



## Letter

## In response to the letter to the editor by Soha Ghanian et al. re our publication “Shorter androgen receptor polyQ alleles protect against life-threatening COVID-19 disease in European males”

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DHT synthesis is reduced only in the prostate, skin, and liver of men treated with the 5 $\alpha$ Ri Dutasteride (Dut), while testosterone (T), the major male androgen and precursor of DHT, increases in the bloodstream and every target tissue, and maintains its ability to activate the androgen receptor (AR). Based on this, 5 $\alpha$ Ri-treated subjects are not androgen-deprived, and 5 $\alpha$ Ri is not a classic antiandrogen. The AndroCoV trial did not measure T and DHT levels; however, as Dut increases tissue and serum T, the reported positive effects observed in this trial in Dut-treated individuals are not due to changes in T levels or activity. Additionally, the effect of Dut among these subjects is attenuated, because 21% of controls and 18% of those on dutasteride were taking T or other drugs (SERMS or aromatase inhibitors), known to increase androgen levels [1].

Of note, viral clearance is almost complete within seven days from the infection, even among individuals with a poor outcome [2]. In contrast, in AndroCoV, most of the time-to remission outcomes were measured after 7–10 days, when virus clearance plays a minor role and the outcome depends on abnormal immune response and endothelial damage. Our paper [3] explains that at this stage, AR function correlates with a beneficial immune-modulatory effect in patients with increased T, that overcomes receptor resistance. As a consequence, we would not expect clinical effects of testosterone-induced modulation of TMPRSS2 in COVID-19 patients seven or ten days after the onset of symptoms, as shown in a study where androgen deprivation therapy did not protect against SARS-CoV-2 [4].

Regarding the other questions, McCoy investigated the AR CAG repeat length in men with androgenic alopecia and found that they are more likely to become infected with COVID-19. Poorer prognosis was reported in those with longer AR CAG repeats [5]. This observation (reference # 37 in our manuscript) agrees with our results, but the interpretation provided is opposite. Going along with the concept that AR with longer CAG repeats is less transcriptionally active, we hypothesized that longer CAG repeats are associated with a more aggressive COVID-19 phenotype. In comparison, we think that less aggressive COVID-19 infections result from more active ARs with shorter CAG repeat [3]. McCoy reached the opposite conclusion, that ARs with longer CAG repeats are more active, due to different expressions of coactivators versus corepressors in the lungs. Hence, the lung's biological environment would be responsible for increased AR transcription and the more aggressive COVID-19 phenotype present in these patients [5]. We are unaware of evidence proving that longer CAG repeats confer decreased or increased transcriptional activity depending on the local environment. For example, Kennedy's disease is caused by a germline mutation, and ARs with longer CAG repeats are present in every tissue. Despite the claim by Ghanian that “*In skeletal muscle long AR CAG confer increased transcriptional activity in response to testosterone*” Kennedy's patients have androgen insensitivity in every tissue, including the muscles, that are affected by a phenotype of generalized weakness.

### Declaration of Competing Interest

The authors have no competing interests.

### Contributors

AI, MM and AR drafted the letter. All authors reviewed and edited the letter.

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