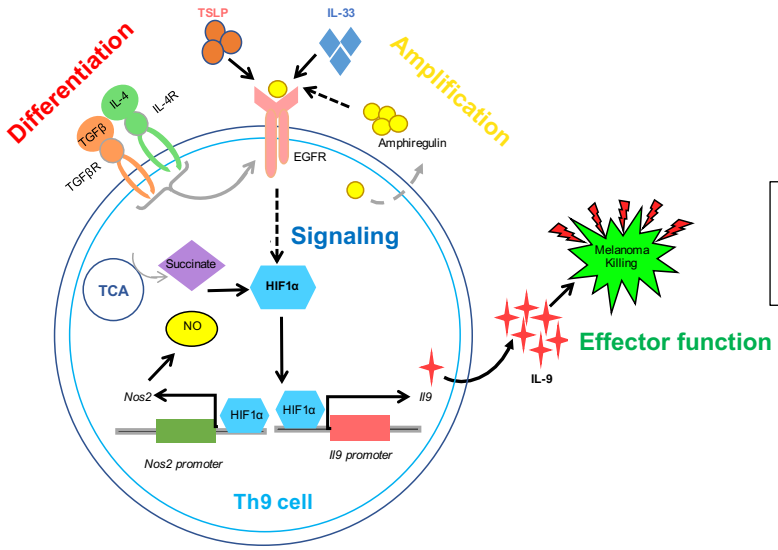
**Signed details of the excellence in research work for which the Sun Pharma Research Award is claimed, including references and illustrations. The candidate should duly sign on the details**

1. **EGFR-HIF1α signaling positively regulates the differentiation of IL-9 producing T helper cells**

Interleukin 9 (IL-9)-producing helper T (Th9) cells are essential for inducing anti-tumor immunity and inflammation in allergic and autoimmune diseases. Although transcription factors that are essential for Th9 cell differentiation have been identified, other signaling pathways that are required for their generation and functions are yet to be explored. Here we identified that Epidermal Growth Factor Receptor (EGFR) is essential for IL-9 induction in Th cells. Moreover, amphiregulin (Areg), an EGFR ligand, is critical for the amplification of Th9 cells induced by TGF-β1 and IL-4. Furthermore, our data show that AREG-EGFR signaling induces HIF1α, which binds and transactivates IL-9 and NOS2




Schematic representation of EGFR-HIF1α signaling pathway in Th9 cells.

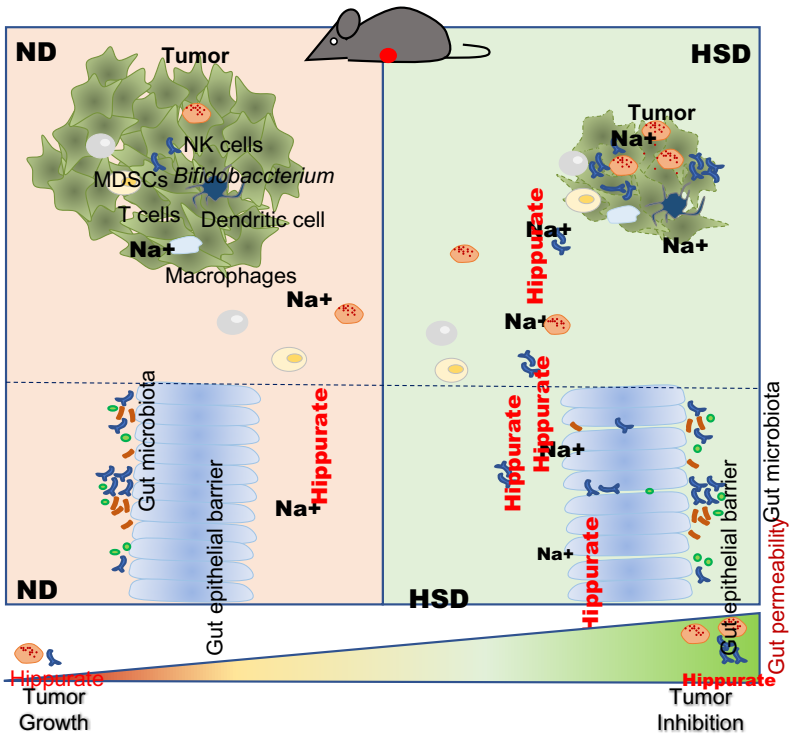
promoters in Th9 cells. Loss of EGFR or HIF1α abrogates Th9 cell differentiation and suppresses their anti-tumor functions. Moreover, in line with its reliance on HIF1α expression, metabolomics profiling of Th9 cells revealed that Succinate, a TCA cycle metabolite, promotes Th9 cell differentiation and Th9 cell-mediated tumor regression.

