Rediscovering Drugs to Inhibit Microbiota-Induced Chemoresistance in Pancreatic Ductal Adenocarcinoma

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Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is the **most aggressive gastrointestinal cancer**, with a **97.8% mortality rate in Pakistan** (Ali et al., 2021).

Standard treatments include gemcitabine, FOLFIRINOX, and capecitabine (Ali et al., 2021). The **gut microbiota** significantly contributes to chemoresistance against gemcitabine in PDAC.

Bacterial cytidine deaminase isoform has **higher affinity for gemcitabine** than the human CDA enzyme, converting the drug before it can reach the tumor microenvironment (Geller et al., 2017). This **microbial interaction limits chemotherapy effectiveness in PDAC.**

Objective

To identify compounds and drugs that could reverse gene signatures associated with Gemcitabine Resistant PDAC

Methodology

Literature review → Data collection → Gene conversion → Drug identification → Drug Data → Venn diagram

Results

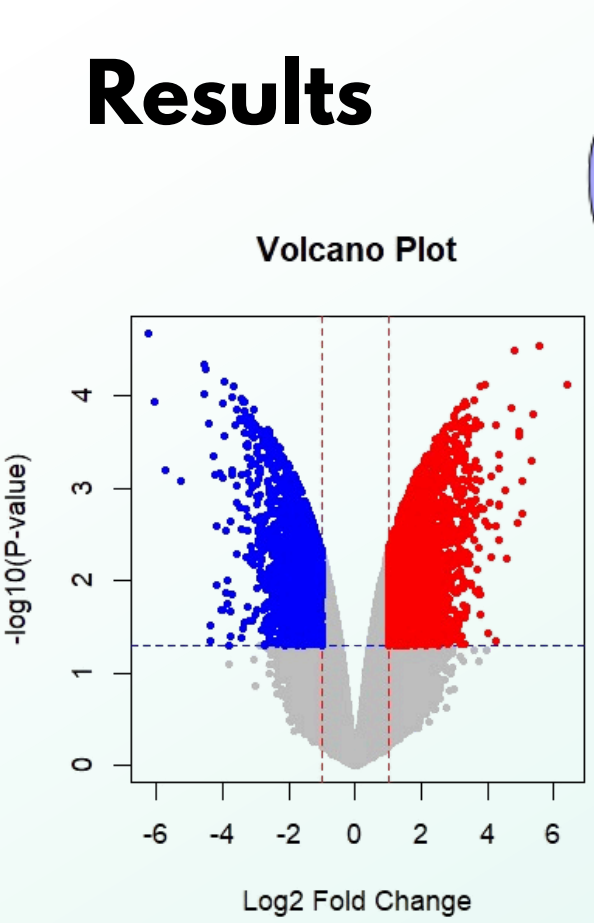

Figure 1. DGE plot for Resistant PDAC

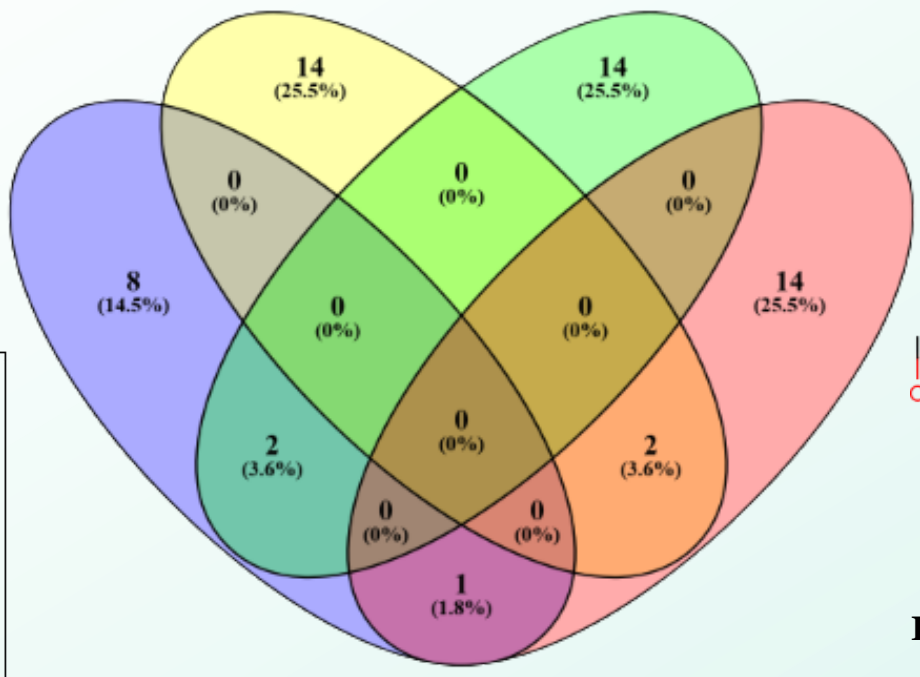

Figure 2. Drug overlap

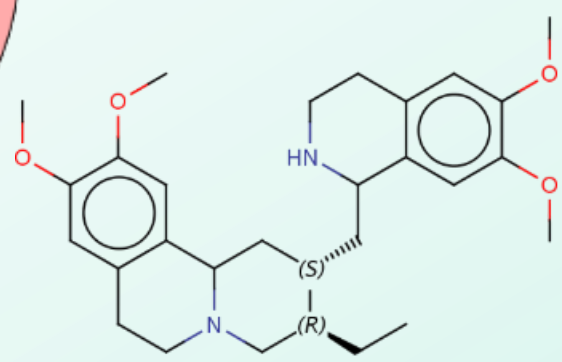

Figure 3. Structure of Emetine

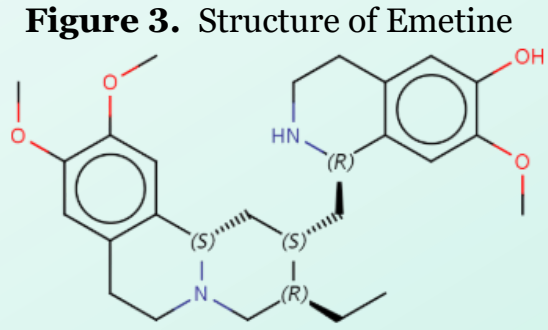

Figure 4. Structure of Cephaline

Conclusion

A panel of **eight drugs and compounds** was identified that effectively reverse gene signatures associated with gemcitabine-resistant pancreatic ductal adenocarcinoma (PDAC).The drugs rediscovered include **Anisomycin, Cephalin, Emetine, QL-X-138, STK17AKO, Navitoclax, Kinetinriboside, and Bortezomib.**

Way forward

Integrate meta-omic analysis.
Replicate study for **FOLFIRINOX, Capecitabine** regimens.
validation on PDAC patient cohort

References

1. Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, Davis A, Mongare MM, Gould J, Frederick DT, Cooper ZA, Chapman PB, Solit DB, Ribas A, Lo RS, Flaherty KT, Ogino S, Wargo JA, Golub TR. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. **Nature**. 2012 Jul 26;487(7408):500-4.
2. Geller LT, Barzily-Rokni M, Danino T, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. **Science**. 2017;357(6356):1156-60.
3. Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, Davis A, Mongare MM, Gould J, Frederick DT, Cooper ZA, Chapman PB, Solit DB, Ribas A, Lo RS, Flaherty KT, Ogino S, Wargo JA, Golub TR. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. **Nature**. 2012 Jul 26;487(7408):500-4. doi:10.1038/nature11183.

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