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Response to "Disparity between vitamin A-induced Th1-dependent oral tolerance in newborn mice and vitamin A-induced atopic sensitization in Guinean girls"

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To the Editor: We thank Dr Kiraly and colleagues[1] for bringing attention on the potential clinical implications of our fundamental work on the beneficial impact of vitamin A supplementation on neonatal oral tolerance induction and prevention of allergic airway inflammation.[2] Importantly, Kiraly and colleagues highlight discrepancies with their observations done in the human where authors found that neonatal vitamin A supplementation increased risk of atopy in two interventional studies performed in Guinea-Bissau. This effect was found only in girls. Kiraly and colleagues propose that gender and vitamin A dosage issues could explain the disparity between their and our results.

Although we did not mention this in our publication,[2] our study of the impact of vitamin A supplementation in neonates on allergy was performed in female as we and others found that allergy induction protocol is more robust in female than in male mice.[3] Thus, we found a protective effect in a mouse model associated with higher risk of atopy in humans.

In all our experiments, vitamin A was given indirectly to neonates through supplementation of diet of lactating mothers. We performed one preliminary experiment (see **Supplementary Figure S5** online)[2] in which we administered vitamin A directly to the neonates; we used a dose scaled to mice neonate weight which is comparable to the one given to human neonates (50,000 IU) and found a similar protective effect.

We propose that most of the disparity between our results and those of Kiraly's study originates from major difference in hygiene status of neonates and their mothers from Guinea-Bissau compared with mice housed in a specific pathogen-free animal facility. Guinea-Bissau is a country where infectious diarrhea still represent a very high burden of disease compared with high-income countries.[4] Gut mucosal inflammation has been shown to dramatically affect immune outcome to mucosal antigen administered in the presence of vitamin A supplement. Vitamin A metabolite retinoic acid was shown to foster inflammatory immune response to dietary antigens given to mice exhibiting gut mucosal inflammation instead of the expected regulatory immune response observed in non-inflammatory conditions.[5] Our hypothesis is supported by epidemiological studies performed in high-income countries, which either showed an inverse correlation between retinol levels in the first months of life and risk of atopy or no significant association, but none of them showed increased risk (reviewed in ref. 6).

We think that evolutionary conserved low-retinol level at birth[7] is not adapted to the new environment of industrialized high-incomes countries and may contribute to allergic disease epidemic in this specific environment. Interventional studies are needed to assess this hypothesis.

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