

Allt er ónæmisfræði

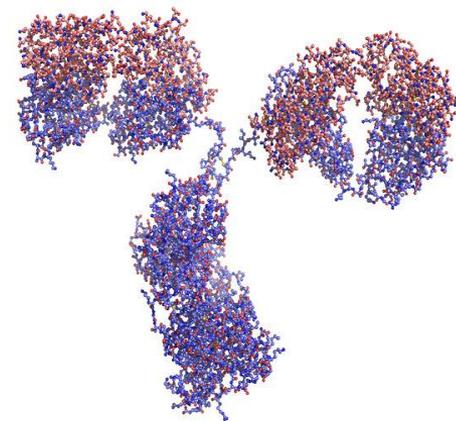
Inngangur

Helstu þættir ónæmiskerfisins

Ræsing ónæmiskerfisins

Helstu sjúkdómar í ónæmiskerfinu

Rannsóknir og nokkrir meðferðarmöguleikar

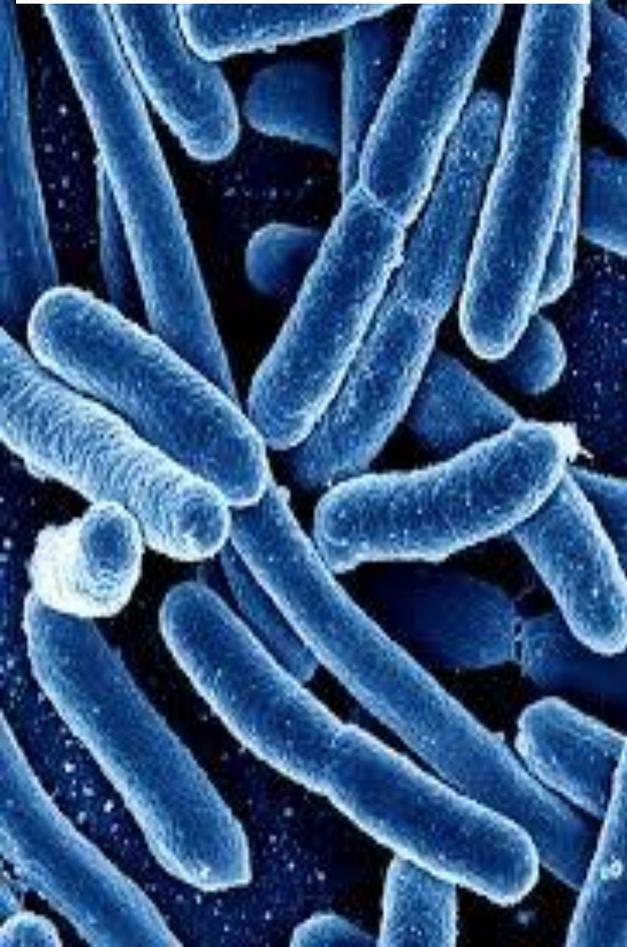


Allt er ónæmisfræði

Inngangur

(ath: útdráttur (og ekki tæmandi) úr
ónæmisfyrirlestrunum sem eru á youtube)

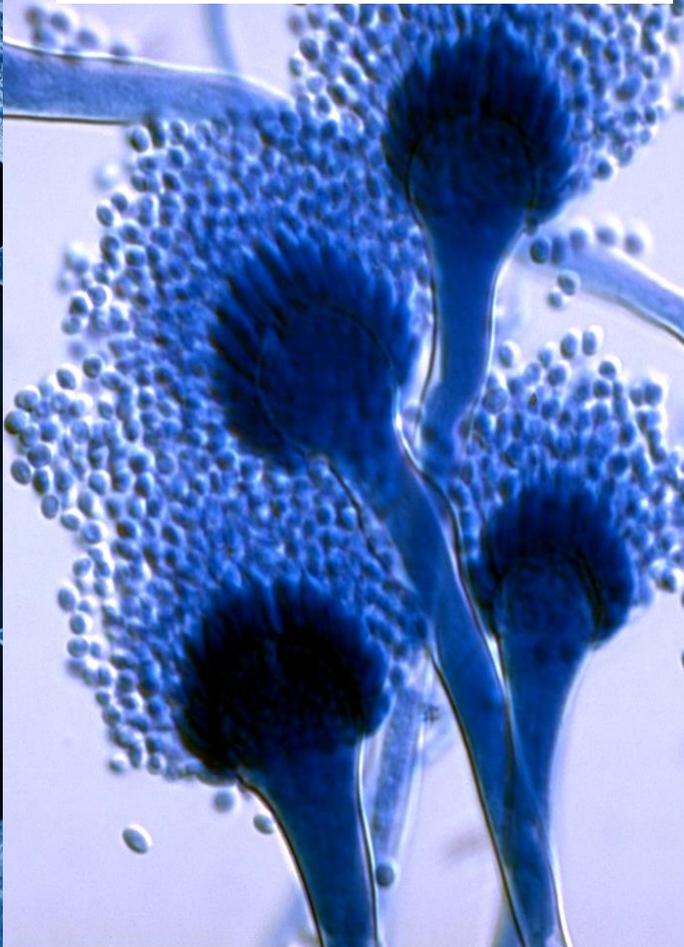
Bakteríur ...



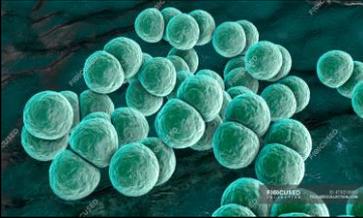
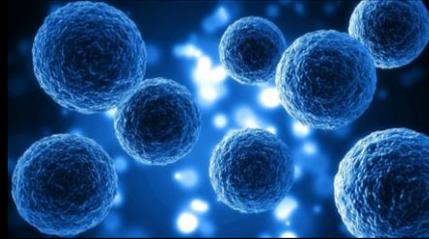
... vírusar!!!



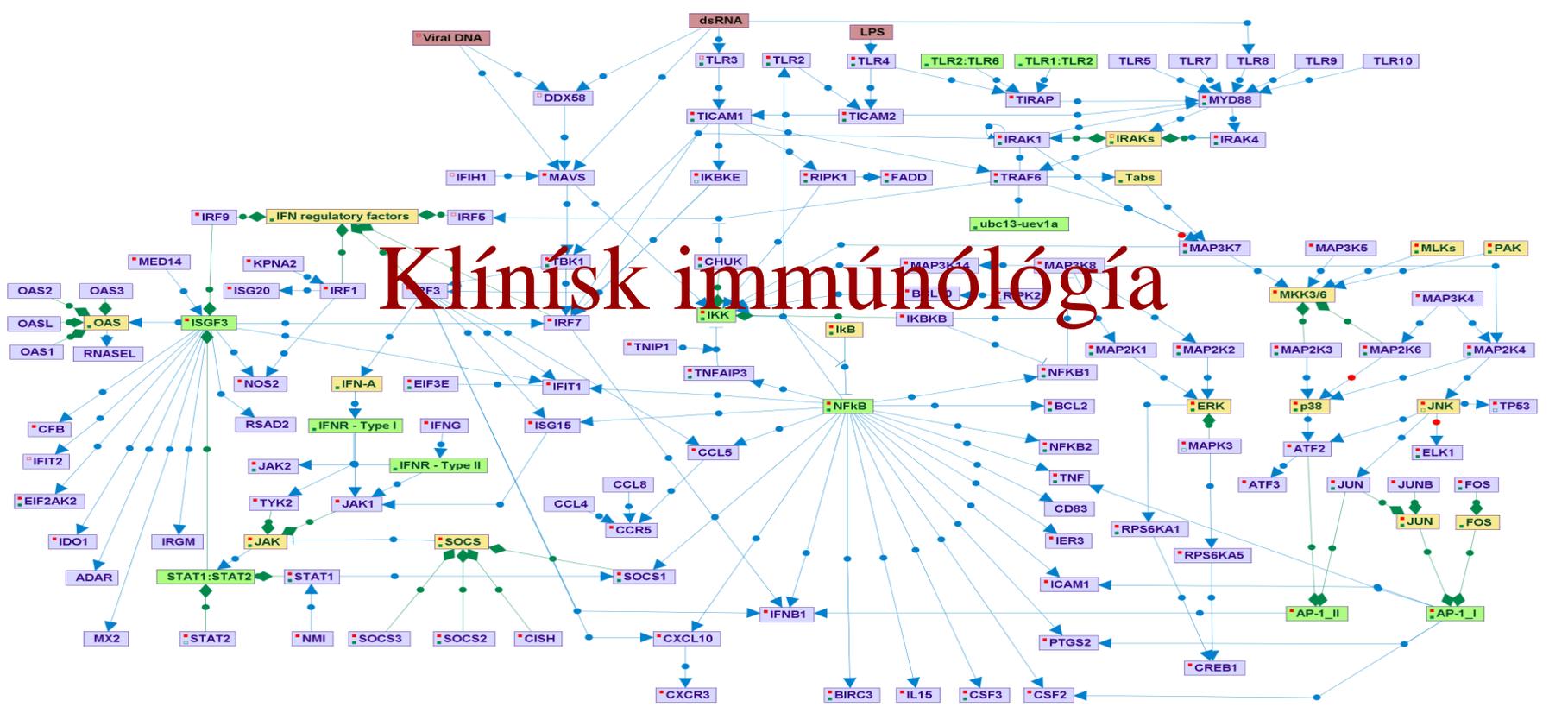
... sveppir!!



Sjálf og non-sjálf



Klinisk immunológia

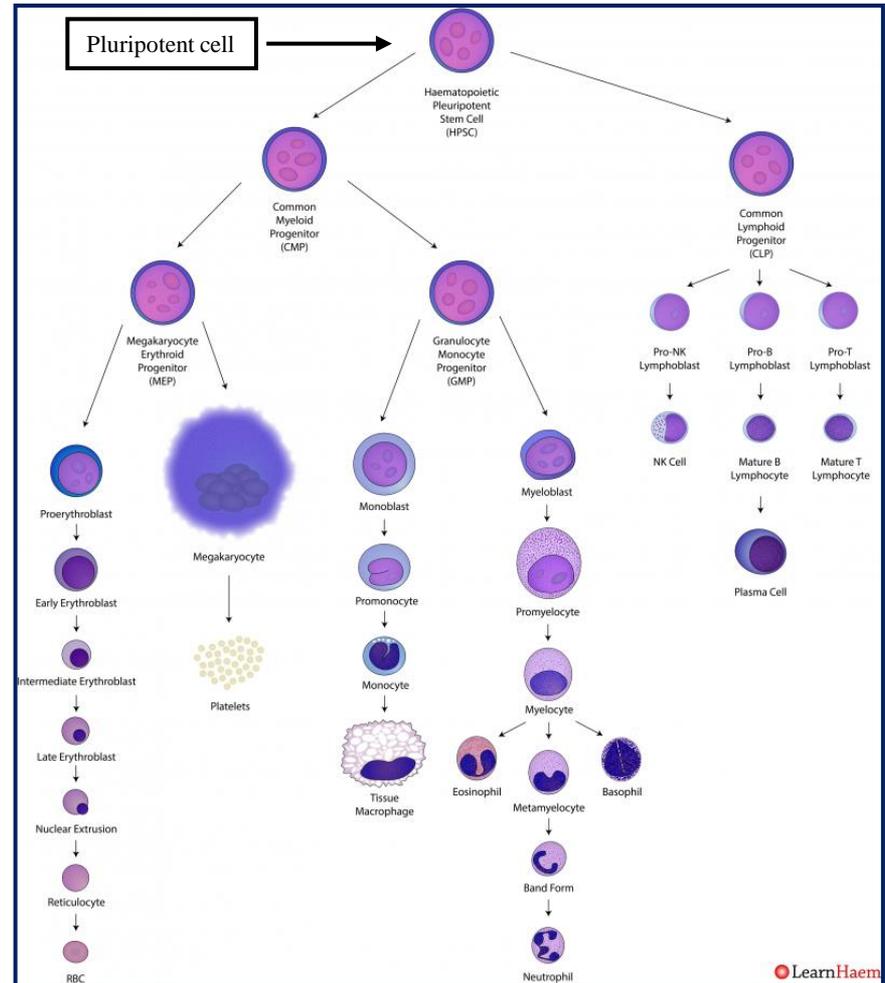


Frumur ónæmiskerfisins

Granulocyta – monocyta lína
Monocyta/macrophagar
Granulocyta
Eosinophilar
Basophilar
Neutrophilar

Lymphocyta lína
B-frumur
T-frumur
NK-frumur
... og undirflokkar

Auk þess ...
Kompliment
Frumuboðefni
..... o.m.fl



The immune system

Innate immunity
(non-specific)

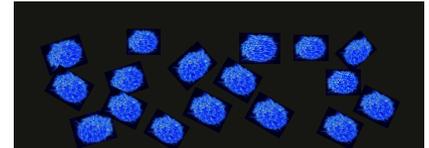
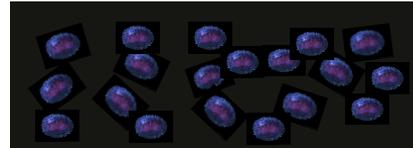
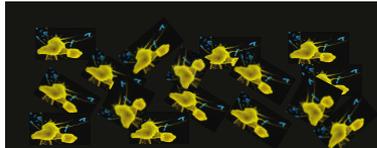
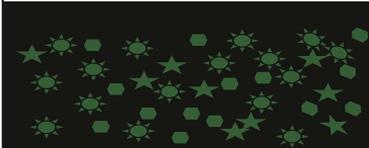
Adaptive immunity
(specific)

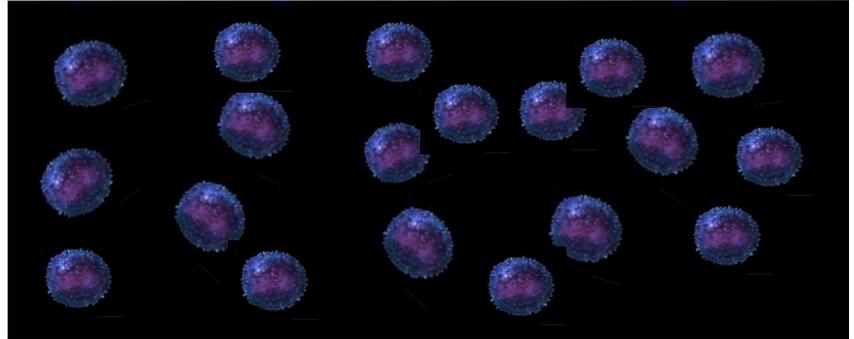
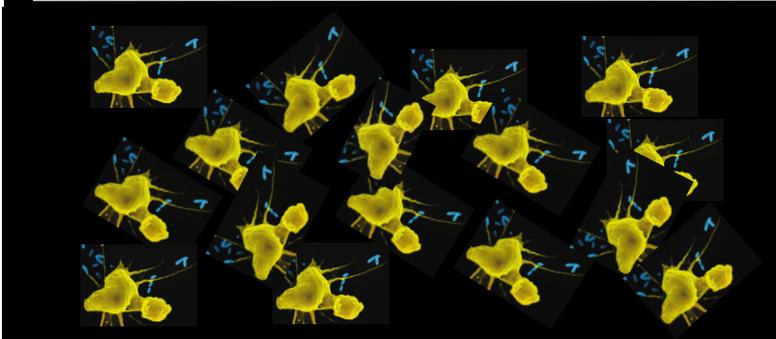
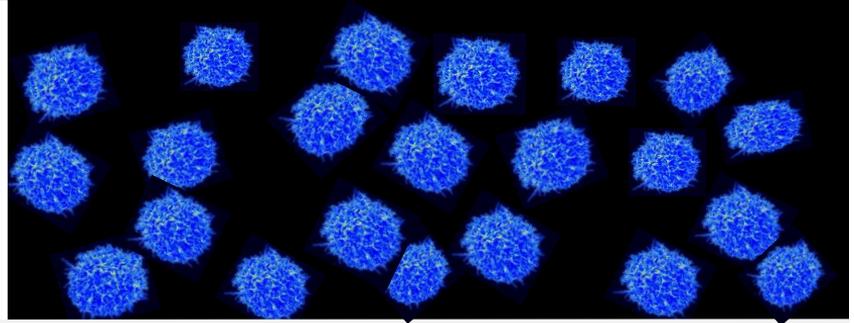
Soluble factors

Phagocytes

Humoral immunity
B-cells

Cellular immunity
T-cells





Soluble factors

Phagocytes

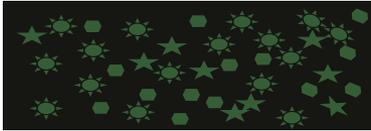
Humoral immunity
B-cells

Cellular immunity
T-cells

Ónæmisgallar / Immune defects

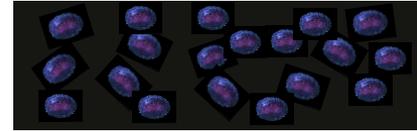
Neutrophil defects

Macrophage function

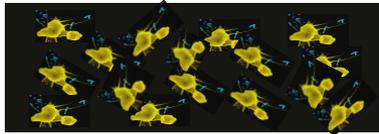


Humoral defects

B-cell defects

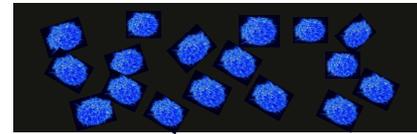


Complement defects



Cellular defects

T-cells defects



Ónæmisgallar / Immune defects

Neutrophil defects

- Number or function
- Skin infections
- Mucous membranes infections
- Granulomas
- Umbilical cord



Humoral defects

- B-cell defects
- Number and function
- Not in first months of life
- Recurrent infections (RTI)
- Bacterial infections (esp. capsulated)



Complement defects

- Recurrent bacterial infections
- Inf with capsulated bacteria
(meningococcus, pneumococcus)
- Autoimmune disorders



Cellular defects

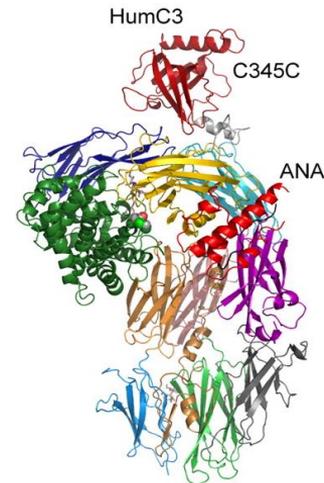
- Early in life
- Recurrent infections,
viral, fungal and parasitic
- Malignancies



Allt er ónæmisfræði

Helstu þættir ónæmiskerfisins

(Um frumurnar og fleira!)

