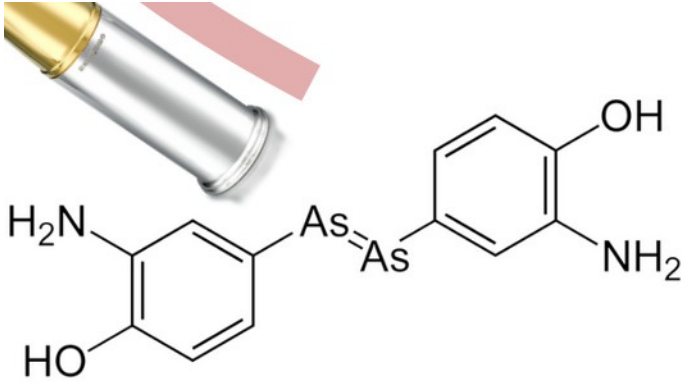
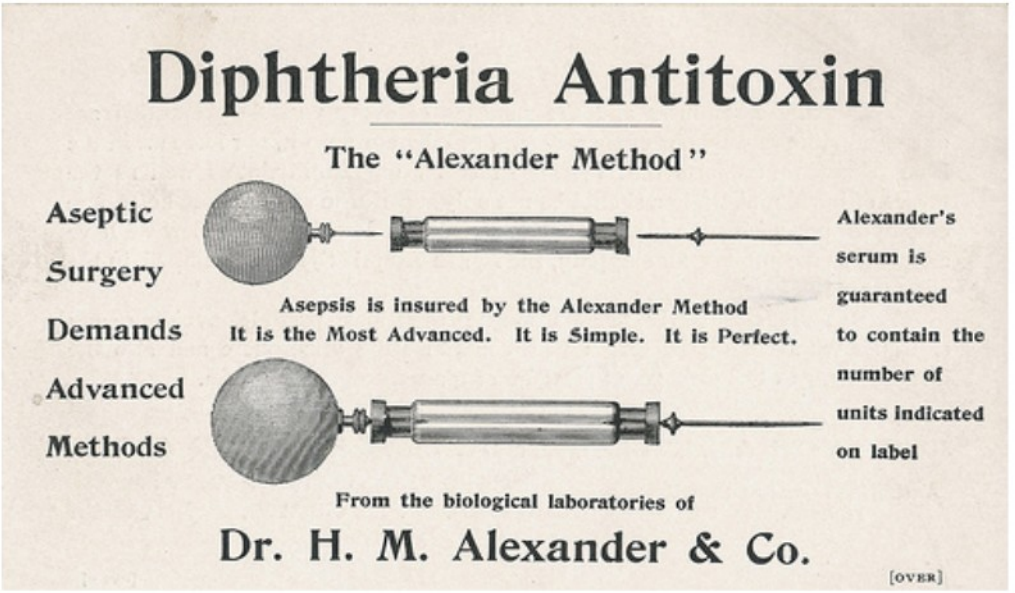
Biyolojik ilaçlar



Arsenik bileşikleri mikropları öldürüyor

Antikorlar mikropları öldürüyor



Diphtheria Antitoxin

The "Alexander Method"

Aseptic Surgery Demands Advanced Methods

Asepsis is insured by the Alexander Method
It is the Most Advanced. It is Simple. It is Perfect.

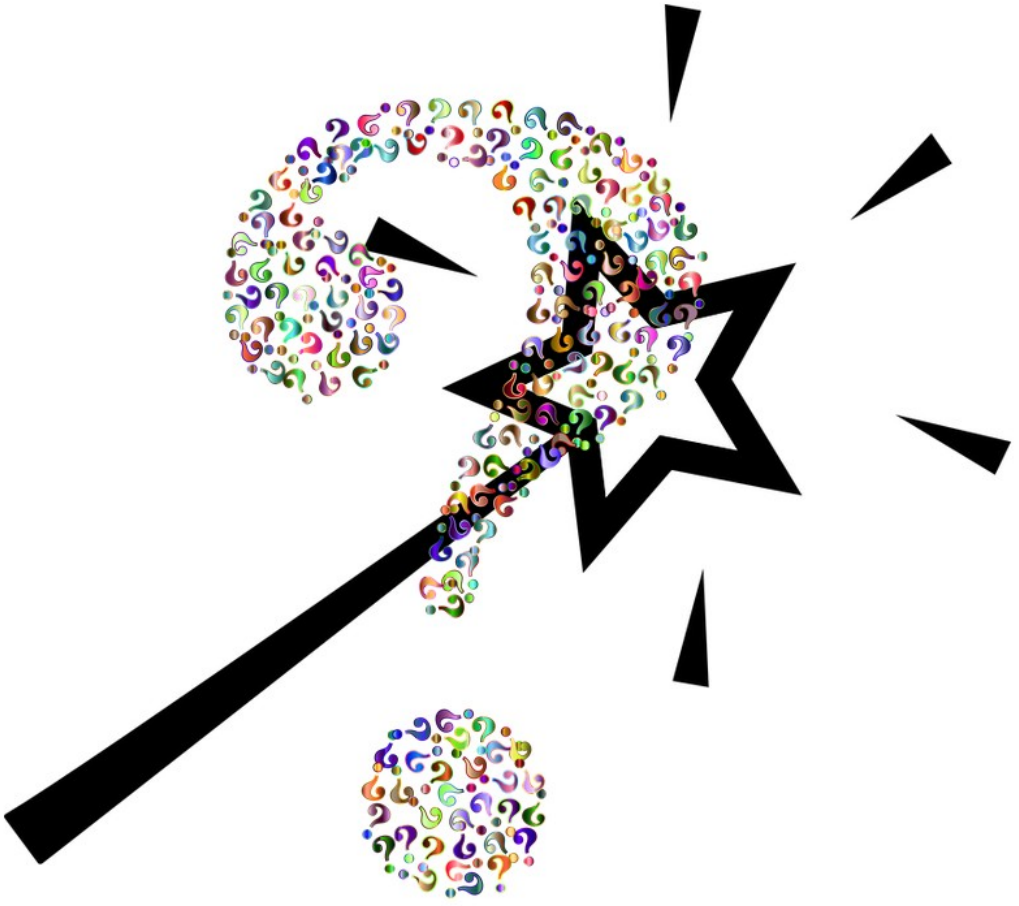
Alexander's serum is guaranteed to contain the number of units indicated on label

From the biological laboratories of

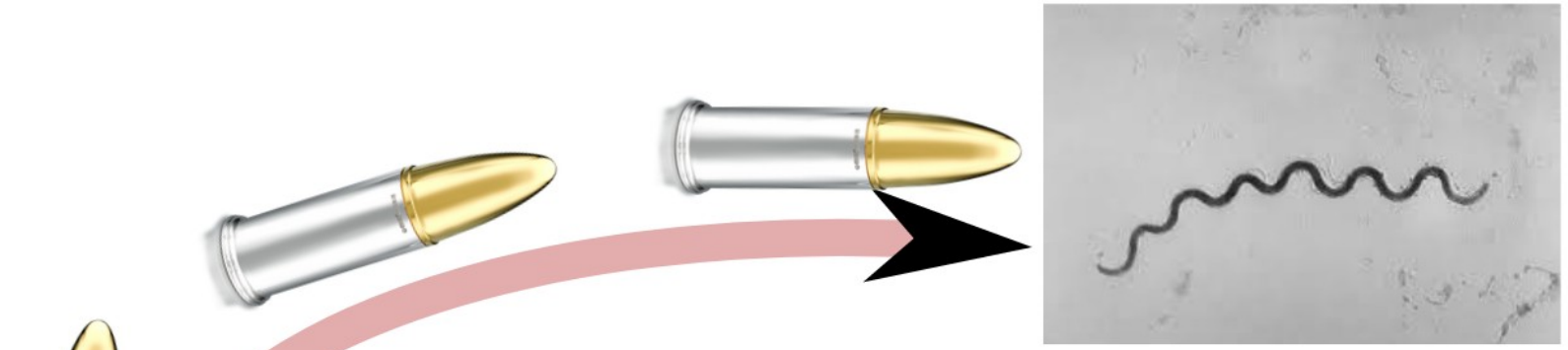
Dr. H. M. Alexander & Co.

