# Ribosomal Stoichiometric Reprogramming and Integrated Stress Response Activation Define a Translational Stalling State in DLBCL Non-Responder CAR-T Infusion Products

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## INTRODUCTION

Elevated ribosomal protein (RP) gene expression in non-responder (NR) CAR-T infusion products for diffuse large B-cell lymphoma (DLBCL) has been dismissed as housekeeping noise.

Emerging evidence indicates that RP stoichiometric shifts can generate compositionally distinct ribosomes with altered translational selectivity.

We therefore asked whether such ribosome-level reprogramming, together with integrated stress response activation, characterises CAR-T products that fail.

## OBJECTIVE

To determine whether NR CAR-T cells harbor **reprogrammed ribosomes** co-occurring with **integrated stress response (ISR) activation**, defining a translational stalling state.
*A state defined at the level of ribosome composition rather than transcriptional exhaustion programmes.*

## METHODS

- scRNA-seq of CAR-T infusion products from 24 DLBCL patients (GSE197268): 12 responders (R), 8 non-responders (NR), 4 partial responders
- Products: 18 axicabtagene ciloleucel, 6 tisagenlecleucel
- Seurat v5 processing of 81,143 T cells (22,853 R / 13,094 NR analysed)
- Per-cell stoichiometric fractions calculated for 72 core RP genes
- Ribosomal composition assessed by PCA and Shannon entropy
- RPL5/RPL11 coupling to p53 targets (CDKN1A, BAX, MDM2, GADD45A, FAS) tested via permutation analysis
- mTORC1, translation initiation/elongation and ISR pathway scores compared between R and NR

## CONCLUSIONS

- NR CAR-T products carry compositionally altered ribosomes alongside active ISR signalling.
- Ribosome biogenesis is uncoupled from effector translation: high mTORC1, initiation and elongation scores coexist with ATF4/CHOP induction and stalled-quadrant enrichment.
- This translational stalling axis is distinct from exhaustion and metabolic dysfunction.
- The ISR is positioned as a therapeutic intervention point for improving CAR-T efficacy in aggressive B-cell lymphoma.

## RESULTS

**71 / 72**
core ribosomal proteins with significantly altered stoichiometric fractions in NR (adj. p<0.05)

**$p < 10^{-300}$**
Shannon entropy — NR ribosomal composition markedly more heterogeneous

**30.5% vs 24.4%**
NR vs R cells in the translationally stalled quadrant ($p=8.1\times10^{-36}$)

**$\rho \approx -0.07$**
mTOR–effector coupling lost, while mTOR–ribosome coupling stays intact ($\rho$≈0.25–0.28)

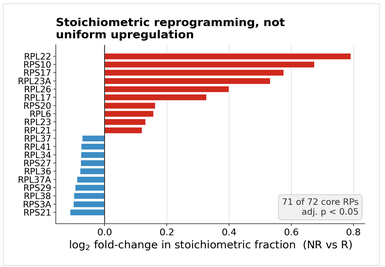


Fig 1. Stoichiometric fractions of the 72 core RP genes, NR vs R. 71/72 shifted (adj. p<0.05): RPL22, RPS10, RPS17, RPL23A, RPL26 over-represented; RPS21, RPS3A, RPL38, RPL34, RPL37, RPL41 depleted.

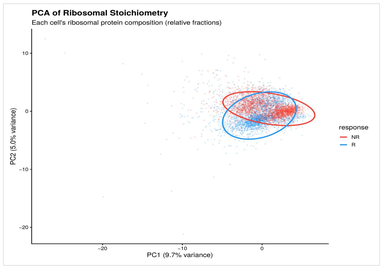


Fig 2. PCA of per-cell ribosomal composition (PC1 9.7%, PC2 5.0%). NR profiles occupy a broader region; Shannon entropy 6.065 (NR) vs 6.034 (R), $p<10^{-300}$.

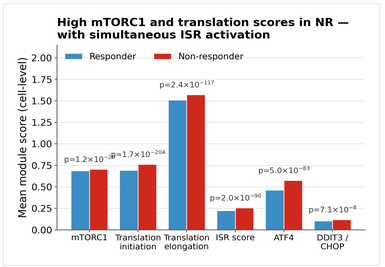


Fig 3. Cell-level module scores. mTORC1, initiation and elongation are all higher in NR, yet the ISR, ATF4 and DDIT3/CHOP are simultaneously elevated.

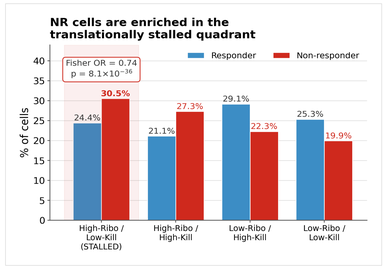


Fig 4. Ribosome biogenesis vs effector translation quadrants. NR cells are enriched in the High-Ribo/Low-Kill (stalled) quadrant; ATF4 is higher in stalled than efficient translators (p=0.017).

**Compositional reprogramming, not uniform upregulation**
71 of 72 core RPs showed significantly altered stoichiometric fractions in NR (adj. p<0.05). RPL22, RPL23A and RPL26 were over-represented; RPL34, RPL37 and RPL41 were depleted.

**Greater ribosomal heterogeneity**
NR ribosomal profiles were markedly more heterogeneous by Shannon entropy ($p<10^{-300}$), consistent with a mixed pool of compositionally distinct ribosomes.

**Nucleolar stress signalling**
RPL11 was elevated in NR ($p=6.2\times10^{-33}$) with rewired coupling to p53 targets — CDKN1A, BAX, MDM2, GADD45A, FAS (permutation p=0.0002).

**A translational paradox**
mTORC1 ($p=1.2\times10^{-20}$), initiation ($p=1.7\times10^{-204}$) and elongation ($p=2.4\times10^{-117}$) scores were all higher in NR, yet ATF4 ($p=5.0\times10^{-83}$) and DDIT3/CHOP ($p=7.1\times10^{-8}$) were simultaneously elevated.

**Enrichment in translational stalling**
NR cells were enriched in the stalled quadrant (30.5% vs 24.4%, Fisher OR=0.74, $p=8.1\times10^{-36}$), and ATF4 was higher in stalled than in efficient translator cells (p=0.017).

**Selective uncoupling of the mTOR axis**
mTOR–ribosome correlation remained intact ($\rho$=+0.28 R, +0.25 NR), whereas mTOR–effector coupling was absent ($\rho$=−0.07 R, −0.08 NR).

### The paradox in non-responder CAR-T cells

**Growth signal is ON**
mTORC1 tells the cell to keep building ribosomes

**Stress signal is ON**
the ISR blocks ribosomes from starting new proteins

**Ribosomes are built and ready**

× **BLOCKED AT THE STARTING STEP** ×

**No killing proteins are made**
GZMB · PRF1 · NKG7

**Machinery present, output absent — and this stalled state is enriched in non-responders: 30.5% of cells vs 24.4% in responders**

## REFERENCES

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