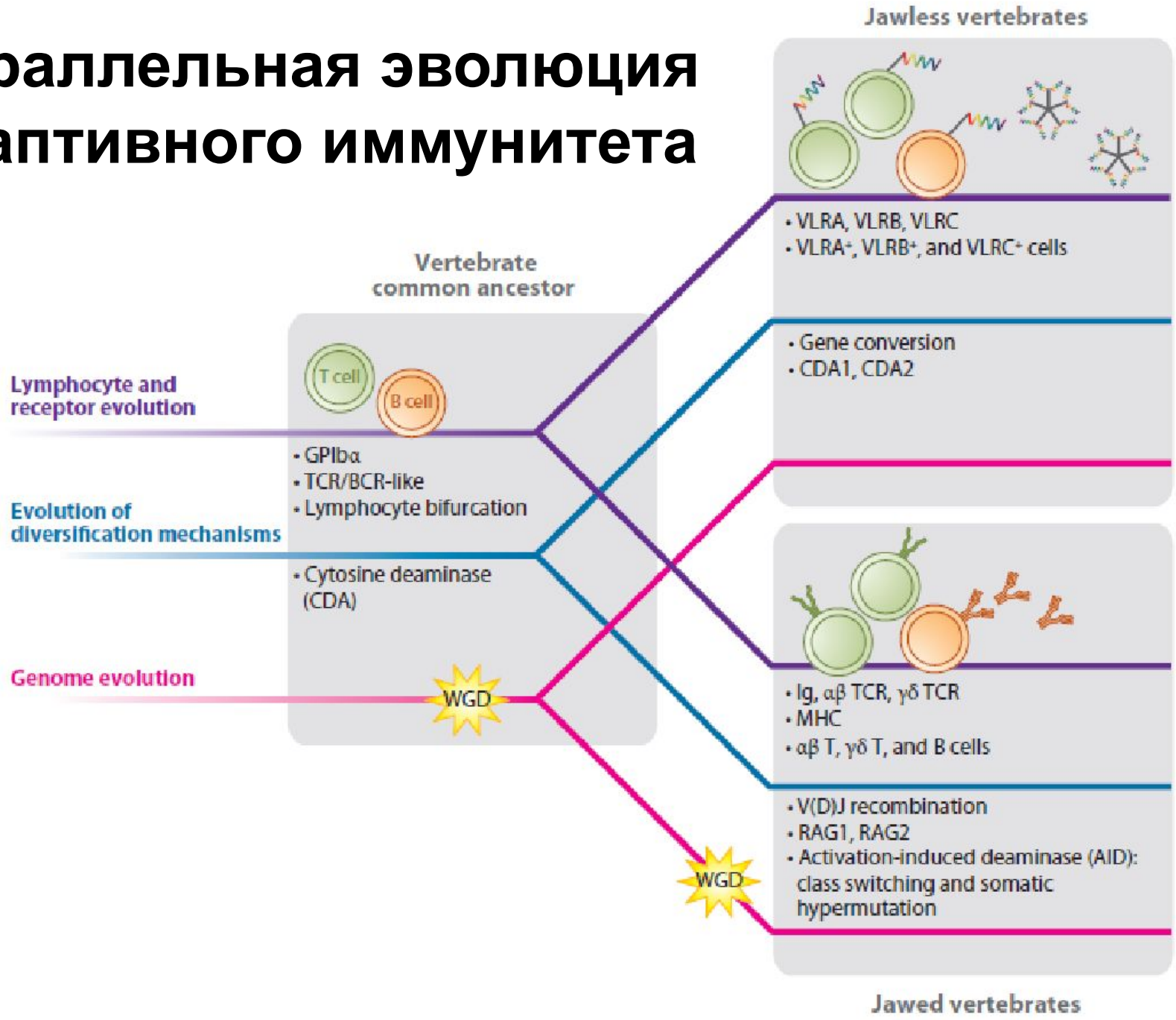
Общее сравнение лимфоцитов круглоротых и челюстноротых



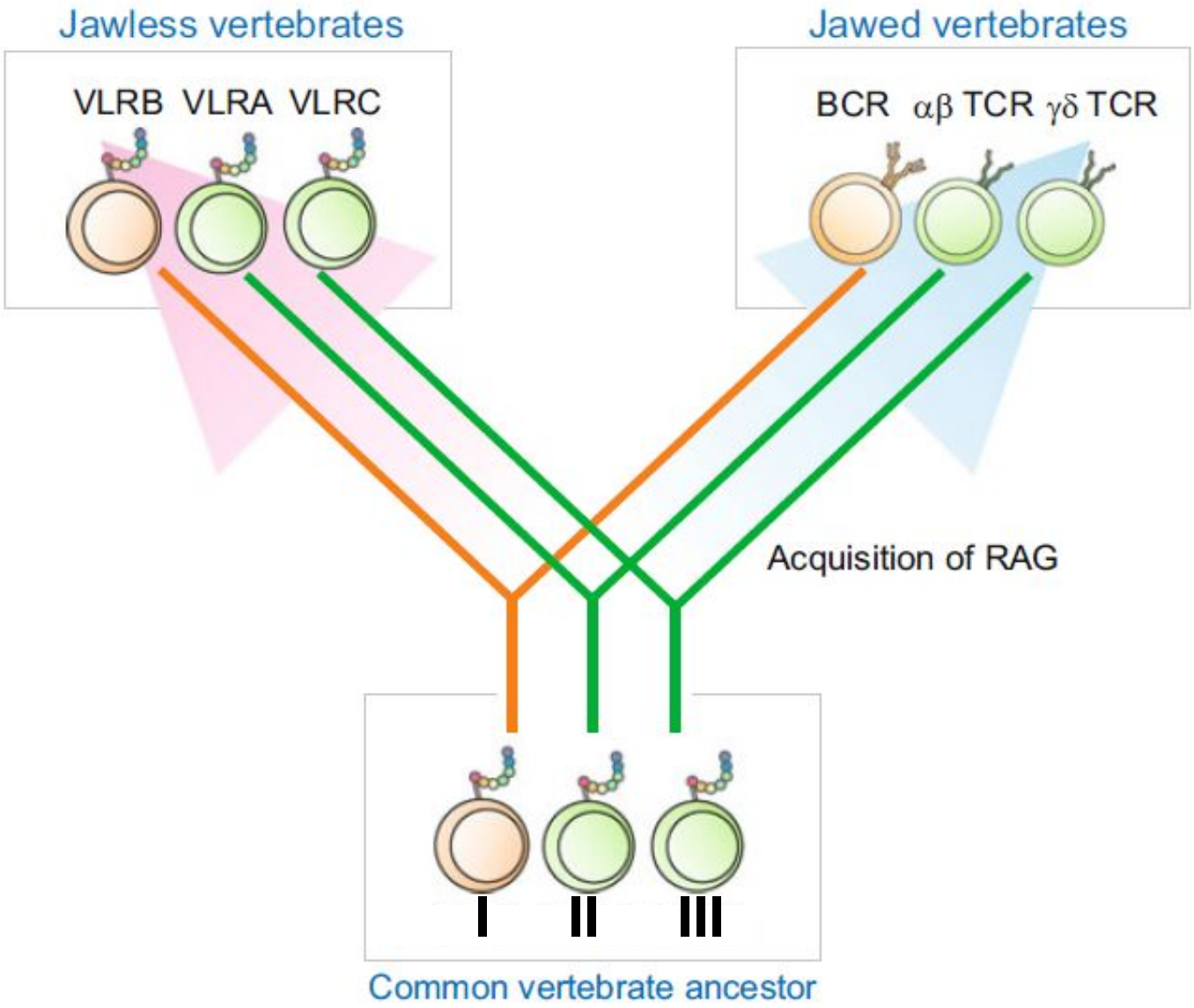
Общее сравнение VLR круглоротых и вариабельных рецепторов челюстноротых

Structure of antibody	Octamer or decamer	Monomer, dimer and pentamer
Complement activation	 VLRB-dependent cytolysis	 Immunoglobulin-dependent cytolysis
Antigen presentation	?	APC expressing MHC molecules

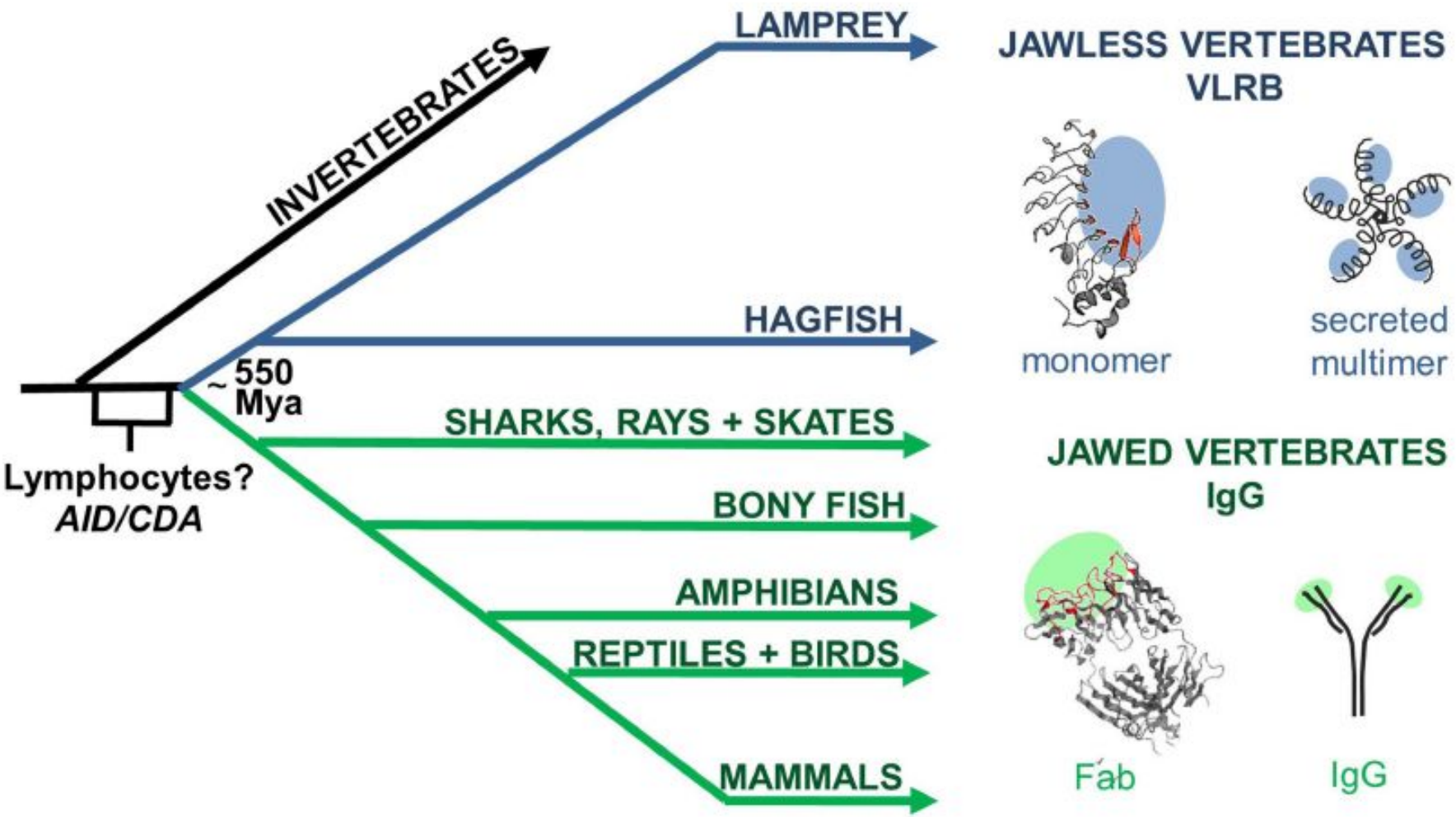
Параллельная эволюция адаптивного иммунитета



