So how does blockade of translational machinery lead to downregulation at the transcriptional level? The researchers used mRNA profiling and microarray analysis to identify mRNA species in melanoma cell lines that were transcriptionally upregulated by IFNγ and translationally downregulated by silvestrol.

The analysis revealed that signal transducer and activator of transcription 1 (*STAT1*) mRNA provides the missing link between eIF4F activity and *PD-L1* transcription. In line with these findings, silvestrol dose-dependently decreased STAT1 protein levels, and melanoma cells from transgenic mice with constitutively upregulated eIF4F activity expressed higher levels of STAT1 protein compared with melanoma cells with normal eIF4F activity.

The authors concluded that activation of eIF4F in response to immune cell-derived IFNγ increases translation of *STAT1* mRNA, elevating the level of this transcription factor and thereby

promoting PD-L1 expression and immune evasion by the tumour.

In immunocompetent mice harbouring melanoma allografts, daily intraperitoneal injection with silvestrol significantly reduced tumour growth and was associated with increased immune cell infiltration of the tumour. Importantly, the same dose of silvestrol had no effect in nude mice, underscoring the key role of the immune system in the drug response.

eIF4F inhibitors have gained increasing attention as potential cancer therapies owing to their direct antitumour effects. The current study suggests that these molecules have an additional, immune-mediated mode of action that might improve immunotherapy efficacy and provides a tractable target for small-molecule intervention.

Katie Kingwell, Associate editor,
Nature Reviews Drug Discovery

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ORIGINAL ARTICLE Cerezo, M. et al. Translational control of tumor immune escape via the eIF4F–STAT1–PD-L1 axis in melanoma. *Nat. Med.* https://doi.org/10.1038/s41591-018-0217-1 (2018)

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an anti-inflammatory profile, and oral administration of butyrate during antibiotic treatment completely prevented T_H1 cell skewing in the colon after recolonization. These data provide a mechanistic link between antibiotic use and predisposition to certain infections and intestinal inflammation.

Meanwhile, Verma et al. identified another microbiota-derived effector component with immunoregulatory function. In an ex vivo screen for T_{reg} cell-inducing bacteria, they identified *B. bifidum* as a top candidate and showed that germ-free (GF) mice that were colonized with *B. bifidum* had a marked increase of memory-phenotype T_{reg} cells in their colonic lamina propria (cLP). Compared with T_{reg} cells from uncolonized GF mice, these expressed higher levels of IL-10 and CTLA4, indicating enhanced suppressive properties.

Further analysis revealed that *B. bifidum* induces T_{reg} cells by upregulating FOXP3 in naive CD4+ T cells, and that these have a broad range of T cell receptor specificities to diverse dietary antigens and the commensal microbiota. The induction

of T_{reg} cells in the intestine was found to be facilitated by cLP-resident CD103+ dendritic cells (DCs).

Using an in vitro system, the authors identified cell surface β-glucan/galactan (CSGG) as the bacterial component responsible for T_{reg} cell induction. CSGG appeared to act by converting conventional DCs into regulatory DCs, which secrete increased levels of IL-10 and TGFβ and decreased levels of IFNγ. In an in vivo colitis model, intraperitoneal administration of CSGG induced CD4+FOXP3+ T_{reg} cells capable of suppressing the progression of intestinal inflammation.

These studies provide new insights into the role of specific bacterial metabolites and components in immune tolerance and may point to novel strategies to treat certain inflammatory diseases.

Alexandra Flemming

ORIGINAL ARTICLES Scott, N. A. et al. Antibiotics induce sustained dysregulation of intestinal T cell immunity by perturbing macrophage homeostasis. *Sci. Transl Med.* **10**, eaao4755 (2018) | Verma, R. et al. Cell surface polysaccharides of *Bifidobacterium bifidum* induce the generation of Foxp3+ regulatory T cells. *Sci. Immunol.* **3**, eaat6975 (2018)

Web watch

A NEW GUIDE TO IMMUNOPHARMACOLOGY

The International Union of Basic and Clinical Pharmacology (IUPHAR) guide to immunopharmacology (www.guideto immunopharmacology.org) is a new, Wellcome Trust-funded, open-access resource that brings an immunological perspective to the high quality, expert-curated pharmacological data found in the existing IUPHAR/British Pharmacological Society guide to pharmacology (www.guidetopharmacology.org).

A unique aspect of this resource is that all data are manually curated, with support from 96 target class-specific IUPHAR subcommittees, comprising over 500 scientists. The guide to immunopharmacology extension delivers a knowledge base that, for the first time, connects immunology with pharmacology, bringing added value and supporting research and development of drugs targeted at modulating immune, inflammatory or infectious components of disease. Its integration with the guide to pharmacology comes with enhanced search mechanisms and new ways to browse and visualize immunological data (see Further Reading). The importance of extending into immune-relevant data is underlined by a new partnership between IUPHAR and the International Union of Immunological Sciences (IUIS) to create standard tools and nomenclature.

> " a knowledge base that, for the first time, connects immunology with pharmacology "

The guide to immunopharmacology has extended the information stored about drug targets by associating them with biological processes, cell types and diseases of relevance to immunology. In total, over 540 targets and 1,000 ligands are tagged in the database as being relevant to immunopharmacology. To date, we have curated approximately 300 associations between targets and immune cell types; approximately 3,000 associations between targets and immune or inflammatory system processes; approximately 53 associations between targets and immunological diseases; and approximately 700 associations between ligands and immunological diseases.

This expert curation seeks to bring the most valuable pharmacological data into the hands of immunology researchers, facilitating the crossover of their research into drug discovery and therapeutics.

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The authors declare no competing interests.

FURTHER READING Harding, S. D. et al. The IUPHAR/BPS guide to pharmacology in 2018: updates and expansion to encompass the new guide to immunopharmacology. *Nucleic Acids Res.* **46**, D1091–D1106 (2018)