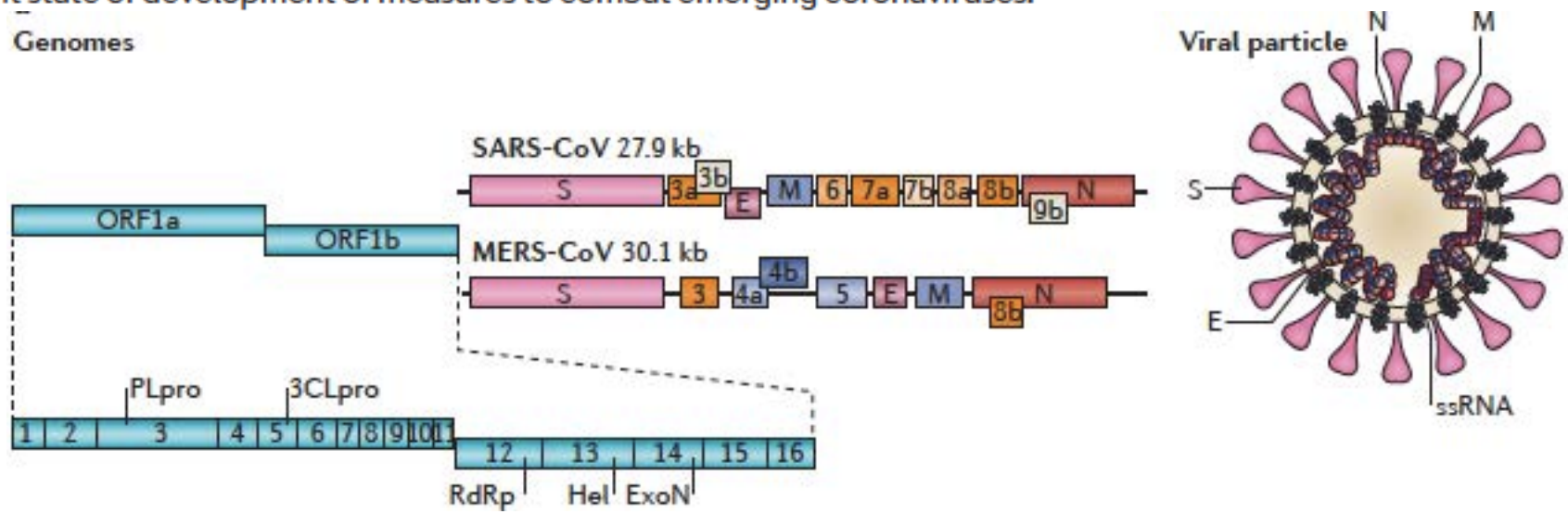
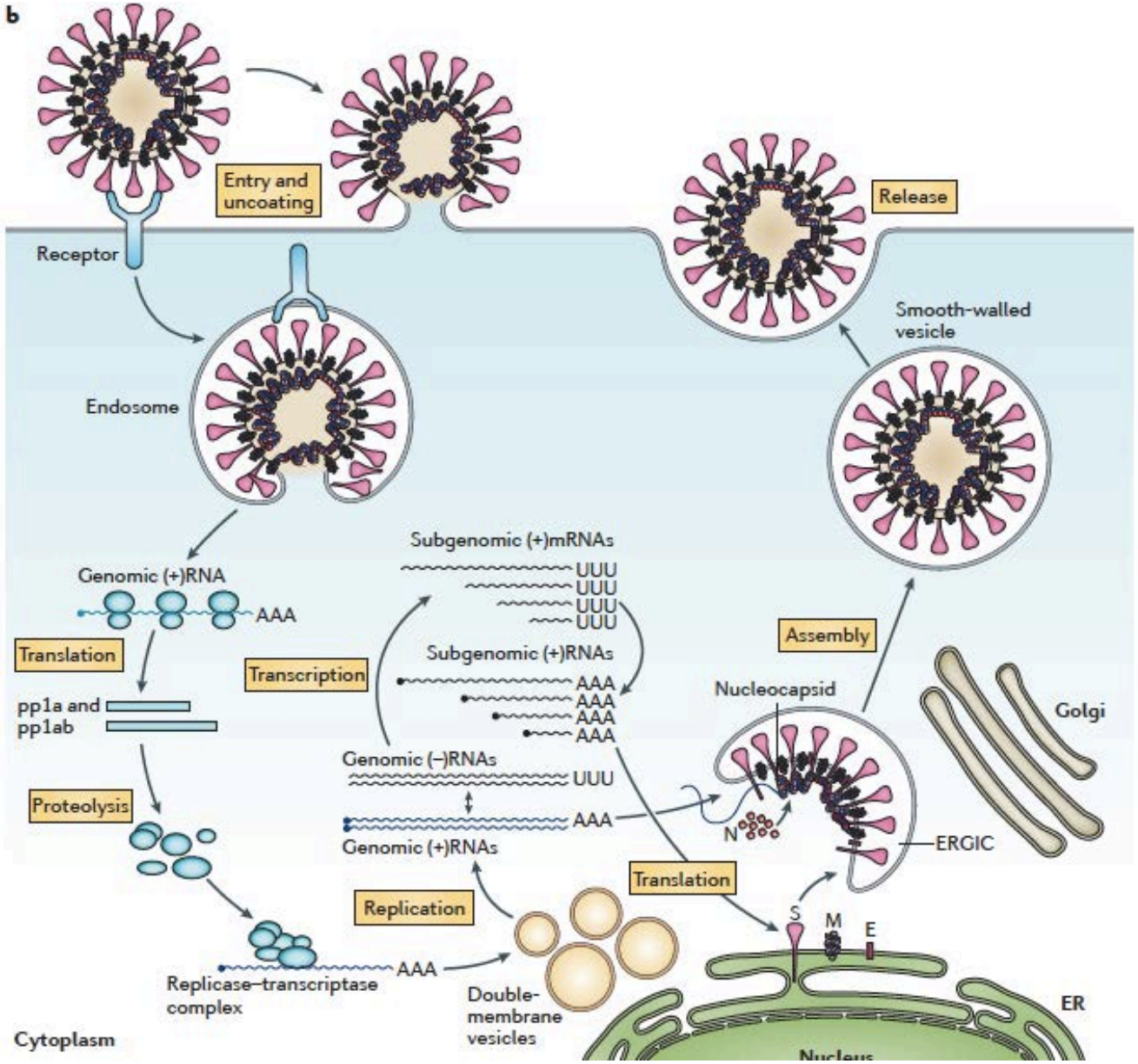
SARS and MERS: recent insights into emerging coronaviruses

Emmie de Wit[1], Neeltje van Doremalen[1], Darryl Falzarano[2] and Vincent J. Munster[1]

