Mitochondria, Corona & the Spike Protein: An Underestimated Problem

Basics

We now know that Covid-19 is not the modern equivalent of the medieval plague, which depopulated entire regions and reduced Europe's population by an estimated 30%. Rather, it has been clear for a long time that Corona infection mainly endangers clearly defined risk groups, but is regularly unproblematic for people outside these risk groups. Few take the trouble to think a little more carefully about the criteria that define these groups. For an acute respiratory infectious disease, one would spontaneously associate risk factors such as the following: Prior respiratory disease (COPD, asthma, emphysema, fibrosis, etc.) and, of course, immune deficiency. The latter is also on the list of officially recognised risks - in the form of advanced age. This brings with it a phenomenon called "immune senescence", an age-related loss of function of the immune system, especially at the level of the adaptive (i.e. learning) defence. However, one looks in vain for diseases of the respiratory organs or immune-damaging processes (e.g. cancer). Instead, overweight (obesity) and type 2 diabetes mellitus have been identified as the main risks. This actually calls for an explanation, since these pathologies have no direct connection to the virus defence or vulnerability of the respiratory organs. In fact, there are three phenomena common to all three "Major Risks" (age, diabetes, obesity) that explain their disruptive effects on covid morbidity: Inflammation, Radical and Mitochondriopathy. The scientific debate on the causes and mechanisms of ageing has now coined the term "inflammaging" - ageing through inflammation[1] . Obesity and diabetes are persistent inflammation ("Silent inflammation") and radical formation and promote their development, progression and complications[2] . Both chronic inflammation and radical stress ultimately lead to another phenomenon: the loss of mitochondrial function, a so-called mitochondriopathy[3,4] . This also results from ageing, as the number and functionality of these cell organelles decrease with age[5] . It is the culmination point and perhaps the morbidity factor par excellence, if one considers chronic diseases (and here in particular those referred to as diseases of civilisation and old age) at the cellular level[6] . From A as in Alzheimer's to Z as in zoster, no matter whether cancer, general degeneration, orthopaedic problems or immune deficiencies - mitochondriopathy always emerges as the cellular-pathological basis. In this context, it is important to say goodbye to the image of mitochondria as pure energy producers. Mitochondria are much more than simple "power plants" of our cells. Besides their task of producing energy, they control and regulate our genome (epigenetics), cell division and controlled cell death (apoptosis). Persistent mitochondriopathies accordingly induce a chain reaction of biochemical and (epi)genetic effects, the pathophysiological consequences of which bring multimorbidity in its purest form.

Mitochondria and the immune system

In the context of our consideration here, we are of course particularly interested in the importance of mitochondria for our immune system, and this cannot be overestimated. Both innate and adaptive defence cells are in terms of

Activation and function extremely dependent on the mitochondria[7] , this applies in particular to the defence against viruses - in the form of the interferon system[8] . Poor mitochondrial function, few interferons. Few interferons, rapid increase in viral load and viral persistence, with all the negative consequences. Particularly critical in corona: interferon deficits increase the probability of excessive but unproductive activity of the non-specific immune system. Possible consequence is the dreaded cytokine storm[9] . Mitochondrial status is predictive of the course of infection[10] . Interferons are also crucial in the elimination of malignant cells - corresponding deficits increase the risk of cancer or dramatically worsen the prognosis of cancer[11,12] .