[OVER]

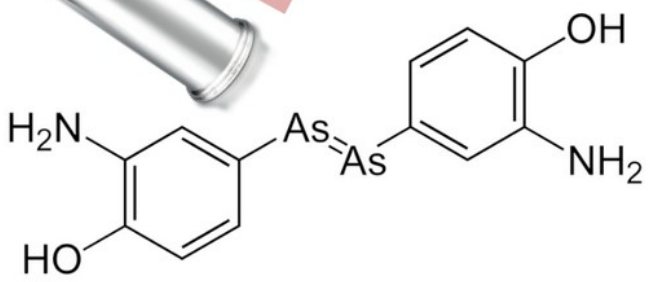
Sihirli mermi - vuracağı hedefi biliyor!



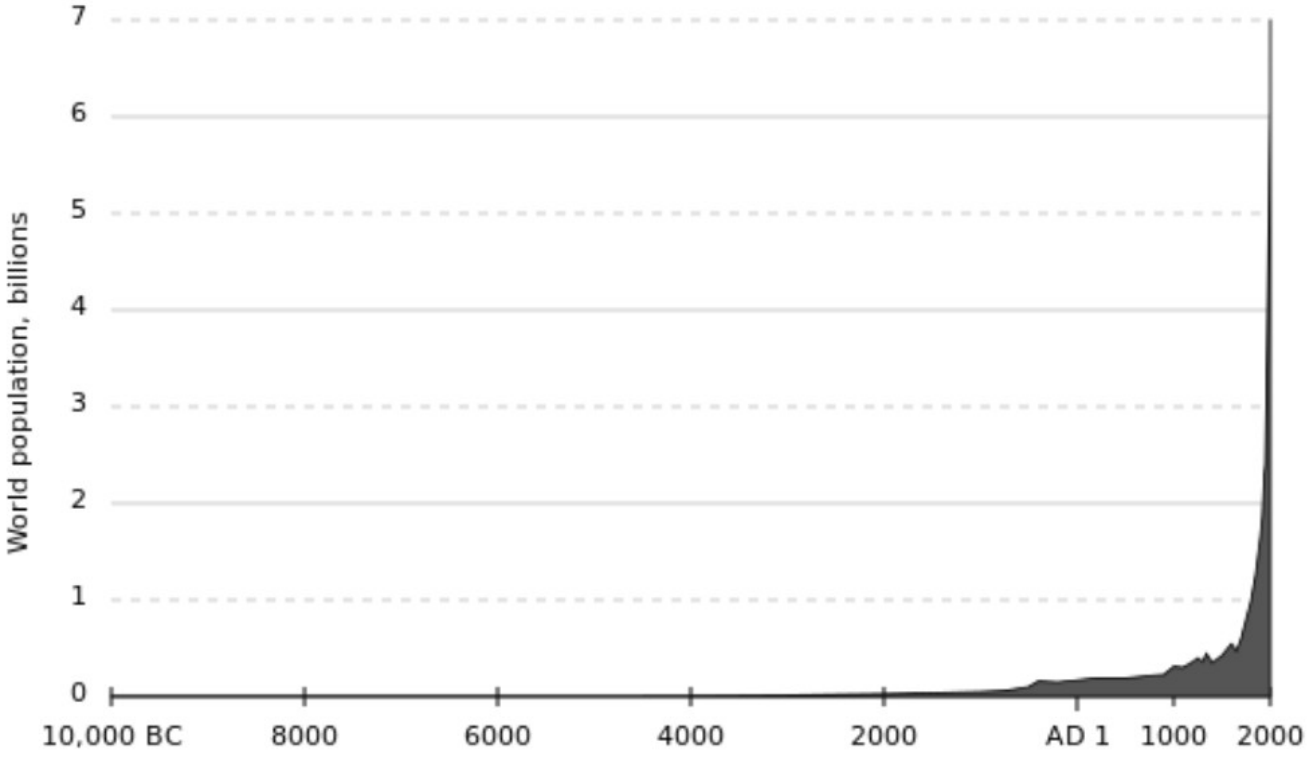
Antikorlar, mikroorganizmaları her zaman öldürmüyor!



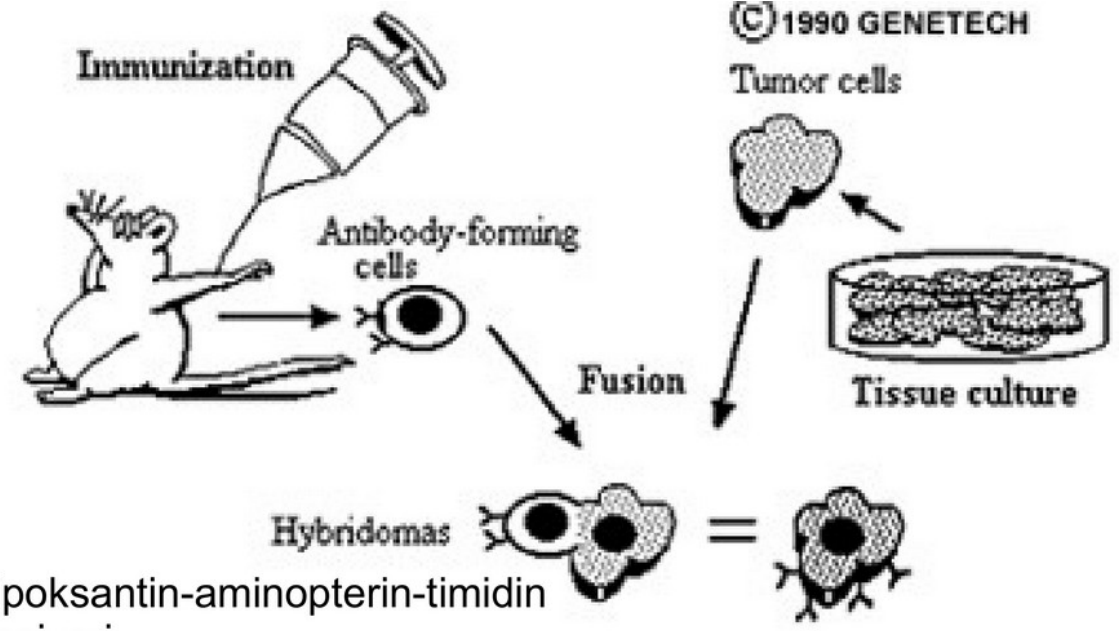
Bu bileşiklerin de antikorlar gibi mikroorganizmların toksinlerine bağlanabilen yan zincirleri olmalı



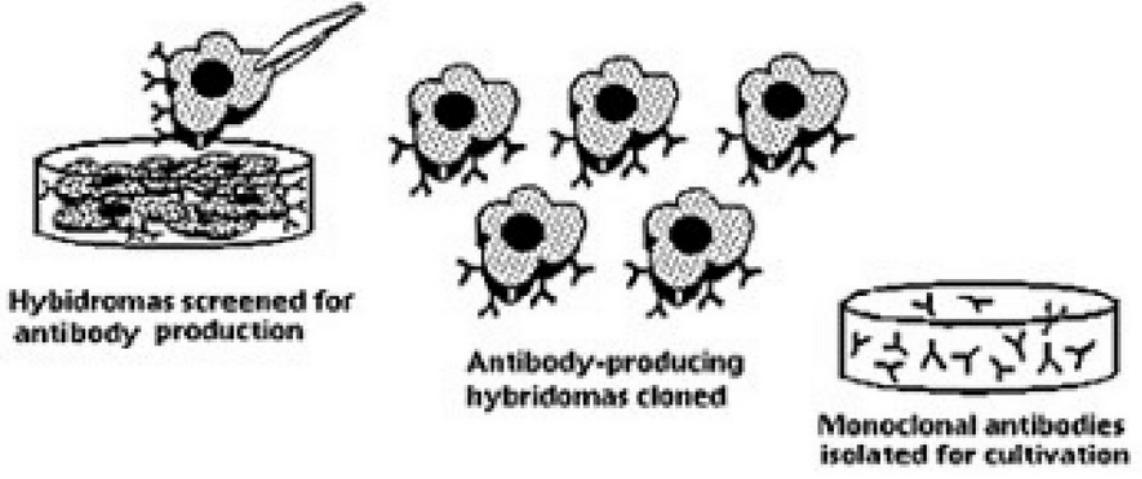
Arsenik bileşikleri mikropları öldürüyor

