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Molecular Medicine Communications

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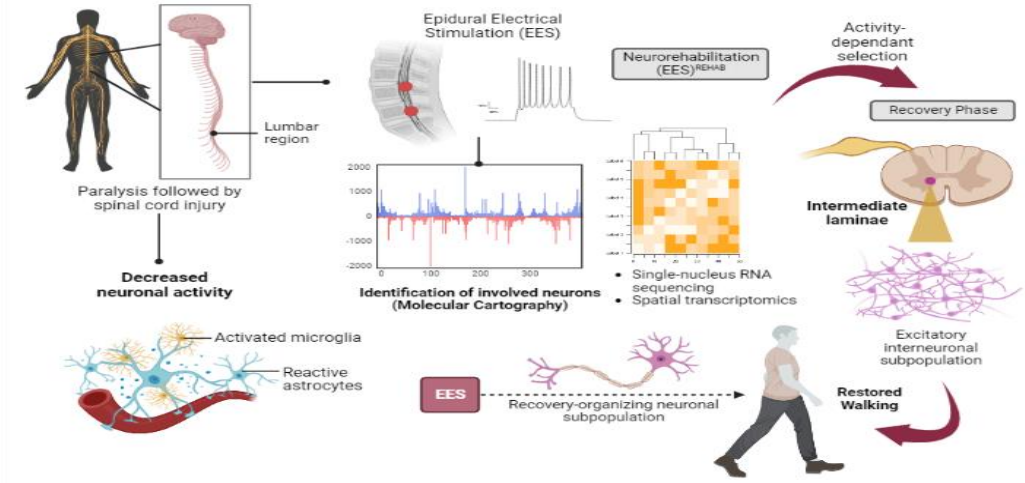
Editor's Choice

Editor's Selection of the Important Research Investigations in the Field of Molecular Medicine Communications from Around the World

Editorial Staff

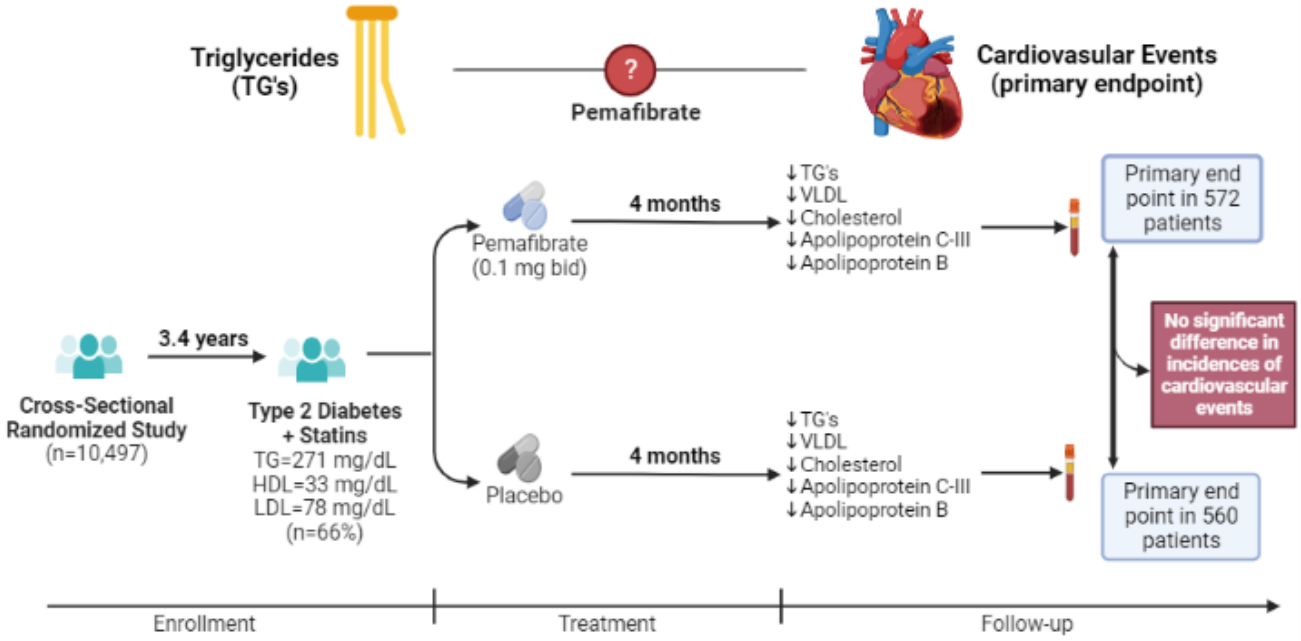
The neurons that restore walking after paralysis (doi.org/10.55627/mmc.002.002.0160)

