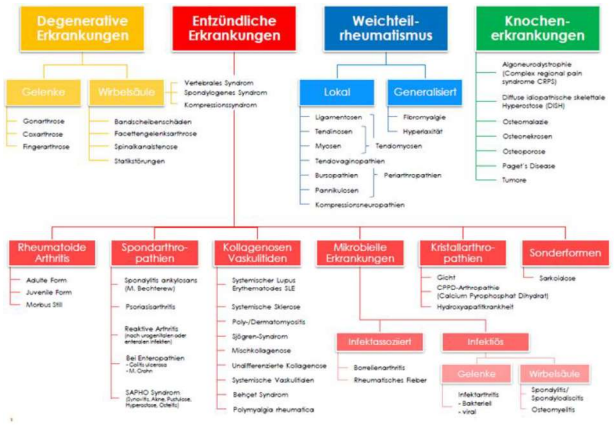
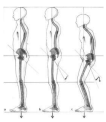
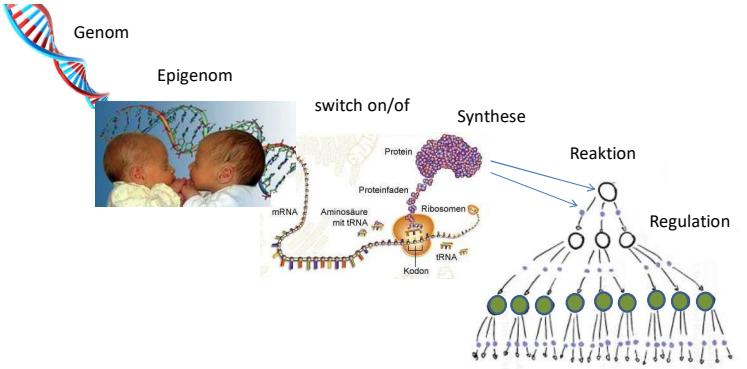
Rheumatischer Formenkreis:



inhomogene Pathogenese rheumatischer Formenkreis



RA	**SLE**	**SPA**
Leukozytose	Leukopenie	(Leukozytose)
BSG hoch	BSG hoch	BSG hoch
CrP hoch	CrP niedrig	CrP hoch
Knochenabbau	Knochenabbau	Knochenanbau

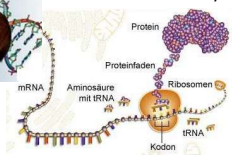


Genom

Epigenom

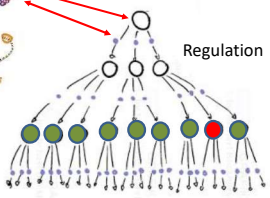
switch **on/of**

Synthese



Reaktion

Regulation



Genom

Genom

HLA: ***human leukocyte antigen*** = Genkomplex der den
MHC ***major histocompatibility complex*** codiert

Rheumatoide Arthritis:	70 % **DR4/DRB1** (Gesunde 25%)
Spondylitis ankylosans:	90 % **HLA B27** (Gesunde 8 %)
Psoriasisarthritis:	30 – 50 % **HLA-B27**
Systemischer Lupus erythematodes:	50 % **DR2/DR 3**
Polymyositis, Dermatomyositis:	**B8/DR3**
Systemische Sklerose:	**DR 1, 4, 8**
Sjögren Syndrom:	**DR2, DR3**

Genom

HLA: ***human leukocyte antigen*** = Genkomplex der den
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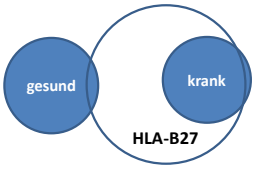
Sjögren Syndrom:	**DR2, DR3**

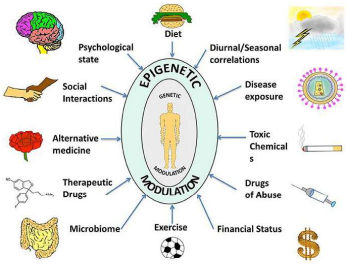


Genom

Epigenom

Genom

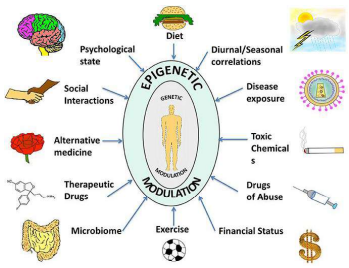
Epigenom



Genom

Epigenom

Einflüsse als
-***prädisponierende(r)*** (?)
-***auslösende(r)*** (?)
-***unterhaltende(r)*** (?)
Faktor(en)



