Біотехнологічні фармацевтичні продукти

«Modern European trends in biomedical higher education: Bionanomaterials.» № 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

Лекція містить контент англійською мовою

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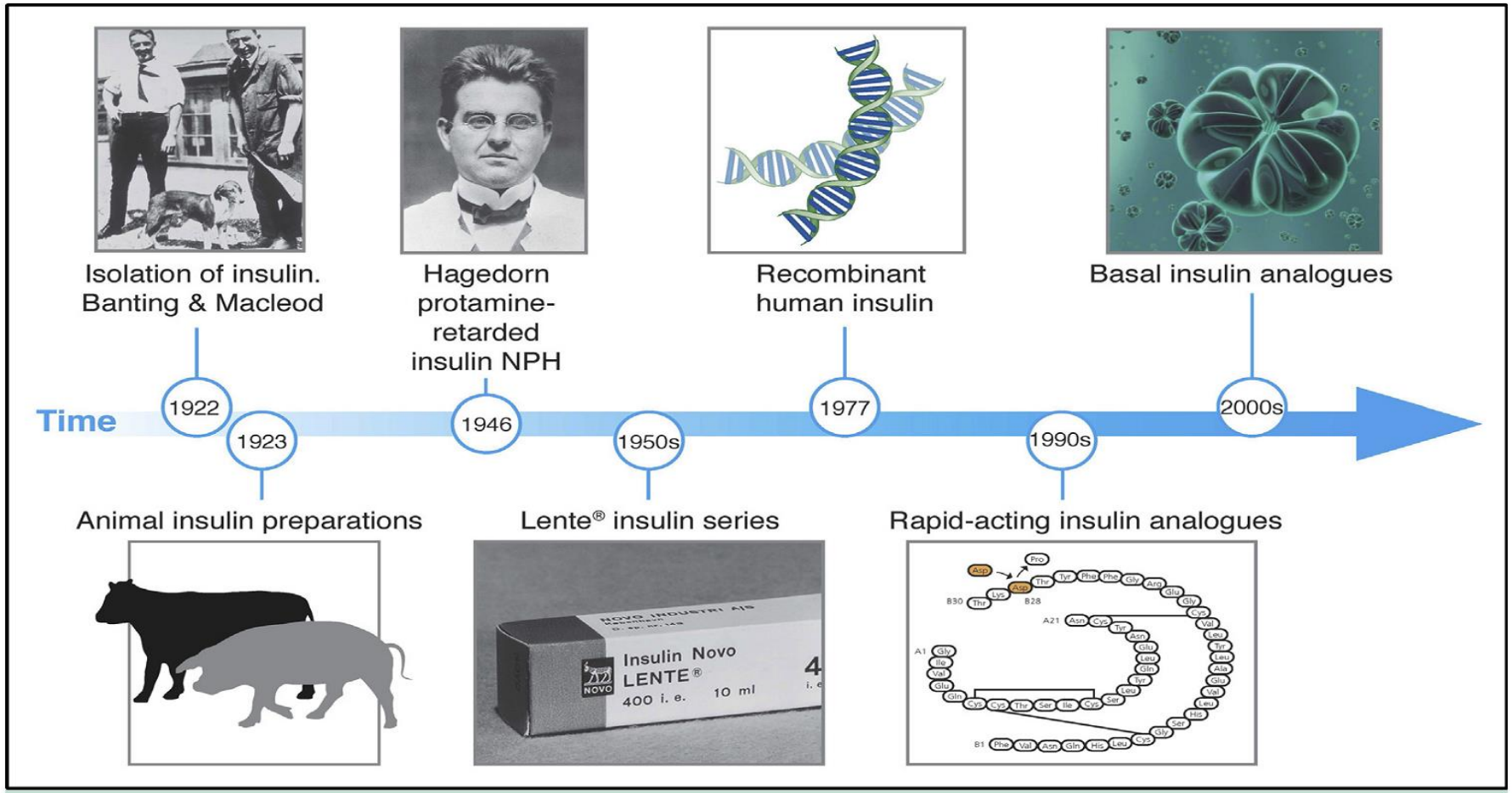

Figure 1 Milestones in the evolution of insulin therapy. NPH = neutral protamine Hagedorn.

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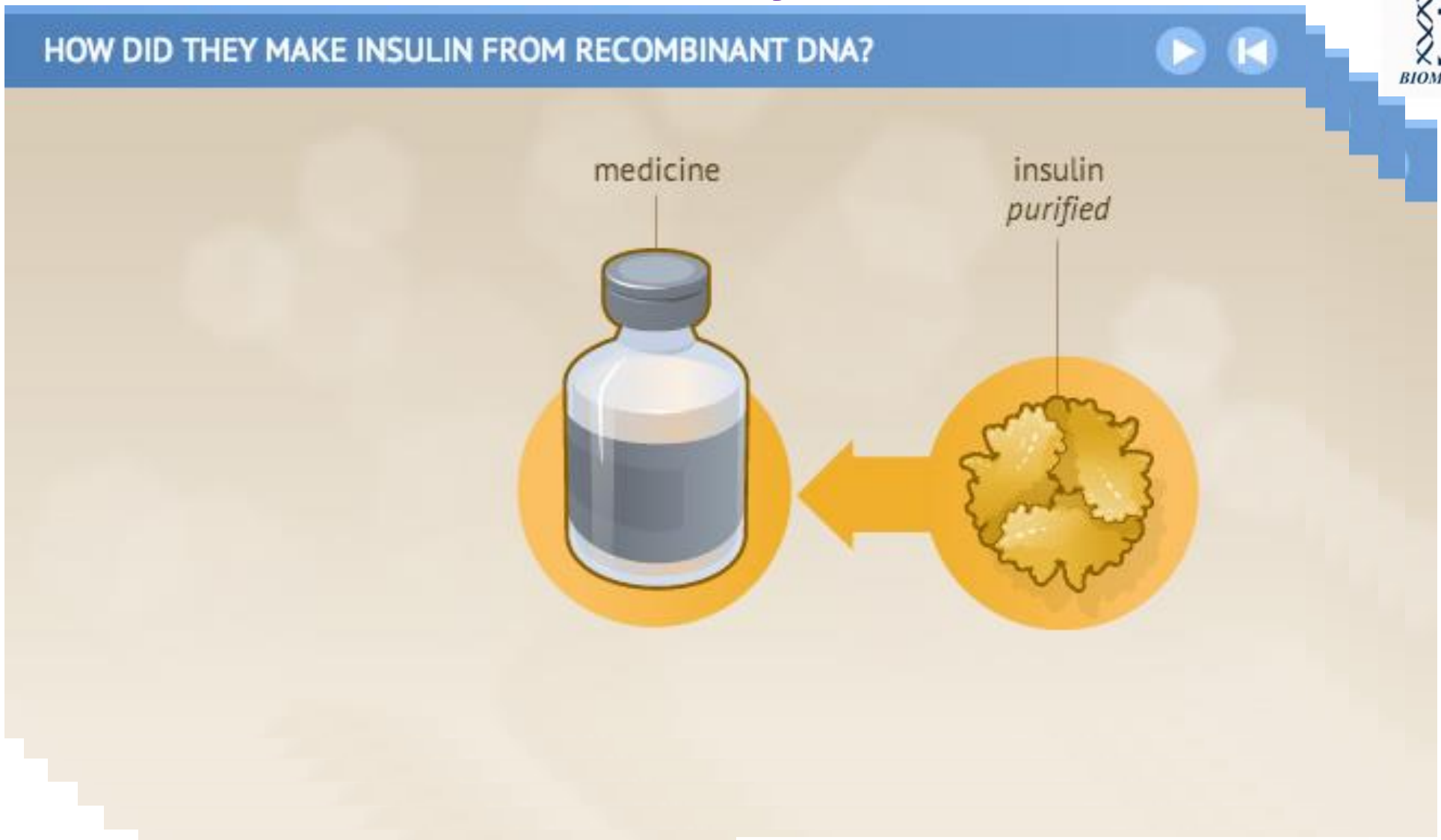
How do they do it?



https://www.nlm.nih.gov/exhibition/fromdnatobeer/exhibition-interactive/recombinant-DNA/r
alternative.html#:~:text=Recombinant%20DNA%20is%20a%20technology,insulin%20gene%20ir

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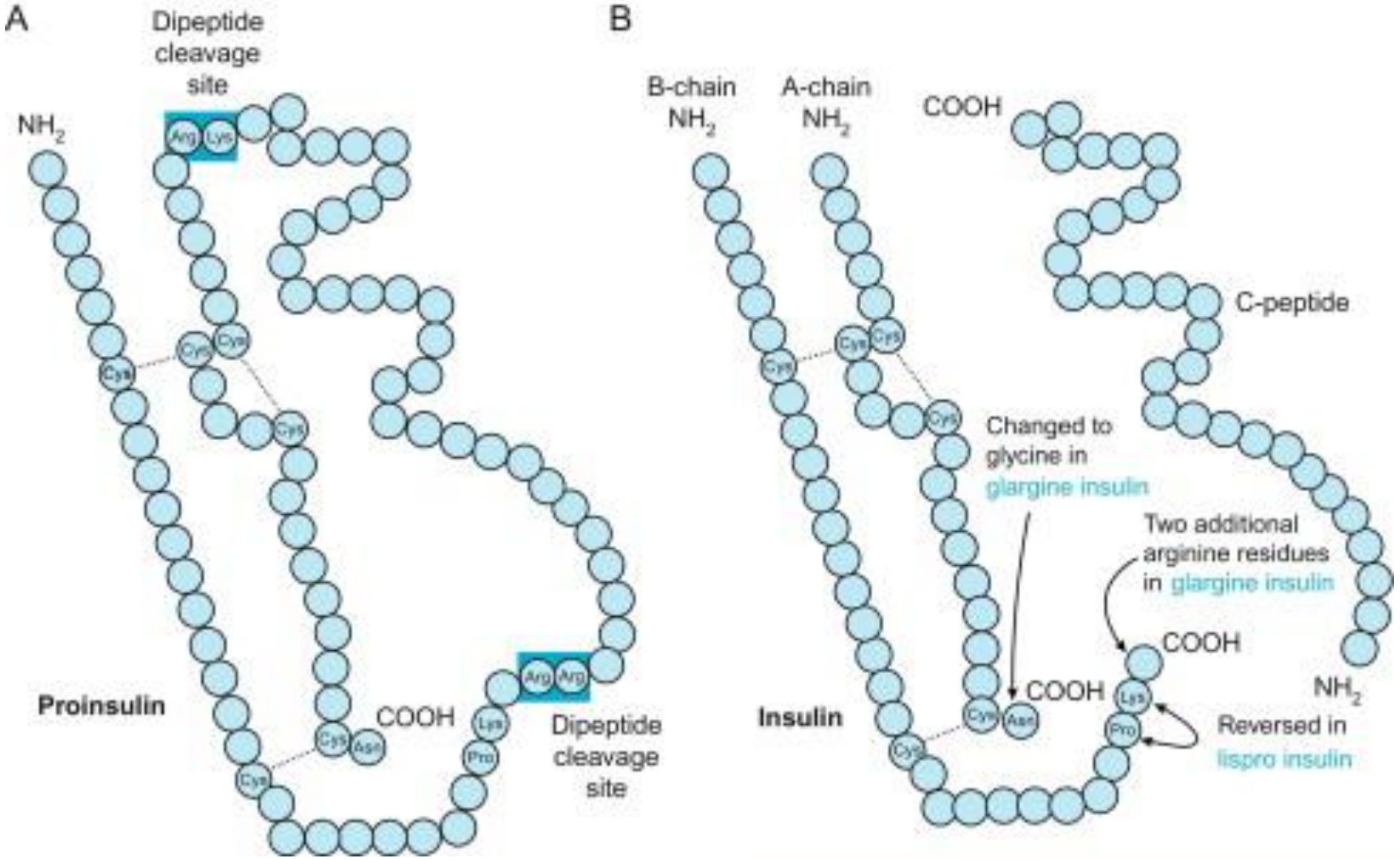