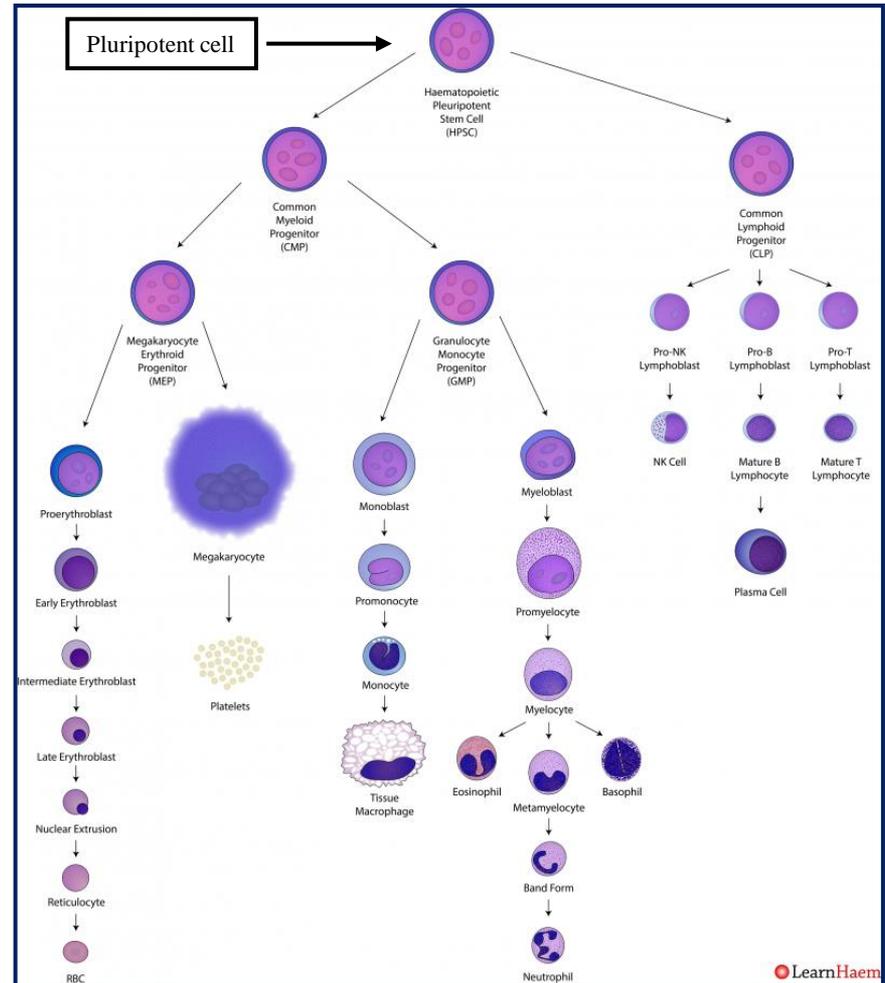


Frumur ónæmiskerfisins

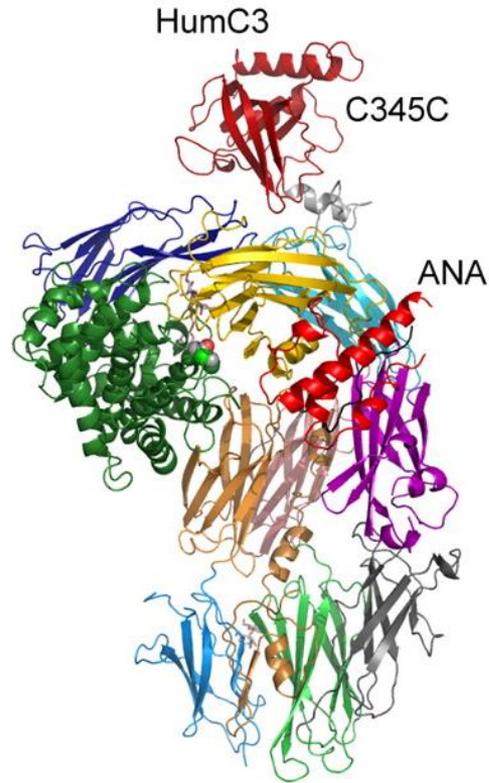
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Basophilar
Neutrophilar

Lymphocyta lína
B-frumur
T-frumur
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... og undirflokkar

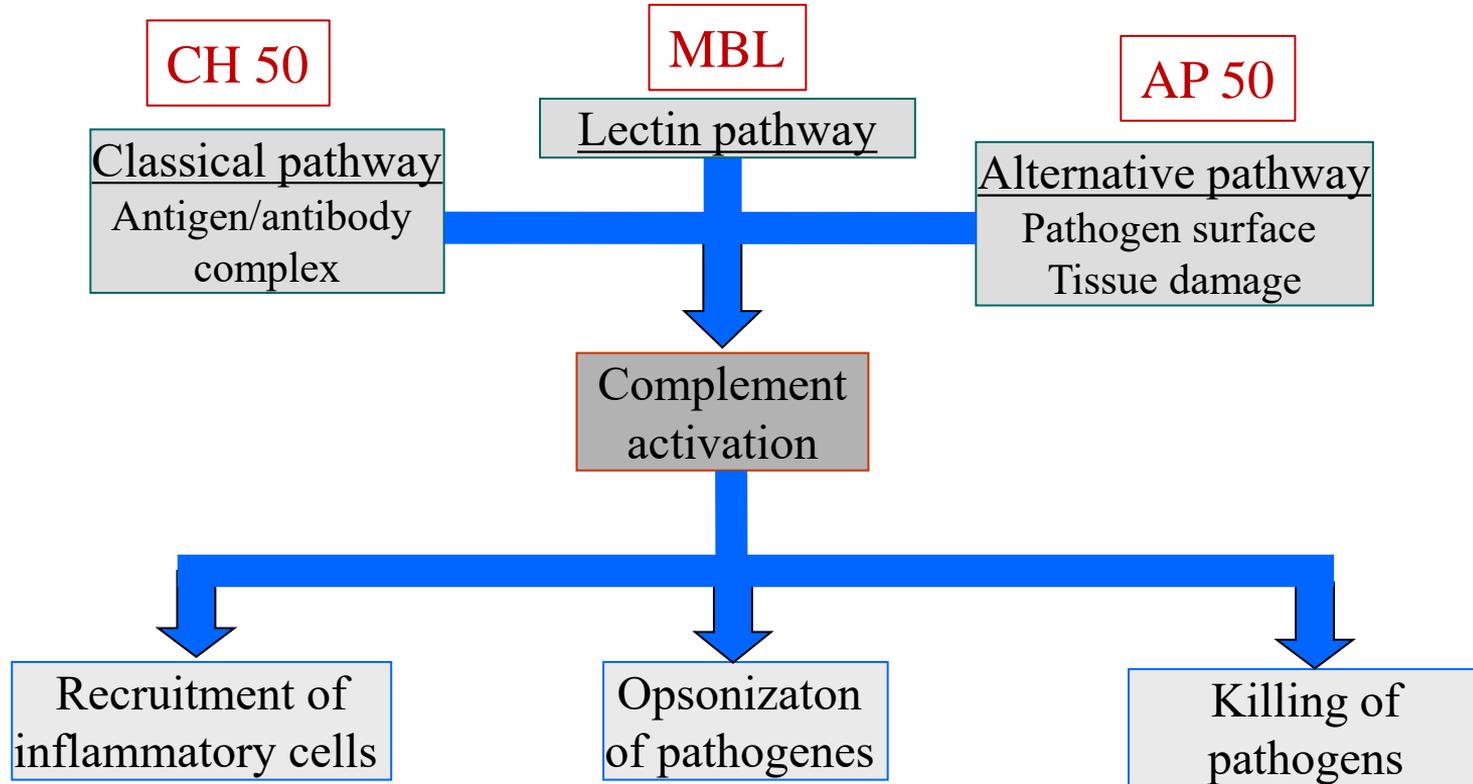
Auk þess ...
Kompliment
Frumuboðefni
..... o.m.fl



Complement



Kompliment kerfið / magnakerfið



Kompliment kerfið / magnakerfið

Complement defects

Recurrent bacterial infections

Inf with capsulated bacteria
(meningococcus, pneumococcus)

Autoimmune disorders

SLE

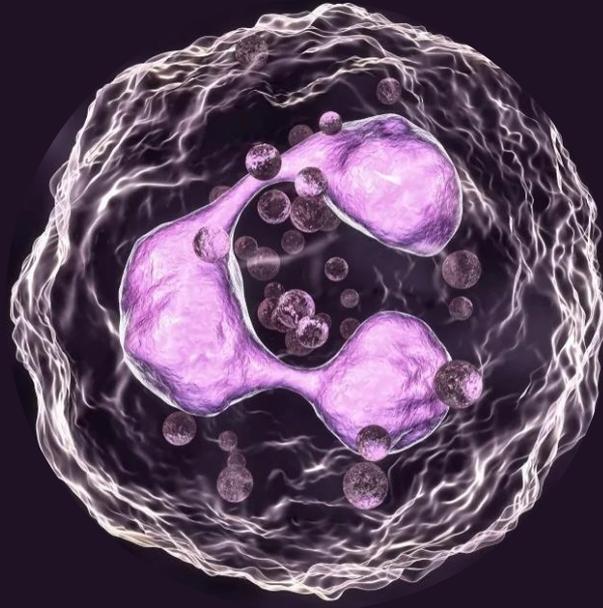
Glomerulonephritis

HUS

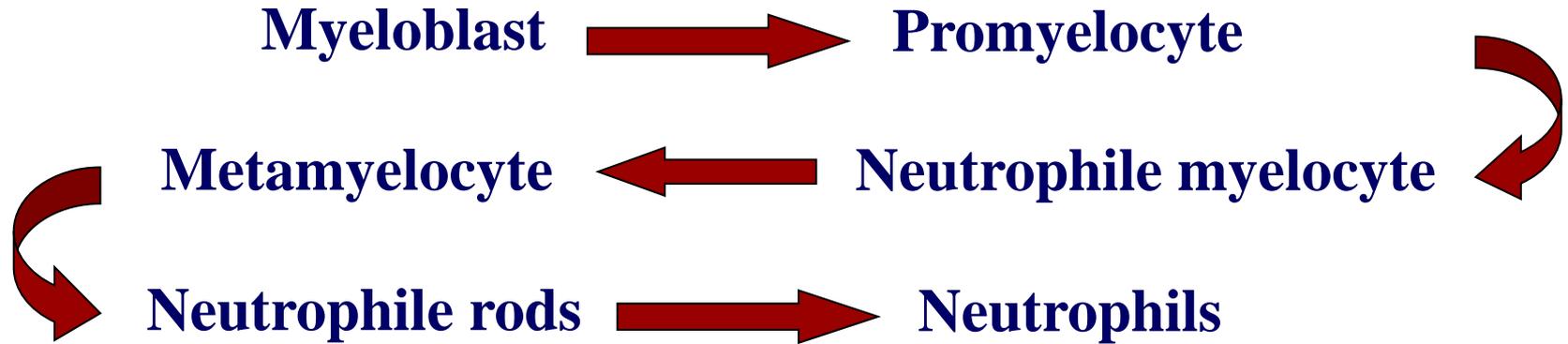
Angio-oedema



Neutrophilar (og aðrir granulocytar)



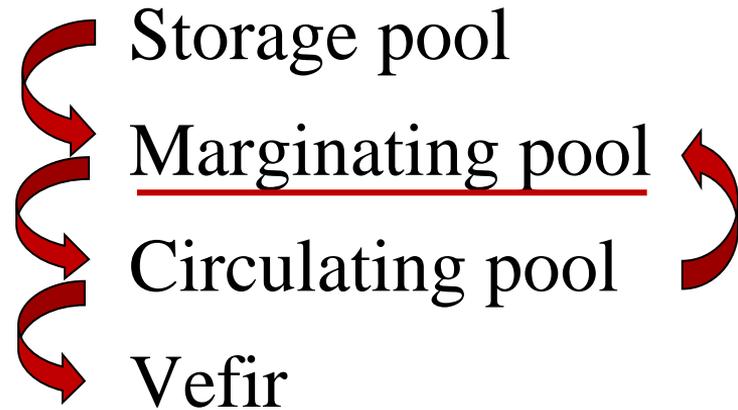
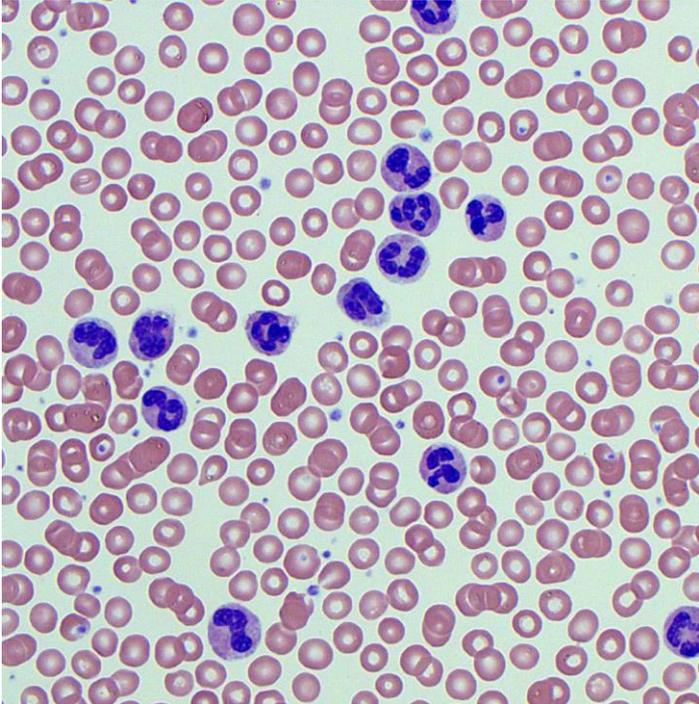
Neutrophilar - þroski



Process 9-11 days, can be 24 h in newborns

G-CSF, GM-CSF, IL-3, IL-6, SCF

Neutrophilar - fjöldi



Neutrophil defects

Neutrophil numbers

Neutrophil function

- Recurrent resp inf
- +/- fever
- Skin infections
- Mucous membranes infections
- GE infections / disorders
- Sepsis
- Granulomas , +/- abscesses
- Unusual pathogens
- Umbilical cord !