Genom

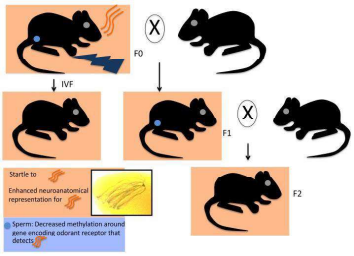
Epigenom

Epigenetik fuktioniert:

in einer Generation

intergenerational

transgenerational



Dias, Ressler et al. Epigenetic mechanisms underlying learning and the inheritance of learned behavior
Trends Neurosci. 2015 Feb;38(2):96-107

Genom

Epigenom

Einflüsse als
-***prädisponierende(r)*** (?)
-***auslösende(r)*** (?)
-***unterhaltende(r)*** (?)
Faktor(en)

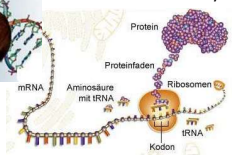
Bewegungstherapie
Ernährungstherapie
Hydrotherapie
Phytotherapie
Ordnungstherapie …

Genom

Epigenom

switch on/of

Synthese



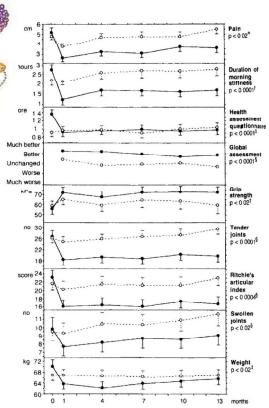
THE LANCET

Vol 338 Saturday 12 October 1991 No 8772

ORIGINAL ARTICLES

Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis

JENS KJELDSEN-KRAGH MARGARETHA HAUGEN CHRISTIAN F. BORCHGREVINK EVEN LAEGREID MORTEN EBE* PETTER MOWINKEL KNUT HOVI ØYSTEIN FORRE

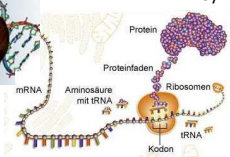


Genom

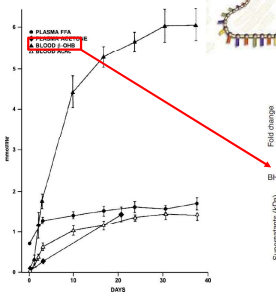
Epigenom

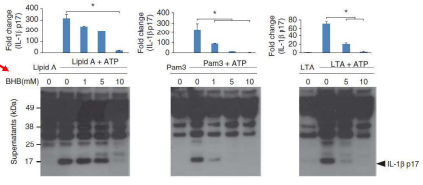
switch on/of

Synthese



NLRP3-Gen: kodiert Inflammasom (IL1beta, IL 18, IL 33)





Cahill G.: Fuel Metabolism in Starvation, Annu Rev Nutr 2006, 26: 1-22
Youm et al: The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease Nat Med. 2015 Feb 16. doi: 10.1038/nm.3804

TRAPS (Tumornekrosefaktor-Rezeptor1-assoziiertes periodisches Fieber-Syndrom)

- Fieberschübe
- Gastrointestinal (Bauchschmerz, Durchfall, Erbrechen)
- Hautauschlag
- Muskelschmerz
- Periorbitale Schwellung
- Nierenbeteiligung
- Hereditäre Häufung (autosomal dominant)
- Extrem selten (200 Fälle weltweit)

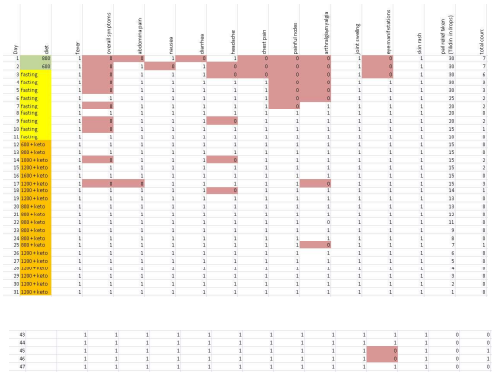
ID:		Age:							Month:				Year:
Autoinflammatory diseases related symptoms today													
Days	Fever ≥38°C (100.4°F) (a)	Overall symptoms (b)	Abdominal pain (c)	Nausea/ vomiting (d)	Diarrhoea (e)	Headaches (f)	Chest pain (g)	Painful nodes (h)	Arthralgia or Myalgia (i)	Swelling of the joints (j)	Eyes manifestations (k)	Skin rash (l)	Pain relief drugs taken
Scored as:	0/1	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	0/1Yes/No	
1													
2													
3													
...													
31													

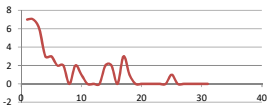
Each line represents a day in a month.

