Review Article

Transfer Factor as an Option for Managing the COVID-19 Pandemic

(cell-mediated immunity / Covid-19 / cytotoxic T lymphocytes / flu / herpes / immunodeficiencies / immunomodulation / transfer factor / vaccines / T cells)

D. VIZA[1*], G. PIZZA[2*], C. DE VINCI[2**], G. BRANDI[3], D. ABLASHI[4]

[1]Immunobiology Laboratory, Faculté de Médicine, Paris 6, France
[2]Immunotherapy dept., S. Orsola-Malpighi University Hospital, Bologna, Italy
[3]Medical Oncology, S. Orsola-Malpighi University Hospital, Bologna, Italy
[4]HHV-6 Foundation, Santa Barbara, CA, USA
[*]fmr Director, [**]fmr Assistant

Abstract. Covid-19 or SARS-CoV-2, a new RNA virus with high infectivity, and seemingly low mutability, which appeared in 2019 in the Wuhan province of China, has created a pandemic with dire consequences. At the end of May 2020, it became the first cause of mortality. As no treatment or vaccine may become available before many months, and because occurrence of similar pandemics is only a matter of time, arguments are presented here for testing the effect of transfer factor (TF), an immunomodulator devoid of toxicity, which has been extensively studied in the past for the treatment and prevention of viral infections.

Introduction

The first case of SARS-CoV-2 or Covid-19 infection, a new coronavirus, was detected on December 27th, 2019 in Wuhan of the Hubei province of China, and its human-to-human transmission was suggested in Taiwan on December 31st. On March 11th, 2020, the World Health Organisation (WHO) declared this viral infection a global pandemic. Meanwhile, the virus has travelled to Europe and to the USA.

The origin of the virus is a matter of debate. Probably stemming from pangolins and bats in China's wet markets, in 120 days since the first observations, it has spread to every country. By the end of May 2020, the pandemic would have officially caused nearly 84,000 infections and 5,000 deaths in China, from where it would have disappeared within three months to reappear in June 2020.

Worldwide, by the end of July 2020, there were nearly 13 million confirmed infections, a largely underestimated number, as only a fraction of the population has been tested – the number of asymptomatic carriers is estimated to be five times higher than it has been predicted – and over 600,000 deaths. According to the CDC (Centers for Disease Control and Prevention in the USA) estimates, asymptomatic infections represent 40 % of the total number.

The infection by Covid-19 produces three main symptoms: fever, cough, and shortness of breath, similar to those seen in the severe acute respiratory syndrome (SARS) virus infections. However, certain older adults, the age group most at risk of severe complications and death, may show none of these symptoms, but sometimes they seem not acting as usual, sleep more, stop speaking, eating, feel dizzy, and even collapse.

Half of the infected patients, including those with a favourable outcome, present seemingly pathognomonic neurological disorders, viz. anosmia, ageusia or dysgeusia, whereas hospitalized older patients often develop a systemic hyperinflammatory syndrome, with increased levels of circulating cytokines, atypical acute respiratory distress syndrome, with loss of neurological control of lung perfusion regulation, and hypoxic vasoconstriction.

Cardiomyopathies and lung lesions are also observed in asymptomatic patients, whereas cases of Kawasaki's

Received June 26, 2020. Accepted July 10, 2020.

Corresponding author: Dharam Ablashi, HHV-6 Foundation, 1482 East Valley Road, Suite 619, Santa Barbara, CA 93109, USA. Phone: (+001) 678-331-1899; e-mail: dharam_ablashi@hhv-6foundation.org

Abbreviations: CMI – cell-mediated immunity, CMV – cytomegalovirus, CFS – chronic fatigue syndrome, DTH – delayed type hypersensitivity, EBV – Epstein-Barr virus, HIV – human immunodeficiency virus, HSV – herpes simplex virus, MW – molecular weight, NPC – nasopharyngeal carcinoma, SAIDS – simian AIDS, SARS – severe acute respiratory syndrome, SIV – simian immunodeficiency virus, TF – transfer factor, VZV – varicella zoster virus, WHO – World Health Organisation.

disease have been described in children (Gattinoni et al., 2020; Harahsheh et al., 2020; Lauer et al., 2020; Meng et al., 2020; Zheng et al., 2020). Moreover, certain patients, months after having recovered from the infection, present symptoms reminiscent of those of the chronic fatigue syndrome (CFS), whose aetiopathology is not totally understood, although certain herpes viruses, viz. HHV-6, seem to play an important role (Buchwald et al. 1990, 1992; Afari and Buchwald, 2003; Rasa et al. 2018; Schreiner et al., 2020). Such manifestations seem to occur even in asymptomatic infected individuals.