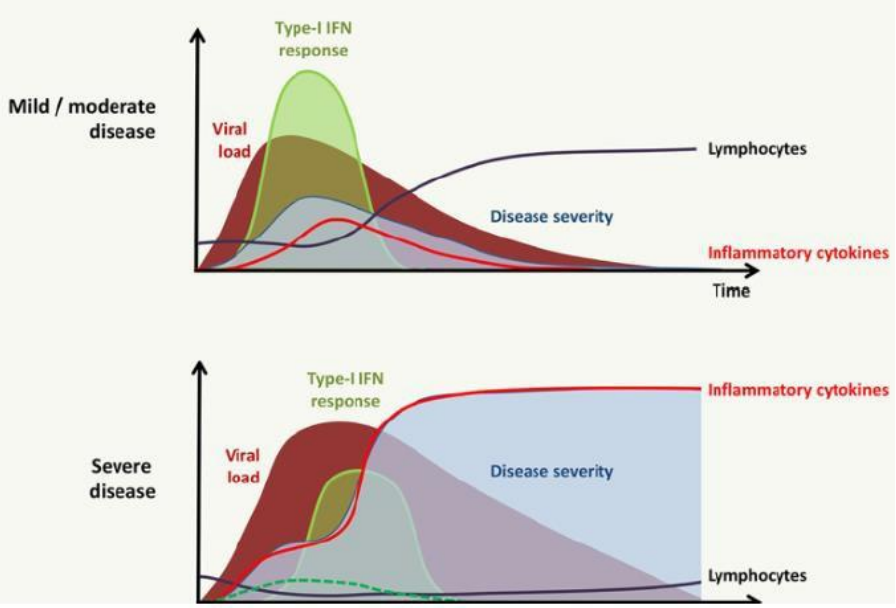

Figure 1: Decreased interferon response increases the risk of severe courses of infection and cytokine storm; source: Jamilloux, 2020

It should also be remembered that the relationship between inflammation, radicals and mitochondria is interactive - the former damage the mitochondria, mitochondriopathy in turn promotes inflammation and radical formation[13] . There is considerable potential here for a vicious circle that ends in a self-accelerating downward spiral. To make matters worse, an intact mitochondrial metabolism is crucial for the successful differentiation of progenitor cells. This affects the formation of mature immune cells as well as the permanent regeneration of tissues subject to wear and tear (epithelium, endothelium, white matter in the nervous system)[14] . However, insufficient differentiation is not only a regeneration problem, but can lead ad extremum to cell degeneration. Consequently, we find the full expression of mitochondriopathy in cancer: complete loss of physiological cell function, uncontrolled cell division with simultaneous lack of differentiation and loss of apoptosis capacity. The mitochondria of malignant cells are numerically depleted, functionally dead and devoid of any epigenetic control function[15] . Cancer is a mitochondrial disease par excellence, mitochondria-oriented therapies at the same time promising tools in oncological therapy[16] . The affected cells are no longer just functional failures, they have developed into enemies of our organism. Mitochondriopathy thus strikes several times in this context: On the level of

of cell metabolism, it promotes the formation of malignant cells, while at the same time sabotaging the immune system and thus the fight against the malignant cells.