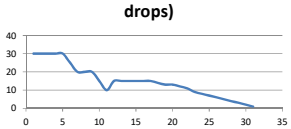
Please complete the diary **during all the time of the attacks** and score symptoms as yes (1) or no (0).

Use a different diary for each month. If you have no flair, bring back the diary empty.

Please note **only symptoms due to your auto-inflammatory disease**







Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes, Piram et al. Ann Rheum Dis. 2014 Dec;73(12):2168-73

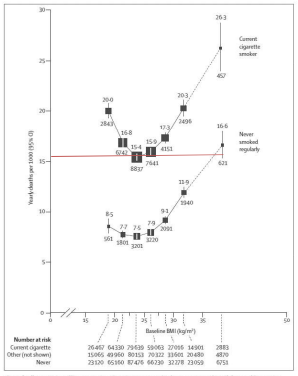
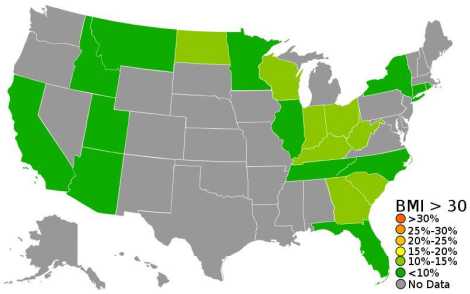
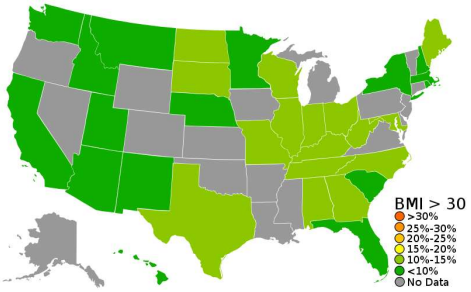


Figure 6: All-cause mortality at ages 35-79 years versus BMI in the range 15-50 kg/m², by smoking status (excluding the first 5 years of follow-up)

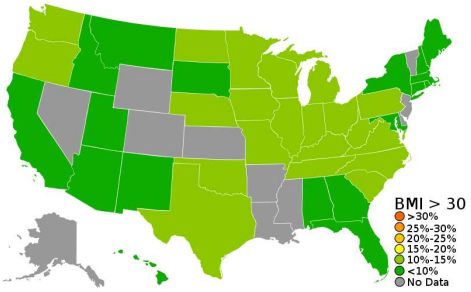


1985

Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies, Lancet 2009



1986



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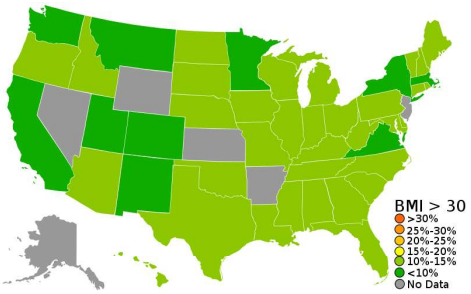

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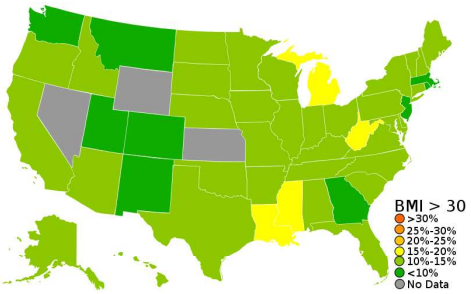
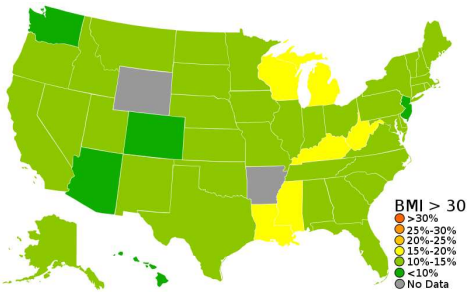


1991



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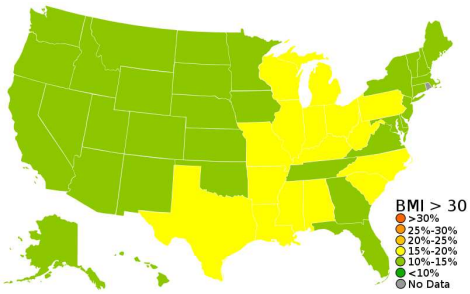

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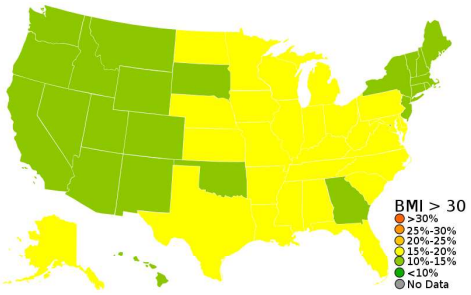

