Pharmacology of Key Emerging Therapies in Chronic Diseases, 2023

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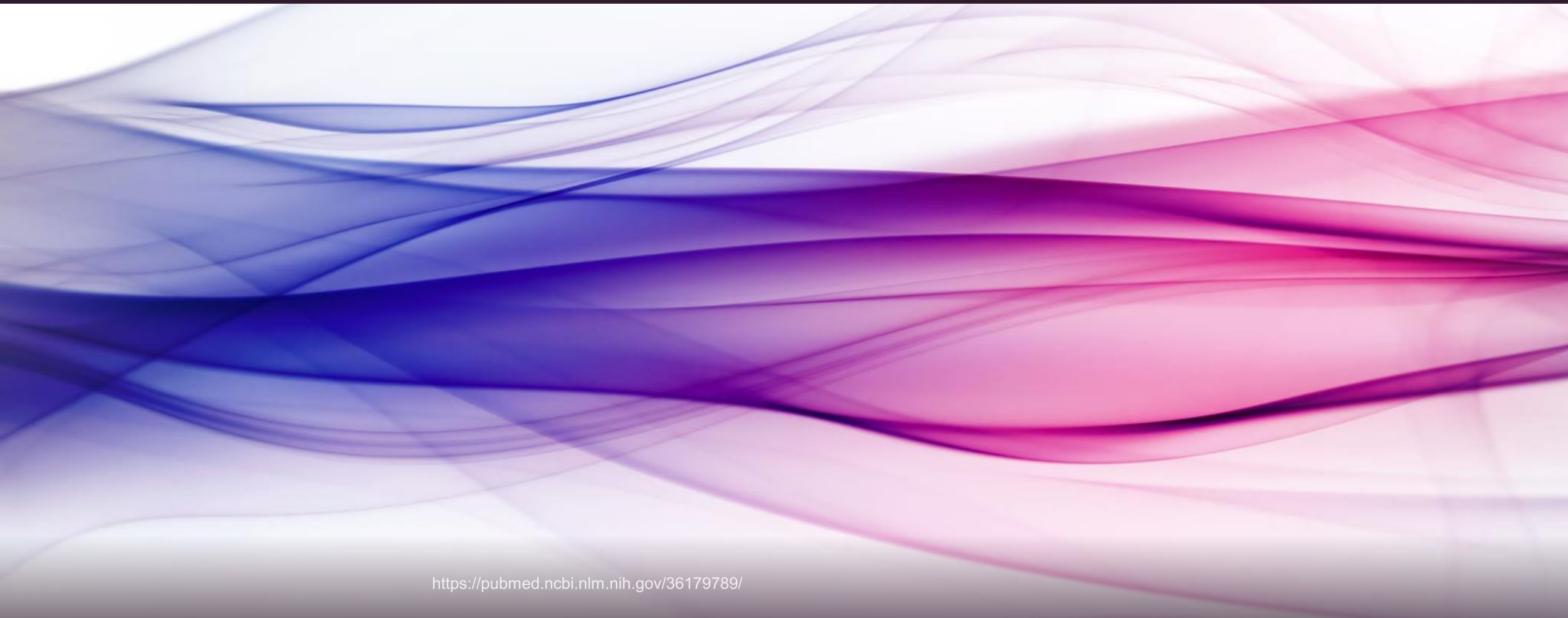

https://pubmed.ncbi.nlm.nih.gov/36179789/

Repurposing of approved drugs

- The pharmaceutical industry often misses important clinical use for a drug
- This is driven by the NDA in the FDA approval process and how the approval process works.
- Advancement in medical science/biochemistry uncovers new uses
- There are major pathologies/illnesses for which new treatments are needed and no new treatments or research is being conducted
- Approval (and patents, intellectual property) is based on ‘indication’, meaning a specific clinical use or disease treated. Often manufacturers choose the lowest cost/highest reward option they can.
- Drugs rarely have just one action, so as time passes and medical science advances, the importance of these effects can be revealed.
- Often there is no business/financial incentive to bring new indications to market

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Repurposed Drugs of interest

- Methylene Blue
- Ivermectin
- Losartan
- LDN
- Oxytocin
- Amlexanox

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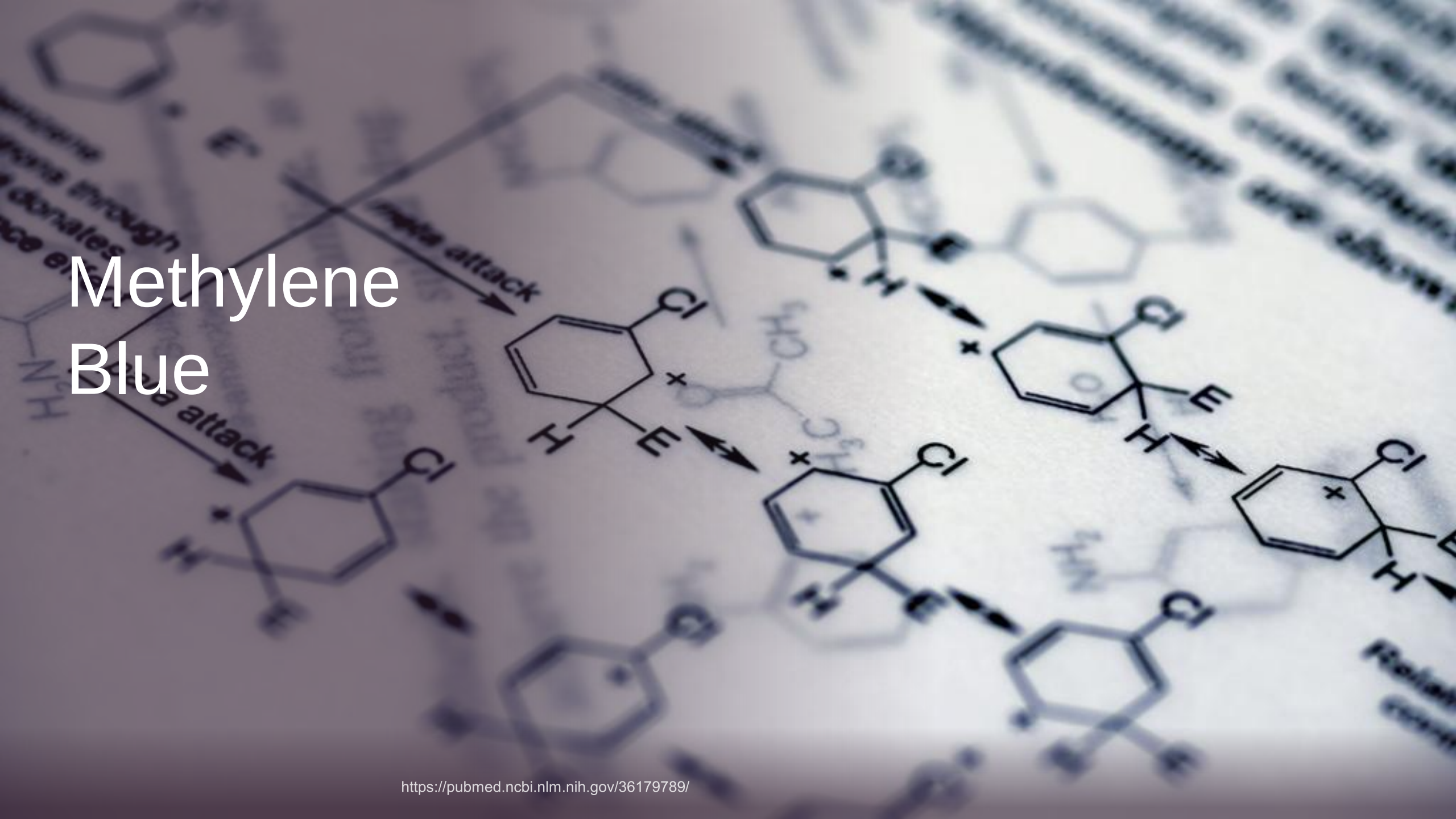
Methylene Blue



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Methylene Blue

- Virtually no one was using or discussing MB at the time CDPMCs brought it forward-no compounding vendor or pharmacy had it and there was no US importer
- MB was viewed as a failed antibiotic for UTI or use in ICU for a rare toxic condition (methemoglobinemia)
- MB is a vital drug for anti-aging because redox drives the exposure memory system, phenotype expression “exposome” and oxidative phosphorylation
- MB and photodynamic therapy are under utilized treatments
- MB has been very well tolerated by patients and our dosage recommendations have been appropriately conservative for our role as educators
- As more patients and docs have worked with MB we have learned more
- 10mg BID orally to start, up to 0.5mg/kg daily. Doses up to 1mg/kg daily are well tolerated. Nausea is usually the first sign of a high dose

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Dosages/Main uses

- **Basic anti aging**: Up to 0.5mg/kg, 5-25mg BID ongoing, take an occasional break
- **Mitochondria/neuroprotection**: Up to 0.5mg/kg, 5-25mg BID, use in balance with NAD+, CoQ10, MB, NAC and GSH. This is the fuel for oxidative phosphorylation. Enzyme function is crucial, and these can be stimulated with exercise, phototherapy, ozone, HBOT, nebulized H202 and by reducing drivers of oxidative stress
- **Oral Care**: MB with PDT for dental or respiratory pathogens-a main cause of chronic infection. 1mg/5ml oral solution, swish and spit/swallow, 3 times weekly
- **Lyme and related**: Generally higher dosages, target is about 1mg/kg daily in 2 or 3 divided doses. Generally, 25mg BID up to 50mg BID or 1mg/kg daily.
- **EBV/CMV** and many other chronic viral infections can be controlled with MB and PDT

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Neurodegenerative Disease

- Methylene Blue is still underutilized in neurodegenerative disease
- The brain utilizes a high percentage of the body's O2 and energy output, yet cannot store energy and relies mainly on mitochondria
- Mitochondrial dysfunction leads to inflammatory signaling that can damage neurons and result in physical changes to the brain itself, leading to neurodegenerative disease
- ALZ is an oxidative stress related illness, not caused by tau protein
- Prevention/early treatment of these diseases is far more effective than any treatment, but restoring mitochondrial function may improve symptoms and reduce speed of disease progression

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Lyme and IV dosage strategies

- Methylene Blue has multiple actions in the management of Lyme and similar
- Direct anti microbial, synergistic effects with key antibiotics Rifampin and Azithromycin, energy support, redox, anti-inflammatory, neuroprotection
- Has role in acute, disseminated, late infection and flares, PDT enhances this
- Higher dosages are used for Lyme as compared to general anti aging.
- Core therapy: MB 10mg BID titrated up to 0.5mg/kg DAILY. Max dose would typically be 1mg/kg, or about 50mg BID, although higher doses have been used temporarily
- Works well with Ozone, HBOT and PDT
- In-Office Strategy: Keep patient on a maintenance dose orally, then add an IV kicker dose with other therapies to manage flares (ozone, Vit C,HBOT, Sauna, PDT)
- Be sure to replete minerals and NAD/NAC/GSH as toxins are eliminated

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Friends of Methylene Blue

- NAD+
- CoQ10
- NAC/GSH
- Azithromycin/Rifampin
- Ivermectin
- LDN
- Ozone, 660nm Red light
- Vit C

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IV Use

Only use D5W if possible, 250ml is a good size

Vials or bags should be at room temp before use.

MB is highly staining, be careful, it may permanently stain and be difficult or impossible to remove

Always use sterile technique and don't store punctured vials longer than a day or two in the fridge.

To avoid waste, you can make up multiple bags using sterile methods, then immediately freeze at -10C for up to 30 days. Thaw to room temp and mix bag to assure it is in solution

Be sure drug is at room temp and shake well before administration

Consider using a filter to assure butterfly doesn't clog, but not absolutely necessary

Administer separately from other drugs, don't mix without advice

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Ivermectin

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Ivermectin

- We have discussed IVM extensively, but some new info has come to light
- The main action of IVM is that of an allosteric modifier. It can bind to proteins and change their shape and ability to function or receive signaling. IVM also can bind to transport proteins or ‘pores’ and block them without necessarily changing the shape.
- IVM had multiple mechanisms in COVID-blocks endocytosis at ACE2, entry into nucleus via importin membrane transport and viral helicase transcription.
- Ivermectin modulates the immune system via inhibition of P2X4 and P2X7 receptors on microglial cells and macrophages
- IVM has anti cancer effects by blockade of FOXA1, increase of mitochondrial ROS in cancer cells and stimulation of PAK1 autophagy

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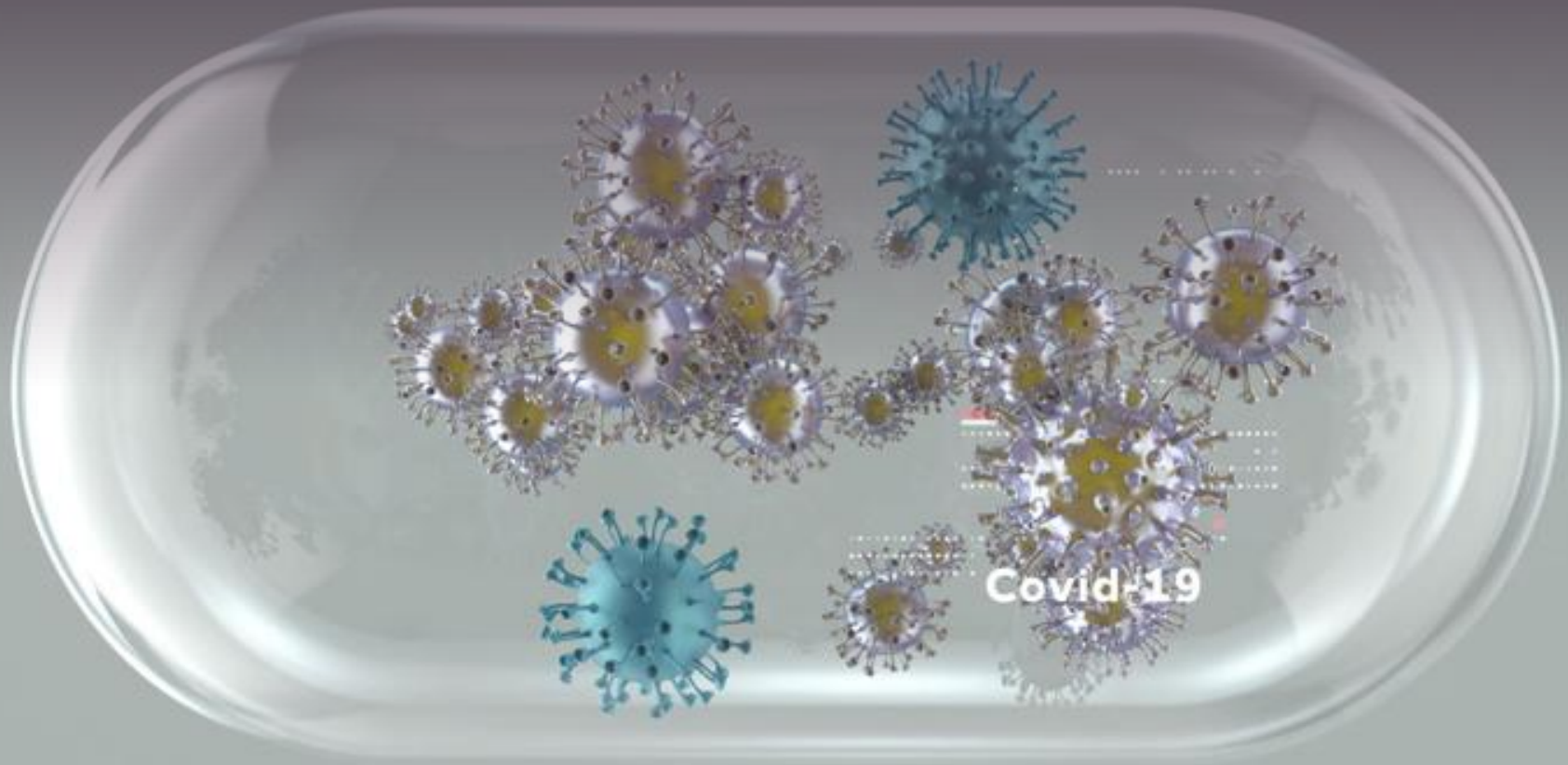
Ivermectin immune system effects



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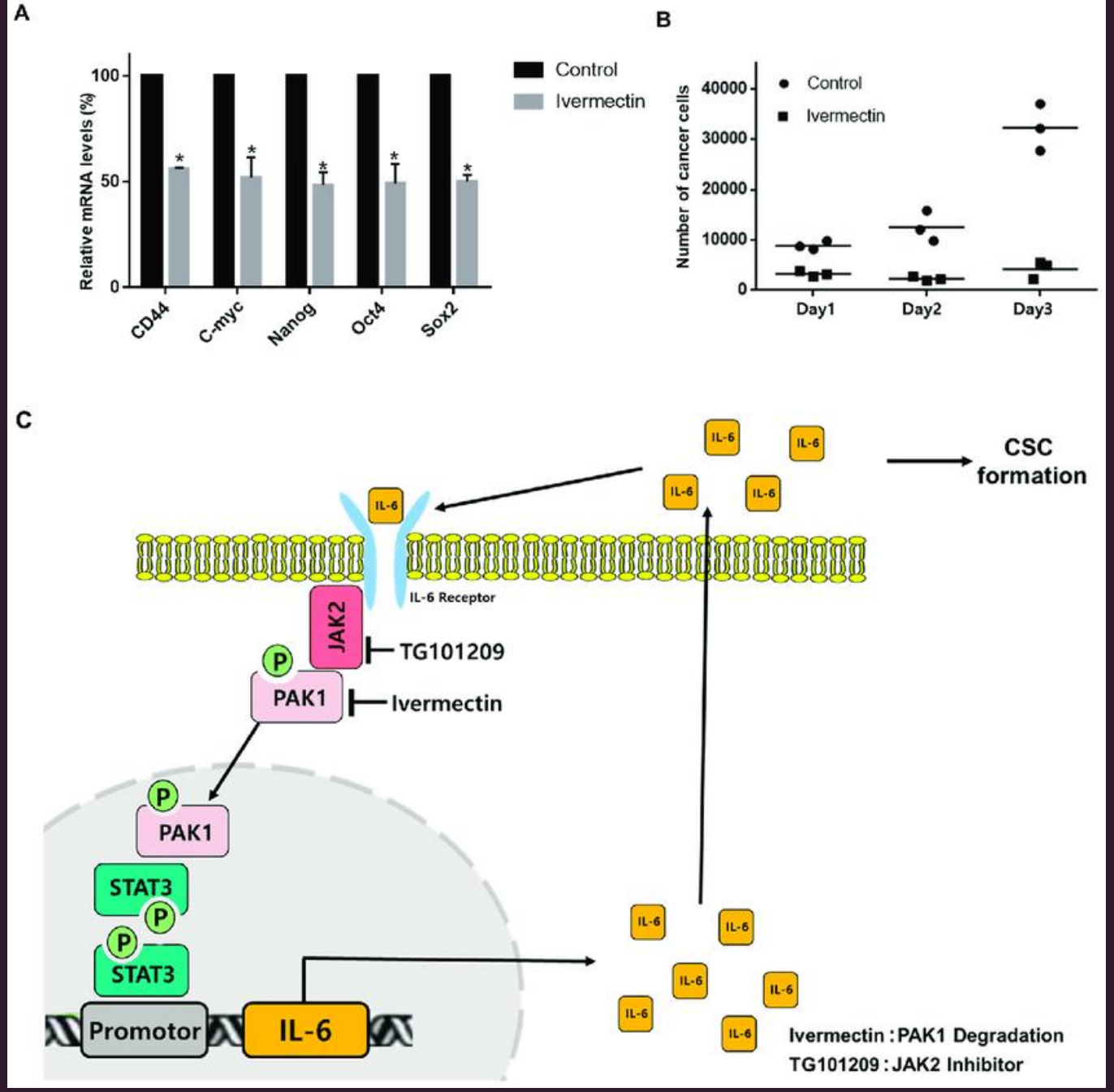
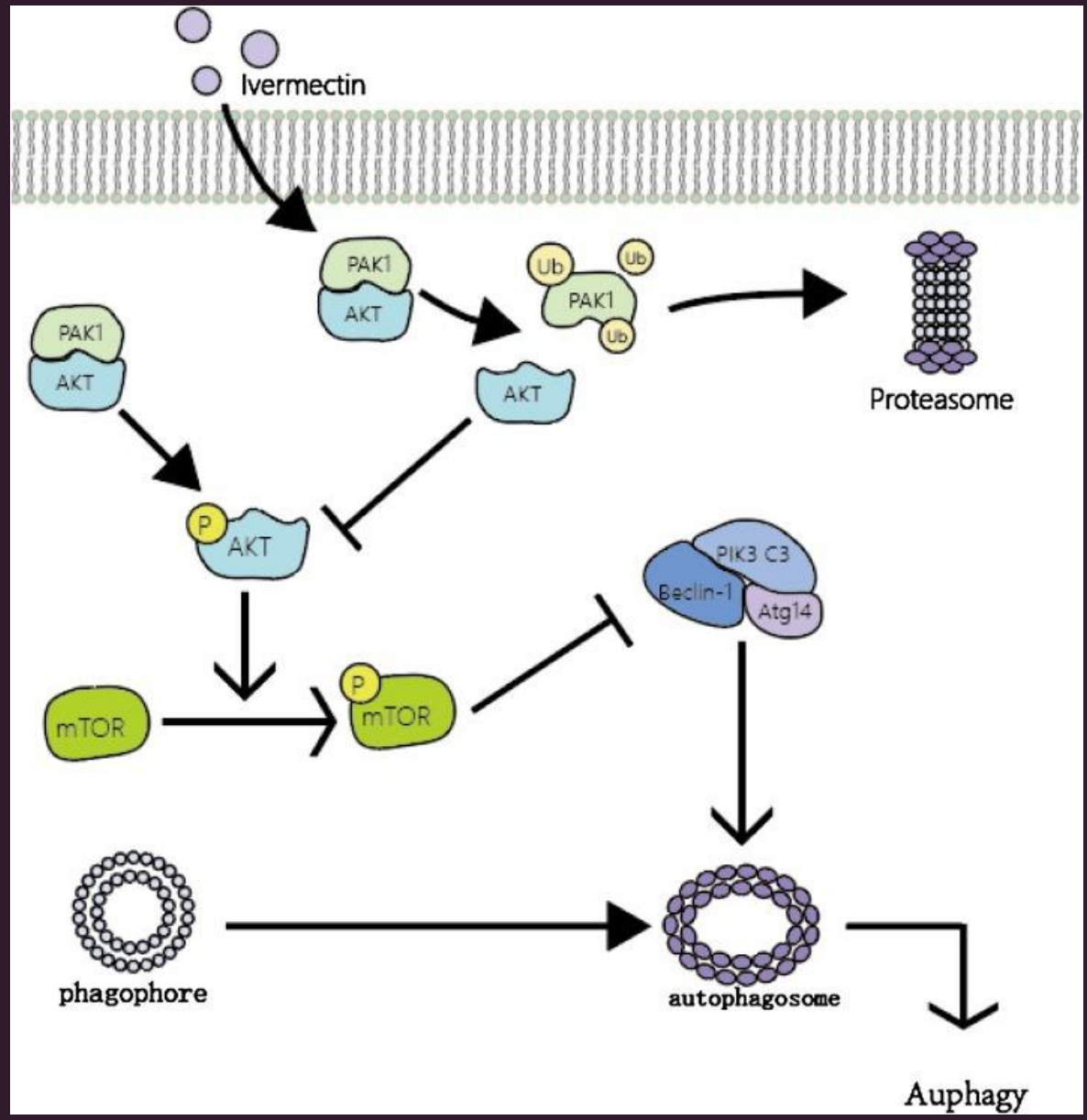
IVM decreases IL6 by inhibition of PAK1