SARS-CoV2, the spike and mitochondria

Back to the initial topic: Viruses know the importance of mitochondria for their host, in particular they know the great danger that these cell organelles pose for them. It is therefore in the nature of things that viruses have developed strategies to switch off the mitochondria or to hijack them for their own needs. SARS-CoV2 is no exception and consequently, on closer inspection, numerous damaging mechanisms are also found. Let us briefly outline the most important ones. As early as 2020, analyses in silico predicted the translation of corona RNA in the mitochondria (and thus not only classically through the ribosomes of the infected cell)[17] . This was confirmed a short time later by the trial and error - the inhibition of mitochondrial translation leads to the collapse of virus replication[18] , transcriptomics analyses (RNA detection in different cell compartments) prove corona RNA in the mitochondria[19] . The mitochondria are thus forced by the virus to build viral proteins - instead of their own proteins that are necessary for their function. Another problem is that the virus enters the cell via the ACE2 receptors, which are destroyed during this process. Unfortunately, ACE2 is a key regulator of mitochondria. Its depletion collapses ATP synthesis, shuts down mitochondrial genes, inhibits the respiratory chain and lowers the membrane potential of mitochondria[20] . We now know that the vaccine spike circulating in free form in the body of vaccinated individuals can also bind to and damage ACE2[21,22] . The level is higher than in acutely ill patients, and the spike formation lasts for months[23] . It is now also known that the toxic effect of a corona infection on our vascular system is largely due to the damage caused by the spike to the mitochondria of endothelial cells. This highly mitotoxic protein destroys a cell's mitochondrial networks and collapses their function[24] . It is also highly inflammatory and induces massive free radical formation[25] . Vaccination and infection also have in common that they trigger inflammation and radicals, which, as we have already seen, are basically co-toxic. The lipid nanoparticles of the vaccination are particularly outstanding here, not only with regard to their general reaction strength[26] , but especially with regard to their inevitable systemic distribution in the body[27] - unlike in the case of an infection, all organs and tissues are automatically acutely threatened. For once, we have decided to base the vaccination on the most toxic SARS-CoV2 component, using a technical platform that ensures maximum damage when spike is introduced into the body. However, there may be room for improvement here in the future with the use of self-replicating mRNA. Another circumstance, problematic for the mitochondria, adds to the misery so far. Antibodies against the IgG-type spike protein have a significant autoreaction potential. This is due to the high similarity of the spike to endogenous structures. At the top of the list of particularly vulnerable structures are neurofilaments - and mitochondria[28] .
If this autoreaction is given, the mitochondria are attacked by the patient's own immune system, and the losses that occur can be enormous. Vaccinated people in particular often have a proportion of non-neutralising spike IgG-AK of over 95%. Here, risks in the sense of the described autoreaction but also in the direction of ADE (infection-enhancing antibodies) must be urgently considered! The situation is exacerbated by the often parallel undersupply of oxygen to the mitochondria. Here the effect is

microclots[29] and endotheliitis[30] are negative, although both are regular findings in long-covid and post-vaccine syndrome. The latter can be passably detected by biomarkers (VEGF, RANTES, IL-6), the former unfortunately not always. Negative D-dimer does not exclude microclots, in which case the probationary use of nattokinase (NSK-SD, >2,000 FU/d) is always recommended. In case of improvement and negative D-dimer, the suspected diagnosis is amyloid clot*. (Link to my amyloid article)*

Mitochondriopathy: consequences and diagnostics

Given this catastrophic hazard situation, it is little wonder that patients with long-covid or post-vaccine syndrome test positive for mitochondriopathy in almost all cases. We have already outlined its consequences for the immune system, including its potential as a precursor to cancer. But what can be expected beyond that? Well, in general, every mitochondriopathic cell will show functional deficiencies due to the obligatory lack of energy. Tissues and whole organs thus become hypofunctional, the symptoms resulting from the abandonment of the individually affected structures. Particularly common are muscle weakness, general fatigue, brain fog, under-functioning of endocrine glands (thyroid, adrenal, ovaries), generally reduced regenerative capacity and susceptibility to infections. The worsening of existing cancers and their recurrence are also frequently observed phenomena. In many cases, mitochondriopathy will make a contribution here (of varying magnitude for each individual). So the question arises as to how we can make mitochondrial damage visible. Unfortunately, conventional medicine does not do this at all; mitochondria do not enjoy any noteworthy attention here - if at all, only as a very rare, primary genetic pathology. A secondary (i.e. acquired) mitochondriopathy is completely unknown in guideline medicine, and is even rejected as a fact. First of all, simple, inexpensive addiction tests are available. The classic test par excellence is the LDH isoenzymes (LDH 1-5). An increase in isoforms 4 and/or 5 is a positive finding, as this proves increased fermentation instead of mitochondrial combustion[31] . A similar logic is followed by the measurement of M2PK in plasma, whose increase also indicates a decrease in cellular respiration[32] . More elaborate but highly useful when specific malignant risks are to be looked at (risk of recurrence, progression of active cancers) is the measurement of TKTL1/Apo10[33] . All the parameters mentioned are routinely offered by the Biovis laboratory, among others. The greatest depth of detail in terms of mitochondrial diagnostics is achieved by the so-called BHI (Bioenergetic Health Index), which represents a kind of mitochondrial MOT. Idle speed, full throttle, acceleration and braking behaviour, exhaust gas composition and fuel consumption - almost all relevant key data and functional values of the mitochondria are tested here[34] . However, such measurements are financially more expensive, and the interpretation requires expertise and experience. Especially in the case of linked toxicological or immunological questions, however, a BHI is definitely useful; the MMD laboratory under the direction of Prof. Brigitte König is particularly recommendable here[35] .