https://www.sciencedirect.com/topics/chemistry/insulin-derivative

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THE FIRST GENERATION OF THERAPEUTIC PROTEINS				
Humulin	Insulin	Eli Lilly	Diabetes	Diabetes
Hematrope	Recombinant somatropin	Eli Lilly	Hormones	Growth failure
Genotropin	Somatropin	Pfizer	Hormones	Growth failure
Saizen	Somatropin	Serono	Hormones	Growth failure
Nutropin/Protropin	Somatropin/Somatrem	Genetech	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 polyneurophathy
Betaseron/Betaferon	Interferon beta-1b	Schering AG	Multiple sclerosis	Multiple sclerosis
Procrit/Eprex	Epoetin alpha	J&J	Blood modifier	Anemia
Epogen	Epoetin alpha	Amgen	Blood modifier	Anemia
NeoRecormon	Epoetin beta	Roche	Blood modifier	Anemia
Kogenate	Factor VIII	Bayer	Blood modifier	Hemophilia
NovoSeven	Factor VIIa	Novo Nordisk	Blood modifier	Hemophilia
Benefix	Factor IX	Wyeth	Blood modifier	Hemophilia
Fabrazyme	Agalsidase beta	Genzyme	Enzymes	Fabry disease
Replagal	Agalsidase alfa	TKT Europe	Enzymes	Fabry disease
Pulmozyme	Domase alpha	Genetech	Enzymes	Cystic fibrosis
Activase/Acitlyse	Alteplase	Genetech	Blood factor	Myocardial infarction

Medical Biotechnology

Phuc V. Pham, in Omics Technologies and Bio-Engineering, 2018

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THE SECOND GENERATION OF THERAPEUTIC PROTEINS

Humalog/Liprolog	Insulin Lispro	Eli Lilly	Diabetes	Diabetes
Lantus	Glargine insulin	Sanofi-Aventis	Diabetes	Diabetes
Levemir	Detemir 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	Anemia
Neulasta	PEG-Filgrastim	Amgen	Blood modifier	Neutropenia
Refacto	Factor VIII	Wyeth	Blood modifier	Hemophilia
Amevive	Alefacept	Biogen Idec	Inflammation/Bone	Plaque psoriasis
Enbrel	Etanercept	Amgen	Anti-arthritic	Arthritis
Ontak	rIL-2-diptheria toxin	Ligand Pharmaceuticals	Cancer	Cancer

Medical Biotechnology

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081211	Fragment Template is pTe102	restrictases
pTe131 pET27b-FGF2-His6	FGF2-cds-2C/2B	NdeI-XhoI
pTe132 pET28b FGF2-His6	FGF2-cds-2A/2B	NcoI-XhoI
pTe133 pET28b-His6-Thrombin-FGF2	FGF2-cds-2C/2D	NdeI-XhoI
pTe134 pColdTF-FGF2	FGF2-cds-2C/2D	NdeI-XhoI
pTe135 pET32a-Trx-His6-Fgf2	FGF2-cds-2A/2D	NcoI-XhoI

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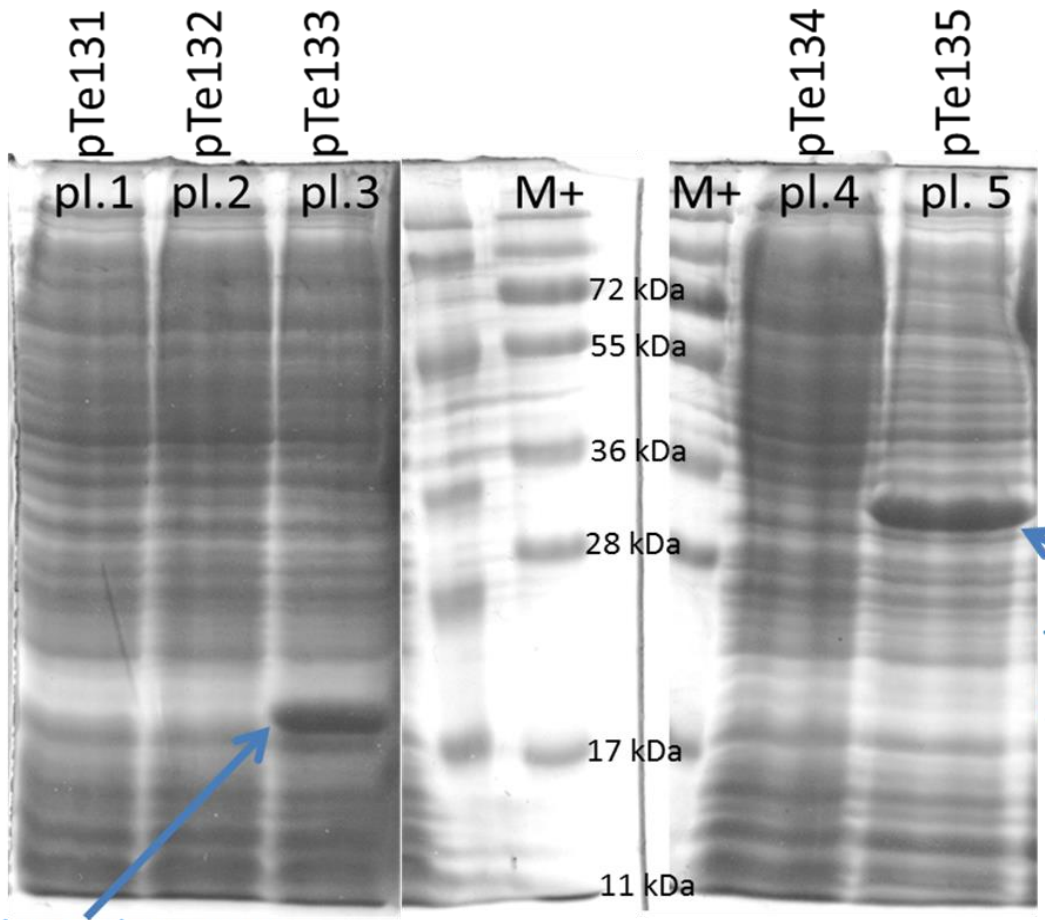
Induction 19Dec2011 in BL21(DE3), soluble fractions



Trx-His6-EK-FGF2
34,4 kDa

His6-Thrombin-FGF2
19,4 kDa

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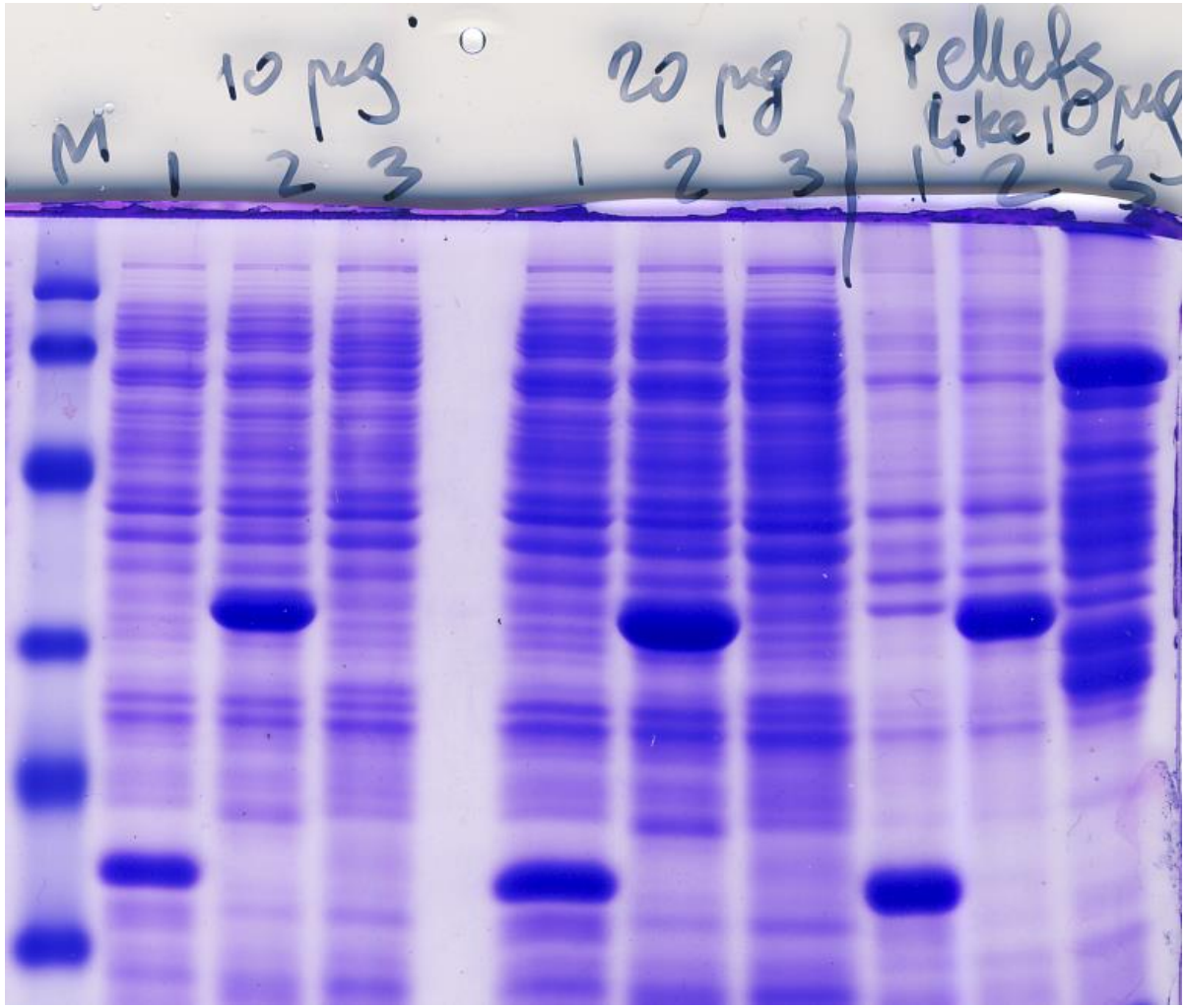
EnBase fermentation 15Feb2012