https://www.researchgate.net/publication/336417477_

IVM promotes autophagy via PAK1 inhibition



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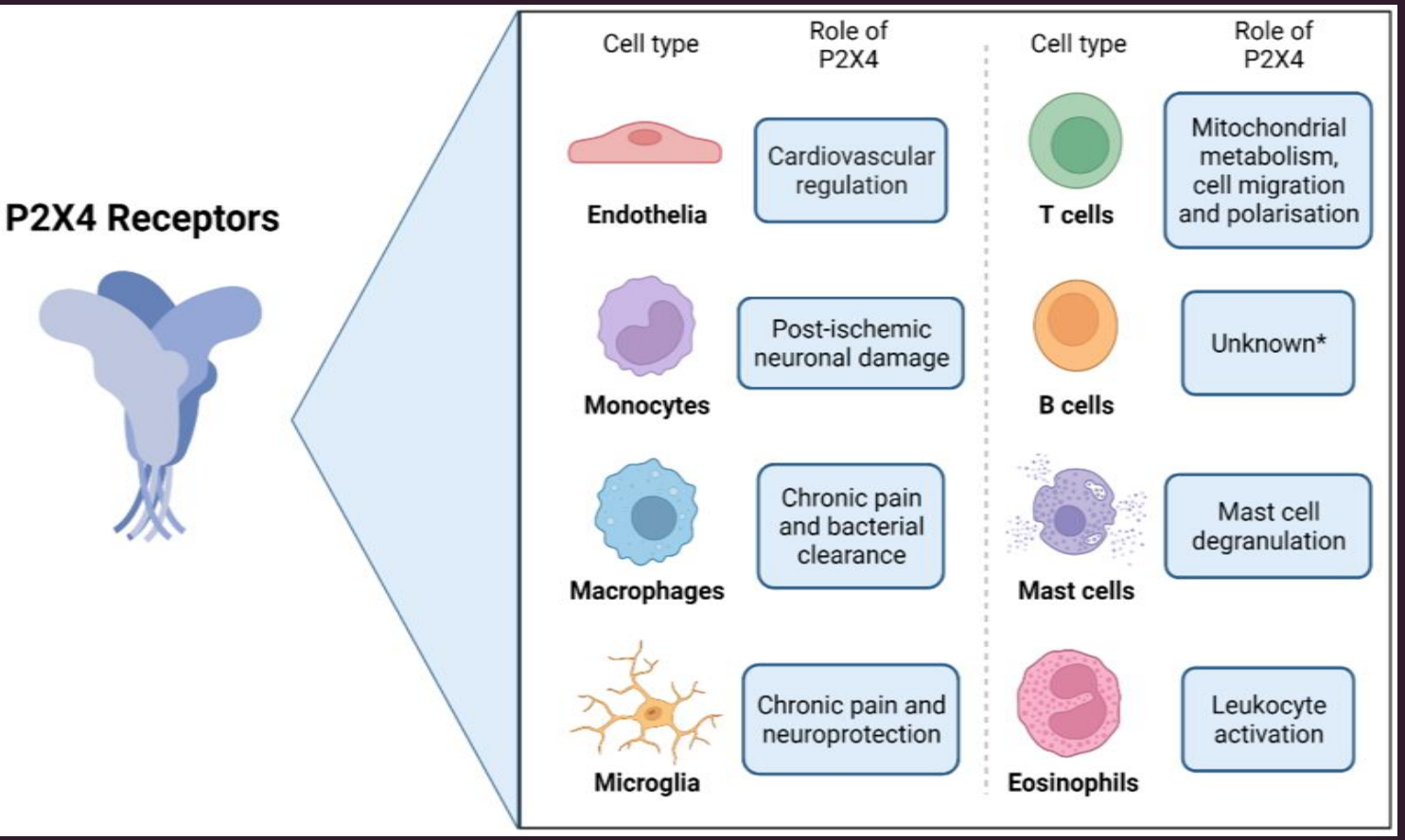
P2X4 Receptors



- P2X4 receptors are ATP gated cation channels that reside in many tissues
- Ivermectin is a P2X4 antagonist
- Regulates neuroinflammatory signaling P2X7 receptor
- Duloxetine and paroxetine are also antagonists

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P2X4 Receptors

- Part of the neuroinflammatory axis responsible for neuron repair (there are other P2X receptors that create an interface between immune and neuronal/CNS responses, including inflammation and apoptosis
- ATP gated /activated P2X4 receptors on microglia and astrocytes release pro-inflammatory cytokines, chemokines and secondary inflammatory messengers, while endothelium and peripheral circulating immune cells regulate crosstalk between circulating immune cells and the CNS.
- Involved in neuropathic pain and allodynia
- P2X4 receptors regulate P2X7 receptors

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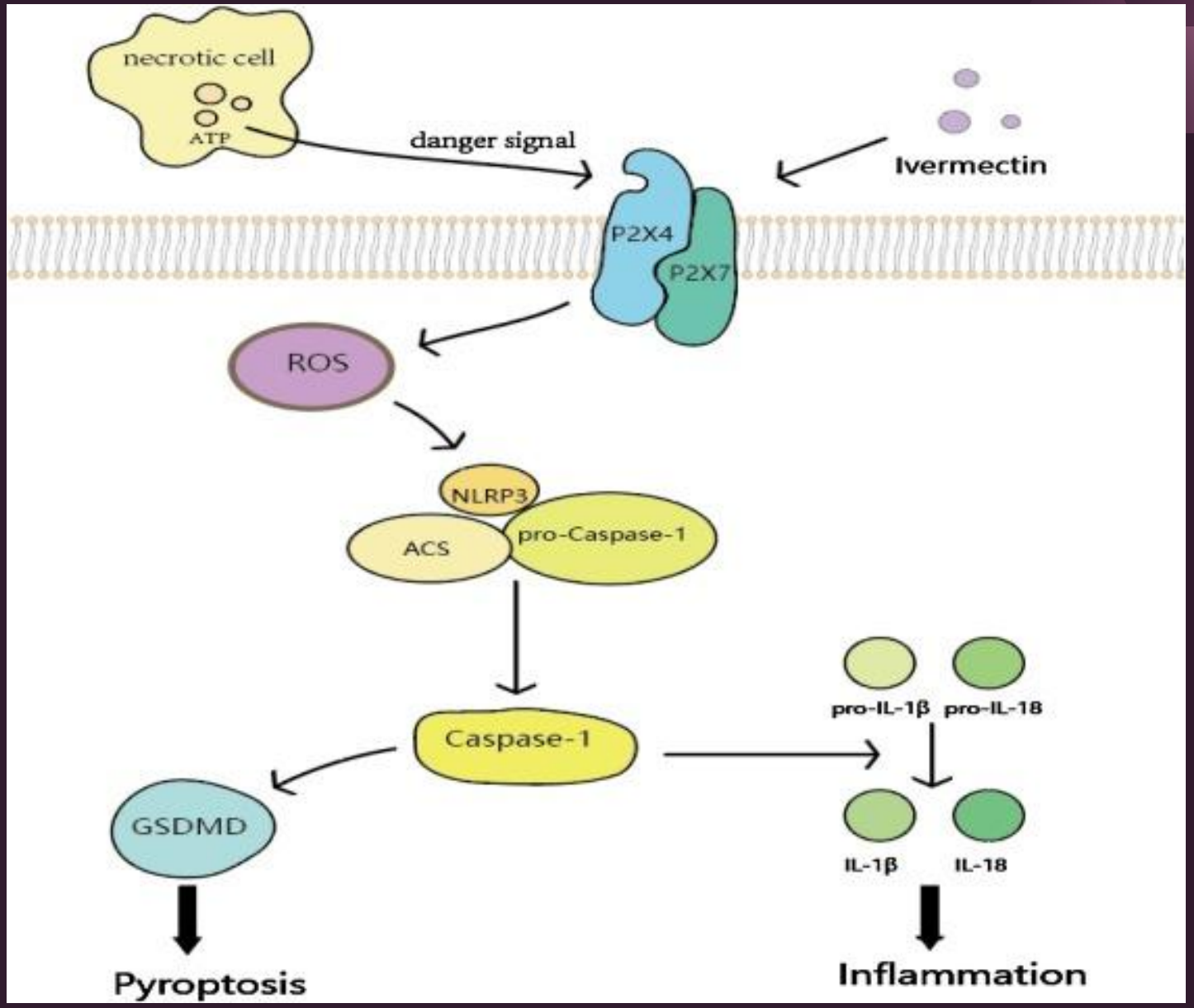
P2X4 Modulates P2X7



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P2X7 receptor

- Several P2X (purine) receptor types reside in the cell wall and monitor ATP levels inside and outside the cell. These are ligand gated ion channels that can open pores in the cell wall and participate in cell destruction or preservation by manipulating concentration of ions
- ATP is not normally present in the cytoplasm or plasma. Its presence indicates damaged or dying cells/danger, so it trigger both innate and adaptive immune responses.
- ATP turns on P2X receptors, which are normally dormant
- In cancer or infectious diseases, P2X7 is either an ‘angel or demon’, depending upon the level of activation and cell type-contrasting effects
- In neuroinflammatory/neurodegenerative diseases, activation of P2X7 contributes to disease progression

https://pubmed.ncbi.nlm.nih.gov/36179789/

P2X7 Receptor activation by free ATP causes…

INNATE RESPONES

- Induces inflammasome maturation and release of IL1b, IL18 and ROS generation
- Signals to activate caspases and apoptosis
- If ATP is detected in the cell, pannexin is signaled to open and release it to help preserve the cell

ADAPTIVE RESPONSES

- Modulates the balance of T cell maturation between TH17 and Treg to favor TH17
- This can be a beneficial or detrimental effect, depending on the illness being treated
- Facilitates conversion of naïve CD4+ cells to Treg

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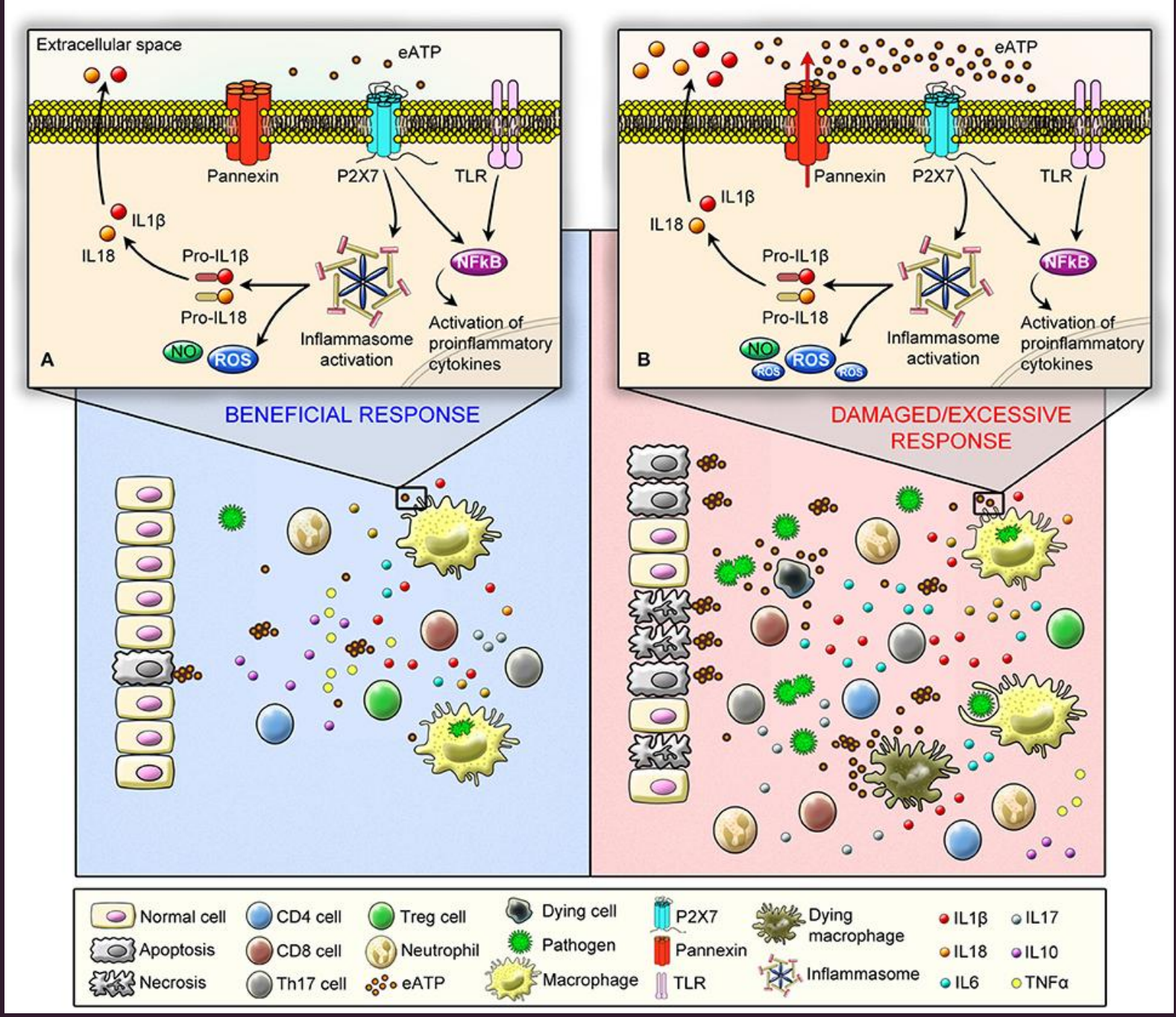

https://www.frontiersin.org/articles/10.3389/fphar.2018.00052/full

Ivermectin in Cancers

- Ivermectin is being investigated for prostate, breast and colon cancers
- Each type of cancer involves different cells and different crucial biochemical pathways, so they are different mechanisms, but all rely on allosteric modification of proteins or enzymes
- Effectiveness in specific cell lines is confirmed but not completely understood due to complexity
- In general, IVM works against cancers by blocking a crucial step in cellular function for that cancer type, plus promotion of cancer cell apoptosis and autophagy
- The immune effects are modulated by purine receptors P2X
- The metabolic anti-cancer effects are centered around PAK1, FOXA1 blockade

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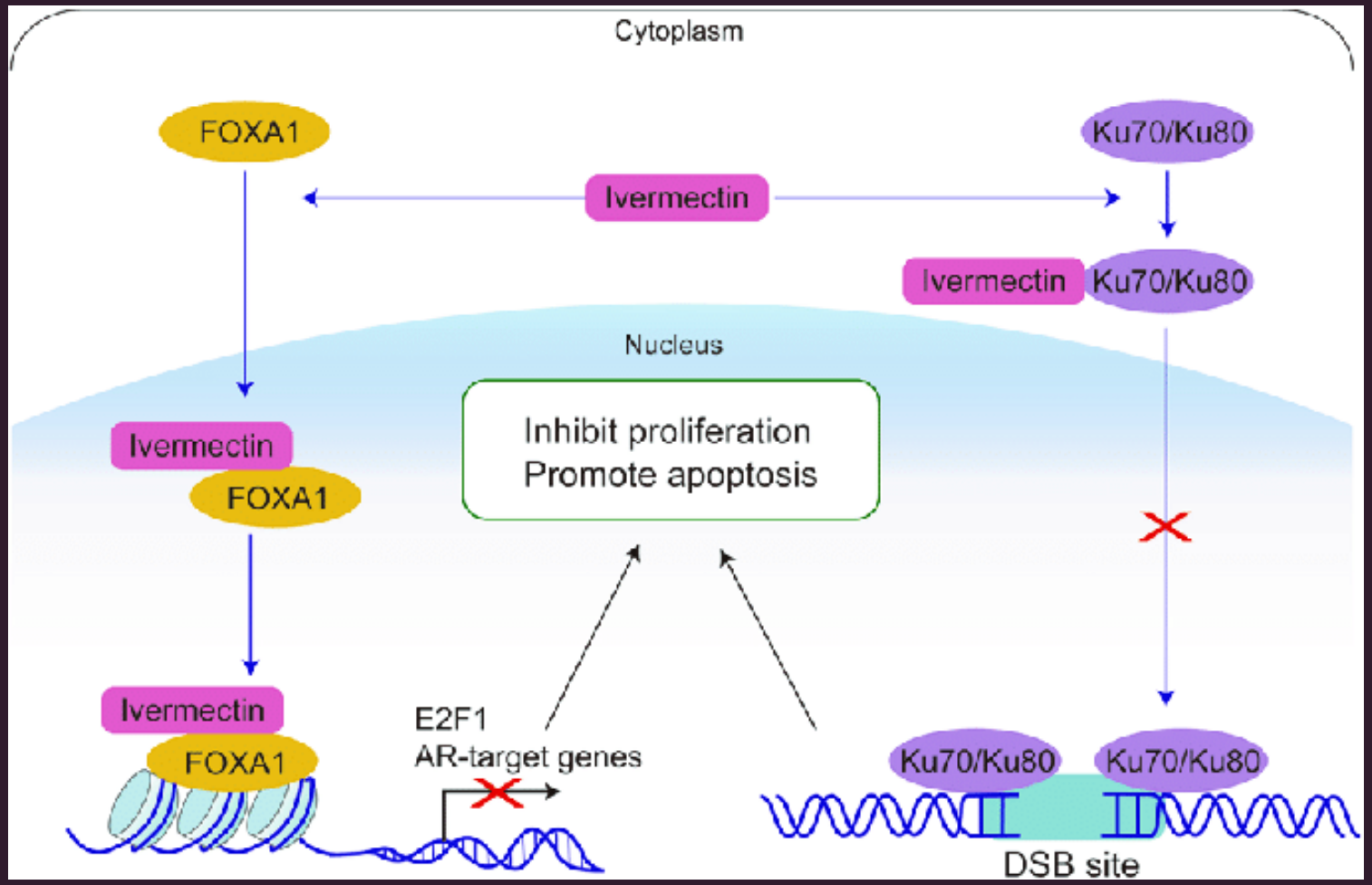
Ivermectin in Prostate-FOXA1 blockade



