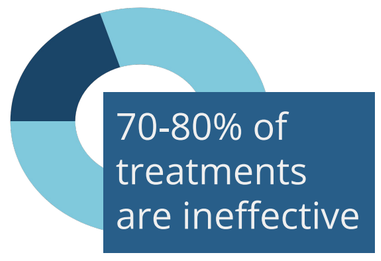
The Role of MYC in *RET* Fusion Tumorigenesis and RET Inhibitor Resistance

Background & Review of Literature

Non-Small-Cell Lung Cancer

- Lung cancer is the leading cause of cancer deaths worldwide
  - Non-small-cell lung cancer (NSCLC) accounts for 85% of all diagnoses
- 5-year survival rate of 15.6%
  - ~1,180,000 deaths per year
- NSCLC mainly treated with surgery and chemotherapy,
  - Only ~20-30% of disease respond

1,180,000
NSCLC deaths each year

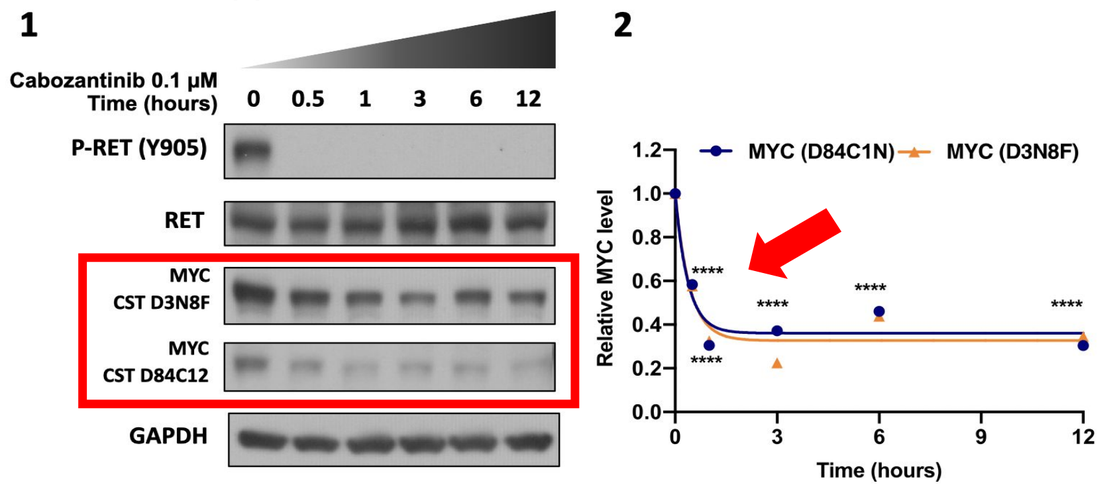


Personalized Medicine

- Standard treatments only effective for subset of the population
  - Patients diagnosed with the same subtype have different genetic causes
- Identifying driving mechanisms opens avenues for targeted therapies
  - Greater efficacy and safety compared to standard approach

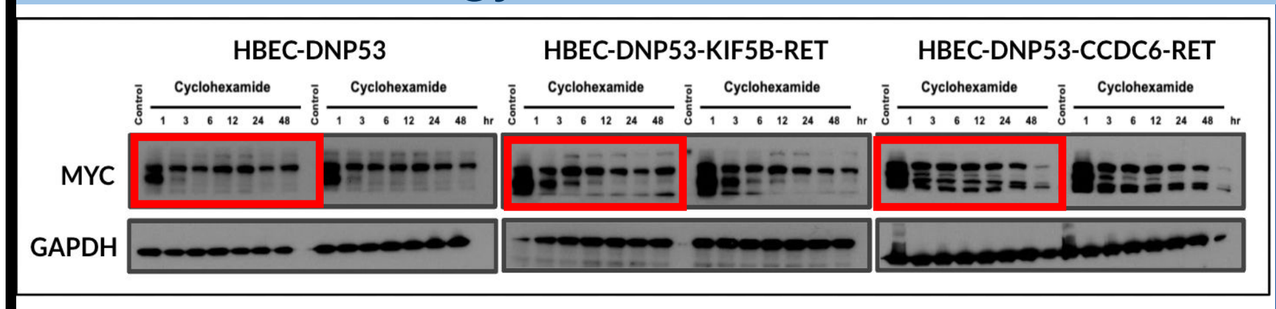
Treatment Resistance in *RET* Fusion NSCLC

