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Analysis of the NeflgArd Part A study confirms Nefecon modulates proteins involved in the intestinal immune network for IgA production

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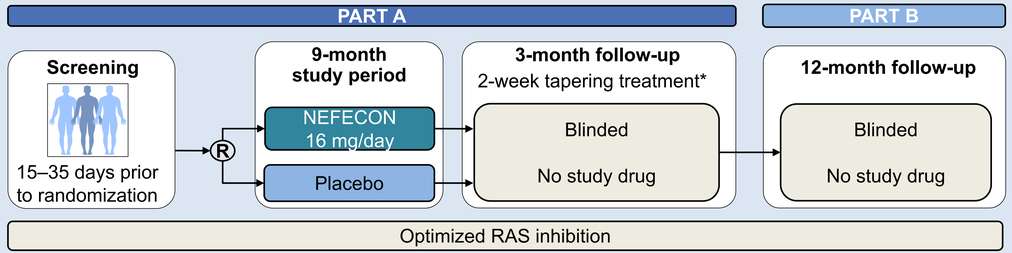
1. Introduction

- Nefecon, the targeted release formulation of budesonide, is delivered to the GALT of the terminal ileum, a major site of IgA production.[1] Results from the Phase 2b NEFIGAN and Phase 3 NeflgArd trials demonstrated that treatment with Nefecon 16 mg/day significantly reduces proteinuria and loss of eGFR compared with placebo.[1-3] A number of serum biomarkers have been measured in the 2 trials and many of those identified to be modulated by Nefecon in the Phase 2b study have now been validated in Part A of the NeflgArd study. The aim of this study was to determine biological pathways modulated by Nefecon treatment using the data currently available from the Part A biomarker analysis program

2. Methods

- NeflgArd is a Phase 3 double-blind, randomized, controlled clinical trial designed to determine the efficacy of Nefecon in patients with IgAN at high risk of progressive kidney disease despite optimized supportive care. The trial comprised 9 months of treatment with placebo or Nefecon 16 mg/day, and a 3-month (Part A) or 12-month (Part B) off drug observational follow-up period (15 months off drug in total).[1,2] An interactome analysis was performed incorporating all serum proteins significantly modulated by treatment with Nefecon 16 mg/day in Part A of the NeflgArd study using the STRING PPI database, which contains known and predicted protein interactions, to determine which biological processes and pathways are modulated by Nefecon treatment

Figure 1. NeflgArd study design[1,2]



*Patients had their blinded treatment reduced from 4 (16 mg/day) to 2 capsules (8 mg/day)

3. Results

- Consistent with the Phase 2b findings[4], functional analysis demonstrated that serum biomarkers significantly modulated by Nefecon treatment in Part A of the NeflgArd trial are enriched for proteins involved in the Kyoto Encyclopedia of Genes and Genomes pathway database for intestinal immune network for IgA production, and biological processes involved in B-cell activation, indicating the mechanism of action of Nefecon is, at least in part, driven by an effect within the GALT

Figure 2A. Functional enrichments in the network of immune system biomarkers that were significantly modulated by treatment with Nefecon 16 mg/day in the NEFIGAN trial (updated 12-SEP-23)

KEGG Pathways

pathway	description	count in network	strength	false discovery rate
hsa04061	Viral protein interaction with cytokine and cytokine receptor	14 of 96	2.06	8.50e-24
hsa04672	Intestinal immune network for IgA production	5 of 43	1.96	2.37e-07
hsa04060	Cytokine-cytokine receptor interaction	23 of 282	1.81	9.59e-38
hsa05323	Rheumatoid arthritis	6 of 83	1.76	9.88e-08
hsa04062	Chemokine signaling pathway	13 of 186	1.74	3.96e-18

Biological Process (Gene Ontology)

GO-term	description	count in network	strength	false discovery rate
GO:2000547	Regulation of dendritic cell dendrite assembly	2 of 3	2.72	0.0018
GO:0072679	Thymocyte migration	2 of 3	2.72	0.0018
GO:0002408	Myeloid dendritic cell chemotaxis	2 of 3	2.72	0.0018
GO:0097029	Mature conventional dendritic cell differentiation	2 of 4	2.6	0.0025
GO:0031296	B cell costimulation	2 of 4	2.6	0.0025

Figure 2B. Key to understanding edges in Figure 2C and Figure 2D

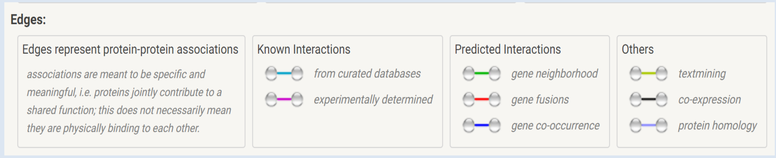


Figure 2C. PPI network of immune system biomarkers significantly modulated by treatment with Nefecon in the NEFIGAN trial (updated 12-SEP-23)

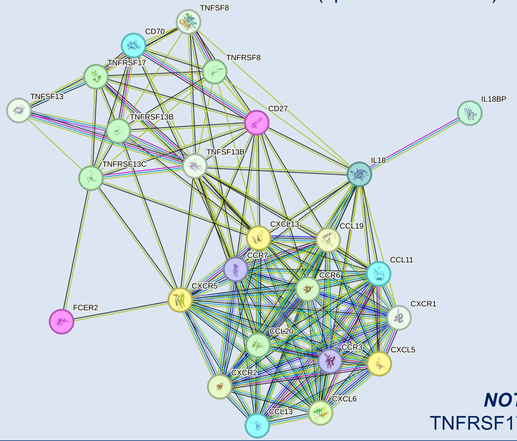
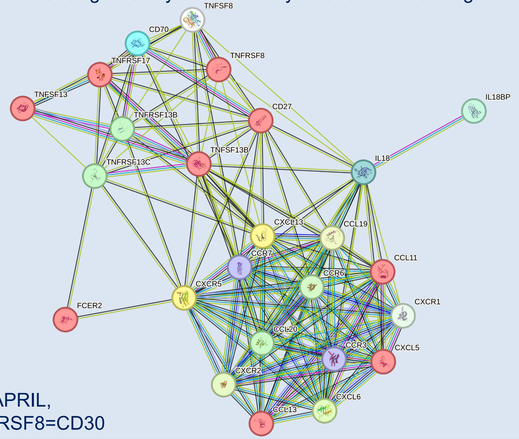


Figure 2D. PPI network from Figure 2C, with red nodes indicating proteins that have been confirmed as significantly modulated by Nefecon in the NeflgArd trial



NOTE: TNFSF13B=BAFF, TNFSF13=APRIL, TNFRSF17=BCMA, FCER2=CD23, and TNFRSF8=CD30

4. Conclusion

- These findings support a disease-modifying effect of Nefecon at the ileal mucosal surface and a direct effect on the ileal GALT, further strengthening the link between the gut and the kidneys in IgAN

APRIL, a proliferation inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, soluble cluster of differentiation; eGFR, estimated glomerular filtration rate; FCER2, Fc Epsilon Receptor II; GALT, gut-associated lymphoid tissue; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; PPI, protein–protein interaction; RAS, renin–angiotensin system; TNFSF, tumor necrosis factor superfamily.

1. Lafayette R, *et al. Lancet* 2023;402(10405):859-870. 2. Barratt J, *et al. Kidney Int* 2023;103(2):391-402. 3. Fellström B, *et al. Lancet* 2017;389(10084):2117-2127. 4. Barratt J, *et al. Kidney Int* 2023 (Accepted for publication)

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