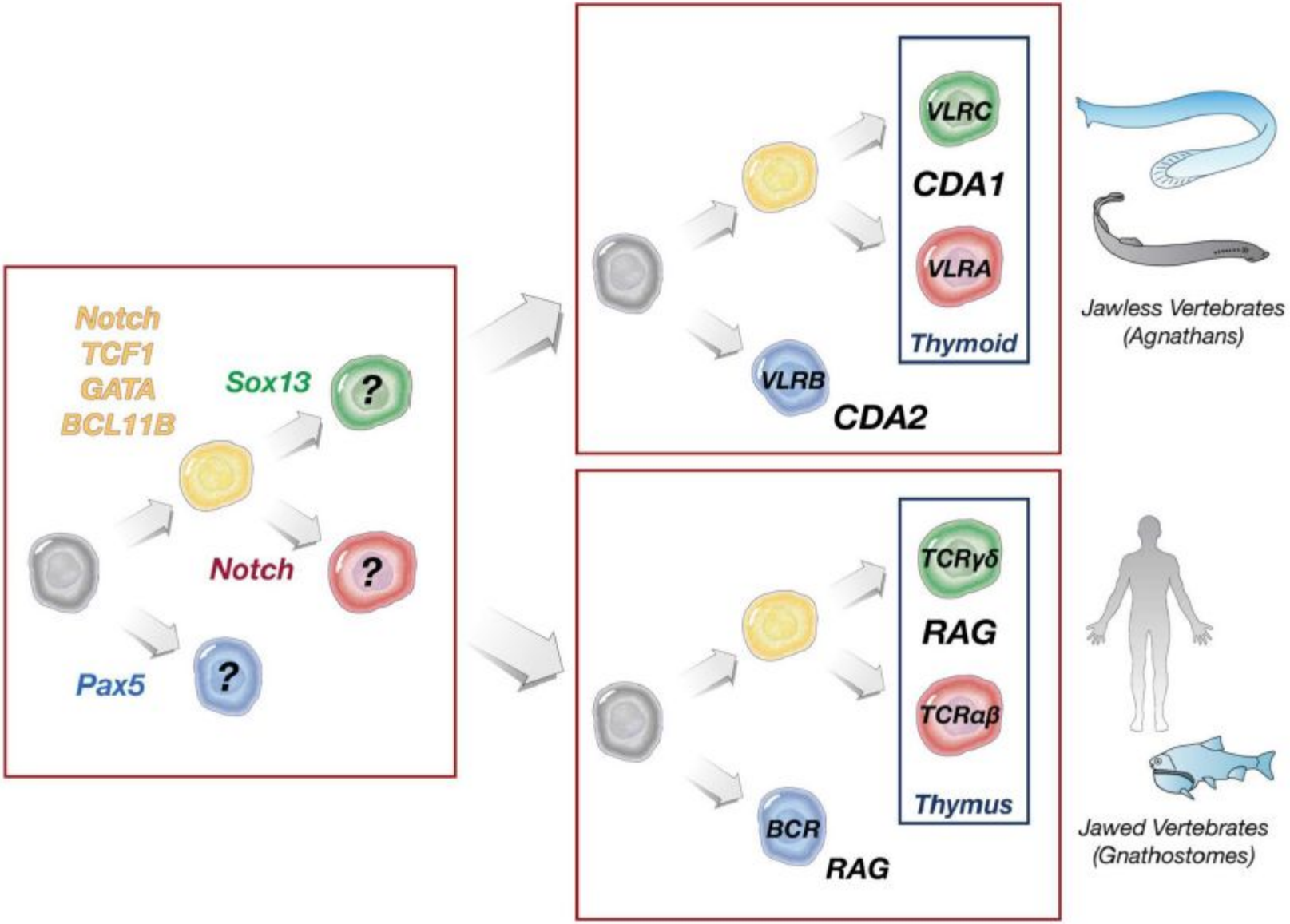
У общего предка позвоночных были дифференцированы аналоги В- и Т- лимфоцитов



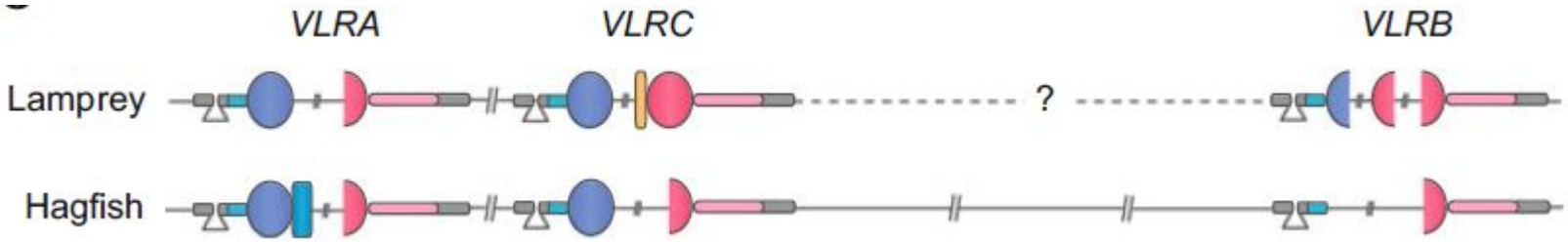
Вариабельные рецепторы лимфоцитов круглоротых связывают антигены



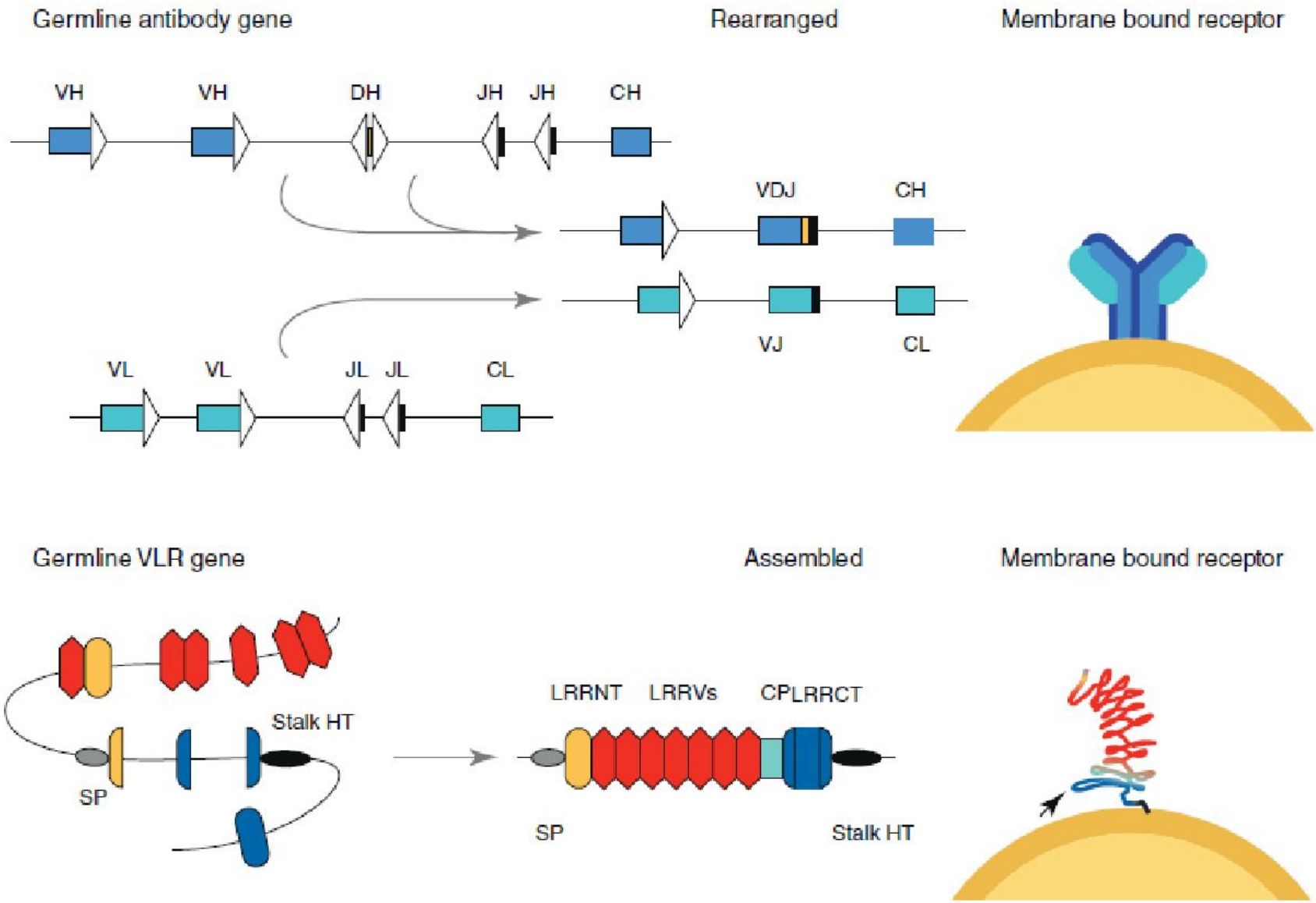
Параллельная эволюция адаптивного иммунитета



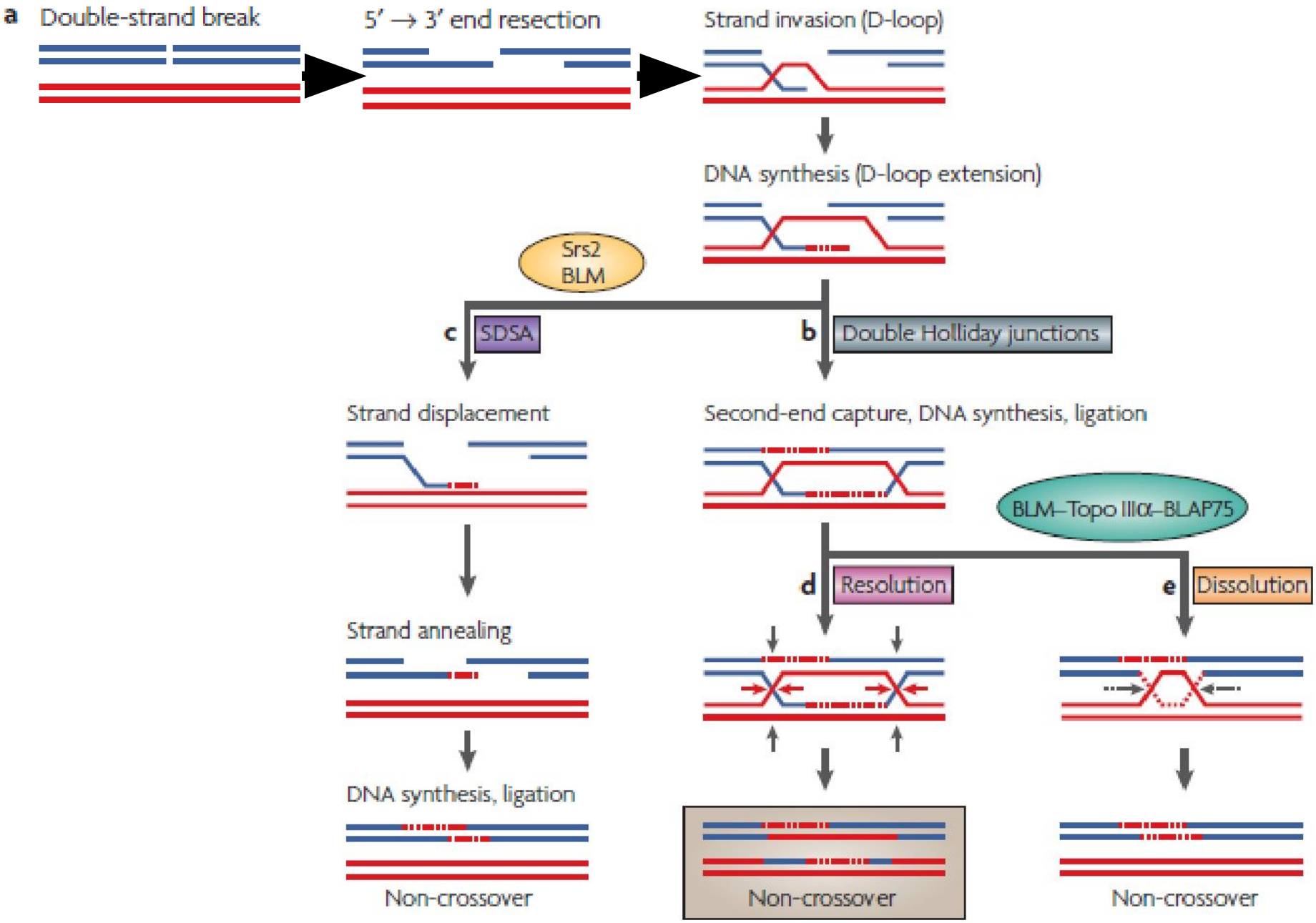
Гены LRR-содержащих вариабельных рецепторов круглоротых находятся вместе