←34,4 kDa

←19,4 kDa

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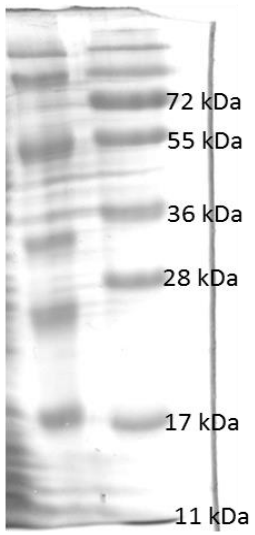
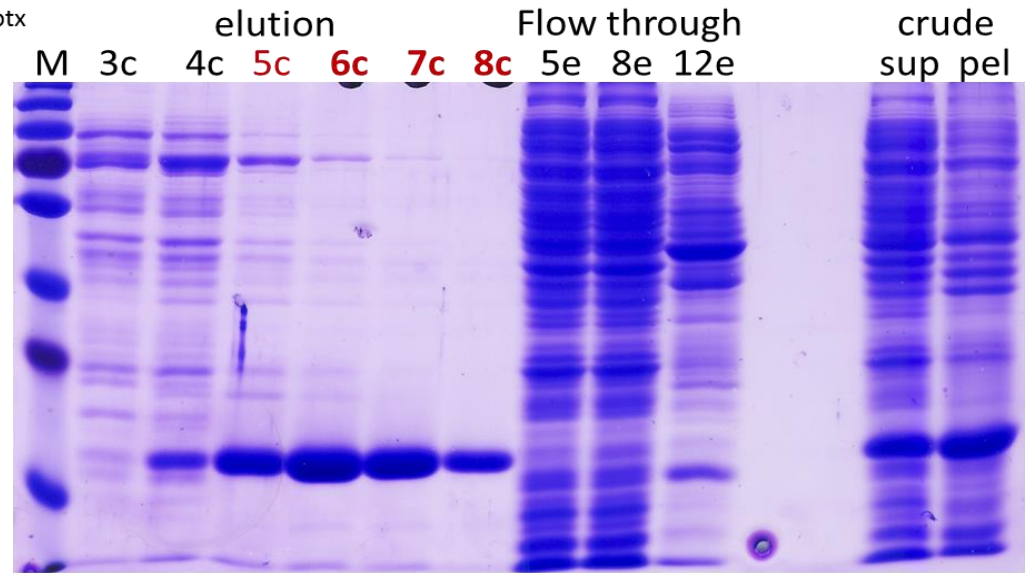
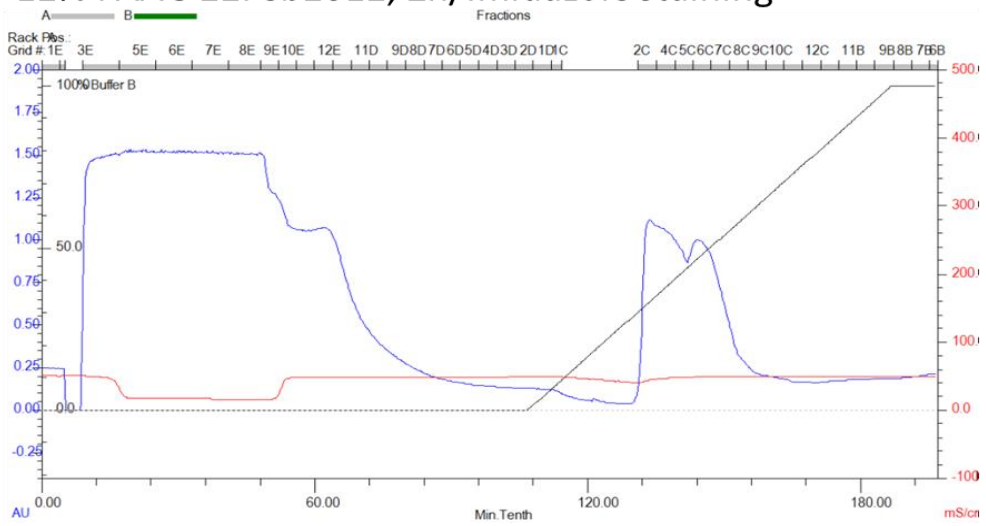
FGF2-133 purification 210212.pptx





FGF2-133
19,4 kDa

12% PAAG 22Feb2012, Zn/Imidazole staining



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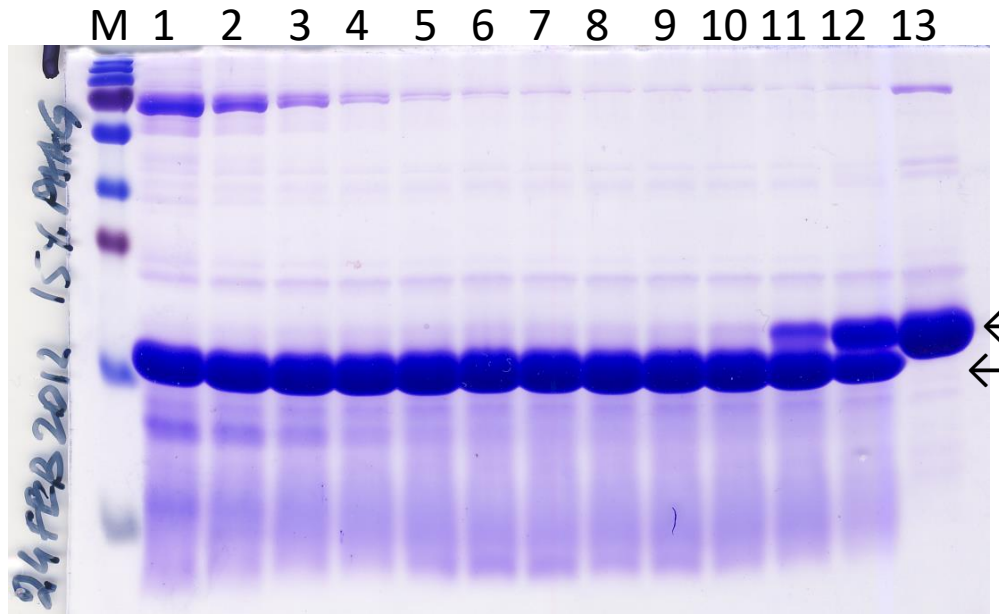
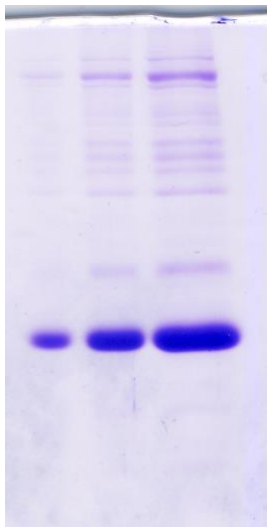
Thrombin cleavage FGF2-133



DP – pellet after dyalysis



0,1ul 0,4ul 1ul loaded

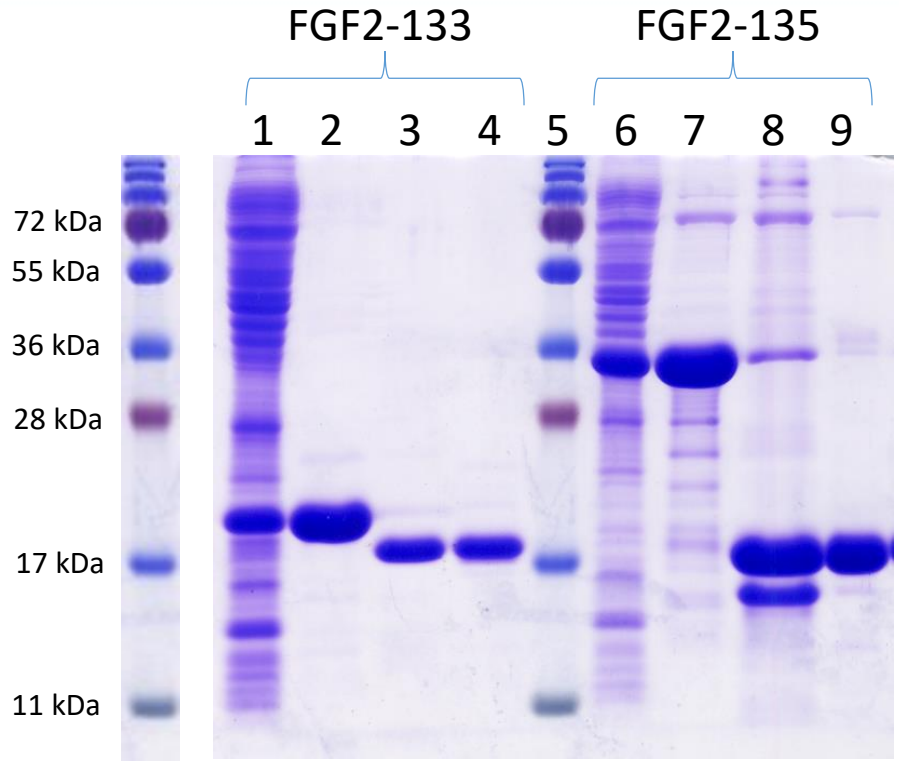
7,5 ul of the soluble dyalyzed protein loaded per lane – from 16 ml of over 2 mg/ml FGF2-133

Info is in the file

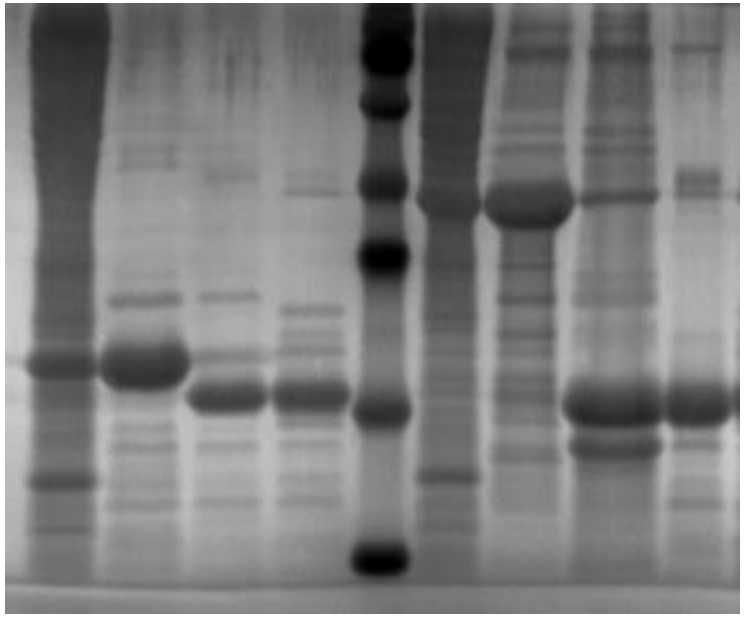
FGF2-133 thrombin cleavage 23Feb2012

We assumed that not more than 18 mg of protein got precipitated, while Over 32 mg of FGF2-133 remained in soluble form. Then, the purity of the Precipitated protein is much worse (5-7 folds more dirt) than the soluble protein.

	1	2	3	4	5	6	7	8	9	10	11	12	13				
	prot 1	prot 2	prot 3	prot 4	prot 5	prot 6	prot 7	prot 8	prot 9	prot 10	prot 11	prot 12					
	100 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF					
	+ 1 u / 1 ul	+ 50 ul pr1	+ 50 ul pr2	+ 50 ul pr3	+ 50 ul pr4	+ 50 ul pr5	+ 50 ul pr6	+ 50 ul pr7	+ 50 ul pr8	+ 50 ul pr9	+ 50 ul pr10	+ 50 ul pr11	------				
excess, x	10	5	2,5	1,25	0,63	0,31	0,16	0,08	0,04	0,02	0,01	0,005	0				
	1 u/100 ul	0,5	0,25	0,125	0,0625	0,031	0,016	0,008	0,004	0,002	0,001	0,0005			1 u per about 200 ug protein...		
Thrombin: 0,005-0,01 units cleaved 100 ul of protein with about 2 or more mg/ml...																	
	which means that for 1 ml of protein we should take 0,05-0,1 units of Thrombin.																
		which means that for our 15 ml protein - around 30 or more mg total - we should use 1,5 units of Thrombin.															
			we could use 1 unit, or 0, 75 units per this amount,														
				and, on the other hand, we can increase this amount safely to at least 3 units per 15 ml													