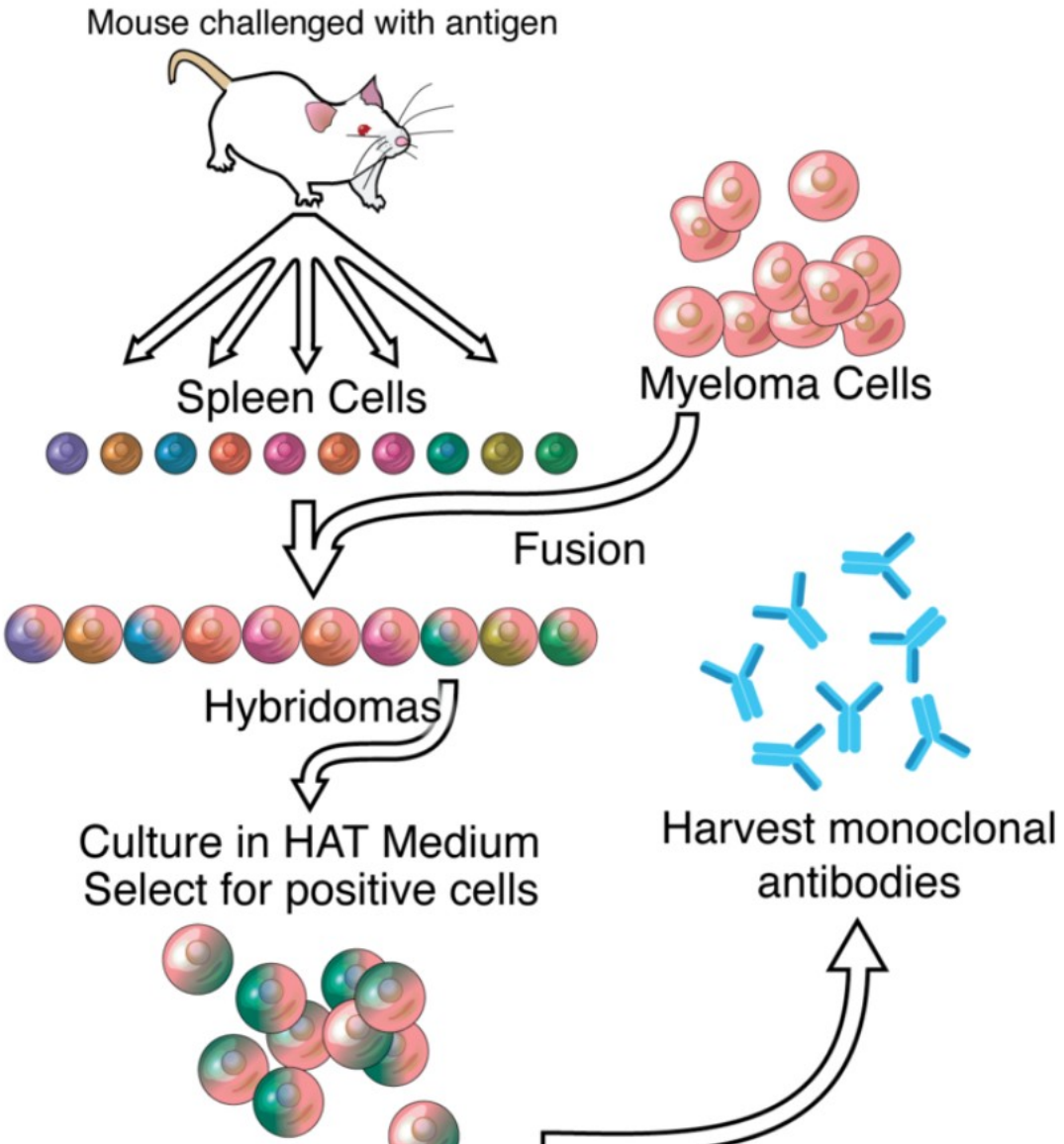


World population milestones in billions (USCB estimates)									
Population	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Year	1804	1927	1960	1974	1987	1999	2011	2024	2042
Years elapsed	—	123	33	14	13	12	12	13	18



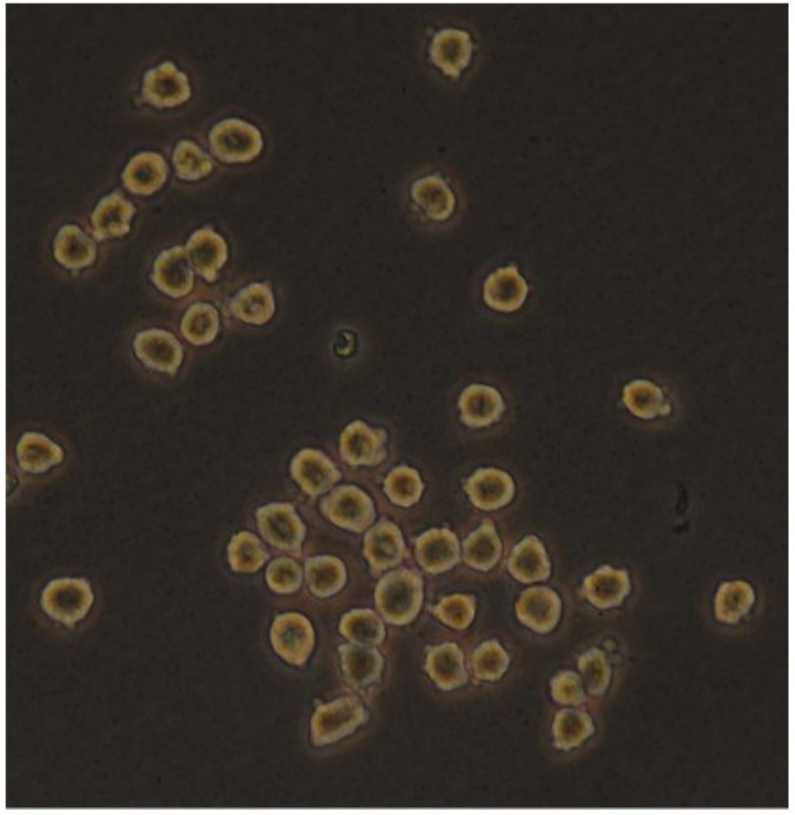
hipoksantin-aminopterin-timidin besiyeri




Mouse challenged with antigen
Spleen Cells
Myeloma Cells
Fusion
Hybridomas
Culture in HAT Medium
Select for positive cells
Harvest monoclonal
antibodies

hipoksantin-guanin fosforiboziltransferaz (HGPRT)

HAT besiyeri ile 14 gün seçim...