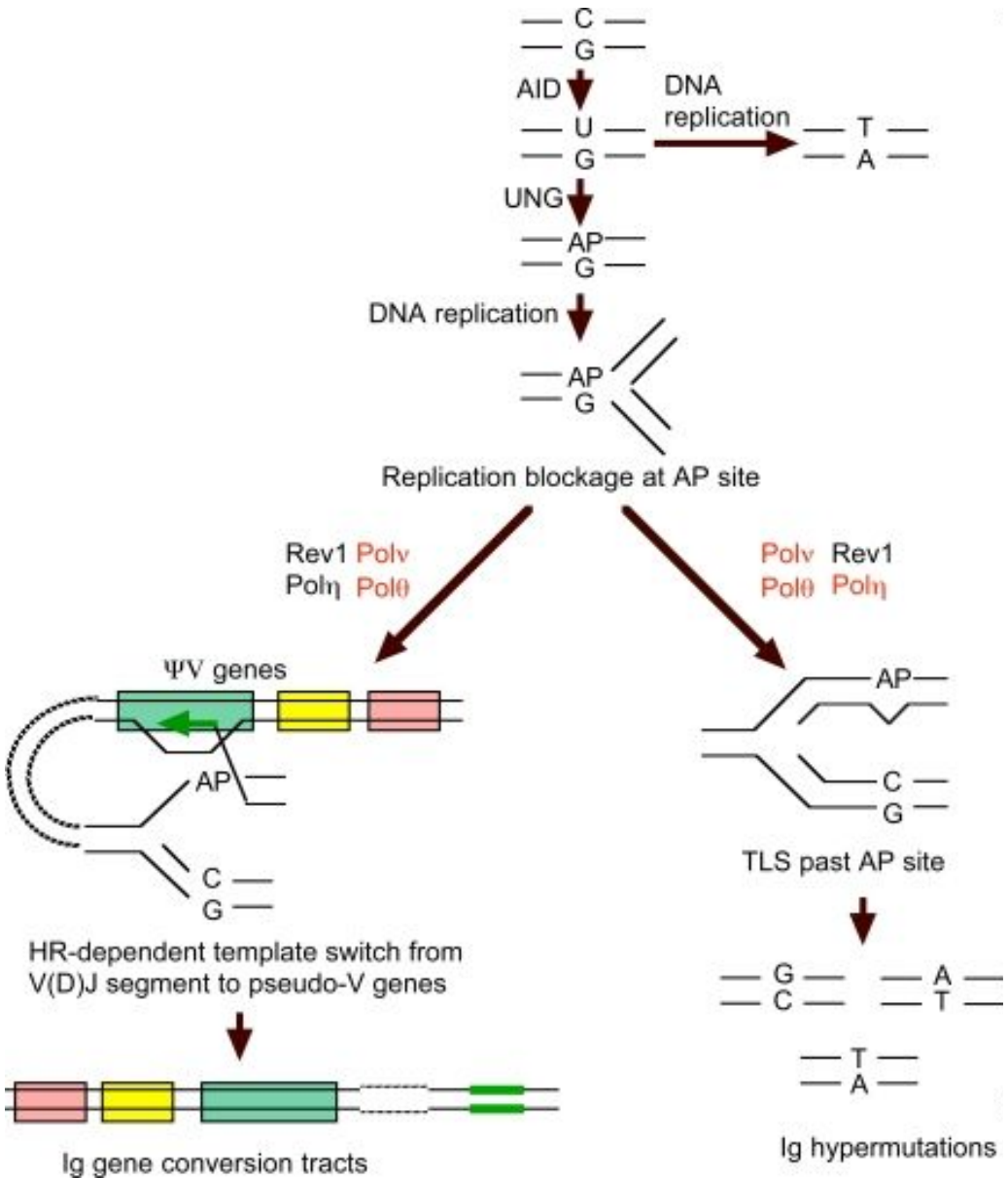
VLR подвергаются генетической конверсии



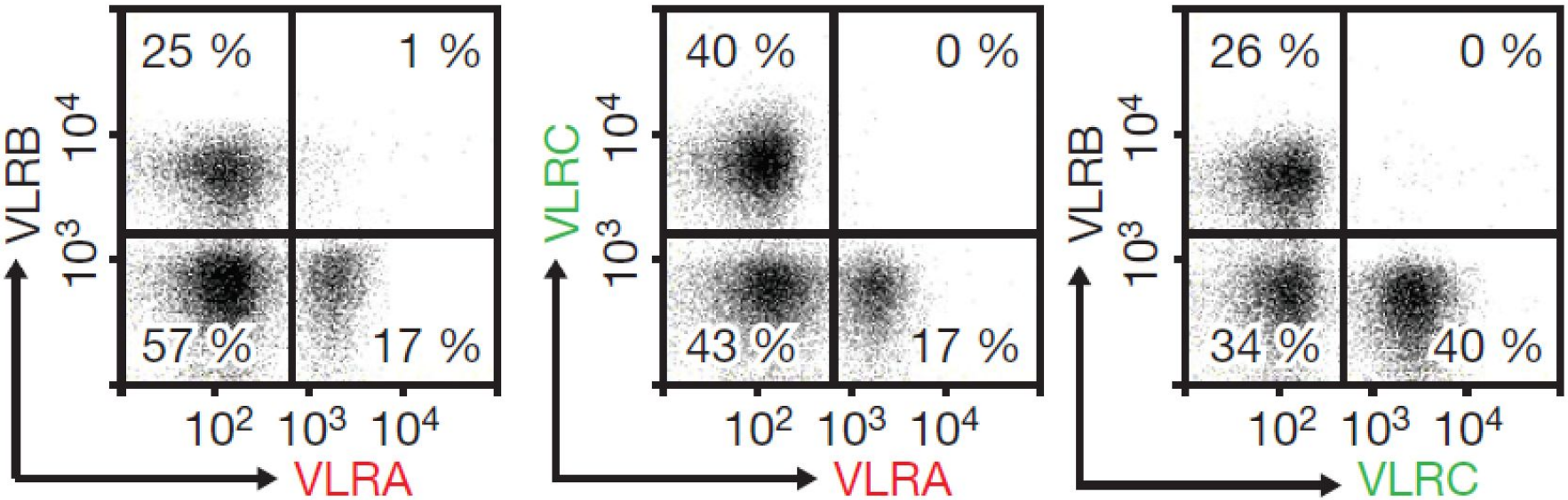
Молекулярная схема генетической конверсии