Improving mitochondrial health

It is advisable to think of mitochondrial health on several levels: education, maintenance and regeneration, functional support and protection. Most fundamental is the activation of mitochondrial genes, which is excellently provided by polyphenols: Apigenin, Curcumin, EGCG, Querctin and Resveratrol[36] . As these simultaneously have an anti-inflammatory effect[37] and an antioxidant effect[38] , and in this way they activate the mitochondria

protect against classical damaging mechanisms, polyphenols represent the royal class of pro-mitochondrial active substances. Approaches such as HBO (hyperbaric oxygen)[39] , intravenous ozone therapy[40] , intravenous oxygen (oxyvenation) and IHHT (interval hypoxia-hyperoxia therapy)[41] have both gene-activating and oxygen-supply-improving effects. Gene activation, however, comes to nothing if the substrates are lacking to convert them. The micro- and macronutrient demand of mitochondria is enormous, dozens of essential, semi-essential and non-essential nutrients are needed here. For the sake of cost efficiency and ease of use, combination preparations are a good choice, for example Mitochondrien Formula Sport[42] . This has a special charm because, in addition to the micro- and macronutrients mentioned, it also provides vitamin D binding protein. This improves the function of the VDR (vitamin D receptor), whose dysfunction in turn represents a classic problem in numerous health disorders - including all chronic inflammatory diseases, post-infectious conditions and CFS. Without an intact VDR, vitamin D does not work as it should - a substitution of the sun hormone then does not produce the desired effects and in the worst case can have a counterproductive effect[43,44] . If left untreated, VDR dysfunction promotes inflammation and inhibits the mitochondria. In chronically ill or directly post-acute patients, the basal "building blocks of life" should also be generously substituted; their depletion is often massive in both cases. These include nucleotides as well as essential amino acids and fatty acids. Especially the nucleotides offer a frequently unused but great potential - be it with regard to general regeneration[45] , antioxidation[46] , immune function[47] or anti-fatigue therapy[48] . Historically, offal and broths were used for recovery/support, but alternatively and especially for vegetarians, nucleotides can also be substituted without problems[49] . The highly stressed inner mitochondrial membrane often suffers from radicals and needs phospholipids, especially phosphatidylcholine, for maintenance. Elegant is the combination of radical scavengers and phospholipids, e.g. by liposomal glutathione[50] . Other mitochondrial scavengers that protect against radical damage include ALA (alpha lipoic acid), the glutathione precursor NAC, NADH and Q10 (which is considerably potentiated by PQQ[51]). Q10 deficits in particular have a considerable impact and often require high-dose substitution[52] . The same applies to NAC; here, too, high doses are often necessary (50 mg/kg/d), especially in the context of long-covid/post-vaccine syndrome. Reason: It is at the same time a spike antidote that neutralises it (at least partially) and keeps it away from ACE2[53] . It should be remembered that this context also requires the clarification and, if necessary, the treatment of endotheliitis and microclots (cf. above). In moderate cases or for general prophylaxis in this regard, polyphenols (set now at the latest), ASA (<100mg/d), nattokinase and serrapeptase[54] can be used instead of the relevant off-label preparations (statins, maraviroc, naltrexone, ivermectin;
https://www.florianschillingscience.org/post/workshop- *for-therapists).* Experience has shown that the most promising approach is a combination of as many of the tools mentioned as possible - especially since this is only a selection of possible candidates, a kind of best-of. The list of possible supporting tools is much longer. In the meantime, a wealth of literature is also available for anyone who wants to take a closer look at the topic of mitochondrial health. Particularly recommendable (although only light fare to a certain extent) in my view are "*Mitochondria: Symptoms, Diagnosis and Therapy*" by Dr. Kuklinski, "*Chronically Healthy*" by HP Ralf Meyer and "*Cancer as a Metabolic Disease*" by Prof. Seyfried.
Finally, I would like to emphasise a few points. Firstly, although there are now

