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Induction of allograft tolerance while maintaining immunity against microbial pathogens: does coronin 1 hold a key?

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Abbreviations:

AC:	Adenylyl cyclase
ATP:	Adenosine triphosphate
cAMP:	Cyclic adenosine mono phosphate
CaMKK:	Calcium/calmodulin dependent kinase kinase
CaMKIV:	Calcium/calmodulin dependent kinase IV
CAR:	Chimeric antigen receptor
CD:	Cluster of differentiation
CSK:	C-terminal Src Kinase
ICER:	Inducible cAMP early repressor
CREM:	cAMP responsive element modulator
F-actin:	Filamentous actin
G protein:	Guanine nucleotide-binding
LCK:	Lymphocyte specific kinase

MHC:	Major histocompatibility complex molecules
PDE:	Phosphodiesterase
PI:	Phosphatidyl inositol
PKA:	Protein kinase A
Ras:	Rat sarcoma
Raf:	Rapidly accelerated fibrosarcoma
RNA:	Ribonucleic acid
Src kinase:	Sarcoma kinase
TCR:	T cell receptor

Abstract

Selective suppression of graft rejection while maintaining anti-pathogen responses has been elusive. Thus far, the most successful strategies to induce suppression of graft rejection relies on inhibition of T cell activation. However, the very same mechanisms that induce allograft-specific T cell suppression are also important for immunity against microbial pathogens as well as oncogenically transformed cells, resulting in significant immunosuppression-associated comorbidities. Therefore, defining the pathways that differentially regulate anti-graft versus anti-microbial T cell responses may allow the development of regimen to induce allograft-specific tolerance. Recent work has defined a molecular pathway driven by the immunoregulatory protein coronin 1 that regulates the phosphodiesterase/cAMP pathway and modulates T cell responses. Interestingly, disruption of coronin 1 promotes allograft tolerance while immunity towards a range of pathogenic microbes is maintained. Here, we briefly review the work leading up to these findings as well as their possible implications for transplantation medicine.

One of the major challenges in transplantation medicine is to overcome tissue incompatibility, mediated not only by HLA but also the minor histocompatibility antigens. Despite decades of research and establishment of state-of-the art screening procedures, it is exceedingly difficult to allow a graft from an unrelated individual to be accepted by a recipient without immunosuppression. The reason for the need of such extensive immunosuppression is that any graft, with the probable exception of that from an identical twin, will be recognized by the recipient's immune system as 'foreign', thereby activating a plethora of immune reactions to initiate graft rejection.

Given that immune system activation against foreign (allo) tissue, as occurs following allotransplantation, is based on the same mechanisms that alert the immune system against invading pathogens, such as viruses, bacteria, parasites, and fungi, immunosuppression is always associated with high risks of vulnerability towards pathogens as well as opportunistic infections. Furthermore, research over the past decades has taught us the importance of a proper functioning immune system for controlling oncogenically transformed cells, and indeed, immunosuppression following allotransplantation is frequently associated with the development of tumors.[1-4] A further complication is presented by the fact that many targets of currently used immunosuppressants are either expressed in many different cell types, and/or may have diverse physiological functions other than immune activation, resulting in nonselective immunosuppression and as well a plethora of unwanted side effects. Thus, while attempting to dampen immune activation to avoid graft rejection, such immunosuppressive treatments cause significant toxicity since they block important biochemical pathways not only in immune cells, but equally in liver, kidney, brain and heart, to name just a few.[5-7] In fact, a significant proportion of patients receiving immunosuppressive therapy succumb to the complications associated with immunosuppression rather than those due to loss of allograft function following transplant rejection.[1,2,8] For example, among organ transplant

recipients who have survived at least 3 years posttransplant, cancer has been shown to be a leading cause of death over the next 20 years.[9-11] There is thus a critical unmet need for therapies that allow graft acceptance while avoiding vulnerability towards infections and malignant transformations.[12,13]