Paralysis after a spinal cord injury is due to the cut-off signaling between the brain and brainstem, especially those pathways that lead to a lumbar spinal cord. Kathe and her colleagues demonstrated that walking in nine patients with spinal cord injury significantly improved during the neurorehabilitation process in which the lumbar spinal cord's spatiotemporal epidural electrical stimulation (EES) was used. A decrease in the lumber spinal cord neuronal activity was counterintuitively accompanied by improved human walking. The authors thought that this decrease in neuronal activity suggests the selection of a particular neuronal subpopulation essential for walking. To find this out, they recapitulated the same study in mouse models. They used transcriptomics and single-nucleus sequencing to chart the molecular circuitry of these mice from paralysis to recovery. They found a subset of neurons within the intermediate laminate. Interestingly, these neurons are not required for normal walking in healthy individuals, but the authors demonstrated that these neurons are essential for walking after a spinal injury. They further confirmed their findings by ablating these neurons, which prevented the recovery from a spinal injury, whereas augmenting these neurons further improved the recovery. The authors found a subset of neurons that organize the rescue of walking after spinal injury and provided a new framework for using molecular cartography to identify neurons required for certain behaviors. *Nature* ***(2022)*** ***DOI:*** https://doi.org/10.1038/s41586-022-05385-7.



Reduction of Cardiovascular Risk with Pemafibrate (doi.org/10.55627/mmc.002.002.0163)

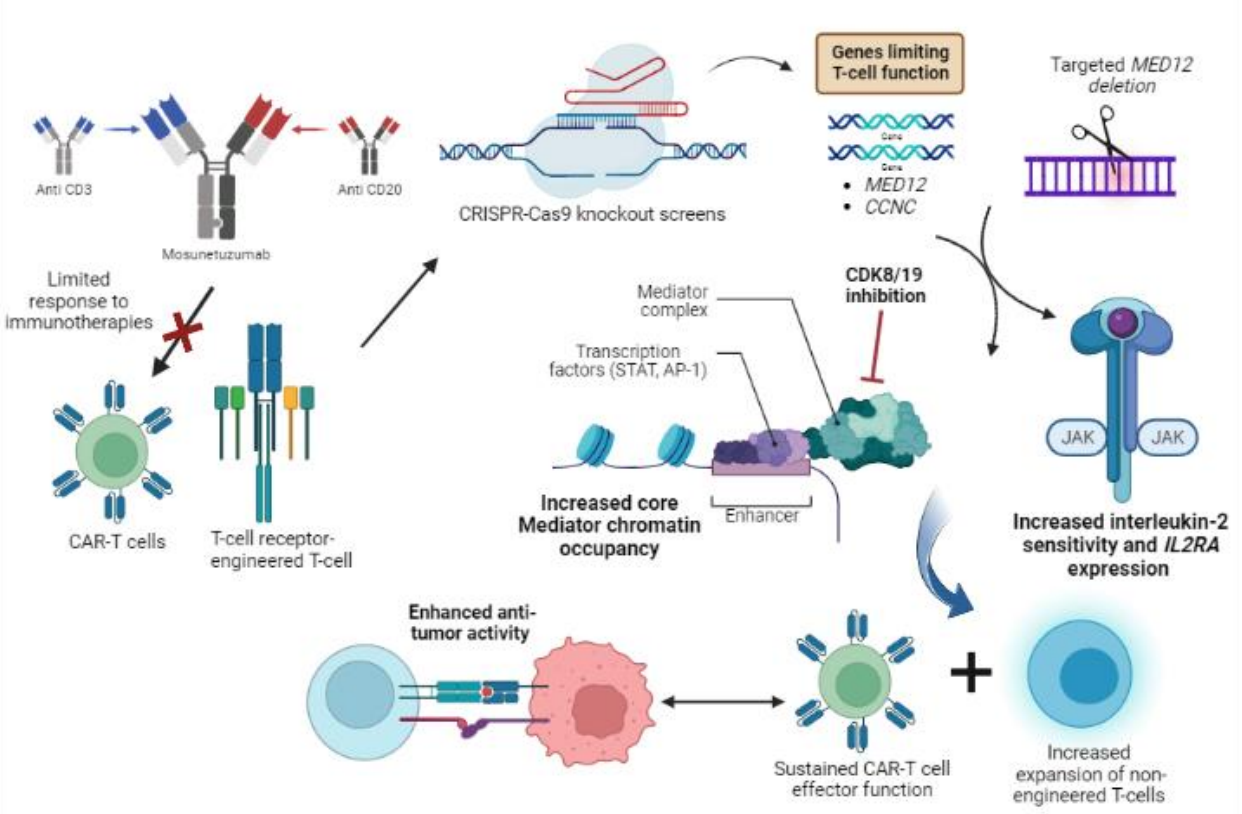
It has been established that increased cardiovascular risk is seen in individuals with elevated triglycerides; however, whether reduction of the same alleviates the risk is still unclear. A decrease in triglycerides and improvement in other lipid levels is observed with Pemafibrate, a selective peroxisome proliferator-activated receptor α modulator. Pradhan and researchers conducted a randomized, double-blind clinical trial on an international scale. Patients with type 2 diabetes mellitus were divided into two groups; high-density lipoprotein (HDL) cholesterol levels of 40 mg per deciliter and or lower and mild to moderate hypertriglyceridemia (200 to 499 mg per deciliter), where one group received a placebo and the other 200µg tablets BD Pemafibrate. A cohort of parameters, namely coronary revascularization, ischemic stroke, myocardial infarction, and death from cardiovascular disease, were factored in as the primary efficacy endpoints. An HDL cholesterol level of 33 mg per deciliter, a median baseline fasting triglyceride level of 271 mg per deciliter, and an LDL cholesterol level of 78 mg per deciliter were observed in a sum-total 10,497 patients, of whom 66.9% had a previous history of cardiovascular disease. After 16 months, a significant reduction of 26.2% for triglycerides, -25.8% for very-low-density lipoprotein (VLDL) cholesterol, 25.6% for remnant cholesterol (cholesterol transported in triglyceride-rich lipoproteins after lipolysis and lipoprotein remodeling), 27.6% for apolipoprotein C-III, and 4.8% for apolipoprotein B were observed in Pemafibrate group in comparison to the placebo group. In both groups, no significant difference was seen in the incidence of adverse events. However, a lower incidence of non-alcoholic fatty liver disease and a higher incidence of venous thromboembolism and adverse renal events were associated with Pemafibrate. ***N Engl J Med (2022) DOI: 10.1056/NEJMoa2210645.***



