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“Remissions leading to a full recovery or relapses progressing to recurrences are characteristic of a significant number of pathological conditions. We are concentrating our efforts toward understanding how the temporal restoration of the body’s homeostasis may induce remission and ideally lead to recovery.”

Like a central command center, the brain area known as the hypothalamus sends out “master” brain hormones, which regulate basic bodily functions. Many of these hypothalamic hormones, including the “stress hormones” corticotropin releasing factor (CRF) and the urocortins (Ucn), as well as their two receptors (CRFR1 and CRFR2), were characterized at the Salk Institute. Because of their broad distribution, CRFs and CRFRs mediate numerous complementary stress-related endocrine, autonomic, metabolic, immune, cardiovascular, gastrointestinal, and cutaneous pathologies.

To test whether molecules that block CRF’s functions may induce remissions, Rivier, in collaboration with Salk colleagues Wylie Vale and Catherine Rivier, developed a series of very effective CRF antagonists. Working with Lixin Wang, Mulugeta Million, and Yvette Taché at UCLA, Rivier and his team then tested the effects of a potent and long-acting version in mice that overexpress CRF. Without treatment, these mice develop symptoms that are typical of Cushing’s syndrome, such as thinning of the skin, loss of fur, and fat accumulation at the midsection of the body as they get older. When treated with a CRF antagonist, however, their fur immediately starts to regrow.

Under stressful conditions, the body responds initially by mounting a multipronged counterattack that normally deals successfully with acute challenges but more likely than not will fail in the face of chronic challenges. When unsuccessful, the body’s defense mechanisms such as the immune system become compromised, triggering a recurrence of the disease. If the chronic stress response is mitigated either psychologically or pharmaceutically, Rivier believes that those systems recover their ability to deal with the insult, thus triggering a remission—the first step toward full recovery. He is now testing this hypothesis in animal models, including in prematurely weaned pigs, which suffer from stress-induced diarrhea. Initial promising results indicate that CRF antagonists could play an important role in treating irritable bowel syndrome and, hypothetically, most other conditions initiated by or relapsing as a result of stress.

For more information, please visit
salk.edu/faculty/rivier.html



Left to right:
Jean Rivier, Judit Erchegyi, Jozsef Gulyas, and Debbie Doan