A number of different approaches are currently being developed to selectively enhance the tolerance to allografts so as to achieve "operational tolerance", a state where immunologic tolerance to allografts is achieved in the absence of any immunosuppressive therapy.[14,15] The induction of such tolerance has been demonstrated following combined kidney and hematopoietic cell transplantation to induce chimerism and donor-specific tolerance[16,17] or by the use of chimeric antigen receptor (CAR)-expressing regulatory T (Treg) cells.[9,18] However, while the induction of mixed chimerism requires conditioning therapy that may result in severe complications, even after successful tolerance induction, the patients may not regain normal immunocompetence.[19] Moreover, given the short half-life of the transferred cells, CAR Treg-mediated tolerance induction may only work transient and may also pose a danger of generalized immunosuppression.[20]

Coronin 1: A Target for Alloselective Tolerance Induction: From Mycobacteria to T lymphocyte and Allograft Survival

Recent work has uncovered an alternative possibility to achieve allograft-selective immune tolerance, based on targeting a pathway that is modulated via the protein coronin 1 in T cells.[21,22] This insight came from quite an unexpected angle, and, in fact, started as a quest for a better understanding of the strategies that are being employed by the notorious pathogen *Mycobacterium tuberculosis*. These pathogens, upon inhalation into the airways, are being phagocytosed by alveolar macrophages, and in contrast to undergoing the fate of most ingested bacilli or particles, namely lysosomal delivery and destruction, pathogenic mycobacteria remodel the inner architecture of their host cells to block phagosome-lysosome

fusion, thereby allowing long term survival.[23,24] Such remodeling of the macrophage phagocytic pathway is one of the strategies that *M. tuberculosis* uses to avoid immune destruction, and that greatly contributes to its virulence.[24-26] A search for the molecular mechanism underlying this remarkable capacity to withstand macrophage-mediated lysosomal delivery and degradation uncovered coronin 1 (also known as Tryptophan Aspartate containing Coat protein (TACO), or P57[27,28]), as a host protein that is actively recruited by the mycobacteria to the phagosomal membrane, and functions to block phagosome-lysosome fusion.[27,29] Coronin 1, encoded by the *coro1a* gene, is a member of the evolutionary conserved protein family of coronins, of which 7 members are expressed in mammals, and that have been ascribed diverse functions ranging from cytoskeletal rearrangement, organelle function, modulation of gene expression, ubiquitylation and signal transduction.[29,30] Coronin 1 is abundantly expressed in all immune cells; however, other than preventing the destruction of pathogenic mycobacteria within phagosomes there does not appear to be any other cellular function for coronin 1 in resting, nonactivated macrophages.[31,32] Together this work suggested that a main function of coronin 1 in macrophages is to ensure a protective environment for *M. tuberculosis*. Given the exquisite ability of mycobacteria to provide adjuvants activity during an immune response[33] it has been speculated that the protection of mycobacteria from destruction could be one role for coronin 1 in macrophages to enable rapid immune responses.[29] But what does protection of *M. tuberculosis* inside macrophages haves to do with T cell-mediated allograft rejection?

Control of Naïve T cell Homeostasis by Coronin 1

A further understanding of the physiological function of coronin 1 came from the development of mouse models lacking coronin 1, and suggested an essential and specific role for coronin 1 in the survival of naïve T cells in peripheral lymphoid organs.[34-37] Similarly, human subjects lacking coronin 1 expression show a profound depletion of naïve CD4 and

CD8 positive T cells.[38,39] Interestingly, upon coronin 1 deletion, thymocyte numbers as well as T cell selection within the thymus are not affected, suggesting that coronin 1 is exclusively required once T cells have emigrated from the thymus into peripheral lymphoid organs.[40,41] The molecular mechanisms via which coronin 1 modulates peripheral naïve T cell survival remain largely unclear. Whereas initial work proposed that coronin 1 may sustain peripheral T cells through a pathway modulating filamentous (F)-actin levels,[35] subsequent work showed no role for coronin 1 in regulating F-actin levels in leukocytes nor a role for F-actin accumulation in T cell death.[31,32,42,43] The other mechanisms that have been reported to be important for peripheral naïve T cell survival are the interaction of the T cell receptor with Major Histocompatibility Complex Molecules (MHC) I and II, as well as interleukin (in particular interleukin 7) signaling.[44-46] However, given the importance of both MHC-TCR as well as interleukin-7 signaling in the thymus[47-49] and the absence of a thymic phenotype upon coronin 1 deletion,[40] any role for coronin 1 in these signaling processes must be specific for peripheral naïve T cells. Alternatively, coronin 1 may be important for the regulation of naïve T cell homeostasis via an as-yet-unknown pathway.