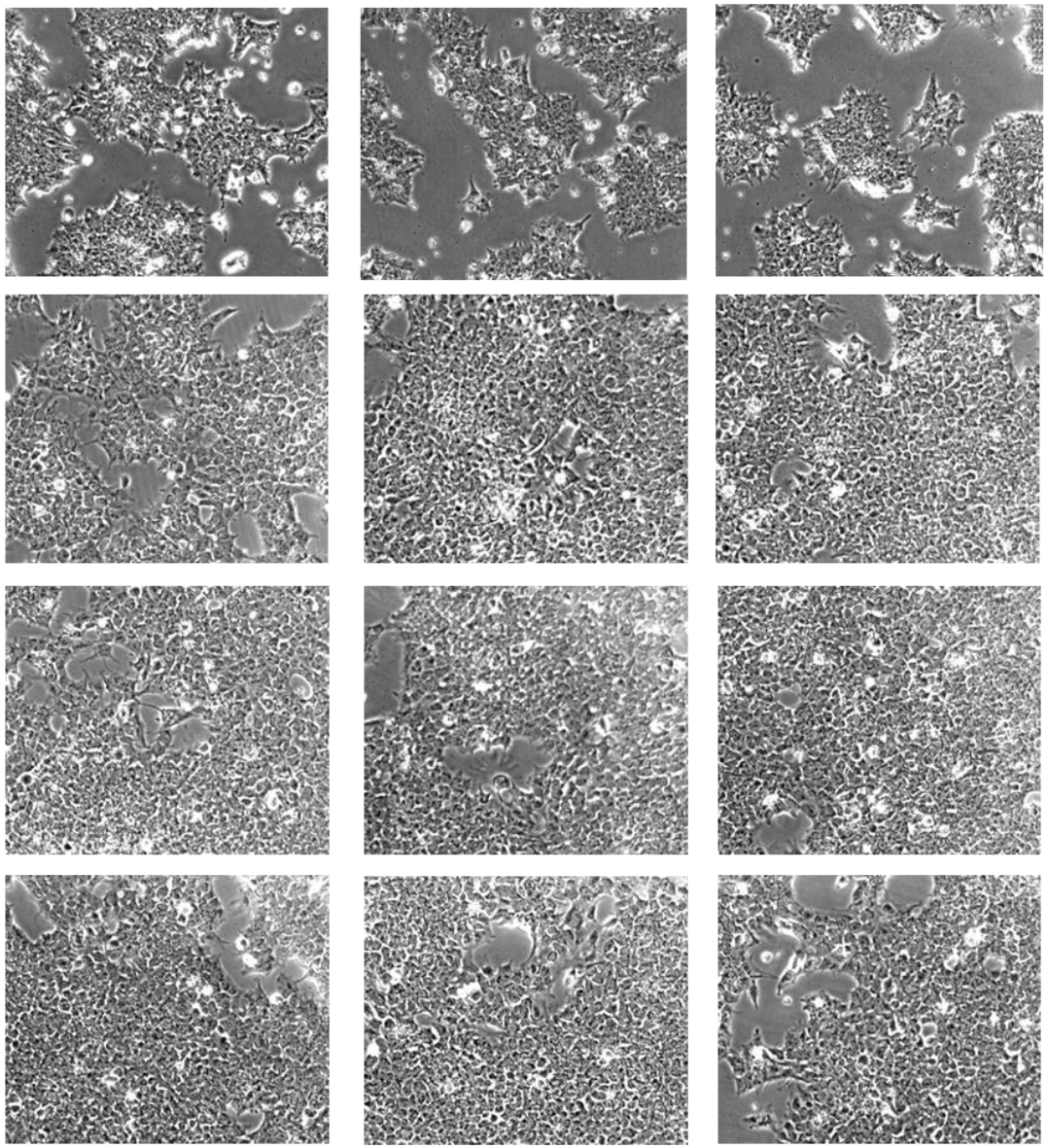
Coomassie staining



Zn-Imidazole staining (more sensitive)

1 – FGF2-133 fusion crude soluble, 19,4 kDa (fused to His-tag)
2 – FGF2-133 fusion Ni-NTA purified, 19,4 kDa
3 – FGF2-133 digested with thrombin, 17,6 kDa
4 – FGF2-133 Heparin purification, 17,6 kDa - final
5 – Mol weight marker
6 – FGF2-135 fusion crude soluble, 34,4 kDa (fused to His-Thioredoxin tag)
7 – FGF2-135 fusion Ni-NTA purified, 34,4 kDa
8 – FGF2-135 digested with Enterokinase, 17,3 kDa
9 – FGF2-135 Heparin purification, 17,3 kDa - final

L12cp36-6 on Matrigel



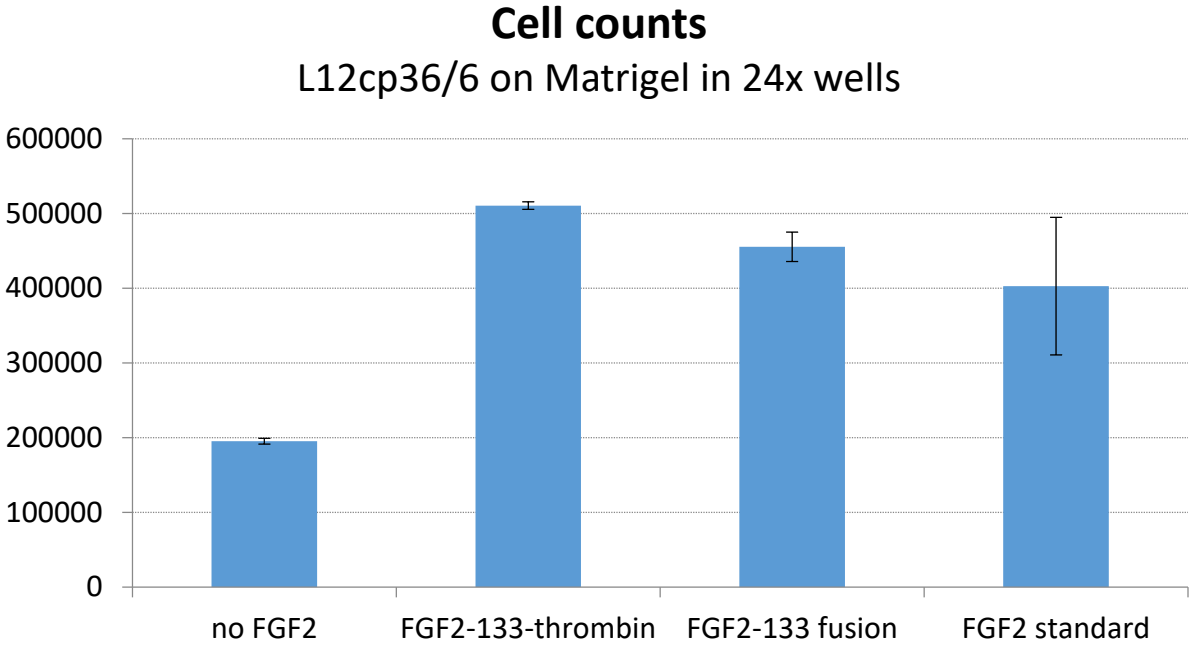
No FGF2

FGF2-133 cleaved

FGF2-133 fused

FGF2 standard

Cells plated at density of 20 000/cm2, grown for 3 days
3 representative pictures shown for each treatment



Cells plated at density of 20 000/cm2, grown for 3 days

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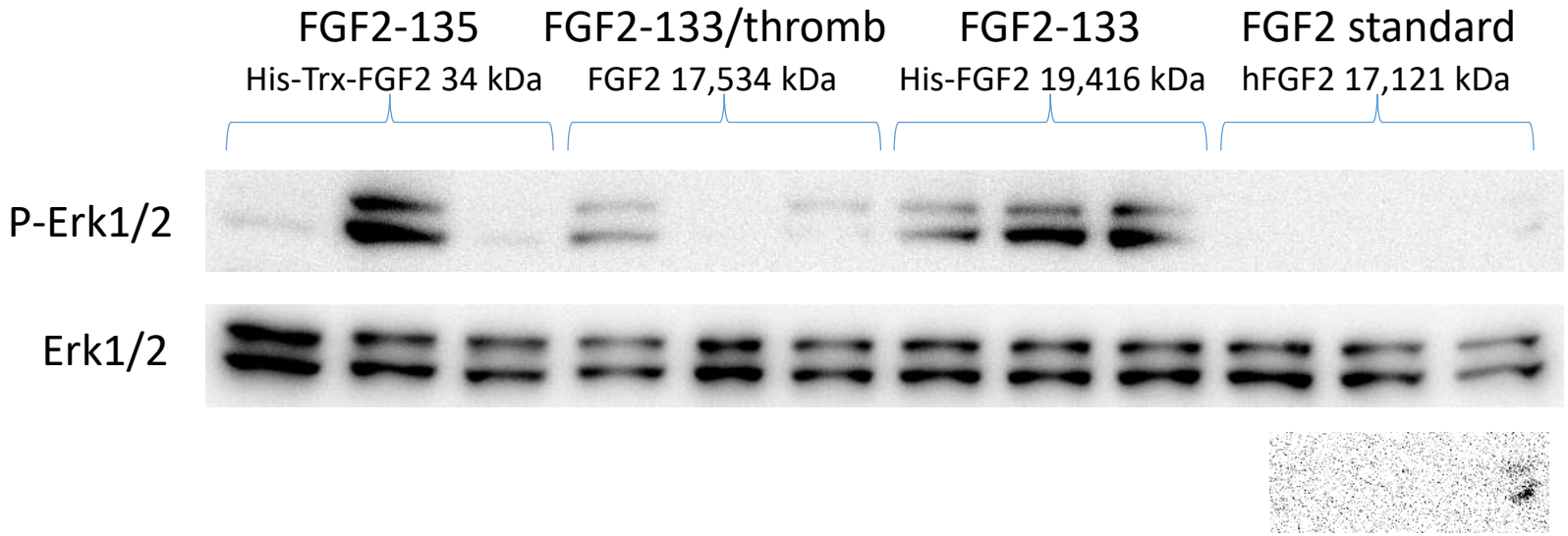

L12cp36/6 were plated at 20 000 cells/cm2 in 24x plate in cHES medium without FGF2.
Cells were allowed to grow for 3 days.
The recombinant FGF2 variants were added each day (3 times), meaning that the controls had FGF2 added 24 hrs before.

For FGF2-135, the cells were used which were not exposed to any FGF2 for all 3 days.

For western, cells were treated with fresh portions of FGF2 variants for 10 min – lyzed in Fermentas´ lysis buffer.