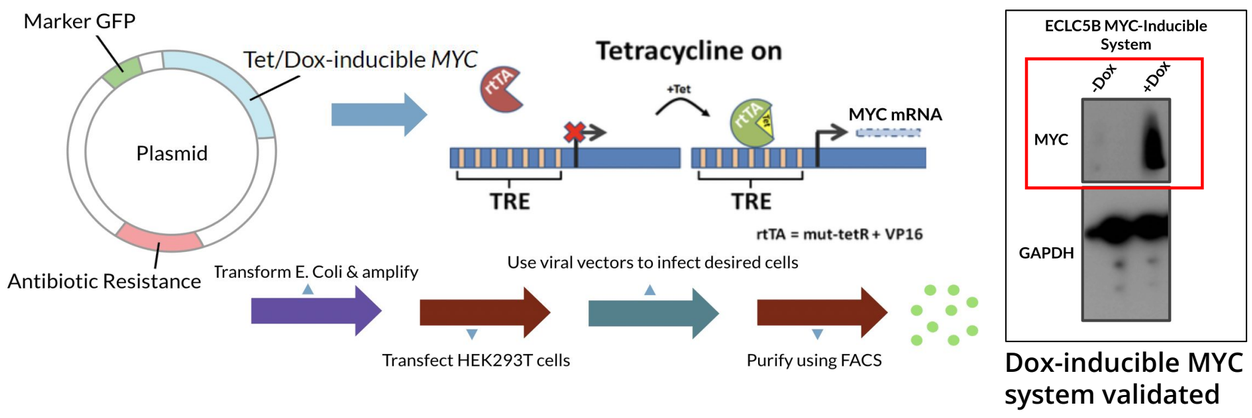
- *RET* encodes for a transmembrane receptor associated with cell proliferation, migration, & differentiation
- *RET*-fusions can be treated with RET inhibitors
  - Selpercatinib, pralsetinib, and cabozantinib
- Resistance to RET inhibitors frequently occurs but mechanisms of resistance are poorly defined
- RET inhibitor application decreases MYC levels



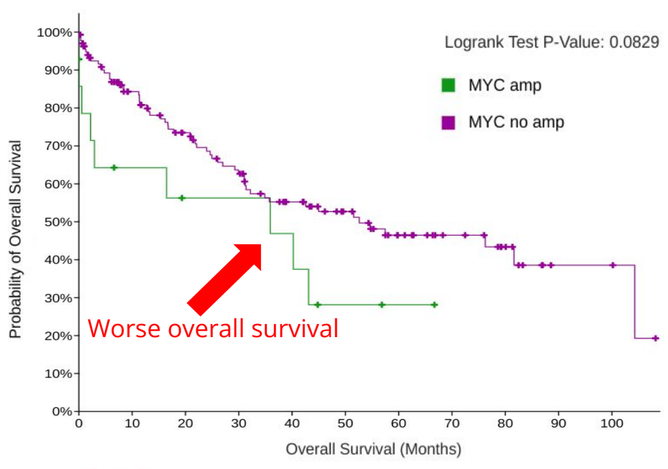
- *MYC* is a family of 'master regulator' transcription factors
  - Regulates ~15% of all genes and is dysregulated in >70% of all cancers)
- Our objective was to determine the role of *MYC* in *RET* fusion NSCLC tumorigenesis and treatment resistance