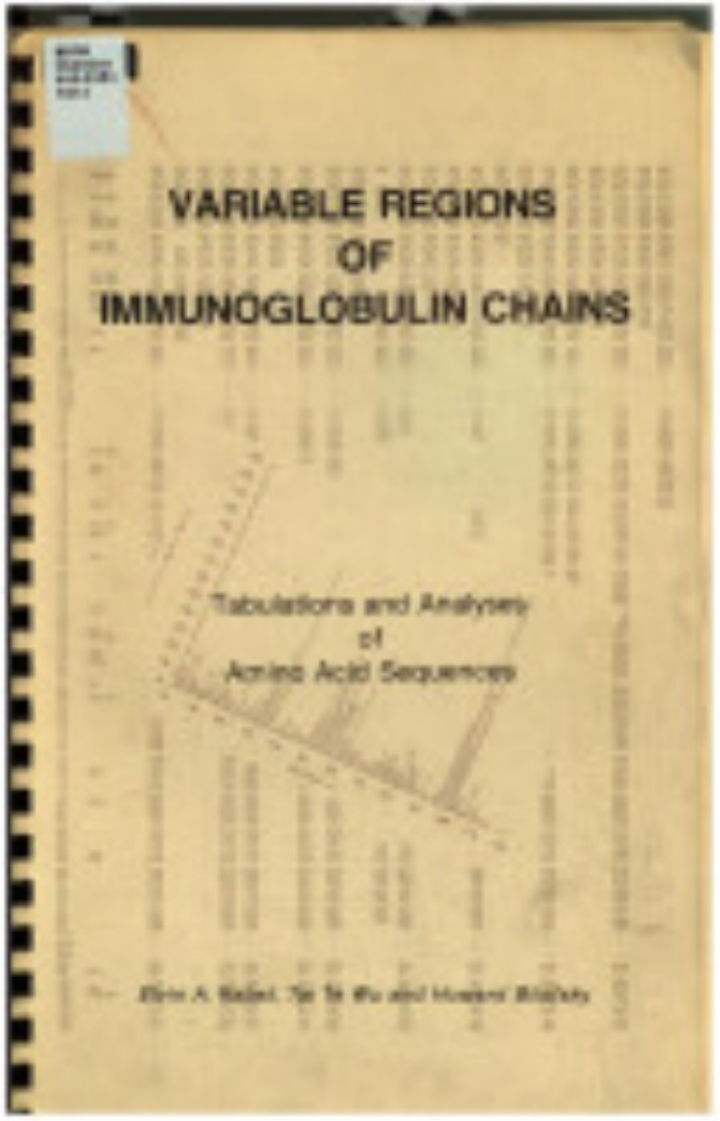


HAT Selection

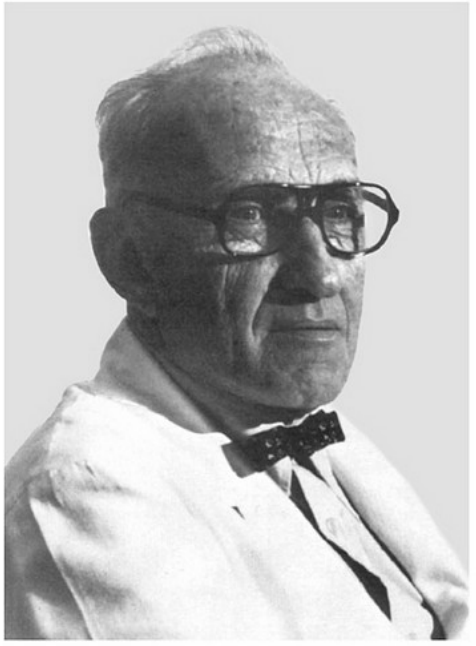
	TK -	TK+/TK -	TK +
Genotype:*			
Cell type:	immortal HAT-sensitive plasmacytoma	fused hybrid	mortal splenic B-cell
HAT fate:	**DIES**	**SURVIVES**	**DIES**
Explanation:	**Unable to synthesize DNA:** (1) Thymidine kinase* mutation causes a loss-of-function in the "salvage" pathway and (2) Aminopterin blocks "De novo" pathway.	**Immortal and restored DNA synthesis:** (1) Immortality from plasmacytoma and (2) rescued ability to synthesize DNA due to restored thymidine kinase* function.	**Mortal:** (1) Functional DNA synthesis, but (2) eventually dies because of limited number of replication cycles

*HGPRT (hypoxanthine-guanine phosphoribosyltransferase) mutants can be used in place of TK (thymidine kinase) mutants

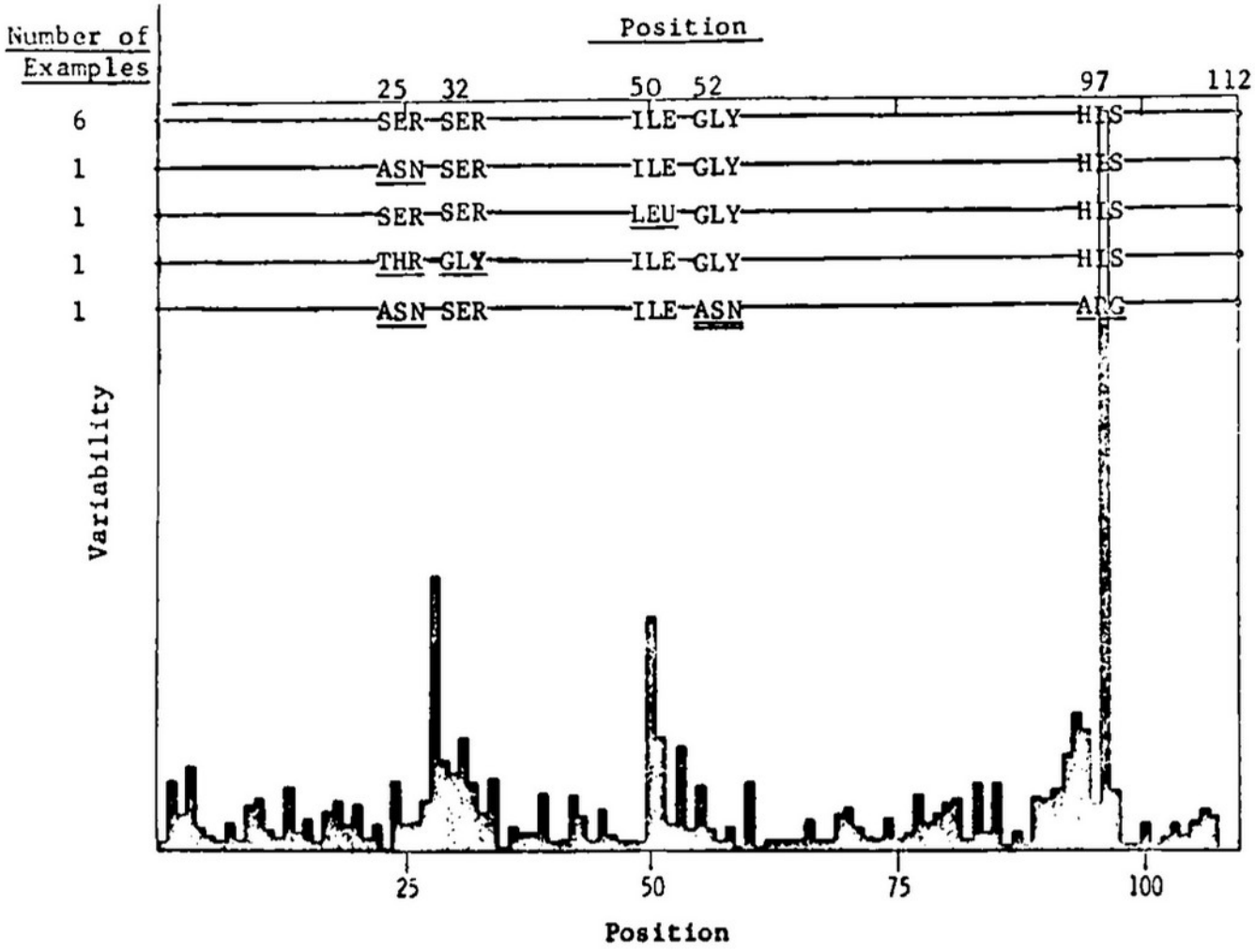
https://en.wikipedia.org/wiki/File:HAT_Selection.png



