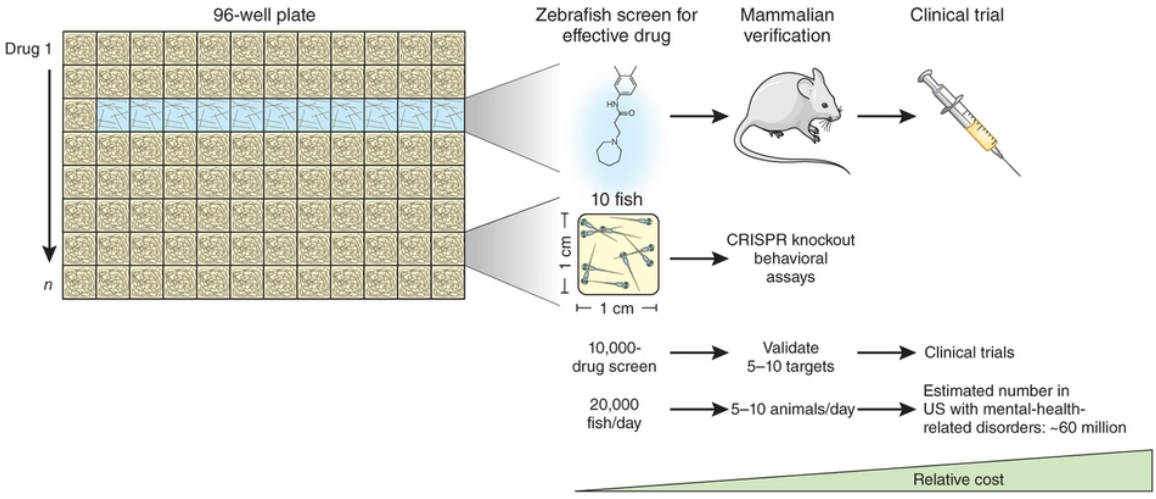
Title:

Target-agnostic CNS drug discovery using high-throughput behavioral chemical screening in zebrafish larvae identifies a new role for sigma-1 receptors in the vertebrate brain.

Abstract:

Since their original (mis)characterization as opioid receptors, sigma-1 receptors have been implicated in substance abuse and addiction. Sigma-1 receptors are one of the molecular targets of cocaine and are involved in self-administration of not only cocaine but also the psychostimulant methamphetamine in rodent models. Sigma-1 receptors have also been studied for their effects on anxiety and neuronal plasticity. The cellular and molecular mechanisms involving sigma-1 whereby addictive processes might be formed are of special interest. My lab is using a chemical-genetics approach to study sigma-1 biology, *in vivo*, in a high-throughput, chemically & genetically tractable system – zebrafish larvae. We, and others, have shown that drugs which affect humans have similar effects and mechanisms of action in zebrafish, and conversely chemicals discovered in zebrafish similarly affect mammals. By using tiny zebrafish larvae, we can collect much more data on the behavioral effects of chemical or genetic perturbations than has been possible with larger animals. I am specifically interested in how sigma-1 ligands induce behavioral changes related to motivation and neuronal processing. By screening libraries of both known drugs and novel chemicals, we are able to identify novel small molecules able to phenocopy the behavioral effects of known drugs and genetic perturbations. We have identified a zebrafish behavior specifically effected by Sigma-1 agonists, and have used it to identify novel Sigma-1 ligands with nanomolar affinities. To confirm sigma-1's involvement in the behavioral modification, we created knockout zebrafish using CISPR-cas9 technology and observed a reversal of the behavioral phenotype. We are now using these new behavioral assays and chemical probes as tools to understand how Sigma-1 activation, *in vivo*, leads to behavioral change.



Biosketch:

Dr. Andrew Rennekamp is a young investigator in the Department of Medicine at *Massachusetts General Hospital* and the Department of Systems Biology at *Harvard Medical School*. He is also affiliated with the *Broad Institute of MIT and Harvard* under the mentorship of Dr. Randall Peterson.

Dr. Rennekamp has more than ten years of experience in cell and molecular biology. He began his career at the *University of Pennsylvania Perelman School of Medicine*, examining zebrafish neurobiology. He also worked in the Penn Department of Microbiology and at the *Wistar Institute* during graduate school. Dr. Rennekamp has successfully collaborated with many researchers and contributed to several peer-reviewed publications. He has been invited to present his work at internationally renowned conferences and meetings.

At Harvard he has been developing a research program focused on the chemical and genetic regulation of freezing and escape behaviors, with an emphasis on using behavioral assays in small zebrafish larvae as tools for high-throughput system-biology and neuroactive drug discovery. His primary interests are in chemical genetics, neuropharmacology and threat response behaviors.