Granulocyta gallar

√ Neutropenia

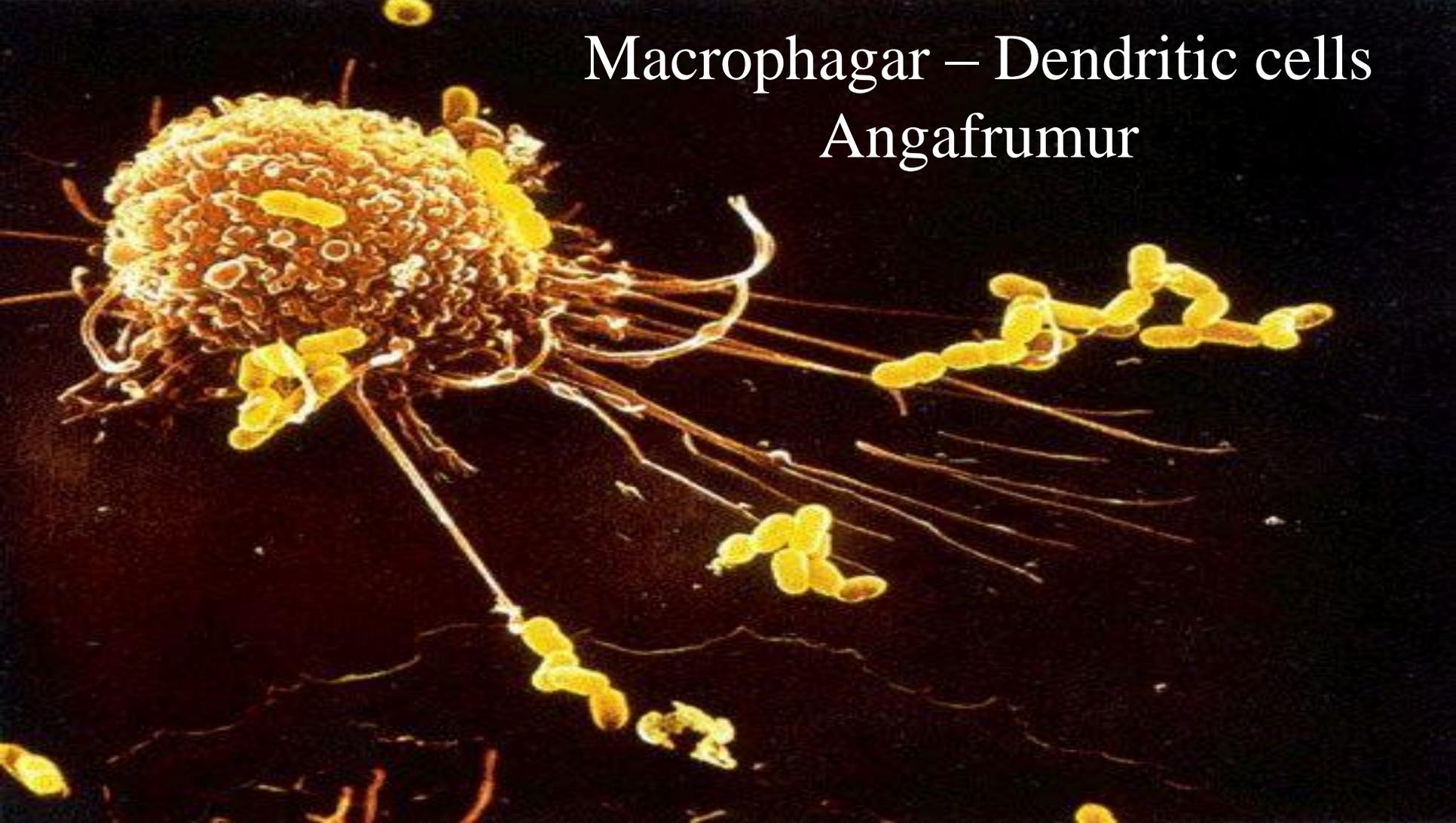
Neutrophils < 1500 = neutropenia

Neutrophils < 1000 = moderately severe neutropenia

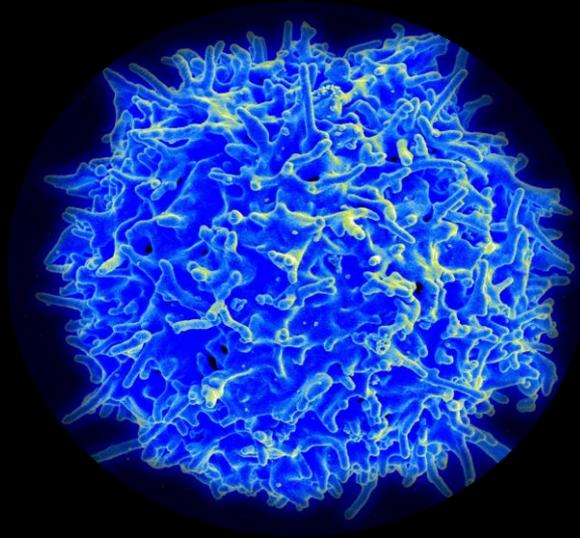
Neutrophils < 500 = severe neutropenia

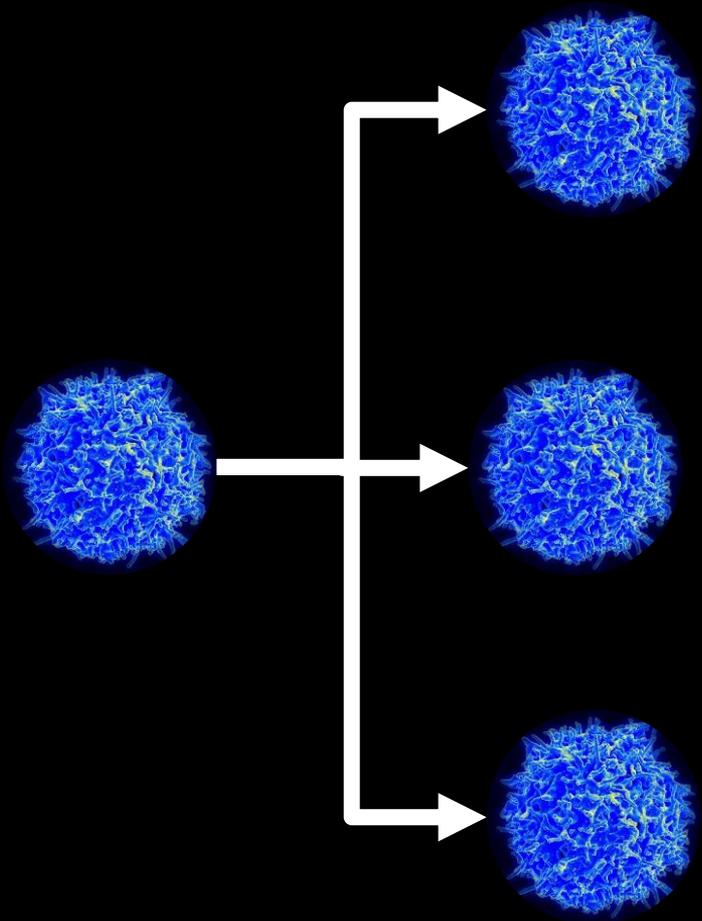
√ Dysfunction of granulocytes

Macrophage – Dendritic cells Angafrumur



T-frumur





Drápsfrumur

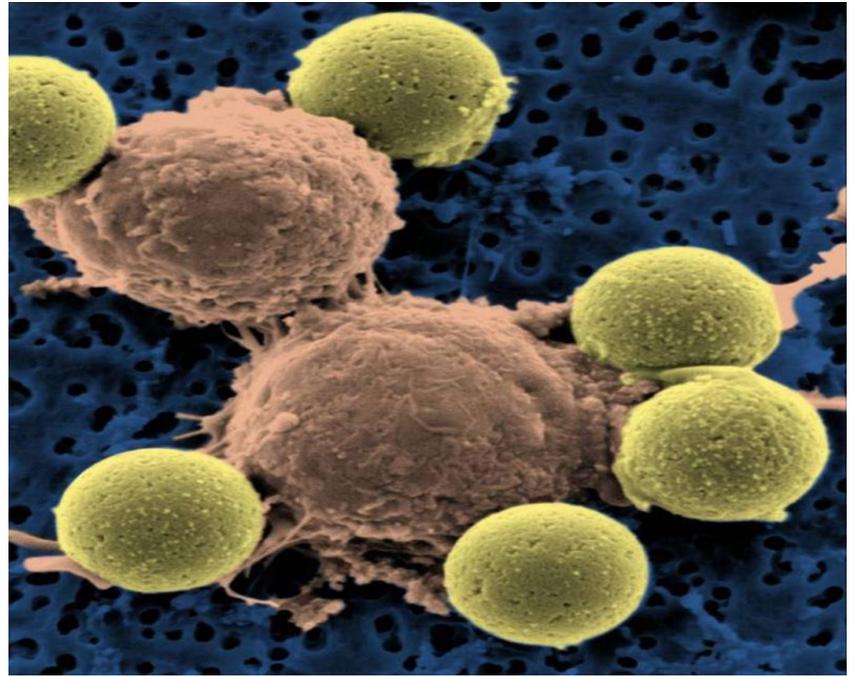
Minnisfrumur

Hjálparfrumur

T-cells



- Helper (CD4+), several subsets
- Cytotoxic (CD8+, CTL), several subsets
- Memory (CD4+ eða CD8+)
- Regulatory (T_{reg})
- NK (NKT fr)
-
-

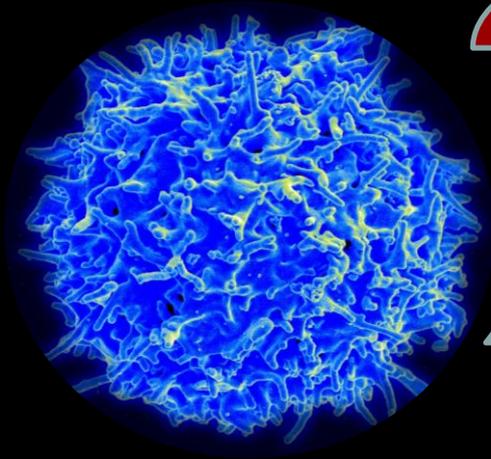


T cell disorders

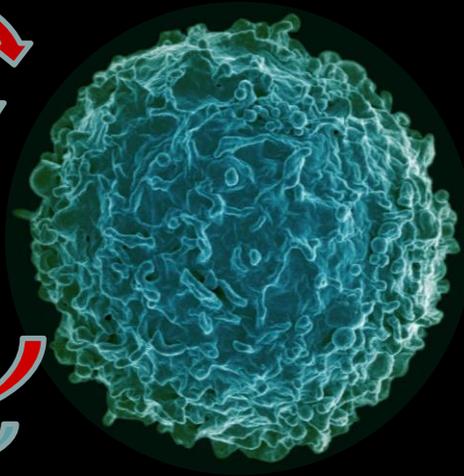
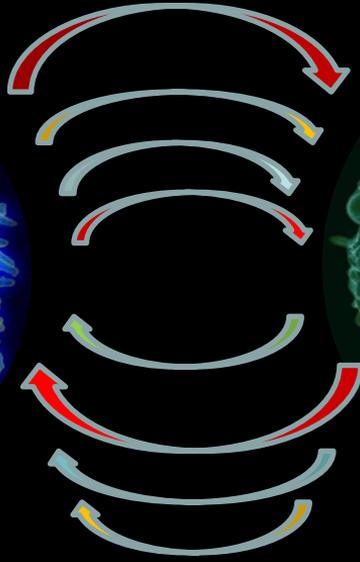
Cellular defects

(with B- cell involvement)

- ✓ Early in life
- ✓ Failure to thrive
- ✓ Recurrent infections,
viral, fungal and parasitic
- ✓ Autoinflammatory
reactions
- ✓ Malignancies
- ✓ etc



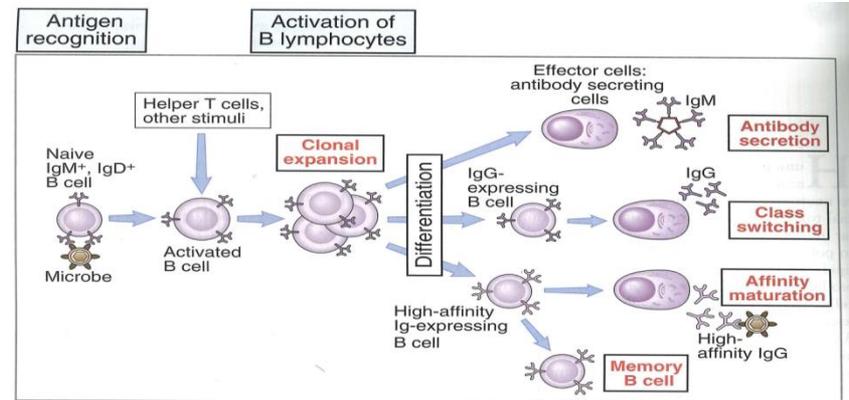
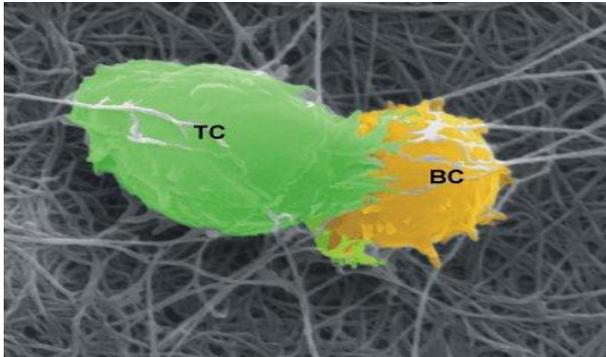
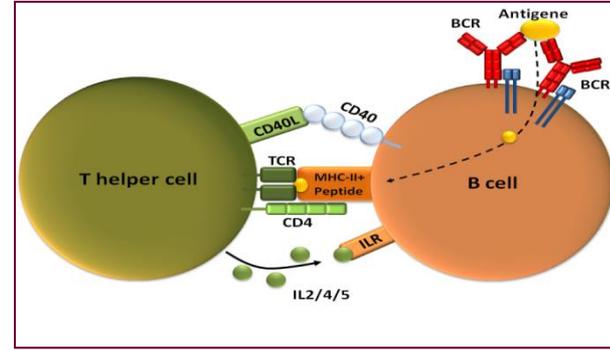
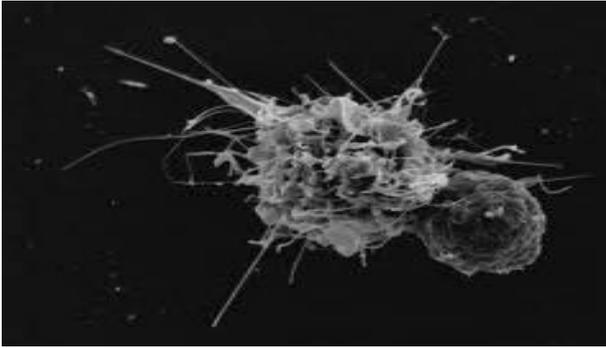
T-frumur



