Farnesyl and geranylgeranyl transferase inhibitors: an anti-inflammatory effect. *Comment to* "Inhibition of protein geranylgeranylation and farnesylation protects against graft-*versus*-host disease via effects on CD4 effector T cells" Haematologica. 2013;98(1):31-40

We read with great interest the article by Hechinger *et al.*[1] pre-published online ahead of print in *Haematologica* in July 2012. In this study, Hechinger *et al.* focused on graft-*versus*-host disease (GvHD), a frequent complication of allogeneic hematopoietic cell transplantation (allo-HCT). Pathogenic donor T cells are dependent on correct attachment of small GTPases to the cell membrane, mediated by farnesyl or geranylgeranyl residues[2] and, therefore, they decided to exploit this feature as a possible target for GvHD prophylaxis. Farnesyl transferase inhibitors (FTIs) and geranylgeranyl transferase inhibitors (GTIs) were used in mouse models to study their impact on GvHD, graft-*versus*-leukemia (GvLD) and murine cytomegalovirus (MCMV) T-cell responses. The results highlighted that mice that had undergone allo-HCT treated with FTIs and GTIs had less severe GvHD due to the decreased expression of pro-inflammatory cytokines (in this study IL-6, INF-γ and TNF-α). Finally, they suggest the use of FTIs, such as Tipifarnib (Tip), in order to reduce GvHD without a negative impact on immune reconstitution.[3,4]

We agree with Hechinger *et al.* in saying that FTIs and GTIs have a potential anti-inflammatory role. In our laboratory, we study a rare auto-inflammatory disease called mevalonate kinase deficiency (MKD)(OMIM #610377), caused by a mutation on the mevalonate kinase gene (*MVK*), the second enzyme of the mevalonate pathway, showing a reduced activity and a shortage of downstream compounds (Figure 1).

In previous *in vitro* studies, we observed that FTIs such as Tip and Lonafarnib (Lon) lead to a redirection of the mevalonate intermediates to geranylgeranylation via geranylgeranyl pyrophosphate (GGPP), eventually reducing the inflammatory response. The effects of Tip and Lon on pro-inflammatory cytokine secretion (IL-1β, TNF-α and IL-18) were proved on a cellular model of MKD obtained treating cells with the aminobisphosphonate alendronate (ALD). ALD inhibits farnesyl pyrophosphate synthase (FPPS), an enzyme of the mevalonate pathway downstream mevalonate kinase (MK). The concomitant administration of ALD with an inflammatory stimulus, such as lipopolysaccharide (LPS), leads to a cytokine-driven inflammatory response (especially IL-1α and IL-1β). These findings have been successfully replicated in monocytes isolated from MKD patients.[5] Tip and Lon were shown to significantly reduce the pro-inflammatory cytokine secretion.[6-8]

In vivo studies were also carried out to evaluate the effect of the FT inhibitor Manumycin A (ManA)[9] in an animal MKD model, chemically obtained treating Balb/c mice with ALD.[10] ALD plus muramyl dipeptide (MDP) treatments induced a huge increase in the inflammatory

