New painkillers reduce overdose risk

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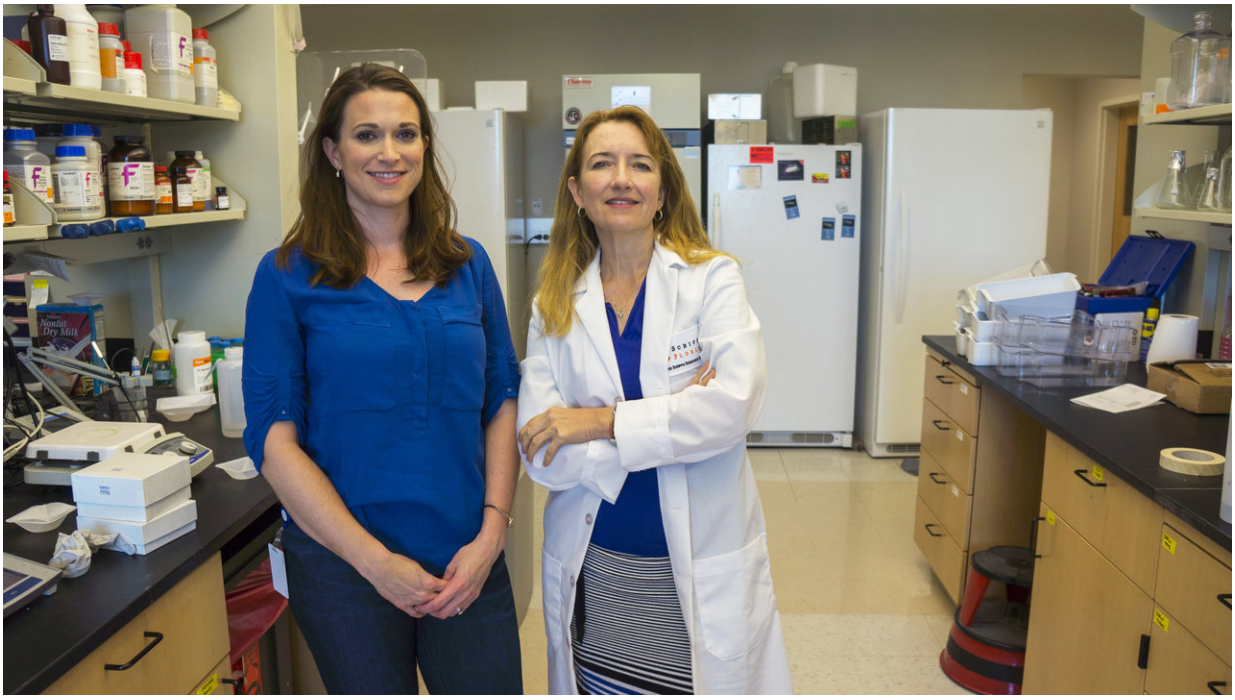

Left to right: This is the study first author Cullen Schmid, staff scientist, and TSRI Professor Laura Bohn. Credit: Laura Bohn, The Scripps Research Institute

Scientists on the Florida campus of The Scripps Research Institute (TSRI) have developed new opioid pain relievers that reduce pain on par with morphine but do not slow or stop breathing—the cause of opiate overdose.

The research, published today in the journal *Cell*, describes a method for

making safer opioid painkillers. According to the U.S. Centers for Disease Control and Prevention, 91 Americans die every day from opioid overdoses—deaths caused when opiates like oxycontin, heroin and fentanyl slow and eventually stop a person's breathing.

Study leader TSRI Professor Laura M. Bohn, Ph.D., said the research shows that a range of compounds can deliver pain-blocking potency without affecting respiration.

The study builds on two decades of research by Bohn and her colleagues, who long questioned whether the painkilling pathway, called the G protein pathway, could be unlinked from the breathing suppression pathway, called the beta-arrestin pathway.

"One of the questions we had was how good we can get at separating out the pathways, and how much separation do we need to see analgesia without respiratory suppression," Bohn said.

For the study, the Bohn worked closely with TSRI chemist Thomas Bannister, PhD, to develope new potential drug molecules; they then tweaked their chemical structures to systematically vary the "bias" between the two pathways—G protein signaling and beta-arrestin recruitment. The group developed more than 500 compounds in the past six years, and they found more than 60 that showed bias between signaling assays. They then selected six compounds to represent a wide range in the degree of bias (from those that preferred barrestin2 recruitment to those that almost exclusively preferred G protein signaling) and determined their overall potency for inducing analgesia and respiratory suppression in mouse models.

The researchers found that the new compounds could indeed enter the brain—and all of the compounds were as potent, if not more so, than morphine. The compounds that were less able to promote barrestin2

associations in cells were also less likely to induce respiratory suppression in mice.

In contrast, the painkiller fentanyl was shown to prefer receptor-barrestin2 associations and also had a more narrow safety margin. In short, the fentanyl dose needed to alleviate the perception of pain was closer to the dose that suppressed breathing, which may be why fentanyl is more likely to trigger respiratory suppression at low doses. Fentanyl is a powerful pain killer, but one with a narrow therapeutic window and a history of overdoses. While this issue requires more research, "this at least brings into question whether this may be part of the reason," Bohn said.

Bohn explained that separating the receptor's ability to engage in the two pathways can provide a way to separate desired drug effects from side effects.

"I think what we have done here is shown that bias isn't all or none—that there is a spectrum." That suggests an opportunity to expand the "therapeutic window," or the range of doses at which a drug may be administered safely, she said.

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