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Losartan and Fibrosis

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Losartan

- Fibrosis is difficult to treat once it has occurred.
- Losartan has been shown to reverse fibrosis in the eye, liver, kidneys and muscle tissue and reduce tumor stromal pressure in cancers
- AT2 is a pro-oxidant, fibrogenic cytokine. It up regulates other pro-oxidant signals such as TGF-B1, thus blocking/regulating overactive AT2 has many benefits
- AT2-1 activation=vasoconstriction, myocardial fibrosis, ventricular hypertrophy, Aldosterone release and Vasopressin Release
- AT2-2 activation=Vasodilation, antiproliferation, neuronal regeneration and antiatherothrombotic

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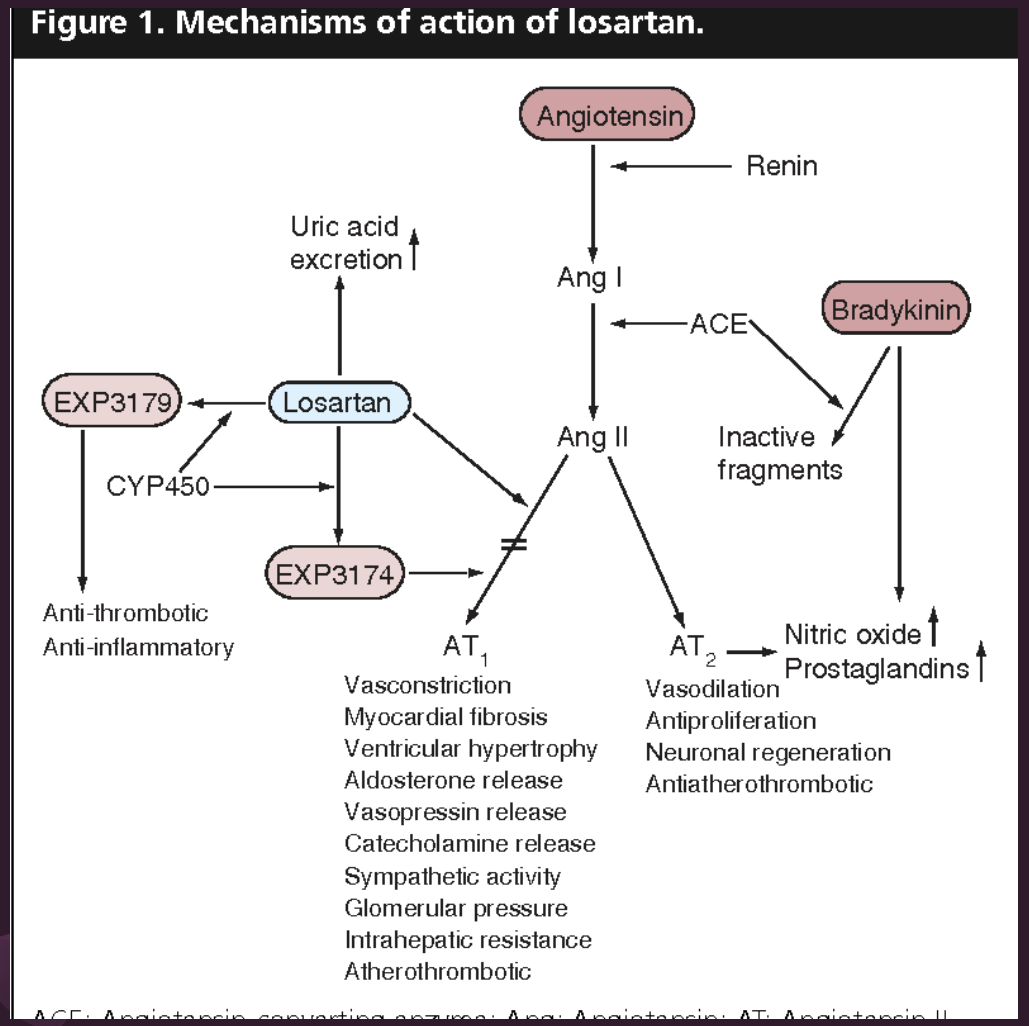
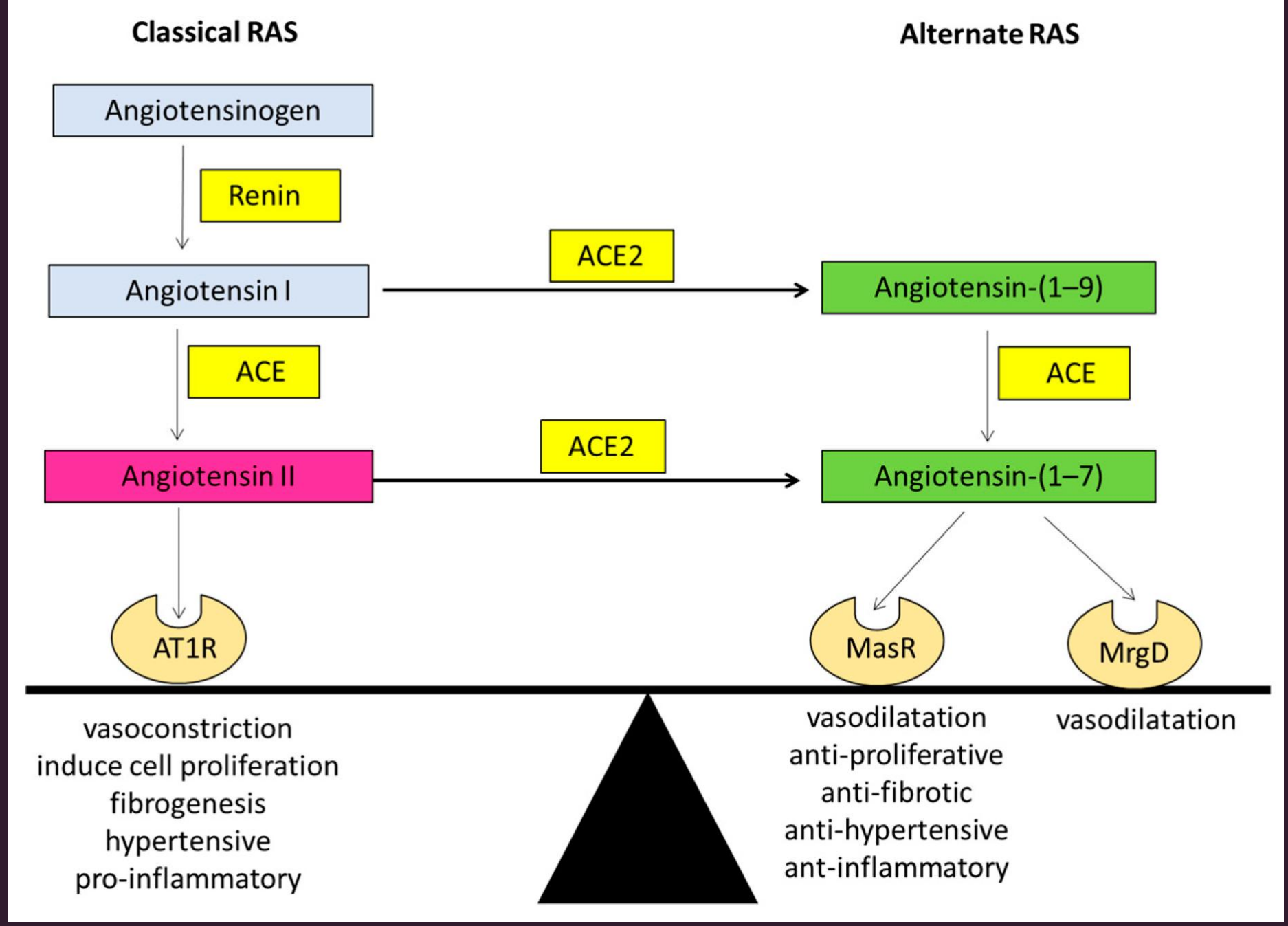
Losartan has a significant active metabolite



- Losartan has 2 active metabolites
- EXP3179 is a potent endothelial COX-2 inhibitor, reduces adhesion molecule binding to endothelium, activates endothelial NOS and PPAR-G
- PPAR-G is a reverse-insulin resistance receptor, regulates fatty acid storage and adipogenesis
- PPAR-G activation causes M2 polarization

https://pubmed.ncbi.nlm.nih.gov/36179789/
https://www.ahajournals.org/doi/full/10.1161/hypertensionaha.109.138883



https://www.mdpi.com/2077-0383/10/4/702

Losartan anti-fibrotic effects

- There is a broad base of literature regarding the antifibrotic effects of losartan in renal, hepatic, prostate, cardiac, pulmonary, ophthalmology, diabetes and fatty tissue
- This is because the AT2-1 receptor is a prolific pro-inflammatory signal in response to injury, so it is related to repair functions like fibrosis, proliferation, ECM, tumor stroma, etc.
- Each specialty has a different way of describing the pathways due to specialized tissues in each organ, etc

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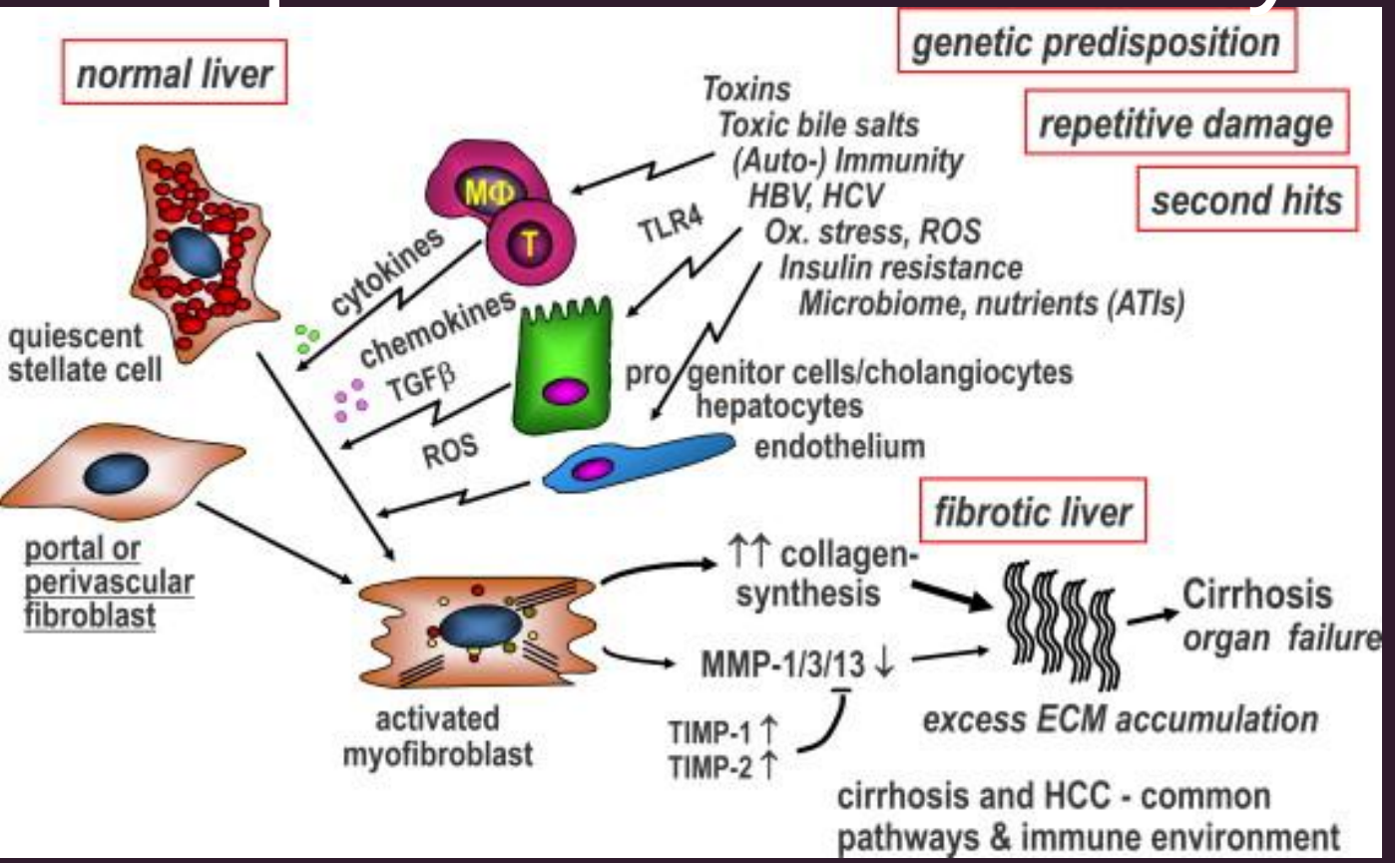
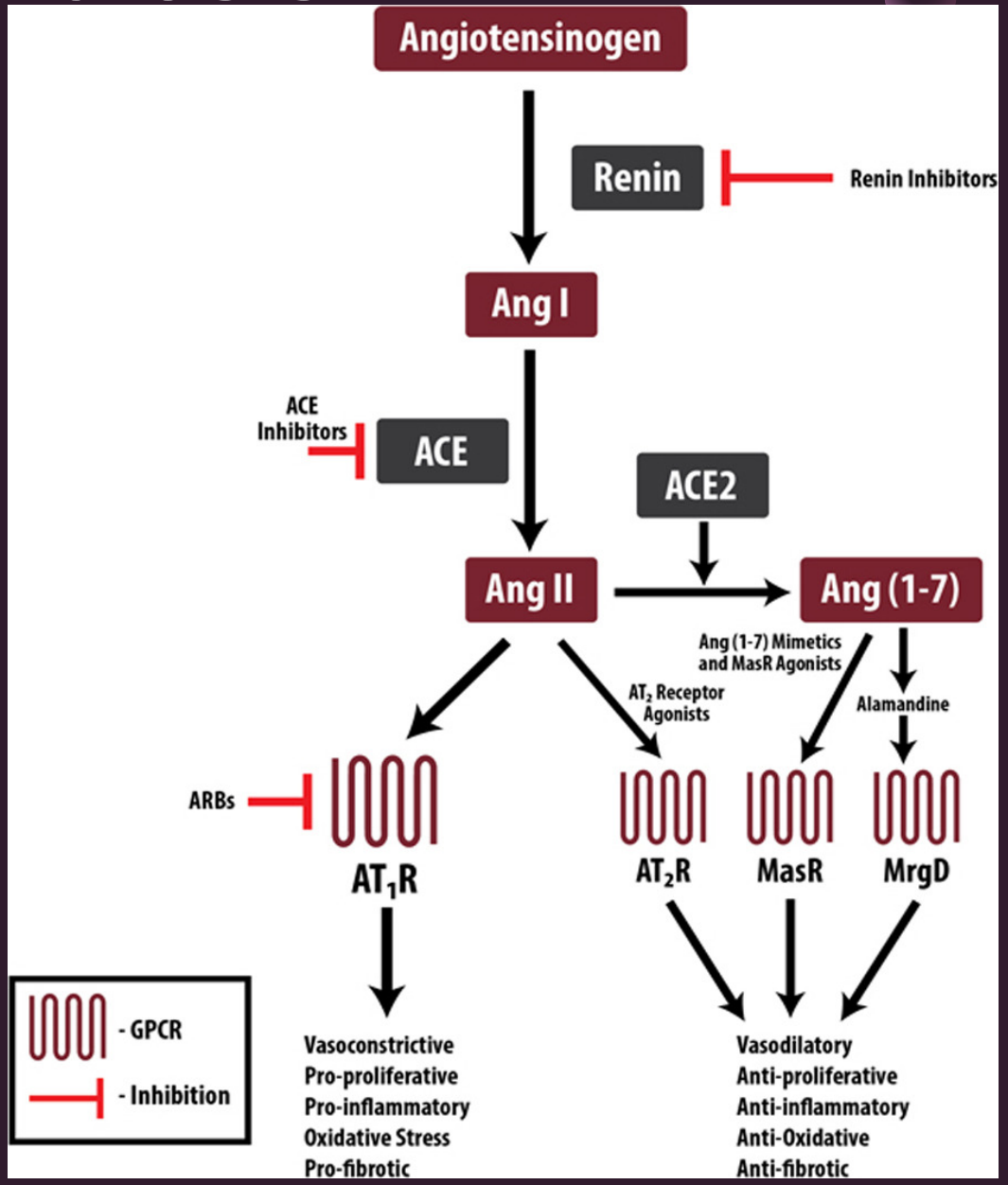
Hepatic and Pulmonary Fibrosis