Coronin 1-induced Naïve T cell deficiency and immunity towards infections

One would assume that the paucity of T cells in the absence of coronin 1 would be a recipe for infectious disease disaster. Interestingly, it turns out that mice lacking coronin 1 withstand infections caused by a broad range of pathogens, from viruses to bacteria as well as fungi (see also Figure 1).[21,22] Moreover, vaccination protects coronin 1-deficient mice against a challenge with virulent bacteria, which is associated with the induction of an effector T cell response (Figure 1D and E).[21] Thus, although coronin 1-dependent T cell activation may be important in cases where the timing of the response may be important,[50] it appears that even in the absence of coronin 1 the remaining T cells are sufficiently capable to induce protective anti-pathogen immunity. Coronin 1-deficiency has also been reported to occur in humans,

and is in all cases associated with profound T cell depletion.[38,39] Also, while in many cases the persons harboring mutations in the *coro1a* gene suffer from recurrent infections, it remains unclear whether this is directly due to the coronin 1-induced T cell lymphopenia or confounding factors, given that all of the thus-far reported individuals carry additional genetic alterations, including in immunity-relevant genes such as the PI3 kinase adaptor protein 1 (*Pik3ap1*), also known as BICAP, Immunoglobulin genes (*Igsf9b),* integrins (*Itgal, Itgb6*)[51]; leukosialin (*SPN*), protein phosphatases regulating tumor necrosis factor (TNF)α and nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) signaling (*Ppp4c*), mitogen-activated protein (MAP) kinase pathway components (*Mapk3*),[52,53] signal transducers and activators of T cells (*Stat2, 5*) as well as inflammasome components (*Nlrp7*),[54] all of which are crucial mediators of anti-infectious immune responses.[55-58]

Induction of Tolerance upon Coronin 1 Deletion

Considering the near normal immune responses against microbial infections in mice lacking coronin 1, including induction of T cell-specific immunity, it was to be expected that T cell activation against allo-antigens would also not be compromised. However, the analysis of coronin 1-deficient mice that had received a major MHC-mismatched heterotopic cardiac transplant showed a striking ability to fully tolerate the graft, while, as expected, wild type recipients rejected the allograft within the first 10 days[21] (see Figure 1A). Cardiac allografts are relatively immune-protected,[59,60] and to analyze whether tolerance can also be achieved for more immunogenic grafts, tolerance of coronin 1-deficient mice towards skin grafts was analyzed, since skin is one of the most immunogenic tissues known, and therefore poses a challenge in terms of graft retention.[61] However, even for skin grafts, allo-tolerance is readily obtained in a coronin 1-deficient background (Figure 1B). For both major as well as minor mismatched antigens, graft retention was observed up to 300 days, which is the approximate life span of a mouse in the wild (ref. 21 and unpublished observations).

Importantly, the tolerance induced by coronin 1 deficiency was not due to the paucity of T cells in the coronin 1-deficient background, since restoration of normal T cell numbers by adoptive transfer still allowed graft retention. Moreover, the presence of coronin 1-deficient T cells prior to transplantation was able to suppress allograft rejection induced by wild type T cells.[21] This suggests an intrinsic ability of coronin 1-deficient T cells to create a tolerogenic environment to suppress alloresponses while leaving immunity against infectious microbes intact. It will be important to understand the precise mechanism via which coronin 1-deficient T cells can suppress wild type T cells in trans, as well as to have a thorough understanding of the stoichiometry required for effective suppression, which may also depend on the nature of the graft being transplanted (liver, heart, kidneys, skin) and/or the level of MHC mismatch.