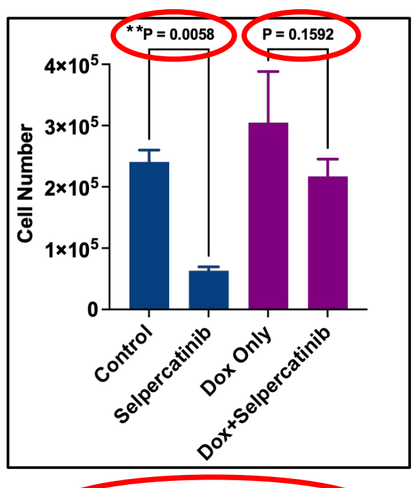
Methodology, Results, and Discussion

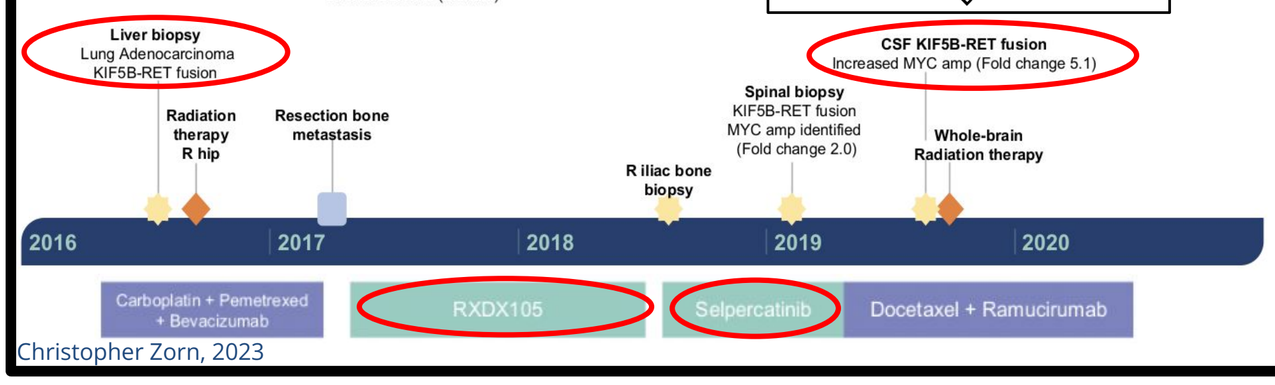




Dox-inducible MYC system validated







Christopher Zorn, 2023

Impact and Application

- Connection between *MYC* and *RET* allows for development of new therapeutic approaches
- New personalized approaches will have improved effectiveness
- *RET* fusions present in ~3% of NSCLC
  - Based on an estimated 1.87 million NSCLC cases, this has potential to benefit 56,100 patients per year

56,100
Patients benefited per year

- *RET* fusion NSCLC is usually seen in young, never-smokers
  - Particularly benefits these groups
- Applications to other cancers
  - Thyroid, medullary, breast

Benefits young, never smokers

Student and Mentor Roles

Student Role

- ❑ Idea for the study
- ❑ Design of purposes and methods
- ❑ All data collection
- ❑ Determination of results, conclusions, implications and future research

Mentor Role

- ❑ Consulting in design of methods
- ❑ Cell line generation
- ❑ Verification of results, conclusions, implications, and future research

Conclusion

Goal

- Determine the role of MYC in *RET*-fusion tumorigenesis and RET inhibitor resistance

Results

- Hypotheses were supported
  1) *RET* fusions increase MYC levels by stabilizing the MYC protein
  2) MYC overexpression is a mechanism of resistance to RET inhibitors in NSCLC
- MYC plays a key role in *RET* fusion tumorigenesis and resistance to current therapies

Future Focuses

- Develop & test combined anti-RET anti-MYC therapy in mice
- Determine more comprehensive model of MYC upregulation with additional inhibitory approaches
  - MYC shRNA, dox-inducible *MYC* system, Omomyc
- Test more *RET* fusion variants
- Verify MYC stabilizing mechanism

Global Impact

- Benefits over 50,000 patients per year
- Benefits young, never-smokers
- Applications to other cancers