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Commentary: Trained immunity and beyond: the not-yet lost chance to win with COVID-19

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Abstract

COVID-19 pandemic has frightened people and governments all around the world. The common opinion is that there are no efficient preventive measures but masks, isolation, and social distancing. The deliverance is hoped from the SARS-CoV-2-specific vaccine, which must be efficient and cheap. But, so far nobody knows when, and if such a vaccine will be developed and mass-produced. Trained immunity with oral polio vaccine (OPV) was recently proposed as a temporal solution against the heavy course of COVID-19. However, politics do not seem to follow, and the scientific world should react because humanity has no time to lose. Below, we support this with our thoughts.

On June 12th 2020, i.e. during the first wave of COVID-19 pandemic, Science journal published the Viewpoint article entitled "Can existing live vaccines prevent COVID-19?" by Konstantin Chumakov, Christine S. Benn, Peter Aaby, Shyamasundaran Kottilil, Robert Gallo[1]. The information cited in this commentary gives great hope that the old and very well-characterized oral polio vaccine (OPV) can be the salvation before the expected development of the SARS-CoV-2-specific vaccine. The authors also hypothesize that the OPV may be the only real solution even in the future if SARS-CoV-2 mutate and the specific vaccine appear weak or inefficient. Similar conclusions were presented by Netea and collaborators[2] who also pointed to the preventive function of the Bacille Calmette-Guérin (BCG) vaccine against many of the respiratory viruses. However, it seems that these two appeals fell on deaf ears. We have followed the world news concerning COVID-19 prevention, and no reaction to these simple solutions has been heard. One of us wrote a newspaper article in the Polish journal Gazeta Wyborcza[3] about the subject, but apparently, it also has been heard only by the deaf ears.

Trained immunity, and especially the use of OPV appears to be an excellent solution for immediate dealing with the current pandemic. If the governments hesitate to order massive vaccinations for organizational or other unknown reasons, they should at least mandate the production of OPV vaccines, advertise its potential benefits, and allow volunteers to be vaccinated. But, of course, the real, even if a transient or partial solution is immediate and global OPV vaccination.

We are the cell and molecular biologists working on the

macrophages and the immune response. The COVID-19 pandemic has also involved us in the emerging field of SARS-CoV-2 immunity and prevention. From our side, we can add to the above-quoted papers (1, 2) that because the adults and elders are much more prone to the severe course of COVID-19, the use of OPV should be focused on them and not on children who were the original recipients of the vaccine. Children and youth are less prone to SARS-CoV-2 infection[4] and aggressive course of COVID-19 with Acute Respiratory Distress Syndrome (ARDS) and cytokine storm[5]. Also, the original recipients of OPV, namely the very young children, have some not yet well-characterized immune defense mechanisms (reviewed in the context of COVID-19 in ref.[6]), which seem sufficient to protect them during the COVID-19 pandemic.

There are also very promising new studies indicating that trained immunity can be induced by the metabolic signals[7,8]. These experiments showed that the activation of the cholesterol synthesis (but not of cholesterol itself) through the mevalonate kinase/mevalonate pathway affects trained immunity on the epigenetic and functional levels. The statins (the popular drugs used to lower cholesterol level), which block the production of mevalonate, prevent the induction of trained immunity[7]. These studies indicate a novel targets for the pharmacologic/matabolic interference with trained immunity to eliminate or decrease symptoms of COVID-19 infection.

Another avenue for the laboratory and clinical studies, which we recently proposed[9] is the potential beneficial effect of the RhoA inhibitors on the monocytes and macrophages to lessen the symptoms of ARDS in the lungs of COVID-19 patients. Our studies on the chronic rejection of transplanted organs showed that the vessel occlusion and tissue fibrosis - the main symptoms of chronic rejection - depend on the monocyte and macrophage infiltration and functions, which are regulated by the actin cytoskeleton and its regulator small GTPase Ras homolog family member A (RhoA). The animal studies showed that the genetic knockout of RhoA in the monocytes/macrophages, or pharmacologic inhibition of RhoA in the transplant recipients, prevents monocyte/ macrophage migration into the transplant and prevents chronic rejection[10-14]. Based on these findings, we postulated that the clinical trials with the clinically approved, for the treatment of multiple sclerosis, RhoA inhibitors such as Fingolimod or Siponimod would also inhibit monocyte/macrophage movement into the lungs of COVID-19 patients, and prevent development, or lessen the symptoms of ARDS[9].