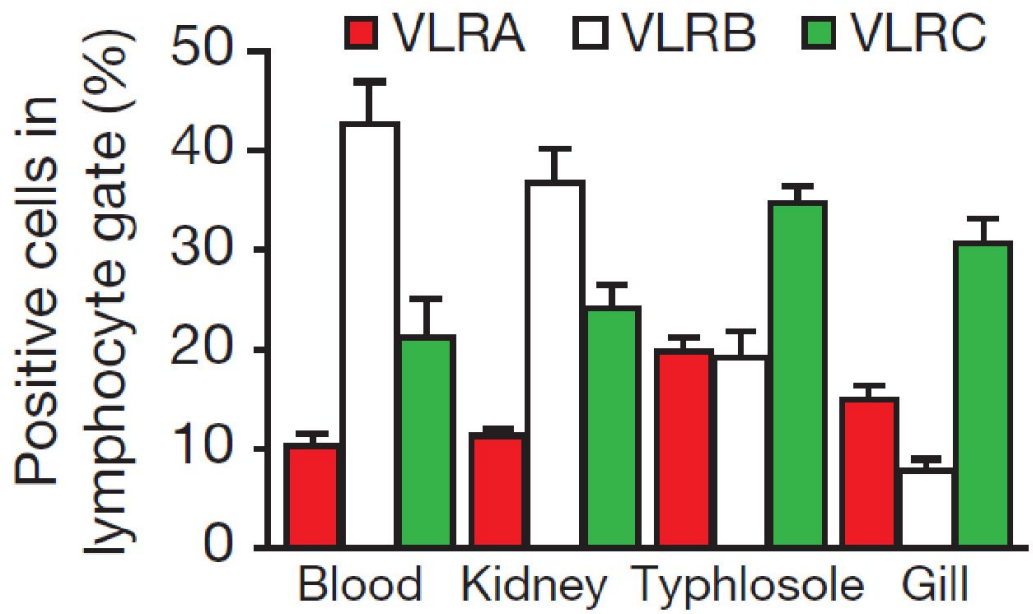


Конверсия иммуноглобулиновых генов



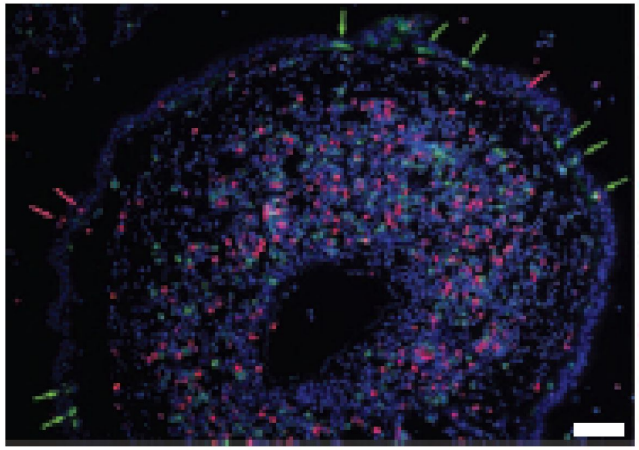
Три типа VLR-несущих клеток



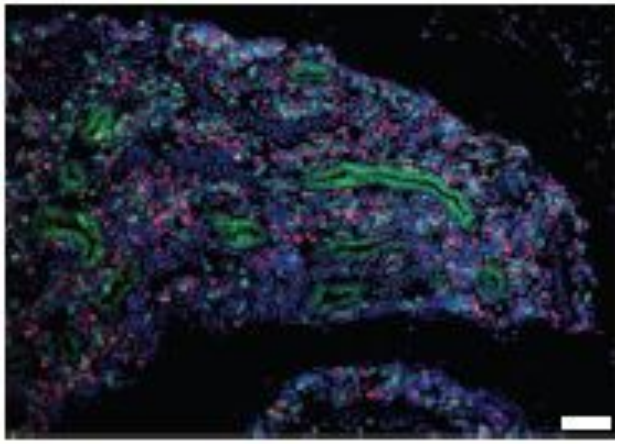


Распределение VLRA и VLRC лимфоцитов в тканях

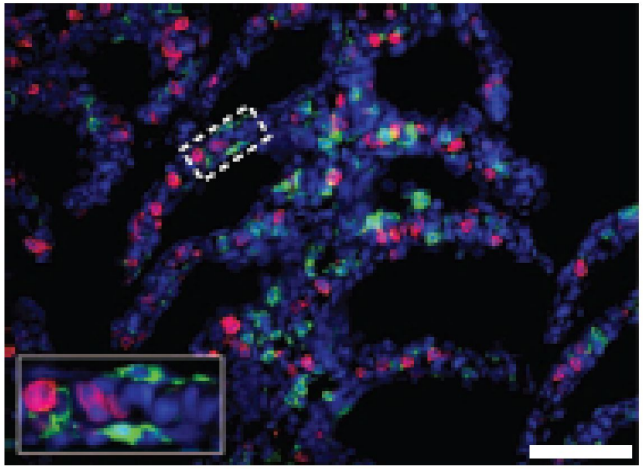
Тифлозоль



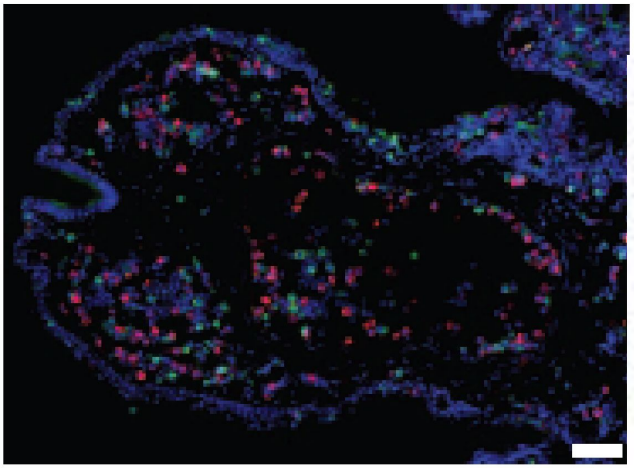
Почка



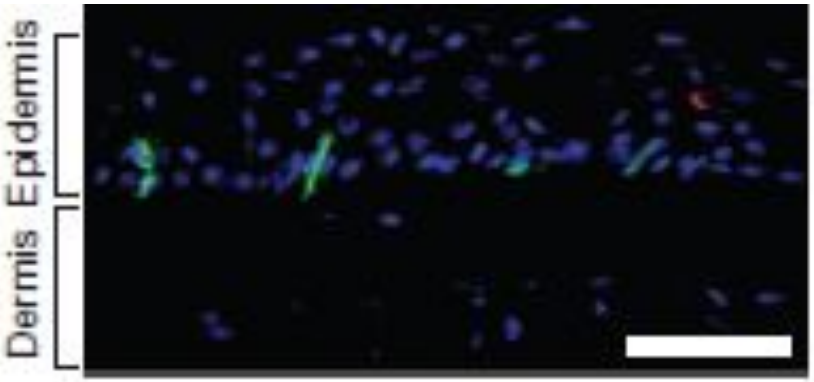
Жабра

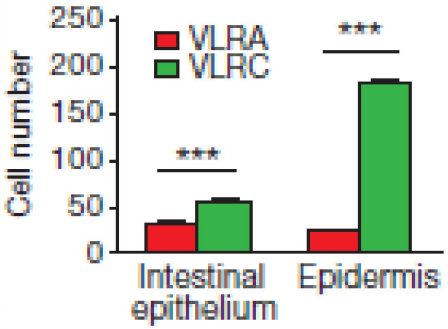


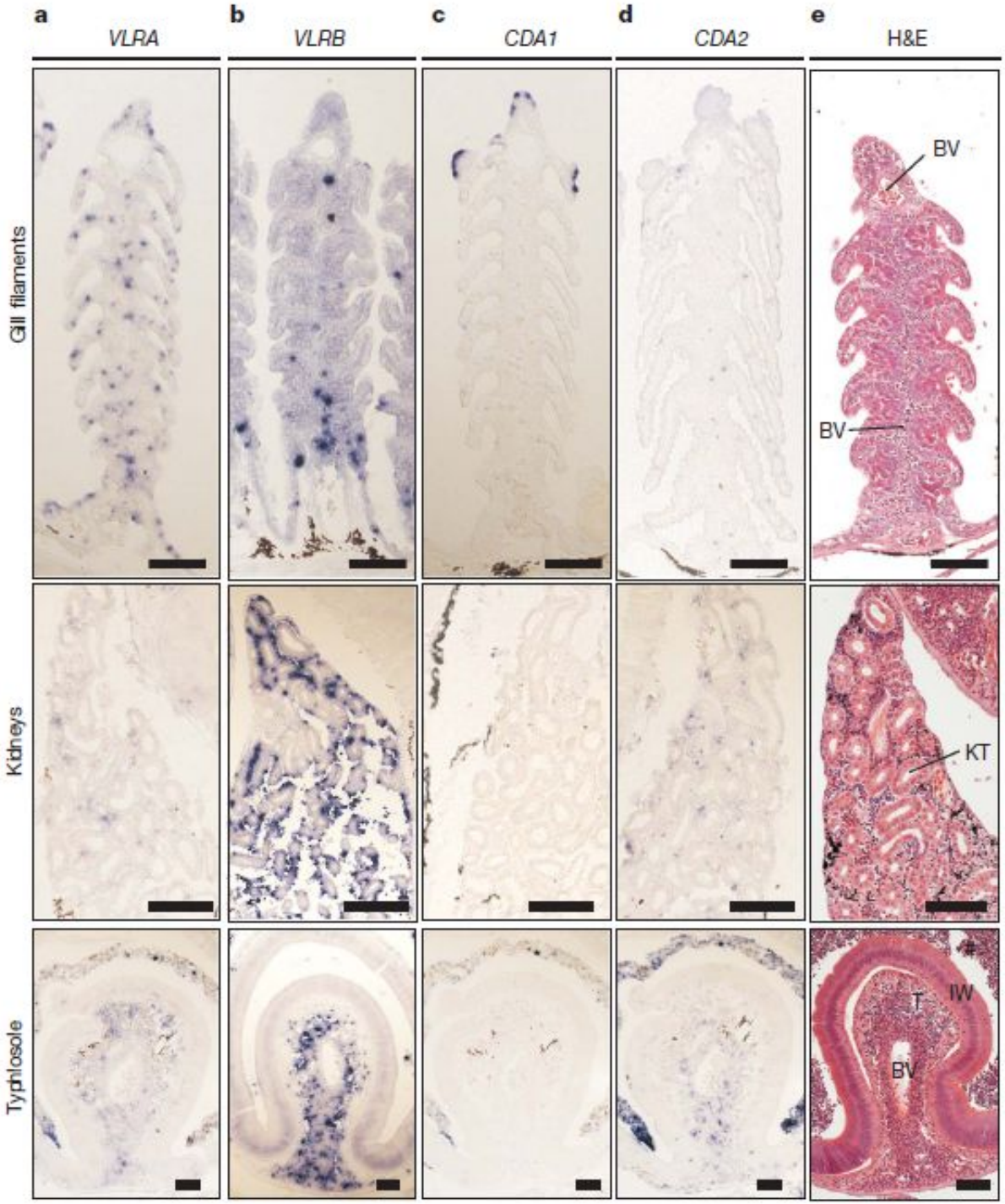
Подглоточная складка

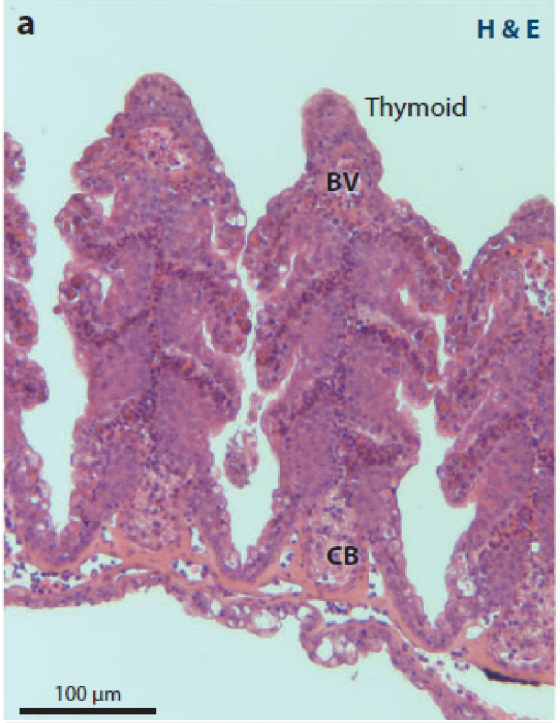


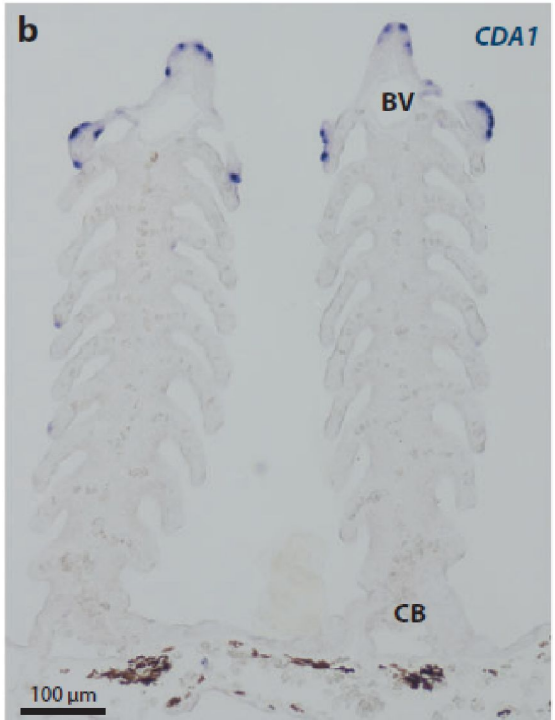
Кожа

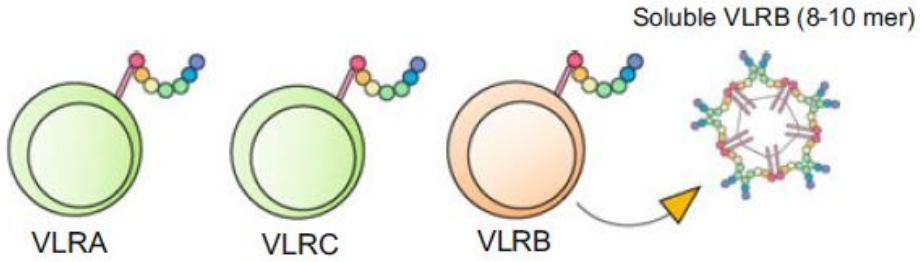





a
VLRA
b
VLRB
c
CDA1
d
CDA2
e
H&E
Gill filaments
Kidneys
Typhlosole
BV
BV
KT
T
IW
BV

