# A novel class of Ribosome Modulating Agents (RMAs) targets ribosome heterogeneity in a subset of Small Cell Lung Cancers

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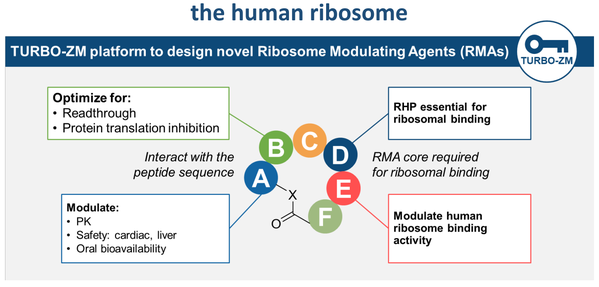
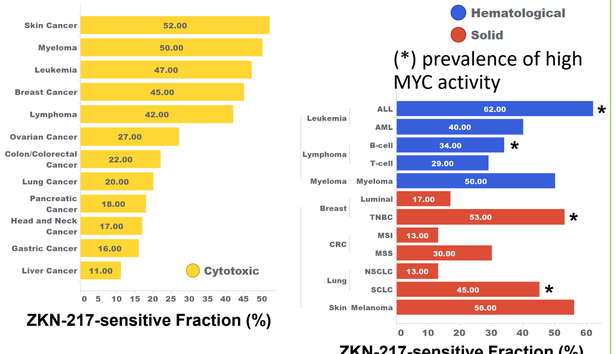
## Introduction

Small cell lung cancer (SCLC) has a very poor prognosis and limited treatment options. Genomic studies in SCLC show that MYC isoforms are key oncogenic drivers in most of SCLC tumors. As a result, these tumors tend to have high proliferation and protein translation rates. We synthesized ribosome modulating agents (RMAs), a novel class of macrolides, capable of selectively inhibiting translation of a subset of molecules enriched for ribogenesis and translation-related proteins in sensitive SCLC cell lines. ZKN-217 selectively inhibits growth and induces apoptosis in a subset of SCLC cell lines characterized by high MYC activity and high ribogenesis rates. Furthermore, ZKN-217 is synergistic with current SCLC standard of care DNA intercalating drugs. The dependency of MYC-driven cancers on abnormally high protein translation rates can therefore be exploited by our RMAs presenting a novel therapeutic opportunity for this recalcitrant disease with high unmet needs.

## Novel synthetic macrolide-based allosteric modulators of the human ribosome



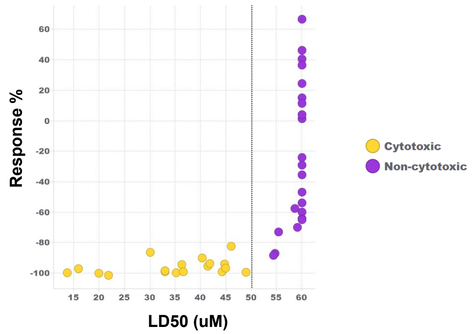

## Several clinical subtypes in solid and hematological cancers are highly sensitive to ZKN-217



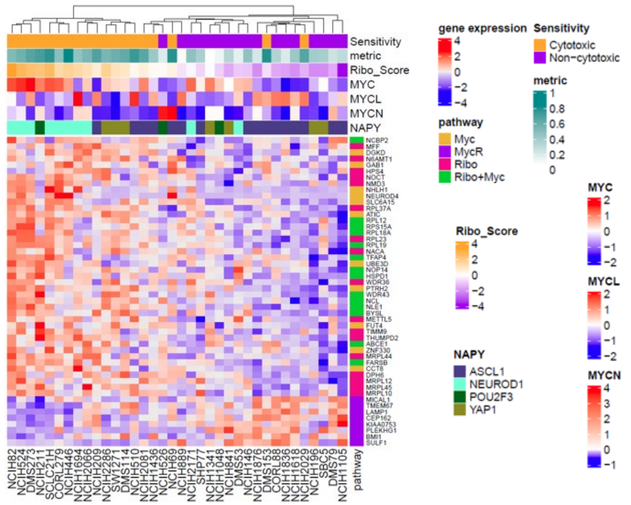


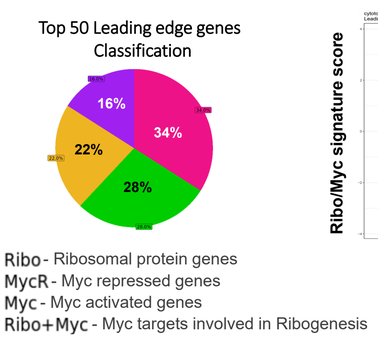


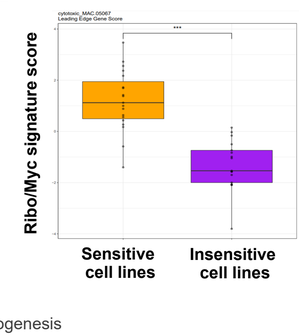
## 45% of SCLC cell lines are highly sensitive to ZKN-217