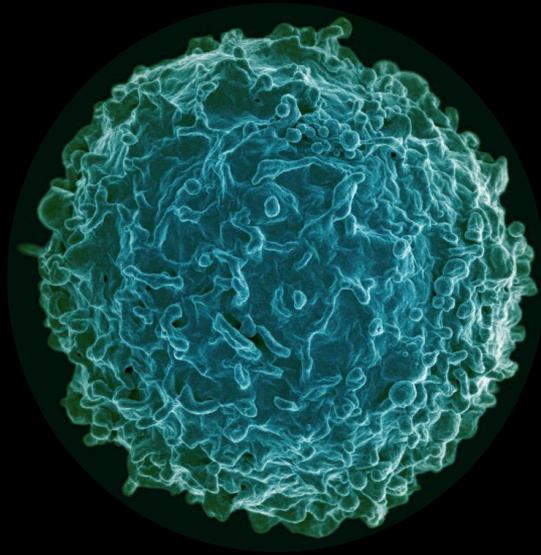
B-frumur

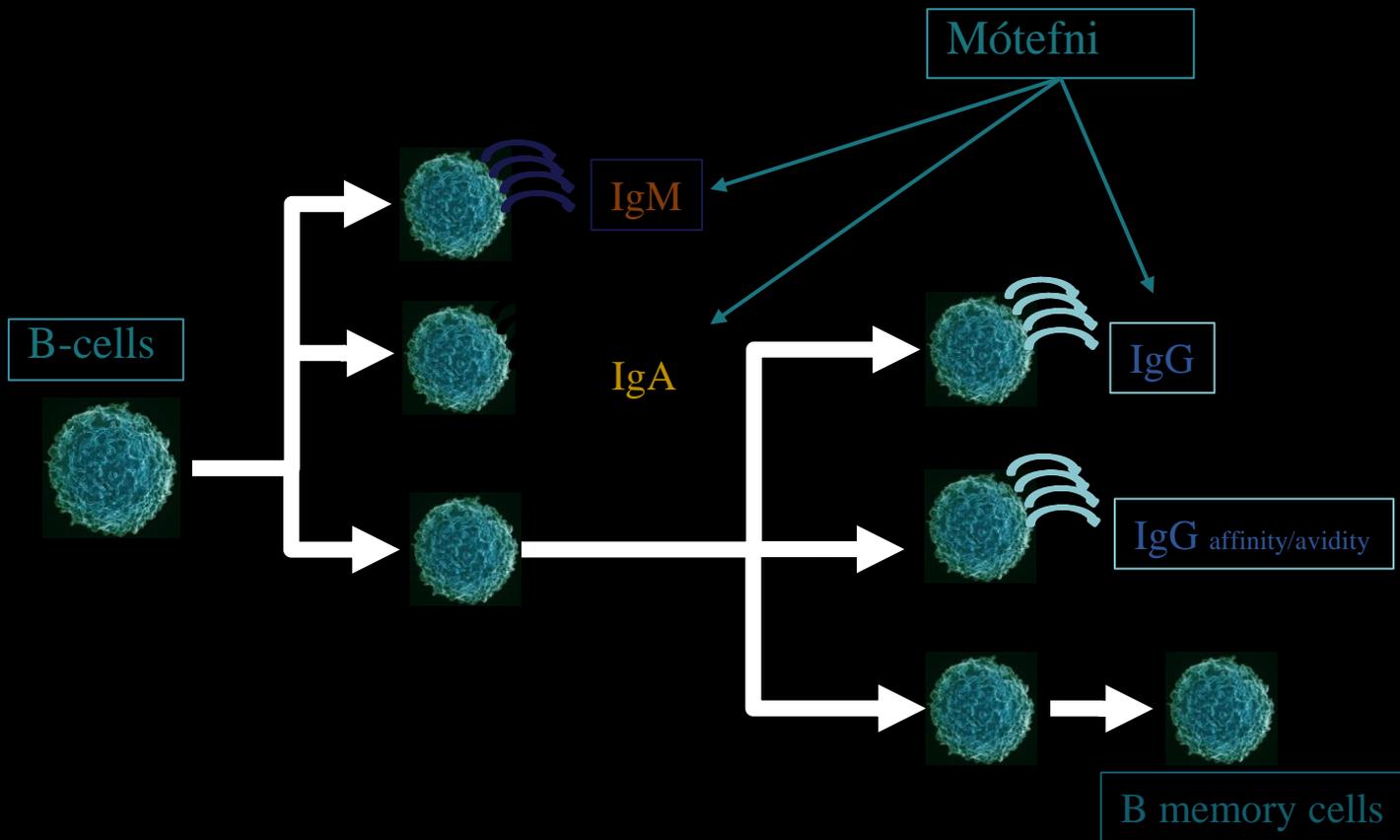
Helper (CD4+), several subtypes

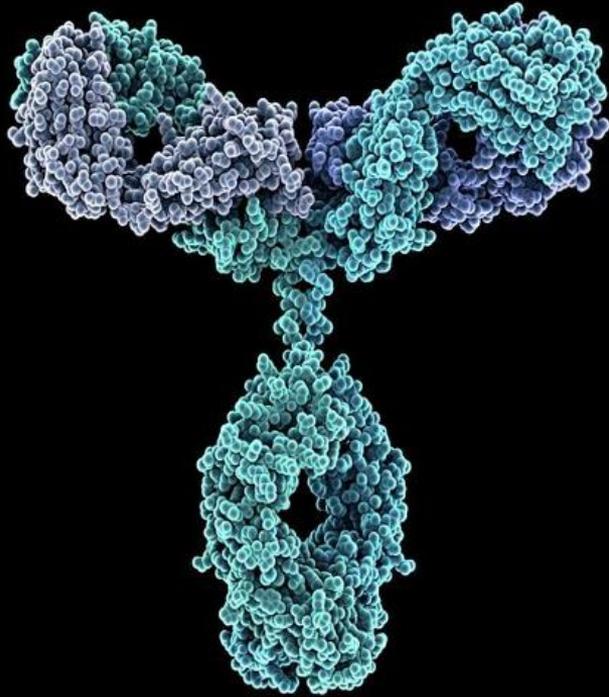
Control/activating/cytokine production



B-frumur







IgG

IgG1

IgG2

IgG3

IgG4

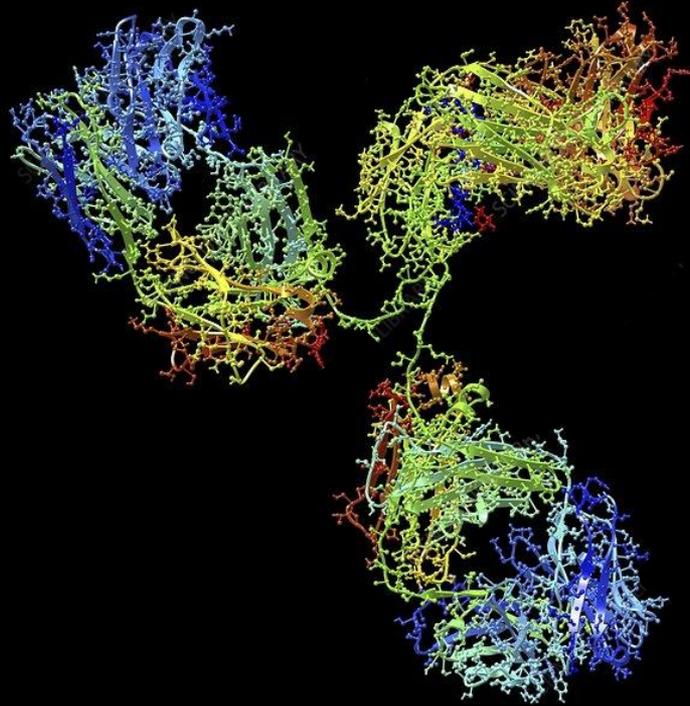
IgA

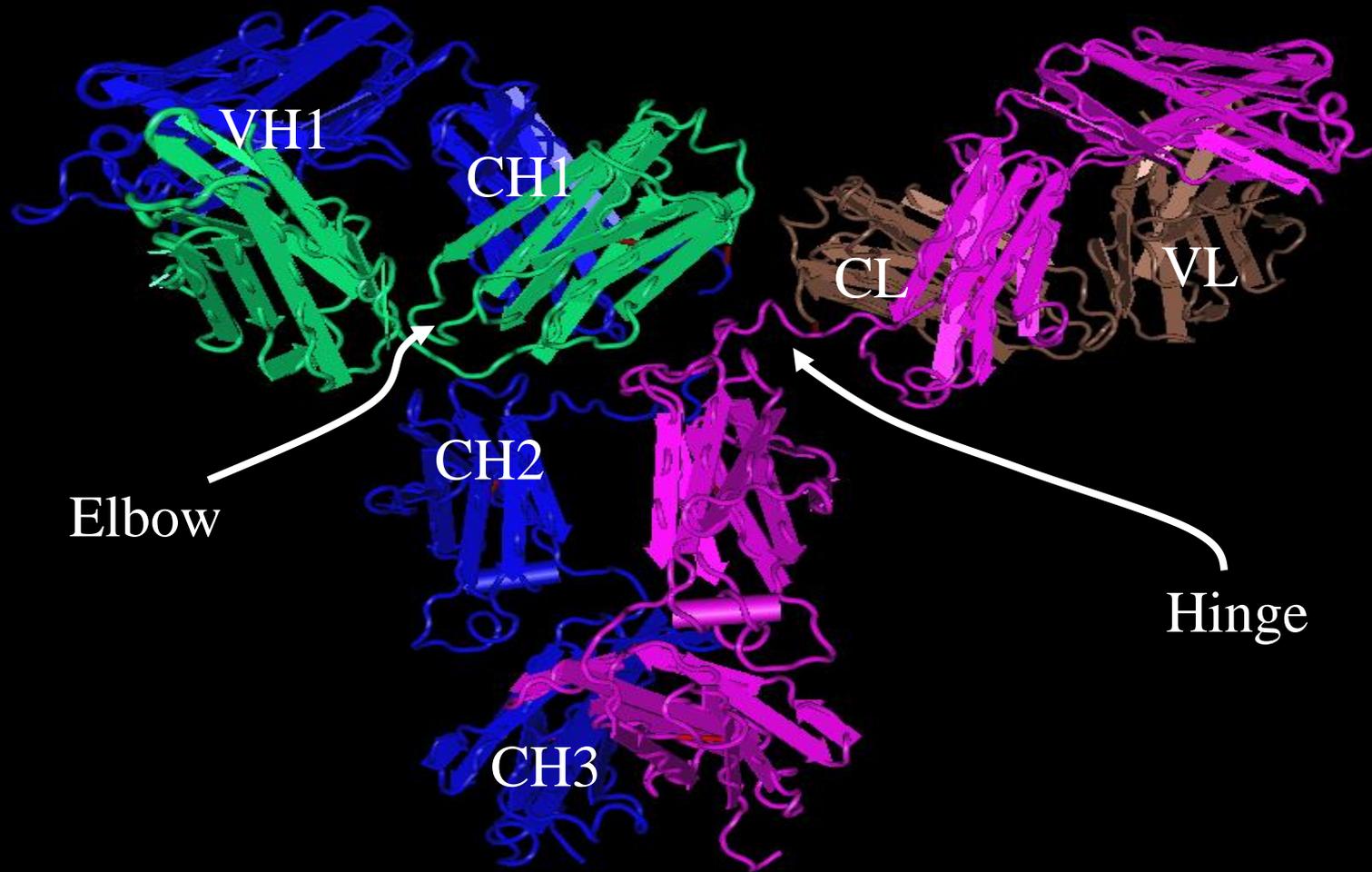
IgM

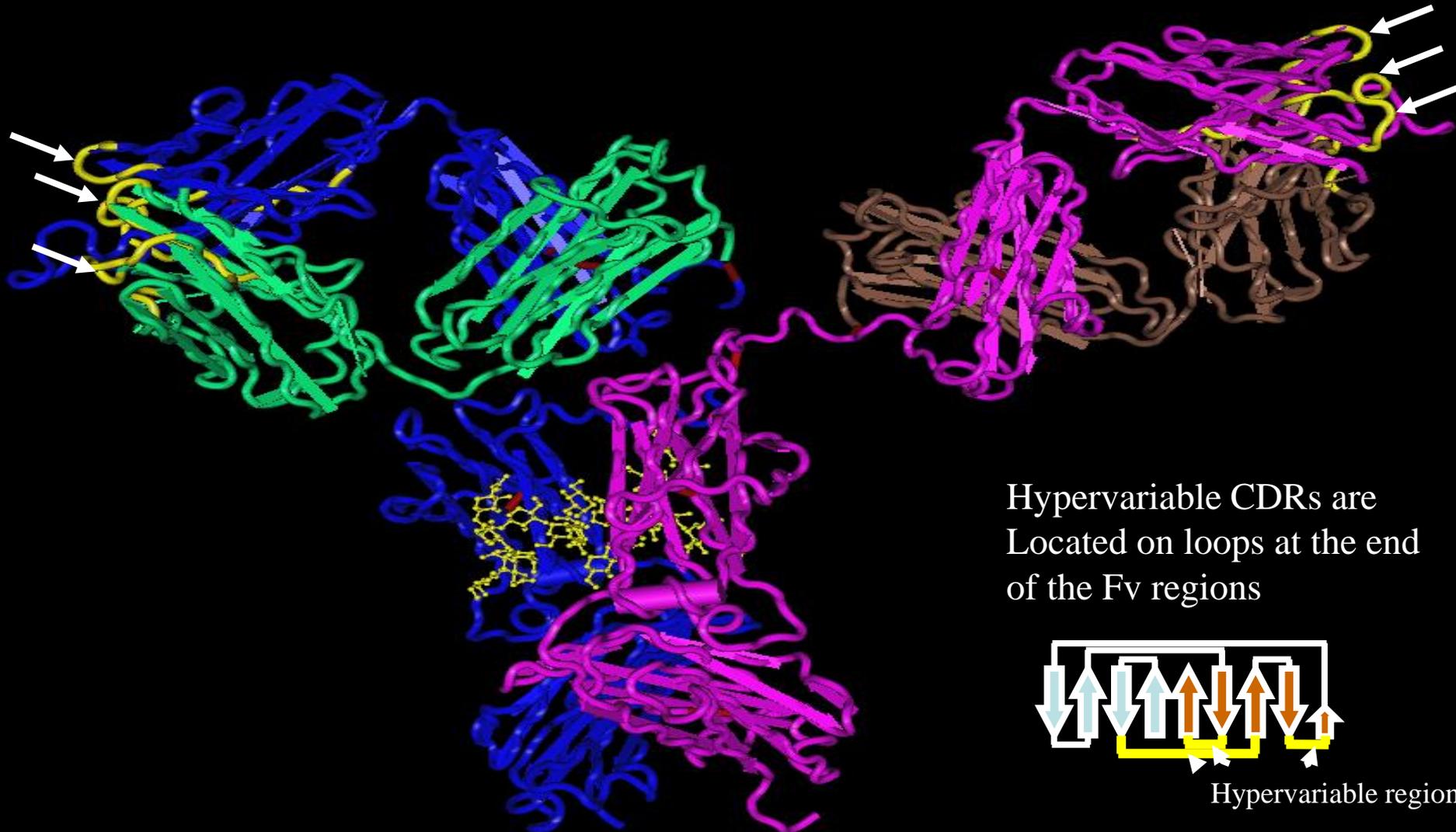
IgE

IgD

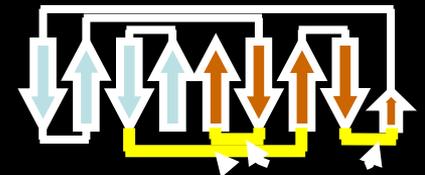
Immunoglobulins







Hypervariable CDRs are Located on loops at the end of the Fv regions



Hypervariable regions

B-cell immune defects

Agammaglobulinaemia

Hyogammaglobulinaemia

Transient hypogamma of infancy

IgA deficiency

S subclass deficiency (i.e. IgG2 def)

Hyper IgE Sx

Hyper IgM Sx

Heavy chain deletion

Kappa chain deficiency

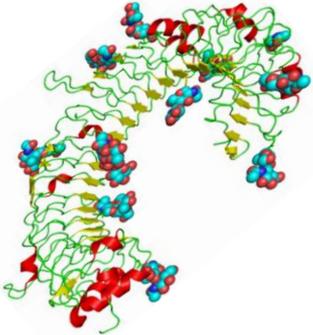
CVID

Humoral defects

- B-cell defects
- Number and function
- Not in first months of life
- Recurrent infections (RTI)
- Bacterial infections (esp. capsulated)

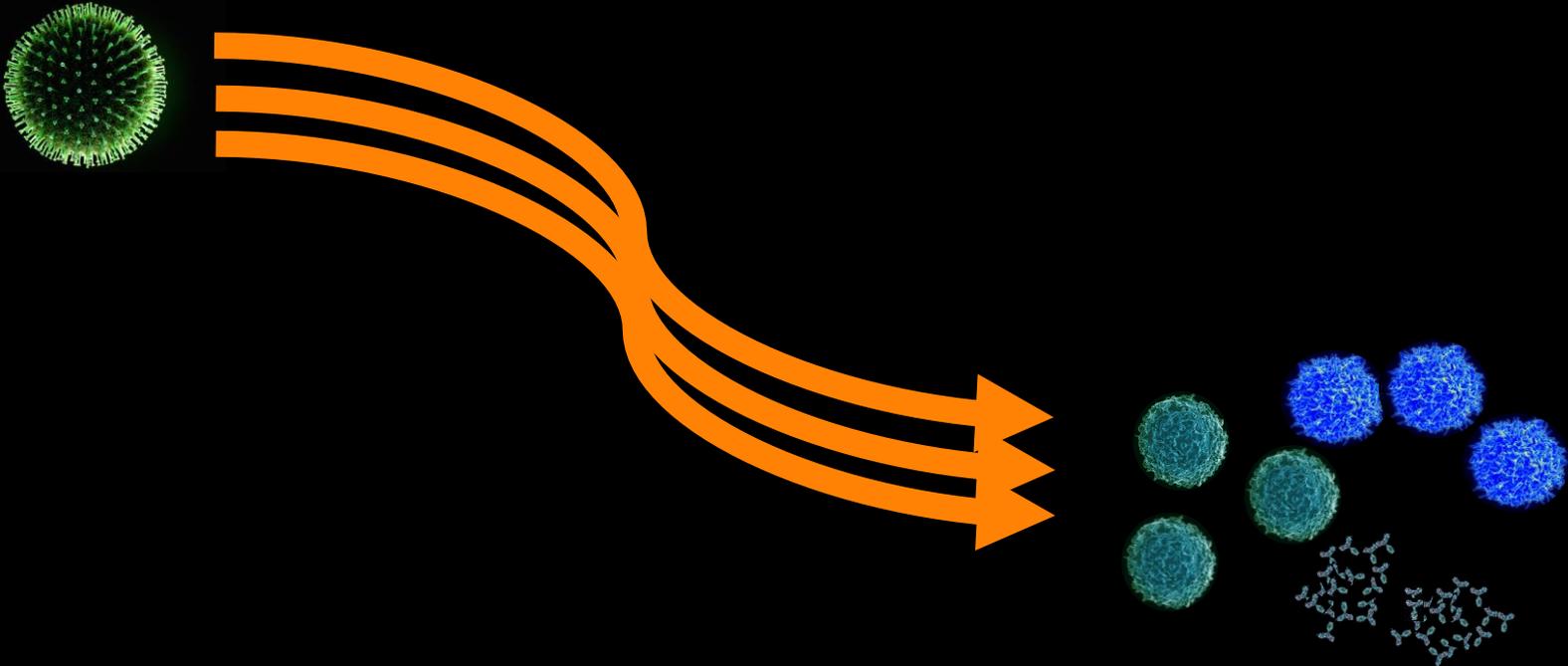
Allt er ónæmisfræði

Virkjun ónæmiskerfisins

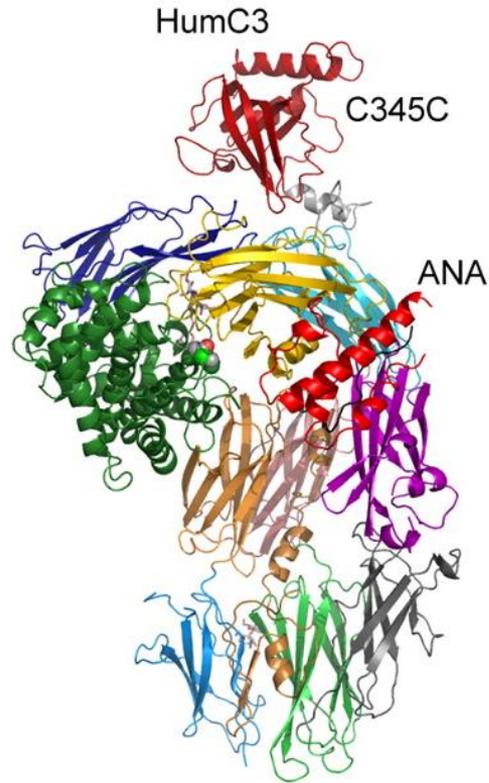


Hvernig þekkir ónæmiskerfið sýkla
og bregst við!