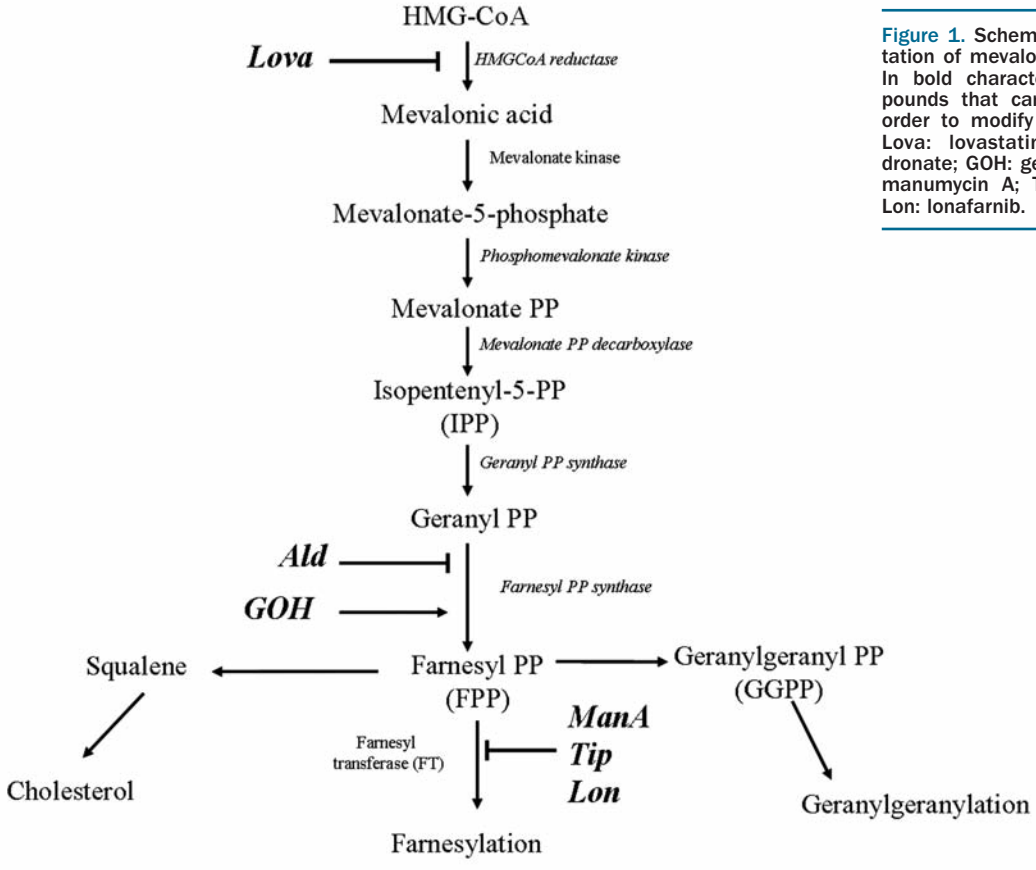

Figure 1. Schematic representation of mevalonate pathway. In bold characters the compounds that can be used in order to modify the pathway. Lova: lovastatin; Ald: alendronate; GOH: geraniol; ManA: manumycin A; Tip: tipifarnib; Lon: lonafarnib.

marker serum amyloid A (SAA). ManA was able to significantly reduce ALD-MDP-induced SAA production in the animal model. Moreover, ManA was able to reduce IL-1β production when administered to human monocytes treated with ALD plus LPS. This finding is of particular interest since it shows the efficacy of ManA not only in chemical models but also against the genetic defect.

Other Authors reported discordant results. The effects of ManA were compared to those of other inhibitors of the mevalonate pathway, such as zaragozic acid (ZAA) and geranylgeranyl transferase inhibitor (GGTI-298).[6] ManA and ZAA showed similar effects in lowering IL-1β secretion in ALD-LPS-treated monocytes, whereas GGTI-298 amplified the induction of this cytokine, highlighting that the mechanism of action of these molecules is not yet clear.

FTIs have a dramatic anti-inflammatory effect in models where the mevalonate pathway is chemically or genetically impaired. In our studies, we considered several compounds, such as Tip, Lon and ManA. The effects of Tip and Lon were confirmed by *in vitro* studies on a cellular model of MKD and on monocytes isolated from MKD patients. The same findings have also been confirmed using the FT inhibitor ManA, according to the results of the *in vivo* studies.

Our findings and those of Hechinger *et al.* all demonstrate the anti-inflammatory effects of FTIs and GTIs. Given this, FTIs could be used as a novel therapeutic approach for the currently orphan disease MKD, as well as an anti-cancer drug,

However, the mechanisms used by these compounds in exerting their anti-inflammatory role in such widely different pathologies are not completely understood. We believe that these mechanisms merit further study.

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