

Author Profile

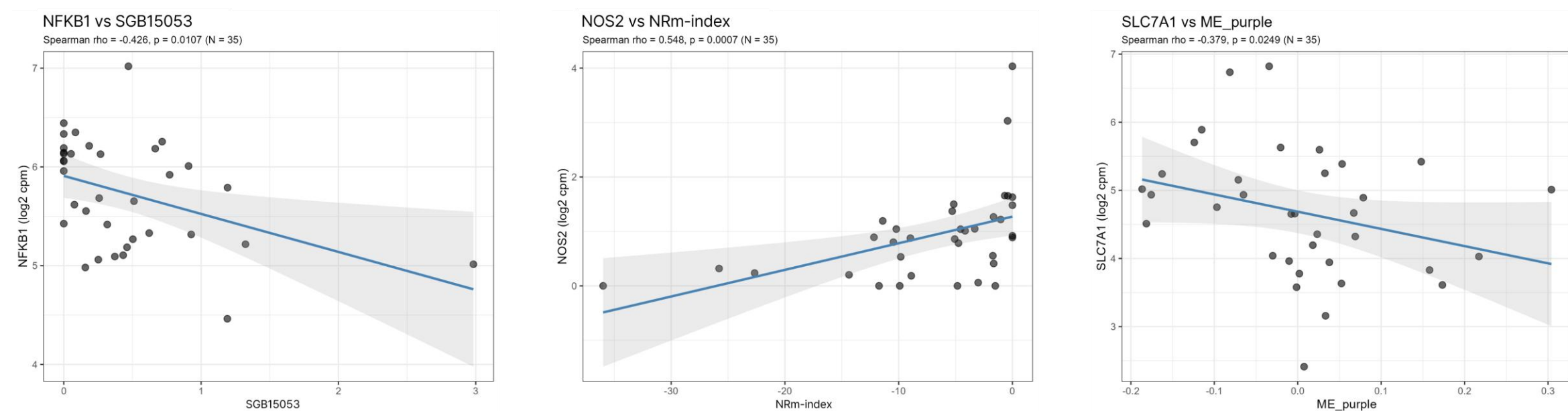
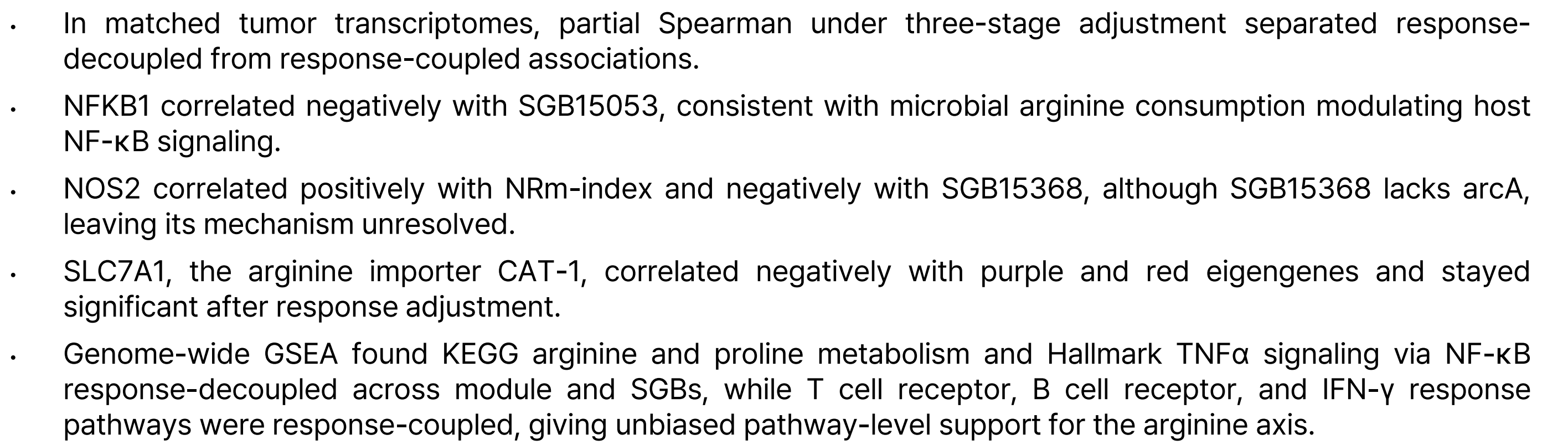
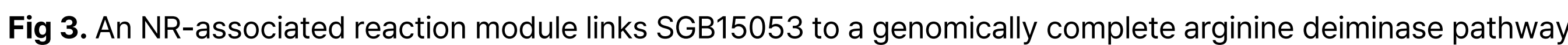
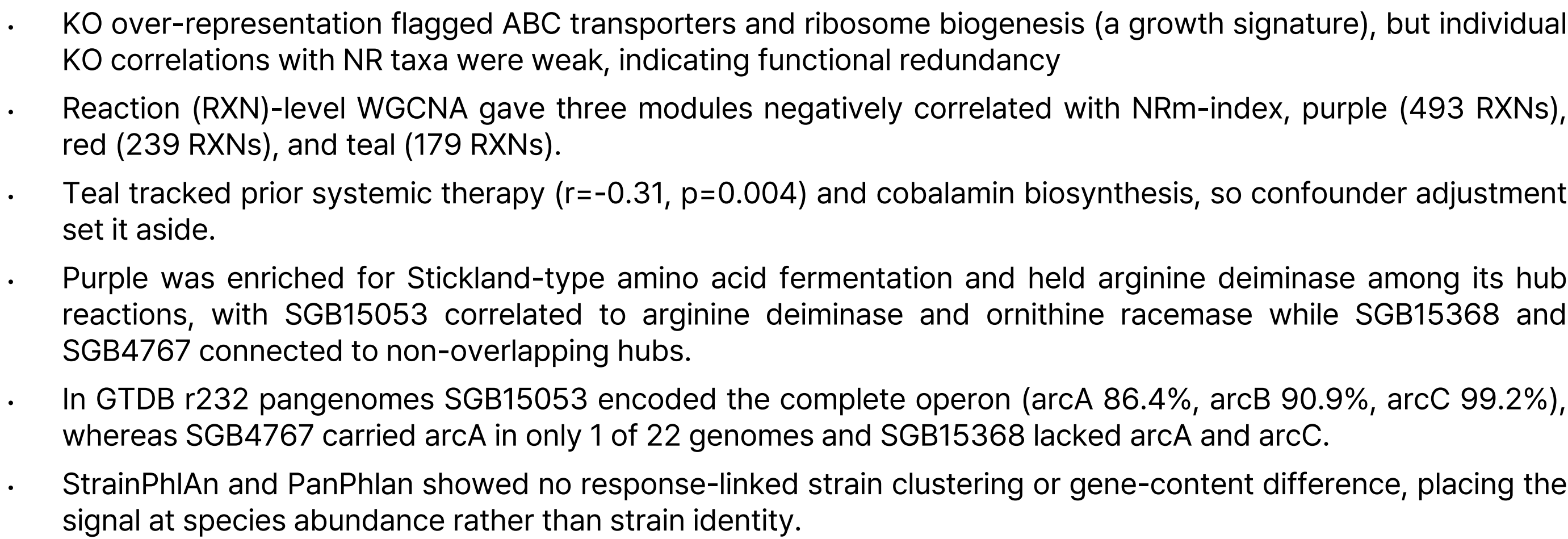