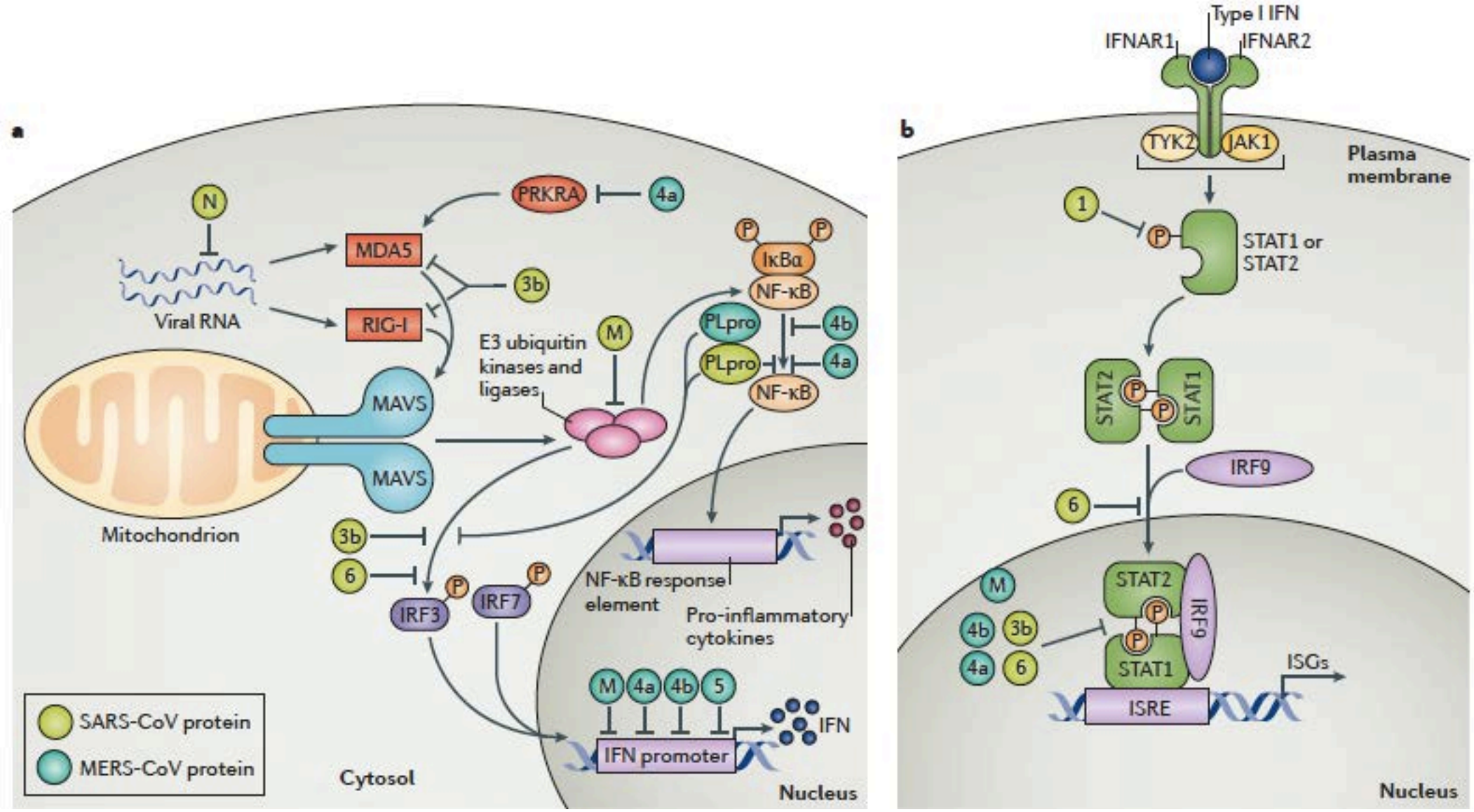
Abstract | The emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 marked the second introduction of a highly pathogenic coronavirus into the human population in the twenty-first century. The continuing introductions of MERS-CoV from dromedary camels, the subsequent travel-related viral spread, the unprecedented nosocomial outbreaks and the high case-fatality rates highlight the need for prophylactic and therapeutic measures. Scientific advancements since the 2002–2003 severe acute respiratory syndrome coronavirus (SARS-CoV) pandemic allowed for rapid progress in our understanding of the epidemiology and pathogenesis of MERS-CoV and the development of therapeutics. In this Review, we detail our present understanding of the transmission and pathogenesis of SARS-CoV and MERS-CoV, and discuss the current state of development of measures to combat emerging coronaviruses.



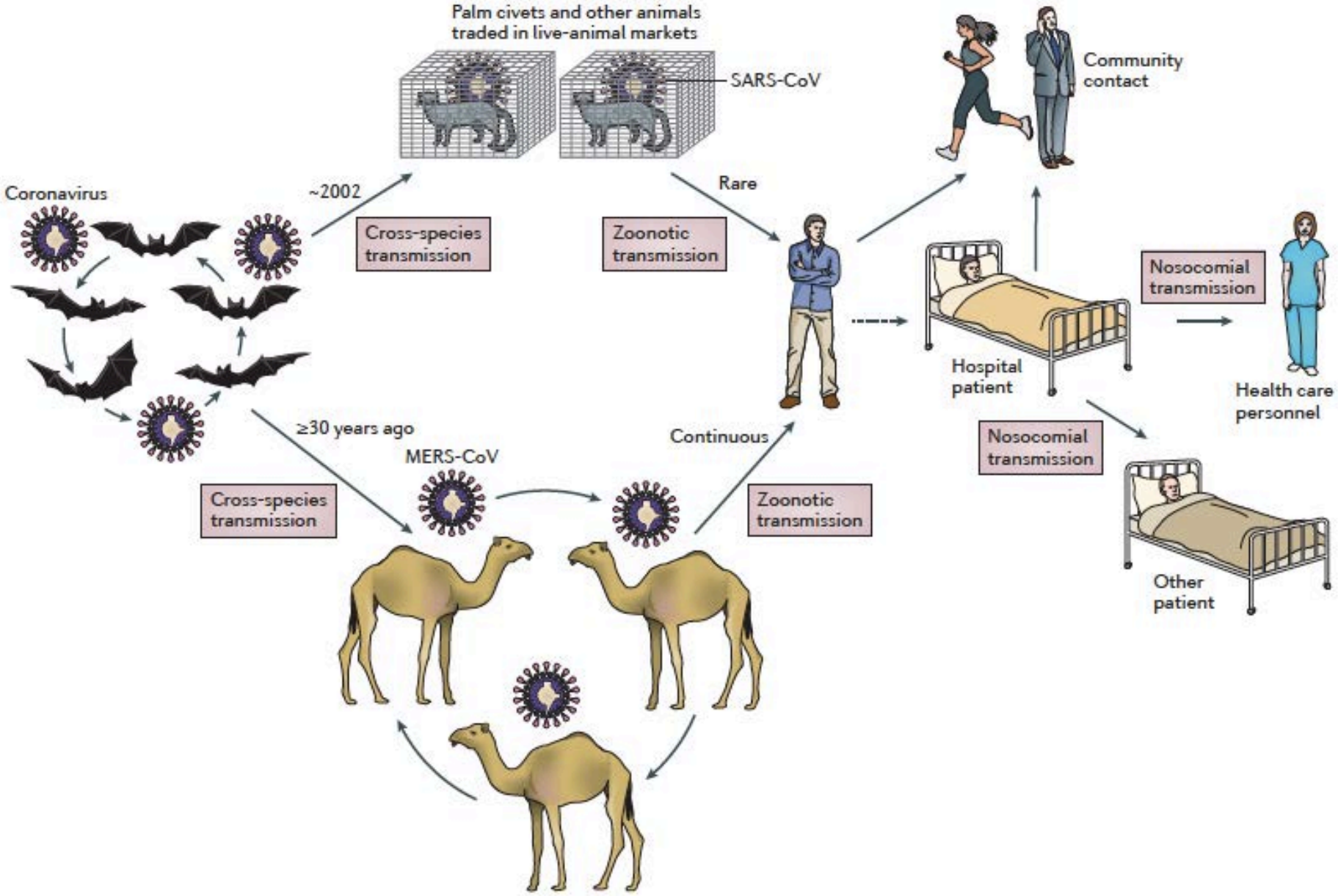
SARS-CoV and MERS-CoV Replication



Evasion of the innate Immune Response by SARS-CoV and MERS-CoV



Emergence of SARS-CoV and MERS-CoV: Bats and Camels harbor many strains of Coronaviruses



Coronavirus outbreak raises question: Why are bat viruses so deadly?

It's no coincidence that some of the worst viral disease outbreaks in recent years — SARS, MERS, Ebola, Marburg and likely the newly arrived COVID-19 virus — originated in bats.

- Generally, vigorous physical activity high metabolic rates lead to higher tissue damage due to an accumulation of reactive molecules, primarily free radicals.

- key trick of many bats' immune systems is the hair-trigger release of a signaling molecule called interferon-alpha, which tells other cells to "man the battle stations" before a virus invades

The Australian black flying fox is a reservoir of Hendra virus, which can be transmitted to horses and sometimes humans.

Premarin= old hormone therapy drug made from **Pre**gnant **Mar**e Uri**ne**:

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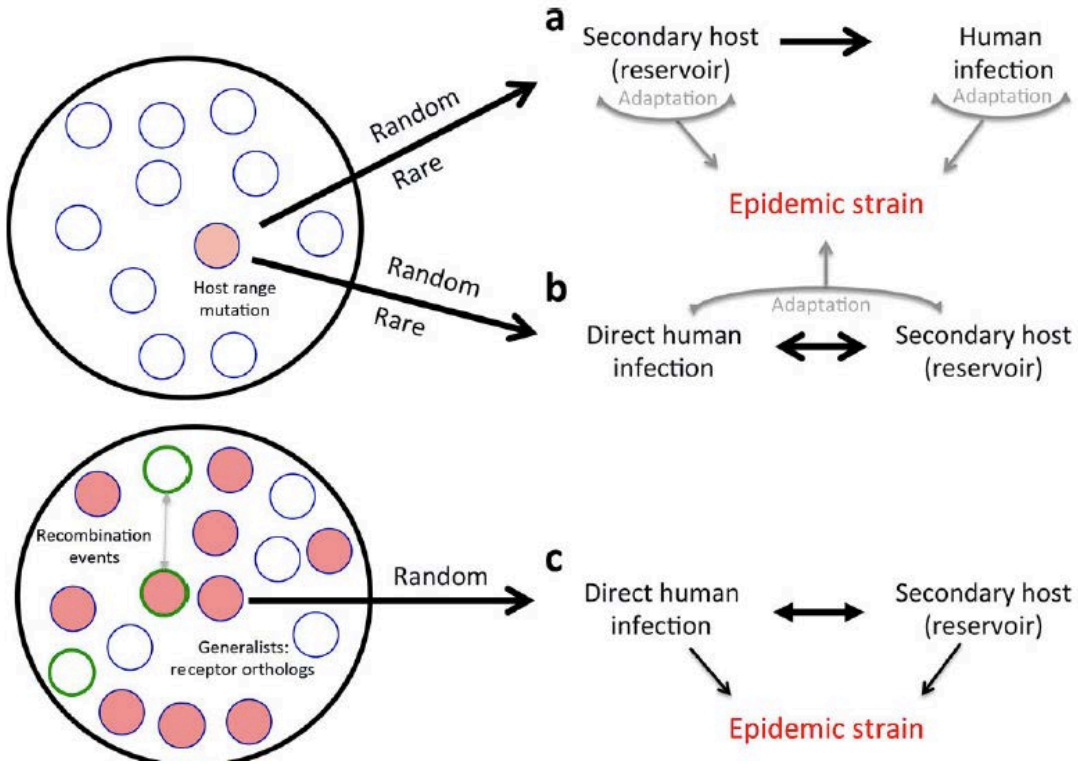
Nat Med. 2015 December ; 21(12): 1508–1513. doi:10.1038/nm.3985.