This semiological and pathological polymorphism should be considered in the attempts to understand the physiopathology of the disease. Systematic serological tests that include everybody are needed to determine, inter alia, the precise percentage of asymptomatic patients and confirm that they are protected from future symptomatic novel infections by the same virus. They should also contribute to determination of the duration of such protection, as well as the role that is played by cell-mediated immunity (CMI).

In the recent past, life-threatening viruses, e.g., SARS-CoV-1, EBOLA, MERS-CoV have appeared, and new viruses will continue to emerge in the future, with often unpredictable and unique behaviour. For instance, SARS, a coronavirus with low risk of transmission, generating a severe illness, has apparently disappeared, whereas new cases of MERS-CoV are periodically diagnosed.

However, despite attempts to extrapolate from the past, the existence of many unknown variables is making the end of the present pandemic uncertain. Many hope that it will spontaneously fade away, as it has been the case for H1N1, H5N1, and SARS-CoV-1 viruses. Alternatively, it may become endemic, producing flu-like, low mortality, seasonally recurring outbreaks.

Conventional strategies to contain viral pandemics consist in testing, to evaluate the number of infected individuals, and preferably isolating them; in using antiviral drugs for treating symptomatic patients, and vaccines for protecting naïve populations. Testing, to be meaningful, should be virus-specific, being able to make the difference between Covid-19 and other coronaviruses, and to be effective, vaccines should provide long-term protection: a short-lived immunity offers a misleading feeling of security.

So far, the search for effective antiviral drugs has not produced satisfactory results, whereas the hunt for an efficacious vaccine, with as many as 133 candidates in the pipeline, 123 in preclinical, 10 in clinical evaluation, and logistical problems ahead, is several months away from reaching its goal, despite daily announcements of imminent breakthroughs boosting the stock market value of the manufacturing companies.

It is worth considering here that the always possible mutations of Covid-19 may render newly developed vaccines at best partially ineffective. Also, if the epidemic were to disappear before new vaccines became profitable for the manufacturers and their shareholders, future stock market gambling to fight new epidemics may be discouraged.

Be that as it may, as long as an effective vaccine is not available, the world will be exposed to successive outbreaks of Covid-19; its fading out by protective '*herd immunity'* requires acquisition of immunity by 70 % of the population, far from the 25 % observed today in the worst infected areas.

Thus, even if the rate of new infections may periodically seem declining in various areas, as long as the virus continues to circulate and a vaccine is not available to be used worldwide, the present pandemic may persist, with possible successive waves or ripples of new infections occurring episodically, as in the case of the seasonal flu and as it has been observed in the USA.

During the 2005 avian flu epidemic, we were suggesting adapting transfer factor (TF) to be used against the H5N1 virus and further studying its possible use for other emerging viruses (Pizza et al., 2006). Today, there is urgent need to contain the COVID-19 pandemic, which has created a medical emergency that may end in social disaster. Studying the use of TF is thus warranted, as it may provide an easy solution to the present crisis.

Transfer Factor

Transfer factor (TF), an immunomodulator capable of transferring antigen-specific information to T lymphocytes, was described over half a century ago by Lawrence (1955). He showed that CMI could be transmitted by acellular extracts of lymphocytes from immune donors to naïve recipients, reminding the passive transfer of humoral immunity by the antibodies present in the plasma of immune patients, except that in the case of TF the transfer triggers an active cellular immune response by recruiting naïve T lymphocytes. He assumed that a low molecular weight (< 12,000 > 3500 Da), dialysable moiety, which he named Transfer Factor, was responsible for this adoptive CMI transfer.

In the last 65 years, TF was used in numerous clinical trials (Viza et al., 2013), inter alia for treating parasitic and viral diseases, such as cutaneous leishmaniasis (Sharma et al., 1979a, b; Delgado et al., 1981), cryptosporidiosis (McMeeking et al., 1990), acute CMV infections (Nkrumah et al., 1985), EBV-induced nasopharyngeal carcinoma (Prasad et al., 1996; Levine et al., 2011), and herpes (HSV-1 and HSV-2) infections (Dwyer, 1983; Viza et al., 1985; Pizza et al., 1995).