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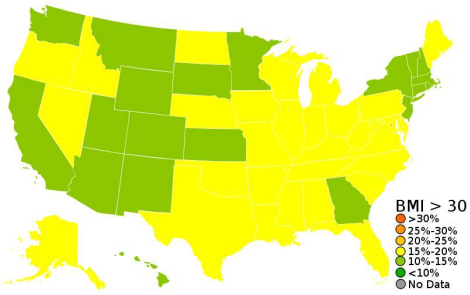

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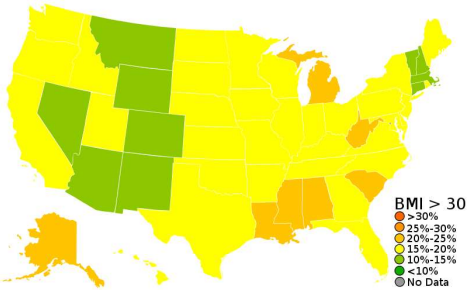
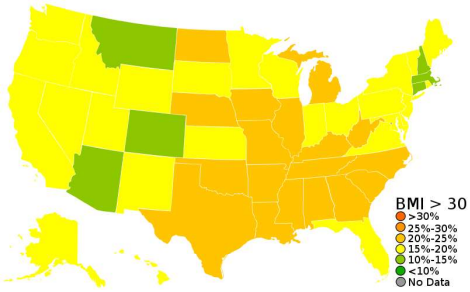


1998



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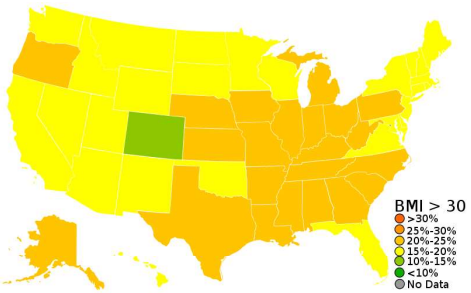

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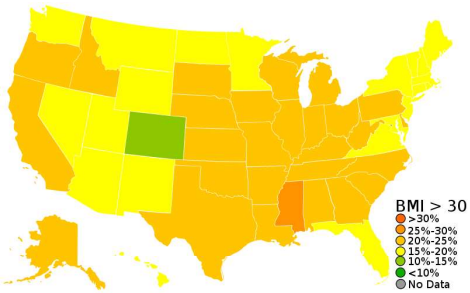

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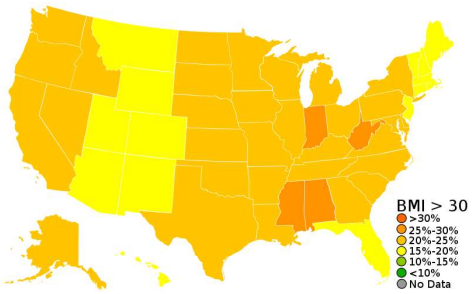

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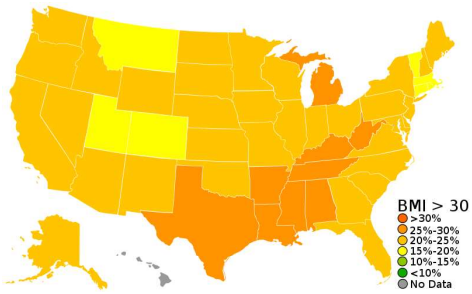
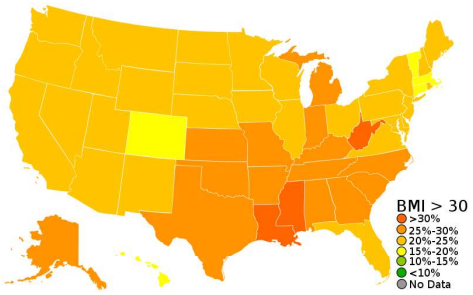
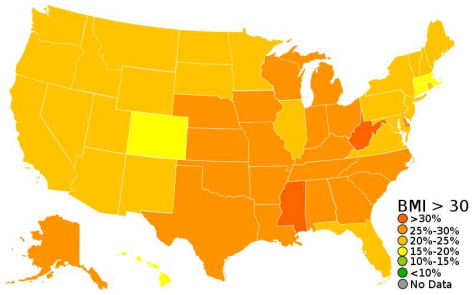