SARS-like cluster of circulating bat coronavirus pose threat for human emergence



Emergence Paradigms for Coronaviruses

Did coronavirus originate in Chinese government laboratory? | Daily Mail Online 2/18

- **Beijing-sponsored South China University of Technology concludes that 'the killer coronavirus probably originated from a laboratory in Wuhan'**
- **It points to research on bats and respiratory diseases carried by the animals at the Wuhan Center for Disease Control and the Wuhan Institute of Virology**
- **WCDC is just 300 yards from the seafood market and is adjacent to the hospital**

Vaccine Excipient & Media Summary

Excipients Included in U.S. Vaccines, by Vaccine

This table includes not only vaccine ingredients (e.g., adjuvants and preservatives), but also substances used during the manufacturing process, including vaccine-production media, that are removed from the final product and present only in trace quantities.
In addition to the substances listed, most vaccines contain Sodium Chloride (table salt).

Last Updated September 2013

All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers may change product contents before that information is reflected here. If in doubt, check the manufacturer's package insert.

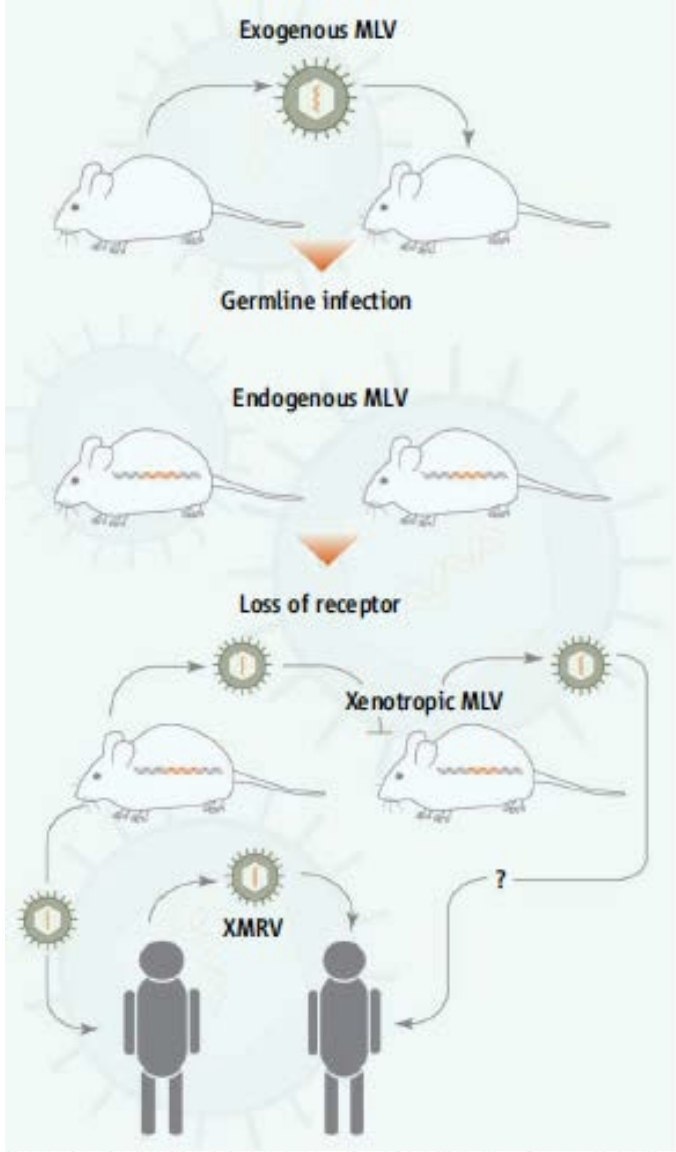
DTaP-HepB-IPV (Pediarix)	formaldehyde, gluteraldehyde, aluminum hydroxide, aluminum phosphate, lactalbumin hydrolysate, polysorbate 80, neomycin sulfate, polymyxin B, yeast protein, calf serum, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium, Vero (monkey kidney) cells	August, 2012
DTaP-IPV/Hib (Pentacel)	aluminum phosphate, polysorbate 80, formaldehyde, gutaraldehyde, bovine serum albumin, 2-phenoxethanol, neomycin, polymyxin B sulfate, Mueller's Growth Medium, Mueller-Miller casamino acid medium (without beef heart infusion), Stainer-Scholte medium (modified by the addition of casamino acids and dimethyl-beta-cyclodextrin), MRC-5 (human diploid) cells, CMRL 1969 medium (supplemented with calf serum), ammonium sulfate, and medium 199	July, 2012

VIROLOGY

A New Virus for Old Diseases?

A retrovirus associated with cancer is linked to chronic fatigue syndrome.

John M. Coffin[1] and Jonathan P. Stoye[2]



2009 Emergence of XMRVS : Zoonosis

- Transmission via to susceptible Humans via contaminated blood supply
- Transmission via Inoculation of proviruses vial contaminated vaccines
- Susceptible too young to have fully developed RNASEL immunity
- Or have mutations in the RNASEL R462Q..Prostate cancer susceptibility
- And MMR injury susceptibility

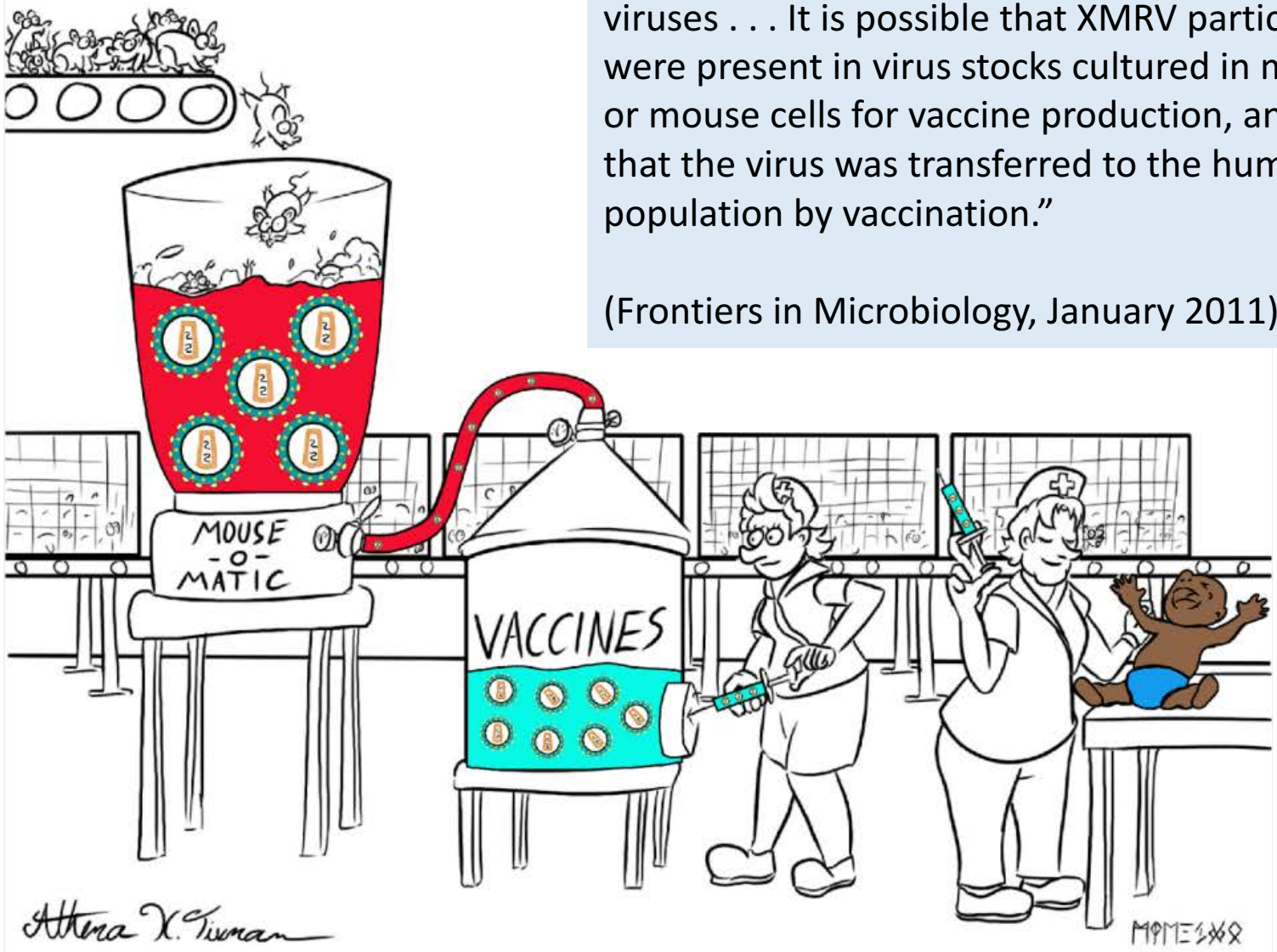
- Cow blood (Bovine Leukemia Virus) in most vaccines
- Pig retroviruses (Rotateq)
- Vero Monkey Kidney Cells (SIV/HIV)
- MRC5 Human Fetal Tissue (Human Endogenous retroviruses)