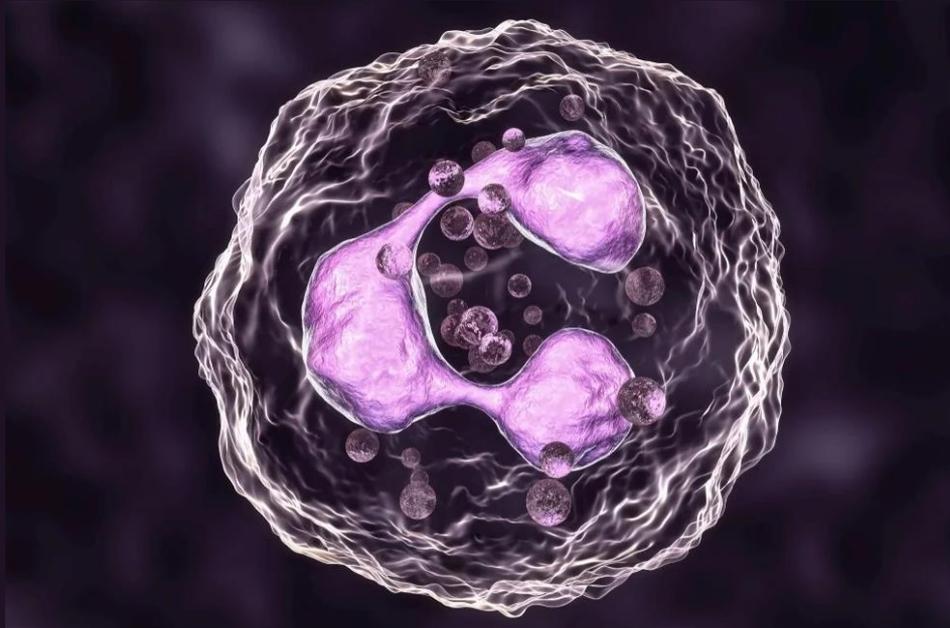
Sýklar → ónæmissvar



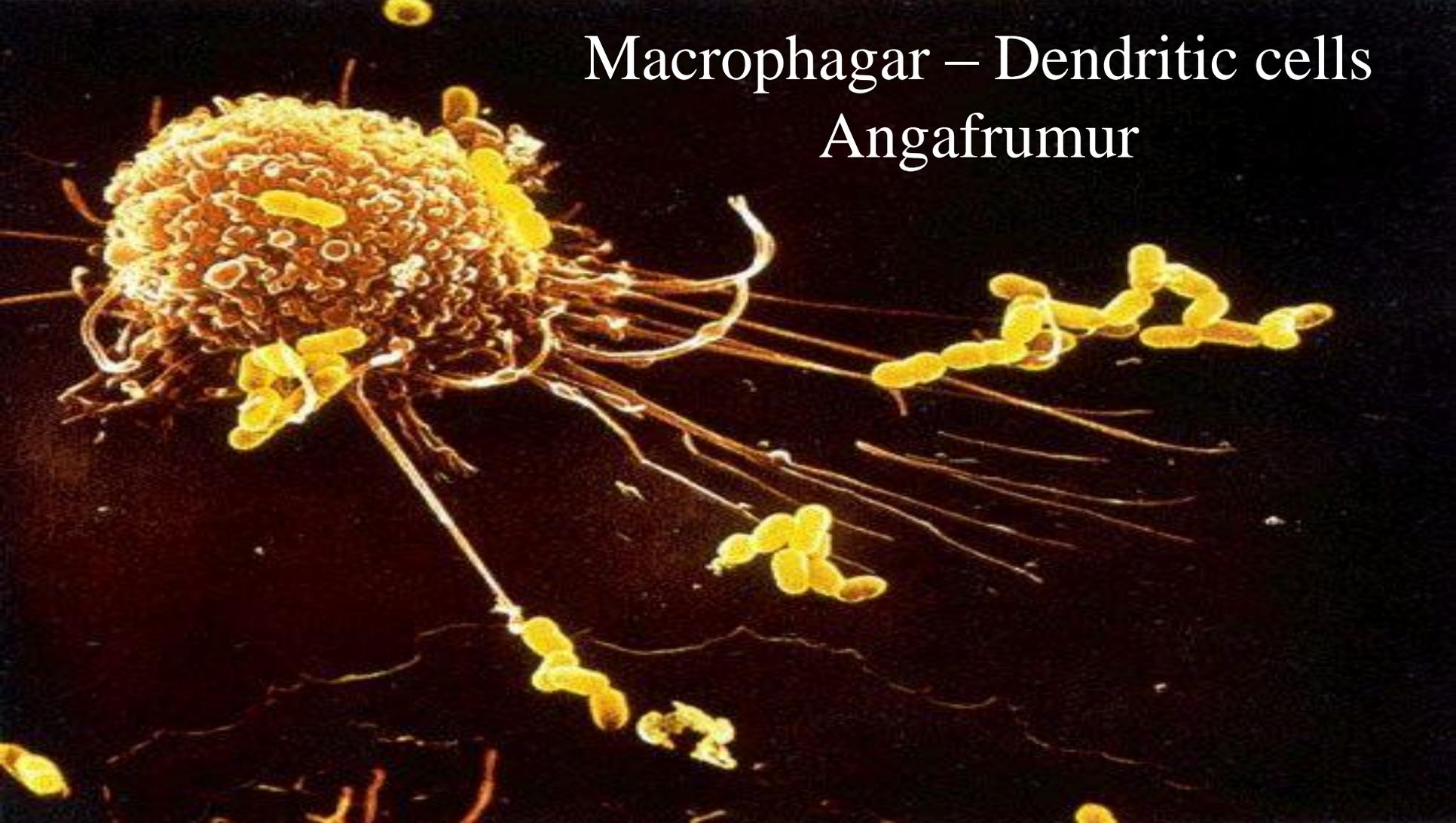
Complement



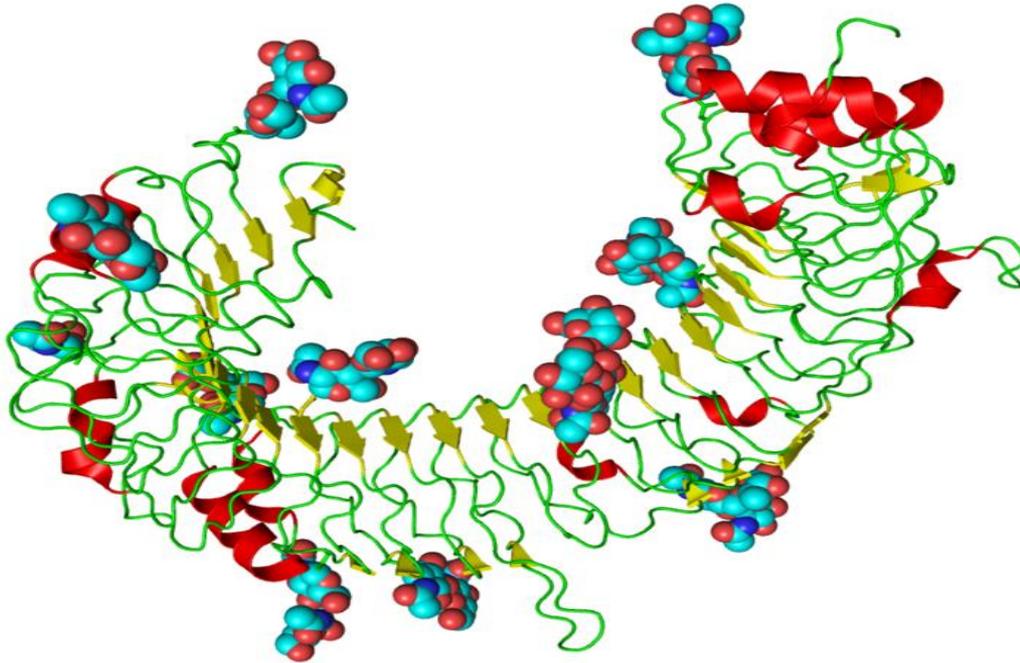
Neutrophilar (og aðrir granulocytar)



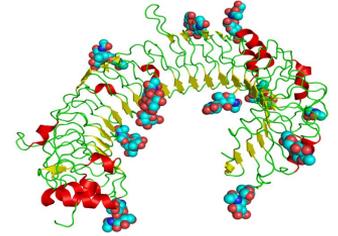
Macrophage – Dendritic cells Angafrumur



Hinir glæsilegu TLR! (Toll like receptors)



Hinir glæsilegu TLR! (Toll like receptors)



TLR1

TLR2

TLR3

TLR4

TLR5

TLR6

TLR7

TLR8

TLR9

TLR10

(TLR 11, 12 og 13 ekki í mönnum)

Cell membrane

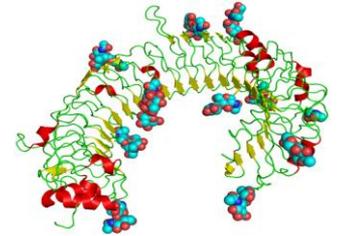
Intracellular vesicles

Eru á macrophögum/dendritic cells,
Einnig NK, T & B, epi & endothleial fr
o.fl

Greina mismunandi sýkla og flokka
af bakteríum, veirum og sveppum

PAMP: Pathogen associated molecular pattern
PRR(P): Pattern recognising receptors (proteins)

Hinir glæsilegu TLR! (Toll like receptors)



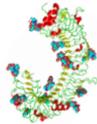
MØ



T-frumur



Ræsing sérhæfða
ónæmissvarsins



Stöðvar prótein
framleiðslu



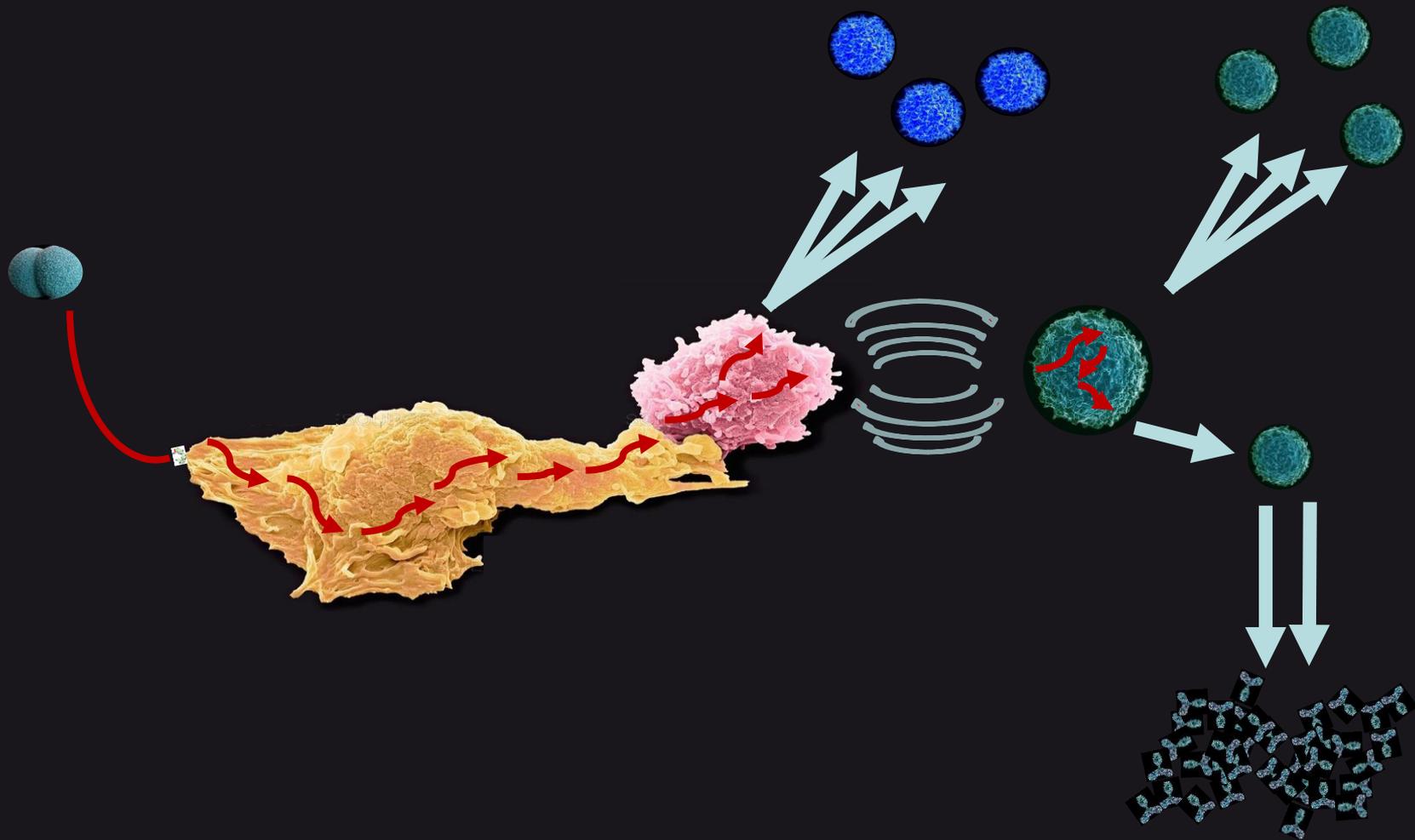
Apoptosis



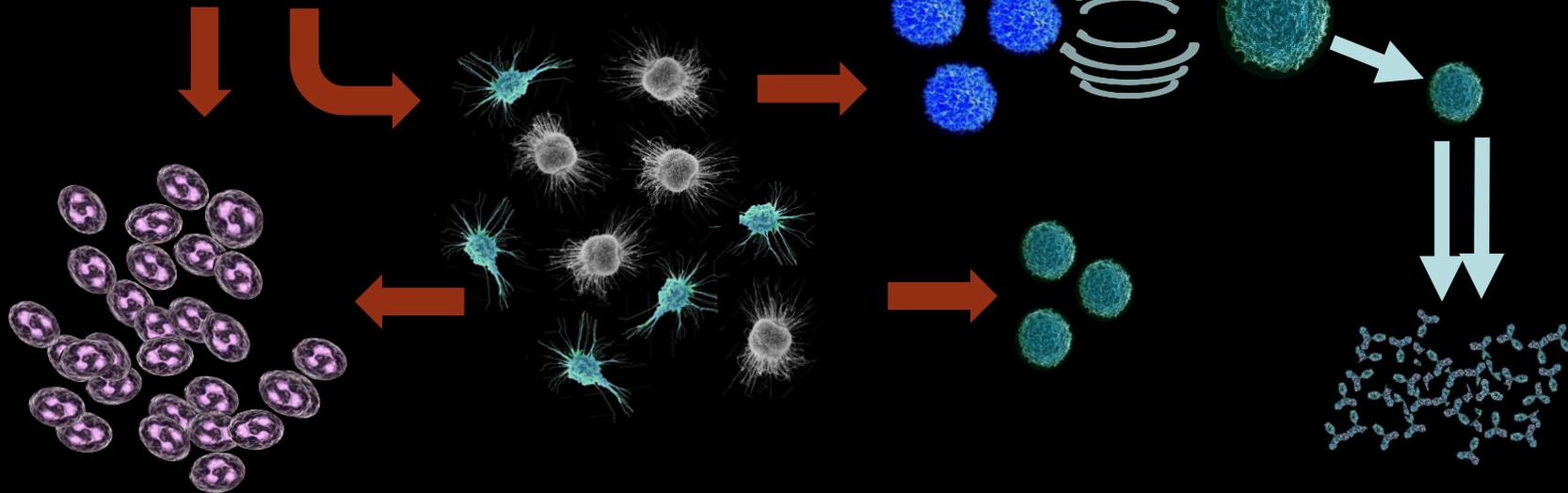
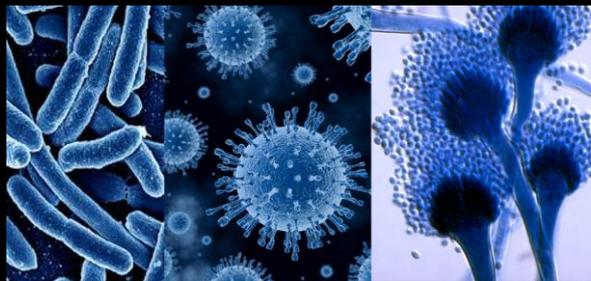
Örvar framleiðslu
antiviral cytokina



Veirudráp



Ræsing ónæmikerfisins

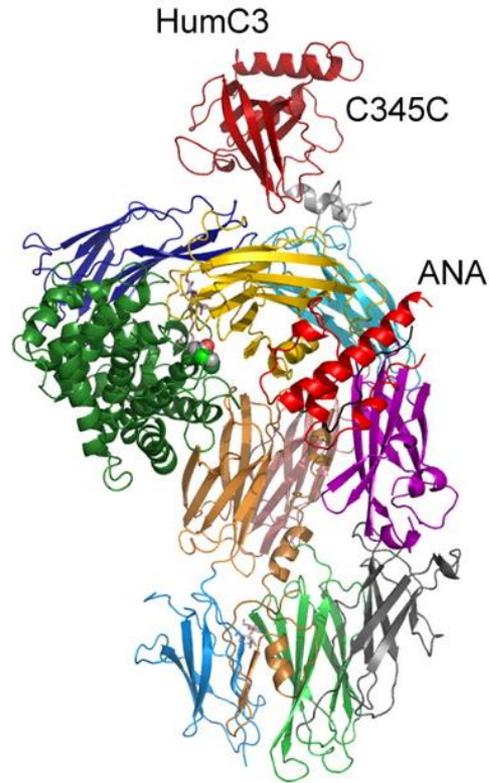


Allt er ónæmisfræði

Ýmsir sjúkdómar í ónæmiskerfinu

... en þeir eru miklu fleiri!

