Multi-Target Anthrax Antitoxin Therapies

Lisa Johansen*, Nicole Sirianni, William Avery, Shannon Shelton, Joseph Lehar, Margaret Lee and Curtis Keith., CombinatoRx, Incorporated, Cambridge, MA

Multi-component drugs are successful in treating a variety of infectious diseases including bacterial and viral infections. Historically, combinations have been discovered through luck or lengthy trials using agents with similar indications. To tap into the vast potential of unexplored combination drugs, we have developed a combination high throughput screening technology (cHTS™) which systematically tests combinations of approved drugs in phenotypic assays. Because anthrax lethal toxin intoxication involves multiple pathways, it is well suited for combination drugs. We have assembled a library of ~2000 approved drugs and biologically active molecules and are applying cHTS™ to identify novel synergistic combinations directed against anthrax lethal toxin.

We have optimized a cell-based assay for rescue from lethal toxin cytotoxicity and are screening our library for unique pairwise combinations that synergistically rescue toxicity. Combinations are screened in multiple doses and ratios in a dose matrix format and data are subjected to several interaction models to identify synergistic combination effects. Our custom analysis tool, Chalice, enables us to characterize complex patterns of combination effects and obtain insights into multi-target mechanisms of action as well as guide clinical co-therapy decisions.

We have identified multiple pairwise combinations possessing significant antilethal toxin activity. These pairs include both combinations of drugs not previously known to possess anti-lethal toxin activity as well as enhancers of known anti-lethal toxin agents. Initial work has begun on examining the efficacy of our anti-toxin combinations in animal models of intoxication.

In summary, we have applied our cHTS™ approach to discover novel multi-target drugs for anthrax lethal toxin and have identified multiple pairwise combinations with synergistic anti-toxin activity. Because there are extensive toxicity and pharmacology data available for approved drugs, promising leads may be rapidly advanced to clinical settings.