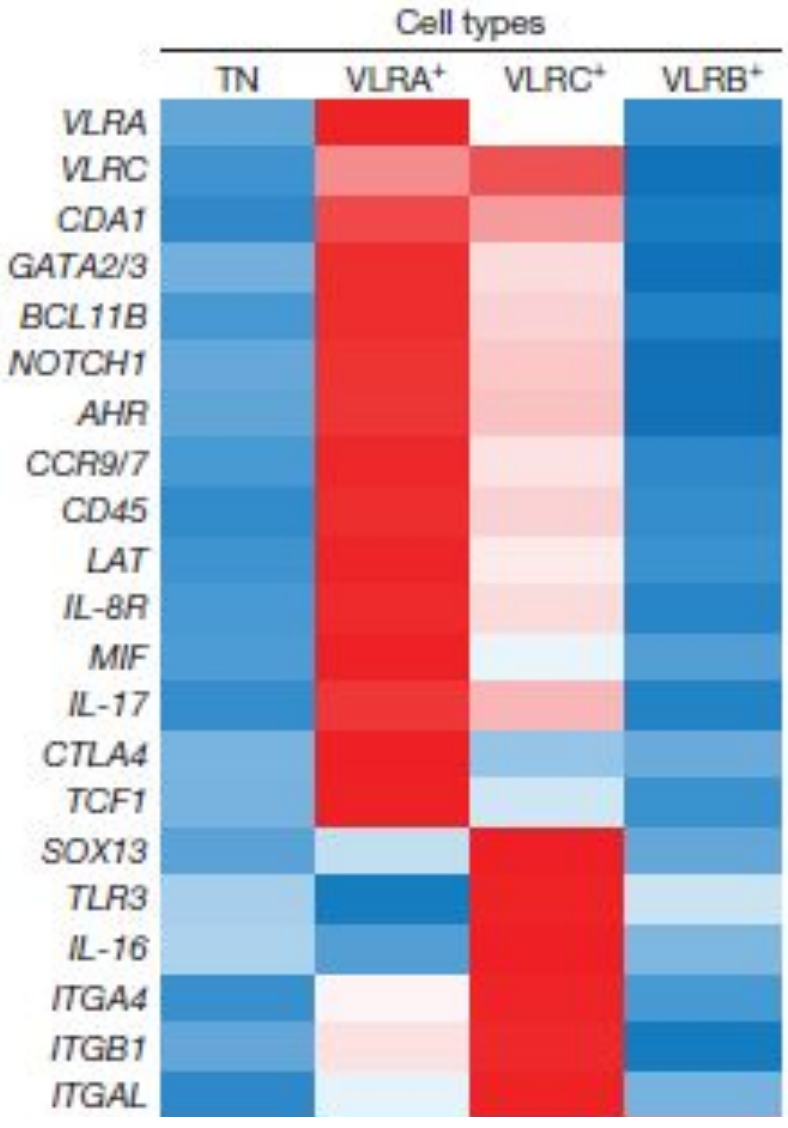

a
H & E
Thymoid
BV
CB
100 µm

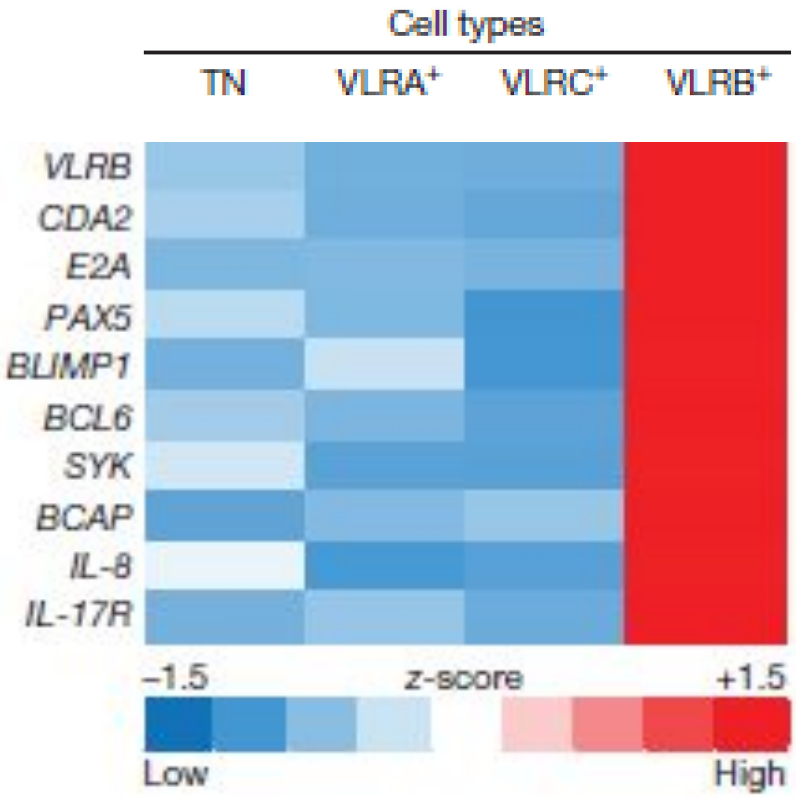

b
CDA1
BV
CB
100 µm



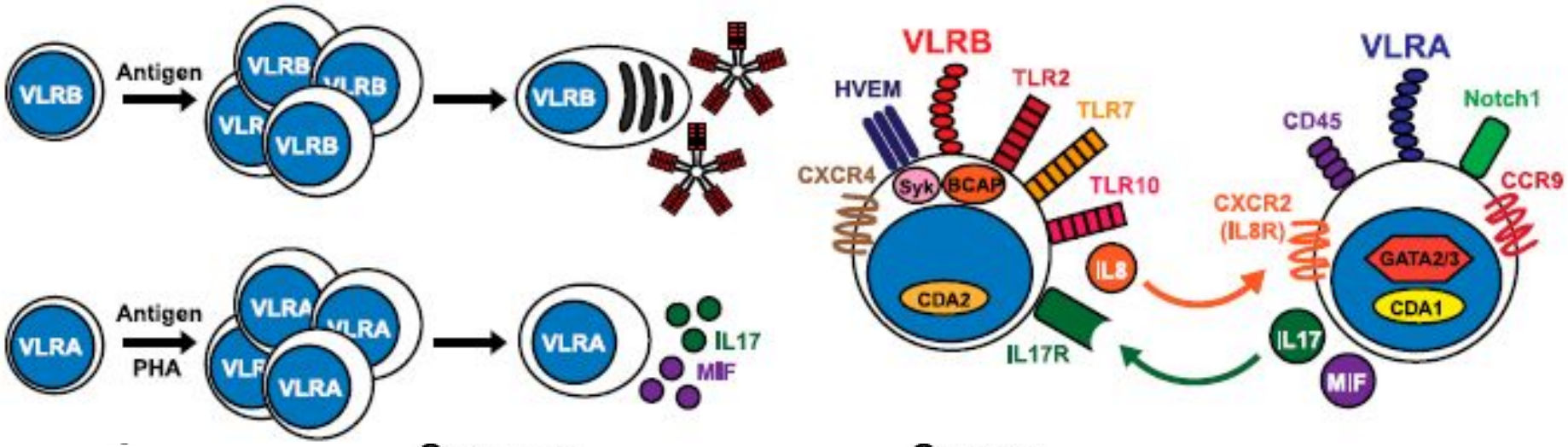
Immune function	Cellular immunity		Humoral immunity
Sites of development	Thymoid		Hematopoietic organ
Response to PHA	Yes		No
Response to poly I:C		Strong	Weak
Tissue distribution	Blood	Blood, Epithelium (skin, intestine)	Blood, intestine/typhlosole
Receptor diversity	High	High, but limited in skin	High
Enzymes involved in the generation of diversity	CDA1		CDA2
Cytokines	MIF, IL-17	IL-16, IL-17	IL-8
Cytokine receptors	IL-8R		IL-17R
Transcription factors	GATA2/3, TCF1	SOX13	BLIMP-1 BCL6, PAX5, E2A
Signaling molecules	LAT		BCAP, Syk
Cell surface molecules	NOTCH, AHR, CCR9/7, CD45, CTLA4	TLR3, ITGA4, ITGB1, ITGAL	