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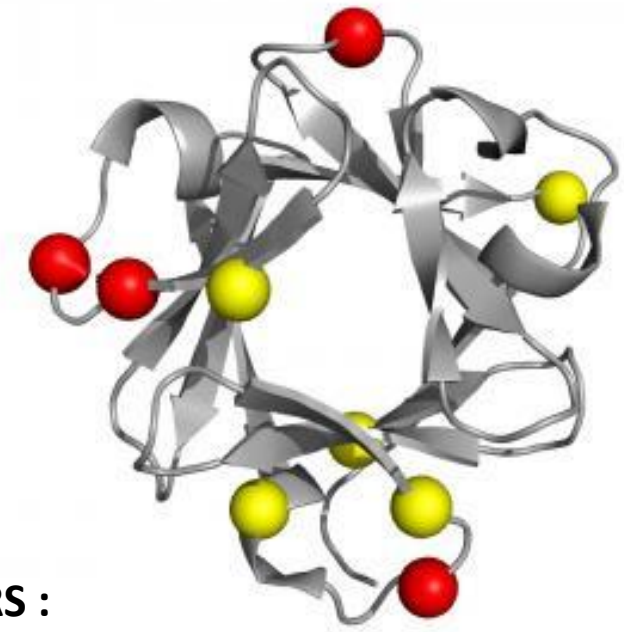
FGF2-STAB

- retains full biological activity even after twenty days at 37°C
- half-life of biological activity of a wild type FGF2 is 9 hours at 37°C

- FGF2 for cultivation media
- FGF2 for cosmetics
- FGF2 for veterinary medicine
- FGF2 for wound healing



TECHNOLOGY / IP OWNERS :
Masaryk University Enantis s.r.o.

https://biospot.eu/technology/hyperstable-fibroblast-growth-factor-2-fgf2-stab/

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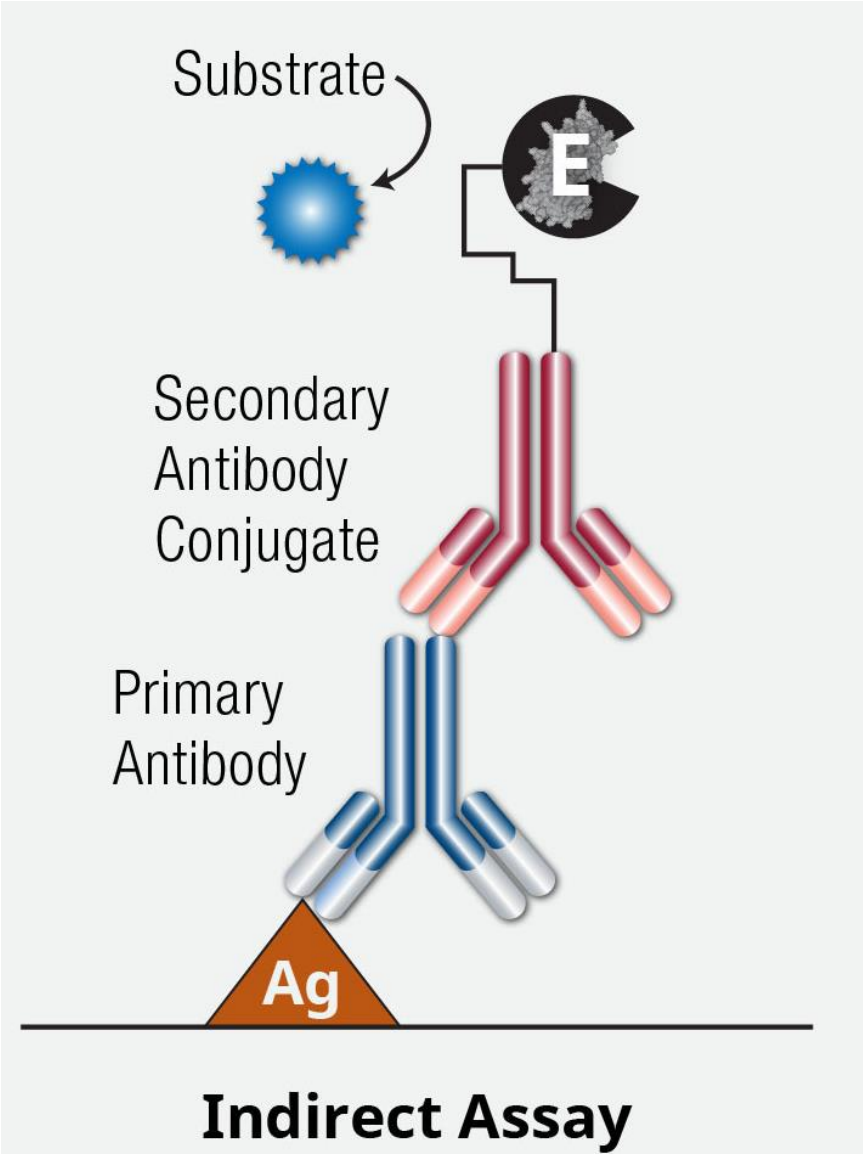
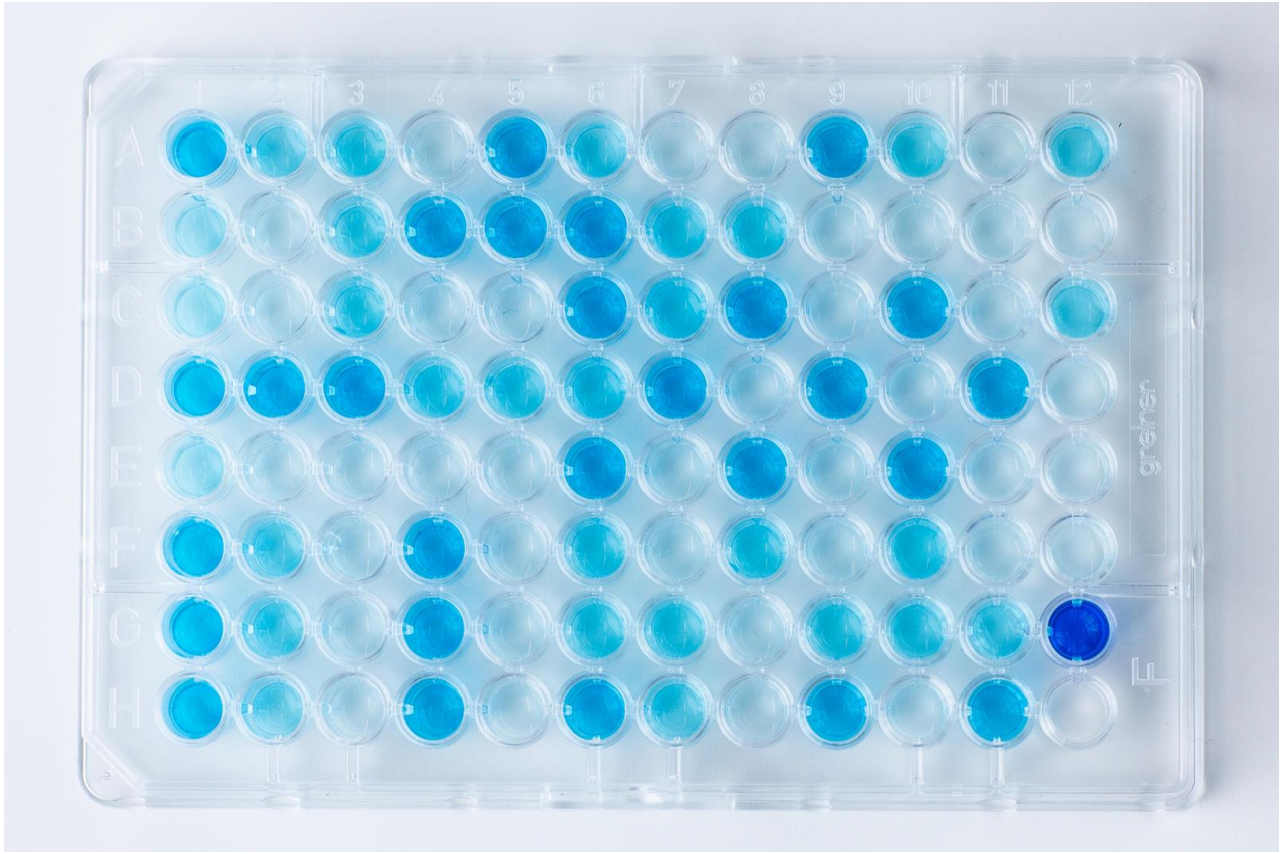
Recombinant antigens



https://media.cellsignal.com/www/images/resources/applications/elisa/elisa-indirect-assay.jpg



https://www.integra-biosciences.com/sites/default/files/styles/large/public/images/elisa-viaflo-96-384-8993.jpg?itok=5rolbtIn

vitrotest.ua/-produkciiya-.html

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- Час проведення аналізу 2-2,5 години;
- Лунки стрипів відокремлюються в усіх наборах;
- Зміна кольору розчинів на різних етапах постановки;
- Можливість постановки вручну та на автоматизованому роботі;
- Усі реагенти мають чітке маркування та кольорову індикацію;
- Діагностичні характеристики підтверджені на комерційних панелях сироваток;

Продукція

Головна / Продукція /

Інфекційні захворювання | **Алергія** | **Компоненти in bulk**

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Імуноферментні тест-системи для діагностики вірусних та бактеріальних інфекцій, протозойних гельмінтних інвазій.

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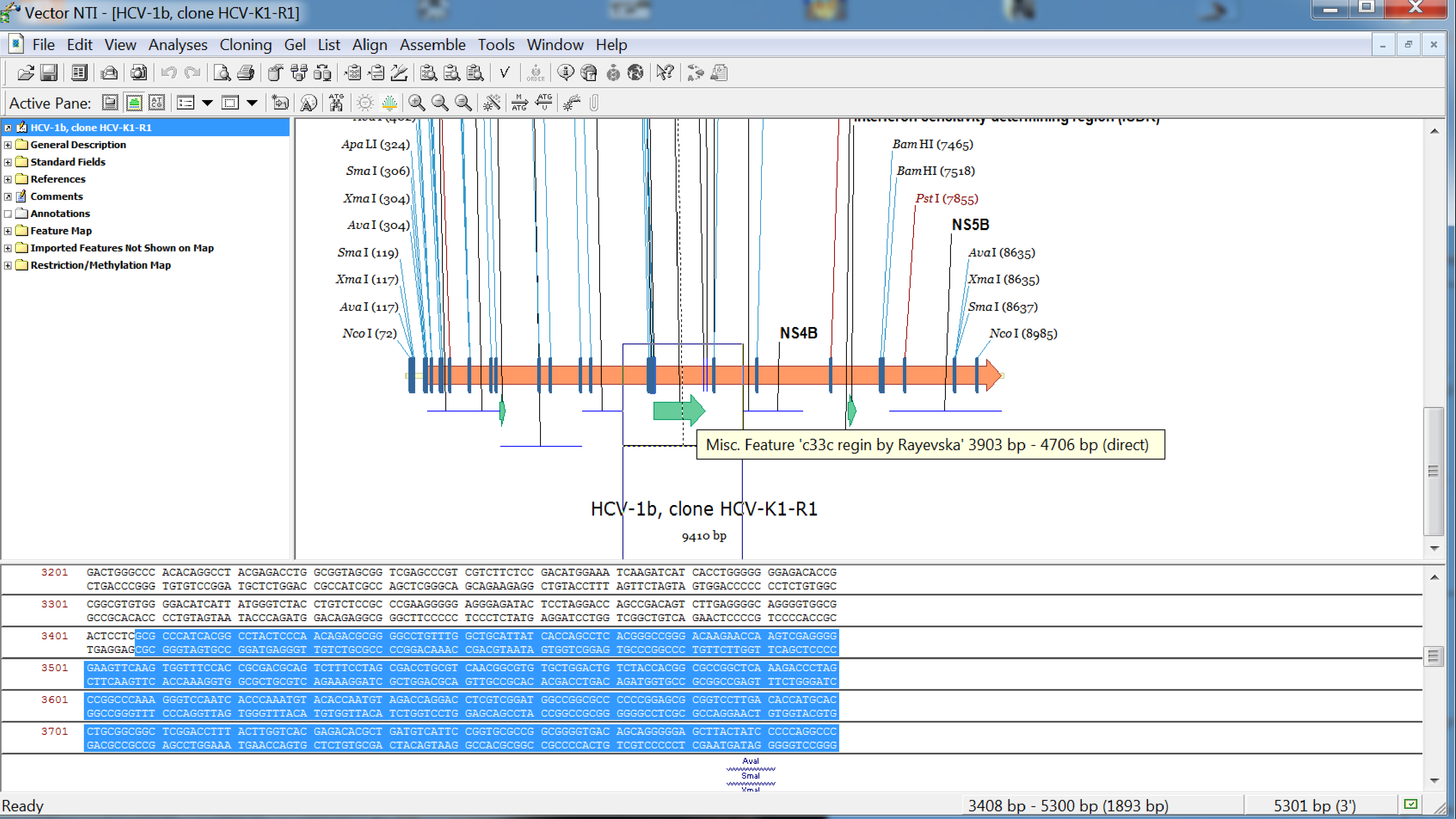
- Вірусний гепатит С
- Вірусний гепатит А
- Токсоплазмоз
- Краснуха
- Цитомегаловірусна інфекція
- Простий герпес
- Інфекційний мононуклеоз
- Мікоплазменна пневмонія
- Урогенітальний мікоплазмоз
- Уреаплазмоз
- Урогенітальний трихомоніаз
- Урогенітальний хламідіоз
- Сифіліс
- Хелікобактеріоз
- Лямбліоз (гіардіоз)
- Аскаридоз
- Опісторхоз
- Токсокароз
- Ехінококоз
- Трихінельоз
- Хвороба Лайма (бореліоз)
- Вірус Варіцелла-Зостер
- Кір
- Дифтерія
- COVID-19