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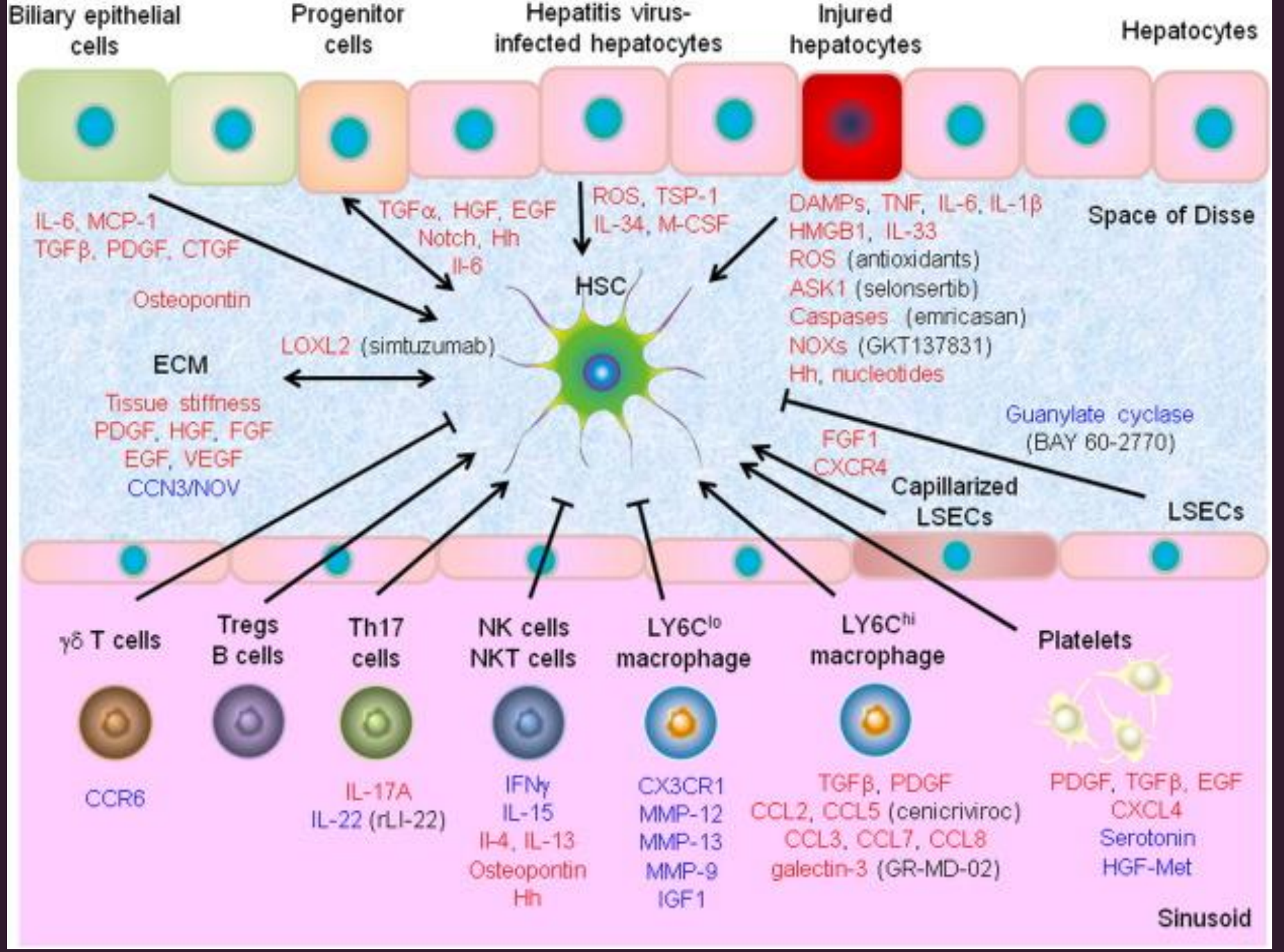
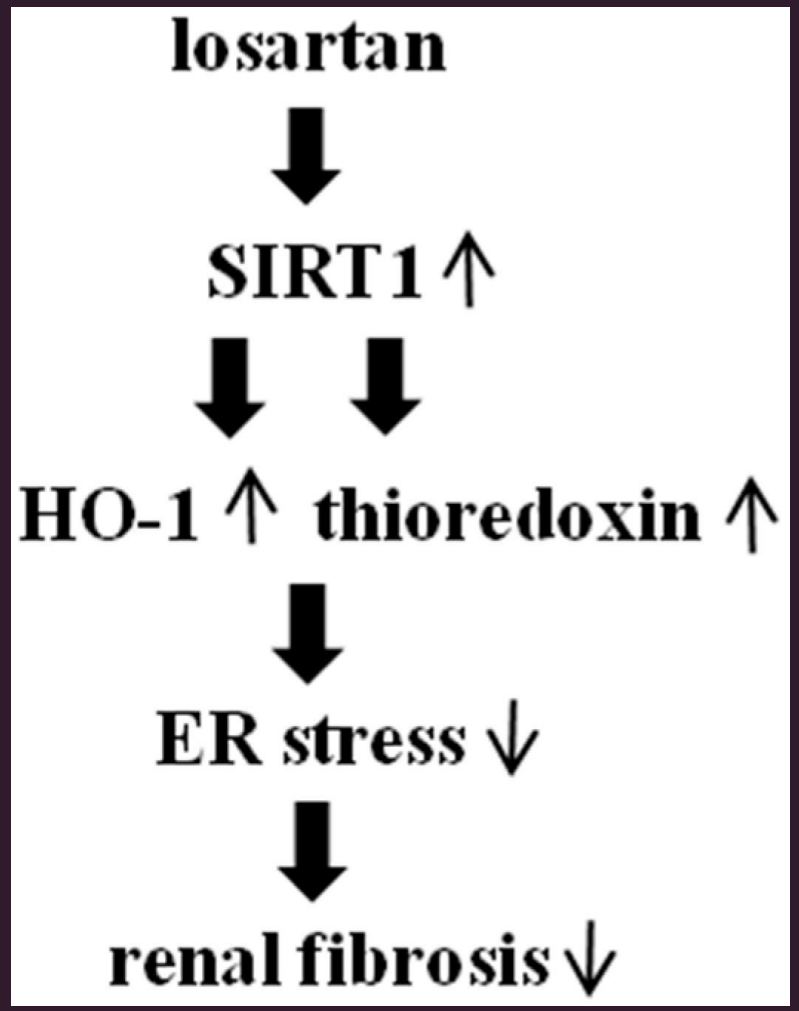


https://www.sciencedirect.com/science/article/pii/S0169409X17300637

Renal Fibrosis



- Losartan induces SIRT1 activity, upregulating HO1 and thioredoxin, two important anti-oxidant enzymes-buffering redox
- SIRT1-reduces renal fibrosis, reduces apoptosis (increased cell life),
- ER stress elicits NF-kB and NLRP3 inflammasome, IFNB, IL23, enothelin-1, TGF-B and Collagen
- SIRT1-reduces renal fibrosis, reduces apoptosis (increased cell life),
- HO-1=Heme oxygenase-1, rate limiting step in heme degradation, clearing free heme reduces oxidative stress

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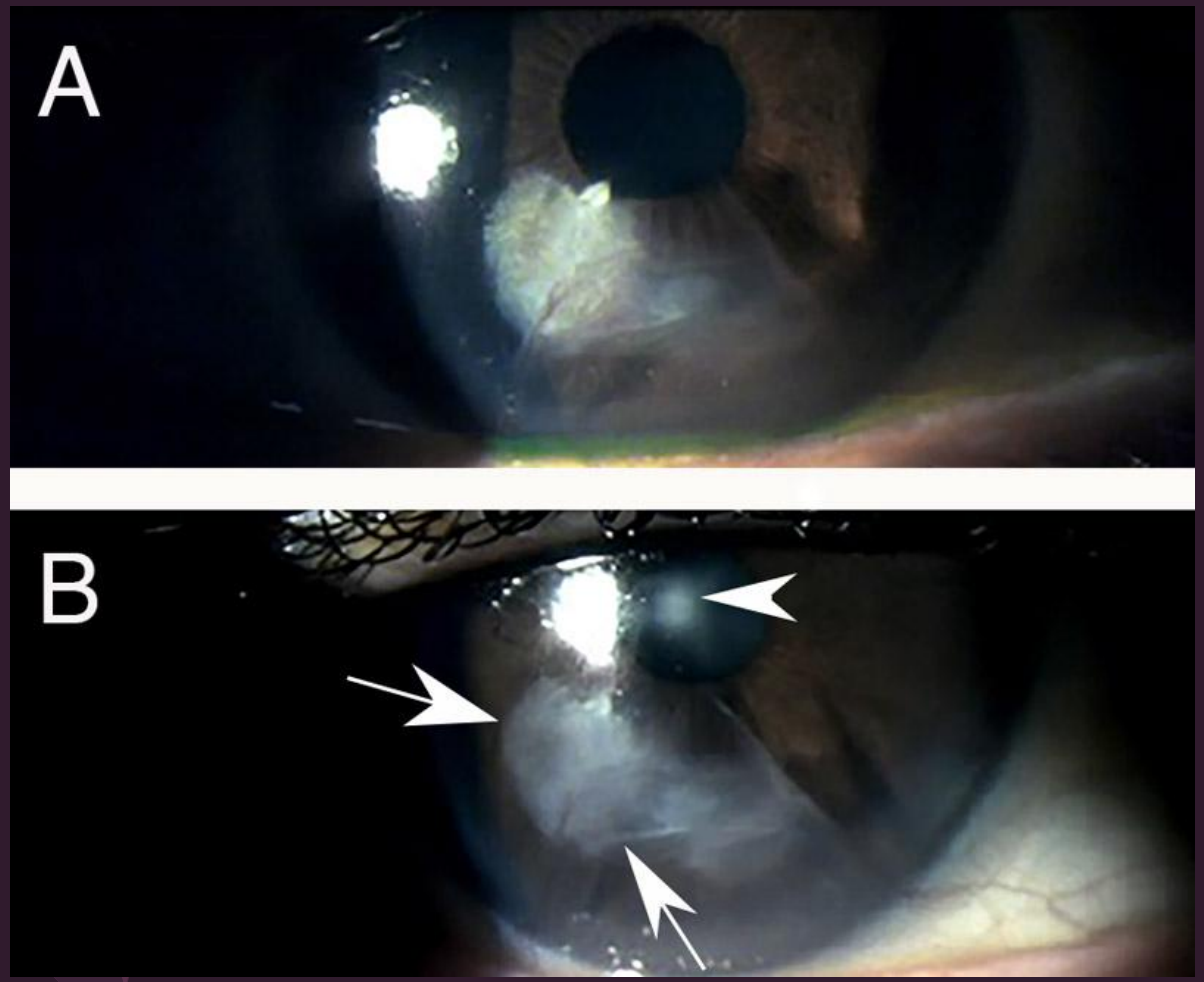
Losartan in the eye…

"If myofibroblasts are the cause of the scarring and the topical drug can reach the site of scarring, losartan is likely to be effective"



- Corneal 'scarring' can be prevented or reversed with losartan
- Reduces or blocks TGF-B signaling
- Anti-TGF drugs don't penetrate all layers of the eye
- 0.8mg/ml 6 times daily for 90-180 days
- Reduces myofibroblast development, relies on TGF-B signaling. Blocking signal causes apoptosis of existing MFB and they are replaced with normal corneal cells

https://consultqd.clevelandclinic.org/hypertension-drug-losartan-reverses-scarring-and-restores-vision-after-cornea-damage/

Losartan Dosage, synergistic ideas

Losartan is CONTRAINDICATED IN PREGNANCY

Oral Dosage: 12.5mg/25mg/50mg/100mg, given once daily. Average dose is 50mg/day for BP, very inexpensive

For those who can’t take losartan due to other needed BP/cardiac meds, we have a 5mg BID lozenge that does not significantly alter BP

Losartan eye drops are available

Supportive items: Methylene Blue, NAC, Curcuminoids, NAD+, Berberine

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Low Dose Naltrexone

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LDN

- In simplest terms, LDN therapy is a transient blockade of of mu, kappa and sigma opioid receptors that induces endogenous opiate peptide production (endorphins, enkephalins, etc) and direct blockade of TLRs. This enhances immune function, reduces inflammation and down regulates TH17 (via decrease in IL10 and TFG-B)
- LDN is an underutilized therapy and not well understood by prescribers-works differently than ‘high dose’ naltrexone
- Used in fibromyalgia, MS, Crohns/UC, Hashimoto’s, Weight Loss, TBI, Cancer, Hailey-Hailey disease, CRPS/chronic pain, Spike Protein/COVID, various dermatology conditions and more
- No labs or special exams are needed to begin therapy safely
- Dosage must be titrated from about 1mg to a target of 4.5mg at bedtime, patients need to be on it for at least 6 months to assess
- Can suppress thyroid function, check TSH after 3-4 months
- Patients frequently report favorable responses to LDN over other options
- Low cost, readily available
- Short term nocturnal blockade of opiate receptors is the primary mechanism of action

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LDN Side effects are low, but present

- Insomnia-most common
- Vivid dreams
- Fatigue
- Low or loss of appetite
- Nausea
- Thinning hair
- Mood swings
- Potential liver or kidney toxicity over time

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Some common uses for LDN therapy

Skin Conditions Reported to Be Improved by LDN

- Alopecia areata
- Atopic dermatitis
- Autoimmune progesterone dermatitis
- Autoimmune thrombocytopenia purpura
- Autoimmune urticaria
- Bachet's syndrome
- Bullous pemphigoid
- Cicatricial pemphigoid
- Dermatitis herpetiformis
- Dermatomyositis
- Diffuse cutaneous systemic sclerosis
- Discoid lupus erythematosus
- Epidermolysis bulls acquisita
- Erythema nodosum
- Essential mixed cryoglobulinemia
- Essential Pruritis
- Hailey-Hailey Disease
- Henoch-Schonlein purpura
- Herpes gestationis
- Kawasaki's disease
- Lichen planopilaris
- Lichen planus
- Lichen sclerosus
- Linear IgA disease
- Microscopic polyangiitis
- Morphea
- Phemphigus vulgaris
- Psoriasis
- Pyoderma gangrenosum
- Vitiligo

Other Conditions:

- Mood disorders -- anxiety, depression, PTSD
- Thyroid disorders -- autoimmunethyroid disease
- DM-1
- GI -- celiac, Chrons, ulcerative colitis
- A variety of cancers -- including melanoma
- Neurologic conditions -- neuropathy, restless leg, Parkinson's, multiple sclerosis, ALS
- Chronic fatigue/Fibromyalgia
- Chronic Lyme

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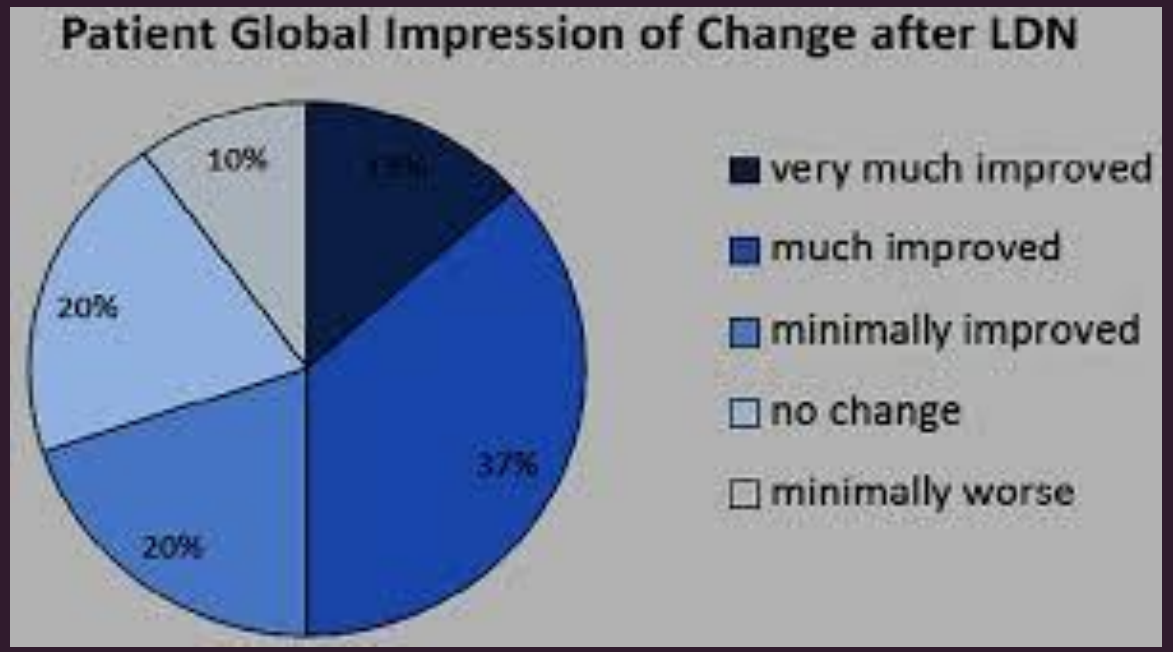

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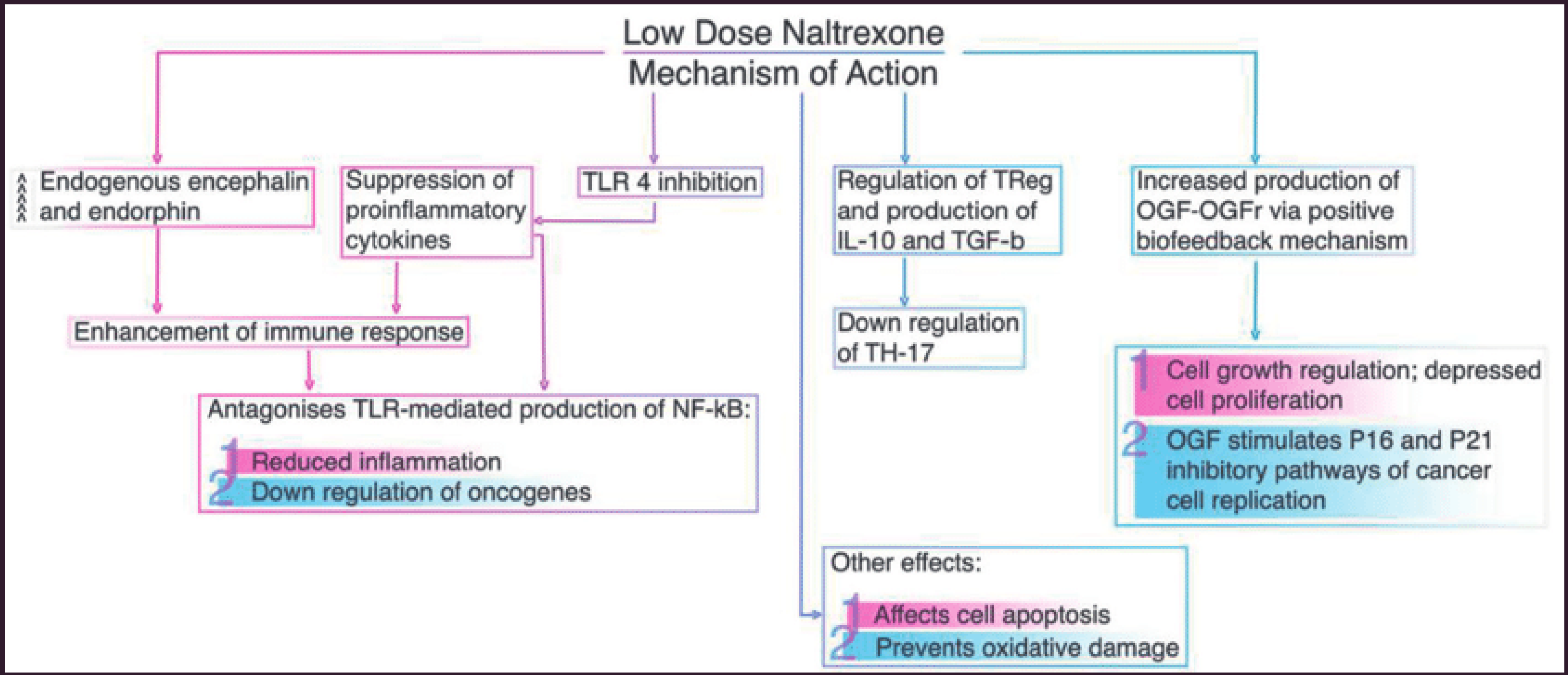

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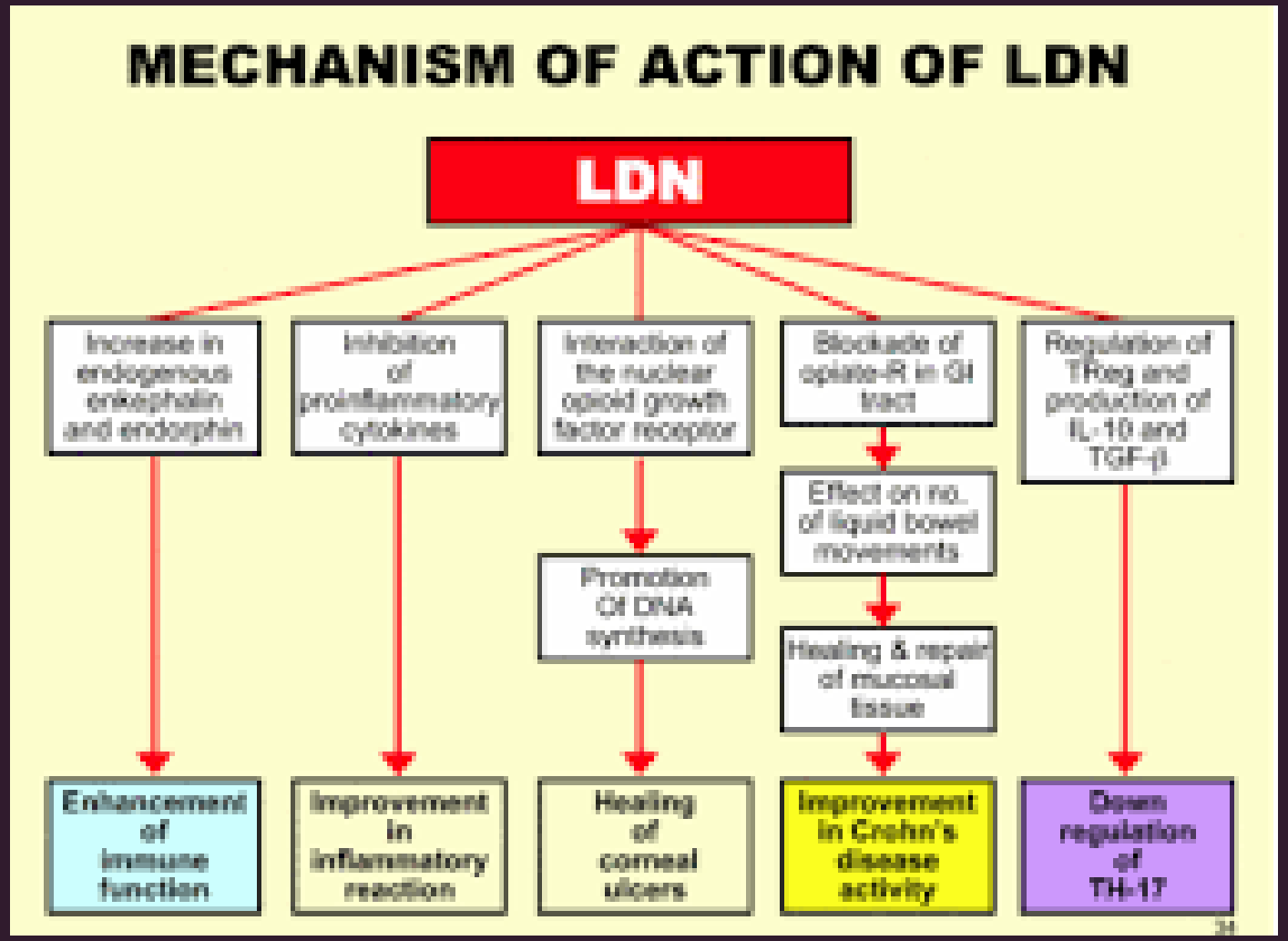
Naltrexone (LDN)