numerous, including quite potent protocols for the treatment of long-covid and post-vaccine syndrome. Among them, however, are many that either mitochondriopathy is not or, conversely, focus "too much" on these without sufficiently acknowledging topics such as amyloids, microclots and endotheliitis (example of the latter is the protocol of the FLCCC, which I otherwise hold in high esteem). Secondly, we should also detach ourselves a bit from the current post-covid/post-vaccination context and see mitochondrial health as a top priority issue for health in general and healthy ageing in particular. If you want to do yourself good here (and anything else amounts to prematurely relieving the pension funds), you cannot avoid pro-active care of your own mitochondria. Guideline medicine (I can no longer call it orthodox medicine or evidence-based medicine, the underlying standards have been undercut too often and too brutally for that) does not know this field of work. Worse still, it frequently and persistently uses active substances that have considerable damaging potential for the mitochondria[55] . Those who seek their salvation here will be disappointed. Thirdly: The findings and laboratory reports will not be very edifying, especially at first. The first commandment is to remain calm and take action. Decades of mitochondrial medicine have given us a bulging toolbox that allows us to confront mitochondriopathy decisively, effectively and sustainably. Even the simplest things like exercise, sunlight, a balanced diet, (intermittent) fasting - behaviours that have proven their worth for years - prove to be effective tools even in times of genome analysis, molecular biology and biochemistry. Nowadays, we can simply interpret them in a more technically adept way than Paracelsus or Hippocrates.

[1] FRANCESCHI, C. & CAMPISI, J. 2014. Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases. The *Journals of Gerontology: Series A,* 69**,** S4-S9.

[2] NEWSHOLME, P., CRUZAT, V. F., KEANE, K. N., CARLESSI, R. & DE BITTENCOURT, P. I. H., JR 2016. Molecular mechanisms of ROS production and oxidative stress in diabetes. *Biochemical Journal,* 473**,** 4527-4550.