Vector NTI - [HCV-1b, clone HCV-K1-R1]
File Edit View Analyses Cloning Gel List Align Assemble Tools Window Help
Active Pane:
HCV-1b, clone HCV-K1-R1
General Description
Standard Fields
References
Comments
Annotations
Feature Map
Imported Features Not Shown on Map
Restriction/Methylation Map
Interferon sensitivity determining region (ISDR)
ApaLI (324)
SmaI (306)
XmaI (304)
AvaI (304)
SmaI (119)
XmaI (117)
AvaI (117)
NcoI (72)
BamHI (7465)
BamHI (7518)
PstI (7855)
NS5B
AvaI (8635)
XmaI (8635)
SmaI (8637)
NcoI (8985)
NS4B
Misc. Feature 'c33c regin by Rayevska' 3903 bp - 4706 bp (direct)
HCV-1b, clone HCV-K1-R1
9410 bp
3201 GACTGGGCCC ACACAGGCCT ACGAGACCTG GCGGTAGCGG TCGAGCCCGT CGTCTTCTCC GACATGGAAA TCAAGATCAT CACCTGGGGG GGAGACACCG
CTGACCCGGG TGTGTCCGGA TGCTCTGGAC CGCCATCGCC AGCTCGGGCA GCAGAAGAGG CTGTACCTTT AGTTCTAGTA GTGGACCCCC CCTCTGTGGC
3301 CGGCGTGTGG GGACATCATT ATGGGTCTAC CTGTCTCCGC CCGAAGGGGG AGGGAGATAC TCCTAGGACC AGCCGACAGT CTTGAGGGGC AGGGGTGGCG
GCCGCACACC CCTGTAGTAA TACCCAGATG GACAGAGGCG GGCTTCCCCC TCCCTCTATG AGGATCCTGG TCGGCTGTCA GAACTCCCCG TCCCCACCGC
3401 ACTCCTCGCG CCCATCACGG CCTACTCCCA ACAGACGCGG GGCCTGTTTG GCTGCATTAT CACCAGCCTC ACGGGCCGGG ACAAGAACCA AGTCGAGGGG
TGAGGAGCGC GGGTAGTGCC GGATGAGGGT TGTCTGCGCC CCGGACAAAC CGACGTAATA GTGGTCGGAG TGCCCGGCCC TGTTCTTGGT TCAGCTCCCC
3501 GAAGTTCAAG TGGTTTCCAC CGCGACGCAG TCTTTCCTAG CGACCTGCGT CAACGGCGTG TGCTGGACTG TCTACCACGG CGCCGGCTCA AAGACCCTAG
CTTCAAGTTC ACCAAAGGTG GCGCTGCGTC AGAAAGGATC GCTGGACGCA GTTGCCGCAC ACGACCTGAC AGATGGTGCC GCGGCCGAGT TTCTGGGATC
3601 CCGGCCCAAA GGGTCCAATC ACCCAAATGT ACACCAATGT AGACCAGGAC CTCGTCGGAT GGCCGGCGCC CCCCGGAGCG CGGTCCTTGA CACCATGCAC
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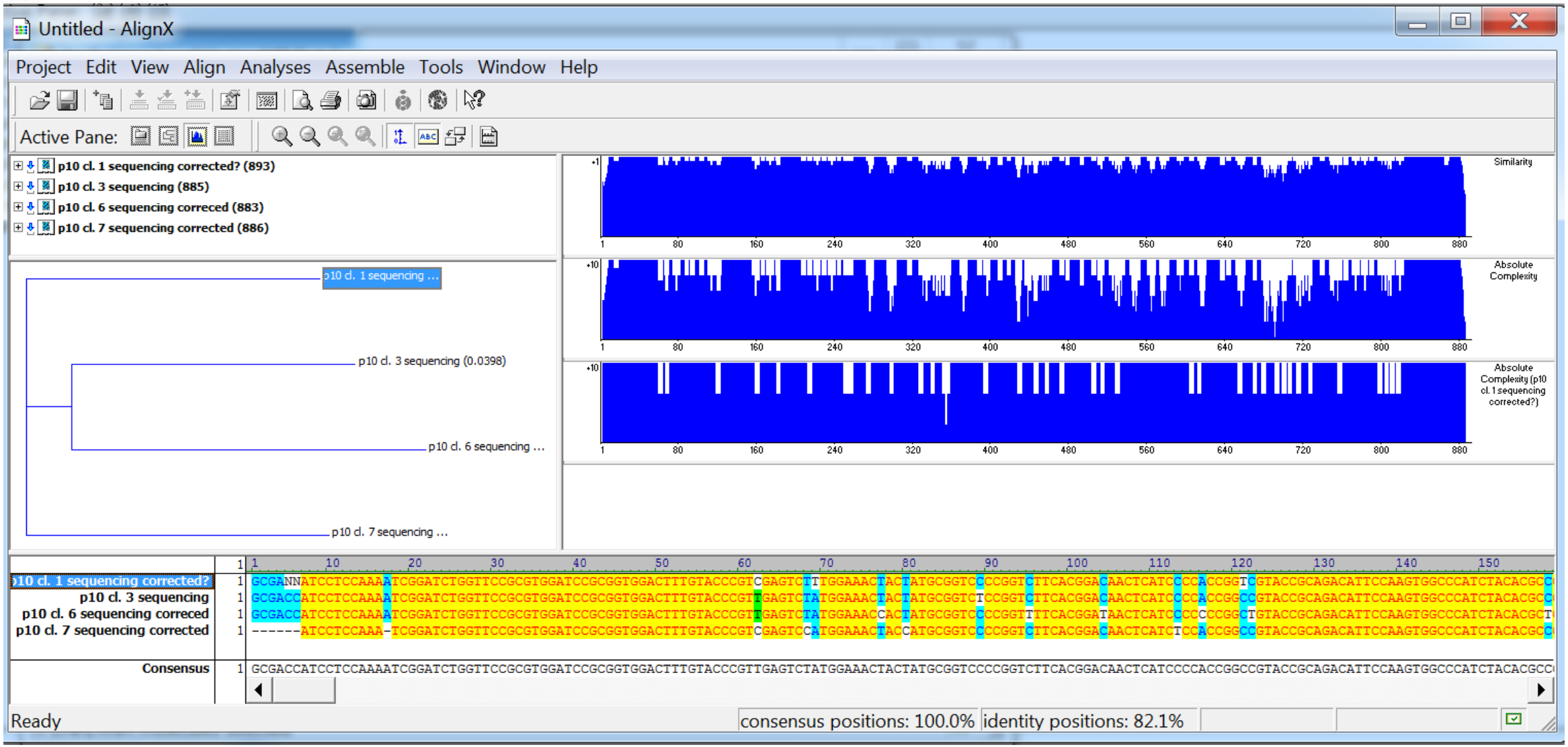
3701 CTGCGGCGGC TCGGACCTTT ACTTGGTCAC GAGACACGCT GATGTCATTC CGGTGCGCCG GCGGGGTGAC AGCAGGGGGA GCTTACTATC CCCCAGGCCC
GACGCCGCCG AGCCTGGAAA TGAACCAGTG CTCTGTGCGA CTACAGTAAG GCCACGCGGC CGCCCCACTG TCGTCCCCCT CGAATGATAG GGGGTCCGGG
AvaI
SmaI
Ready
3408 bp - 5300 bp (1893 bp)
5301 bp (3')

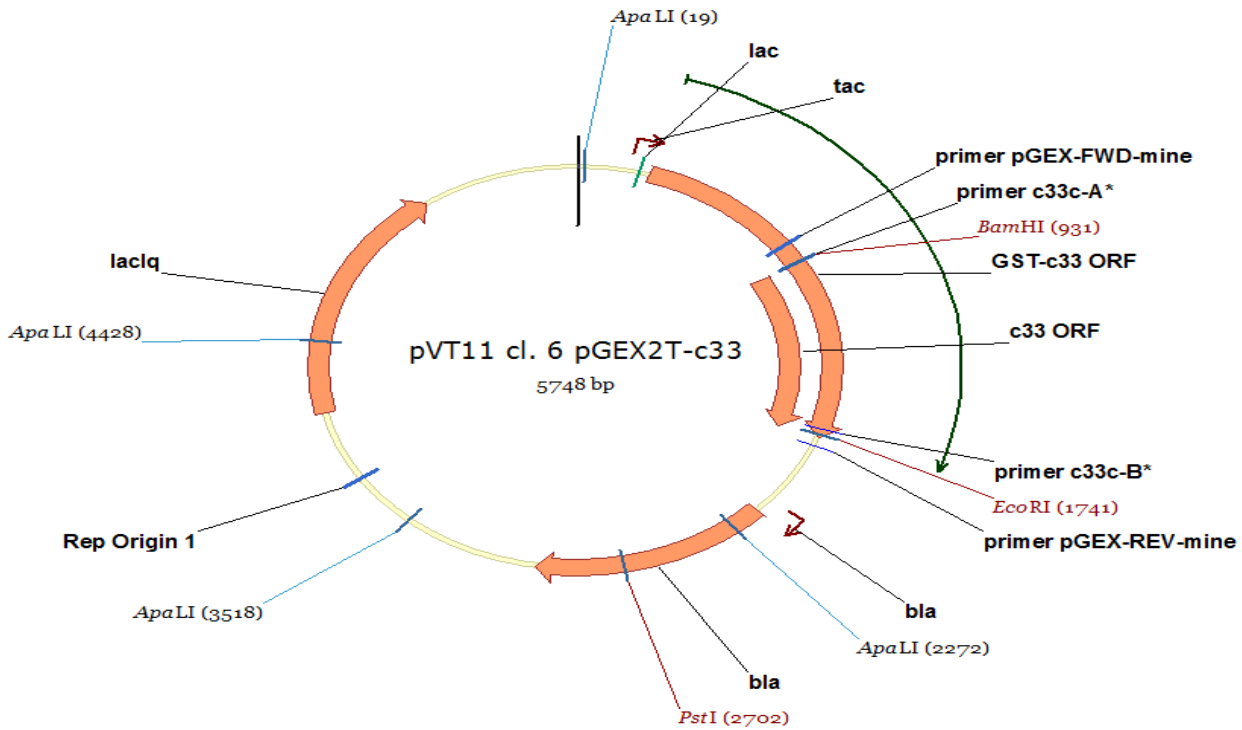

Untitled - AlignX
Project Edit View Align Analyses Assemble Tools Window Help
Active Pane:
p10 cl. 1 sequencing corrected? (893)
p10 cl. 3 sequencing (885)
p10 cl. 6 sequencing correced (883)
p10 cl. 7 sequencing corrected (886)
p10 cl. 1 sequencing ...
p10 cl. 3 sequencing (0.0398)
p10 cl. 6 sequencing ...
p10 cl. 7 sequencing ...
Similarity
Absolute Complexity
Absolute Complexity (p10 cl. 1 sequencing corrected?)
p10 cl. 1 sequencing corrected?
p10 cl. 3 sequencing
p10 cl. 6 sequencing correced
p10 cl. 7 sequencing corrected
Consensus
Ready
consensus positions: 100.0%
identity positions: 82.1%