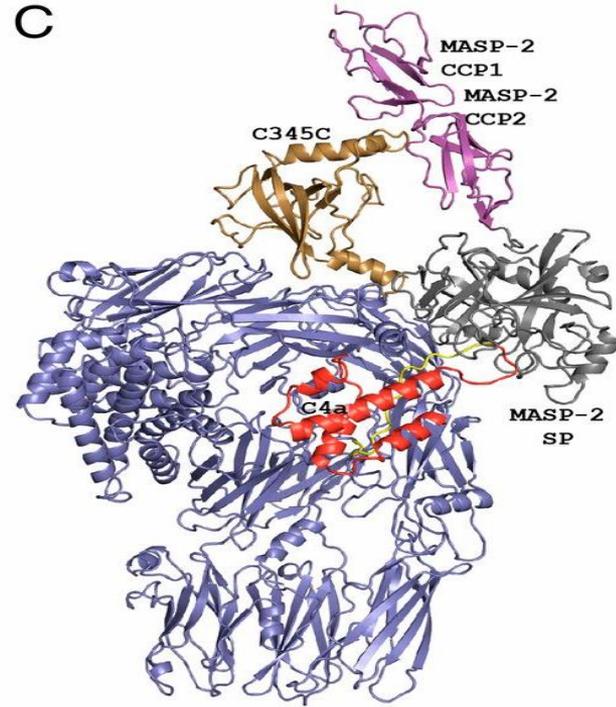
Complement



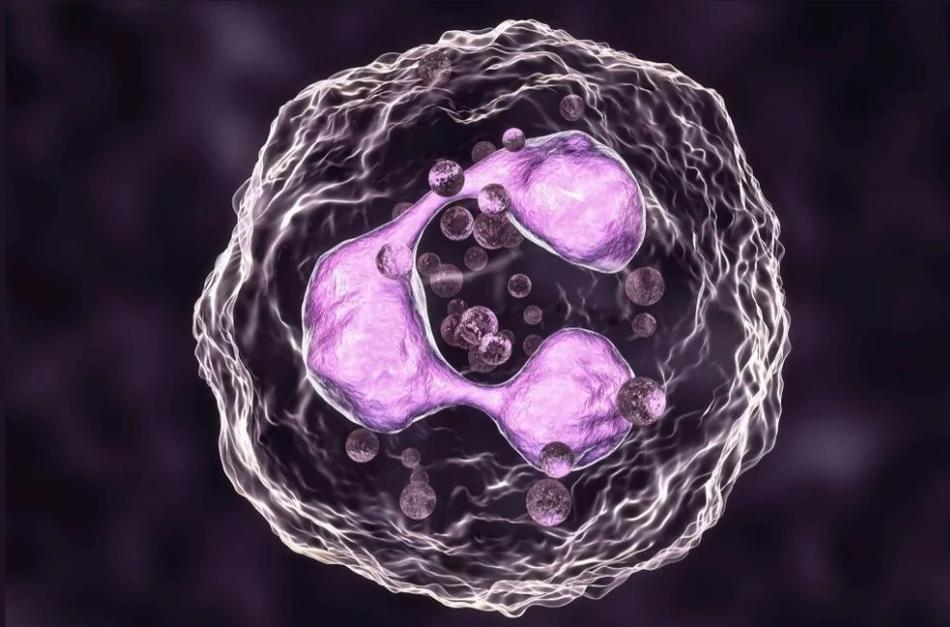
Complement defects

Complement defects

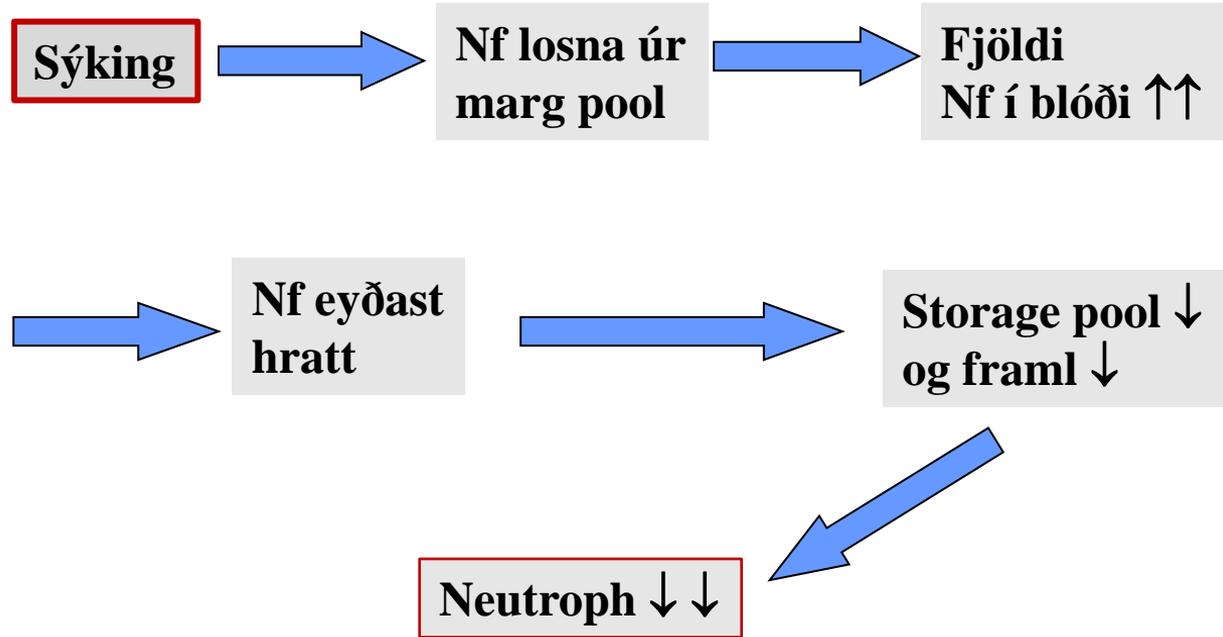
- V** Recurrent bacterial infections
- V** Inf with capsulated bacteria (meningococcus, pneumococcus)
- V** Autoimmune disorders
 - SLE
 - Glomerulonephritis
 - HUS
 - Angio-oedema



Neutrophilar (og aðrir granulocytar)



Neutrophilar í (neonatal) sepsis



Granulocyta gallar

√ Neutropenia

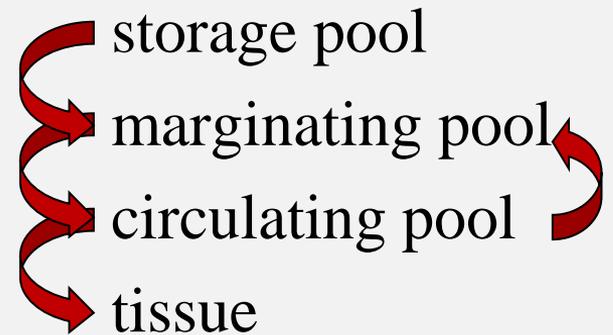
Neutrophils < 1500 = neutropenia

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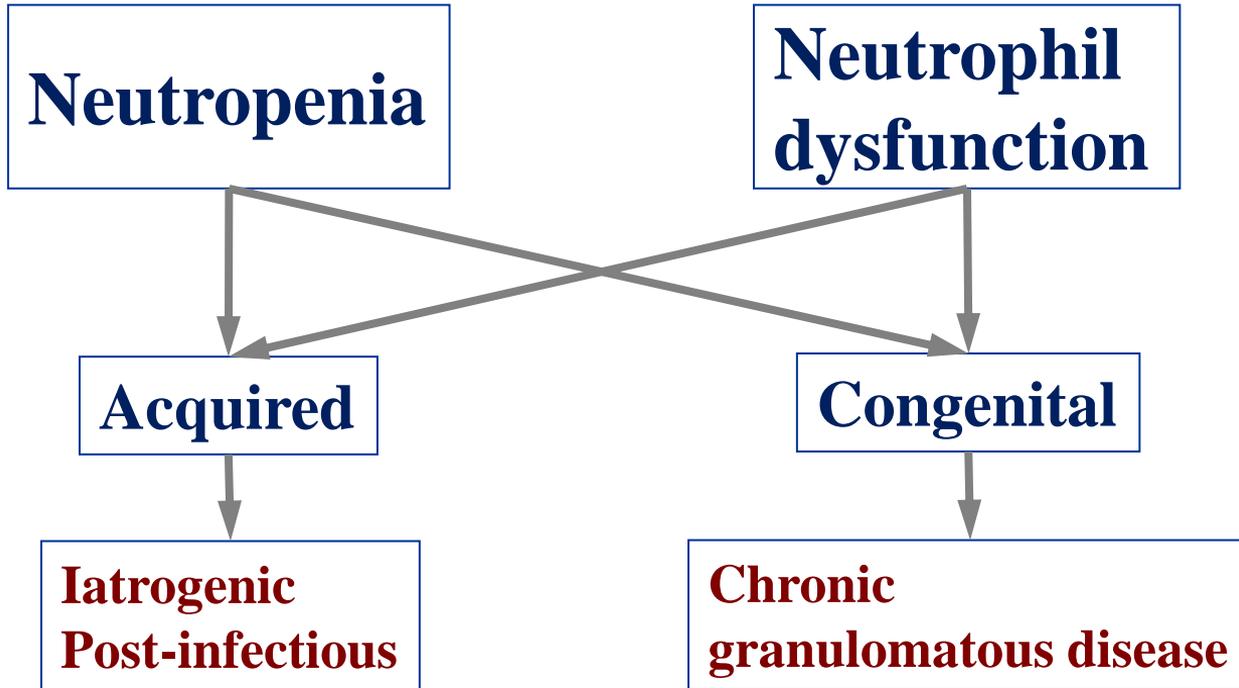
Neutrophils < 500 = severe neutropenia

√ Dysfunction of granulocytes

Neutrophils



Granulocyte disorders



Neutrophil defects

Neutrophil numbers

Neutrophil function

- Recurrent resp inf
- +/- fever
- Skin infections
- Mucous membranes infections
- GE infections / disorders
- Sepsis
- Granulomas , +/- abscesses
- Unusual pathogens
- Umbilical cord !



Áunnar neutropeniur

✓ Aplastic anaemia

Pancytopenia

(drugs, toxins, infections, etc.)

✓ Postinfectious neutropenia

Autoimmune neutropenia

✓ Iatrogen

(drugs, irradiation)

✓ Chronic diseases

Autoimmune dis

Infections

Drugs

Malignant dis

Hypersplenismus

etc

Neutrophile gallar

- ✓ Lazy leukocyte sx
- ✓ Leukocyte adhesion defects
- ✓ Hyperimmunoglobulin E sx
- ✓ Chronic granulomatous disease
- ✓ Glucosa-6-phosphatase def
- ✓ Myelokathexis
- ✓ Def ic killing



Neutropenia and neutrophil dysfunction

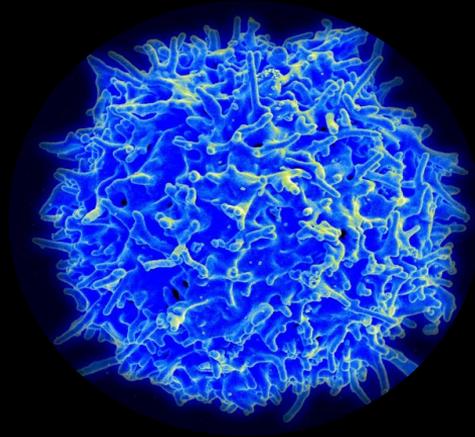
- ✓ Aplastic anaemia
Pancytopenia (drugs, toxins, infections, etc.)

- ✓ Postinfectious neutropenia
Autoimmune / benign

- ✓ Iatrogen
(drugs, irradiation)

- ✓ Chronic granulomatous disease

Ónæmisgallar T-frumur

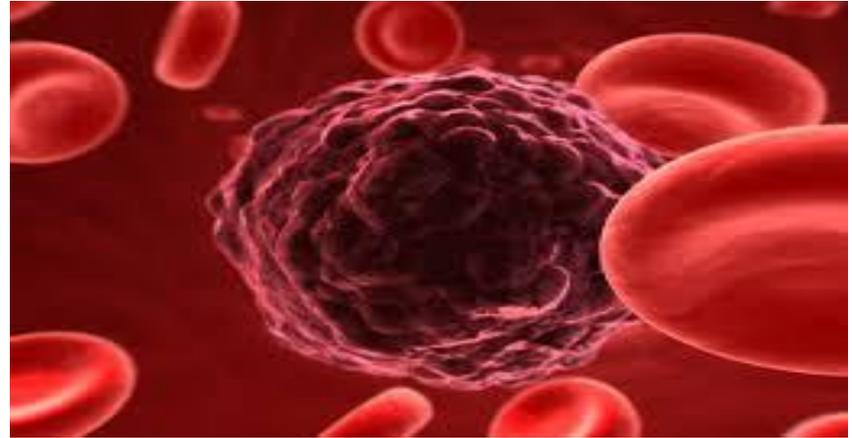


T cell disorders

Cellular defects

(with B- cell involvement)

- ✓ Early in life
- ✓ Failure to thrive
- ✓ Recurrent infections,
viral, fungal and parasitic
- ✓ Autoinflammatory
reactions
- ✓ Malignancies
etc



SCID

WAS

TCR def

Omenn sx

HIV

DiGeorge

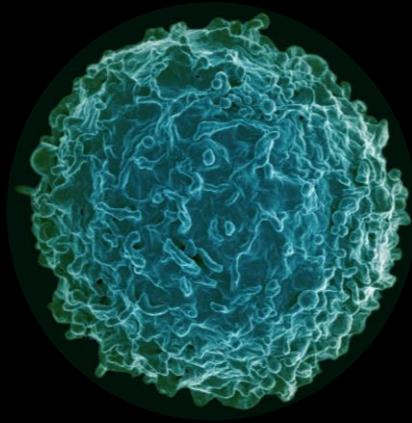
AT

CVID

Meðfæddir T (og B) ónæmisgallar

- Frumubundnir og blandaðir gallar
 - CVID (common variable immunodeficiency) með yfirgnæfandi mótefna / frumubundnum göllum
 - SCID (severe combined immunodef) T-B- / T- B+
 - ADA SCID (adenosine deaminase deficiency)
 - PNP-SCID (purine nucleoside phosphorylase def)
 - MHC class I / class II skortur

Ónæmisgallar B-frumur



B - frumugallar

Agammaglobulinaemia

Hyogammaglobulinaemia

Transient hypogamma of infancy

Antibody deficiency

IgA deficiency

Suclass deficiency

HyprerIgE Sx

Hyper IgM Sx

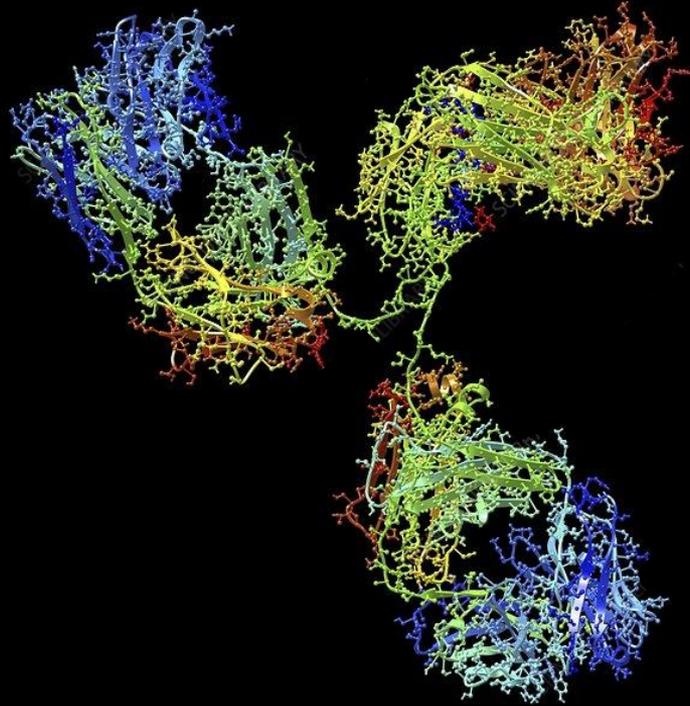
Heavy chain deletion

CVID

Humoral defects

- B-cell defects
- Number and function
- Not in first months of life
- Recurrent infections (RTI)
- Bacterial infections (esp. capsulated)

Immunoglobulins



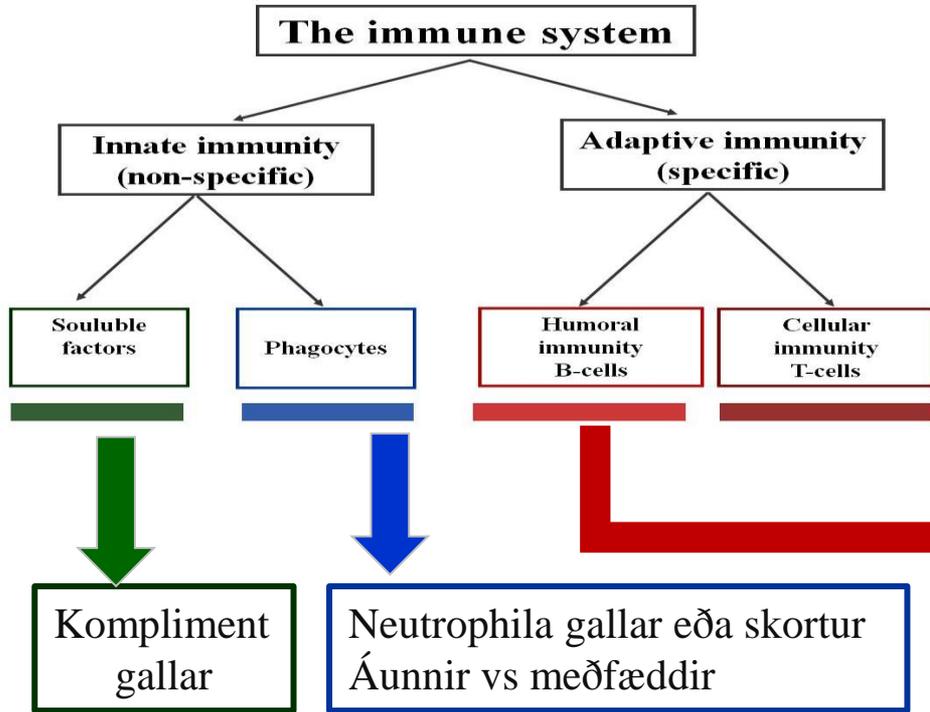
A photograph of a clear blue sky with scattered, wispy white clouds. The clouds are most prominent in the upper half of the frame, with a few smaller ones scattered throughout. The overall tone is bright and airy.

