CalciMedica, Inc.
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CalciMedica
The CRAC Channel Company

CRACing inflammatory disease

CalciMedica, a clinical-stage biopharma company, is developing potentially first-in-class small molecules to combat excessive intracellular calcium levels that drive pathological processes in inflammatory diseases and acute injury, including COVID-19.

Calcium ions (Ca^{2+}) play crucial roles as cofactors for enzymes and second-messengers in signal-transduction pathways in many cell types. Calcium release-activated calcium (CRAC) channels on the cell surface control the entry of Ca^{2+} and are an important way of regulating levels within the cell. Different cellular insults, including infection, trauma, and toxins, can cause CRAC channels to become overactive in certain tissues, leading to excessive amounts of calcium entering cells. Inappropriately high levels of Ca^{2+} lead to cell injury and death, resulting in a variety of disease conditions. Ca^{2+} from CRAC channels also controls expression of proinflammatory proteins, such as cytokines by immune cells, which can lead to serious inflammatory disorders.

CalciMedica, headquartered in La Jolla, California, is a leading CRAC-channel company dedicated to reversing the pathology of Ca^{2+} dysregulation by the modulation of active and overactive CRAC channels with novel small-molecule inhibitors. These inhibitors, delivered in proprietary formulations for intravenous and oral administration, have the potential for a two-hit effect: they can simultaneously protect cells with overactive CRAC channels by preventing the accumulation of dangerously high levels of calcium caused by a disease insult, while also modulating immune-cell function to counter the inflammatory response associated with the same condition.

Auxora, CalciMedica's lead compound, has completed initial phase 2 trials in severe coronavirus disease 2019 (COVID-19) pneumonia and predicted severe acute pancreatitis (AP); it is currently also in phase 2 trials for intubated COVID-19 patients with acute respiratory distress syndrome (ARDS) and for AP patients with systemic inflammatory response syndrome (SIRS). In addition, Auxora is being studied preclinically in ARDS caused by agents other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). CalciMedica's additional drug candidate, CM6018, is currently in preclinical development for chronic pancreatitis. The company is also exploring further indications in which an excessive influx of calcium through CRAC channels negatively affects cells, or activation of the immune system plays a role, such as acute kidney injury (AKI) and traumatic brain injury (TBI).

CRAC-channel biology

Intracellular Ca^{2+} stores within certain organelles, especially the endoplasmic reticulum (ER), are released to the rest of the cell as needed, thereby depleting reserves. Nearly four decades ago, the idea was put forward that 'store-operated calcium channels' (SOCs) at the cell surface were linked to Ca^{2+} levels in the ER. And just over 15 years ago, two of the key proteins comprising the channels—stromal interaction molecule 1 (STIM1) and CRAC modulator 1 (Orai1)—were identified, in large part by CalciMedica's founders.

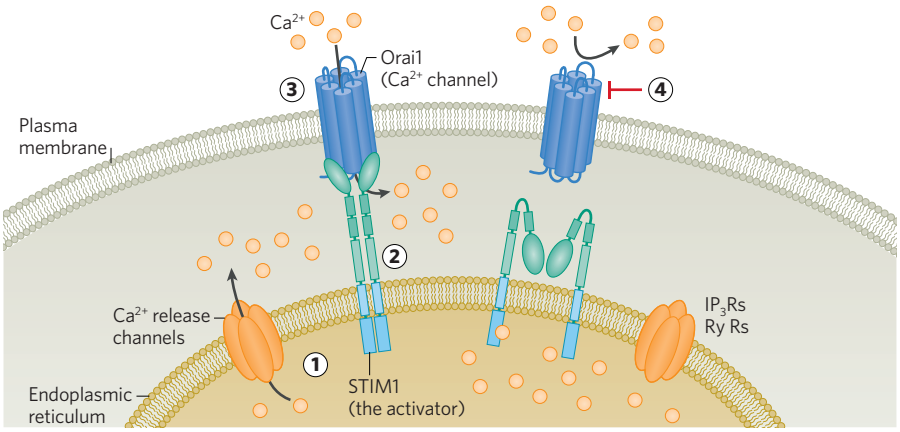

Fig. 1 | Store-operated calcium-channel (SOC) entry pathway. When levels of calcium ions (Ca^{2+}) stored in the endoplasmic reticulum drop (1), stromal interaction molecule 1 (STIM1) 'senses' the change and activates calcium release-activated calcium (CRAC) modulator 1 (Orai1) (2), to allow Ca^{2+} into the cell to replenish stores (3). When CRAC channels are overactivated, an excess of Ca^{2+} enters the cell, a process blocked by CalciMedica's CRAC channel inhibitors (4). This not only protects the cells from Ca^{2+} toxicity, but also prevents the expression of proinflammatory cytokines by immune cells that drive systemic inflammation. IP3Rs, inositol 1,4,5-trisphosphate receptors; RyRs, ryanodine receptors (both are ion channels that release Ca^{2+}).