23 OCTOBER 2009 VOL 326 SCIENCE www.sciencemag.org

How did mouse retroviruses get into humans?

"One of the most widely distributed biological products that frequently involved mice of mouse tissue, at least up until recent years, are vaccines, especially vaccines against viruses . . . It is possible that XMRV particles were present in virus stocks cultured in mice or mouse cells for vaccine production, and that the virus was transferred to the human population by vaccination."

(Frontiers in Microbiology, January 2011)



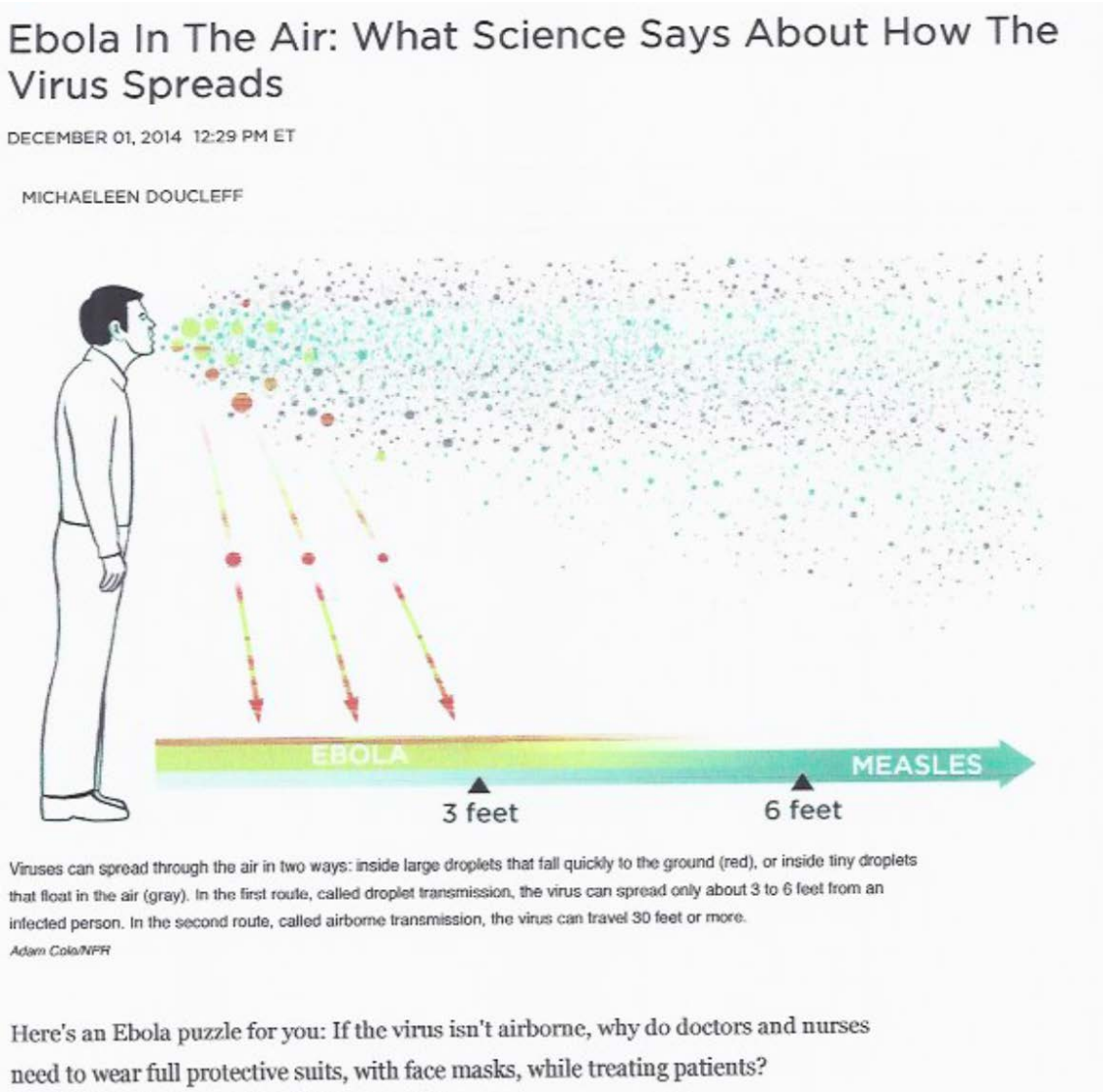
21st Century Acquired Endocannabinoid Immune Dysfunction: *Unintended* Consequences of 21st century Vaccination Schedule

Prostate*	Lupus	ME/CFS*
Breast*	Crohn's*	Gulf War Syndrome*
Multiple Myeloma*	Hashimoto's Thyroiditis*	Autism/ASD*
Non Hodgkin's Lymphoma*	Polymyositis	MS*
Chronic Lymphocytic Leukemia*	Sjogren's Syndrome	Parkinson's*
Mantle Cell Lymphoma*	Bechet's Disease*	ALS*
Hairy Cell Leukemia	Primary Billary Cirrhosis*	Fibromyalgia
Bladder*	IBD*	Chronic Lyme Disease*
Coloretal	Psoriasis, Dermatitis	OCD
Kidney*		ADHD
Ovarian*		PTSD

Table 1: Conditions and Diseases in Which Activation of The ECS has Shown Benefit[78]

Emesis	Epilepsy	Obesity	Tourette's syndrome
Pain	Glaucoma	Anorexia	Anxiety
Inflammation	Schizophrenia	Parkinson's disease	Depression
Multiple sclerosis	Cardiovascular disorders	Huntington's disease	Panic
Autism	Stroke (Ischemia)	Insomnia	Prion diseases
PTSD	Cancer	Alzheimer's disease	Psychosis
Obsessive compulsive behavior	Amyotrophic lateral sclerosis	Metabolic syndrome related diseases	

2014 Ebola Outbreak in Liberia : Zaire Strain By Way of BSL4 Facility Ft Detrick MD
Ft Detrick houses National Cancer Institute and USAMRIID



Ebola In The Air: What Science Says About How The Virus Spreads

DECEMBER 01, 2014 12:29 PM ET

MICHAELEEN DOUCLEFF

Viruses can spread through the air in two ways: inside large droplets that fall quickly to the ground (red), or inside tiny droplets that float in the air (gray). In the first route, called droplet transmission, the virus can spread only about 3 to 6 feet from an infected person. In the second route, called airborne transmission, the virus can travel 30 feet or more.