An Immunosuppressive cAMP-PDE Axis Regulated by Coronin 1

The ability of mice lacking coronin 1 to fight a wide range of infectious microbes while tolerating cardiac and skin grafts suggests the existence of different pathways governing anti-pathogen immunity and the activation of alloimmunity, that may be regulated by coronin 1. A further understanding of the molecular basis of such pathway(s) came from carrying out an unbiased approach through total transcriptome analysis (RNAseq) of wild type versus coronin 1-deficient T cells, showing the differential expression of a number of genes involved in the cyclic adenosine mono phosphate (cAMP) pathway resulting in drastically enhanced cAMP levels upon coronin 1 deletion. This is interesting because of 2 reasons: First, coronin 1, as well as coronin A, the coronin 1 homologue expressed in the slime mold *Dictyostelium discoideum*, was recently reported to play important roles in the modulation of cAMP signaling.[62-64] Second, modulation of the cAMP pathway has been known since a long time to modulate immune responses[65,66] (see also below).

cAMP is an important second messenger molecule in virtually all cell types, linking extracellular stimuli with intracellular responses. cAMP is synthesized from adenosine triphosphate (ATP) by adenylate cyclases, that in turn can be activated by different stimuli including Ca^{2+}/calmodulin and trimeric G protein activation following the triggering of G protein-coupled receptors.[67,68] The production of cAMP can have a number of downstream effects, including the activation of the cAMP-dependent protein kinase A, the Exchange proteins activated by cAMP (Epacs) as well as modulation of a number of cyclic nucleotide-gated channels.[69-71] Importantly, the cAMP/PKA pathway is subject to a range of regulatory mechanisms, including subunit assembly, subcellular localization through interaction with A-kinase anchoring proteins, and the presence of cAMP-degrading phosphodiesterases.[72-76]

As mentioned, the potential for sustained elevated levels of cAMP to create an immunosuppressive environment has been well documented.[65,66] For example, cAMP is a potent negative regulator of T cell receptor-mediated T cell activation, through protein kinase A-mediated activation of the inhibitory C-terminal Sarcoma (Srk) kinase (Csk), thereby dampening activity of the lymphocyte-specific protein tyrosine kinase (Lck).[66] Also, cAMP-dependent protein kinases can activate a number of transcriptional regulators such as the cAMP responsive element binding proteins (CREB)-1 and -2, as well as the cAMP responsive element modulator (CREM) and the inducible cAMP early repressor (ICER), the latter 2 being involved in the transcriptional repression of a number of genes important for T cell activation.[77] Besides these, cAMP has also been shown to modulate the activity of a plethora of other signaling molecules, including NF-kB, Ras, Raf and mitogen activated kinases.[69,78] Furthermore, cAMP may act to dampen T cell responses through the activation of Epac.[79] Finally, it has also been shown that cAMP can work in trans, via a direct cell-to-cell contact using a gap-junction-mediated pathway through which cAMP is transferred to neighboring cells.[80] While the ability of cAMP to confer immunosuppression is widely

documented, the exact upstream triggers activating cAMP-dependent suppression is less clear. One pathway implicated in the activation of cAMP production in T cells is the prostaglandin (PG) E2-mediated activation of the E-prostanoid (EP) family of G protein-coupled receptors, of which EP2 and EP4 activate adenylate cyclase activity to induce cAMP, but also other stimuli are known to elevate cAMP in T cells.[81]

One crucial cAMP regulatory mechanism, especially in T cells, relies on the activity of the cAMP degrading enzymes, the phosphodiesterases (PDEs). The PDEs comprise more than 100 enzyme variants divided into 11 families based on their structure and mechanism of regulation.[76,82] One of the most abundantly expressed PDEs in T cells is PDE4, that plays an important role in the regulation of cAMP levels as well as dampening immune responses through elevation of cAMP levels.[76] In fact, several PDE4 inhibitors are being used in clinics for the attenuation of inflammatory responses.[83,84]

It turns out that in T cells, as in other cell types such as neurons, coronin 1 is required for stimulation-induced activation of the cAMP pathway[21,62,64]: while cAMP production following stimulation of the adenylate cyclase pathway requires coronin 1, upon coronin 1 deletion, T cells accumulate large amounts of cAMP, most probably as a result of the downregulation of PDE4.[21] Whether or not coronin 1 is required for stabilization of PDE4, or whether the destabilization of PDE4 is a compensation for the long-term lack of coronin 1 thereby inducing T cells to maintain appropriate cAMP levels even in the absence of coronin 1 is presently unclear.[85,86] How, exactly, coronin 1 modulates cAMP levels is not known, but may be related to the structural homology of coronin 1 with the beta subunit of trimeric G-proteins possibly involving a mechanism wherein coronin 1 interacts with Gαs subunits to modulate the GPCR pathway.[62,63,87-90]