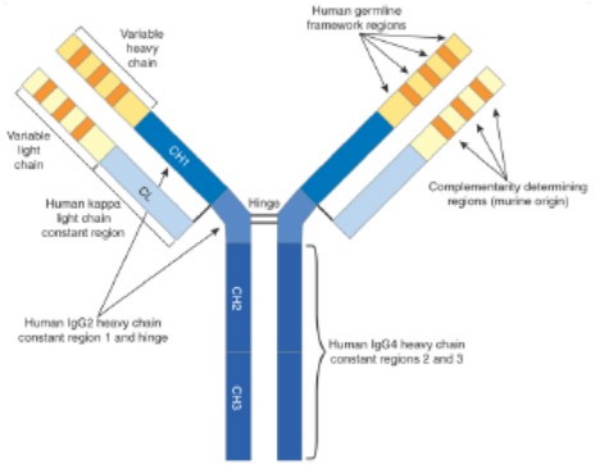
Variable Regions of Immunoglobulin Chains: Tabulations and Analyses of Amino Acid Sequences

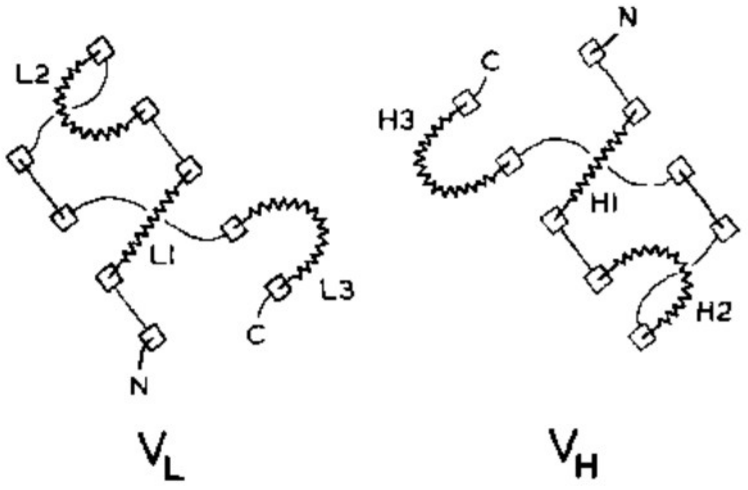


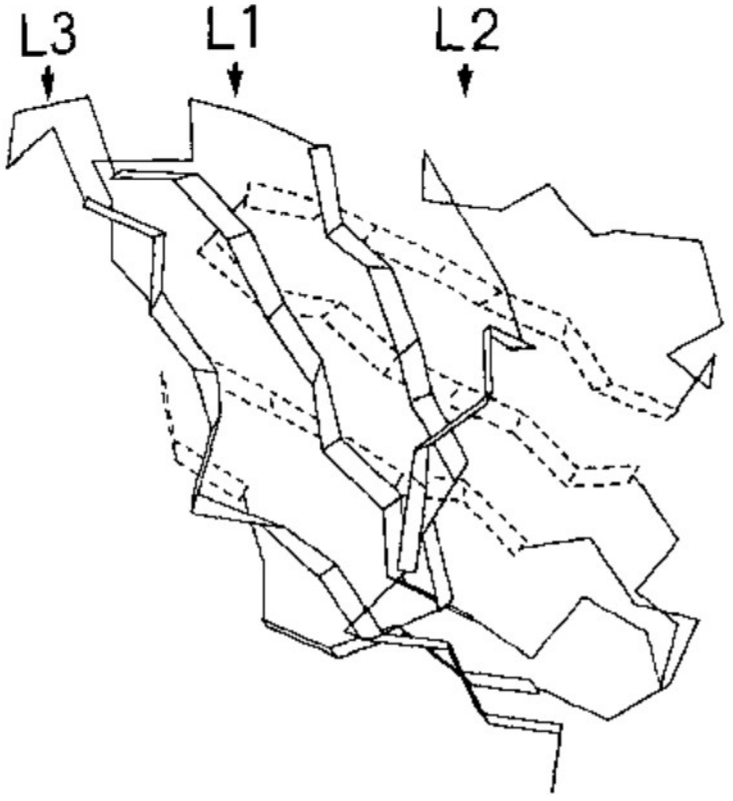
Elvin A. Kabat



Kabat EA, Wu TT. Attempts to Locate Complementarity-Determining Residues in the Variable Positions of Light and Heavy Chains *. Annals of the New York Academy of Sciences 1971;190(1):382–393.

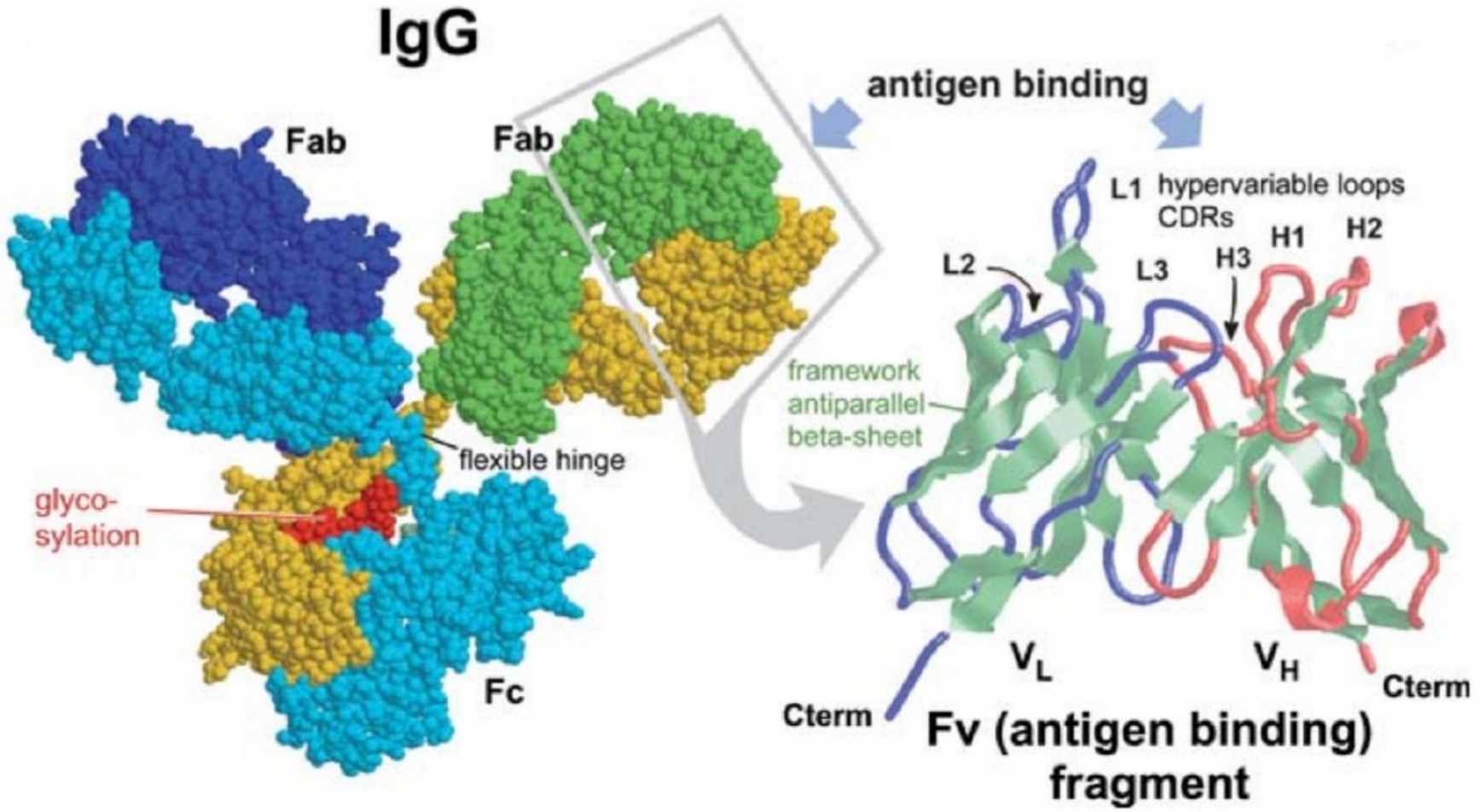


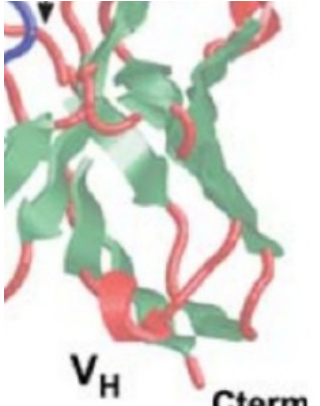




Chothia C, Lesk AM. Canonical structures for the hypervariable regions of immunoglobulins. J. Mol. Biol. 1987 Aug;196(4):901–917.