[3] HUNTER, R. L., DRAGICEVIC, N., SEIFERT, K., CHOI, D. Y., LIU, M., KIM, H.-C., CASS, W. A., SULLIVAN, P. G. & BING, G. 2007. Inflammation induces mitochondrial dysfunction and dopaminergic neurodegeneration in the nigrostriatal system. *Journal of Neurochemistry,* 100**,** 1375-1386.
[4] GUO, C., SUN, L., CHEN, X. & ZHANG, D. 2013. Oxidative stress, mitochondrial damage and neurodegenerative diseases. *Neural Regen Res,* 8**,** 2003-14.
[5] CREE, L. M., PATEL, S., PYLE, A., LYNN, S., TURNBULL, D., CHINNERY, P. & WALKER, M. 2008. Age-related decline in mitochondrial DNA copy number in isolated human pancreatic islets. *Diabetologia,* 51**,** 1440-1443.
[6] DUCHEN, M. R. 2004. Mitochondria in health and disease: perspectives on a new mitochondrial biology. Molecular *Aspects of Medicine,* 25**,** 365-451.
[7] MILLS, E. L., KELLY, B. & O'NEILL, L. A. J. 2017. Mitochondria are the powerhouses of immunity. *Nature Immunology,* 18**,** 488-498.
[8] WEST, A. P., SHADEL, G. S. & GHOSH, S. 2011. Mitochondria in innate immune responses. *Nature Reviews Immunology,* 11**,** 389-402.
[9] JAMILLOUX, Y., HENRY, T., BELOT, A., VIEL, S., FAUTER, M., EL JAMMAL, T., WALTZ, T., FRANÇOIS, B. & SÈVE, P. 2020. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmunity Reviews***,** 102567.
[10] BURTSCHER, J., CAPPELLANO, G., OMORI, A., KOSHIBA, T. & MILLET, G. P. 2020. Mitochondria: In the Cross Fire of SARS-CoV-2 and Immunity. *iScience,* 23**,** 101631.
[11] DUNN, G. P., KOEBEL, C. M. & SCHREIBER, R. D. 2006. Interferons, immunity and cancer immunoediting. Nature *Reviews Immunology,* 6**,** 836-848.
[12] MARTH, C., FIEGL, H., ZEIMET, A. G., MÜLLER-HOLZNER, E., DEIBL, M., DOPPLER, W. & DAXENBICHLER, G. 2004. interferon-γ expression is an independent prognostic factor in ovarian cancer. *American Journal of Obstetrics and Gynecology,* 191**,** 1598-1605.
[13] ANGAJALA, A., LIM, S., PHILLIPS, J. B., KIM, J.-H., YATES, C., YOU, Z. & TAN, M. 2018. Diverse Roles of Mitochondria in Immune Responses: Novel Insights Into Immuno-Metabolism. *Frontiers in Immunology,* 9.
[14] CHEN, C. T., SHIH, Y. R., KUO, T. K., LEE, O. K. & WEI, Y. H. 2008. Coordinated changes of mitochondrial biogenesis and antioxidant enzymes during osteogenic differentiation of human mesenchymal stem cells. *Stem Cells,* 26**,** 960-8.
[15] SEYFRIED, T. N. & SHELTON, L. M. 2010. Cancer as a metabolic disease. *Nutr Metab (Lond),* 7**,** 269-270.
[16] SEYFRIED, T. N., FLORES, R., POFF, A. M. & D'AGOSTINO, D. P. 2013. Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis***,** bgt480.
[17] WU, K. E., FAZAL, F. M., PARKER, K. R., ZOU, J. & CHANG, H. Y. 2020. RNA-GPS Predicts SARS-CoV-2 RNA Residency to Host Mitochondria and Nucleolus. *Cell Systems,* 11**,** 102-108.e3.
[18] CHENG, Z., ZHANG, D., CHEN, J., WU, Y., LIU, X., SI, L., ZHANG, Z., ZHANG, N., ZHANG, Z., LIU, W., LIU, H., ZHANG, L., SONG, L., DUNMALL, L. S. C., DONG, J., LEMOINE, N. R. & WANG, Y. 2020. A novel viral protein. translation mechanism reveals mitochondria as a target for antiviral drug development. *bioRxiv***,** 2020.10.19.344713.
[19] BURTSCHER, J., CAPPELLANO, G., OMORI, A., KOSHIBA, T. & MILLET, G. P. 2020. Mitochondria: In the Cross Fire of SARS-CoV-2 and Immunity. *iScience,* 23**,** 101631.
[20] SHI, T.-T., YANG, F.-Y., LIU, C., CAO, X., LU, J., ZHANG, X.-L., YUAN, M.-X., CHEN, C. & YANG, J.-K. 2018. Angiotensin-converting enzyme 2 regulates mitochondrial function in pancreatic β-cells. *Biochemical and Biophysical Research Communications,* 495**,** 860-866.
[21] OGATA, A. F., CHENG, C.-A., DESJARDINS, M., SENUSSI, Y., SHERMAN, A. C., POWELL, M., NOVACK, L., VON, S., LI, X., BADEN, L. R. & WALT, D. R. 2021. Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients. *Clinical Infectious Diseases,* 74**,** 715-718.
[22] MOBEEN, S. Spike Protein Spills in the Blood of the Vaccinated Individuals (Study).
[23] BANSAL, S., PERINCHERI, S., FLEMING, T., POULSON, C., TIFFANY, B., BREMNER, R. M. & MOHANAKUMAR, T. 2021 Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer-BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines. The *Journal of Immunology,* 207**,** 2405-2410.
[24] LEI, Y., ZHANG, J., SCHIAVON, C. R., HE, M., CHEN, L., SHEN, H., ZHANG, Y., YIN, Q., CHO, Y., ANDRADE, L., SHADEL, G. S., HEPOKOSKI, M., LEI, T., WANG, H., ZHANG, J., YUAN, J. X.-J., MALHOTRA, A., MANOR, U., WANG, S., YUAN, Z.-Y. & SHYY, J. Y.-J. 2021. SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2. *Circulation Research,* 128**,** 1323-1326.
[25] LI, F., LI, J., WANG, P.-H., YANG, N., HUANG, J., OU, J., XU, T., ZHAO, X., LIU, T., HUANG, X., WANG, Q., LI, M., YANG, L., LIN, Y., CAI, Y., CHEN, H. & ZHANG, Q. 2021. SARS-CoV-2 spike promotes inflammation and apoptosis.