Low levels of Ca^{2+} within the ER lumen are detected by STIM1, an ER membrane-spanning protein, causing it to change conformation and cluster together with other STIM family proteins. These clusters move to positions close to the cell membrane, where they interact with and activate the plasma-membrane Orai proteins. Orai1 forms an ion channel, also known as a CRAC channel, which opens to allow Ca^{2+} into the cell to both replenish the ER stores and participate in cellular signaling (Fig. 1).

STIM1 and Orai1 are essential for a fully functional immune system. Loss-of-function mutations in *ORAI1* and *STIM1* lead to severely immunodeficient phenotypes. The crucial roles of Orai1 and STIM1 in adaptive immunity are due to the importance of Ca^{2+} influx for effective T cell activation. Antigen binding to a T cell receptor leads to depletion of ER stores of Ca^{2+}, which then stimulates STIM1–Orai1 channels to open and to allow Ca^{2+} into the cell, activating an immune response; when STIM1 or Orai1 proteins are non-functional, there is no entry of Ca^{2+} and the immune response is blunted.

In healthy lymphocytes, Ca^{2+} signaling activates several pathways, including those involving the nuclear factor of activated T cells (NFAT) and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) families of transcription factors. Their activation leads to nuclear translocation of these factors and the expression of many immune-related genes, including proinflammatory cytokines. This has made these transcription factors important drug targets, and some of the molecules that modulate them have been approved for clinical use. However, they target individual transcription factors, whereas CRAC-channel inhibitors, acting upstream in the signaling pathways at the level of the initiating Ca^{2+} signal, can affect multiple pathways.

CalciMedica's CRAC-channel inhibitors therefore treat inflammatory diseases (such as AP and COVID-19 pneumonia) and, potentially, some

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acute injuries (such as ARDS and AKI) differently than other immunomodulators (such as cyclosporine or corticosteroids)—not only by cutting off the flow of Ca^{2+} that is required to activate the signaling pathways for transcription factors (such as NFAT, NF-κB, and others) in immune cells, but also by limiting excess intracellular calcium that is toxic in many distressed cell types. To date, CalciMedica has two pipeline candidates: Auxora, an IV formulation which is on the verge of phase 3 trials; and CM6018 for oral administration, which is currently in late preclinical development.

Auxora

CalciMedica's lead candidate, Auxora, is a small-molecule inhibitor of Orai1 that both downregulates the expression of proinflammatory cytokines—dampening the immune response—and protects cells from calcium-induced cytotoxicity when CRAC channels are overactivated. In human peripheral blood mononuclear cells, stimulated with plate-bound anti-cluster of differentiation 3 (CD3)/anti-CD28 antibodies to express inflammatory proteins, Auxora reduced expression of a variety of interleukins, as well as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α).

Auxora also prevents the cell damage and death that contributes to disease. This dual mechanism of action is illustrated in CalciMedica's phase 2 program in patients with AP and accompanying SIRS.

Auxora for AP with SIRS. AP—sudden inflammation of the pancreas—has a variety of causes, from gallstones and alcohol use to systemic disease and trauma, and results in about 275,000 hospitalizations in the US annually. When CRAC channels become overactive as a result of these diverse causes, pancreatic cells are damaged or die. Factors released from the pancreatic cells, combined with other inflammatory mediators, recruit and activate inflammatory cells, resulting in both local and systemic inflammation.

AP is often mild, with patients spending just a few days in hospital before discharge; however, it can be more serious, with high mortality. One frequent complication of AP is SIRS, which is a kind of 'cytokine storm' that occurs in a large percentage of AP patients and can lead to organ failure, particularly respiratory failure that can necessitate ventilator assistance. CalciMedica is developing Auxora for seriously ill AP patients with unmet medical needs.

Auxora addresses the two core pathological processes that drive AP simultaneously (Fig. 2). In pancreatic cells, Auxora blocks the rapid build-up of toxic levels of Ca^{2+} to avert cell damage and death. At the same time, Auxora prevents the activation of lymphocytes and the expression of proinflammatory mediators that drive SIRS. Consistent with this two-hit model, multiple studies in animal models of AP have shown that Auxora protects pancreatic cells from damage, and downregulates multiple cytokines and other markers of inflammation in both pancreas and lung.

In a completed phase 2a trial in patients with AP plus SIRS and hypoxemia, Auxora plus standard-of-care compared with standard-of-care alone reduced the median hospital stay from 6 to 3.7 days, the severity of AP according to radiologic imaging in patients presenting with moderate or severe disease, and the incidence of persistent SIRS, as well as rapidly restoring appetite and tolerance of solid food. CalciMedica is currently conducting a dose-optimization phase 2b trial of Auxora in more than 200 patients with AP and SIRS.