Bağlanmanın anatomisi...





binding)
ent

L1 L2 L3 — Canonical
H1 H2 H3 — Noncanonical Extensive Variability

10 sınıf
Canonical sınıf üyeleri hemen hemen aynı omurga konformasyonuna sahip
— loop uzunluğu
— CDR'lardaki anahtar amino asitler
— Framework'deki anahtar aminoasitler

H3 tahmini
— dB taraması
— Ab initio modeller
— Conformasyonel arama
— Hepsi :)

CDR-L1
5 belirgin κ
4 belirgin olmayan λ
1 belirgin olmayan κ
Toplam 10 sınıf

CDR-L2
çoğunluk bir yapıya uyuyor

CDR-L3
Sınıf 1+2 → 9 üye
Sınıf 3 → 8 üye
Benzer hairpin loop'lardan oluşuyor
Farklılıklar Prolinin pozisyonundan kaynaklanıyor
Sınıf 4 → 7 üye
Sınıf 5 → 8 üye

CDR-H1
Sınıf 1 → 10 üye
Sınıf 2 → ?
Sınıf 3 → 11 üye
Sınıf 4 → 12 üye

CDR-H2
Sınıf 1 → 9 üye
Sınıf 2 → 10 üye
Sınıf 3 → 10 üye
Sınıf 4 → 12 üye

CDR-H3
Canonical sınıflar yerine korunmuş yan zincirler bulunuyor

FRs and CDRs of Antibody and TCR Variable Regions

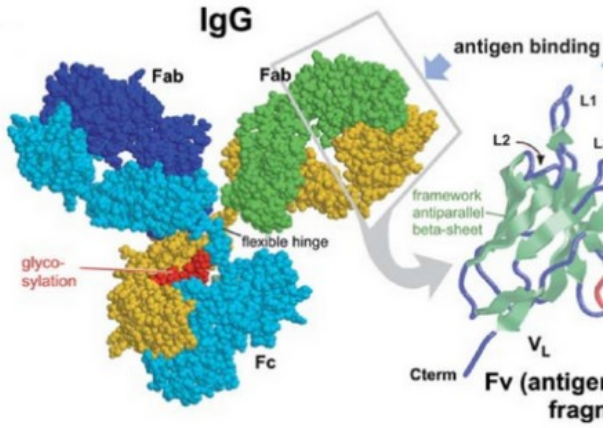
FR or CDR	V_L	V_H	V_α	V_β	V_γ	V_δ
FR1	1–23	1–22	1–22	1–23	1–21	1–22
CDR1	24–34	31–35B	23–33	24–33	22–34	23–34A
FR2	35–49	36–49	34–47	34–49	35–49	35–49
CDR2	50–56	50–65	48–56	50–56	50–59	50–57
FR3	57–88	66–91	57–92	57–94	60–95	58–89
CDR3	89–97	95–102	93–105	95–107	96–107	90–105
FR4	98–107	103–113	106–116	108–116A	108–116C	106–116

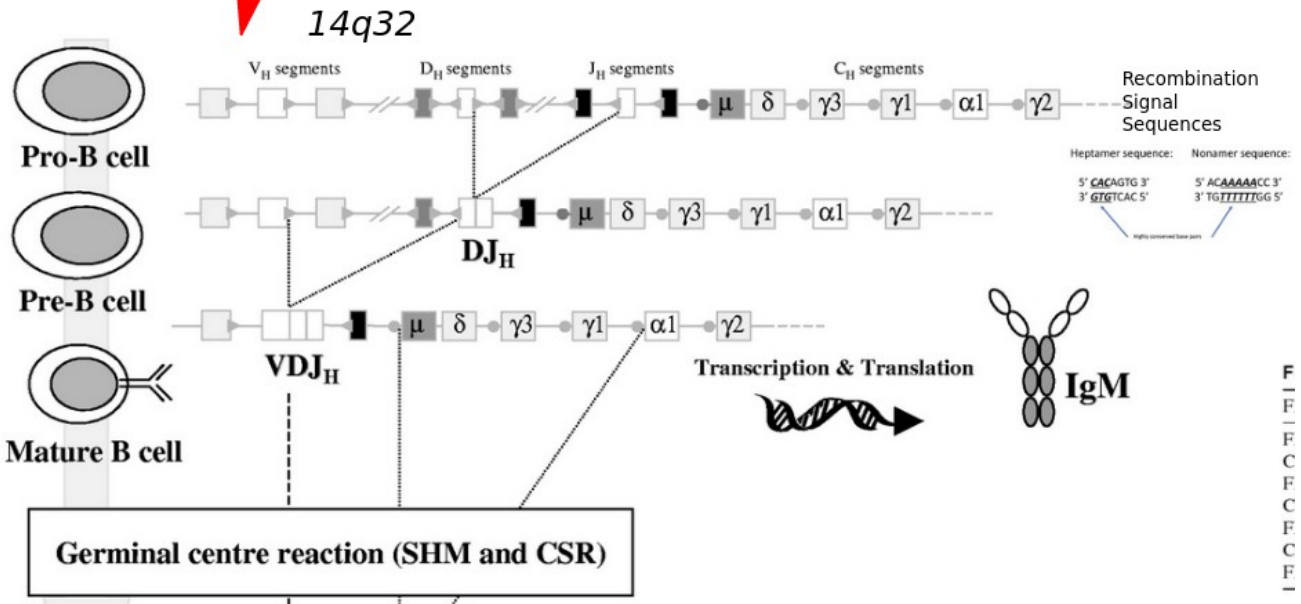
Soru: Bir memelide kaç farklı genom bulunur?

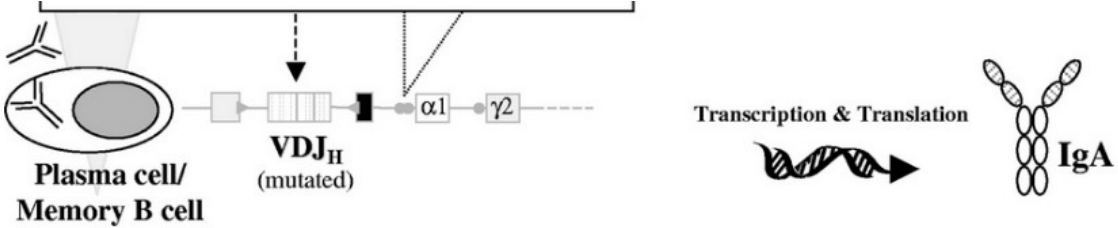
10^11 - 10^12

Ama nasıl?

