Immunotherapy Treatment for Stress-Related Disorders

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Technology description

Corticotropin Releasing Hormone (CRH) Antibody Reduces Stress Response

This immunotherapy is a first-in-class approach targeting a hormonal peptide, CRH, to treat stress-related disorders. In response to psychologically stressful situations, the body initiates an orchestrated hormonal signaling cascade that begins with the release of CRH by neurons within the hypothalamus in the brain. CRH has direct action within the brain, but its most studied action is on the pituitary gland, where it triggers release of adrenocorticotropic hormone (ACTH), which in turn controls release of cortisol from the adrenal glands. Collectively, this system is referred to as hypothalamus-pituitary-adrenal (HPA) axis. Chronic psychological stress and perturbation of the HPA-axis has been associated with many diseases and conditions including Alzheimer’s disease, anxiety disorders, major depression, post-traumatic stress disorder, addiction, metabolic syndrome, osteoporosis, sarcopenia and others. Further, chronic stress, HPA-axis dysfunction, and elevated cortisol have been implicated as an accelerant with regard to the negative physiological consequences of aging. Despite great interest, small-molecule approaches to targeting the HPA-axis have had limited benefit in human studies. Antagonist of the high affinity CRH receptor (CRHR1) have not proven efficacious, with concerns including off-target toxicity, insufficient target engagement, CRH-signaling through alternate receptors and to no effect on ↑-arrestin mediated receptor signaling. Glucocortocoid antagonists (e.g., mifepristone) suffer from lack of specificity and many side effects, thus limiting clinical utility. Researchers at the University of Florida have developed an antibody against corticotropin-releasing hormone (CRH). This high-affinity anti-CRH antibody (KD of ~1 pM) shows excellent target engagement in preclinical studies. In a dose-dependent fashion, it blocks both acute and chronic stress-induced elevations in cortisol. Further, it blocks chronic-stress-induced weight loss and increases lean body mass and muscle weight in mice. Extensive multi-organ pharmaco-transcriptomic studies reveal profound effects on pathways implicated in major depression, metabolic syndrome, and sarcopenia. Ongoing preclinical studies are rigorously and extensively evaluating the potential of the anti-CRH immunotherapy in preclinical models of Alzheimer’s disease pathologies, age-associated and stress-related cognitive dysfunction, sarcopenia, and metabolic syndrome. Notably, with respect to Alzheimer’s disease, blocking CRH may reduce both amyloid and tau pathologies. Further given extensive and reproducible data that high cortisol is associated with more rapid declines in cognition

and rates of hippocampal atrophy, targeting CRH in the setting of cognitive decline may have effects on brain function independent of effects on pathology.

Technology

This high-affinity (KD < 1 picomolar) antibody effectively blocks the actions of CRH (corticotropin-releasing hormone) following a stressor in mice. CRH is a central mediator of stress response generated by the HPA (hypothalamus-pituitary-adrenal) axis in brain. In addition, we have a lower-affinity antibody (KD ~10 nM) and a peptide target for the development of an active vaccine targeting CRH. Combined together, these data establish a unique approach to using an antibody targeting a CNS produced peptide involved in complex negative behavioral and metabolic syndromes such as depression, anxiety, Alzheimer’ s disease, metabolic syndrome, sarcopenia and many more.

Application area

Passive immunotherapies for stress-related disorders using either a humanized anti-CRH antibody or a vaccine targeting CRH

Advantages

First-in-class approach to counter stress using high-affinity antibody for CRH
Conservation of CRH from mouse to human means target engagement will remain constant through IND-enabling studies
No evidence exists for toxicity in studies to date
Many possible indications in common diseases and syndromes provide a unique pathway for clinical development. Phase 1 studies can provide unambiguous and rapid assessment of target engagement

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