Adam Cole/NPR

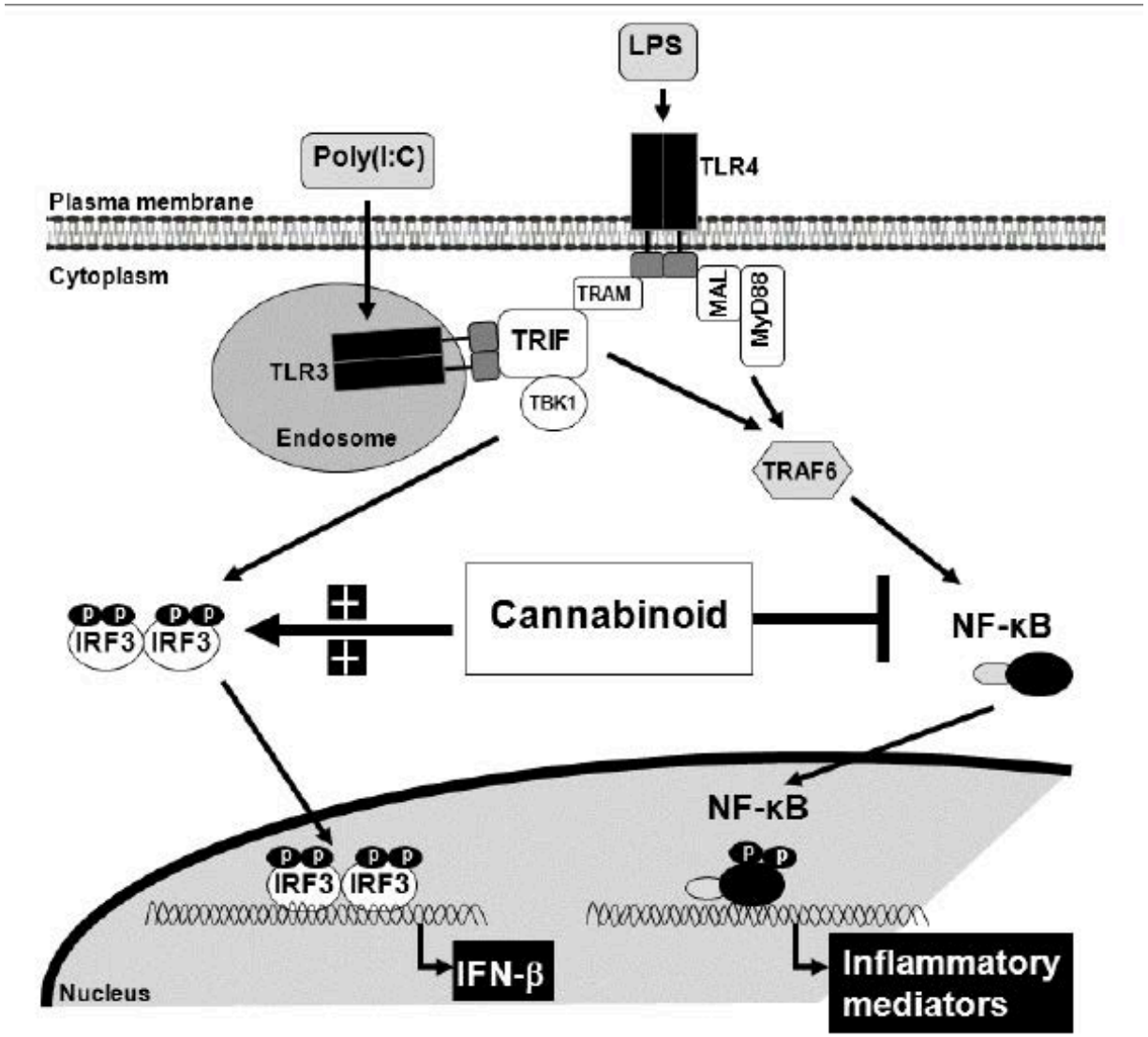
Here's an Ebola puzzle for you: If the virus isn't airborne, why do doctors and nurses need to wear full protective suits, with face masks, while treating patients?

Harold Varmus was NIH Director who implemented the xenotransplantation program in 1999. This included xenografts for cancer research, gene therapy. Varmus also started the NIH Vaccine Research Program.

Many infectious diseases of animals can be transmitted to humans via routine exposure to or consumption of animals (e.g., rabies). Viruses that are not pathogenic in their natural host reservoirs may**, in some cases, be highly pathogenic when transmitted to a new host species.** Several zoonotic viruses have produced significant outbreaks when introduced into human hosts under normal circumstances of exposure (e.g., Ebola, Hanta Virus, Influenza).

Consequently, the recipient of a xenotransplant is potentially at risk for infection with infectious agents already known to be transmissible from animals to humans as well as with infectious agents, which may become transmissible only through xenotransplantation and which may not be readily identified with current diagnostic tools. Infected xenograft recipients could then potentially transmit these infectious agents to their contacts and subsequently to the public at large.

Cannabinoids are Anti-Viral and Reduce Inflammation

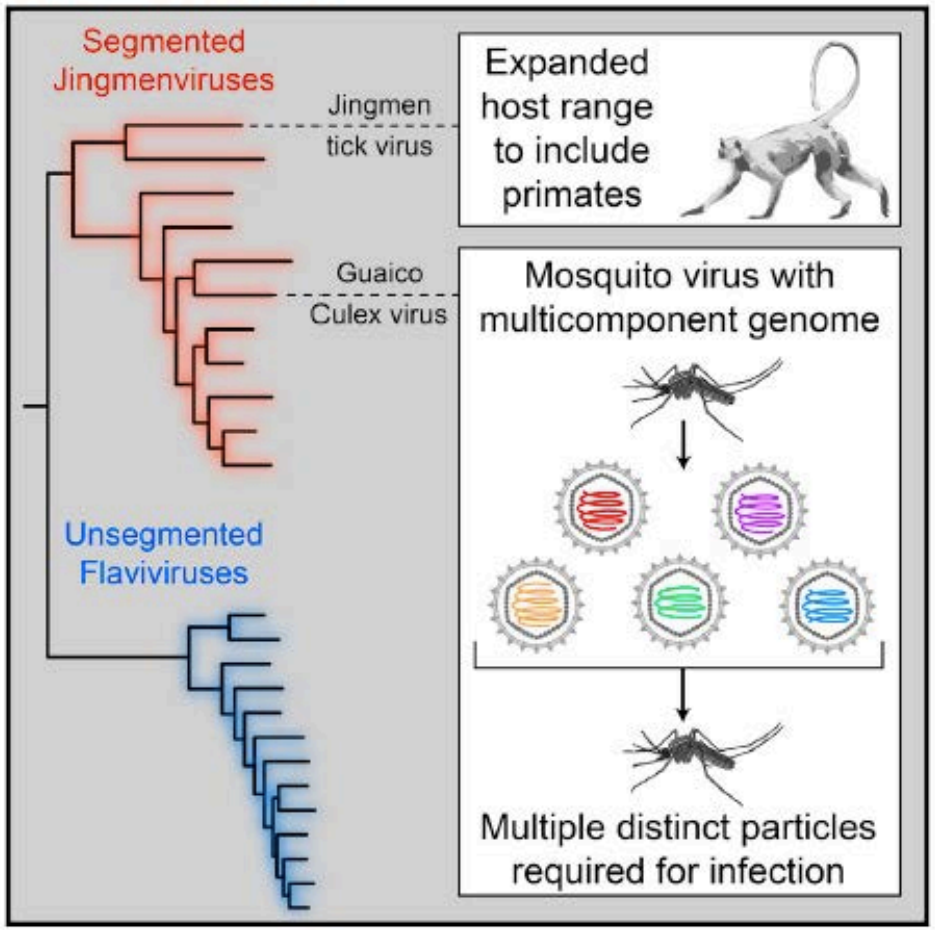


2016 Zika Outbreak Zoonosis caused by DTP vaccination & bioengineered Mosquito in Brazil

Cell Host & Microbe

A Multicomponent Animal Virus Isolated from Mosquitoes

Graphical Abstract



Authors

Jason T. Ladner, Michael R. Wiley, Brett Beitzel, ..., Laura D. Kramer, Robert B. Tesh, Gustavo Palacios