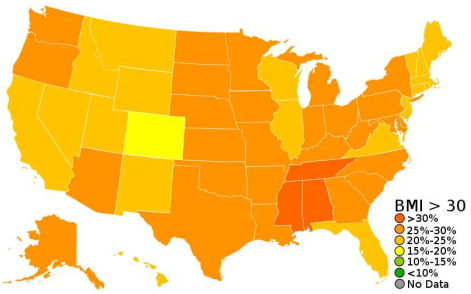
2004



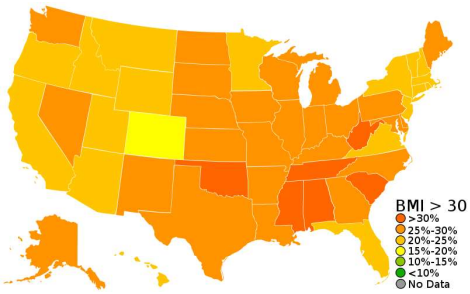
2005



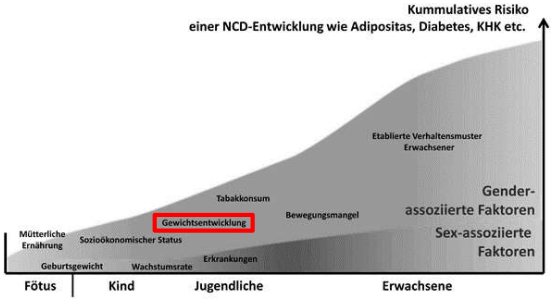
2006



2007



2008



Schiebinger L, Klinge I, Sánchez de Madariaga I, et al.
Gendered Innovations in Science, Health & Medicine, Engineering and Environment.
2011–2015.

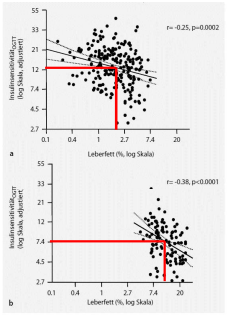


Abb. 2 ◂ Zusammenhang zwischen Leberfett und Insulinsensitivität (bestimmt über OGTT: oraler Glukosetoleranztest) bei Menschen mit (a n=221) und ohne (b n=105) Fettleber in der TULIP-Studie

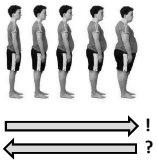
„Prävention des T2DM und seiner Gefäßkomplikationen – Identifizierung metabolischer und genotypischer Merkmale zur Vorhersage von Notwendigkeit und Ansprechen präventiver Maßnahmen"

Tübinger Lebensstil-Interventionsprogramm (TULIP)

cut off: Fettleber ja oder nein ?: 5,56% Leberfettgehalt

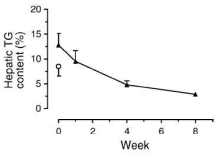
Im Vergleich zur **viszeralen Adipositas** ist die **Fettleber** für die Progression eines Prädiabetes die **wichtigere** Determinante.

N. Stefan, H.U. Häring: Nichtalkoholische Steatohepatitis –Prädiktor und Folge des Diabetes, Internist 2011, 52, 389-394
Kantartzis K et al: The impact of liver fat vs visceral fat in determining categories Of prediabetes. Diabetologia 2010, 53: 882-889



Intervention:
caloric restriction:

T2DM (< 4 a): n = 11
8 Wochen **600 kcal**
Technik: MRT



Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol; Lim et al.; Diabetologia 2011

Fatty Liver Index **(FLI)** = f (TG, GGT, BMI; waist)
(Fettleber? ja: > 60; indifferent: 30 – 60; nein: < 30)

Intervention: **periodic fasting** (n=697)

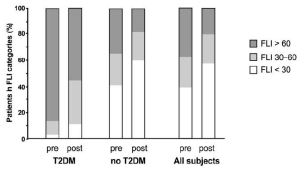
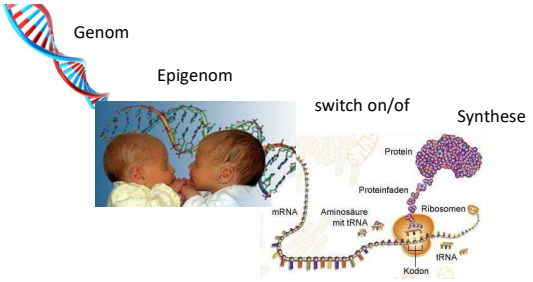


Figure 2. Frequency distribution of FLI categories before and after therapeutic fasting in patients with T2DM (n = 38), in non-diabetic subjects (no T2DM; n = 659), and in all subjects (n = 697).