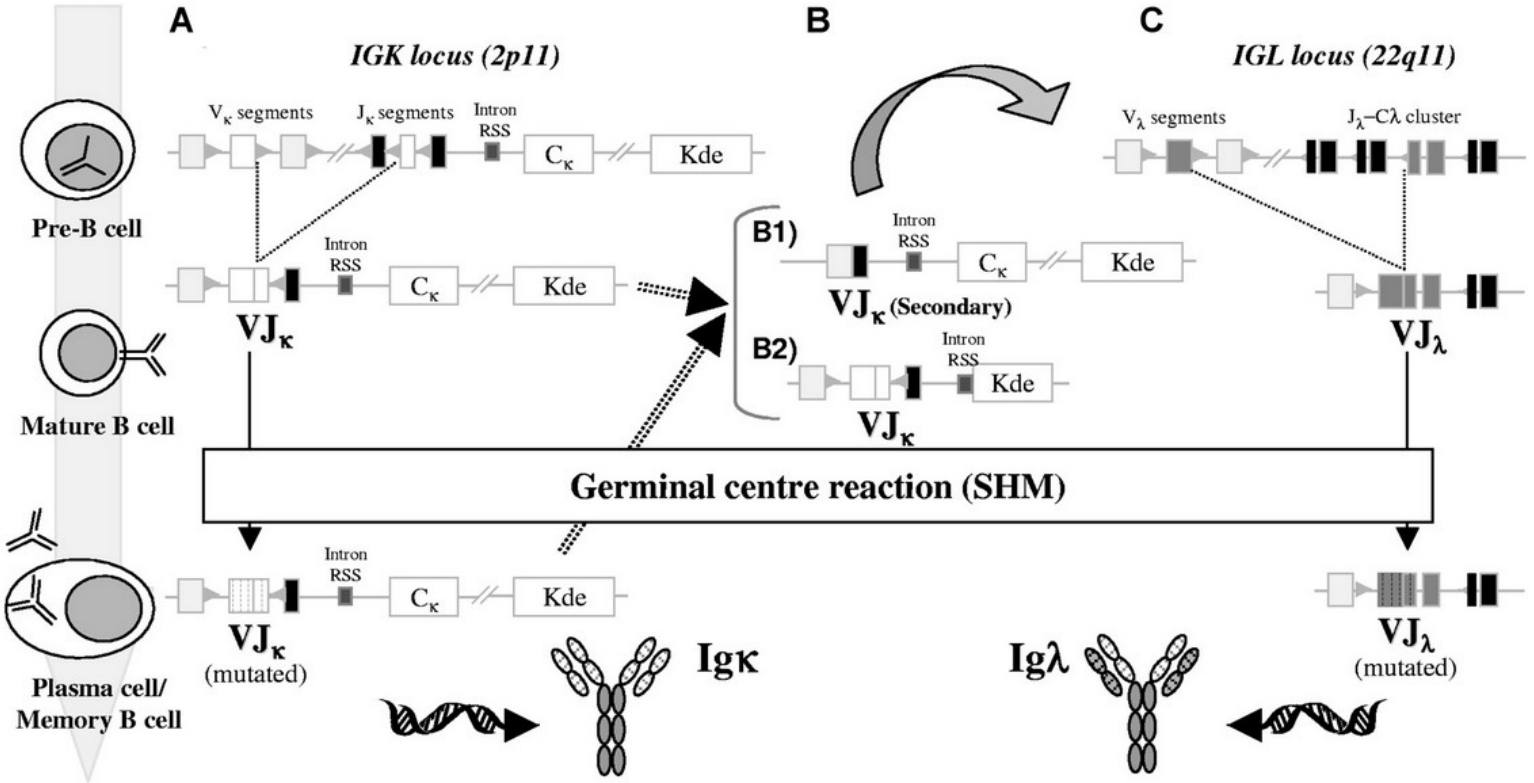
Bağlanmanın anatomisi...







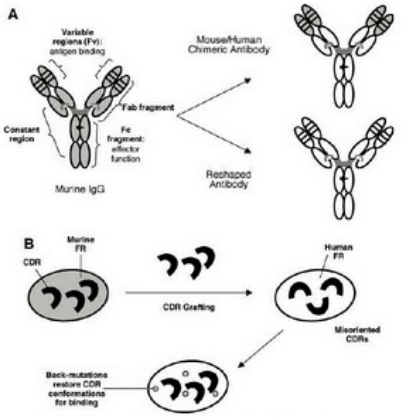
Immunoglobulin gene rearrangements and the pathogenesis of multiple myeloma
David González, Mirjam van der Burg, Ramón García-Sanz, James A. Fenton, Anton W. Langerak, Marcos González, Jacques J. M. van Dongen, Jesus F. San Miguel and Gareth J. Morgan. Blood 2007 110:3112-3121



VDJ recombinase

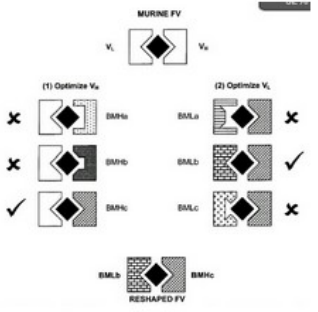
- recombination activating genes 1 and 2 (RAG)
- terminal deoxynucleotidyl transferase (TdT)
- Artemis nuclease (ubiquitous non-homologous end j oining (NHEJ) pathway for DNA repair)
- DNA-dependent protein kinase (DNA-PK)
- X-ray repair cross-complementing protein 4 (XRCC4)
- DNA ligase IV
- Cernunnos or XRCC4-like factor [XLF]: non-homologous end-joining factor 1
- Paralog of XRCC4 and XLF (PAXX)
- DNA polymerases λ and μ

Yıllar içinde biyolojik peptid ilaçlar...



Tüm bu manipülasyonlar, "orijinal" konformasyonu bozuyor :/

O halde ciddi bir optimizasyona gereksinim var!



1

Brand	Generic	Company	Therapeutic category	Indications
Humulin	Insulin	Eli Lilly	Diabetes	Diabetes
Humatrope	Recombinant Somatropin	Eli Lilly	Hormones	Growth failure
Genotropin	Somatropin	Pfizer	Hormones	Growth failure
Saizen	Somatropin	Serono	Hormones	Growth failure
Nutropin/Protropin	Somatropin/Somatrem	Genentech	Hormones	Growth failure
Intron A &	Interferon alpha-2b/	Schering-Plough	Anti-infective	Viral infections
Avonex	Interferon beta-1a	Biogen Idec	Multiple sclerosis	Chronic inflammatory demyelinating polyneuropathy
Betaseron/Betaferon	Interferon beta-1b	Schering AG	Multiple sclerosis	Multiple sclerosis
Procrit/Eprex	Epoetin alpha	J&J	Blood modifier	Anaemia
Epogen	Epoetin alpha	Amgen	Blood modifier	Anaemia
NeoRecormon	Epoetin beta	Roche	Blood modifier	Anaemia
Kogenate	Factor VIII	Bayer	Blood modifier	Haemophilia
NovoSeven	Factor VIIa	Novo Nordisk	Blood modifier	Haemophilia
Benefix	Factor IX	Wyeth	Blood modifier	Haemophilia
Fabrazyme	Agalsidase beta	Genzyme	Enzymes	Fabry disease
Replagal	Agalsidase alfa	TKT Europe	Enzymes	Fabry disease
Pulmozyme	Dornase alpha	Genentech	Enzymes	Cystic fibrosis
Activase/Actilyse	Alteplase	Genentech	Blood factor	Myocardial infarction

http://laborant.pl/index.php/recombinant-protein-therapeutics-the-future-is-here

2

Brand	Generic	Company	Therapeutic category	Indications
Humalog/Liprolog	insulin lispro,	Eli Lilly	Diabetes	Diabetes
Lantus	Glargine insulin	Sanofi-Aventis	Diabetes	Diabetes
Levemir	Datemir insulin	Novo Nordisk	Diabetes	Diabetes
Pegasys	Pegylated interferon alpha-2a	Roche	Interferon	Hepatitis C
Peg-Intron	Pegylated interferon alpha-2a	Schering Plough	Interferon	Hepatitis C
Aranesp	Darbepoetin alpha	Amgen	Blood modifier	Anaemia
Neulasta	PEG-Filgrastim	Amgen	Blood modifier	Neutropenia
ReFacto	Factor VIII	Wyeth	Blood modifier	Haemophilia
Amevive	alefacept	Biogen Idec.	Inflammation/Bone	Plaque psoriasis
Enbrel	Etanercept	Amgen	Anti-arthritic	Arthritis
Ontak	rIL2-diptheria toxin	Ligand Pharmaceuticals	Cancer	Cancer

http://laborant.pl/index.php/recombinant-protein-therapeutics-the-future-is-here

3

Brand	Generic	Company	Therapeutic category	Indications
ReoPro	Abciximab	Eli Lilly	Blood modifier	Acute coronary syndrome
Rituxan	rituxumab	Genentech	Cancer	Non-Hodgkin's lymphoma
Herceptin	Trastuzumab	Genentech	Cancer	Breast cancer
Synagis	Palivizumab	MedImmune	Respiratory	Respiratory syncytial virus
Campath	Alemtuzumab	Schering AG	Cancer	Non-Hodgkin's lymphoma
Humira	Adalimumab	Abbott Labs	Anti-arthritic	Rheumatoid arthritis
Xolair Omalizumab	Omalizumab	Genentech	Respiratory diseases	Paediatric asthma, peanut allergies
Erbitux	Cetuximab	Imclone Systems	Cancer	Colon cancer
Avastin	Bevacizumab	Genentech	Cancer	Colon cancer