Correspondence

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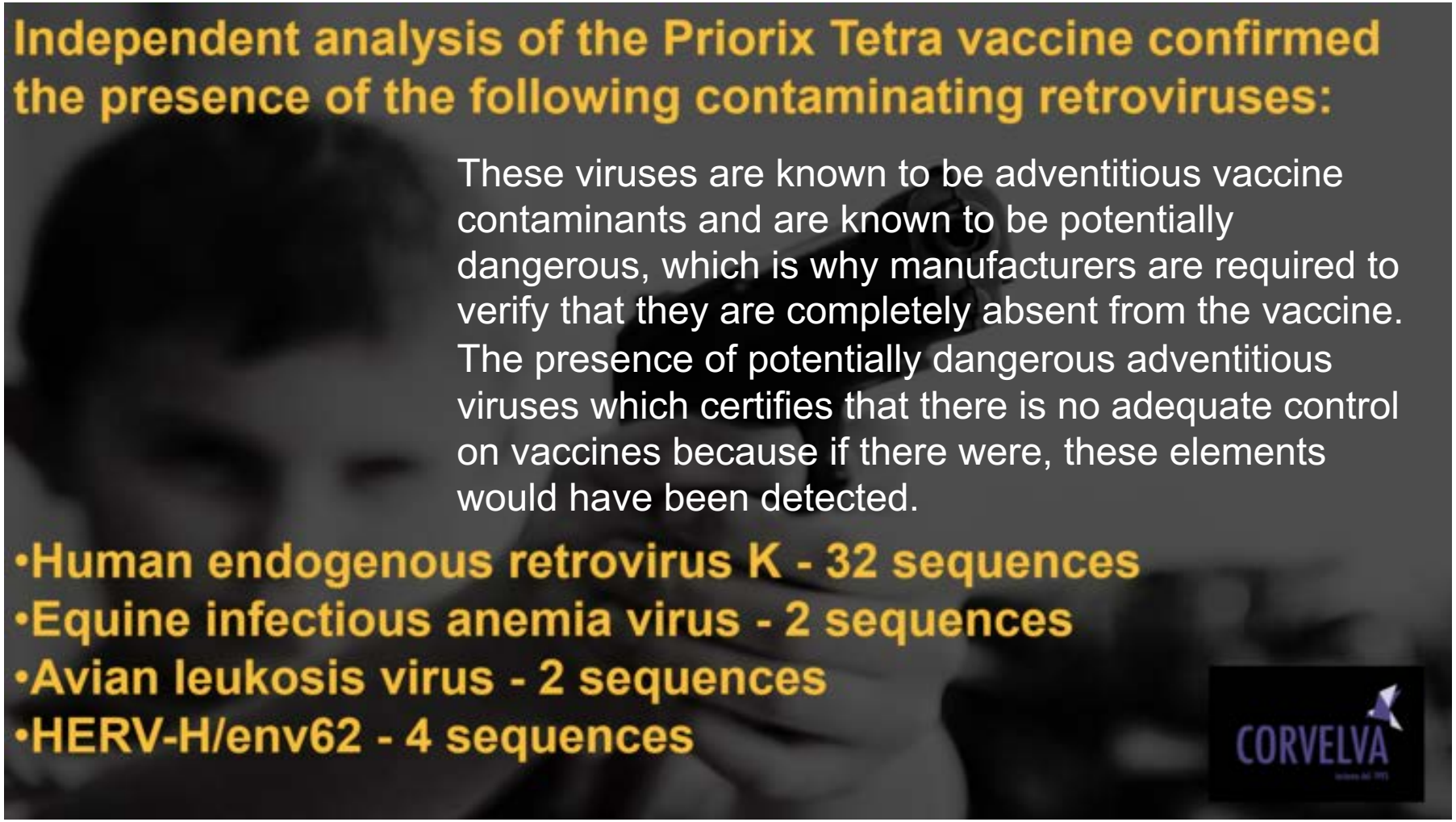
In Brief

Multicomponent viruses, which separately package different genome segments, were thought to be restricted to plant and fungal hosts. Ladner et al. characterize a multicomponent mosquito virus and describe an evolutionarily related, segmented virus in a nonhuman primate. These findings provide evidence for multicomponent animal viruses and suggest relevance to animal health.

Ladner et al., 2016, Cell Host & Microbe *20*, 357–367
September 14, 2016
http://dx.doi.org/10.1016/j.chom.2016.07.011



Residual DNA/RNA deriving from cultured cells - Total amount of DNA: 1.7-3.7 µg/dose, the 80% of which was human (Human fetal DNA / RNA from the MRC-5 cell line). Other amount of DNA: chicken

PaxImune Homeopathic Immunity Booster Can Prevent and Treat Corona Virus , retroviral illness, influenza, Zika, Ebola

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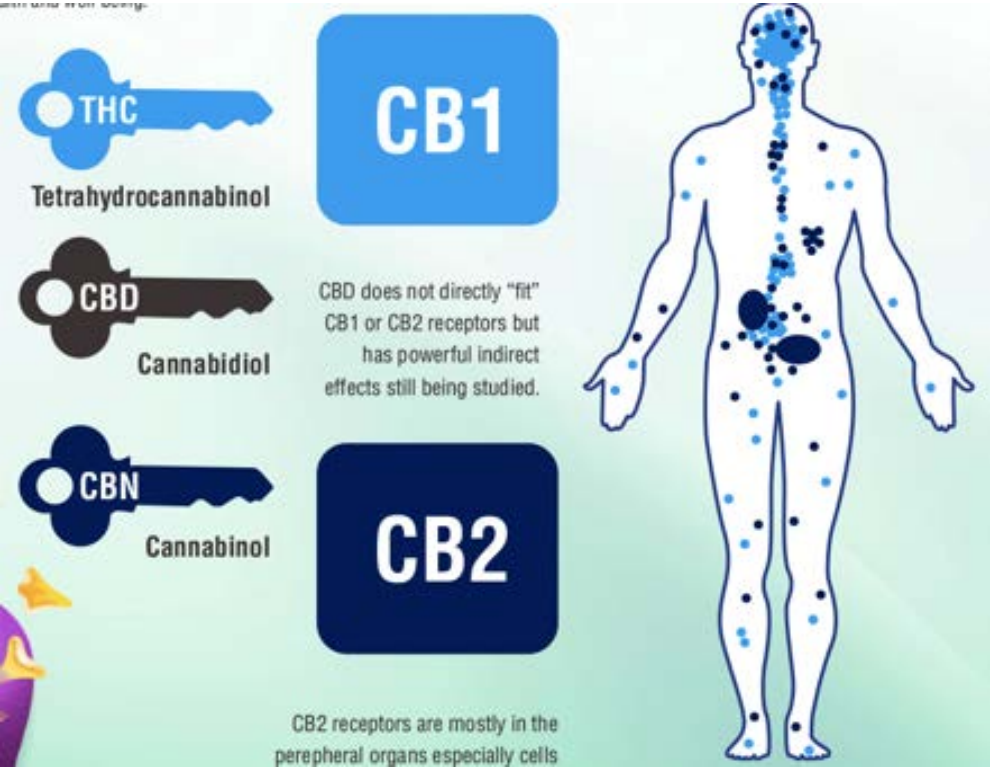
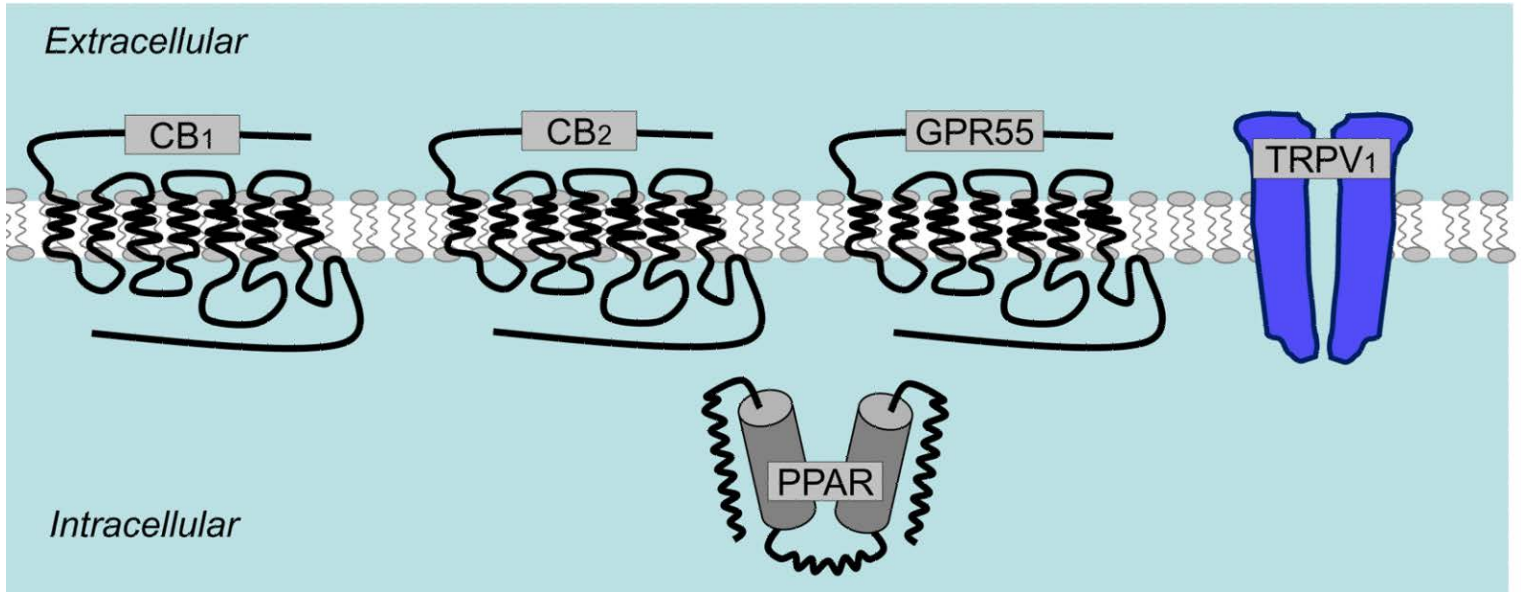
Key Regulator of stem cell development, Immune Homeostasis & Neuroimmune Health

A signaling system that helps to modulate all other physiological, behavioral, and energetic processes in the body.



