

# SMALL MOLECULE INHIBITORS TO PREVENT TETRACYCLINE RESISTANCE

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**Disease indication** – Tetracycline resistant infections

**Drug format** – Small molecule (anhydrotetracycline (aTC) or analogs)

**Drug class** – Combination therapy

**Research stage and Preliminary data**

- In vitro:
  - Enzymatic activity assays demonstrated that aTC inhibits tetracycline destructases from degrading tetracycline
  - When aTC and tetracycline are administered together in liquid culture, *E. coli* expressing tetracycline destructases become up to five times more susceptible to tetracycline
  - Similar findings observed for combinations of four semisynthetic aTC derivatives co-administered with five tetracycline analogs

**Target** – Tetracycline destructases (Tet(X), Tet(50), etc)

**Background** – Tetracycline is one of the three most commonly used antibiotic classes in both clinical and agricultural settings, and some tetracyclines are used as last-resort antibiotics against multidrug resistant pathogens. Bacteria can develop resistance to these broad-spectrum antibiotics with tetracycline destructases – enzymes that degrade and thereby inactivate tetracyclines before they can interrupt bacterial protein production. Enzymatic inactivation of tetracyclines has now been reported in many multidrug resistant pathogens from both clinical and agricultural settings and against all known tetracyclines, including the recently FDA-approved derivatives tigecycline, eravacycline, and omadacycline. Because the genes encoding these destructases are highly transferable, this mechanism of resistance could continue to spread quickly throughout microbial communities and threaten the effectiveness of yet another key class of antibiotics.

**Keywords** – Antibiotics, antibiotic resistance, multidrug resistance, infectious disease

**Mode of action** – aTC and its analogs are competitive and mechanistic inhibitors of tetracycline destructases, blocking their active site and rendering them noncatalytic. Because they are not degraded themselves, these inhibitors can be administered together with tetracyclines to circumvent this resistance mechanism and treat infections.

**Competitive edge** – First therapy developed for rapidly emerging antibiotics resistance mechanism, which has already been observed to evade recently developed and last-resort antibiotics in clinical and

agricultural pathogens.

**Publications** – Park, J. *et al.* [Plasticity, dynamics, and inhibition of emerging tetracycline resistance enzymes](#). *Nat. Chem. Biol.* **13**, 730 (2017).

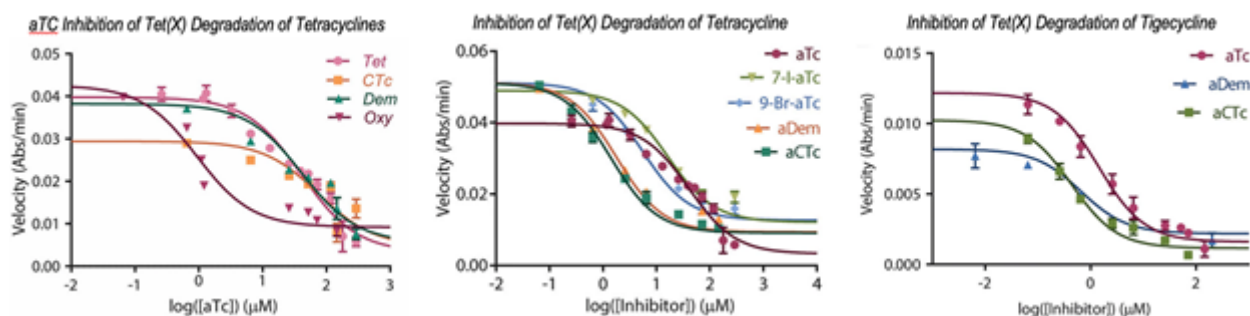
L. Markley, J. *et al.* [Semisynthetic Analogues of Anhydrotetracycline as Inhibitors of Tetracycline Destructase Enzymes](#). *ACS Infect. Dis.* **5**, 618–633 (2019).

**Related Publications** – He, T. *et al.* [Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans](#). *Nat. Microbiol.* **4**, 1450–1456 (2019).

**Patent status** – [Inhibition and Diagnostics of Emerging Tetracycline Resistance Enzymes](#) (US Patent No. 10,273,468 B2)

## Web Links

- [Tim Wencewicz lab](#)
- [Gautam Dantas lab](#)
- [Niraj Tolia lab \(NIH\)](#)



*In vitro* kinetic assays with Tet(X) show that aTC inhibits the degradation of first-generation tetracyclines (left) and that aTC analogs inhibit the degradation of tetracycline (middle) and the recently FDA-approved tigecycline (right).