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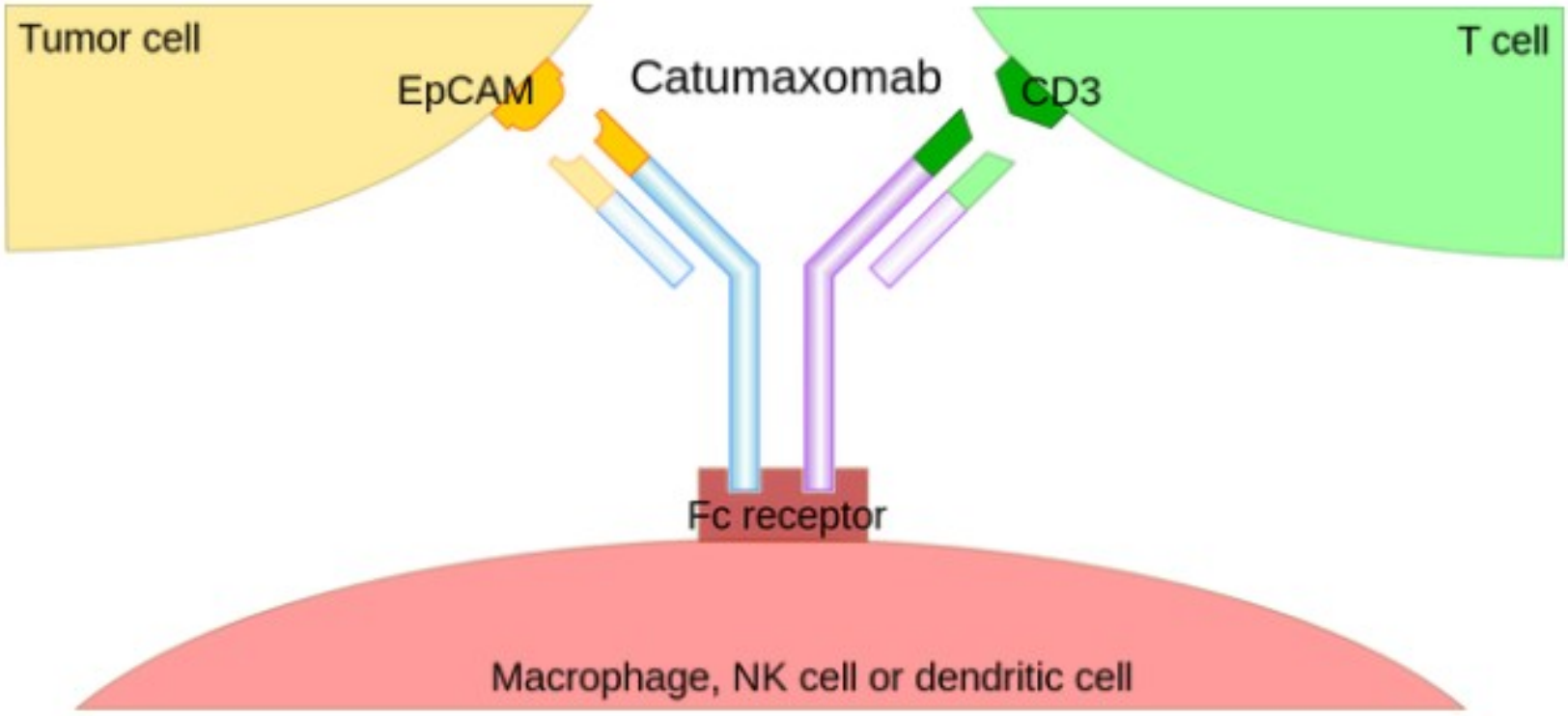
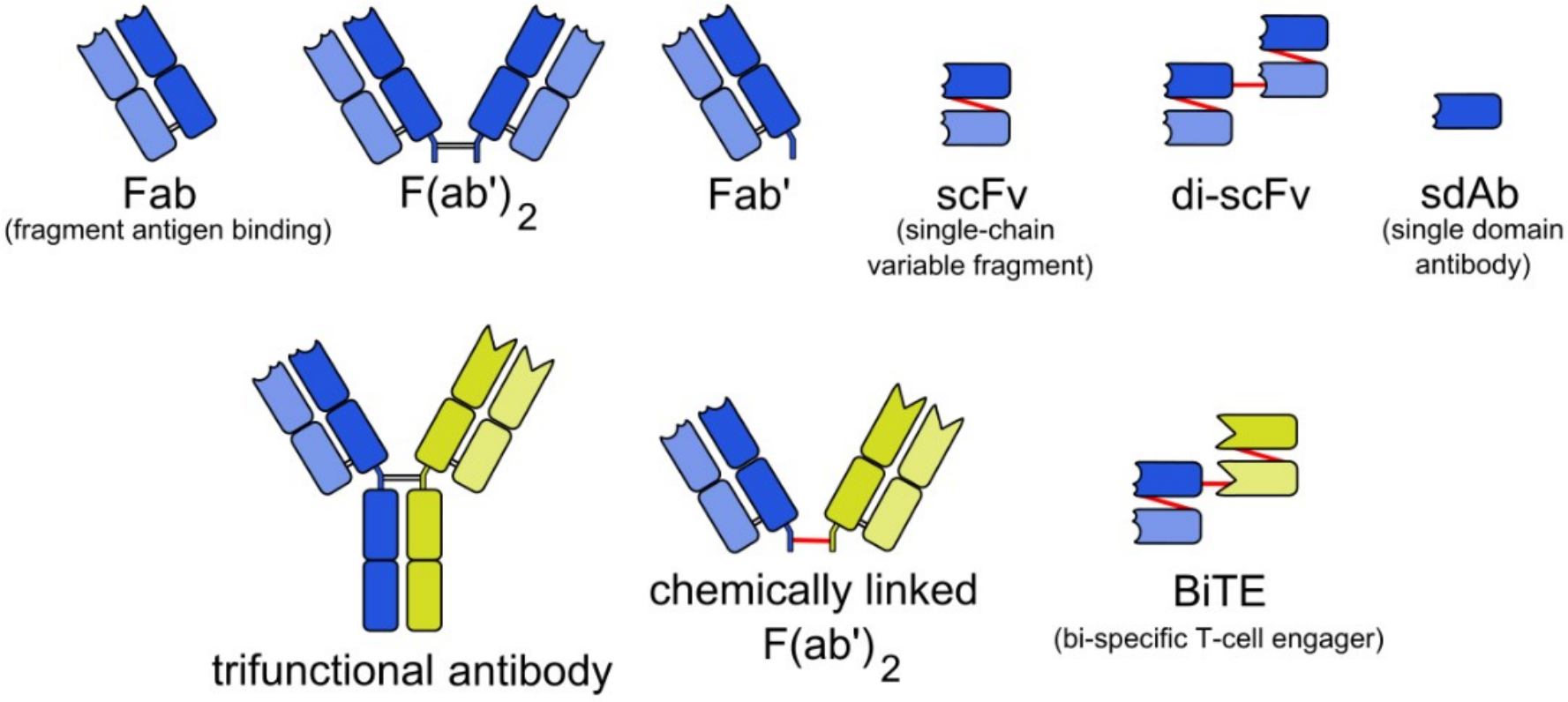


çoklu hedeleme...



daha küçük... daha kompakt... hücre içi hedefler?

çoklu hedefleme...

Daha yaratıcı kombinasyonlar...