Effects of Periodic Fasting on Fatty Liver Index—A Prospective Observational Study Drinda et al.; Nutrients 2019

Leben
Lebendigkeit — Ernährung — Lebensraum
(gesundheitliche) Lebensqualität



Zur Krankheit ggf. «prädisponierende» Gene können an– und abgeschaltet werden.
Dies wird durch epigenetische Faktoren, u.a. Ernährung, beeinflusst.

Diese Faktoren sind bislang nur unvollständig untersucht und wenig therapeutisch genutzt.
(Möglicherweise auch, weil sie finanziell unprofitabel sind?)

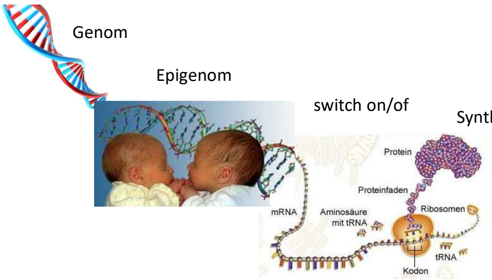
Sie haben gelegentlich einen guten psychologischen Aspekt (Selbsthilfe).

Genom

Epigenom

switch on/of

Synthese



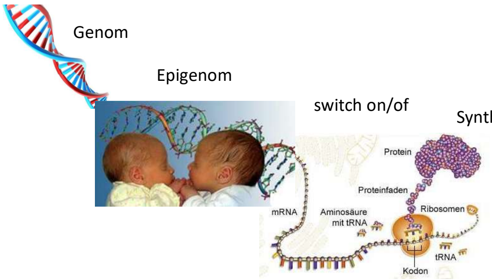
Wirkstoff	Vertreter	Ziel	Indikation
Methotrexat	Metex	**Purinsynthese**	RA, PSA, SA
Leflunomide	Arava	**Pyrimidinsynthese**	RA
Azathioprin	Imurek	**Purinsynthese**	SLE