- Immune checkpoint inhibitors (ICIs) transformed standard of care in advanced non-small cell lung cancer (NSCLC), yet single-agent objective response remains <30%, and many patients lack durable benefit.
- The gut microbiome is an extrinsic determinant of ICI response, and responder fecal transplantation restores antitumor immunity in preclinical models.
- Human associations replicate poorly across cohorts, with taxa reversing direction and genus-level profiling obscuring species or strain-level functions.
- Prior systemic therapy, especially platinum-based chemotherapy, simultaneously shortens survival and reshapes the microbiome, yet is rarely modeled as a confounder.

- In a prospective single-center cohort, characterize the non-responder (NR)-associated gut microbiome under explicit control for prior systemic therapy.
- Resolve it within one cohort under consistent confounder control, moving from community composition to species-level enzymatic and genomic potential and then to the matched host tumor transcriptome.

- Baseline fecal samples were prospectively collected from 83 patients with advanced stage IIIB-IV NSCLC at Samsung Medical Center before single-agent pembrolizumab or atezolizumab. Patients were classified as pre-treated (N=56) if they had received prior ICI, targeted therapy, or platinum-based chemotherapy within six months of ICI initiation, and as treatment-naïve (N=27) otherwise.
- Responders were defined by RECIST v1.1 as complete or partial response or stable disease with progression-free survival (PFS) of at least six months, and non-responders as progressive disease or stable disease with PFS under six months.
- Taxonomic composition was profiled with MetaPhlAn4 and community function with HUMAnN4a after shotgun metagenomic sequencing.
- Species-level pangenomes were assembled from all GTDB r232 genomes within each species cluster.
- Matched tumor whole-transcriptome sequencing was available for 35 patients, obtained from a previously published dataset.

- Pretreated patients showed worse survival in univariate Cox, HR 2.64 for PFS (95% CI 1.43-4.88, p=0.001) and HR 3.21 for OS (95% CI 1.49-6.92, p=0.002).
- Prior systemic therapy explained the largest compositional variance among all clinical variables, Bray-Curtis PERMANOVA $R^2=2.03\%$ (p=0.032), above treatment line 1.78%, PD-L1 expression 1.74%, and ICI regimen 1.43%.
- Beta-diversity PCoA showed partial separation of naive and pretreated communities.
- Shannon diversity was unchanged (p=0.518), so the effect lies in community structure rather than richness.
- Acting on both outcome and composition, prior systemic therapy meets the definition of a confounder.



Conclusion

- A treatment history-controlled analysis separates response-specific microbiome biology from the imprint of prior therapy and resolves it from community composition to species-level genomic potential to host transcriptome.
- The NR-associated microbiome acts through parallel taxon-specific channels that partially converge on arginine metabolism, with SGB15053 giving a genomically supported NF- κ B link.

Discussion

- SGB15053 arginine deiminase activity may consume arginine, a shared substrate for microbial Stickland fermentation and host immune effector functions.
- Reduced arginine availability could suppress host NF- κ B signaling and impair antitumor immunity in the tumor microenvironment.
- Parallel taxon-specific channels (NFKB1, NOS2, SLC7A1) partially converge on this arginine axis rather than a single dominant species-pathway link.
- This remains a formal hypothesis, since circulating and tissue arginine were not measured.
- Cross-sectional design, host associations hypothesis-generating with limited power (N=35), single-center cohort, and no direct arginine metabolite measurement.

Acknowledgements: This research was supported by the Bio&Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (RS-2023-00225255). This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (RS-2025-00519956). This author also thanks Korea Institute of Science and Technology Information (KISTI) for the usage of the Global Science Experimental Data Hub Center (GSDC) and Korea Research Environment Open Network (KREONET/GLORIAD) resources, and for the technological supports.