Furthermore, several reports suggest that when a virus-specific TF is administered before the encounter with a pathogen, the recipient may be protected. For instance, using a varicella-zoster-specific (VZV) TF, Steele and co-workers succeeded in protecting leukaemic children from VZV infections during chemotherapy treatments (Steele, 1980; Steele et al., 1980). Prevention against HSV infections was also observed in primates (Steele et al., 1976), rodents (Viza et al., 1986), whereas macaques were protected from the progression of simian AIDS (SAIDS), Viza et al. (1988).

In the early days, TF was prepared from the lymphocytes of patients' asymptomatic household contacts. Subsequently, once it was established that TF was not species specific, from immunized animals (Klesius et al., 1978). It may thus be used for the treatment of even unknown, newly emerged pathogens: the immune system needs not a laboratory label to recognize a new virus. For instance, HIV-specific TF was prepared before the AIDS virus was identified (Viza et al., 1987).

Discussion

It has been suggested that the Covid-19 infection may primarily affect CMI, viz. $CD4^+$ and $CD8^+$ T lymphocytes, whose numbers may be in correlation with the disease severity (Chen G. et al., 2020; Wang et al., 2020). By stimulating CMI and increasing the number of cytotoxic lymphocytes, TF should contribute in reducing the viral load; and by modulating the overreaction of the immune system that most steroids fail to restrain, and which is mainly responsible for the mortality, it should be able to control the disease. Thus, following its administration, an increased number of asymptomatic patients should be observed along with decreased mortality.

For initial pilot studies, Covid-19-specific TF may be obtained from plasma dialysates of convalescent patients. Plasma from such patients has already been used with encouraging results in treating Covid-19 symptomatic patients (Chen L., et al., 2020; Duan et al., 2020). Its activity has so far been attributed to the antiviral antibodies it contains, which will be absent from the dialysates. Once effectiveness has been confirmed, the onset of bulk production may be speedily undertaken by establishing new or by inducing existing lymphoblastoid cell lines (Viza et al., 1975, 1982) and/or by animal immunization.

As TF has been utilized in the past for treating thousands of patients without any adverse side effect, testing its therapeutic and preventative activity in the Covid-19 pandemic may be carried out speedily, skipping phase 1 trials. Several past clinical studies, some carried out over long periods, have confirmed that, and as it may have been expected, no toxicity concerns are warranted for dialysates containing low molecular weight (< 12000 Da) moieties (Viza et al., 2013).

The main problem with TF is not toxicity, nor credibility of all the numerous clinical reports and animal experiments that have not been challenged, but the partial failure to unravel its molecular structure and comprehend its mode of action (Kirkpatrick, 2000; Myles et al., 2017). As a result, and for many, its reality remains speculative. Today, the fear of the irrational makes it safer to dismiss an unexplained fact than to get mixed up with a possible fluke. And so far, the easy way out of the TF conundrum has been to attribute all clinical results to placebo effects, disregarding even easily reproducible animal data.

Getting rid of the placebo effect, sometimes capable of healing patients by unclear unscientific mechanisms, is an obsession of modern scientific medicine, which abhors ignorance and credulity, hallmarks of a superstitious past. Hence, the passionate and occasionally shameful debates, resembling more religious medieval controversies than scientific arguments of the 21st century, have recently erupted regarding the use of hydroxychloroquine for lack of double-blind clinical trials validating its efficacy in treating Covid-19 patients. Following two reports (Boulware et al., 2020; Mehra et al., 2020) confirming a previous quasi-consensus regarding the inefficacy and side effects of this rather '*ancient'* drug, contradicting previous reports to the contrary, the WHO decided to discontinue clinical trials pertaining to its use, but promptly reinstate them when the credibility and impartiality of these publications became problematic. Far from being over, the controversy persists as the inefficacy of the drug continues to be denied and reconfirmed.

And yet, observation and experimentation, conjectures and refutations are the pillars of modern science, and opposition and dissent should be welcome, except when they are becoming pretexts for petty bickering, trying to reject what lies outside the comfort of the dominant paradigm. Science progresses only by conjectures and refutations. Each hypothesis should be continuously tested (*falsified*) until proven false, in order to be replaced by a novel one (Popper, 1959, 1963, 1975). In science, or even in politics, rigging or denial of facts should be unforgivable.

The season is not suitable to theoretical quarrels. Inaction or negligence to explore all possible avenues will only cost additional lives. To the grim predictions of Covid-19 mortality that many models forecast, there are the no less severe psychological consequences for the survivors of the virus that lockdowns to prevent its spread will cause.