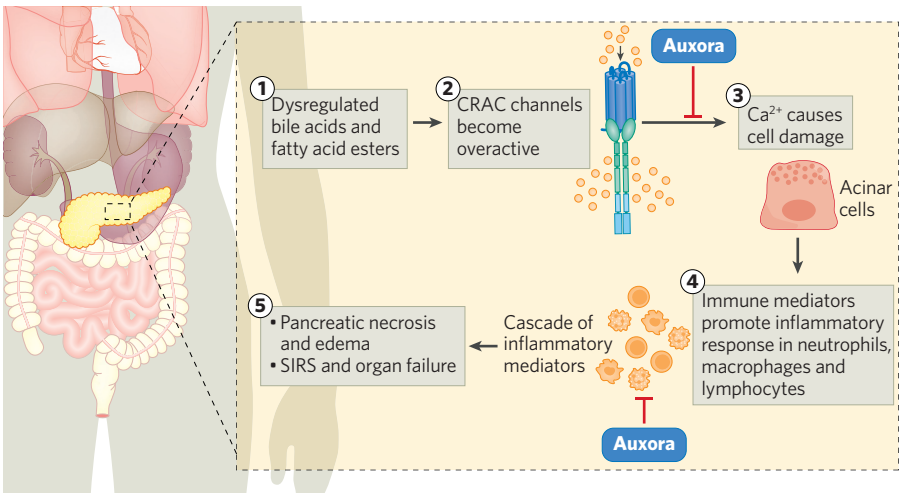

Fig. 2 | Auxora for the treatment of acute pancreatitis (AP) with systemic inflammatory response syndrome (SIRS). Alcohol misuse and gallstones, the leading causes of AP, lead to dysregulation of levels of bile acids and the production of fatty-acid esters (1), which result in the overstimulation of calcium release-activated calcium (CRAC) channels that allow excess Ca^{2+} into cells (2), leading to cellular dysfunction, activation of digestive enzymes within the pancreas, and cell injury or death (3), resulting in the release of cellular debris and inflammatory mediators that activate immune cells (4), which can lead to more local inflammation within the pancreas and SIRS, potentially progressing to organ failure (5). Auxora has a two-hit mechanism-of-action, working to protect pancreatic cells and to downregulate the inflammatory response.

Auxora in COVID-19 pneumonia. Like SIRS, COVID-19 pneumonia is characterized by severe dysregulation of normal immune functioning that can affect the lungs. Although only a minority of COVID-19 patients develop pneumonia, they account for almost all COVID-19 morbidity and mortality. When the pandemic struck, CalciMedica immediately saw the potential for Auxora to help the most seriously ill patients with COVID-19 pneumonia. In an open-label phase 2 trial, patients receiving Auxora in addition to standard-of-care were less likely to need intubation or to die, and they recovered faster; the US Food and Drug Administration strongly recommended switching from an open-label trial to a blinded trial.

In September 2020, following this advice, CalciMedica initiated a randomized, blinded, placebo-controlled phase 2b trial of Auxora on top of standard-of-care, which included universal application of steroids and anticoagulation, specifically in patients requiring low-flow or high-flow supplemental oxygen therapy. This study enrolled 284 patients with COVID-19 pneumonia, and those receiving Auxora showed statistically significant improvement in mortality at 30 days post-treatment compared with placebo, with the effects on mortality continuing through 60 days (56% and 33% relative-risk reduction, respectively). Effects of Aurora on immune cells as well as protection of endothelial cells—the two-hit mechanism-of-action—are thought to be responsible for the clinical benefit.

CalciMedica is also currently running a phase 2 trial in COVID-19 pneumonia patients who require invasive mechanical ventilation. The data generated in this dose-escalation trial, being performed at Northwestern University and involving an array of pharmacodynamic and biomarker analyses, will also be used to guide the design of further trials of Auxora in COVID-19 pneumonia, acute hypoxemic respiratory failure (ARHF), and ARDS.

CalciMedica's Auxora programs also include an ongoing phase 1/2 trial in AP that can develop in pediatric patients as a result of asparaginase therapy for acute lymphoblastic leukemia. This study, which is being run by St Jude Children's Research Hospital, Memphis, Tennessee, and includes other sites, has primary endpoints of safety, tolerability, and the reduction of complications of AP including necrotizing pancreatitis.

Looking to the future, in the first half of 2022, CalciMedica expects to initiate another clinical trial on COVID-19, to file an investigational new drug (IND) application for CM6018 in chronic pancreatitis based on strong preclinical data, and to start phase 1/1b safety studies, as well as beginning a phase 2 trial of Auxora in AHRF/ARDS. Furthermore, CalciMedica expects to file an IND application for Aurora in AKI, and to begin designing phase 2 trials of CM6018 in chronic pancreatitis in the second half of 2022. Continuing research into other respiratory diseases, acute brain injury, and fibrosis is planned. CalciMedica welcomes discussions with potential partners interested in joining this exciting journey and bringing a new class of therapies to market, to address serious and unmet clinical needs.

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