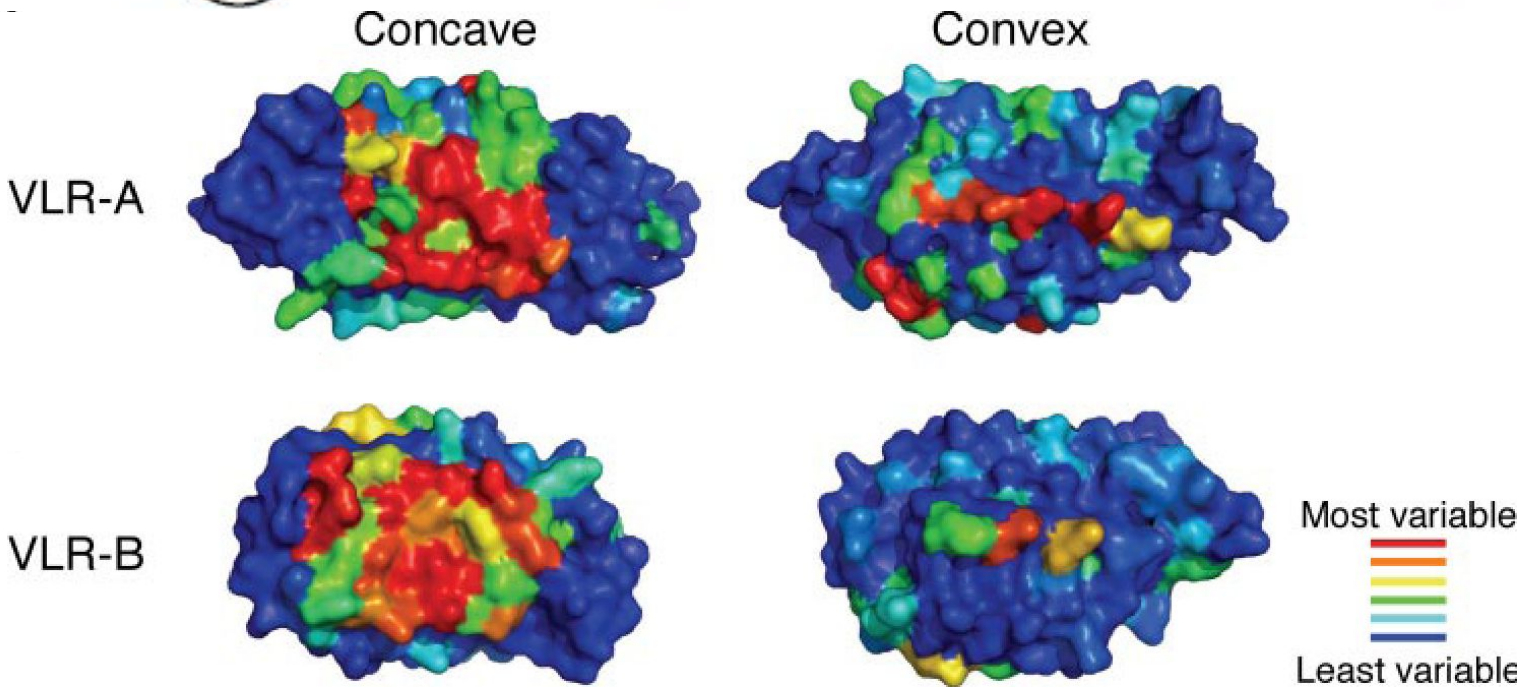
Профили экспрессии лимфоцитов миноги



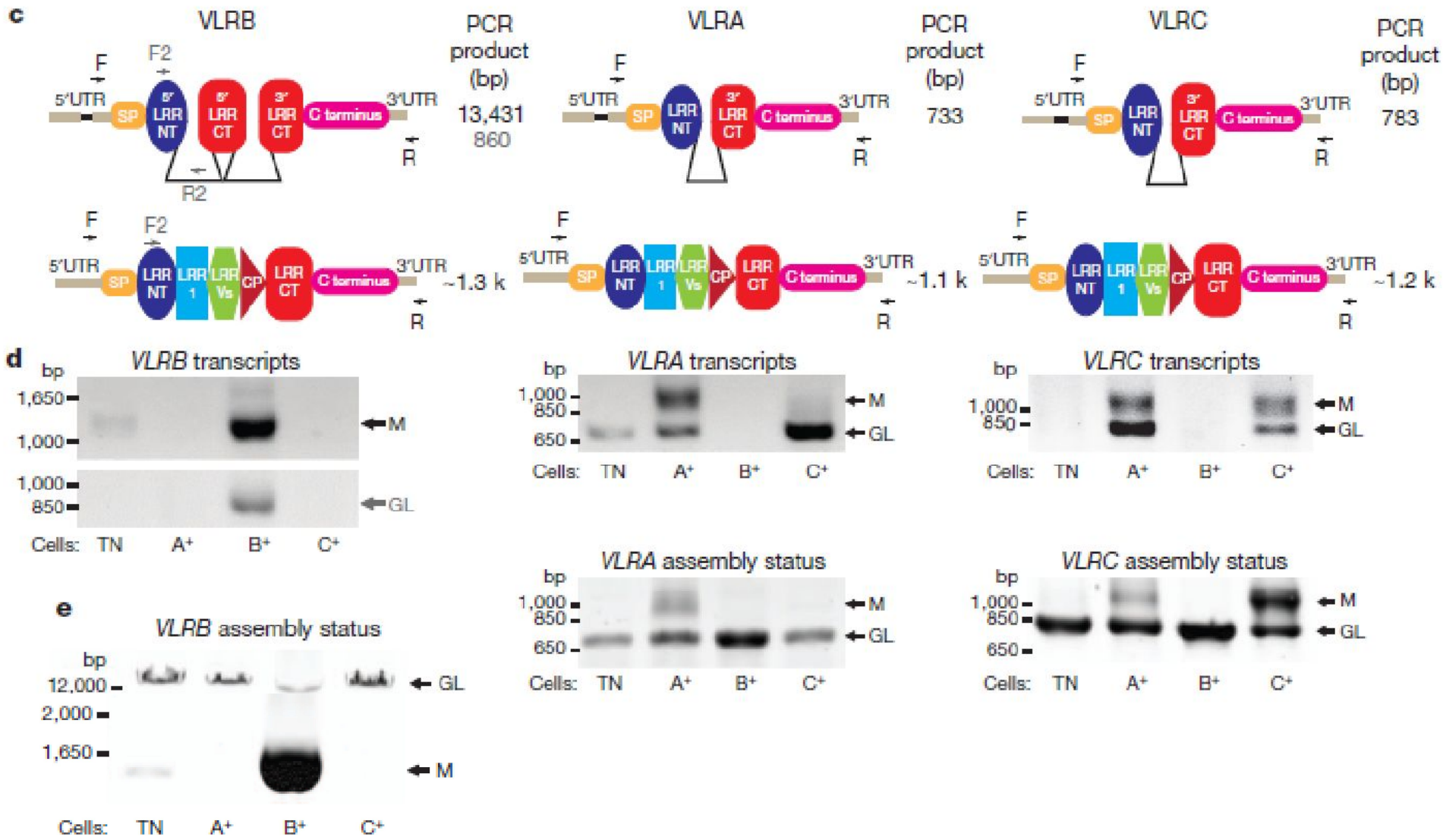


Популяции лимфоцитов круглоротых

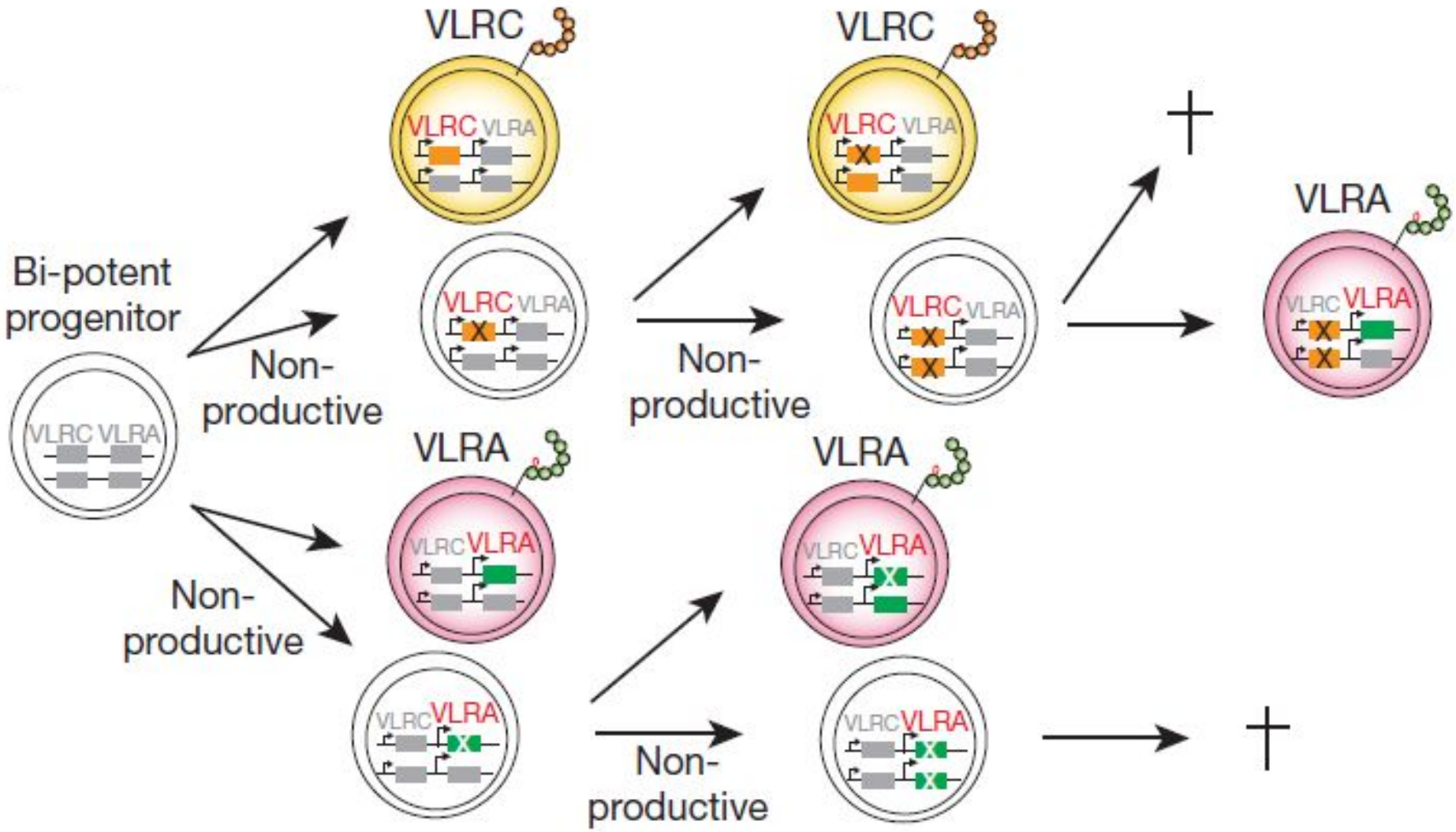




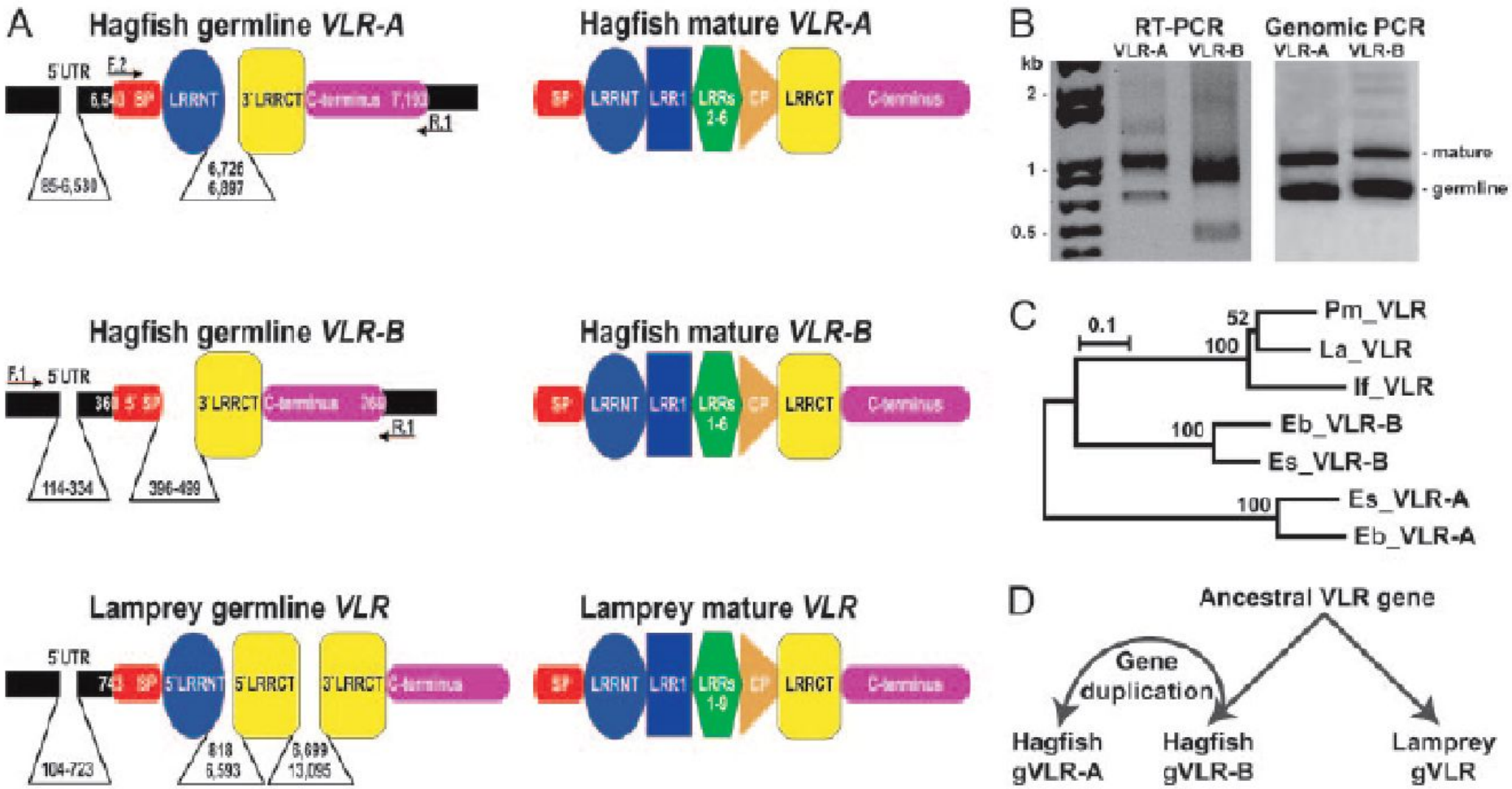
Одновременная экспрессия VLRA и VLRC на уровне мРНК