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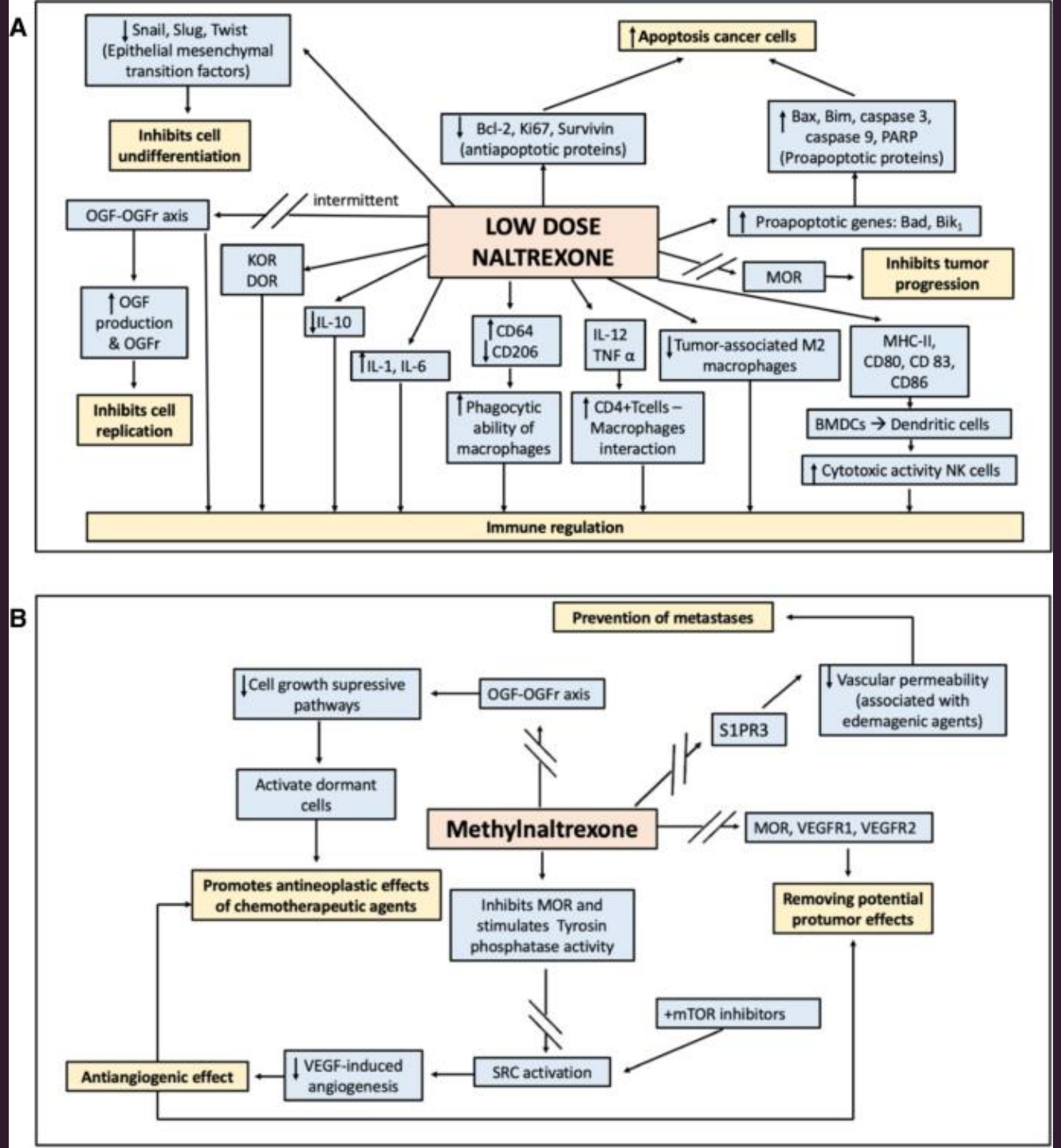
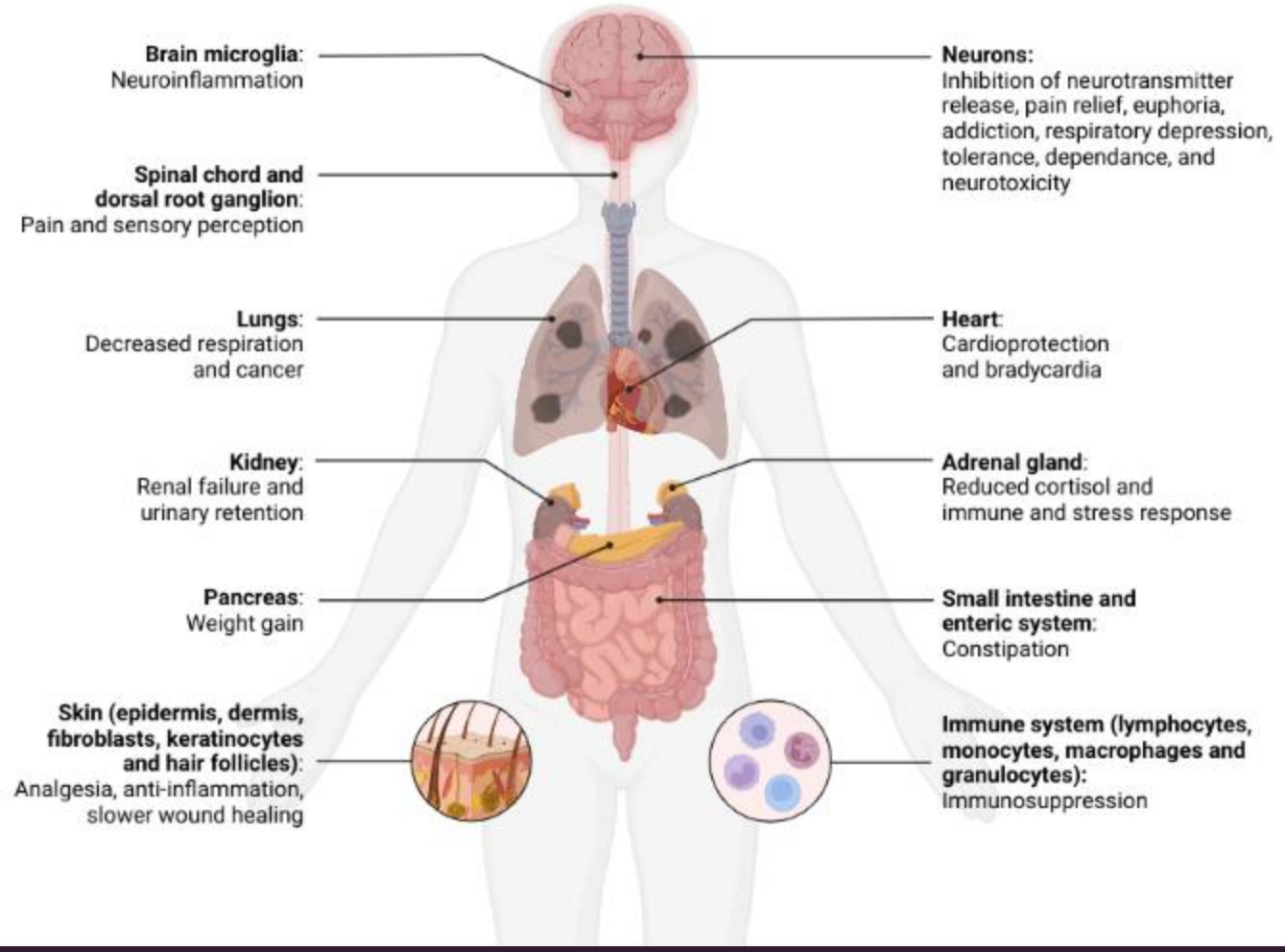

A
↓Snail, Slug, Twist (Epithelial mesenchymal transition factors)
Inhibits cell undifferentiation
↑Apoptosis cancer cells
↓Bcl-2, Ki67, Survivin (antiapoptotic proteins)
↑Bax, Bim, caspase 3, caspase 9, PARP (Proapoptotic proteins)
intermittent
OGF-OGFr axis
LOW DOSE NALTREXONE
↑Proapoptotic genes: Bad, Bik1
KOR DOR
MOR
Inhibits tumor progression
↑OGF production & OGFr
Inhibits cell replication
↓IL-10
↑IL-1, IL-6
↑CD64 ↓CD206
IL-12 TNF α
↓Tumor-associated M2 macrophages
MHC-II, CD80, CD 83, CD86
↑Phagocytic ability of macrophages
↑CD4+Tcells – Macrophages interaction
BMDCs → Dendritic cells
↑Cytotoxic activity NK cells
Immune regulation
B
Prevention of metastases
↓Cell growth supressive pathways
OGF-OGFr axis
↓Vascular permeability (associated with edemagenic agents)
S1PR3
Activate dormant cells
Methylnaltrexone
MOR, VEGFR1, VEGFR2
Promotes antineoplastic effects of chemotherapeutic agents
Inhibits MOR and stimulates Tyrosin phosphatase activity
Removing potential protumor effects
+mTOR inhibitors
Antiangiogenic effect
↓VEGF-induced angiogenesis
SRC activation

Where do we find opioid receptors?

- CNS: Areas related to pain perception, reward, emotion (PAG, thalamus, ventral tegmental area, nucleus accumbens and amygdala)
- Immune Cells have mu receptors: glial cells, macrophage, granulocyte, T cells, B cells
- Mu-brain, euphoria, decrease GI motility, cortex, thalamus, PAG, medulla, spinal cord, sensory neurons (glial cells), GI
- Sigma Opioid expressed in similar CNS tissues and monocytes, T cells and B cells
- Kappa: CNS and spinal cord, macrophages and T cells, dissociative effects, sedation
- Delta: analgesia, cardiovascular function, GI motility, antidepressant, dependence
- Zeta: Anxiety, depression, appetite, regulates cancer cell proliferation
- Nociceptin: CNS, anxiety, ,depression, appetite, tolerance to mu agonists
- All opiate receptor expression is affected by mitogens and various cytokines
- Known to cause addiction, tolerance, respiratory depression and immunosuppression
- LDN antagonizes mu, kappa and delta/sigma to a lesser extent in partial blockade, cannot fully antagonize any opioid receptor

https://pubmed.ncbi.nlm.nih.gov/36179789/

Effects of Opioids on the Human Body



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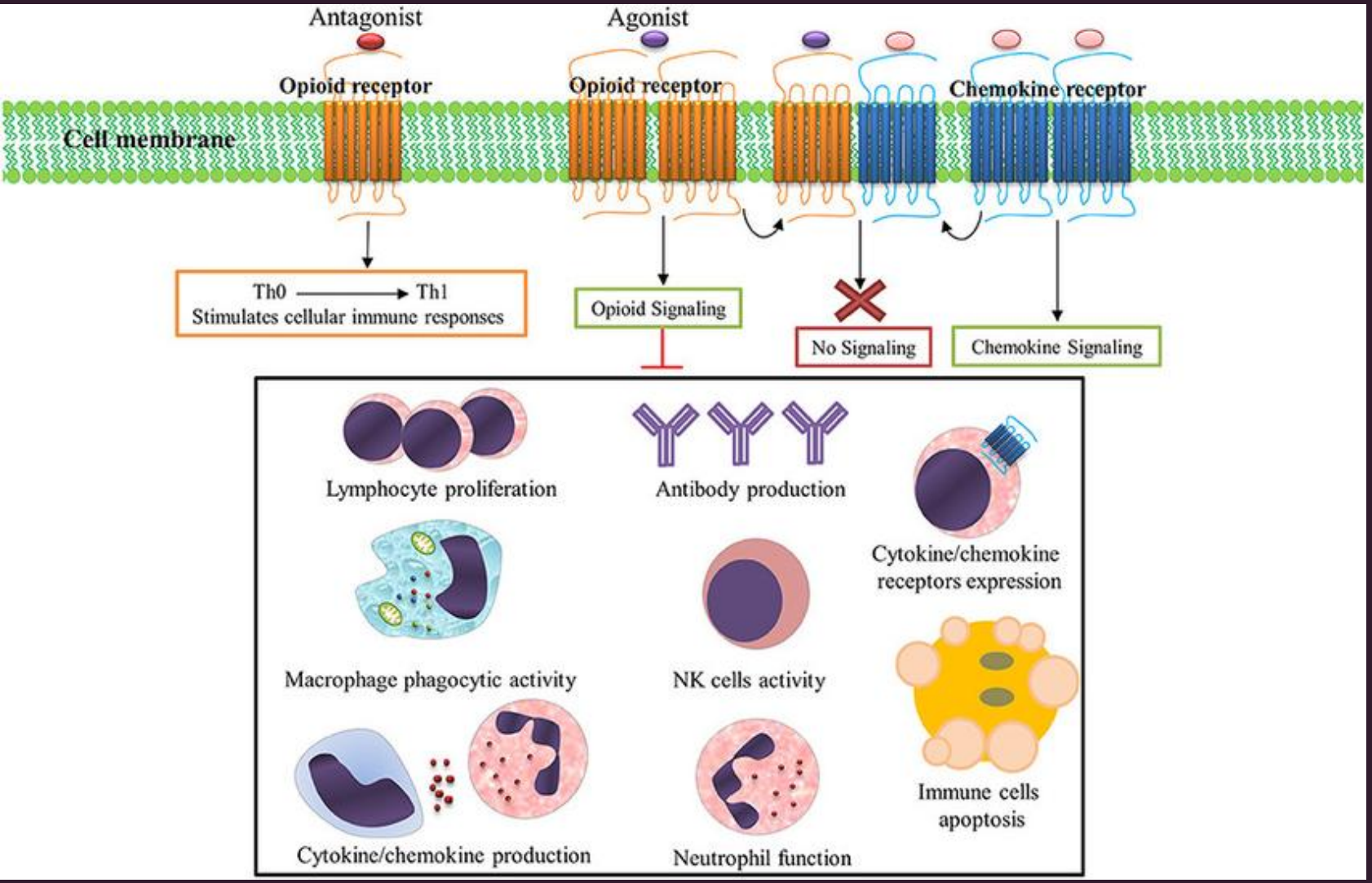
Effect of Exogenous Opioids on Immune System

- Endogenous and exogenous opioid agonists and antagonists have different effects based on receptor binding affinity and location of receptors.
- Exogenous opioids are immunosuppressive, likely part of analgesic effects
- Predisposes to opportunistic infections by suppression of TH1
- Endogenous and exogenous opiates act on different primary receptors, naltrexone is an anagonist for mu, delta and kappa
- Down regulates TH1 and promotes TH2, Treg and TH17
- Down regulates antibody production by B cells
- Suppresses macrophage function

https://pubmed.ncbi.nlm.nih.gov/36179789/

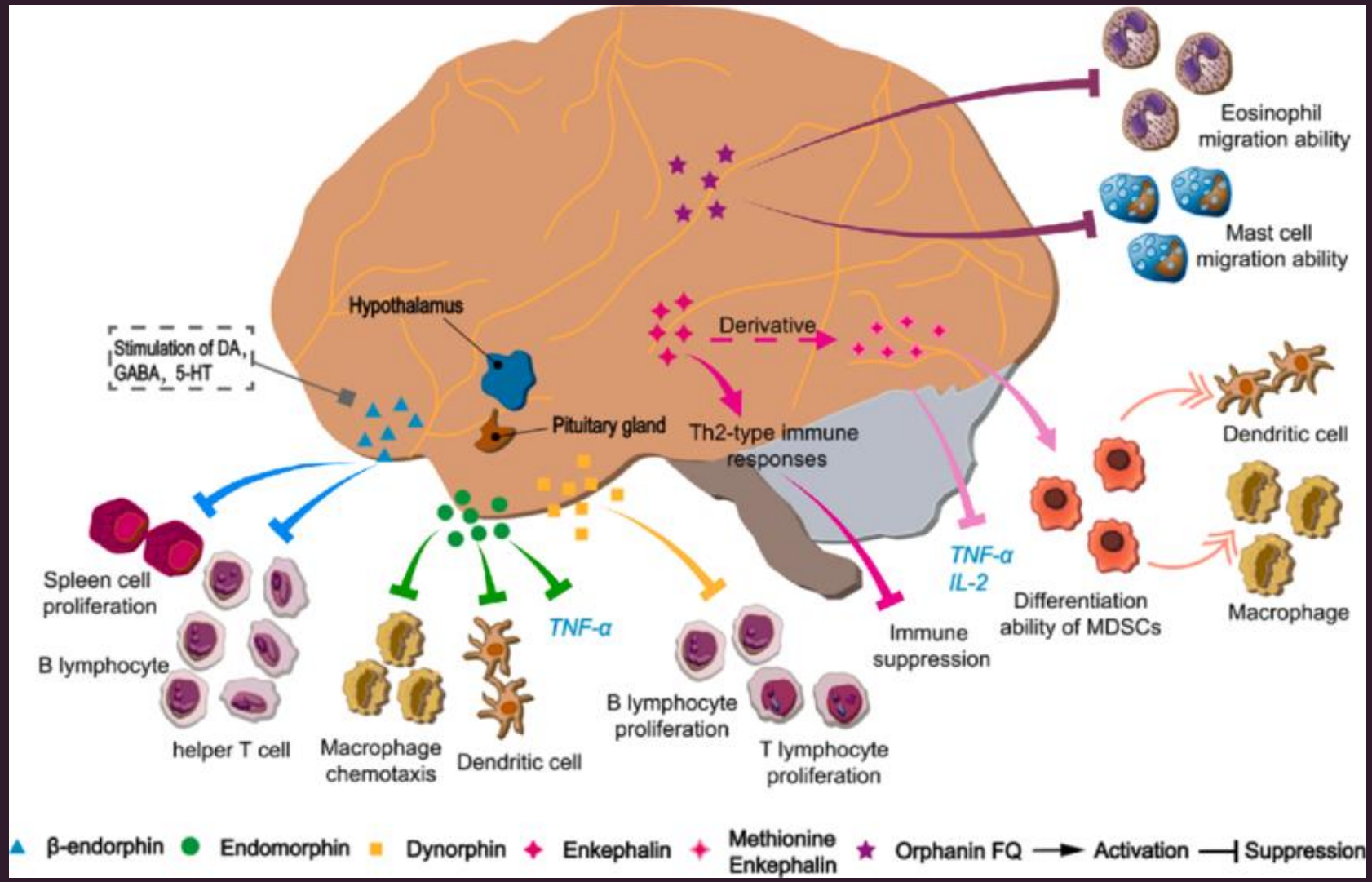
Effect of opiates on immune system in viral infection



