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# Words of Wisdom

**Re: Gut Microbiome Influences Efficacy of PD-1-based Immunotherapy Against Epithelial Tumors**
Routy B, Le Chatelier E, Derosa L, et al

Science 2018;359:91–7

**Experts' summary:**
We read with interest the paper by Routy et al [1]. They found that primary resistance to immune checkpoint inhibitors "can be attributed to abnormal gut microbiome composition". They observed the efficacy of "fecal microbiota transplantation" or oral supplementation with *Akkermansia muciniphila* in restoring response to anti-PD-1 agents in mouse models of epithelial tumors. The authors suggested that this is dependent on IL-12 because of the increase in the recruitment of $CCR9^{+}CXCR3^{+}CD4^{+}$ T lymphocytes.

**Experts' comments:**
*A. muciniphila* acts as a mucus-degrading bacterium in the mucus layer and produces short-chain fatty acids (SCFAs), mainly acetate and propionate, through the hydrolysis and fermentation of dietary polysaccharides. SCFAs are absorbed into any cell type and used as a source of energy. SCFAs act as ligands of two orphan G-protein–coupled receptors (GPRCs), GPR41 and GPR43. On this basis, we hypothesized a model involving the dual activity of *A. muciniphila* on both cancer and immune cells to explain the restored responsiveness to anti-PD-1 agents.

In particular, GPR43 can exert tumor suppressor activity via regulation of the SCFA-induced apoptosis of cancer cells. Propionate produced by *A. muciniphila* can induce histone hyperacetylation by inhibiting histone deacetylases (HDACs), thus promoting relaxation of chromatin and increasing the accessibility of DNA to transcription factors, and activates cell cycle inhibitor p21, leading to G1 phase arrest and cancer cell apoptosis [2]. This pro-apoptotic activity is also sustained by reducing the expression of several members of the inhibitor of apoptosis (IAP) family and the activation of initiator caspases 6, 7, and 8 and executioner caspase 3 (Fig. 1) [3].

The inhibition of HDAC expression, in particular HDAC6 and HDAC9, by SCFAs in murine colonic regulatory T cells leads to activation of the mTOR-S6K and STAT3 pathways [4]