With its cohort of deaths, the cost of global recession will further widen the gap between the rich and the poor, the white and the coloured, transforming Giovanni Boccaccio's stories in the Decameron, following the 1347 Black Death epidemic in Italy, to a forewarning (Ahmed et al., 2020).

In Boccaccio's time, epidemics were God's punishment for the sinners. Today, for many who confuse cause and effect, the culprits are loss of biodiversity and pollution. If unlimited population growth is periodically pointed out, criticisms are usually quickly dismissed as ridiculous fears by those who prefer to sacrifice the living to the unborn. And yet, common sense suggests that it is difficult to handle epidemics, limiting viral circulation and implementing lockdowns in overcrowded places and metropolises. With soon eleven billion inhabitants (United Nations News, 2017), earth is an overcrowded planet, and the unpredictable but certain emergence of new viruses in the future will be all the more difficult to control.

Certain hope, while others fear that the Covid-19 pandemic may be the beginning of awareness, and the last nail on globalization, borders' suppression, and unlimited economic growth. Be that as it may, it would be a

mistake if at the end of this virus outbreak we were to continue business as usual, waiting unprepared for the onset of the next one. Equally inexcusable will be to neglect investigating all means, including the potential of TF, for fighting the present and future epidemics.

References

Afari, N., Buchwald, D. (2003) Chronic fatigue syndrome: A review. *Am. J. Psychiatry* **160**, 205-207.

Ahmed, F., Ahmed, N., Pissarides, C., Stiglitz, J., (2020) Why inequality could spread COVID-19. *The Lancet* **5**, 5.

Boulware, D. R., Pullen, M. F., Bangdiwala, A. S., Pastick, K. A., Lofgren, S. M., Okafor, E. C., Skipper, C. P., Nascene, A. A., Nicol, M. R., Abassi, M., Engen, W. N., Cheng M. P., LaBar, D., Lother, S. A., MacKenzie, L. J., Drobot, D., Marten, N., Zarychanski, R, Kelly, L., E., Schwartz, I., S., McDonald, E.,G., Rajasingham, R., Lee, T. C., Hullsiek, K., H. (2020) A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N. Eng. J. Med.* **1**, 9.

Buchwald, D., Freedman, A. S., Ablashi, D. V., Sullivan, J. L., Calligiuri, M., Weinberg, D. S., Hall, C. G., Bashir, R., Singer, R. M., Ashley, R. L., Saxinger, C., Balachandran, N., Ritz, J., Nadler, L. M., Komaroff, A. L. (1990) A chronic "post-infectious" fatigue associated with benign lymphoproliferation, B-cell proliferation and active replication of human herpesvirus-6. *J. Clin. Immunol*. **10**, 335-344.

Buchwald, D., Cheney, P., Peterson, D. L., Henry, B., Wormsley, S. B., Geiger, A., Ablashi, D. V., Salahuddin, S. Z., Saxinger, C., Biddle, R., Kilkinis, R., Jolesz, F. A., Folks, T., Balachandran, N., Gallo, R. C., Komaroff, A. L. (1992) A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus-6 infection. *Ann. Intern. Med.* **116**, 103-113.

Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., Wang, T., Zhang, X., Chen, H., Yu, H., Zhang, X., Zhang, M., Wu, S., Song, J., Chen, T., Han, M., Li, S., Luo, X., Zhao, J., Ning, Q. **(**2020**)** Clinical and immunological features of severe and moderate coronavirus disease 2019**.** *J. Clin. Invest.* **130**, 2620-2629.

Chen, L., Xiong, J., Bao, L., Shi, Y. (2020) Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect. Dis.* **20**, 398-400.

Delgado, O., Romano, E. L., Belfort, E., Pifano, F., Scorza, J. V, Rojas, Z. (1981) Dialyzable leukocyte extracts therapy in immunodepressed patients with cutaneous leishmaniasis. *Clin. Immunol. Immunopathol.* **19**, 351-358.

Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., Zhou, M., Chen, L., Meng, S., Hu, Y., Peng, C., Yuan, M., Huang, J., Wang, Z., Yu, J., Gao, X., Wang, D., Yu, X., Li, L., Zhang, J., Wu, X., Li, B., Xu, Y., Chen, W., Peng, Y., Hu, Y., Lin, L., Liu, X., Huang, S., Zhou, Z., Zhang, L., Wang, Y., Zhang, Z., Deng, K., Xia, Z., Gong, D., Zhang, W., Zheng, X., Liu, Y., Yang, H., Zhou, D., Yu, D., Hou, J., Shi, Z., Chen, S., Chen, Z., Zhang, X., Yang, X. (2020) Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc. Natl. Acad. Sci. USA* **117**, 9490-9496.