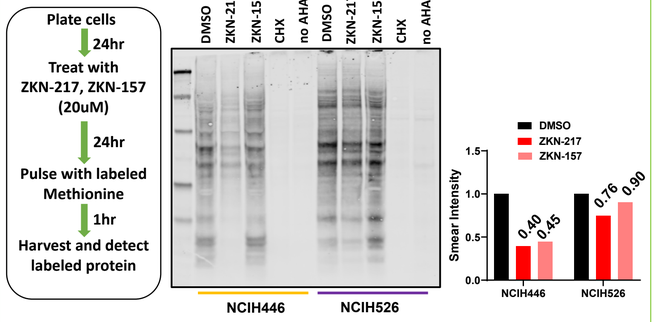

## Sensitivity to ZKN-217 is associated with high expression of Ribogenesis, protein translation, and MYC pathway genes



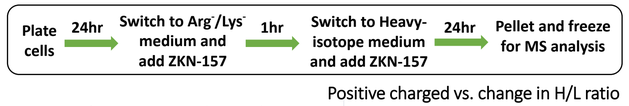



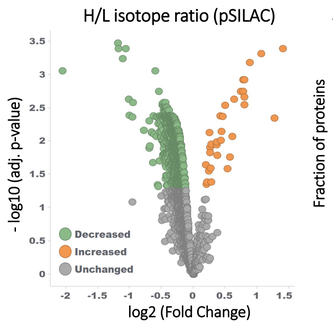



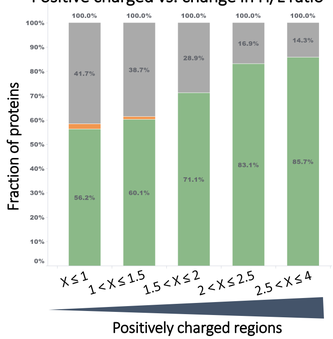

## Anti-proliferative effect of RMAs is driven by selective inhibition of new protein synthesis



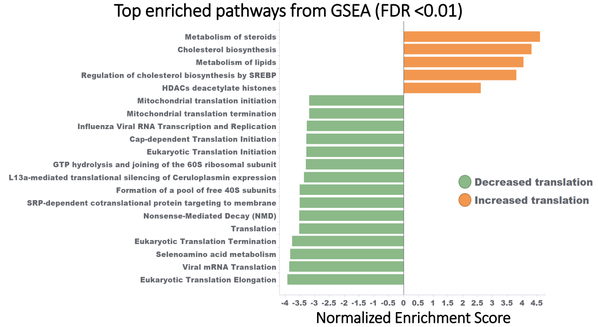

## Proteins with higher positively charged regions are more sensitive to translation inhibition by RMAs



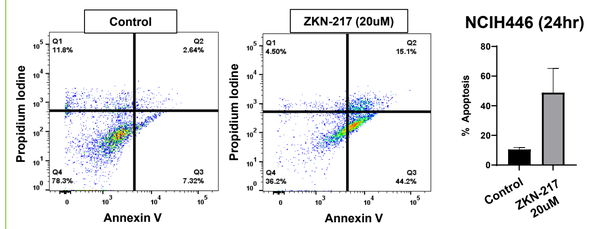



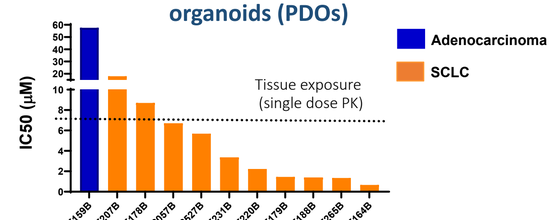

## Decreased proteins show large impact on Ribogenesis and protein translation machinery



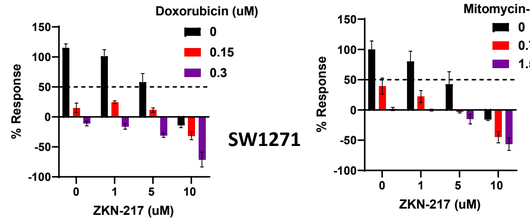

## ZKN-217 selectively induces apoptosis in sensitive cells




## ZKN-217 selectively inhibits SCLC patient-derived organoids (PDOs)




## ZKN-217 shows combination synergy with DNA targeting chemotherapeutics known to inhibit rRNA synthesis




## Multiple levels of selectivity of allosteric inhibition by RMAs

| Novel Activity | Cause | Effect (of RMAs) |
|---|---|---|
| Ribosome selectivity | Ribosome heterogeneity | Target Ribosomes in a subset of cancers |
| Translation inhibition selectivity | Proteins containing regions with high density of positively charged amino acids | Inhibit translation of a subset of proteins |

## Conclusion

- Several cancer subtypes with prevalence of high MYC activity are sensitive to novel allosteric ribosome modulators
- Sensitivity in SCLC is associated with high expression of MYC target genes involved in Ribogenesis and protein translation
- Anti-proliferative effect is driven by selective inhibition of ribogenesis and new protein synthesis
- RMAs show additive and synergistic effects with major chemotherapy backbone agents