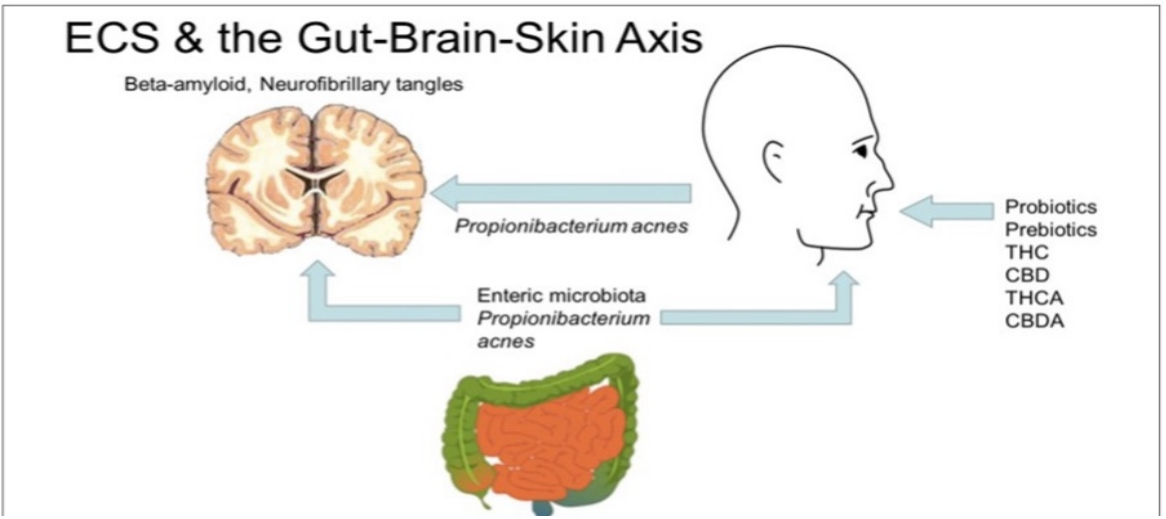
Glia. 2010 July ; 58(9): 1017–1030



Anxiety
Depression
Sleep Disorders
Pain
Itch
Wound healing

- ***neuroprotection & plasticity***
- ***immunity & inflammation***
- ***apoptosis &carcinogenesis***
- ***pain and emotional memory***
- ***Supports detoxification:***
  - ***repairs Fibrosis***
  - ***fatty Liver disease***

Cannabis Can be consumed in Multiple ways: Capsules, Powder or Raw juice



Cannabis capitate glandular

Cannabis Harlequin Leaves

VerdeVida
get juiced

Mixtures of different Phytocannabinoids are more active biologically than single: Targeting by extraction and Formulations

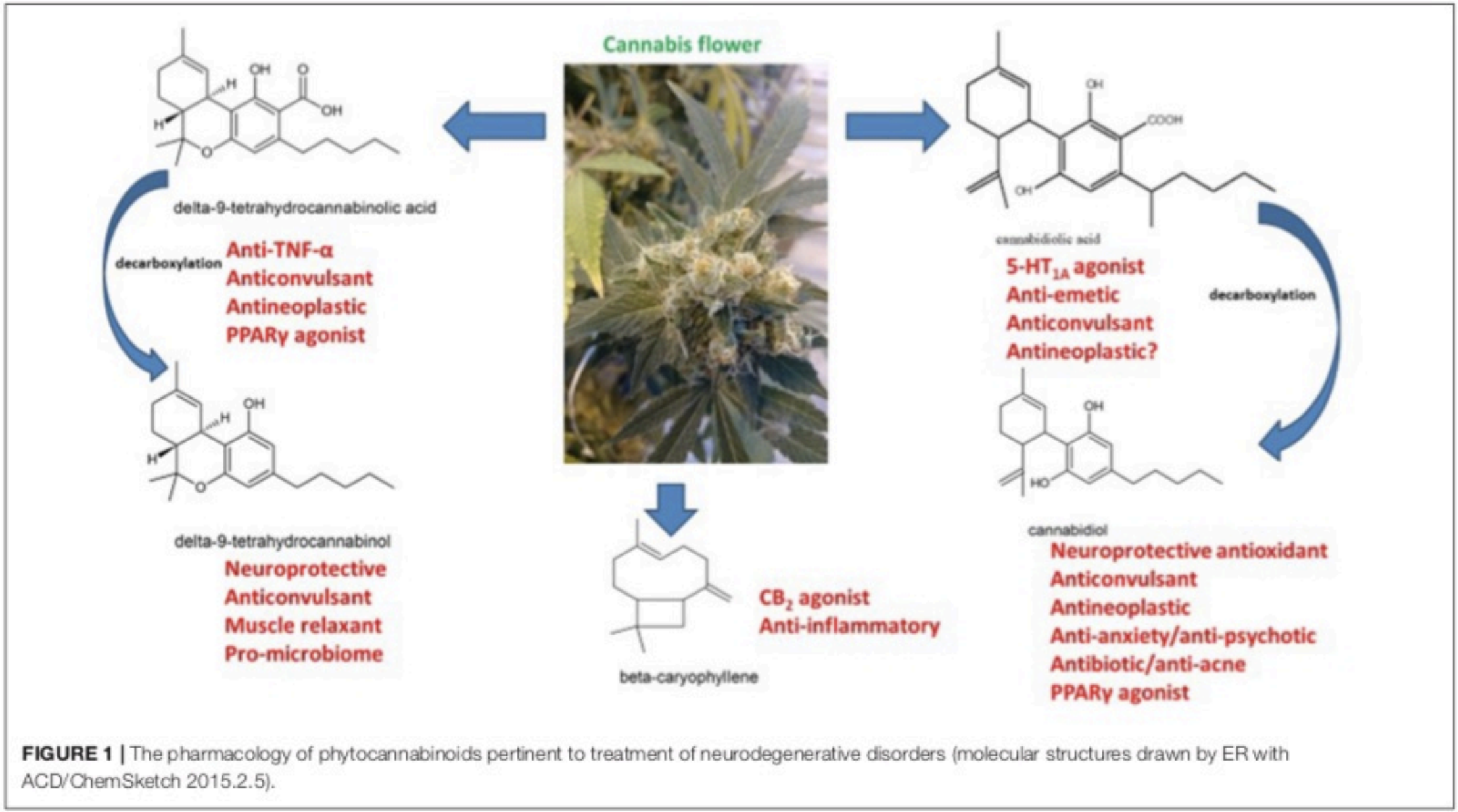


FIGURE 1 | The pharmacology of phytocannabinoids pertinent to treatment of neurodegenerative disorders (molecular structures drawn by ER with ACD/ChemSketch 2015.2.5).

BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2011.01238.x
www.brjpharmacol.org

Themed Issue: Cannabinoids in Biology and Medicine, Part I

REVIEW

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

Ethan B Russo

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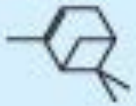
Keywords
cannabinoids; terpenoids; essential oils; THC; CBD; limonene; pinene; linalool; caryophyllene; phytotherapy

Received
19 November 2010
Revised
29 December 2010
Accepted
12 January 2011

Terpenoid	Structure	Commonly encountered in	Pharmacological activity (Reference)	Synergistic cannabinoid
Limonene		 Lemon	Potent AD/immunostimulant via inhalation (Komori *et al.*, 1995)	CBD
			Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006) via 5-HT$_{1A}$ (Komiya *et al.*, 2006)	CBD
			Apoptosis of breast cancer cells (Vigushin *et al.*, 1998)	CBD, CBG
			Active against acne bacteria (Kim *et al.*, 2008)	CBD
			Dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010)	CBG
			Gastro-oesophageal reflux (Harris, 2010)	THC
α-Pinene		 Pine	Anti-inflammatory via PGE-1 (Gil *et al.*, 1989)	CBD
			Bronchodilatory in humans (Falk *et al.*, 1990)	THC
			Acetylcholinesterase inhibitor, aiding memory (Perry *et al.*, 2000)	THCT, CBD
β-Myrcene		 Hops	Blocks inflammation via PGE-2 (Lorenzetti *et al.*, 1991)	CBD
			Analgesic, antagonized by naloxone (Rao *et al.*, 1990)	CBD, THC
			Sedating, muscle relaxant, hypnotic (do Vale *et al.*, 2002)	THC
			Blocks hepatic carcinogenesis by aflatoxin (de Oliveira *et al.*, 1997)	CBD, CBG
Linalool		 Lavender	Anti-anxiety (Russo, 2001)	CBD, CBG?
			Sedative on inhalation in mice (Buchbauer *et al.*, 1993)	THC
			Local anesthetic (Re *et al.*, 2000)	THC
			Analgesic via adenosine A_{3A} (Peana *et al.*, 2004)	CBD
			Anticonvulsant/anti-glutamate (Elisabetsky *et al.*, 1995)	CBD, THCV, CBDV
			Potent anti-leishmanial (do Socorro *et al.*, 2003)	?