Enhanced T cell effector activity by targeting the Mediator kinase module

(doi.org/10.55627/mmc.002.002.0161)

T cells play important roles in combating various diseases, including cancers. To find out what genes hinder the function of T cells, Freitas and colleagues performed genome-wide CRISPR knock-out experiments in human chimeric antigen receptor T cells. They found that two genes, *MED12* and *CCNC*, which are part of the Mediator kinase module, had the most significant effect. They discovered that antitumor activity was increased when *MED12* was selectively deleted, and the effector phenotype was maintained in chimeric antigen receptor and T cell receptor-engineered T cells. They found increased occupancy of core Mediator chromatin at transcriptionally active enhancers in *MED12*-deficient cells. This effect was most evident for enhanced *IL2RA* expression and STAT and AP-1 transcription factors. The authors concluded that Mediator plays a vital role in T cell effector programming and that antitumor T cell response may be enhanced by targeting the Mediator kinase module. ***Science* (2022). *DOI: 10.1126/science.abn5647.***

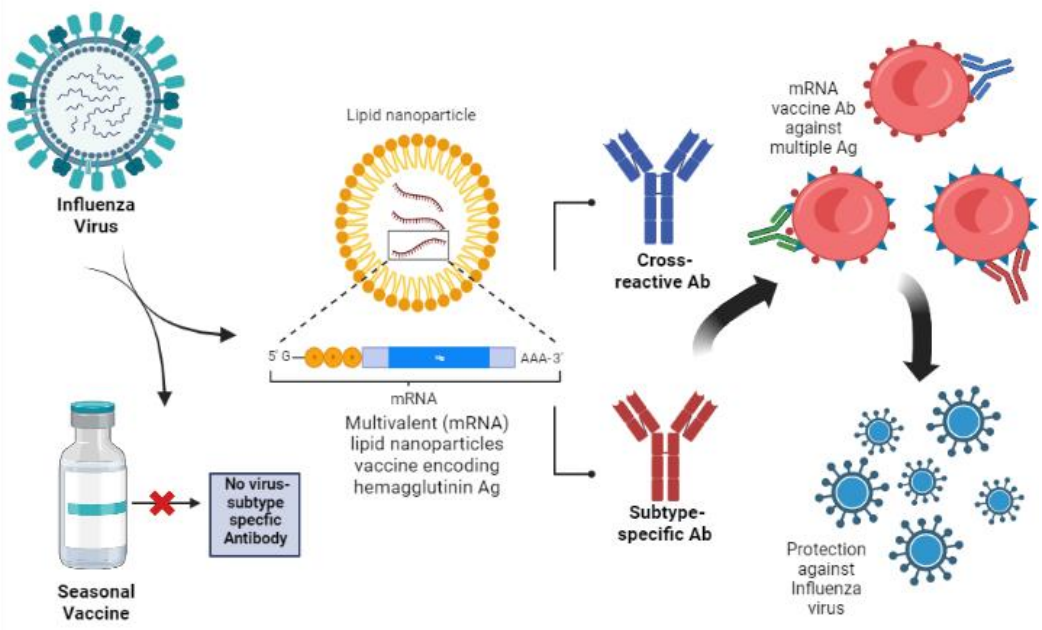


One mRNA vaccine to rule them all

(doi.org/10.55627/mmc.002.002.0164)