Dwyer, J. M. (1983) The use of antigen-specific transfer factor in the management of infections with herpes viruses. In: C. H. Kirkpatrick: *Immunobiology of Transfer Factor*, pp. 233-244. Academic Press, New York.

Gattinoni, L., Coppola, S., Cressoni, M., Busana, M., Rossi, S., Chiumello, D. (2020) Covid-19 does not lead to a "typical" acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med*. **201**, 1299-1300.

Harahsheh, A. S., Dahdah, N., Newburger, J. W., Portman, M. A., Piram, M., Tulloh, R., McCrindle, B. W., de Ferranti, S. D., Cimaz, R., Truong, D. T., Jane C. Burns , J. C. (2020) Missed or delayed diagnosis of Kawasaki disease during the 2019 novel coronavirus disease (COVID-19) pandemic. *J. Pediatr*. **222**, 261-262.

Kirkpatrick, C. H., (2000) Transfer factors: identification of conserved sequences in transfer factor molecules. *Mol. Med.* **6**, 332-341.

Klesius, P. H., Qualls, D. F., Elston, A. L., Fudenberg, H. H. (1978) Effects of bovine transfer factor (TFd) in mouse coccidiosis (Eimeria ferrisi). *Clin. Imm. Immunopath.* **10**, 214-221.

Lauer, S. A., Grantz, K. H., Bi, Q., Jones, F. K., Zheng, Q., Meredith, H. R., Azman, A. S., Reich, N. G., Lessler, J. (2020) The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann. Intern. Med.* doi: 10.7326/M20-0504.

Lawrence, H. S. (1955) The transfer in humans of delayed skin sensitivity to streptococci M substance and to tuberculin with disrupted leukocytes. *J. Clin. Invest.* **34**, 219-32.

Levine, P. H., Pizza, G., Ajmera, K., De Vinci, C., Viza, D. (2011) Transfer factor in virus-associated malignancies: an underestimated weapon in prevention and treatment of cancer. *Adv. Tumor Virol.* **2**, 7-20.

McMeeking, A., Borkowski, W., Klesius, P. H., Bonk, S., Holzman, R. S., Lawrence, H. S. (1990) A controlled trial of bovine dialyzable leukocyte extract for cryptosporidiosis in patients with AIDS. *J. Infect. Dis.* **161**, 108-112.

Mehra, M. R., Desai, S. S., Ruschitzka, F., Patel, A. N. (2020) Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *The Lancet*. RETRACTED.

Meng, H., Xiong, R., He, R., Lin, W., Hao, B., Zhang, L., Lu, Z., Shen, X., Fan, T., Jiang, W., Li, T., Chen, J., Geng, Q. (2020) CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan. *J. Infect*. **81**, 33-39.

Myles, I. A., Zhao, M., Nardone, G., Olano, L. R., Reckhow, J. D., Saleem, D., Break, T. J., Lionakis, M. S., Myers, T. G., Gardina, P. J., Kirkpatrick, C. H., Holland, S. M., Datta, S. K. (2017) $CD8^+$ T cells produce a dialyzable antigen-specific activator of dendritic cells. *J. Leukoc. Biol.* **101**, 307-320.

Nkrumah, F., Pizza, G., Viza, D., Phillips, J., De Vinci, C., Levine, P. (1985) Regression of progressive lymphadenopathy in a young child with acute cytomegalovirus (CMV) infection following the administration of transfer factor with specific anti-CMV activity. *Lymphokine Res.* **4**, 237-241.

Pizza, G., Amadori, M., Ablashi, D., De Vinci, C., Viza, D., (2006) Cell mediated immunity to meet the avian influenza A (H5N1) challenge. *Med. Hypotheses* **67**, 601-608.

Pizza, G., Meduri, R., De Vinci, C., Scorolli, L., Viza, D. (1995) Transfer factor prevents relapses in herpes keratitis patients: A pilot study. *Biotherapy* **8**, 63-68.

Popper, K. R. (1959) *The Logic of Scientific Discovery*. Hutchinson, London.

Popper, K. R. (1963) *Conjectures and Refutations*. Routledge and Kegan, London.

Popper, K.R., (1975) *Objective Knowledge*. Oxford University Press.

Prasad, U., bin Jalaludin, M. A., Rajadurai, P., Pizza, G., De Vinci, C., Viza, D., Levine, P. H. (1996) Transfer factor with anti-EBV activity as an adjuvant therapy for nasopharyngeal carcinoma: A pilot study. *Biotherapy* **9**, 109-115.