Reference:

Roy, Rizvi ZA, Clarke A, Macdonald F, Pandey A, Zaiss D, Dr. Simon KA, **Awasthi A**. EGFR-HIF1α signaling positively regulates the differentiation of IL-9 producing T helper cells. **Nature Communication 2021**, 12(1):3182. doi: 10.1038/s41467-021-23042-x

1. **High salt diet mediates interplay between NK cells and gut microbiota to induce potent tumor immunity**

Dietary salt (NaCl) is known to modulate gut microbiota, and thereby contributing to inflammation in autoimmunity. Within immunosuppressive tumor microenvironment, high salt diet (HSD)-induced inflammatory response could enhance tumor immunity. However, HSD-induced antitumor immunity and its association with gut microbiota is yet to understood. In the current study, we report that HSD-induced tumor immunity via enhancing IFN-γ production, NK cells functions and downregulation of key checkpoint inhibitor, PD1, programmed cell death protein 1. While depletion of NK cells abrogated HSD-induced anti-tumor functions, combination of salt with anti-PD1 antibody leads to a




robust anti-tumour immune response. It seems that HSD modulates gut microbiota in mounting tumor immunity, as depletion of microbiota blunted HSD-induced tumor immunity. Faecal matter transfer (FMT) from HSD mice restored anti-tumor immunity

associated with NK cell activity. Metagenomic profiling revealed that HSD enriches *Bifidobacterium* abundance, as colonizing *Bifidobacterium* resulted in NK cell functions in tumor regression. Our results, thus, indicate a potential use of salt, as an adjuvant, to enhance cancer immunotherapy via modulation of gut microbiota-dependent NK cell activation.

Reference:
Rizvi ZA, Dalal R, Sadhu S, Kumar Y, Kumar S, Gupta SK, Tripathy MR, Rathore DK, **Awasthi A**. High salt diet mediates interplay between NK cells and gut microbiota to induce potent tumor immunity. **Science Advances 2021,** 7(37):eabg5016. doi: 10.1126/sciadv.abg5016.

**Cellular Immune Responses are Preserved and may Contribute to Vaccine Effectiveness Despite Reduced Virus Neutralization Against Infection due to SARS-CoV-2 B.1.617.2 Variant.**

Of the 2766 cases of confirmed SARS-CoV-2 infection, 3·1% were fully vaccinated compared with 7·1% of the 2377 controls giving an adjusted OR of 0·37 (95%CI 0·28, 0·48); this translated to 63·1% (95%CI 51·5, 72·1) vaccine effectiveness against SARS-CoV-2 B·1·617·2 variant, seen in 80% of the infected population. Full vaccination prevented moderate-severe COVID-19 in 81·5% (95%CI: 9·9, 99·0). The effectiveness of single-dose vaccine was 46·2% (95%CI: 31·6, 57·7) against infection but 79·2% (95%CI: 46·1, 94·0) in preventing moderate-severe COVID-19. Among healthy vaccinated persons, plasma live virus neutralisation was 2·5-6·8 fold lower against B·1·1·7, B·1·351, B·1·617·1 and B·1·617·2 being lowest against B·1·617·2 (Delta). However, both CD4+ and CD8+ T-cell responses were preserved against the virus spike protein of the Delta variant suggesting cell-mediated immune protection. ChAdOx1 nCoV-19 VE was 63.1% against B·1·617·2 infection and 81·5% in preventing severe disease. Spike-specific T-cells responses against virus variants were maintained

Reference:

Thiruvengadam R, **Awasthi A**, Medigeshi GR, Bhattacharya S, Mani S, Sivasubbu S, Shrivastava S, Samal S, Murugesan DR, Desiraju BK, Kshetrapal P, Pandey R, Scaria V, Malik PK, Taneja J, Binayke A, Vohra T, Zaheer A, Rathore D, Khan NA, Shaman H, Ahmed S, Kumar R, Deshpande S, Subramani C, Wadhwa N, Gupta N, Pandey AK, Bhattacharya J, Agrawal A, Vrati S, Bhatnagar S, Garg PK. Cellular Immune Responses are Preserved and may Contribute to Vaccine Effectiveness Despite Reduced Virus Neutralization Against Infection due to SARS-CoV-2 B.1.617.2 Variant. **Lancet Infectious Disease 2021, accepted, in press**