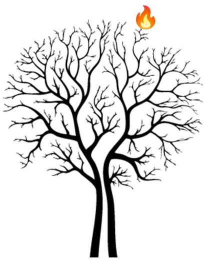
Genom

Epigenom

switch on/of

Synthese



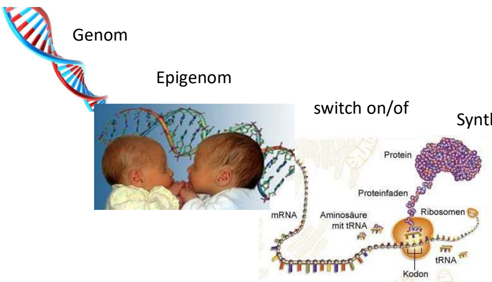


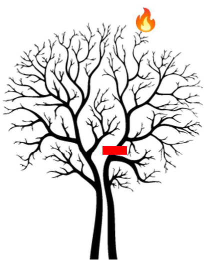
Genom

Epigenom

switch on/of

Synthese



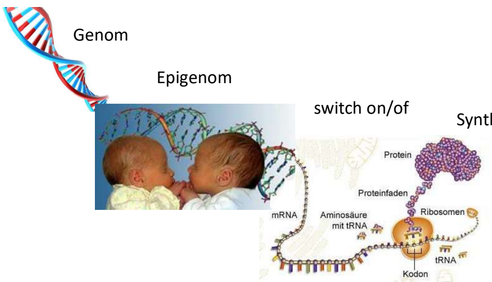


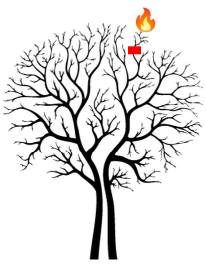
Genom

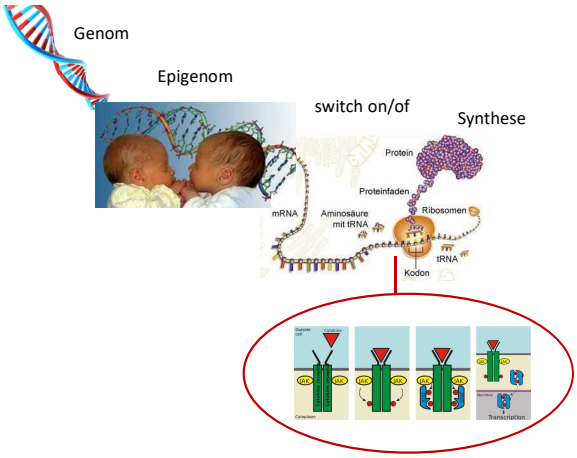
Epigenom

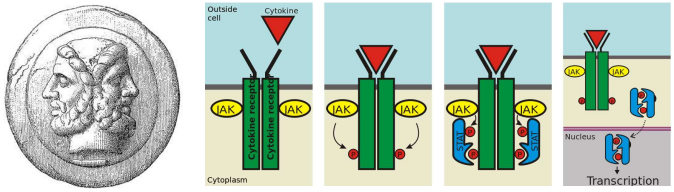
switch on/of

Synthese

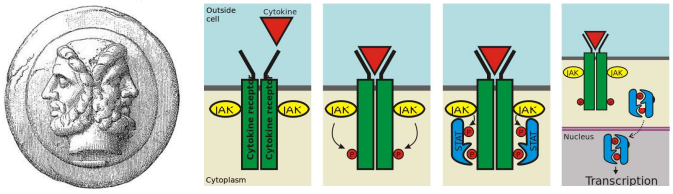


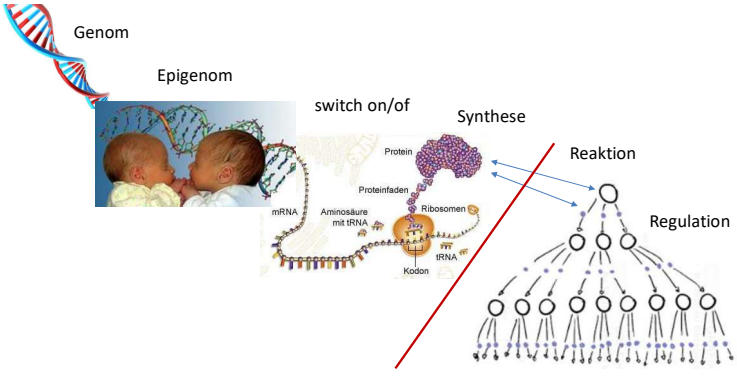






Janus: der doppelköpfige, römische Gott: ein Torwächter
Januskinasen phosphorylieren (aktivieren) STAT-Proteine (signal transducer and activator of transcription); STAT = Transkriptionsfaktor u.a. für Synthese von **Zytokinen, Interferonen, Interleukinen**, Erythropoetin, Wachstumshormon, Prolaktin, Leptin.





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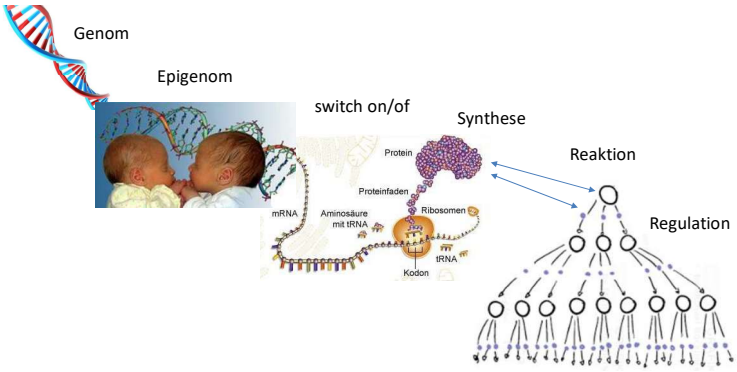
Wirkstoff	Vertreter	Ziel	Indikation
Tofacitinib	Xeljanz	**JAK1/2/3**	RA
Baricitinib	Olumiant	**JAK 1/2**	RA

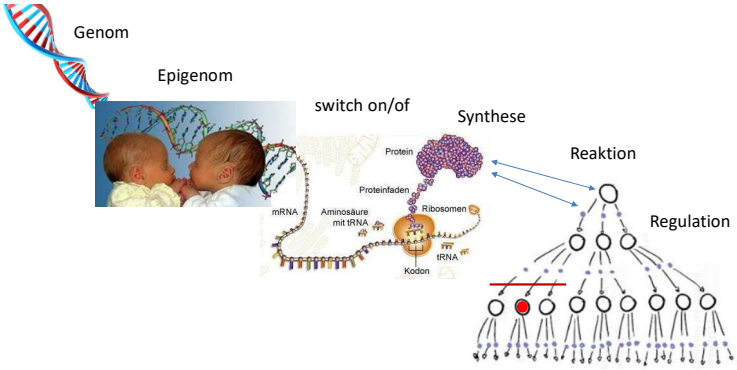
Wirkungsbereich		Ursprungsorganismus des Antikörpers		Wortstamm
neu	Bedeutung		Bedeutung	
—	Angiogenese (inhibitor)	-a-	Ratte	
-b(a)-	Bakterien	-e-	Hamster	
-c(i)-	Blutkreislauf	-i-	Primaten	
-f(u)-	Fungi	-o-	Maus	
-k(i)-	Interleukin	-u-	human	
—	Läsion	-xi-	chimär (human/fremd)	
-l(i)-	Immunsystem	-zu-	humanisiert	
–	Stütz- und Bewegungsapparat	-xi/zu-*	chimärer/humanisierter Hybrid	
-n(e)-*	Nervensystem	-axo-	Ratte/Maus-Hybrid	
-s(o)-	Knochen			-mab
-tox(a)-	Toxin			
t(u)	Darmkrebs			
	Hodenkrebs			
	Eierstockkrebs			
	Brustkrebs			
	Melanom			
	Prostatakarzinom			
	verschiedene Tumoren			
-v(i)-	Virus			