Дифференцировка лимфоцитов миног

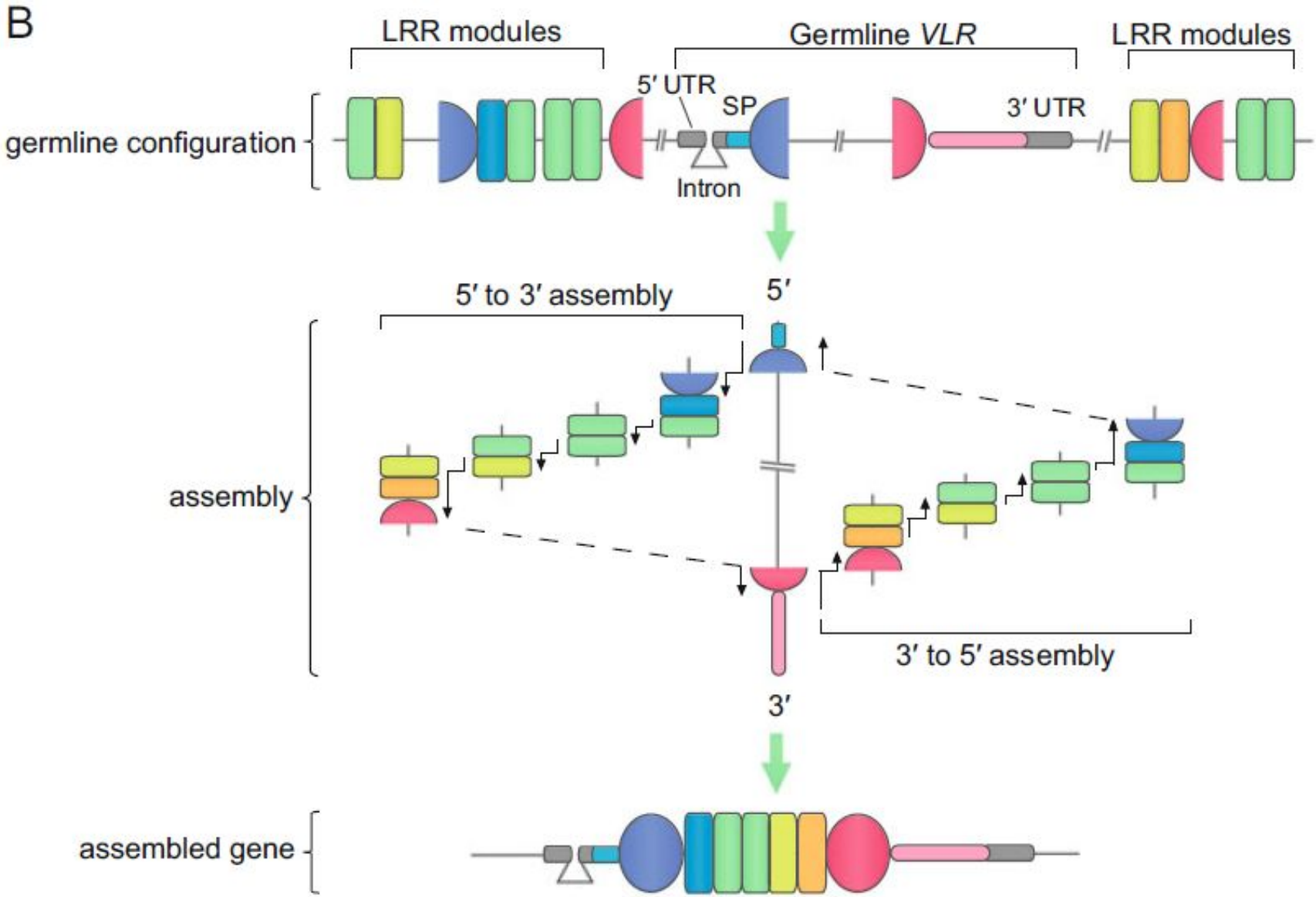


Генерация разнообразия VLR

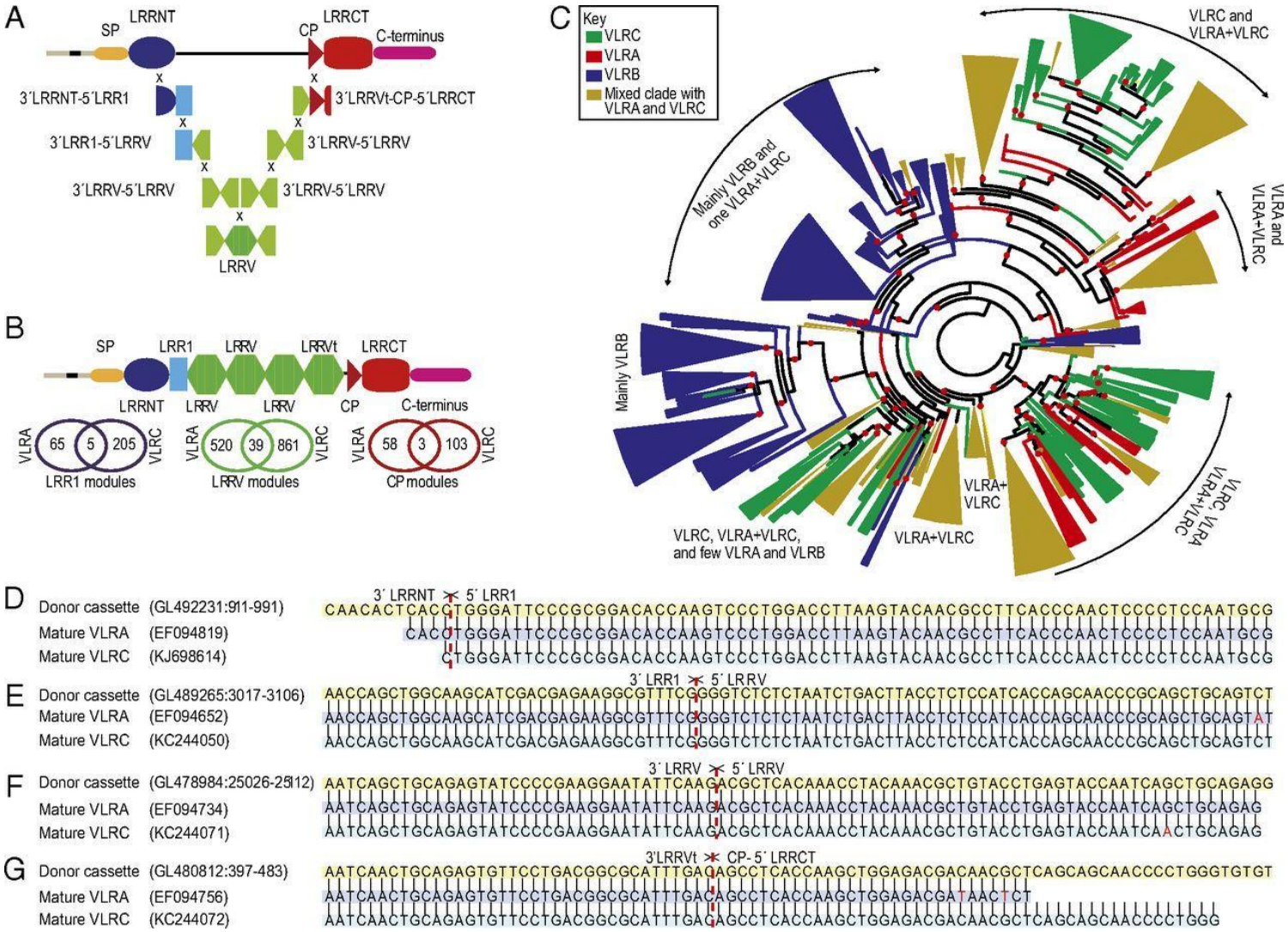


Лейциновый повтор имеет последовательность XLXXLXXLXLXXNXLXXLPXXXFX

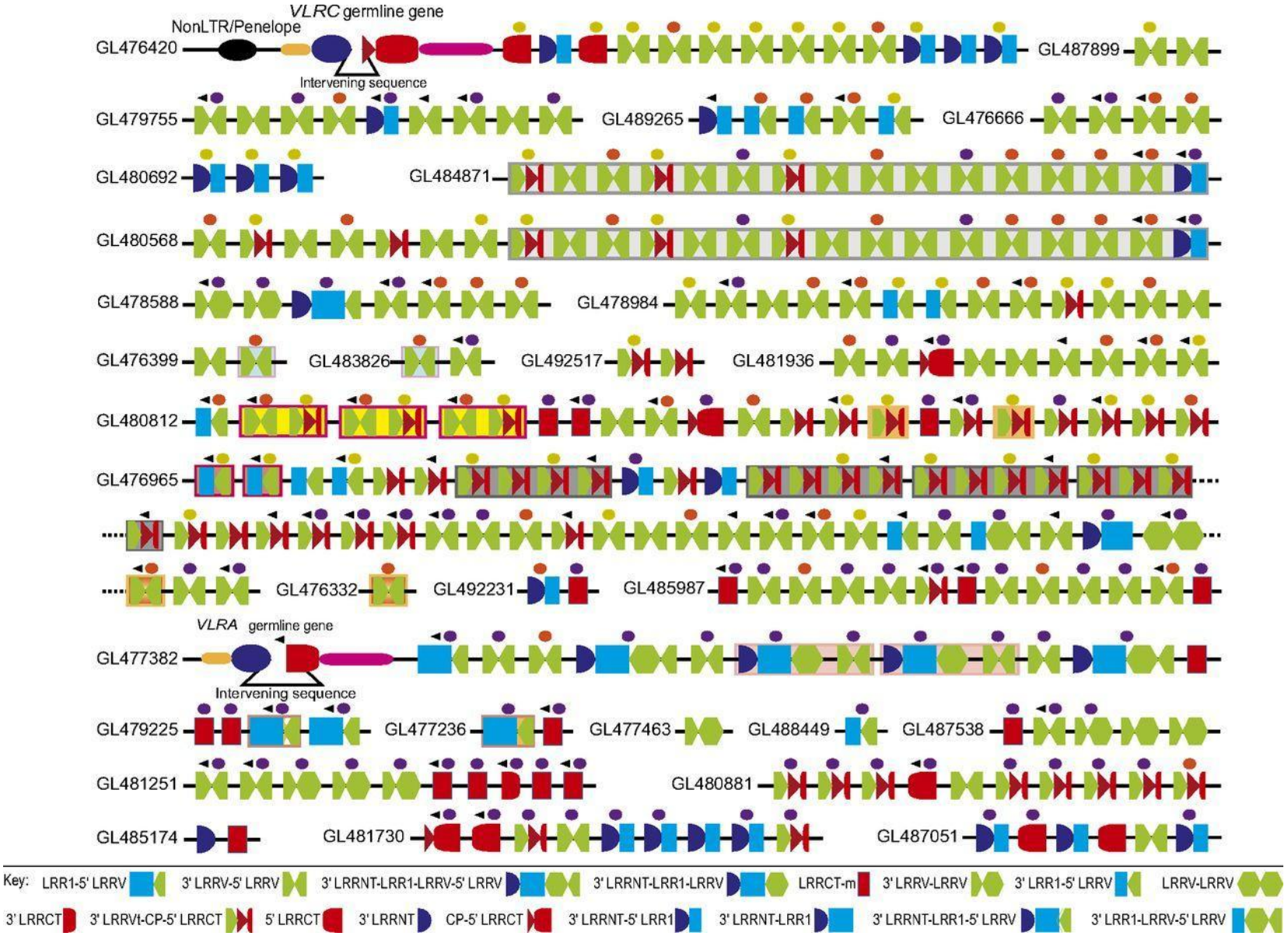
Генерация разнообразия VLR



VLRA и VLRC используют одни и те же элементы кассет генов



Геномная организация локуса VLRA/VLRC



Характеристики первых VLR к лимфоцитарным антигенам человека

Screening results of monoclonal VLR antibodies to PBMCs

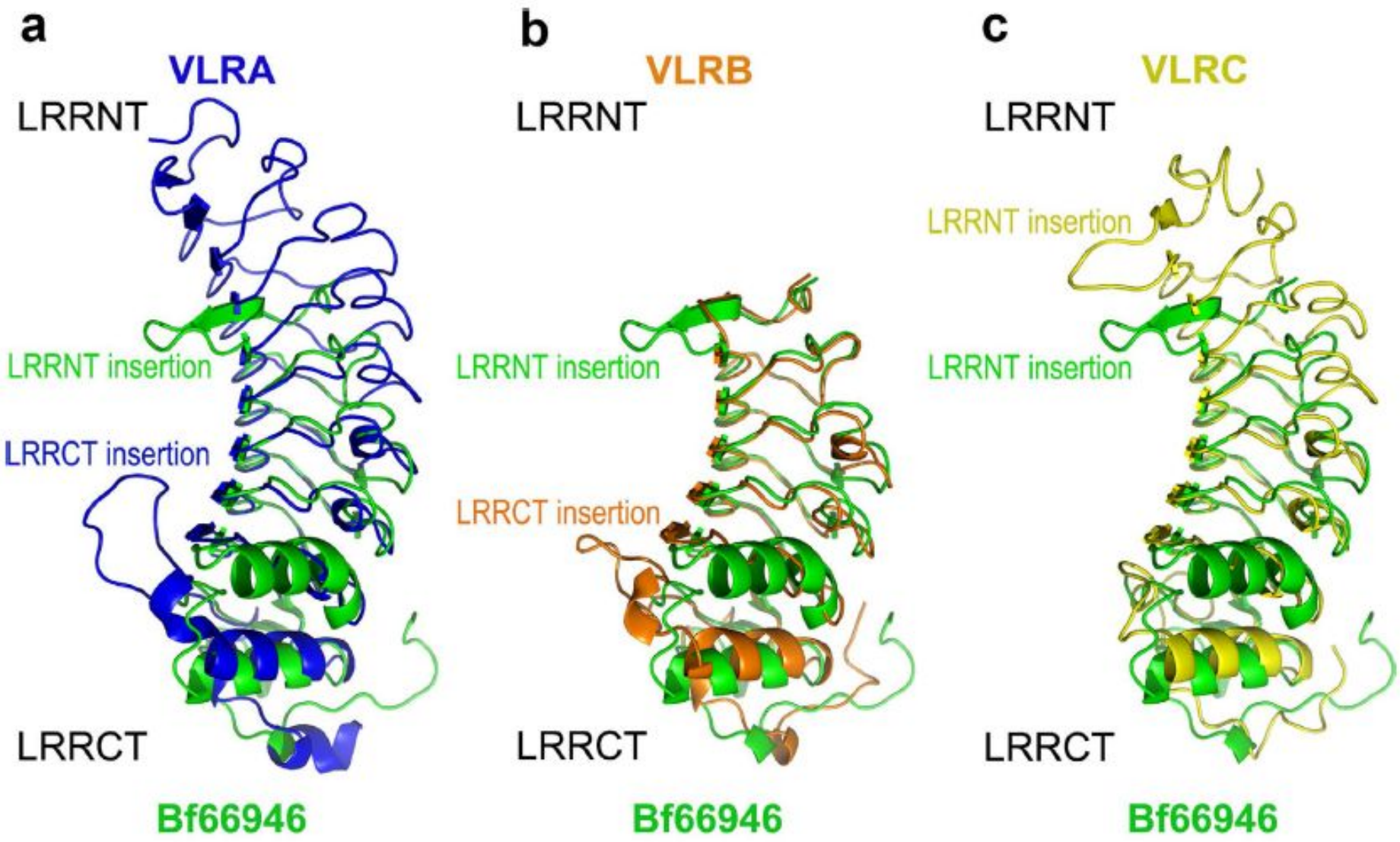
VLR clone	T cells	B cells	non B/T cells	monocytes
VLR6	+	−	−	−
VLR18	+	+	+	−
VLR25	+	+	+	−
VLR32	+	−	−	−
VLR33	+	−	+[1]	−
VLR37	+	−	+[1]	−
VLR73	+	−	+[1]	−
VLR87	+	+	+	−
VLR97	+	−	−	−
VLR99	−	−	−	+
VLR109	+	−	+[1]	−
VLR139	+	+	+	−

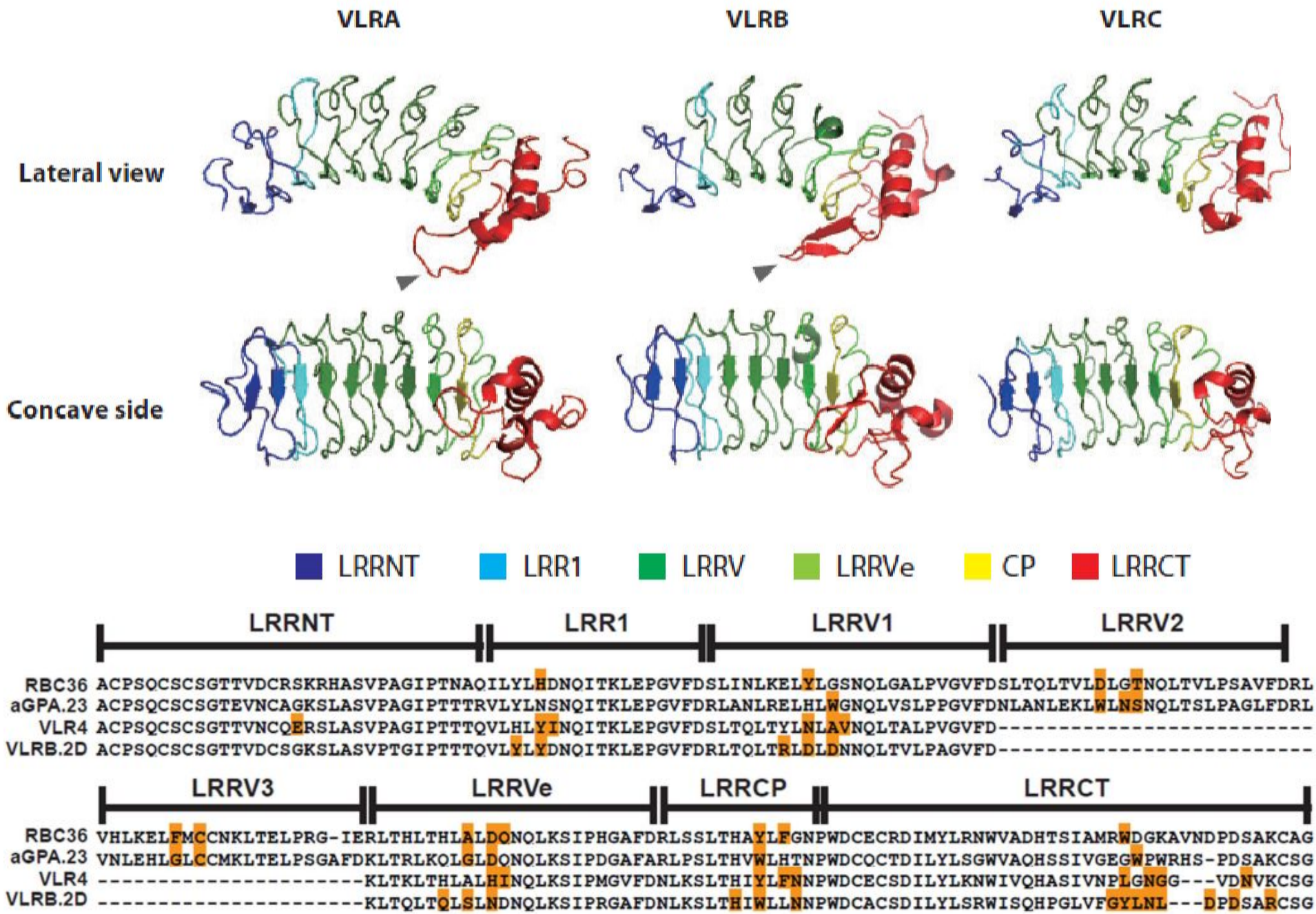
SP LRR-NT
MWIKWITTLVAFGALVQSAVACPSQCSCSGTEVHCQRKSLASVPAGIPTT
LRR-1 LRR-v
TRVLYLHVNEITKFEPGVFDRLVNLQQLYLGGNQLSALPDGVFDRLTQLT
LRR-v LRR-v CP
RLDLYNNQLTVLPAGVFDRLVNLQTLDLHNNQLKSIPRGAFDNLKSLTHI
LRR-CT
WLFGNPWDCACSDILYLSGWLGQHAGKEQGQAVCSGTNTPVRAVTEASTS
Stalk HA-His epitope tag
PSKCPGYVATTTTPTTTTPEFIPETTTSTGYPYDVPDYASHHHHHHVITT
Stalk
QKPKPLWNFNCTSIQERKNDGGDCGKPACTTLLNCANFLSCLCSTCALCR
KR

T cells: $CD3^+$, B cells: $CD19^+$, non B/T cells: $CD3^-/CD19^-$, monocytes identified by FSC/SSC profile.