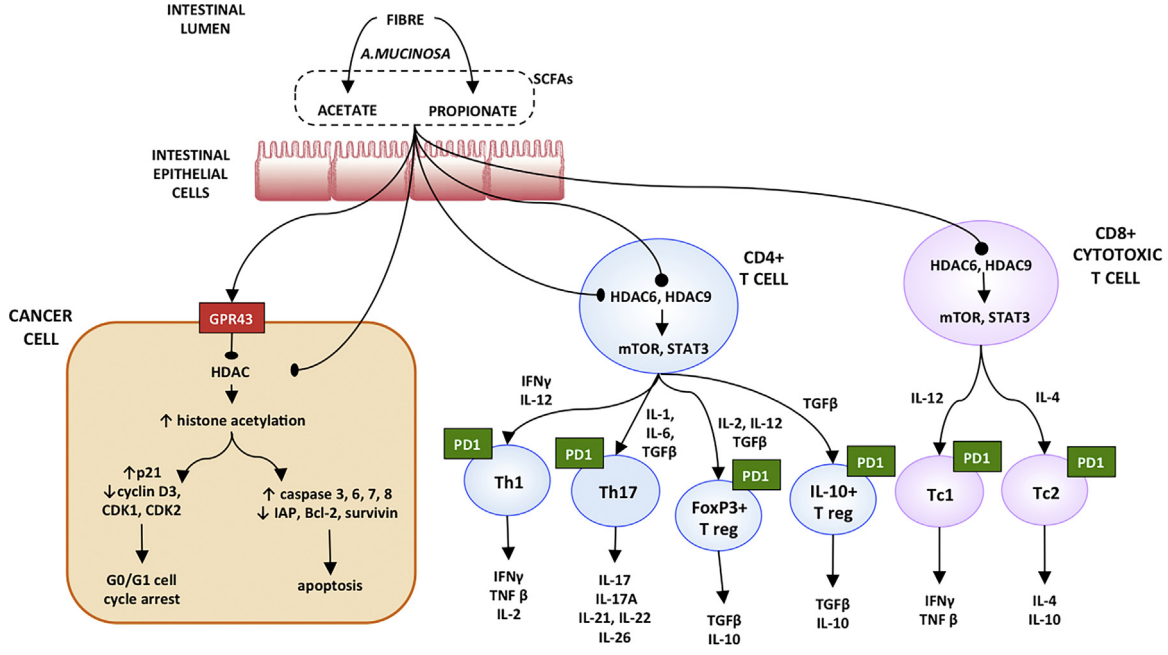


**Fig. 1 – Proposed model of the role of microbiota in restoring the response to immune checkpoint inhibitors.**

and promotes the generation of Th17, Th1, FoxP3$^+$, and IL-10$^+$ T cells and expression of IL-10, IFN-γ, and IL-17 in CD8$^+$ T cells in both Tc1- and Tc17-cell subsets (Fig. 1) [4]. Propionate increases the expression of ICAM-1 and E-selectin on vascular endothelial cells [5], thus promoting T cell migration (Fig. 1).

The activity of microbiota in restoring response to immune checkpoint inhibitors might involve both cancer and immune cells, thus opening the way to the identification of novel biomarkers of response to these agents. Understanding these mechanisms will be crucial for patients with genitourinary tumors to reduce the rate of primary, adaptive, and acquired resistance to immunotherapy due to tumor-cell intrinsic and extrinsic factors [6] as well as the risk of immune-related adverse events.

***Conflicts of interest:*** The authors have nothing to disclose.

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## Re: Tamsulosin and the Risk of Dementia in Older Men with Benign Prostatic Hyperplasia

Duan Y, Grady JJ, Albertsen PC, Wu ZH

Pharmacoepidemiol Drug Saf 2018;27:340–8

### Experts' summary:

Duan et al [1] used Medicare data to study the association between tamsulosin and the risk of dementia. Men (≥65 yr) taking tamsulosin ($n$ = 253 136) were matched at a 1:1 ratio to six comparison cohorts (no medication $n$ = 180 926, doxazosin $n$ = 28 581, terazosin $n$ = 23 858, alfuzosin $n$ = 17 934, dutasteride $n$ = 34 027, finasteride $n$ = 38 767). Assessment began following the first filling of prescriptions for benign prostatic hyperplasia (BPH) medications to identify incident dementia according to ICD-9 diagnosis codes. The median follow-up for all cohorts was 19.8 mo. The risk of dementia was significantly higher in the tamsulosin cohort than in the no-medication cohort (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.14–1.21) and in each of the alternative BPH-medication cohorts (doxazosin: HR 1.2, 95% CI 1.12–1.28; terazosin: HR 1.11, 95% CI 1.04–1.19; alfuzosin: HR 1.12, 95% CI 1.03–1.22; dutasteride: HR 1.26, 95% CI 1.19–1.34; finasteride: HR 1.13, 95% CI 1.07–1.19). The significance of these findings persisted in sensitivity analyses. These data suggest that use of tamsulosin may be associated with a diagnosis of dementia among older men with BPH.

### Experts' comments:

Given the high prevalence of BPH and lower urinary tract symptoms (LUTS) and of cognitive impairment among elderly men, and the popularity of medical BPH/LUTS therapeutic agents and their long-term use, any potential impact of these drugs on cognitive function is of relevant clinical importance. Duan et al [1] report on the first study to observe an association between prescription of tamsulosin and a new diagnosis of dementia. It remains unclear whether this represents a statistical artefact or a clinical reality, and arguments exist for both interpretations.

Two facts, however, argue against a cause-effect relationship. First, therapeutic doses of the other α-blockers cause similar $\alpha_1$-adrenoceptor inhibition as that for tamsulosin. If the association was because of $\alpha_1$-adrenoceptor antagonism, it should occur with all members of the drug class. However, associations with intraoperative floppy iris syndrome have been observed more frequently with tamsulosin than with other α-blockers [2]. Second, several studies have shown that tamsulosin exhibits little passage through the blood-brain barrier [3]. It remains unclear how a drug could promote the occurrence of dementia with minimal penetration into the brain. Irrespective of these mechanistic considerations, the associations observed by Duan et al [1] were over a median time of <2 yr, which is probably too short to cause dementia and, if anything, represents an accelerated time to diagnosis.