Ixe-ki-zu-mab

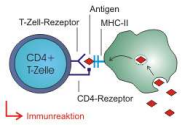
https://www.pei.de/DE/arzneimittel/antikoerper/monoklonale-antikoerper/monoklonale-antikoerper-node.html;jsessionid=19DD1DA8A09F7BC4568935EBDCDFC33A.intranet232?cms_tabcounter=0&cms_tabcounter=0#anchor



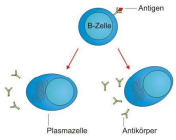
Wirkstoff	Vertreter	Ziel	Indikation
Anakinra	Kineret	IL1-R	RA (+MTX); M. Still – nicht in CH
Tozilizumab	Actemra	IL6-R	RA
Ustekinumab	Stelara	IL12/23	PSA
Secukinumab	Cosentyx	IL-17A	PSA, SPA
Mepolizumab	Nucara	IL-5	Eosinoph. Asthma; EGPA (Churg Strauss Syndrom)



Wirkstoff	Vertreter	Ziel	Indikation
Infliximab	Remicade, Remsima	**TNF α**	RA, PSA, SPA
Adalimumab	Humira	**TNF α**	RA, PSA, SPA
Eternacept	Enbrel	**TNF α**	RA, PSA, SPA
Golimumab	Simponi	**TNF α**	RA, PSA, SPA
Certolizumab	Cimzia	**TNF α**	RA, PSA, SPA



antigenpräsentierende Zelle
CD 80; CD 86; CTLA4

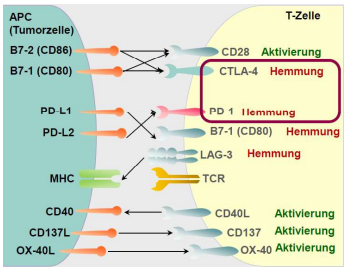


B-Zelle
CD 20

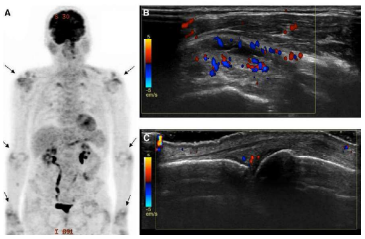
Wirkstoff	Vertreter	Ziel	Indikation
Abatacept	Orencia	**CD 80, 86, CTLA 4; somit indirekt T-Zelle**	RA, PSA
Rituximab	MabThera, Truxima	**CD 20; somit B-Zelle**	RA

Immunologische Checkpoints:

- begrenzen dauerhafte Immunantwort
- Regeln die T-Zell-Aktivität nach «immunologischen Bedarf»
- Verhindern die Zerstörung von gesundem Gewebe durch negative Costimulation Bsp. PD-1, CTLA-4, LAG 3
- werden vor allem in onkologischen Therapie genutzt



Padroll, Nat Rev Cancer 2016;12:252-264



Wirkstoff	Vertreter	Ziel	Indikation
Atezolizumab	Tecentriq	**Anti PD-L1**	NSCLC
Ipilimumab	Yervoy	**Anti-CTLA4**	Melanom
Pembrolizumab	Keytruda	**Anti-PD-1**	Melanom
Nivolumab	Opdivo	**Anti-PD-1**	NSCLC, Nierenzell-CA, Melanom, Hodgkin
Avelumab	Bavencio	**Anti PD-L1**	Merkelzell-CA (kutaner neuroendokriner Tumor)

(S)AE: Autoimmunphänomene! an Haut, Lunge, Auge, GI-Trakt, Herz, Blutbild
Arthralgien, Arthritiden, Polymyalgia rheumatica, Myositis

Widmann et al. Curr Radiol Rep 2017;5:59

Therapiestrategien - Entwicklung

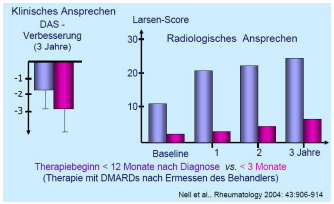
cDMARDS zu bDMARDS

Hit hard and erly – time is bone

Treat to target

Absetzten / Pausieren DMARDS?

EBM-komplementäre Ansätze



Danke.

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