**Supplementary figures:**

**Supplementary Fig 1. Tango-GPCR screening for P17**

**(A**) 32 Tango-GPCRs positive hits **(i and ii)** upon the single dose (100 nM) activation of P17 with SCTR as a positive control. Fold change (treatment/basal) were obtained from the basal constitutive activity. All values are means ± SD. **(B)** TANGO β-arrestin recruitment assayin comparison with Tango-MRGPRX2 construct treated with P17 and few representative candidates (Tango-MRGPRF, -CCR2, -CCR3, -HTR1A, -HTR1B, -HTR4, -HTR5 and -HTR6) with P17 in dose response. All values are means ± S.E.M. (N=3, n=3). \*\*\*\* p-value ≤ 0.0001; \*\*\* p-value ≤ 0.001; \*\* p-value ≤ 0.01; \* p-value ≤ 0.05 and ns p-value > 0.05. SCT was used as positive control.

**Supplementary Fig 2. *In silico* analysis of peptide receptor interaction site**

**(A) (i)** The Ramachandran plot represents 98.8 % aa residues in the allowed and favored region.

**(ii)** Validation of 3D model by virtual docking of a small compound agonist ZINC72453573 with known binding sites on the MRGPRX2 **(iii)** Docking of P17(5-13) in MRGPRX2 *in silico* model. **(B)** Image showing the **(i)** P17(5-13**)** and **(ii)** P17(5-11) binding with the MRGPRX2 3D model. Interaction site of MRGPRX2 amino acids with **(iii)** P17(5-13) and **(iv)** P17(5-11). Videos are attached in supplementary documents.

**Supplementary Fig 3. P17 alanine mutants with Tango β-arrestin recruitment assay and β-hexosaminidase release assay**

**(A) (i)** P17 alanine mutants ([Ala1]P17, [Ala3]P17, [Ala5]P17, [Ala6]P17, [Ala9]P17 and [Ala13]P17) showing similar dose response as P17. **(ii)** P17 alanine mutants ([Ala2]P17, [Ala8]P17, [Ala10]P17 and [Ala12]P17) showing decreased efficacy and/or potency compared to P17 in β-arrestin recruitment assay. **(B)** P17 alanine mutants ([Ala2]P17, [Ala8]P17, [Ala10]P17 and [Ala12]P17) showing decreased β-hexosaminidase release compared to P17 in LAD2 cells. **(C) (i)** Percentage β-arrestin recruitment in pre-treated MRGPRX2 transfected HTLA cells with [Ala8]P17 (10 μM) and **(ii)** Percentageβ-hexosaminidase release in pre-treated LAD2 cells with [Ala8]P17 (10 μM). All values are means ± S.E.M. (N=3 and n=3). \*\*\*\* p-value ≤ 0.0001; \*\*\* p-value ≤ 0.001; \*\* p-value ≤ 0.01; \* p-value ≤ 0.05 and ns p-value > 0.05. compound 48/80 or/and CST-14 were used as positive controls.

**Supplementary Fig 4. qRT-PCR verification of MRGPRX2 knockdown in LAD2 cells and MRGPRX2-Mutants expression in HTLA cells.**

**(A)** LAD2 cells were used for stable knockdown of MRGPRX2 using two shRNA using lentiviral system. **(i)** Relative expression of MRGPRX2 in stably knocked down LAD2 cells is compared with the control shRNA treated LAD2 cells. **(ii)** Relative expression of MRGPRX2 and its mutants (MRGPRX2\*F172A and MRGPRX2\*172-175) are compared with the non-transfected HTLA cells. All values are means ± SD. (N=3 and n=3). \*\*\*\* p-value ≤ 0.0001; \*\*\* p-value ≤ 0.001; \*\* p-value ≤ 0.01; \* p-value ≤ 0.05 and ns p-value > 0.05.

**Supplementary Fig 5. Transwell migration model and P17 control on THP-1 migration**

**(A) (i)** Cartoon of THP-1 monocytes Transwell migration model. **(ii)** Representative image showing the migratory effect of P17 alone on THP-1 monocytes (N=3).

**Supplementary Fig 6. Flow cytometry dot blots showing the human monocyte verification**

**(A)** Representative flow cytometry dot blot of CD11b-PE and CD14-FITC double stained markers in human blood monocytes with their isotype controls (PE conjugated IgG1kappa and FITC conjugated IgG2a, kappa) (N=2).

**Supplementary Fig 7. Flow cytometry dot blots showing the human monocyte verification**

**(A)** Representative flow cytometry dot blot of CD11b-PE stained marker in human blood monocytes with their isotype controls (PE conjugated IgG1kappa) (N=2). (B) Representative flow cytometry dot blot of CD14-FITC stained marker in human blood monocytes with their isotype controls (FITC conjugated IgG2a, kappa) (N=2).

**Supplementary Fig 8. Flow cytometry dot blots showing the THP-1 monocyte differentiation**

**(A)** Representative flow cytometry dot blot of CD11b marker and PE conjugated IgG1kappa isotype control on THP-1 cells treated with water and P17 (N=3).

**Supplementary Fig 9. Histology and H&E staining of P17 injected ear tissues**

Mouse ears intradermally injected (N=6/group) with P17 (10 μM), saline, saline (DMSO), P17 (DMSO) and P17 (10 μM) co-treated with quercetin (100 μM) were recovered at 24 hr post-injection, embedded in paraffin. 10 μm thick paraffin sections were then stained with **(A)** CD11b (green), and DAPI (blue). **(B)** H&E staining showing the thickness of the ear tissues after drug injection and the graph showing thickness measured.

**Supplementary Fig 10. qRT-PCR verification of MRGPRX2 expression and calcium release in immune cells.**

**(A) (i)** Relative expression of MRGPRX2 in immune cells, THP-1 and THP-1 derived macrophage via PMA induction compared to LAD2 cells. All values are means ± SD. (N=3 and n=3) **(ii)** THP-1 cells and LAD2 cells showing the calcium release upon graded concentrations of P17 and compound 48/80. All values are means ± S.E.M. (N=3 and n=3).\*\*\*\* p-value ≤ 0.0001; \*\*\* p-value ≤ 0.001; \*\* p-value ≤ 0.01; \* p-value ≤ 0.05 and ns p-value > 0.05.

**Supplementary Fig 11. Fluorescence intensity quantification of immune cell population infiltration in mice ear.**

**(A)** Mean fluorescence intensity of **(i)** CD11b+ and **(ii)** F4/80+ cells in IF were quantified using Zeiss Zen Microscope Software. All values are means ± SD (N=6) \*\*\*\* p-value ≤ 0.0001; \*\*\* p-value ≤ 0.001; \*\* p-value ≤ 0.01; \* p-value ≤ 0.05 and ns p-value > 0.05.