

Name	Department	Degree	Abstract title	Group members
Andrew Rowley	EOH	MPH	Epinephrine Worsens Cerebral Microcirculation After Experimental Pediatric Cardiac Arrest	Andrew Rowley
Qiao Lin	EOH	PhD	Eradicate Multi-Drug Resistant Pseudomonas aeruginosa Biofilms and Persisters with Splunc1-Derived Novel Antimicrobial Peptides	Berthony Deslouches, Yung-Chih (Jerry) Wang

**Andrew Rowley - EOH**

## **Epinephrine worsens cerebral microcirculation after experimental pediatric cardiac arrest**

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### **Introduction**

Epinephrine is given at resuscitation from cardiac arrest (CA) to produce vasoconstriction of the peripheral vessels and enhance heart contractility. While epinephrine is important in resuscitation to enhance heart contractility and maximize the chances of resuscitation, some reports suggest that it diminishes blood flow in the capillaries of the brain and concern was expressed about worsening outcome. In a recent study in adults, epinephrine was shown to be associated with worse neurological outcome in survivors. Hence, we sought to analyze the efficacy of withholding epinephrine administration during resuscitation in a pediatric model of asphyxial CA (ACA)<sup>3-7</sup>.

### **Hypothesis**

The exclusion of epinephrine administration during resuscitation will attenuate cognitive deficits seen in pediatric rats that have sustained an ACA.

### **Methods**

Post-natal day 16-18 rat pups received either a 9.5-minute ACA intravenous infusion of epinephrine (E) or normal saline (NS) prior to resuscitation. In the cohort tested, the two groups studied were ACA-E (epinephrine), and ACA-NS (normal saline), n=6/group, with brain tissue oxygen and cerebral blood flow monitoring performed for 2 hours post-ACA. Cerebral blood flow was monitored via 2-photon microscopy and fluorescent dye to measure individual and overall bloodflow through the vasculature of the brain

### **Results**

While the administration of epinephrine was beneficial from the standpoint of faster Return Of Spontaneous Circulation (ROSC), there was a statistically significant difference in the capillary diameters observed with 2-photon microscopy. In addition, a statistically significant difference was observed in the amount of capillaries with flow disturbances following ROSC as the recovery period continued, with normal saline animals having less disruption in their capillary flow 45 and 75 minutes following ROSC.

### **Conclusions**

The study finds that while epinephrine is beneficial to reducing resuscitation time following ACA, it restricts blood flow to brain tissue and may lead to neurological impairment after CNS injury. The inclusion of epinephrine comes at the cost of vasoconstriction, which can result in reduced bloodflow to vulnerable regions of the brain following cardiac arrest.

### **Research/Grant support**

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**Qiao Lin - EOH**

**TITLE:** ERADICATE MULTI-DRUG RESISTANT PSEUDOMONAS AERUGINOSA BIOFILMS AND PERSISTERS WITH SPLUNC1-DERIVED NOVEL ANTIMICROBIAL PEPTIDES

**Background:** *Pseudomonas aeruginosa* (*P. aeruginosa*) is one of the most lethal pathogens that causes chronic respiratory infections in cystic fibrosis (CF) patients. With the current shortage of newly developed antibiotics, respiratory failure induced by bacterial infection is still the main cause of death in CF. Antimicrobial peptides (AMPs) are a new class of promising therapeutics that could potentially target current difficult-to-treat multi-drug resistant (MDR) bacterial infections. The goal of this study is to understand the bacterial killing mechanism, efficacy against MDR *P. aeruginosa* and in vivo safety of novel AMPs that were derived from respiratory host defense protein SPLUNC1 (collectively named A4-AMPs).

**Methods:** Rationally designed novel AMPs were synthesized based on an antimicrobial motif of SPLUNC1 and screened against a panel of more than 50 MDR clinical *P. aeruginosa* isolates. Antimicrobial potency was determined by growth inhibition and various biofilm prevention assays. Mode-of-action through bacterial membrane permeation was confirmed by changes of membrane potential and microscopic images including SEM, TEM, and AFM. Cellular toxicity was evaluated using RBC, WBC, and airway epithelial cells. Safety profile and efficacy were determined using murine Pneumonia models.

**Results:** De novo synthesized A4-AMPs overcome multiple shortcomings that are normally associated with natural AMPs and demonstrated excellent antimicrobial activity that are not achievable by natural AMPs. Multiple A4-AMPs also showed superior bactericidal and anti-biofilm activities against MDR-*P. aeruginosa* isolates compared to current standard-of-care antibiotics including Tobramycin, Ceftazidime, and Ciprofloxacin. The lead compound A4-112 has demonstrated significantly lower toxicity and better efficacy than colistin, the last resort of antibiotics. A4-112 directly perturbs bacterial membrane that results in instant bacterial lysing and killing. In vitro and in vivo studies also showed negligible RBC and WBC toxicity and high efficacy against *P. aeruginosa*-induced murine respiratory infection with a therapeutic index >100 in eliminating *P. aeruginosa*-induced pneumonia.

**Conclusions:** Our data demonstrated promising therapeutic potential of A4-AMPs as the next generation novel antimicrobials. The low toxicity and high efficacy against MDR-*P. aeruginosa* warrant further investment and exploration of A4-112 in eradicating persistent *P. aeruginosa*-associated biofilm, colonization, and infection in CF sufferers.