through autophagy by ROS-suppressed PI3K/AKT/mTOR signalling. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease,* 1867**,** 166260.
[26] NDEUPEN, S., QIN, Z., JACOBSEN, S., ESTANBOULI, H., BOUTEAU, A. & IGYÁRTÓ, B. Z. 2021. The mRNA-LNP. platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. *bioRxiv***,** 2021.03.04.430128.
[27] TINARI, S. 2021. The EMA covid-19 data leak, and what it tells us about mRNA instability. *BMJ,* 372**,** n627.
[28] VOJDANI, A., VOJDANI, E. & KHARRAZIAN, D. 2021. Reaction of Human Monoclonal Antibodies to SARS-CoV-2 Proteins With Tissue Antigens: Implications for Autoimmune Diseases. *Frontiers in Immunology,* 11.
[29] GROBBELAAR, L. M., VENTER, C., VLOK, M., NGOEPE, M., LAUBSCHER, G. J., LOURENS, P. J., STEENKAMP, J., KELL, D. B. & PRETORIUS, E. 2021. SARS-CoV-2 spike protein S1 induces fibrin(ogen) resistant to fibrinolysis: implications for microclot formation in COVID-19. *Bioscience reports,* 41**,** BSR20210611.
[30] PATTERSON, B. K., FRANCISCO, E. B., YOGENDRA, R., LONG, E., PISE, A., RODRIGUES, H., HALL, E., HERRERA, M., PARIKH, P., GUEVARA-COTO, J., TRICHE, T. J., SCOTT, P., HEKMATI, S., MAGLINTE, D., CHANG, X., MORA-. RODRÍGUEZ, R. A. & MORA, J. 2022. Persistence of SARS CoV-2 S1 protein in CD16+ monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection. *Frontiers in Immunology,* 12.
[31] OLIVER, J. A., ELHILALI, M. M., BELITSKY, P. & MACKINNON, K. J. 1970. LDH isoenzymes in benign and malignant prostate tissue. The LDH V/I ratio as an index of malignancy. *Cancer,* 25**,** 863-866.
[32] YANG, W. & LU, Z. 2013. Nuclear PKM2 regulates the Warburg effect. *Cell Cycle,* 12**,** 3154-8.
[33] COY, J. F. 2017. EDIM-TKTL1/Apo10 Blood Test: An Innate Immune System Based Liquid Biopsy for the Early Detection, Characterization and Targeted Treatment of Cancer. *International journal of molecular sciences,* 18**,** 878.
[34] BIOVIS (2022) 'Mitochondriale Diagnostik', Available: https://biovis.eu/wp-content/uploads/Biovis_Mitochondriale_Diagnostik_DE.pdf (Accessed).
[35] MMD (2022) 'Bioenergetic Health Index', Available: http://www.mmd-web.de/mediapool/69/693400/data/Info_Bioenergetic_Health_Index_09042017.pdf (Accessed). [36] WHITAKER, R. M., CORUM, D., BEESON, C. C. & SCHNELLMANN, R. G. 2016. Mitochondrial Biogenesis as a Pharmacological Target: A New Approach to Acute and Chronic Diseases. *Annual Review of Pharmacology and Toxicology,* 56**,** 229-249.
[37] YAHFOUFI, N., ALSADI, N., JAMBI, M. & MATAR, C. 2018. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients,* 10**,** 1618.
[38] TEIXEIRA, J., DEUS, C. M., BORGES, F. & OLIVEIRA, P. J. 2018. Mitochondria: Targeting mitochondrial reactive oxygen species with mitochondriotropic polyphenolic-based antioxidants. The *International Journal of Biochemistry & Cell Biology,* 97**,** 98-103.