- Mu opiod receptors modulate immune function
- Opiates suppress many important immune functions
- Endorphins and Enkephalins are endogenous mu-opiod agonists, so they produce similar effects

https://pubmed.ncbi.nlm.nih.gov/36179789/

Endogenous opioid functions



https://pubmed.ncbi.nlm.nih.gov/36179789/

LDN dosage and administration

- Begin at 0.5mg-1mg daily and titrate up weekly or bi-weekly as tolerated
- 1mg, 2mg, 3mg, 4mg etc
- Target dose is about 4.5-5mg daily
- Must be given at bedtime to work, preferably 11pm or so
- Plan on patients using for at least 6 months, you can’t assess effectiveness quickly
- Main side effect is insomnia, this is usually temporary

https://pubmed.ncbi.nlm.nih.gov/36179789/

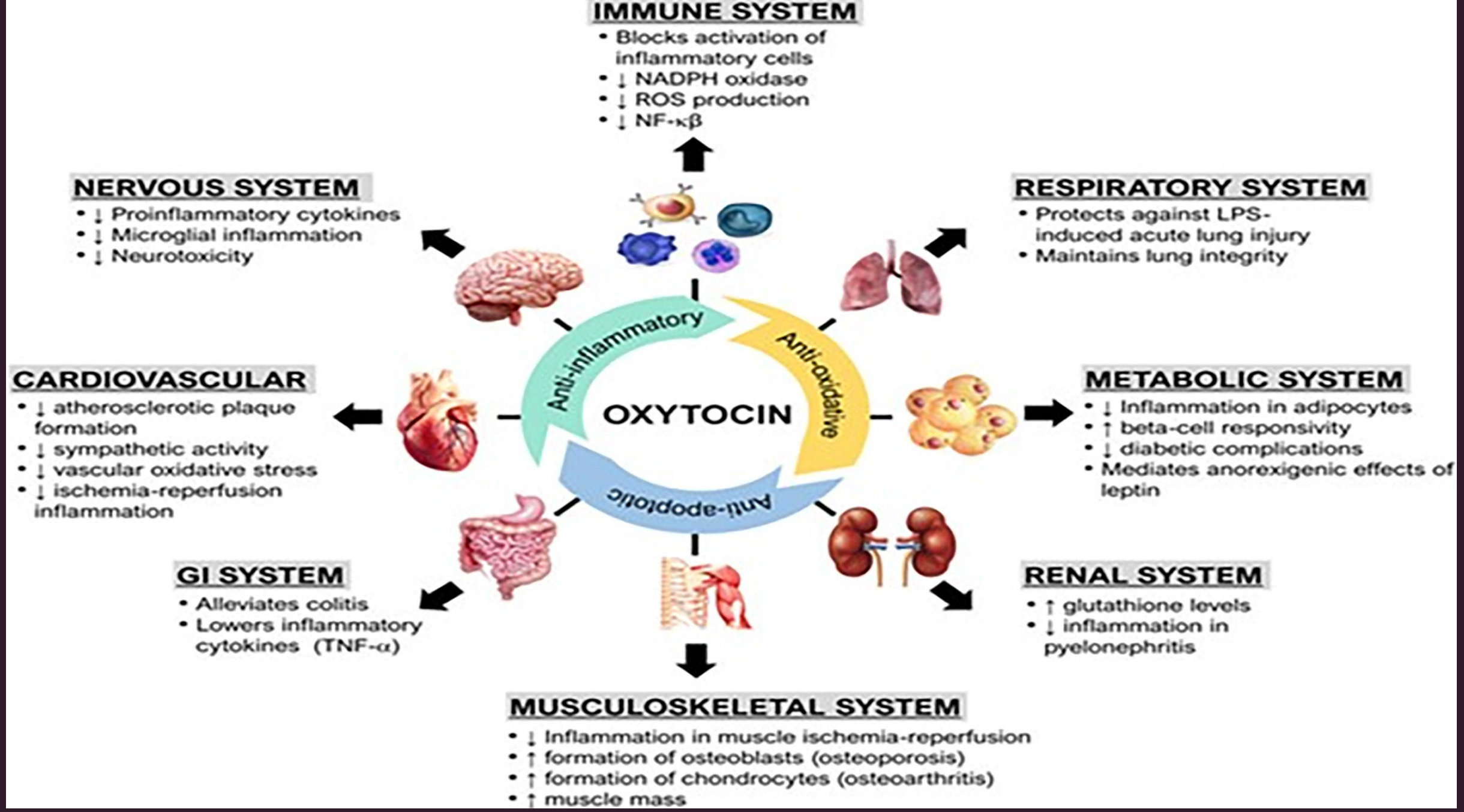
Oxytocin

https://pubmed.ncbi.nlm.nih.gov/36179789/

Oxytocin

- Oxytocin has a wide variety of functions, not just in childbirth/milk production
- ‘Abolishes’ sepsis induced TNF-a, inhibits NF-kB, IL6 and cortisol release in response to stress/infection
- Reduces innate immune response by suppression of TRL4
- Inhibits platelet aggregation, increases eNOS
- Up regulates PPAR-g (reduces inflammatory responses in macrophages)
- Decreases NADPH oxidase, thus increasing NADPH
- Cardioprotective
- Reduces mast cell activation

https://pubmed.ncbi.nlm.nih.gov/36179789/



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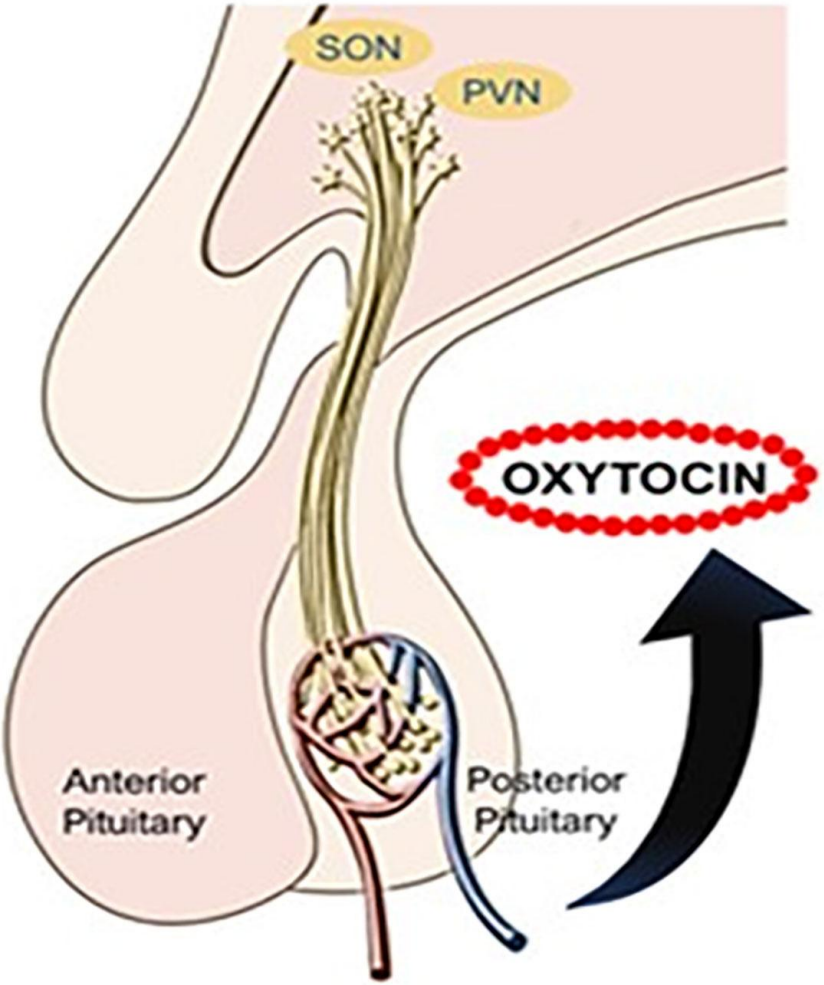
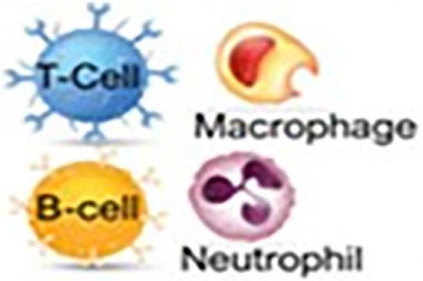
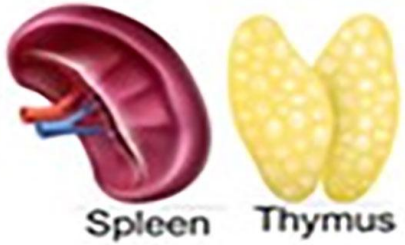
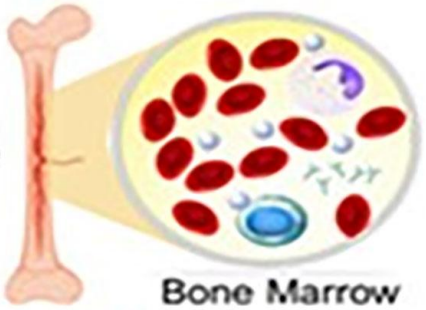




- ↓ IL-1, IL-1β, IL-2, IL-6, TNF-α, NF-κB
- ↓ neutrophils migration, MPO
- ↑ production of IL-10 from T-reg cells
- ↑ expression of PPAR-γ on macrophages
- ↑ IgG, IgM, IgA from B-cells



- ↑ thymic T-cells differentiation
- ↓ self-reactive T-cells
- ↑ growth of thymus gland
- ↑ pathogen clearance from spleen
- ↑ coordination between T and B cells



- ↑ mesenchymal stromal cells
- ↑ formation of blood cell lineages
- ↑ differentiation of HSCs
- ↑ transport of HSCs to lymphatic organs
- ↑ osteoblastic activity

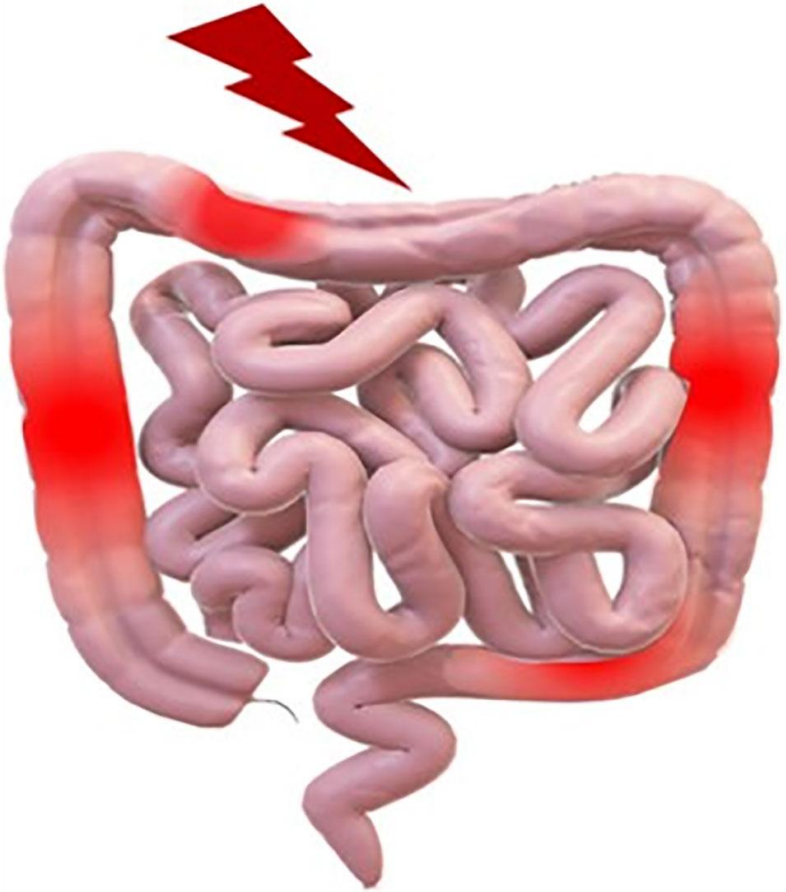
- ↑ cholinergic outflow
- ↓ sympathetic outflow
- ↑ release of nitric oxide
- ↑ prostacyclin release
- ↓ ACTH, TSH

https://www.frontiersin.org/articles/10.3389/fimmu.2022.864007/full

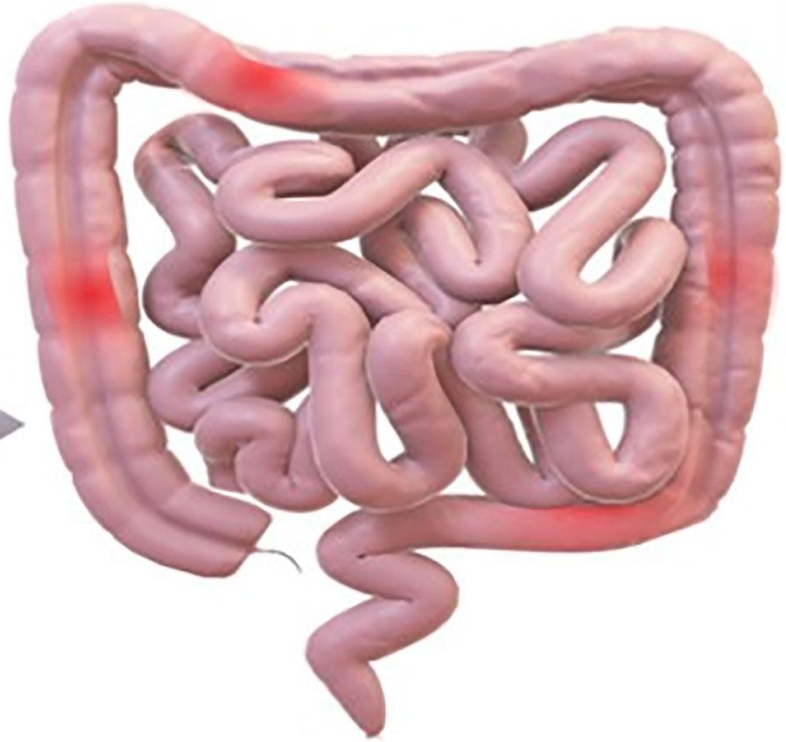
Oxytocin

stress, thermal damage
dextran sodium sulphate

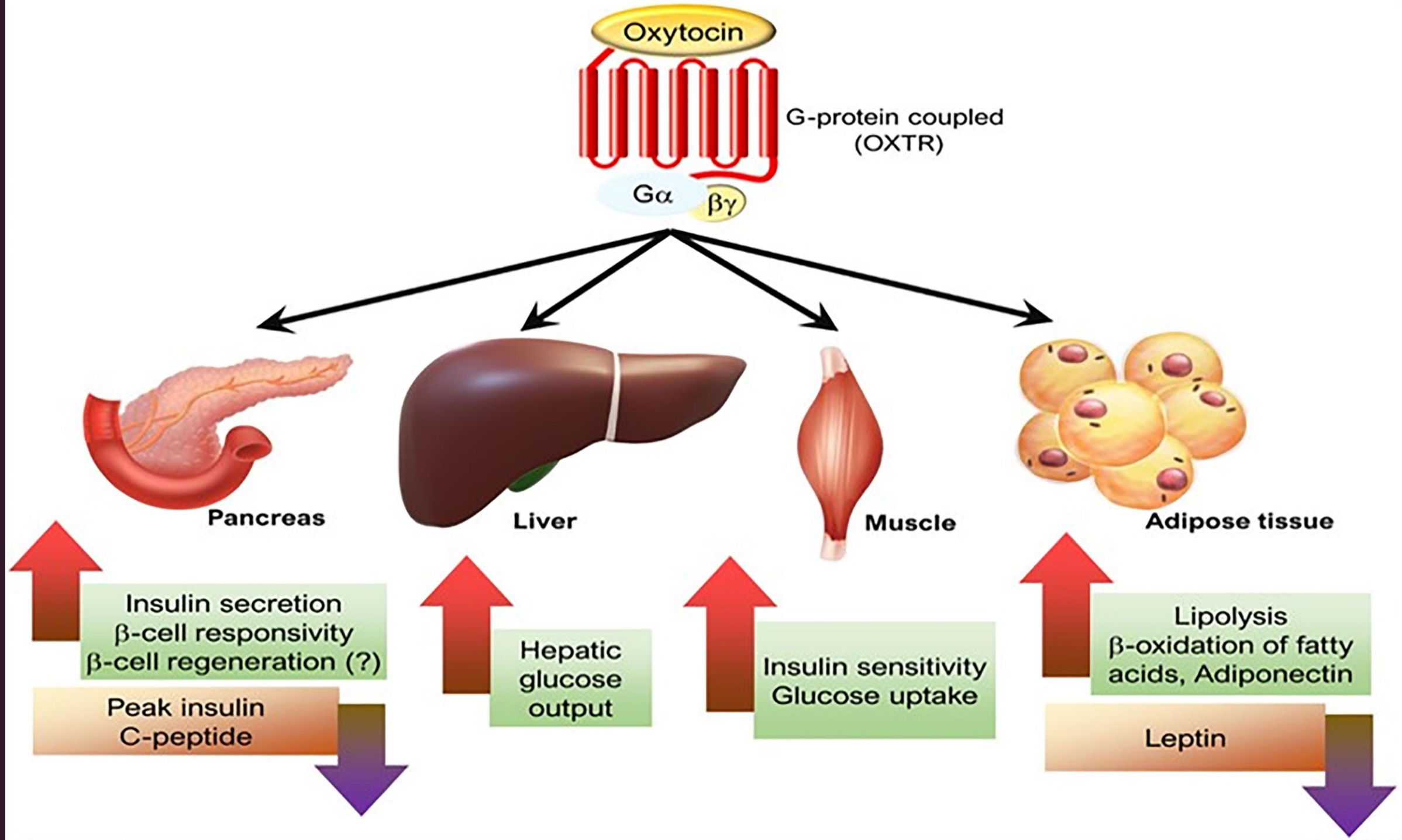
↓ NF-Kβ signaling
↓ TNF-α, MPO, MDA, LDH
↓ Inflammatory cells (e.g., PMNs)
↑ GSH levels
↑ M2 type of cells
↓ Anxiety-like behavior