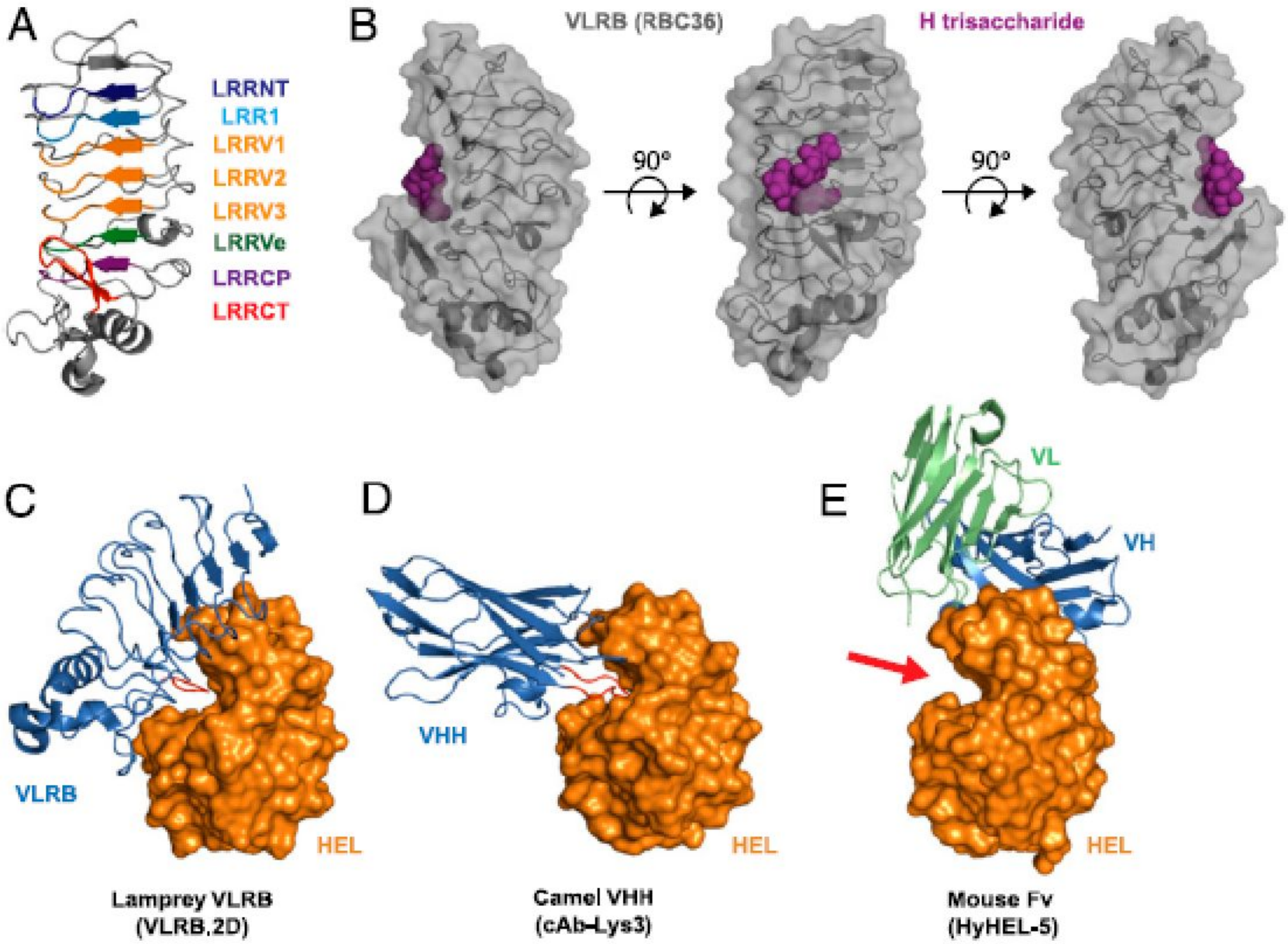
[1] indicates partial staining of the cell population.

Характер связывания антигена

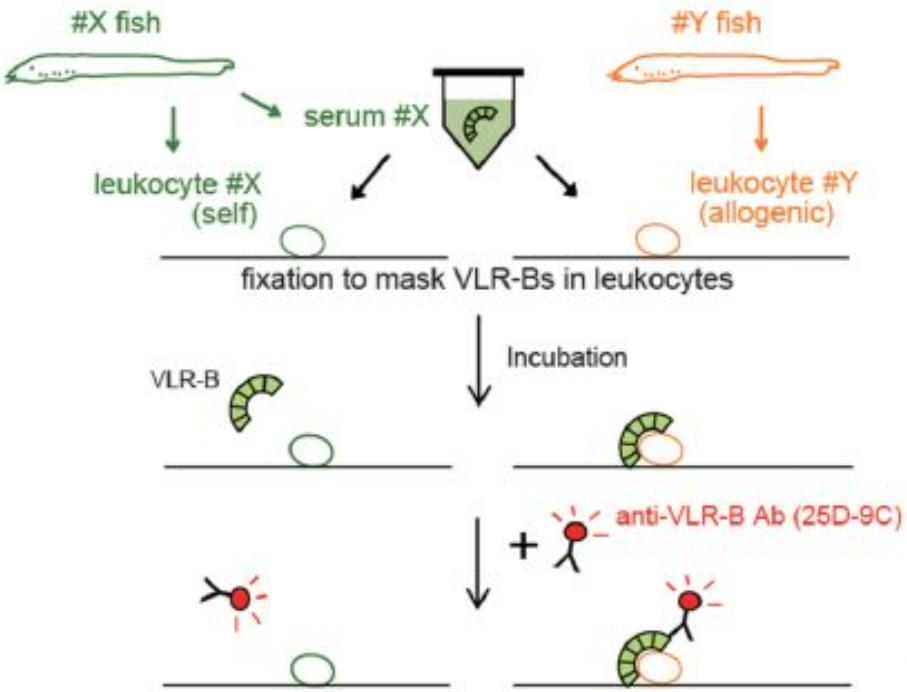


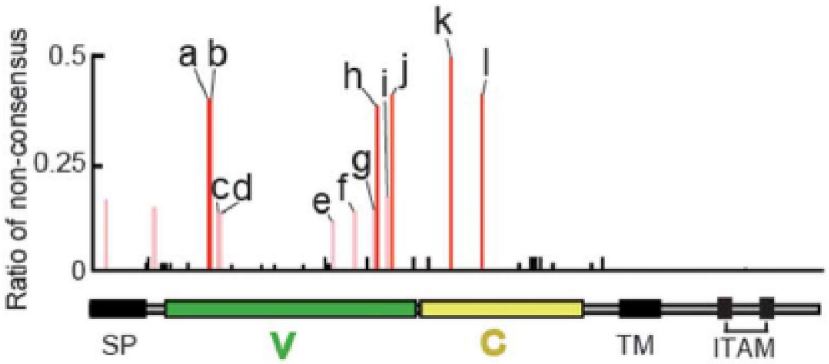

VLRA
VLRB
VLRC
Lateral view
Concave side
LRRNT
LRR1
LRRV
LRRVe
CP
LRRCT
LRRNT
LRR1
LRRV1
LRRV2
RBC36 ACPSQCSCSGTTVDCRSKRHASVPAGIPTNAQILYLHDNQITKLEPGVFDSLINLKELYLGSNQLGALPVGVFDSLTQLTVLDLGTNQLTVLPSAVFDRL
aGPA.23 ACPSQCSCSGTEVNCAGKSLASVPAGIPTTTRVLYLNSNQITKLEPGVFDRLANLRELHLWGNQLVSLPPGVFDNLANLEKLWLNSNQLTSLPAGLFDRL
VLR4 ACPSQCSCSGTTVNCQERSLASVPAGIPTTTQVLHLYINQITKLEPGVFDSLTQLTYLNLAVNQLTALPVGVFD----------
VLRB.2D ACPSQCSCSGTTVDCSGKSLASVPTGIPTTTQVLYLYDNQITKLEPGVFDRLTQLTRLDLDNNQLTVLPAGVFD----------
LRRV3
LRRVe
LRRCP
LRRCT
RBC36 VHLKELFMCCNKLTELPRG-IERLTHLTHLALDONQLKSIPHGAFDRLSSLTHAYLFGNPWDCECRDIMYLRNWVADHTSIAMRWDGKAVNDPDSAKCAG
aGPA.23 VNLEHLGLCCMKLTELPSGAFDKLTRLKQLGLDONQLKSIPDGAFARLPSLTHVWLHTNPWDCQCTDILYLSGWVAQHSSIVGEGWPWRHS-PDSAKCSG
VLR4 ----------KLTKLTHLALHINQLKSIPMGVFDNLKSLTHIYLFNNPWDCECSDILYLKNWIVQHASIVNPLGNGG---VDNVKCSG
VLRB.2D ----------KLTQLTQLSLNDNQLKSIPRGAFDNLKSLTHIWLLNNPWDCACSDILYLSRWISQHPGLVFGYLNL---DPDSARCSG

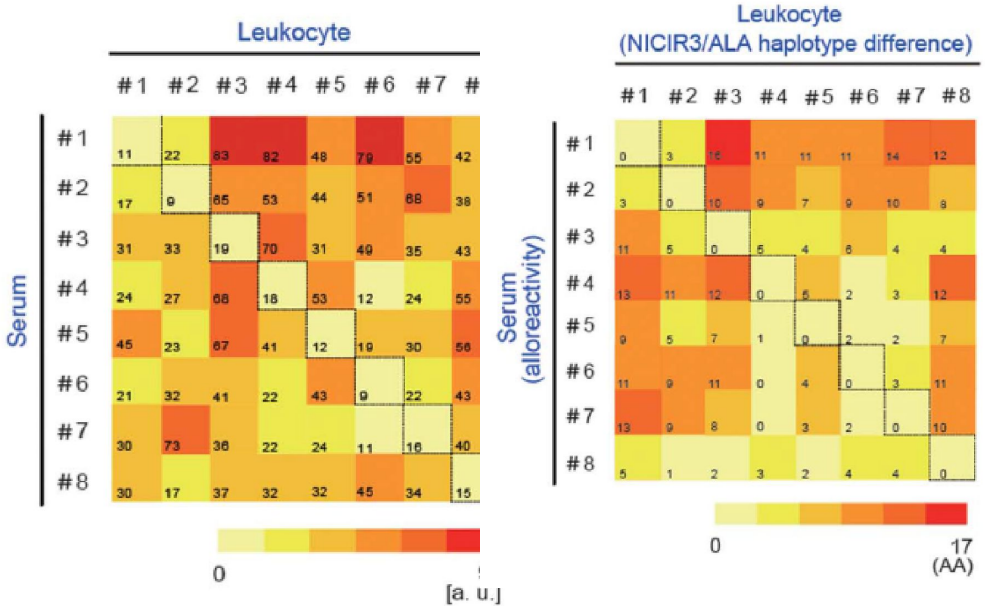
Распознавание антигена при помощи VLRB и АТ



Возможно, за аллораспознавание у миног отвечает иммуноглобулин NICIR3







Property/molecule/cell	Jawless verts (Lamprey, Hagfish)	Jawed verts (e.g. Humans, Bony fish)
Adaptive immunity	+	+
a/b T cells	+ (VLRA)	+ (a/b TCR)
g/d T cells	+ (VLRC)	+ (g/d TCR)
NK cells	?	+ (many types of receptors)
Innate Lymphoid cells (ILC)	?	+ (so far only found in mammals)
B cells	+ (VLRB)	+ (Ig)
Thymus	+ ('thymoid')	+
Enzymes for GOD	+(APOBEC, CDA1, CDA2)	+ (RAG)
Enzymes for affinity maturation	+(?) (APOBEC: CDA1, CDA2)	+ (APOBEC: AID)
Spleen	–	+
Lymph nodes	–	+ (warm-blooded)
MHC classI/II/b2m	–	+
Non-classical class I	–	+
Immunoproteasome	–	+
TAP	+ TAP-L	+ TAP-1/2/L
Developmental Transcription factors	TCF1, BCL11B, Notch, PAX5, SOX13, GATA	TCF1, BCL11B, Notch, PAX5, SOX13, GATA
Adaptive cytokines	+ IL-17 (others?)	+ IL-17, gIFN, IL-2, IL-4, IL-5, IL-7, IL-10, IL-13, IL-15, IL-21 (and many more*)
Beta5T	–	+
AIRE	–	+
Costim B7 family	+ (a few)	+ (many)
TNF family	+ (a few)	+ (many)
C′ alternative pathway	+	+
C′ classical pathway	–	+
C′ lectin pathway	+	+
C′ MAC	–	+

- Следующая лекция 9 апреля – об общих чертах иммунных систем отдельных классов Челюстноротых