Vector NTI - [pVT11 cl. 6 pGEX2T-c33]

File Edit View Analyses Cloning Gel List Align Assemble Tools Window Help

Active Pane:

- pVT11 cl. 6 pGEX2T-c33
- General Description
- Standard Fields
- Comments
- Annotations
- Component Fragments
- Feature Map
- Imported Features Not Shown on Map
- Restriction/Methylation Map
- Open Reading Frames



ApaLI

```
     1  ACGTTATCGA CTGCACGGTG CACCAATGCT TCTGGCGTCA GGCAGCCATC GGAAGCTGTG GTATGGCTGT GCAGGTCGTA AATCACTGCA TAATTCGTGT
        TGCAATAGCT GACGTGCCAC GTGGTTACGA AGACCGCAGT CCGTCGGTAG CCTTCGACAC CATACCGACA CGTCCAGCAT TTAGTGACGT ATTAAGCACA

   101  CGCTCAAGGC GCACTCCCGT TCTGGATAAT GTTTTTTGCG CCGACATCAT AACGGTTCTG GCAAATATTC TGAAATGAGC TGTTGACAAT TAATCATCGG
        GCGAGTTCCG CGTGAGGGCA AGACCTATTA CAAAAAACGC GGCTGTAGTA TTGCCAAGAC CGTTTATAAG ACTTTACTCG ACAACTGTTA ATTAGTAGCC
  +3
```

Ready 1 bp

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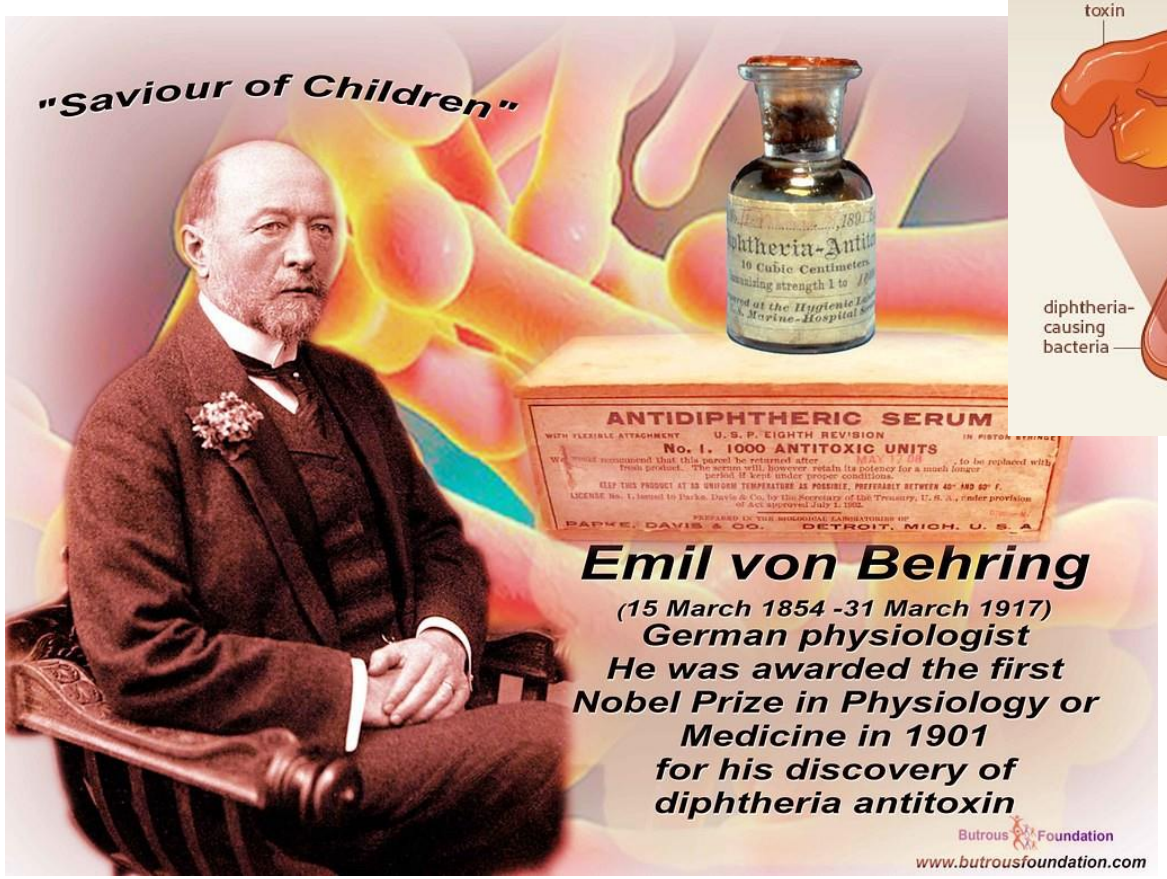

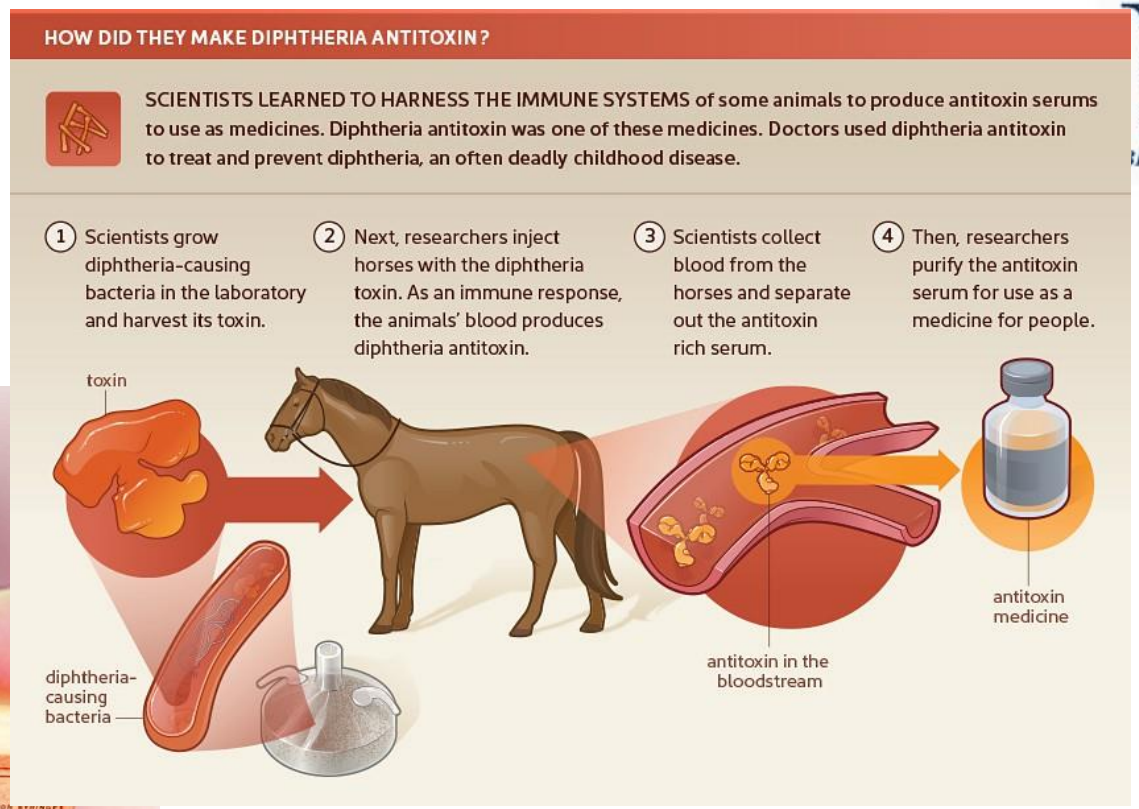

https://denispombriant.medium.com/lets-make-an-antiserum-for-corona-virus-bb1a96dc5808

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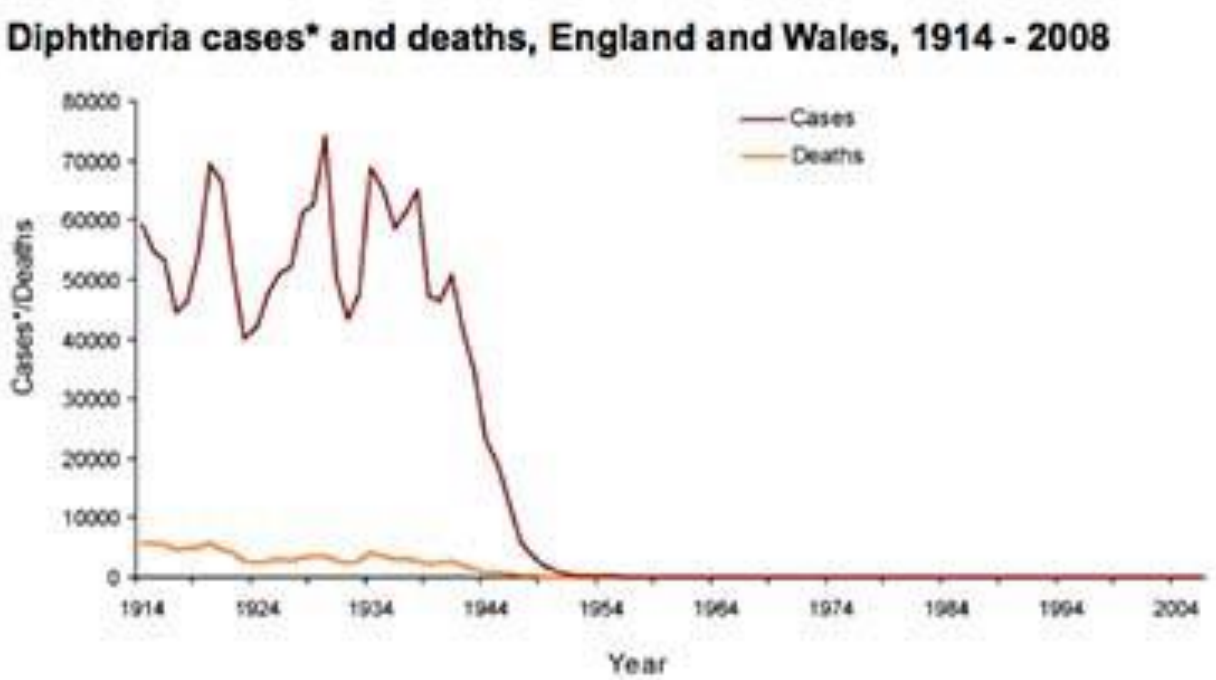

https://denispombriant.medium.com/lets-make-an-antiserum-for-corona-virus-bb1a96dc5808

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Research Highlight | Published: 12 January 2021

AUTOIMMUNITY

mRNA vaccine shows promise in autoimmunity

Alexandra Flemming

Nature Reviews Immunology **21**, 72(2021) | Cite this article

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Recombinant antibodies

COVID-19 treatment:

1.2 grams of both

- **casirivimab**
- **imdevimab**

https://www.nytimes.com/2020/11/21/health/regeneron-covid-antibodies-trump.html

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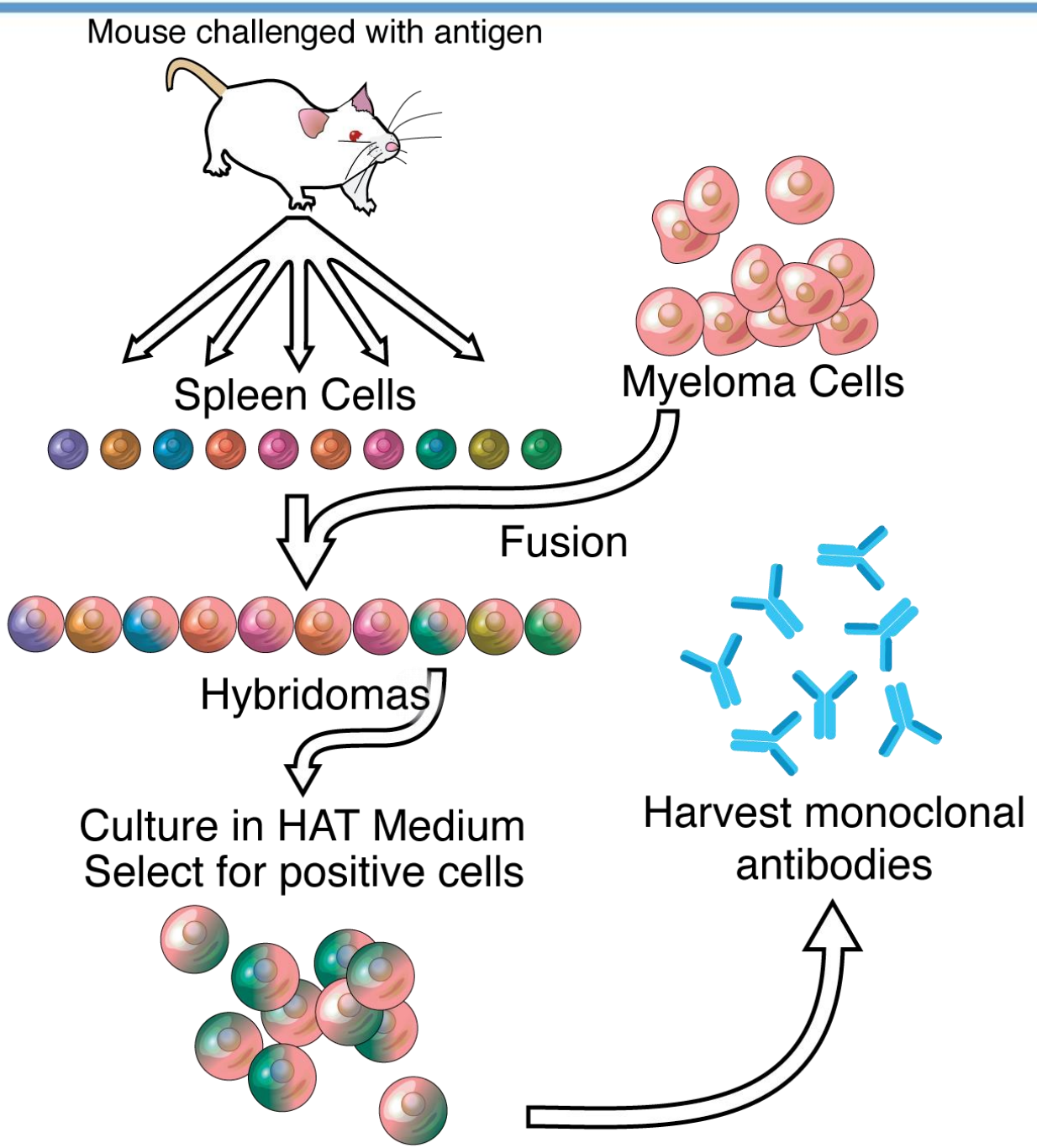


https://upload.wikimedia.org/wikipedia/commons/9/9a/Monoclonals.png

The Nobel Prize in Physiology or Medicine 1984

Photo from the Nobel Foundation archive.

Niels K. Jerne

Prize share: 1/3

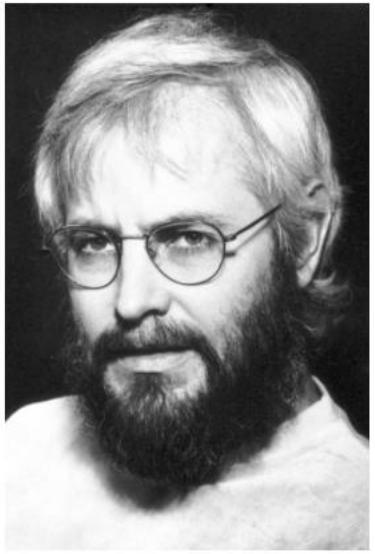


Photo from the Nobel Foundation archive.

Georges J.F. Köhler

Prize share: 1/3

Photo from the Nobel Foundation archive.

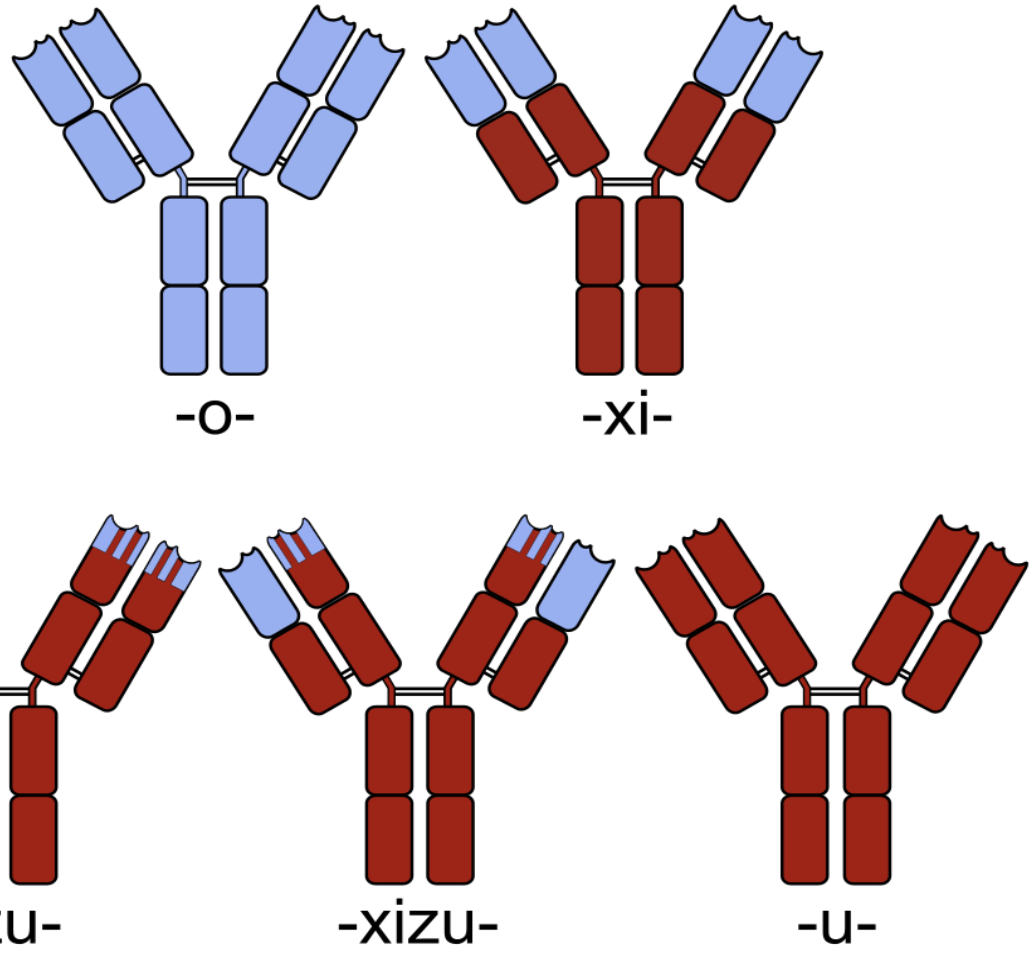
César Milstein

Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein "for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies."

https://www.nobelprize.org/prizes/medicine/1984/summary/

Recombinant antibodies



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US FDA-approved monoclonal antibody on the market

mAb	Brand name	Company	Target	Format	Technology	Indication[&]	US[#] Approval
Muromonab-CD3	Orthoclone OKT3	Centocor Ortho Biotech Products LP.	CD3	Murine IgG2a	Hybridoma/Janssen Biotech, Inc	Kidney transplant rejection	1986*
Abciximab	Reopro	Centocor Inc./Eli Lilly/Janssen Biotech Inc.	GPIIb/IIIa	Chimeric IgG1 Fab	Hybridoma	Prevention of blood clots in angioplasty	1994
Rituximab	MabThera, Rituxan	Biogen Inc./Roche, F. Hoffmann-La Roche Ltd./Genentech Inc.	CD20	Chimeric IgG1	Hybridoma	Non-Hodgkin lymphoma	1997
Palivizumab	Synagis	MedImmune/AbbVie Inc.	RSV	Humanized IgG1	Hybridoma	Prevention of respiratory syncytial virus infection	1998
Infliximab	Remicade	Janssen Biotech Inc.	TNFα	Chimeric IgG1	Hybridoma	Crohn's disease	1998
Trastuzumab	Herceptin	Roche, F. Hoffmann-La Roche, Ltd./Genentech Inc.	HER2	Humanized IgG1	Hybridoma	Breast cancer	1998
Alemtuzumab	Campath, Lemtrada	Berlex Inc./Genzyme Corp./Millennium Pharmaceuticals Inc.	CD52	Humanized IgG1	Hybridoma	Chronic myeloid leukemia	2001
Adalimumab	Humira	AbbVie Inc.	TNFα	Human IgG1	Phage display	Rheumatoid arthritis	2002
Ibritumomab tiuxetan	Zevalin	Biogen Inc./Schering AG/Spectrum Pharmaceuticals Inc.	CD20	Murine IgG1	Hybridoma	Non-Hodgkin lymphoma	2002
Omalizumab	Xolair	Roche, F. Hoffmann-La Roche, Ltd./Genentech	IgE	Humanized IgG1	Hybridoma	Asthma	2003

https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-019-0592-z

US FDA-approved monoclonal antibody on the market

						carcinoma	
Emapalumab	Gamifant	NovImmmune	IFNγ	Human IgG1	Phage display	Primary hemophagocytic lymphohistiocytosis	2018
Fremanezumab	Ajovy	Teva Pharmaceutical Industries, Ltd.	CGRP	Humanized IgG2	Hybridoma	Migraine prevention	2018
Ibalizumab	Trogarzo	Taimed Biologics Inc./Theratechnologies Inc.	CD4	Humanized IgG4	Hybridoma	HIV infection	2018
Moxetumomab pasudodox	Lumoxiti	MedImmune/AstraZeneca	CD22	Murine IgG1 dsFv	Phage display	Hairy cell leukemia	2018
Ravulizumab	Ultomiris	Alexion Pharmaceuticals Inc.	C5	humanized IgG2/4	Hybridoma	Paroxysmal nocturnal hemoglobinuria	2018
Caplacizumab	Cablivi	Ablynx	von Willebrand factor	Humanized Nanobody	Hybridoma	Acquired thrombotic thrombocytopenic purpura	2019
Romosozumab	Evenity	Amgen/UCB	Sclerostin	Humanized IgG2	Hybridoma	Osteoporosis in postmenopausal women at increased risk of fracture	2019
Risankizumab	Skyrizi	Boehringer Ingelheim Pharmaceuticals/ AbbVie Inc.	IL-23 p19	Humanized IgG1	Hybridoma	Plaque psoriasis	2019
Polatuzumab vedotin	Polivy	Roche, F. Hoffmann-La Roche, Ltd.	CD79β	Humanized IgG1 ADC	Hybridoma	Diffuse large B-cell lymphoma	2019
Brolucizumab	Beovu	Novartis Pharmaceuticals Corp.	VEGF-A	Humanized scFv	Hybridoma[$]	Macular degeneration	2019
Crizanlizumab	Adakveo	Novartis Pharmaceuticals Corp.	P-selectin	Humanized IgG2	Hybridoma	Sickle cell disease	2019

https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-019-0592-z

Fibrin sealant

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