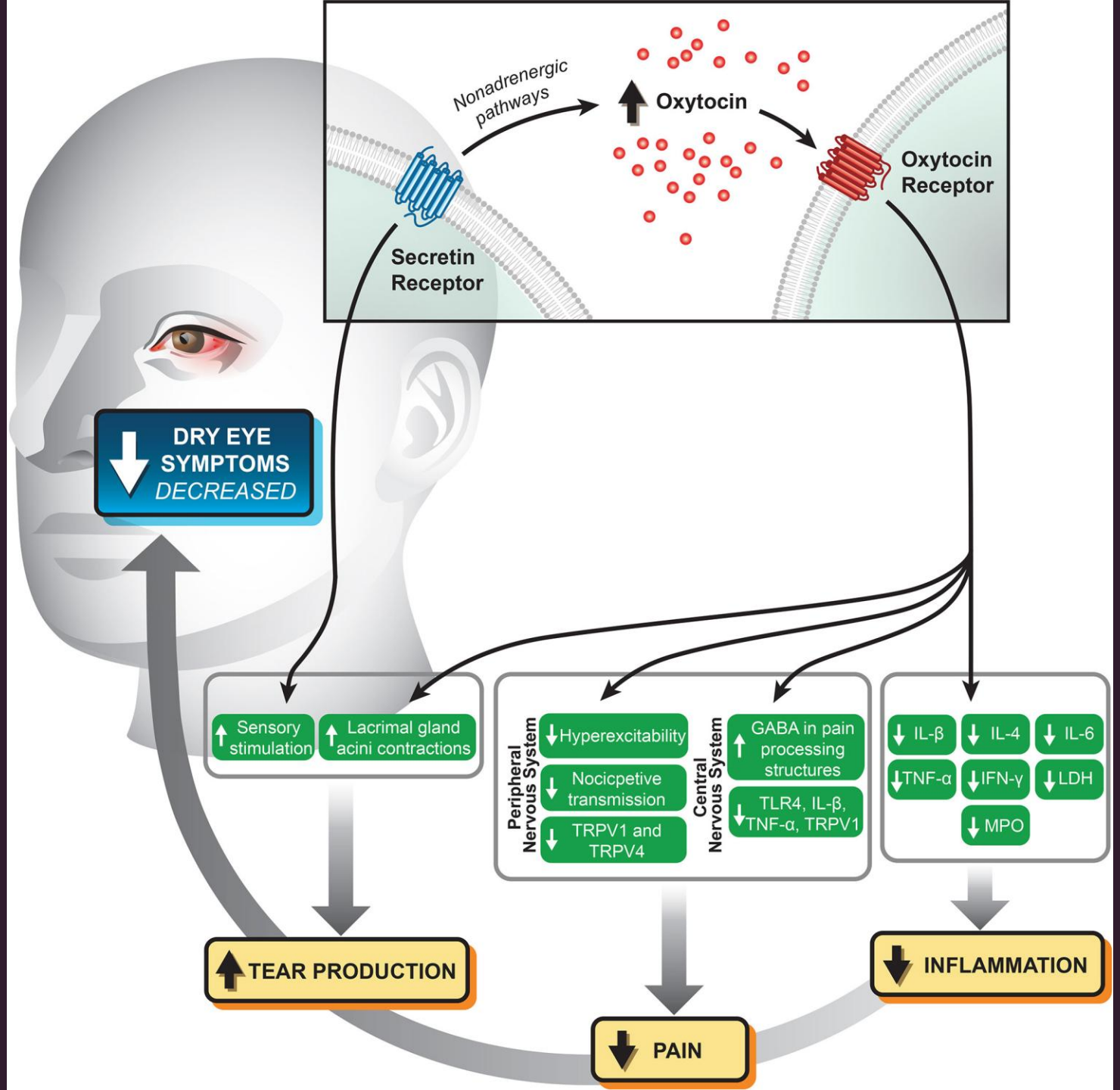


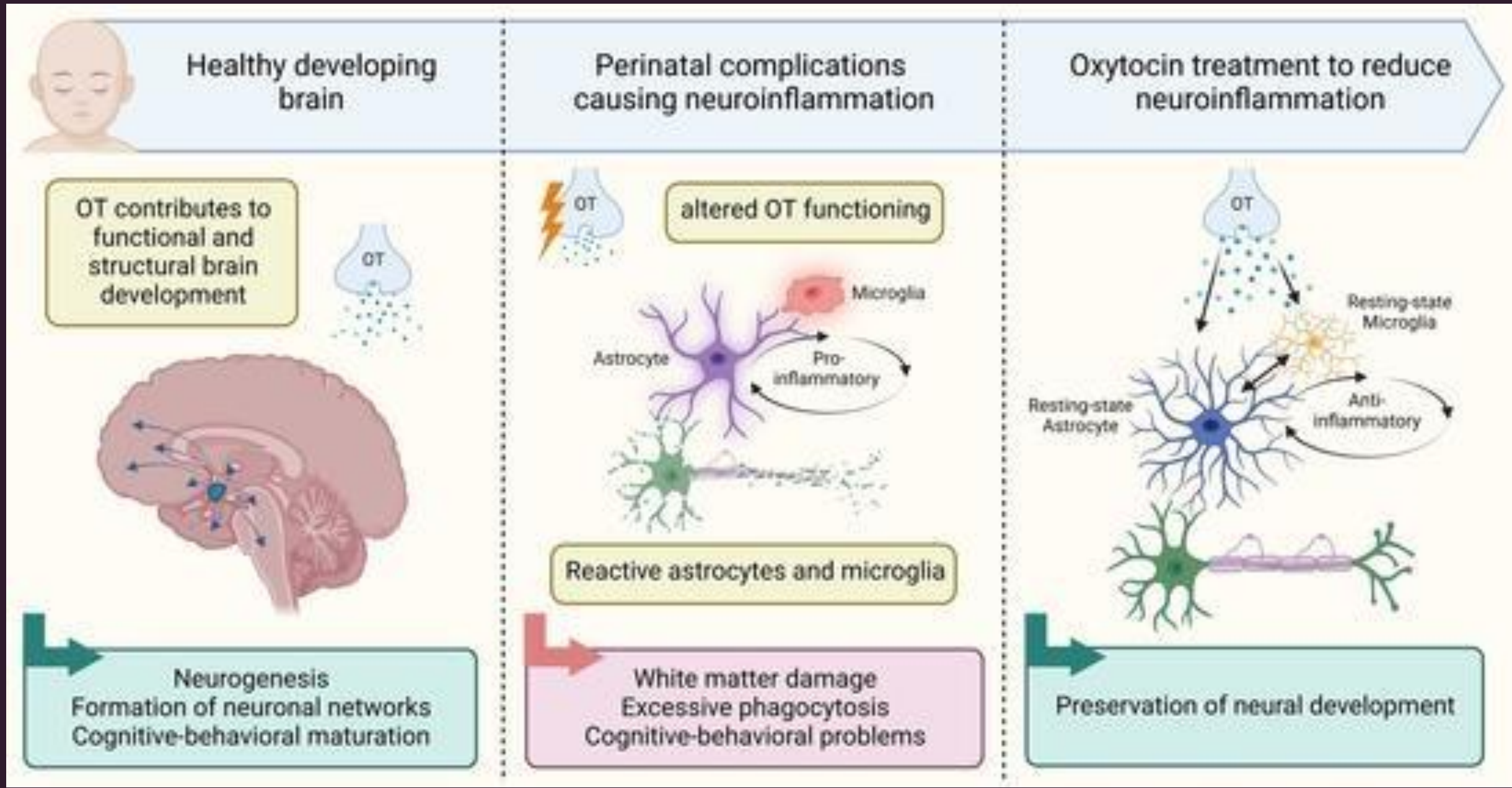
UNTREATED COLITIS



TREATED COLITIS


Oxytocin
G-protein coupled
(OXTR)
Gα
βγ
Pancreas
Liver
Muscle
Adipose tissue
Insulin secretion
β-cell responsivity
β-cell regeneration (?)
Peak insulin
C-peptide
Hepatic
glucose
output
Insulin sensitivity
Glucose uptake
Lipolysis
β-oxidation of fatty
acids, Adiponectin
Leptin


Nonadrenergic pathways
Oxytocin
Oxytocin Receptor
Secretin Receptor
DRY EYE SYMPTOMS DECREASED
Sensory stimulation
Lacrimal gland acini contractions
Peripheral Nervous System
Hyperexcitability
Nocicpetive transmission
TRPV1 and TRPV4
Central Nervous System
GABA in pain processing structures
TLR4, IL-β, TNF-α, TRPV1
IL-β
IL-4
IL-6
TNF-α
IFN-γ
LDH
MPO
TEAR PRODUCTION
PAIN
INFLAMMATION



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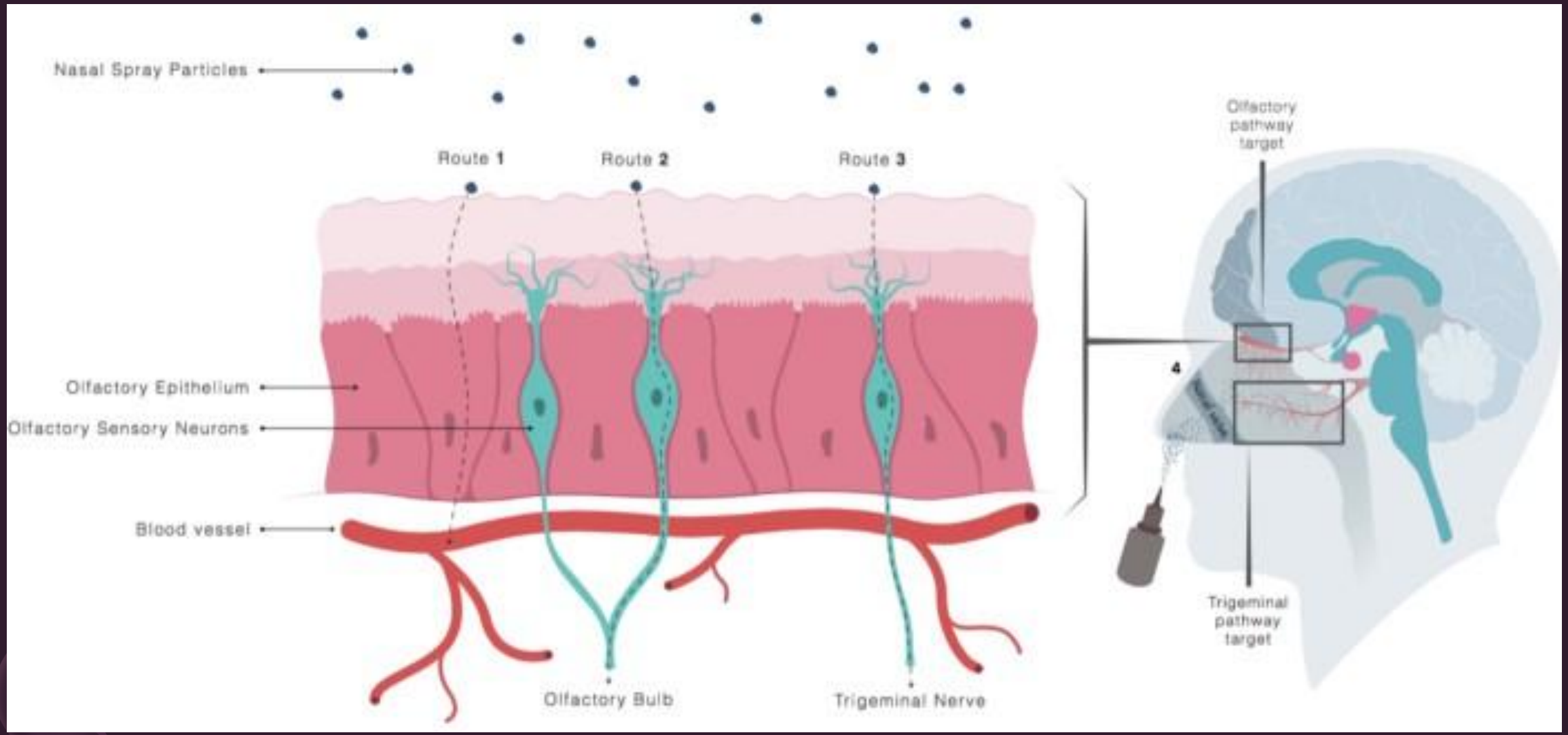
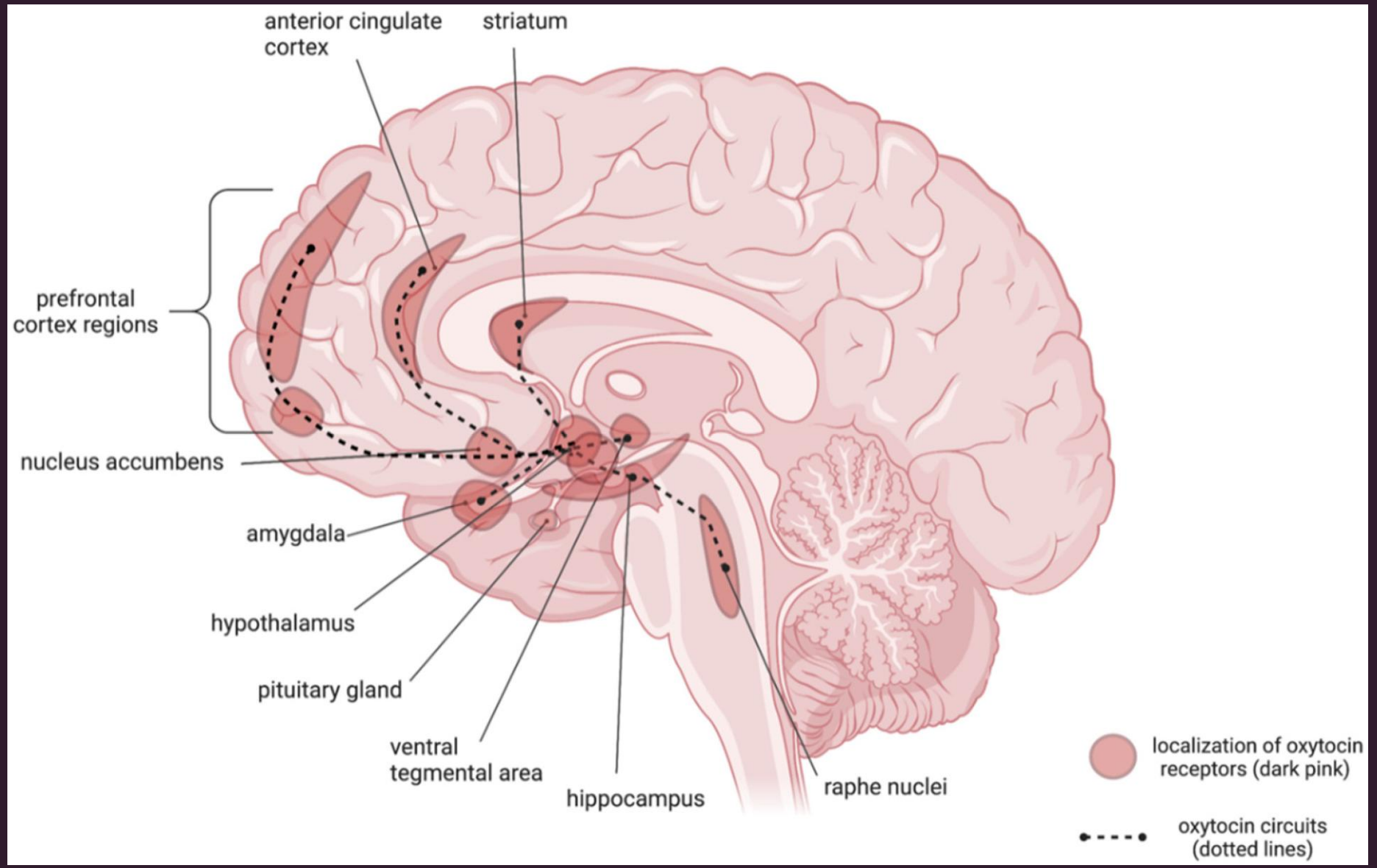
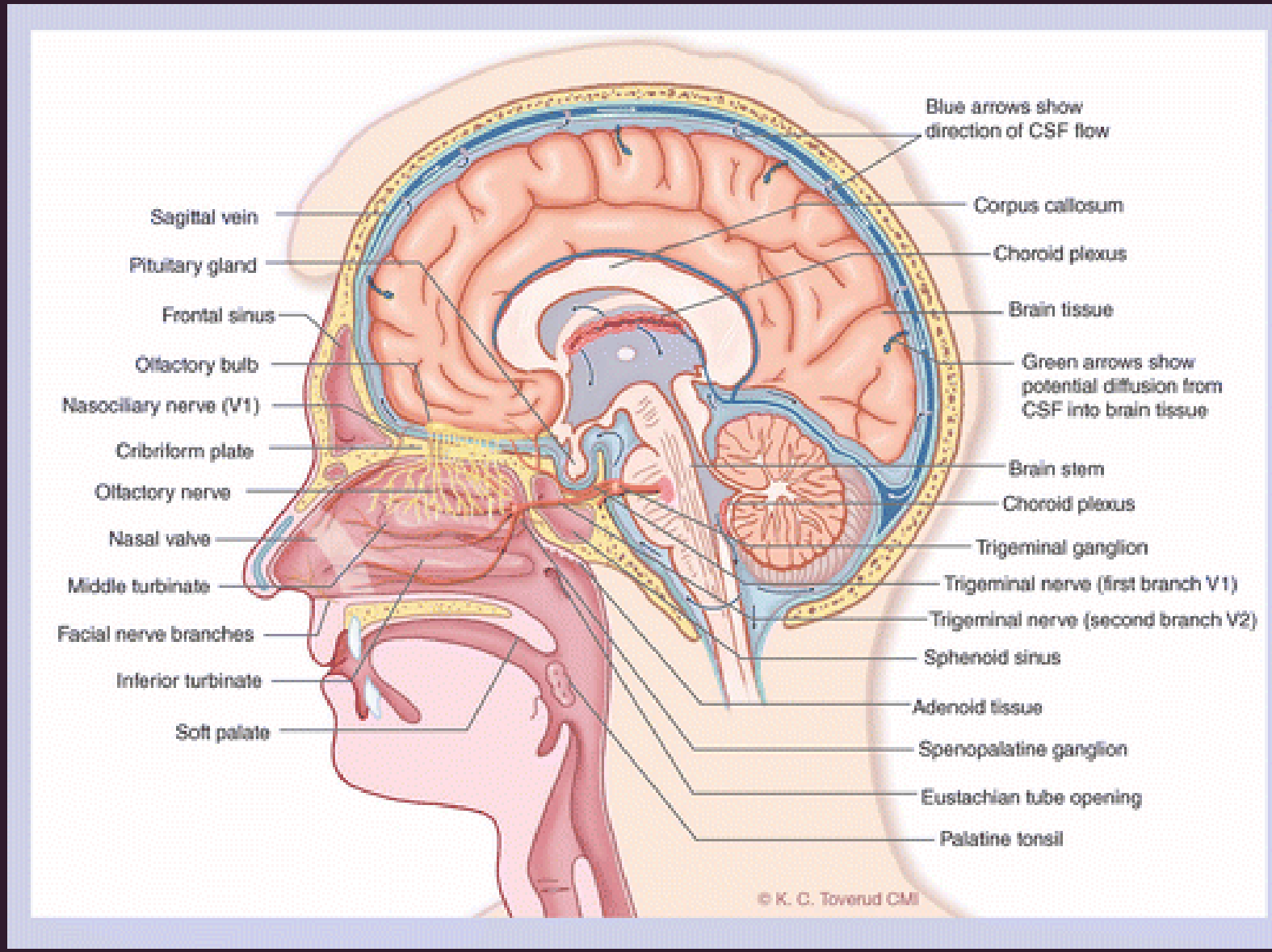

Nasal Spray Particles
Route 1
Route 2
Route 3
Olfactory Epithelium
Olfactory Sensory Neurons
Blood vessel
Olfactory Bulb
Trigeminal Nerve
Olfactory pathway target
4
Trigeminal pathway target

Key anatomical structures involved

- Olfactory receptor neurons extend to the mucous layer of the olfactory epithelium
- Olfactory fibers pass through small openings the cribriform plate, passing through the subarachnoid space and terminating in the olfactory bulbs. These are unsheathed bundles of @1000 olfactory nerve fibers providing an uninterrupted pathway from the nasal epithelium to the CNS.
- This is not a highly efficient pathway, mainly due to anatomical barriers,
- Likely less than 5% bioavailable to target areas in the brain, but this is sufficient for clinical effects
- Intracellular transport has an effect but takes hours, not minutes.
- The nasociliary branch of the ophthalmic division of the trigeminal nerve also has neurons that reach the olfactory bulb similarly to the olfactory nerves.
- Oxytocin in CSF has increased after nasal administration in rodents, monkey and human studies, but it is not fully proven that the cribriform/neuronal transport is the only mechanism operating
- Intranasal administration does also result in increased peripheral levels but this does not readily cross back over the BBB.
- Signaling from peripheral Oxytocin receptive tissues in GI, endothelium may also send feedback to the CNS

https://www.mdpi.com/2075-4426/12/7/1067/htm




Blue arrows show direction of CSF flow
Sagittal vein
Corpus callosum
Pituitary gland
Choroid plexus
Frontal sinus
Brain tissue
Olfactory bulb
Green arrows show potential diffusion from CSF into brain tissue
Nasociliary nerve (V1)
Cribriform plate
Brain stem
Olfactory nerve
Choroid plexus
Nasal valve
Trigeminal ganglion
Middle turbinate
Trigeminal nerve (first branch V1)
Facial nerve branches
Trigeminal nerve (second branch V2)
Sphenoid sinus
Inferior turbinate
Adenoid tissue
Soft palate
Spenopalatine ganglion
Eustachian tube opening
Palatine tonsil
© K. C. Toverud CMI

Studies done to date include

- Sexual Performance/pleasure
- Autism
- Borderline Personality Disorder
- PTSD
- Schizophrenia
- Inflammation
- Pain
- Weight control
- Dementia
- Age related cognitive decline

Challenges/Questions?