We hope that our short letter can help to increase awareness of the subject among the scientists and governing bodies and stimulate awakening from the apparent global inertia. Honestly, we don't understand the reason for no answer from the world of politics to this clear appeal of prominent scientists[1-2]. We are aware of trials with BCG vaccine conducted in France, Netherlands, and Australia, mostly among health professionals (quoted here: https://presse.inserm.fr/en/the-bcg-vaccine-against-covid-19-really/38920/) and with OPV in Bandim Health Project in Guinea Bissau (quoted here: https://clinicaltrials.gov/ct2/show/NCT04445428). However, it will take a long time before these trials give definite conclusions, while the prevention should start immediately. Thus, it seems that the easy solution would be to first vaccinate the population with the existing and proven vaccines, which are known to have only limited secondary side effects, and test their preventive effects on the COVID-19 in parallel. Of course, the ruling bodies hesitate to take such a decision because from theirs, trained for decades, political point of view it is better not to undertake any non-standard actions. However, only the novel and courageous approach can help in winning the battle against COVID-19.

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References

1. Chumakov K, Benn CS, Aaby P, et al. Can existing live vaccines prevent COVID-19? Science. 2020; 368 (6496): 1187-1188. DOI: 10.1126/science.abc4262

2. Netea MG, Giamarellos-Bourboulis EJ, Dominguez-Andres J, et al. Trained Immunity: a Toolfor Reducing Susceptibility to andthe Severity of SARS-CoV-2 Infection. Cell. 2020; 181: 969-977. https://doi.org/10.1016/j.cell.2020.04.042

3. Kubiak JZ, Gazeta Wyborcza 14.06.2020 (in polish): https://wyborcza.pl/7,75400,26029123,nieoczekiwana-bron-na-koronawirusa-zywe-szczepionki-na-polio.html

4. Kuchar E, Załęski A, Wronowski M, et al. Children were less frequently infected with SARS-CoV-2 than adults during 2020 COVID-19 pandemic in Warsaw, Poland. European Journal of Clinical Microbiology and Infectious Diseases, Published Online 28 Sept. 2020. https://doi.org/10.1007/s10096-020-04038-9

5. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020; 20: 355–362. https://doi.org/10.1038/s41577-020-0331-4

6. Kloc M, Ghobrial RM, Kuchar E, et al. Development of child immunity in the context of COVID-19 pandemic. Clinical Immunology. 2020; 217: 108510. doi: 10.1016/j.clim.2020.108510

7. Bekkering S, Arts RJW, Novakovic B, et al. Metabolic Induction of Trained Immunity through the Mevalonate Pathway. Cell. 2018; 172(1-2): 135-146.e9. doi: 10.1016/j.cell.2017.11.025

8. van Tuijl J, Joosten LAB, Netea MG, et al. Immunometabolism orchestrates training of innate immunity in atherosclerosis. Cardiovasc Res. 2019 Jul 15; 115(9): 1416–1424. doi: 10.1093/cvr/cvz107

9. Kloc M, Ghobrial RM. The multiple sclerosis (MS) drugs as a potential treatment of ARDS in COVID-19 patients. Mult Scler Relat Disord. 2020 Oct; 45: 102437. Published online 2020 Jul 31. doi: 10.1016/j.msard.2020.102437

10. Liu Y, Chen W, Wu C, et al. Macrophage/monocyte-specific deletion of RhoA down-regulates fractalkine receptor and inhibits chronic rejection of mouse cardiac allografts. J HEART LUNG TRANSPL. 2017 Mar; 36(3): 340–354. doi: 10.1016/j.healun.2016.08.011

11. Liu Y, Kubiak JZ, Li XC, et al. Macrophages and RhoA Pathway in Transplanted Organs. RESULTS PROBL CELL DIFFER. 2017; 62: 365-376. doi: 10.1007/978-3-319-54090-0_15.

12. Chen W, Chen S, Chen W, et al. Screening RhoA/ROCK inhibitors for the ability to prevent chronic rejection of mouse cardiac allografts. Transpl Immunol. 2018; pii: S0966-3274(18)30029-7. doi: 10.1016/j.trim.2018.06.002. PMID:29885441

13. Chen W, Ghobrial RM, Li XC, et alMInhibition of RhoA and mTORC2/Rictor by Fingolimod (FTY720) induces p21-activated kinase 1, PAK-1 and amplifies podosomes in mouse peritoneal macrophages. Immunobiology. 2018; pii: S0171-2985(18)30046-9. doi: 10.1016/j.imbio.2018.07.009.

14. Uosef A, Vaughn N, Chu X, et al. Siponimod (Mayzent) Downregulates RhoA and Cell Surface Expression of the S1P1 and CX3CR1 Receptors in Mouse RAW 264.7 Macrophages. Arch Immunol Ther Exp. 2020; 68: 19. https://doi.org/10.1007/s00005-020-00584-4