Secondary immunodeficiencies

Secondary immunodeficiencies

- Congenital diseases and metabolic disorders
(trisomy 21, malnutrition, nephrotic sx, protein losing enteropathy, etc)
- Immunosuppression
- Infections
 - Congenital (CMV, parvo, rubella)
 - Acquired (HIV, EBV, sepsis)
- Haematological diseases and malignancies
- Surgery, trauma, burn injuries, splenectomy
- Others (SLE, toxins, medications, liver failure etc)

Ónæmisgallar - yfirlit



CVID

Antibody/ cellular defects

SCID (severe combined immunodef)

T-B- / T- B+

O.s.frv.

Transient hypogammaglobulinaemi of
infancy

“Antibody deficiency”

IgA skortur

IgG undirflokkaskortur

.... O.s.frv.

Allt er ónæmisfræði

Rannsóknir á ónæmiskerfinu
Helstu meðferðarmöguleikar

Rannsóknir á ónæmiskerfinu



Helstu blóðrannsóknir

Status og diff!

Kompliment

Immúnóglóbúlín

Deilitalning eitelfrumna

Neutrophil function



Rtg thorax (thymus)

Beinmergur

HLA – flokkun

Lymphocyte stimulation tests

Cytokine production

TLR

O.fl!

Helstu blóðrannsóknir

Status og diff!



Kompliment

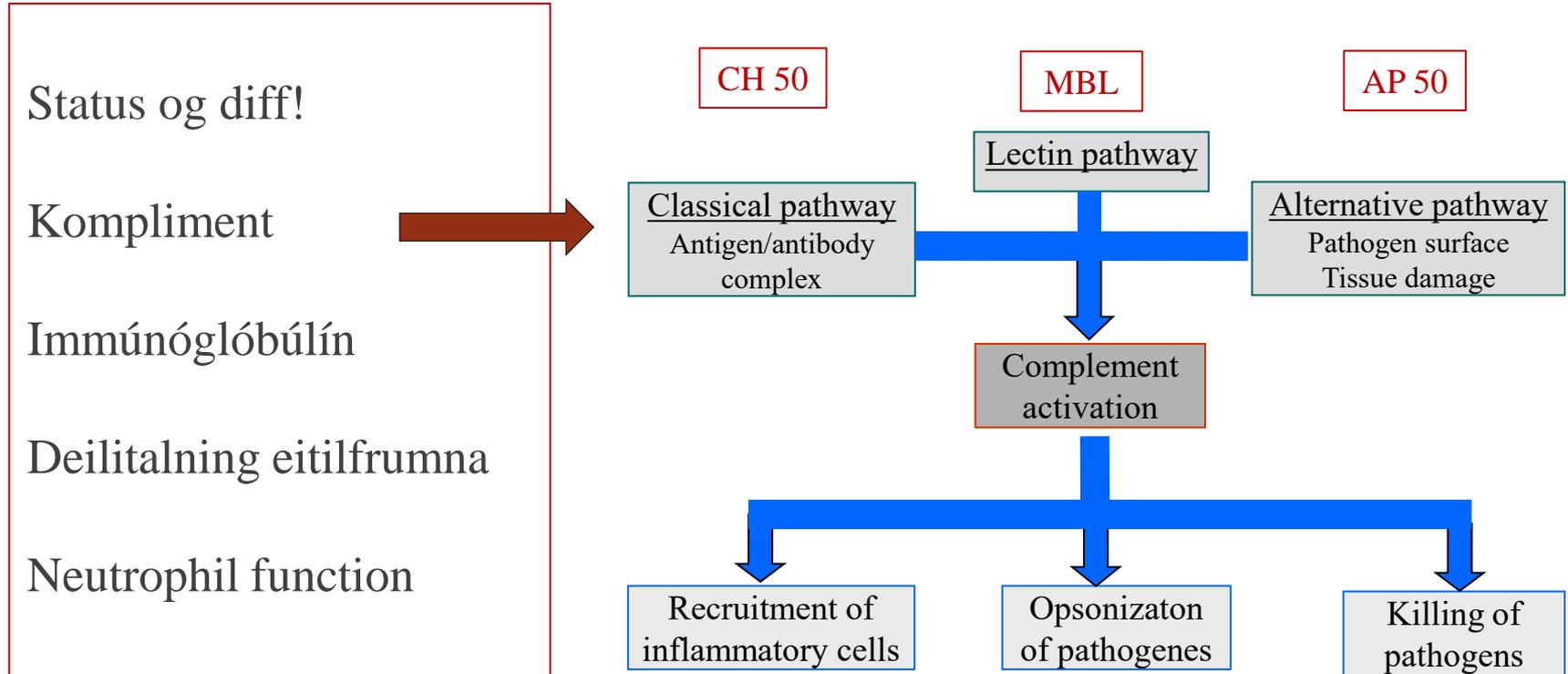
Immúnóglóbúlín

Deilitalning eitilfrumna

Neutrophil function

Blóðhagur			
B-Hvít blóðkorn	x10E9/L	7,6	2,2 L
B-Rauð blóðkorn	x10E12/L	4,49	3,99 L
B-Hemóglóbín	g/L	114	100 L
B-Hematókrít	L/L	0,34	0,31
B-MCV	fL	75	77
B-MCH	pg	25,4	25,1
B-MCHC	g/L	339	326
B-RDW		15,9 H	16,6 H
B-Blóðflögur	x10E9/L	328	263
B-MPV	fL	10,4	10,6
B-Neutrófilar	x10E9/L	0,0 L	0,3 L
B-Lymfócytar	x10E9/L	6,6	0,7 L
B-Mónócytar	x10E9/L	0,6	1,1
B-Eósínófilar	x10E9/L	0,2	0,0
B-Basófilar	x10E9/L	0,1	0,1
B-Forstig Granulocyta	%	0,1	0,0

Helstu blóðrannsóknir



Helstu blóðrannsóknir

Status og diff!

Kompliment

Immúnóglóbúlín

Deilitalning eitilfrumna

Neutrophil function



Ónæmisfræðideild / Department of Immunology		Viðmið / Norm	Eining /
Mótefnamælingar:			
<input type="checkbox"/> IgM	Ⓢ ↓ 0,40 (Ónæmisfræði)	0,55-3,15	g/l
<input type="checkbox"/> IgA	Ⓢ ↑ 2,65 (Ónæmisfræði)	0,58-2,56	g/l
<input type="checkbox"/> IgG	Ⓢ 10,80 (Ónæmisfræði)	6,40-15,20	g/l
<input type="checkbox"/> IgE	Ⓢ 4,70 (Ónæmisfræði)	<148	kU/l
IgG undirflokkar: 0			
<input type="checkbox"/> IgG1	Ⓢ 6,59 (Ónæmisfræði)	3,48-12,14	g/l
<input type="checkbox"/> IgG2	Ⓢ 3,20 (Ónæmisfræði)	1,18-6,62	g/l
<input type="checkbox"/> IgG3	Ⓢ 0,162 (Ónæmisfræði)	0,130-1,580	g/l
<input type="checkbox"/> IgG4	Ⓢ 0,072 (Ónæmisfræði) [1]	0,030-2,540	g/l

Aldurstöðluð
viðmiðunarmörk

Helstu blóðrannsóknir

Sérhæfð mótefni

Status og diff!

Kompliment

Immúnóglóbúlín

Deilitalning eítílfrumna

Neutrophil function



Sértæk mótefni gegn bakteríum:		
<input type="checkbox"/> Upplýsingar um bólusetningu	ℓ	
<input type="checkbox"/> Pneumokokkar hjúpperð 4	ℓ	1,86 (Ónæmisfræði)
<input type="checkbox"/> Pneumokokkar hjúpperð 6B	ℓ	1,71 (Ónæmisfræði)
<input type="checkbox"/> Pneumokokkar hjúpperð 7F	ℓ	0,41 (Ónæmisfræði)
<input type="checkbox"/> Pneumokokkar hjúpperð 19F	ℓ	0,82 (Ónæmisfræði) [3]
<input type="checkbox"/> Pneumokokkar hjúpperð 8	ℓ	2,24 (Ónæmisfræði)
<input type="checkbox"/> Pneumokokkar hjúpperð 12F	ℓ	0,06 (Ónæmisfræði)
<input type="checkbox"/> Tetanus toxoid	ℓ	1,33 (Ónæmisfræði) [3]

<input type="checkbox"/> Varicella zoster veira IgM / Varicella zoster virus IgM	gℓ	Neikvæð (< 0.8 Ratio) (Blóðsýni)
<input type="checkbox"/> Varicella zoster veira IgG / Varicella zoster virus IgG	gℓ	
<input type="checkbox"/> Varicella zoster veira IgG / Varicella zoster virus IgG	gℓ	Neikvæð (< 80 IU/l) (Blóðsýni)
<input type="checkbox"/> Cytomegaloveira IgM (ECLIA) / Cytomegalovirus IgM	gℓ	Neikvæð (Blóðsýni)
<input type="checkbox"/> Cytomegaloveira IgG (ECLIA) / Cytomegalovirus IgG	gℓ	Jákvæð (Blóðsýni)
<input type="checkbox"/> Epstein Barr VCA IgM (ELISA) / Epstein Barr virus VCA IgM	gℓ	Neikvæð (< 0.8 Ratio) (Blóðsýni)
<input type="checkbox"/> Epstein Barr VCA IgG (ELISA) / Epstein Barr virus VCA IgG	gℓ	Jákvæð (>= 1.1 Ratio) (Blóðsýni)

Helstu blóðrannsóknir

Status og diff!

Kompliment

Immúnóglóbúlín

Deilitalning eitifrumna

Neutrophil function



FACS greining á hvítfrumum í blóði 7. september 2021

Hvítfrumur	Dagsetning: 7. sept.		Áður 8. júní		Viðmið Hlutfall %	10-16 ára Abs fj.x10 ⁹ /L
	Hlutfall %	2021 Abs fj.x10 ⁹ /L	Hlutfall %	2021 Abs fj.x10 ⁹ /L		
Monocytar	7,2		9,9			
Granuloeytar	39,3		36,1			
Lymphocytar	51,5	2,3	48,0	1,9		1.0-5.3
<i>B frumur CD19+</i>	17,5	0,4	17,1	0,3	8-24%	0.2-0.6
Memory IgDneg	2,49		0,99			
Naive B frumur	93,25		94,29			
<i>T frumur CD3+</i>	65,5	1,5	61,0	1,1	52-78%	0.8-3.5
CD4+ T fr.og CD3+	32,6	0,8	24,6	0,4	25-48%	0.4-2.1
Naive CCR7+ CD45RA+	72,48		68,08			
Eff. CCR7neg CD45RAneg	13,36		18,23			
Activ. HLA-DR+ CD38+	4,19		2,85			
CD8+T fr. og CD3+	28,6	0,7	28,0	0,5	9-35%	0.2-1.2
Naive CCR7+ CD45RA+	19,84		12,43			
Eff. CCR7neg CD45RAneg	40,61		48,74			
Activ. HLA-DR+ CD38+	15,66		1,01			
Hlutfall CD4+/ CD8+	= 1,15		= 0,85		0.9-3.4	
<i>NK frumur CD16+ og CD56+</i>	14,7	0,3	20,9	0,4	6-27%	0.07-1.2

Eðlileg deilitalning og ekki merki um ræsingu. Niðurstöður frá 8. júní til samanburðar.

Helstu blóðrannsóknir

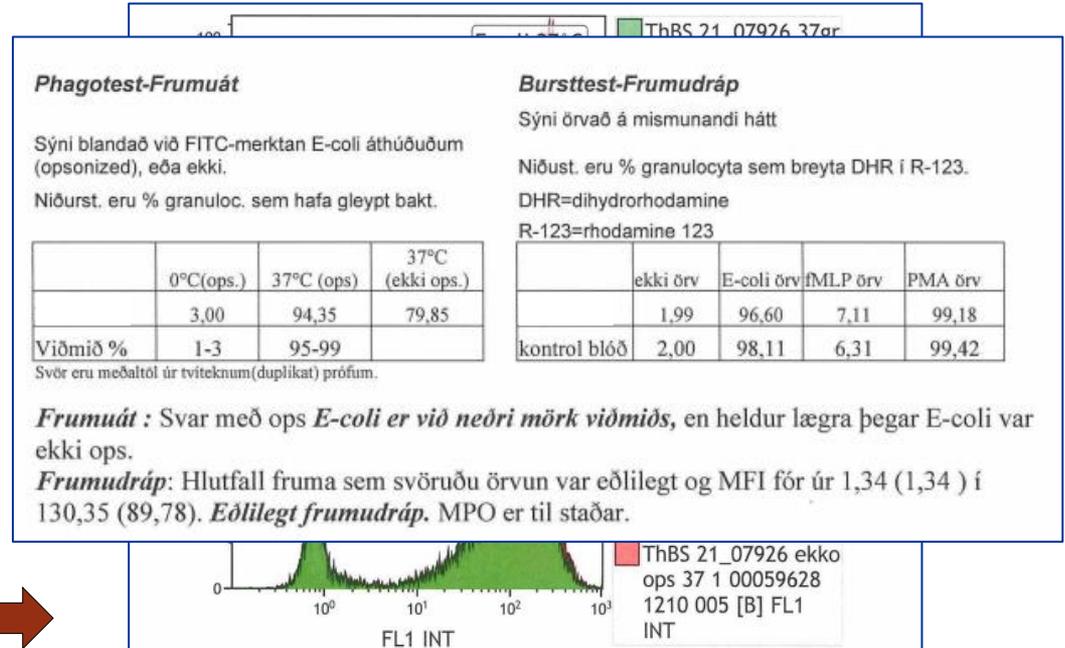
Status og diff!

Kompliment

Immúnóglóbúlín

Deilitalning eitifrumna

Neutrophil function



Helstu blóðrannsóknir

Status og diff!

Kompliment

Immúnóglóbúlín

Deilitalning eitelfrumna

Neutrophil function



Allt er ónæmisfræði

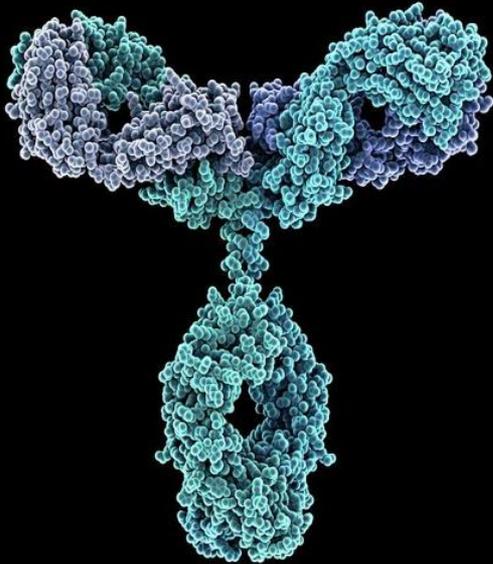
Meðferð við ónæmisgöllum og
frávikum í ónæmiskerfinu

Nokkrir meðferðarmöguleikar

Sýklalyf – en af skynsemi!



Mótnagjafir / IVIG - ScIG



IgG

IgG1

IgG2

IgG3

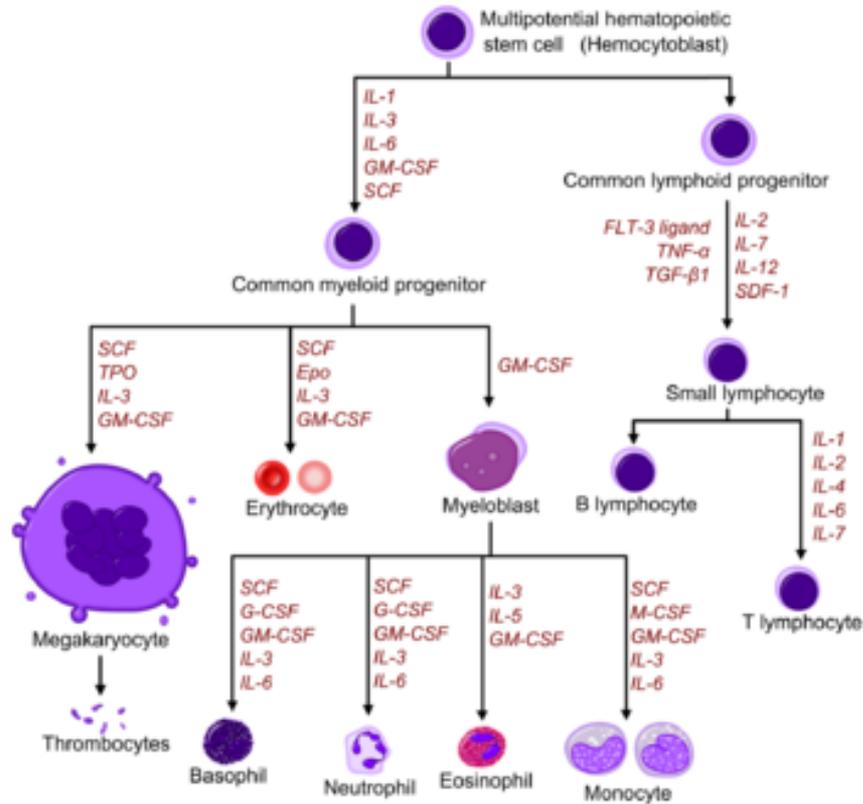
IgG4

Sérhæfð mótefni !