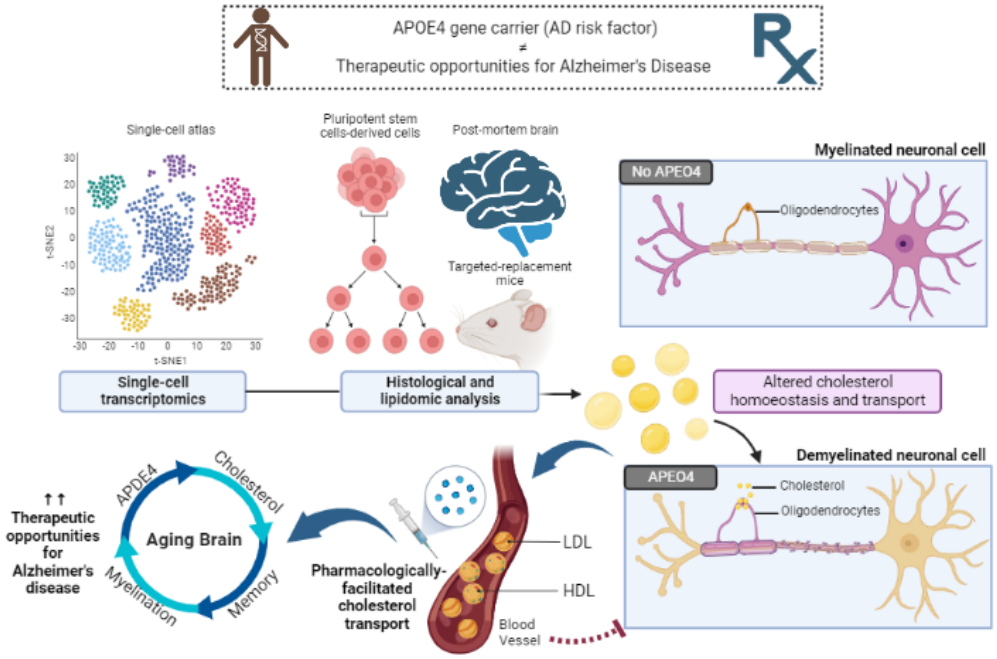
Vaccines for seasonal influenza do not confer protection against the pandemic strains of the influenza virus. Due to the uncertainty in identifying which viral strain of influenza may cause the next pandemic, it is challenging to develop pre-pandemic vaccines. A nucleoside-modified messenger RNA (m-RNA) encapsulated in a lipid nanoparticle that codes for hemagglutinin protein for all 20 strains of both influenza A and influenza B virus were formulated by Arevalo and colleagues. In mice and ferrets administered with this multivalent vaccine, cross-reactive and subtype-specific antibodies targeting all 20 encoded antigens

were developed. The immunized mice and ferrets exhibited strong resistance once challenged with matched and mismatched viral strains. The antibodies developed were in part responsible for conferring this protection. Their studies indicate that mRNA vaccines can provide protection against antigenically variable viruses by inducing antibodies against multiple antigens simultaneously. ***Science (2022) DOI: 10.1126/science.abm0271.***



Disruption in myelination in the brain by APOE4 (doi.org/10.55627/mmc.002.002.0162)

How the brain is affected by *APOE4* -one of the most important genetic risk factors in patients with Alzheimer's disease (AD), is still not clear. This missing piece is a substantial barrier to understanding the risk factors of AD and their use as therapeutic targets.



Blanchard and colleagues performed a study to delineate the function of *APOE4* by post-mortem transcriptomic analysis of the brains of non-carriers and carriers of *APOE4*. The data from their results point to the fact that *APOE4* influences a host of expression profiles and signaling mechanisms in all of the studied cell types. The most significant effects were observed in the cholesterol homeostasis and transport mechanisms. It was observed that the oligodendrocytes were subjected to abnormal cholesterol metabolism, which subsequently affected the electrical activity of neurons. These results were affirmed using induced pluripotent stem cells, post-mortem human brains, and targeted replacement mice. It was also seen that altered deposition of cholesterol in *APOE4* carrier brains reduced myelination. Pharmacological improvement in axonal myelination of *APOE4* mice demonstrated better memory and learning. By providing a single-cell atlas of the partaking signaling events, the authors concisely represented the transcriptomic effects of *APOE4*. A working relationship between cholesterol transport, myelination, and subsequent effects on learning and memory with *APOE4* was also provided, thus unveiling potential targets for treating AD. ***Nature (2022) DOI: 10.1038/s41586-022-05439-w.***

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