molecules

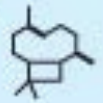
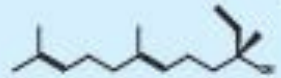
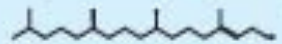
MDPI

Article

Terpenoids and Phytocannabinoids Co-Produced in *Cannabis Sativa* Strains Show Specific Interaction for Cell Cytotoxic Activity

Dvora Namdar [1,*], Hillary Voet [1], Vinayaka Ajjampura [1], Stalin Nadarajan [1], Einav Mayzlish-Gati [2], Moran Mazuz [1], Nurit Shalev [1] and Hinanit Koltai [1]

1 Institute of Plant Sciences, Agricultural Research Organization, Volcani Center, Bet Dagan 7505101, Israel
2 Israeli Gene Bank, Volcani Center, Bet Dagan 7505101, Israel
* Correspondence: dvoran@volcani.agri.gov.il

β-Caryophyllene		 Pepper	AI via PGE-1 comparable phenylbutazone (Basile *et al.*, 1988) — CBD
			Gastric cytoprotective (Tambe *et al.*, 1996) — THC
			Anti-malarial (Campbell *et al.*, 1997) — ?
			Selective CB_2 agonist (100 nM) (Gertsch *et al.*, 2008) — THC
			Treatment of pruritus? (Kamak *et al.*, 2007) — THC
			Treatment of addiction? (Xi *et al.*, 2010) — CBD
Caryophyllene Oxide		 Lemon balm	Decreases platelet aggregation (Lin *et al.*, 2003) — THC
			Antifungal in onychomycosis comparable to ciclopiroxolamine and salconazole (Yang *et al.*, 1999) — CBC,CBG
			Insecticidal/anti-feedant (Bettarini *et al.*, 1993) — THCA, CBGA
Nerolidol		 Orange	Sedative (Barel *et al.*, 1972) — THC, CBN
			Skin penetrant (Cornwell and Barry, 1994) — –
			Potent antimalarial (Lopes *et al.*, 1999; Rodrigues Goulart *et al.*, 2004) — ?
			Anti-leishmanial activity (Amado *et al.*, 2005) — ?
Phytol		 Green tea	Breakdown product of chlorophyll — –
			Prevents Vitamin A teratogenesis (Arnhold *et al.*, 2002) — –
			TGABA via SSADH inhibition (Bang *et al.*, 2002) — CBG

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European Neuropsychopharmacology (2014) 24, 608–620

www.elsevier.com/locate/euroneuro

The cannabinoid CB_2 receptor-selective phytocannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain

biomolecules

Review

Therapeutic Potential of α- and β-Pinene: A Miracle Gift of Nature

Int. J. Mol. Sci. **2014**, *15*, 13637-13648; doi:10.3390/ijms150813637

OPEN ACCESS
International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Article

Celastrol Attenuates Inflammatory and Neuropathic Pain Mediated by Cannabinoid Receptor Type 2

Molecules **2012**, *17*, 3524-3538; doi:10.3390/molecules17033524

OPEN ACCESS
molecules
ISSN 1420-3049
www.mdpi.com/journal/molecules

Review

Terpenoids as Potential Anti-Alzheimer's Disease Therapeutics

Phytocannabinoids can Enhance Vaccine Efficacy and Reduce Neuroinflammation

www.nature.com/scientificreports

OPEN

Transient Cannabinoid Receptor 2 Blockade during Immunization Heightens Intensity and Breadth of Antigen-specific Antibody Responses in Young and Aged mice

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Published: 17 February 2017

Emmanuel Dotsey[1], Irina Ushach[1], Egest Pone[2], Rie Nakajima[1], Algis Jasinskas[1], Donovan A. Argueta[3], Andrea Dillon[3], Nicholas DiPatrizio[3], Huw Davies[1], Albert Zlotnik[4], Peter D. Crompton[5] & Philip L. Felgner[1]

Censorship & Cover-up of Scientific Discovery led to Plague of Chronic Disease

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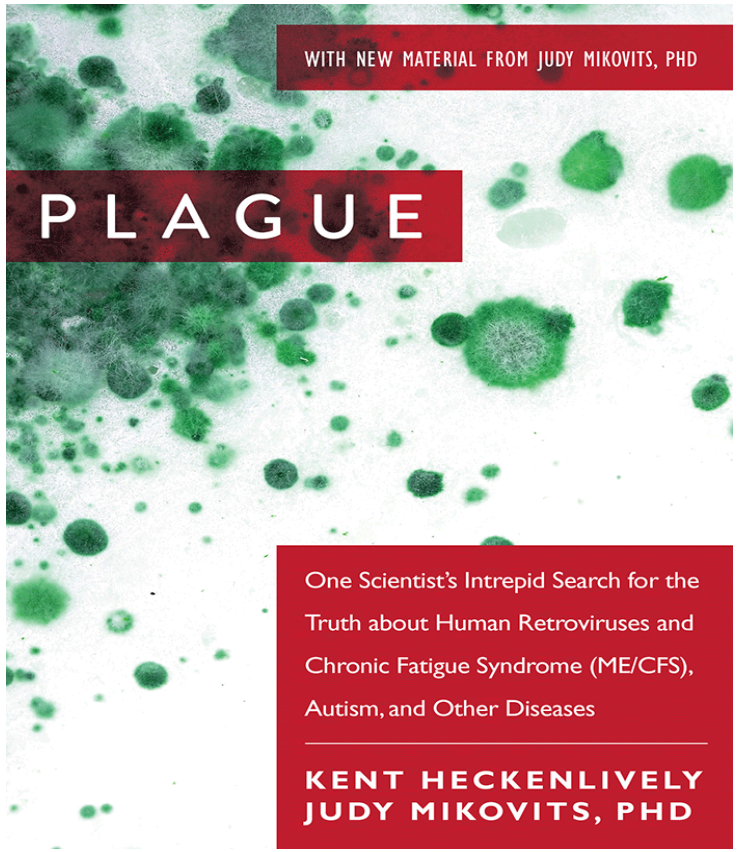

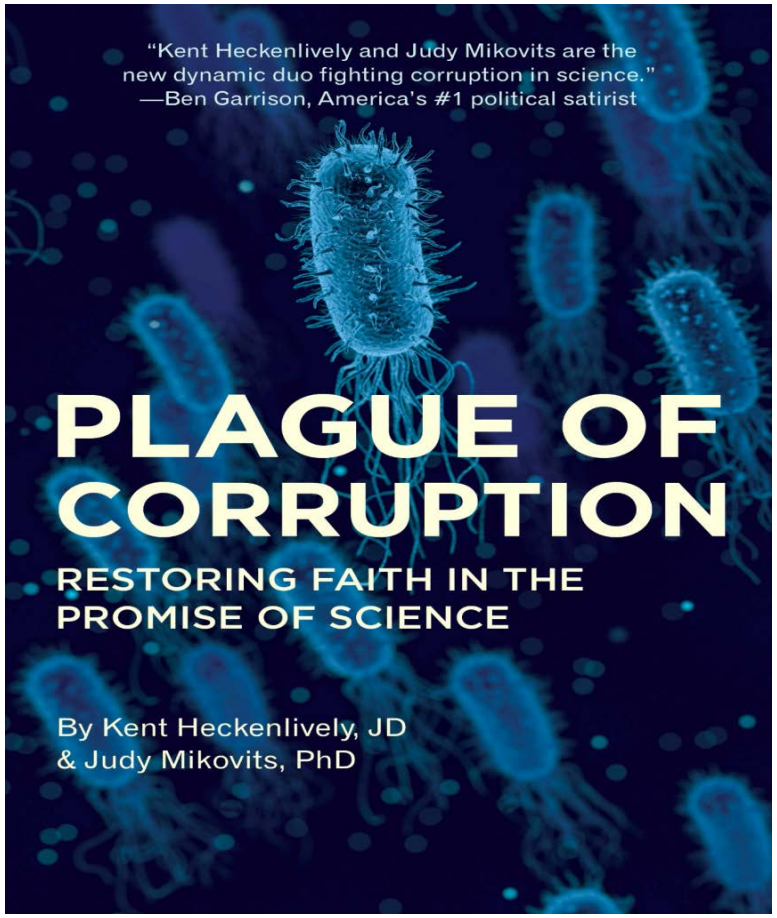

In Plague of Corruption we raise the broader question

of the enormous risk of using animal tissue in research & mixing of it with human tissue
for the development of medical therapies while covering up value and efficacies
of natural product therapies like cannabis, homeopathy, energy therapies and other medicinal plants