



THE  
FRONT  
ROW  
at Scripps Research



A Century  
of Science  
Changing Life



## Bringing precision therapy to mental disorders

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#### ABOUT THE LECTURE

Although mental disorders like anxiety, depression and schizophrenia affect millions of people across the globe, related medications haven't advanced much over the past few decades. But physician-scientist Hugh Rosen, MD, PhD, has made strides in producing new therapeutics. In his Front Row lecture, Rosen explained how together with Ed Roberts and their labs, they discovered a new medication by examining novel ways to target a neural receptor responsible for a range of mental illnesses.

#### TOP TAKEAWAY POINTS

1. During clinical trials, drugs are evaluated on how effective they are at treating as many people as possible. This model conflicts with the concept of precision medicine, which encompasses a treatment plan specifically tailored for each patient. Although precision medicine may involve developing a drug with a specific indication, it's difficult to do this for mental illnesses because the brain is such an intricate organ.
2. The kappa opioid receptor expressed in the brain regulates a variety of neuronal circuits that impact addiction, cognition, dysphoria and emotion. Activating this receptor via the neuropeptide dynorphin—which is produced in response to stress—induces several negative emotions by inhibiting dopamine secretion. Dopamine is essential for pleasure, motivation and satisfaction. There's also evidence that activating the kappa opioid receptor induces psychosis. Thus, Rosen and Roberts were intrigued by how targeting the receptor could potentially influence a new line of treatment for mental illnesses.
3. A key issue with traditional first-line medications for depression and other psychological disorders is that they have a range of side effects, including sedation, weight gain, brain fog and sexual dysfunction. Such medications include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Rosen and his team hypothesized that if they could selectively block the kappa opioid receptor, they could also “block” feelings of anxiety without the patient feeling sedated. Moreover, Rosen postulated that blocking the receptor would not only stop the progression of chronic anxiety to depression, but it could also interrupt processes involved in psychotic behavior.
4. Rosen tested his hypothesis by making a reversible blocker of the kappa opioid receptor. This led to his co-invention of navacaprant, a medication for depression that's currently in phase 3 clinical trials. Some related data is expected to be released later this year. Two phase 3 studies are scheduled for completion by mid 2025. Phase 2 studies for using navacaprant in cases of bipolar disease are also expected to wrap up next year.
5. Other areas of potential therapeutic application for navacaprant include mitigating substance abuse withdrawal as well as sleep disturbance—another common side effect of SSRIs and SNRIs. Researchers at Scripps Research are also planning to test whether navacaprant can be used specifically for decreasing alcohol consumption in cases of alcohol addiction. Another topic being explored is how navacaprant may help alleviate post-traumatic stress disorder.

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