- Oxytocin has a wide but definite therapeutic window. 24u to 200u/daily in divided doses
- Oxytocin works differently when administered intranasally to the brain as opposed to peripherally by injection, crossing the BBB is essentially a one-way street brain to body
- The target tissue is deep in the nasal cavity and difficult to reach with mechanical spray pumps, spraying the anterior nasal cavity is not effective for CNS therapy. Does the dosage device deliver a predictable dose?
- We have quantitative (measurements) evidence that the drug crosses the BBB and reaches the target tissue?
- We have qualitative (expected effects) evidence that the drug is having the expected effect based on the proposed mechanism
- No serious side effects been reported regarding the drug administered

Dosage and Administration

- Intranasal works, SL does not and SQ works differently
- Intranasal dose is 12u sprayed in each nostril once daily at bedtime.
- May increase to am and pm if no response after 5 days of use.
- A safe max dose is is 2 sprays in each nostril 3 times daily (75 units still far less than the 200u/day max)
- Be sure that the nasal passages are open prior to administration
- Main noted side effect is drippy nose, increases nasal secretions

https://pubmed.ncbi.nlm.nih.gov/36179789/

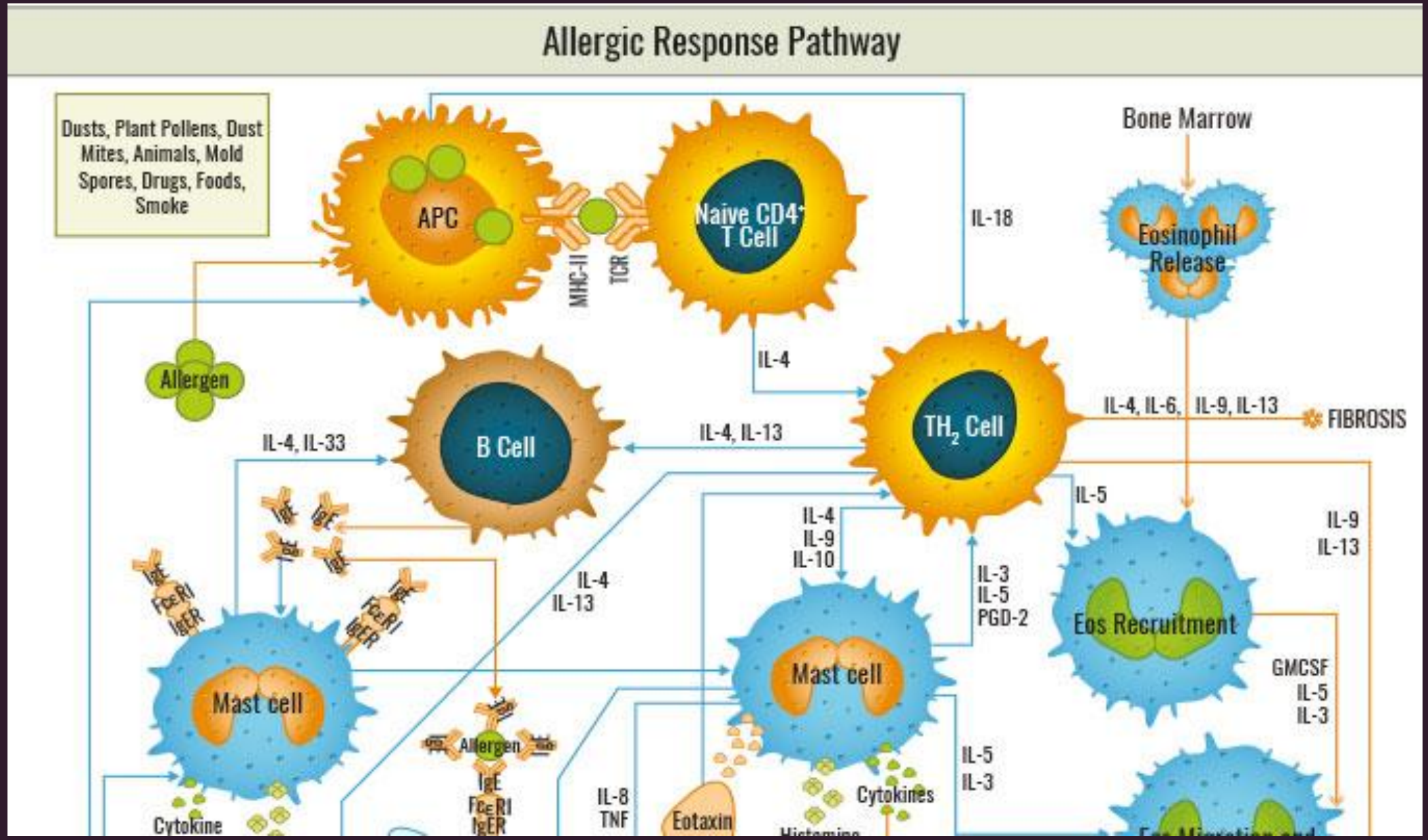
Amlexanox

https://pubmed.ncbi.nlm.nih.gov/36179789/

Amlexanox

- Amlexanox is an FDA approved drug for atopic apthous ulcers that has no current product in production
- Atopia is defined as a TH2/Th17 hyper polarization that results in excessive IgE production in response to an antigen
- It is under study for inflammatory and allergic conditions as well as type 2 diabetes and obesity
- Potent inhibitor of TBK1 and IKK-e
- Ultimately, inhibits NF-kB, mTOR, regulates macrophages, mast cells and T cells.
- Suppresses TH17 and TH2, still need to use IFNg or Ta1 to stimulate TH1
- Stimulates AMPK, helps with diabetes management
- TBK1 regulates innate immunity, inflammatory cytokine production, autophagy, mitochondrial metabolism
- In innate immune system, TBK1 mediates pathogen detection signals and IFN response to infection
- Mast cell stabilizer

https://pubmed.ncbi.nlm.nih.gov/36179789/



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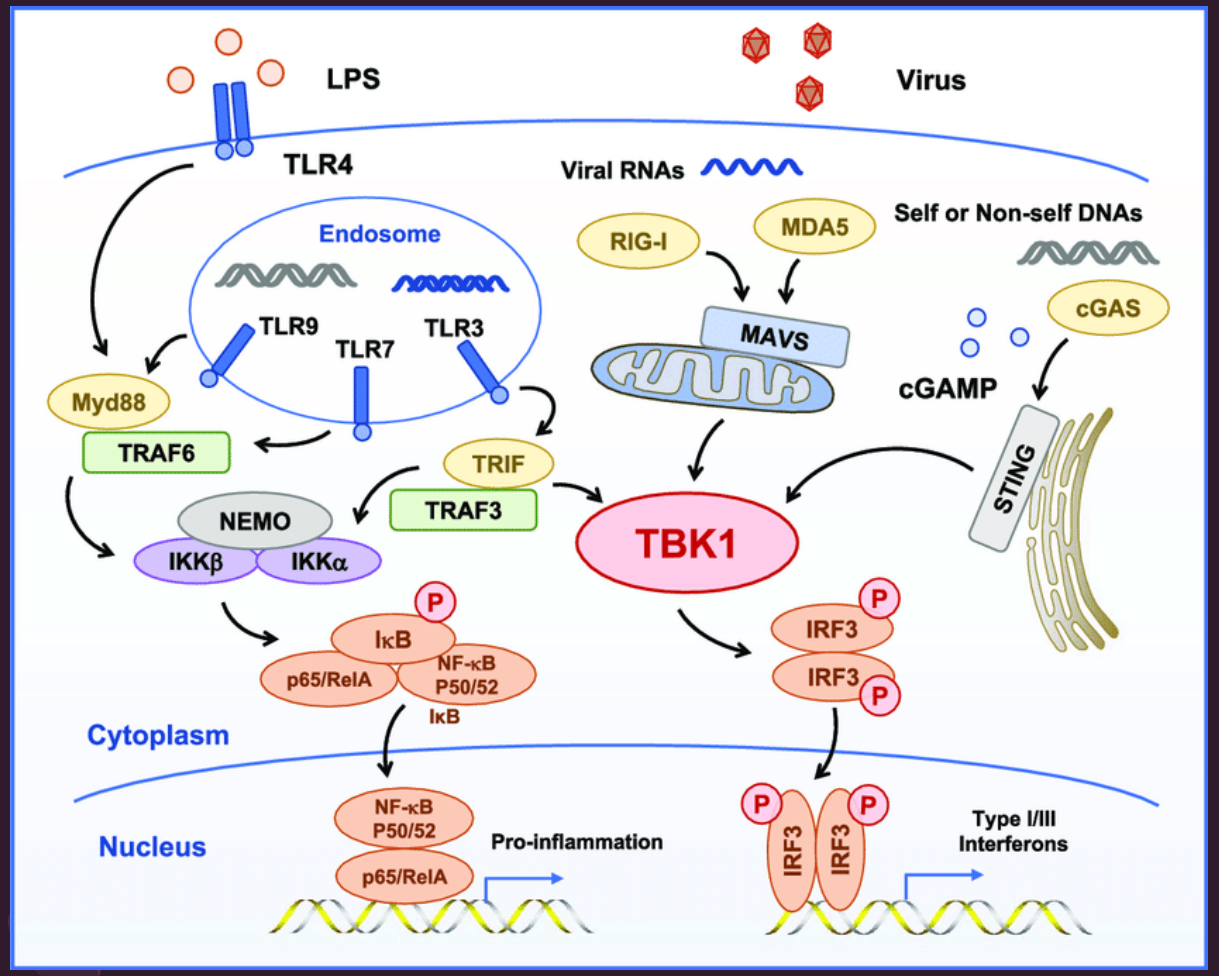
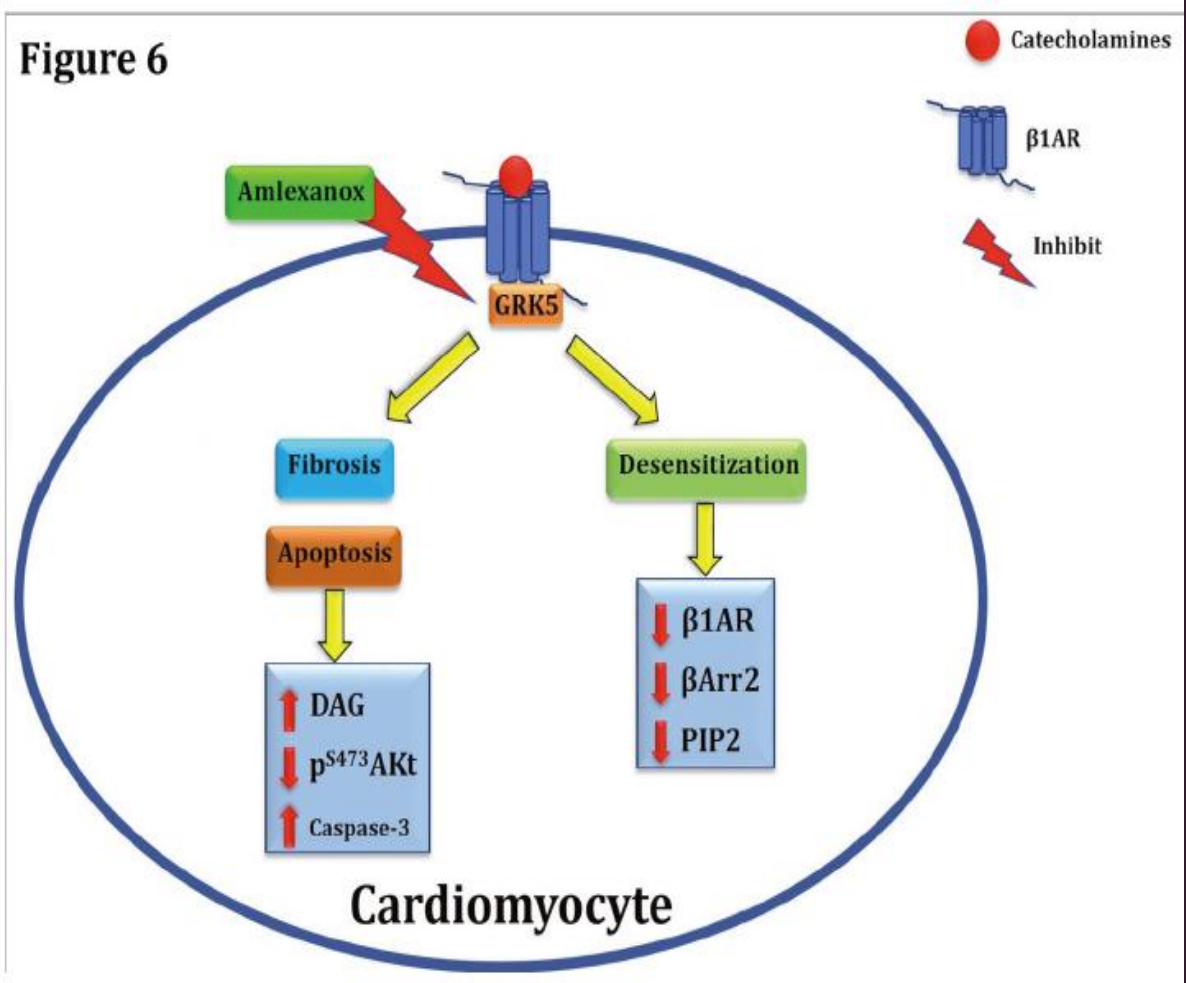
Innate immune system regulation



- Amlexanox modifies the innate immune response by suppressing the downstream effects of TLR4 activation at TBK1/IKKa

https://pubmed.ncbi.nlm.nih.gov/36179789/

Cardioprotective effects

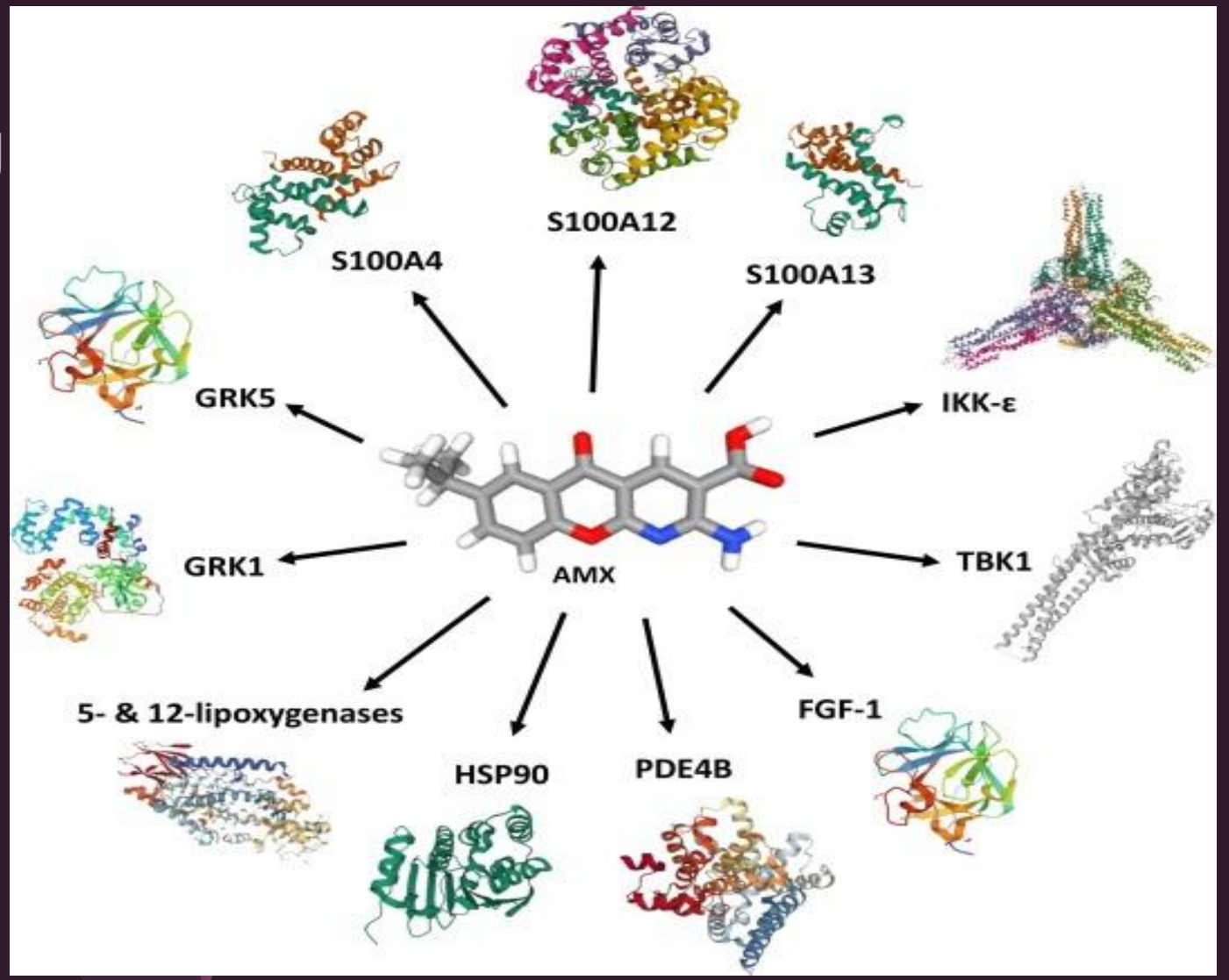


- Amlexanox has been shown to have cardioprotective effects.
- Proposed mechanism is inhibition of GRK5 mediated fibrosis and reduction in apoptosis
- GRK=G-protein receptor kinase

https://www.scielo.br/j/bjps/a/yZTVggCn8K8VWKDmyLt3SVs/?lang=en#

Amlexanox in Cancers

Amlexanox is a potent kinase inhibitor, blocking phosphorylation of at least 10 proteins/enzymes associated with cancer growth



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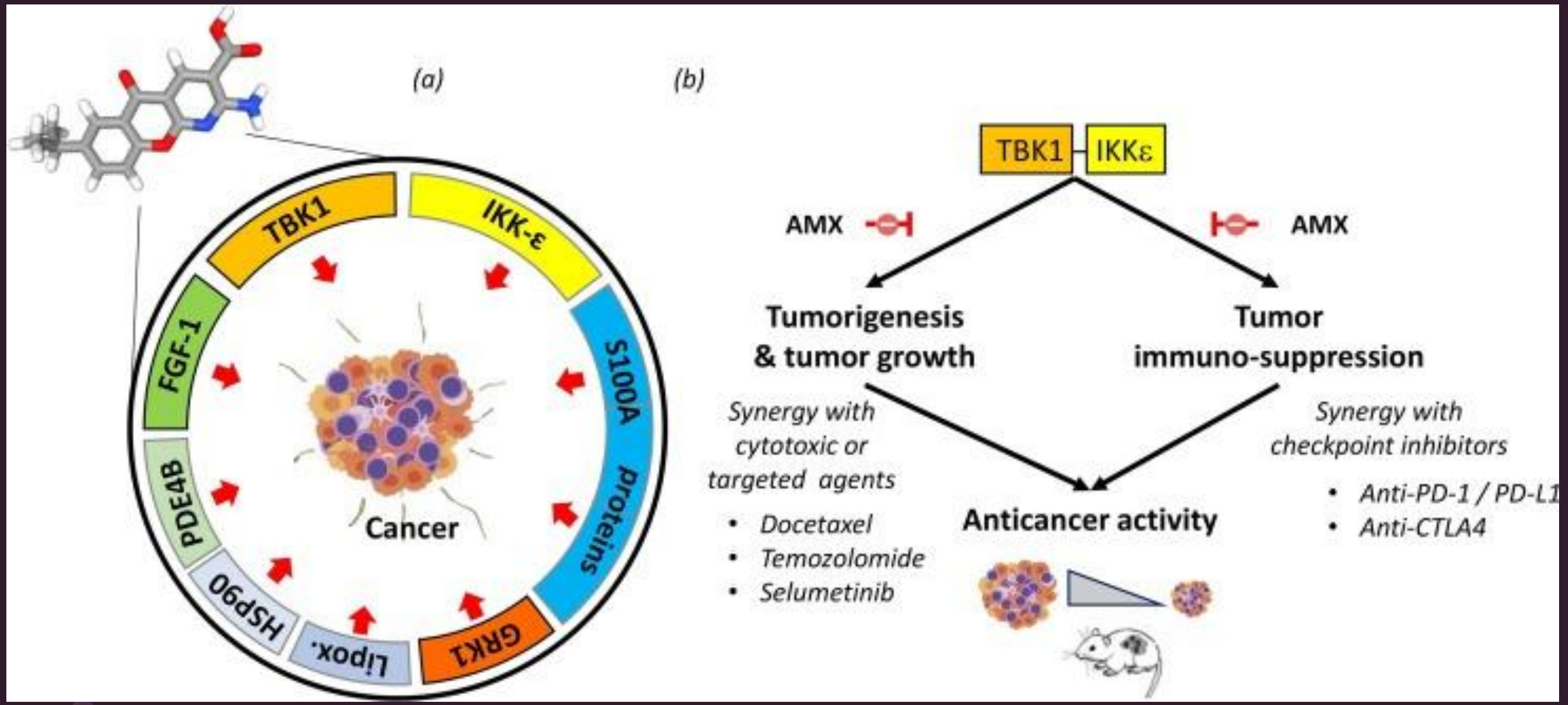

https://pubmed.ncbi.nlm.nih.gov/36179789/

Amlexanox Dosage and Administration

- Dosage is 3 times daily or every 8 hours
- Typical dosage is 40-50mg TID
- We stock 20mg, 30mg, 40mg and 50mg Capsules
- Topicals should be prescribed at 2%
- We have had no reports of side effects thus far

https://pubmed.ncbi.nlm.nih.gov/36179789/