Rasa, S., Nora-Krukle, Z., Henning, N., Eliassen, E., Shikova, E., Harrer, T., Scheibenbogen, C., Murovska, M., Bhupesh, K. P. (2018) Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *J. Transl. Med.* **16,** 268.

Schreiner, P., Harrer, T., Scheibenbogen, C., Lamer, S., Schlosser, A., Naviaux, R. K., Prusty, B. K. (2020) Human herpesvirus-6 reactivation, mitochondrial fragmentation, and the coordination of antiviral and metabolic phenotypes in myalgic encephalomyelitis/chronic fatigue syndrome. *Immunohorizons* **4**, 201-215.

Sharma, M., Firouz, R., Ala, F. (1979a) Transfer factor therapy in human cutaneous leishmania infection (CLI): A double-blind clinical trial in immune regulators. In: *Transfer Factor,* eds. Khan, A., Kirkpatrick, C. H., Hill, N. O., pp. 563-570. Academic Press, N.Y.

Sharma, M. K., Anaraki, F., Ala, F. (1979b) Preliminary results of transfer factor therapy of persistent cutaneous leishmania infection. *Clin. Immunol. Immunopathol.* **12**, 183-190.

Steele, R. W., Heberling, R. L., Eichberg, J. W. (1976) Prevention of herpes simplex virus type 1 fatal dissemination in primates with human transfer factor. In: Ascher, M. S., Gottlieb, A. A., Kirkpatrick, C. H.: *Transfer Factor. Basic Properties and Clinical Applications*, pp. 381-384. Academic Press, New York.

Steele, R. W., (1980) Transfer factor and cellular reactivity to varicella zoster antigen in childhood leukaemia. *Cell. Immunol*. **50**, 282-289.

Steele, R. W., Myers, M. G., Vincent, M. M., (1980). Transfer factor for the prevention of varicella zoster infection in childhood leukaemia. *N. Eng. J. Med*. **303**, 355-359.

United Nations News, Department of Economic and Social Affairs. (2017) *World population projected to reach 9.8 billion in 2050, and 11.2 billion in 2100*. June 21, New York.

Viza, D., Goust, J. M., Moulias, R., Trejdosiewicz, L. K., Collard, A., Müller-Bérat, N., (1975) 'In vitro' production of transfer factor by lymphoblastoid cell lines. *Transplant.* **VII (suppl. 1)**, 329-333.

Viza, D., Boucheix, C., Cesarini, J. P., Ablashi, D. V., Armstrong, G., Levine, P., Pizza, G., (1982) Characterization of a human lymphoblastoid cell line, LDV/7, used to replicate transfer factor and immune RNA. *Biol. Cell*. **46**, 1-10.

Viza, D., Vich, J. M., Phillips, J., Rosenfeld, F. (1985) Orally administered specific transfer factor for the treatment of herpes infections. *Lymphok. Res*. **4**, 27-30.

Viza, D., Vich, J. M., Phillips, J., Rosenfeld, F., Davies, D. A. L. (1986) Specific transfer factor protects mice against lethal challenge with herpes simplex virus. *Cell. Immun.* **100**, 555-562.

Viza, D., Lefesvre, A., Patrasco, M., Phillips, J., Hebbrecht, N., Laumond, G., Vich, J. M., (1987) A preliminary report on three AIDS patients treated with anti-HIV specific transfer factor. *J. Exp. Pathol.* **3**, 653-659.

Viza, D., Vich, J. M., Minarro, A., Ablashi, D. V., Salahuddin, S. Z. (1988) Soluble extracts from a lymphoblastoid cell line modulate SAIDS evolution. *J. Virol. Methods* **21**, 241-253.

Viza, D., Fudenberg, H. H., Palareti, A., Ablashi, D., De Vinci, C., Pizza, G. (2013) Transfer factor: an overlooked potential for the prevention and treatment of infectious diseases. *Folia Biol. (Praha)* **59**, 53-67.

Wang, F., Nie, J., Wang, H., Zhao, Q., Xiong, Y., Deng, L., Song, S., Ma, Z., Mo, P., Zhang, Y. (2020) Characteristics of peripheral lymphocyte subset alteration in COVID-19. *Pneumonia J. Infect. Dis*. **221**, 1762-1769.

Zheng, Y. Y., Ma, Y. T., Zhang, J. Y., Xie, X. (2020) COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol*. **17**, 259-260.