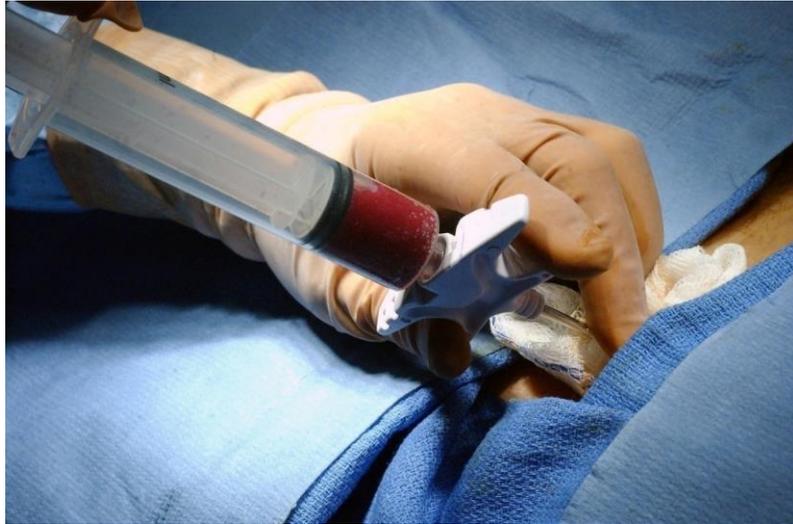
Líftækniyf



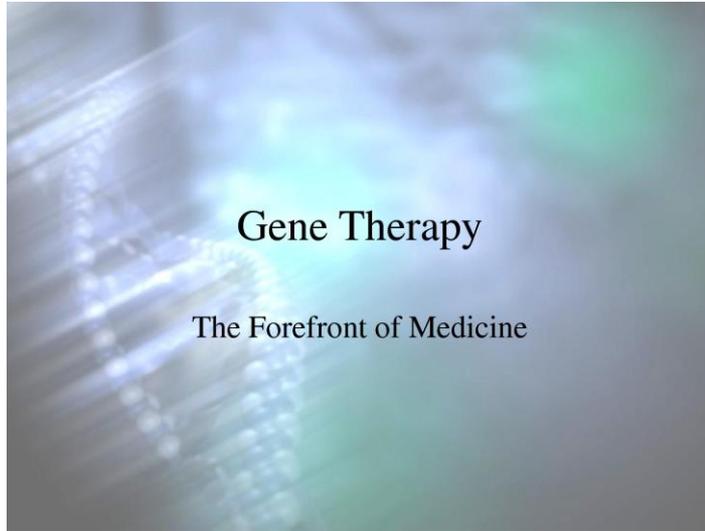
Frumubođefni



Beinmergsskipti / stofnfrumumeðferð



Genalækningar !



Ábendingar

- I. Illkynja sjúkdómar í beinmerg
- II. Krónískir sjúkómar í beinmerg
- III. Meðfæddir ónæmisgallar
- IV. Blóðsjúkdómar
- V. Haemoglobinopathiur
- VI. Storage diseases
- VII. Sjálfnæmsisjúkdómar?
- VIII. „Rescue“ meðferð?



SCID – ýmsar tegundir
T-frumugallar - ýmsar tegundir
Chronic granulomatous disease
Severe congenital neutropenia
Hyper IgE sx, WAS, FEL
o.s.frv.

Aukaverkanir og áhætta

Snemmkomnar aukaverkanir

Sýkingar

Höfnun

Graft vs host disease
(og Graft vs tumor effect)

Hemorrhagic cystitis,

Mucositis

Veno-occlusive disease

Lymphoproliferative sx

Síðkomnar aukaverkanir

Illkynja sjúkdómar

Áhrif á vöxt og þroska

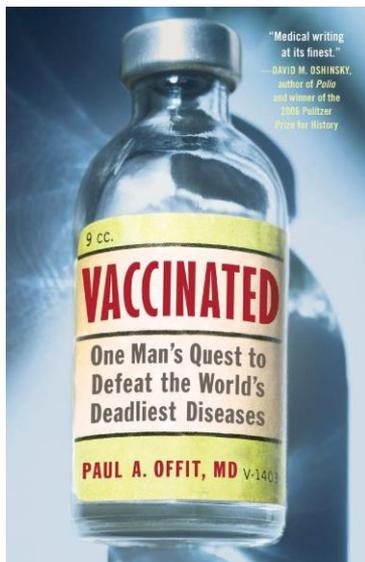
Graft vs host disease

Lymphoproliferative sx

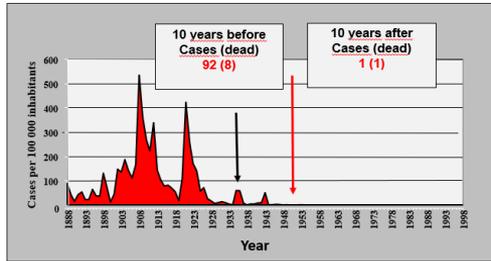
o.s.frv.

Að ógleymdri fyrirbyggjandi meðferð...

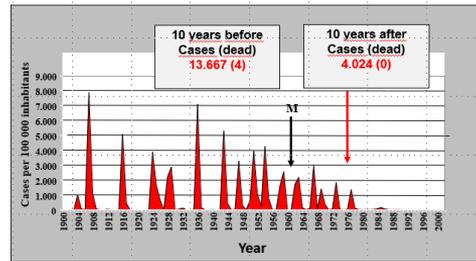
**Sem bjargað hefur fleiri mannlífum
nokkur önnur heilbrigðismeðferð
– að hreinu vatni undanskildu**



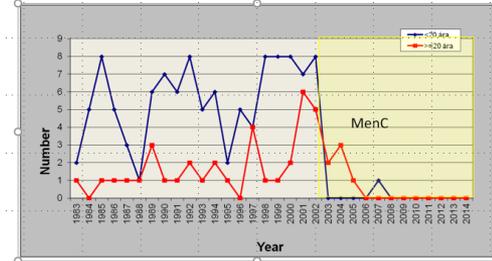
Diphtheria in Iceland



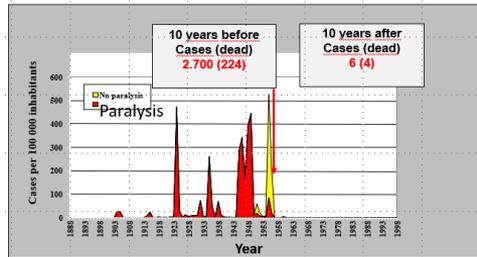
Measles in Iceland



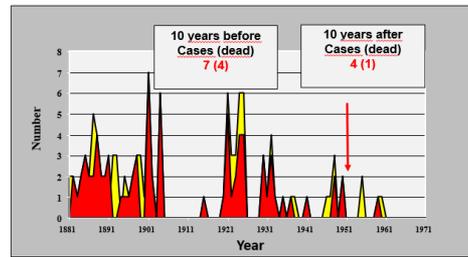
Men C in Iceland



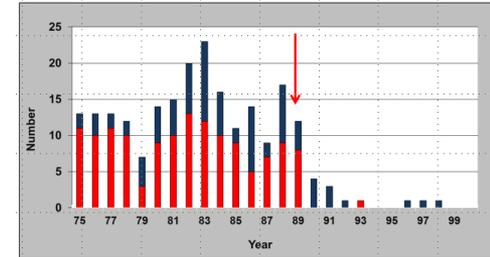
Poliomyelitis in Iceland



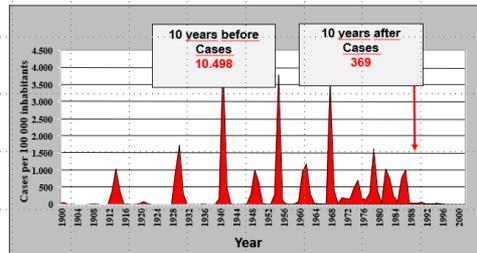
Tetanus in Iceland



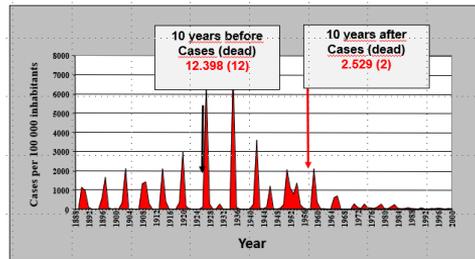
Hib in Iceland



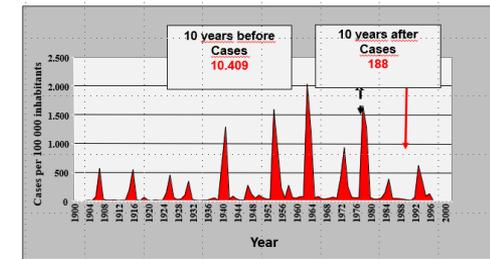
Mumps in Iceland



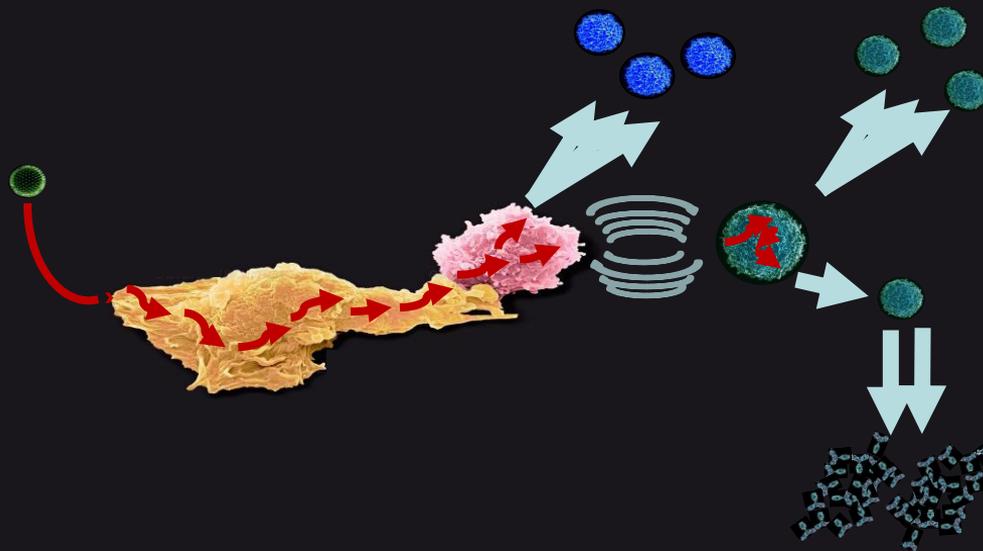
Pertussis in Iceland



Rubella in Iceland



Getum við notað þessa þekkingu til að þróa bóluefni ???



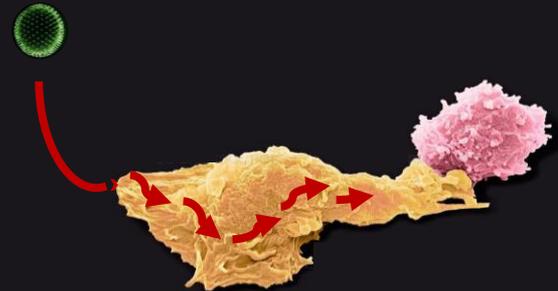


Dauðar veirur
Veiklaðar veirur
Veiruhluta

Dautt dauðir sýklar (oftast veirur)
Inflúensa, IV polio, Hepatitis A

Veiklaðir sýklar
MMR, Hlaupabóla
Rotaveira, Bólusótt, Yellow fever

Veiruhluta
Toxin: Tetanus, Barnaveiki





Dauðar veirur
Veiklaðar veirur
Veiruhluta

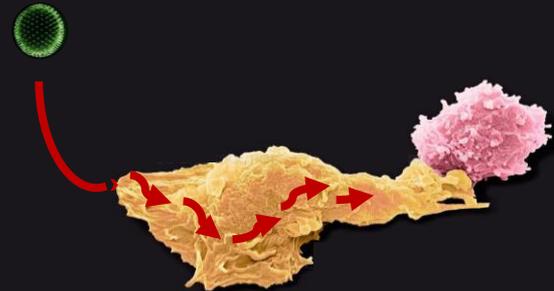
Polysaccharide vaccine
PPV (pneumococcal polysaccharide vaccine)
(Hepatitis B, HPV)



Dauðir sýklar
Sýklahlutar
Með trikkum!

Protein conjugated vaccine
Haemmophilus influenzae, type b,
PCV (pneumococcal conjugated vaccine)
MenC

BCG (úr öðrum tegundum)
Kúabóla





Dauðar veirur
Veiklaðar veirur
Veiruhluta



Dauðar bakteríur
Bakteríuhluta
Með trikkum!



Eitthvað annað?
Beta?
Vir kara?
Ódýrara?
Markvissara?
.....?

RNA vaccine:

mRNA sem skráir fyrir próteini, pakkað inn í vector (veiru, lipid nanópartikkla).
Dæmi: SARS CoV-2

DNA vaccine:

DNA úr veiru komið fyrir í manna eða dýrafrumum, DNA/mRNA-protein !
Væntanlega afar langvinnt ónæmissvar.
Dæmi: enn í tilraunum (hestar og West-Nile virus, monoclonal Ab?)

Recombinant vector:

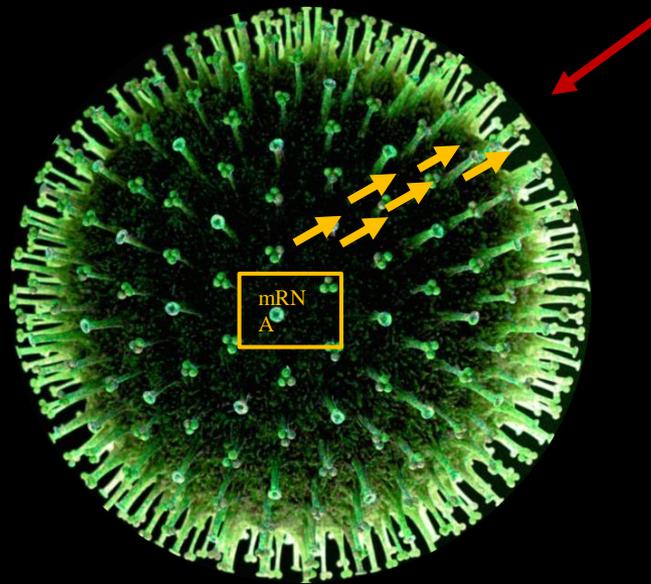
Samþætta eiginleika ákveðins sýkils við DNA úr öðrum.
Dæmi: RSV-ZEBOV (Ebóla bóluefni!)

T-cell receptor peptide vaccines:

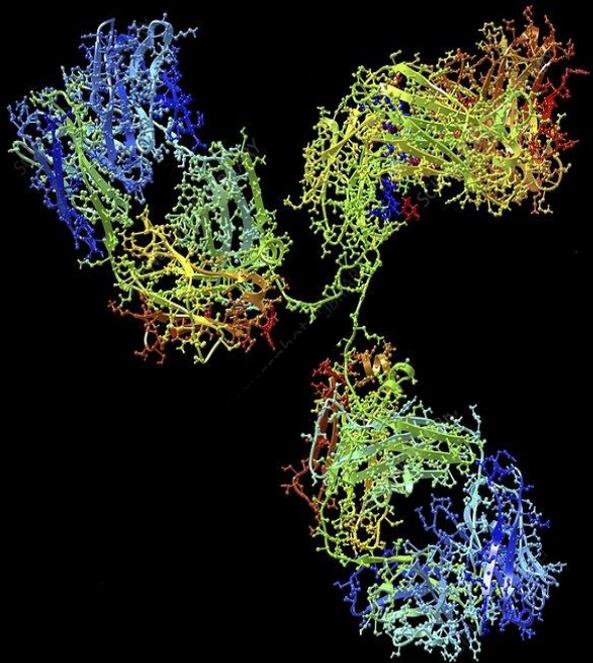
Breytir T-frumu samskiptum og frumuboðenfun.
Bóluefni gegn sjúkdómum (atopic dermatitis o.fl). Dæmi: enn í tilraunum

Dendritic cells (angafrumurnar):

Bóluefni gegn sjúkdómum
(brain tumor, mal melanoma), ex-vivo mRNA (DNA?) programming



Lokaniðurstaðan!



Allt

er ónæmisfræði !!!