[39] ROCKSWOLD, S. B., ROCKSWOLD, G. L. & DEFILLO, A. 2007. Hyperbaric oxygen in traumatic brain injury. Neurological *Research,* 29**,** 162-172.
[40] ELVIS, A. M. & EKTA, J. S. 2011. Ozone therapy: A clinical review. *Journal of natural science, biology, and medicine,* 2**,** 66-70.
[41] MANKOVSKA, I. N. & SEREBROVSKA, T. V. 2015. Mitochondria as a Target of Intermittent Hypoxia. *International Journal of Physiology and Pathophysiology,* 6.
[42] MITOCARE (2022b) 'MITOCHONDRIEN FORMULA', Available: https://mitocare.de/products/mitochondrien-formula-sport (Accessed 14.07.21).
[43] SCHILLING, F. 2021. Vitamin D - Modern Myths and Ambivalent Immunology. *OM & Nutrition*.
[44] SCHILLING, F. 2022. VITAMIN D - Modern Myths and Ambivalent Immunology.
[45] DE LAS PEÑAS, R., MAJEM, M., PEREZ-ALTOZANO, J., VIRIZUELA, J., DIZ, P., DONNAY, O., HURTADO, A., JIMENEZ-FONSECA, P. & OCON, M. 2019. SEOM clinical guidelines on nutrition in cancer patients (2018). *Clinical and translational oncology,* 21**,** 87-93…,
[46] HU, L., PENG, X., QIN, L., WANG, R., FANG, Z., LIN, Y., XU, S., FENG, B., WU, D. & CHE, L. 2018. Dietary nucleotides supplementation during the suckling period improves the antioxidative ability of neonates with intrauterine growth retardation when using a pig model. *RSC advances,* 8**,** 16152-16160.
[47] CARVER, J. 1999. Dietary nucleotides: effects on the immune and gastrointestinal systems. *Acta Paediatrica,* 88**,** 83-88.
[48] XU, M., LIANG, R., LI, Y. & WANG, J. 2017. Anti-fatigue effects of dietary nucleotides in mice. *Food & nutrition research,* 61**,** 1334485.
[49] MITOCARE 2022c. Premium nucleotides.
[50] MITOCARE (2022a) 'Lipo Glutathione Booster', Available: https://mitocare.de/products/lipo-glutathion-booster (Accessed).
[51] (2021) 'PQQ TOTAL', Available: https://mitocare.de/Produkte/MITOcare-Neuheiten/PQQ-TOTAL.aspx (Accessed 14.07.2021).

[52] QUINZII, C. M., LÓPEZ, L. C., VON-MOLTKE, J., NAINI, A., KRISHNA, S., SCHUELKE, M., SALVIATI, L., NAVAS, P., DIMAURO, S. & HIRANO, M. 2008. respiratory chain dysfunction and oxidative stress correlate with severity of primary CoQ10 deficiency. *Faseb j,* 22**,** 1874-85.

[53] DE FLORA, S., BALANSKY, R. & LA MAESTRA, S. 2020. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. *The FASEB Journal,* 34**,** 13185-13193.

[54] METKAR, S. K., GHOSH, S., GIRIGOSWAMI, A. & GIRIGOSWAMI, K. 2019. The Potential of Serratiopetidase and Lumbrokinase for the Degradation of Prion Peptide 106-126 - an In Vitro and In Silico Perspective. *CNS Neurol Disord Drug Targets,* 18**,** 723-731.

[55] WILL, Y., SHIELDS, J. E. & WALLACE, K. B. 2019. Drug-Induced Mitochondrial Toxicity in the Geriatric Population: Challenges and Future Directions. *Biology,* 8**,** 32.