Although the exact mechanism involved in immunosuppression following coronin 1 deletion remains unclear, it involves modulation of the CalModulin Kinase IV (CaMKIV)- cAMP Response Element Binding (pCREB) pathway; in T cells, an increase in cAMP levels are known to activate Protein Kinase A (PKA) which inhibits Ca^{2+}-dependent activation of CaMKIV by CaMKK.[91,92] As a result, phosphorylation of Thr196 in CaMKIV by CaMKK is significantly reduced leading to attenuation of the CAMKIV/pCREB pathway (Figure 2) and consequently a defective T cell functioning.[93] It remains to be determined whether the altered CAMKIV/pCREB pathway is also involved in the observed increase in surface expression of various immunosuppressive receptors (ICOS, LAG3, 2B4, LAP1) in coronin 1-deficient conventional T cells as compared to wild type T cells, and whether these elevated levels of these receptors are responsible for the observed allograft tolerance.[21] A number of cAMP immunoregulatory pathways, in particular those that directly inhibit T cell receptor signaling and T cell activation, have been reported.[66] Given the fact that coronin 1 deletion does not affect thymic development or selection as well as the above-mentioned capacity of coronin 1-deficient T cells to respond towards a range of T cell receptor triggers, it seems unlikely that the elevated cAMP in coronin 1-deficient T cells is involved in a direct inhibition of T cell receptor signaling.[34-37] However, T cell receptor ligation is under the control of a myriad of regulatory mechanisms, and differences in local environment as well as the expression of differentially regulated costimulatory molecules, perhaps also in an organ-specific manner, may explain the observed differential requirement for coronin 1 in T cell functionality against allografts versus infections. Future work, possibly involving 'omics' approaches including transcriptomics and (phospho)proteomics may allow the definition of the molecular mechanisms involved in allograft-selective immunosuppression induced through deletion of coronin 1.

Overcoming cAMP-mediated Immunosuppression through Costimulation

One of the surprising observations in coronin 1-deficient mice was the fact that cAMP-mediated immune suppression allows graft tolerance while maintaining T cell responses against microbial pathogens. Interestingly, it turns out that cAMP-mediated suppression by T cells is neutralized by costimulatory signals delivered by microbe-infected antigen processing and presenting cells (APC's).[21] In particular, cAMP-dependent suppression is overcome through the activation of CD28 signals on T cells induced by CD80 on APC's (Figure 3). These data also raise the interesting possibility to promote allotolerance through cAMP-mediated suppression in the presence of reagents that block CD28 costimulation, a number of which are currently being tested in clinical trials.[22,94]

While inhibitors of phosphodiesterase-4 activity are currently being used to treat inflammatory disorders, they have not yet been applied for tolerance induction towards allografts; however, because cAMP is an important and ubiquitous second messenger, the overall modulation of cAMP may cause significant side effects.[83,95] In that light, the induction of cAMP-based graft-selective immunosuppression upon coronin 1 deletion together with the finding that coronin 1 is dispensable for immunity against microbial pathogens may allow a more targeted approach, possibly avoiding side effects such as vulnerability towards infections and the occurrence of tumors. Also, further delineation of the molecular mechanism underlying the coronin 1-PDE4-cAMP axis will be important for a thorough understanding of this tolerance pathway.

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Figure Legends

Figure 1: Tolerance toward cardiac and skin Allografts while maintaining anti-pathogen immunity in the absence of coronin 1

A: Survival of heterotopic cardiac transplants of BALB/c donor hearts onto C57BL/6 wild type (blue) or coronin 1-deficient (red) recipient mice. Inset: hematoxylin-eosin (H/E) staining at the time of rejection (in WT recipients. B: Survival of major mismatched skin graft (BM12, I-A^{bm12}) transplanted onto C57BL/6 wild type (blue) or coronin 1-deficient (red) mice. *Inset*: Representative image of a skin graft onto either a wild type (day 10) or coronin 1-deficient recipient (day 14). C: Kinetics of MCMV clearance in wild type or coronin 1-deficient mice. D: T cell responses in wild type or coronin 1-deficient mice upon adoptive transfer of Cell Trace Violet-labeled OTII $CD4^+$ T cells and infection with normal *Salmonella* or OVA-expressing *Salmonella*. E: Consequences of vaccination with avirulent Salmonella on a challenge (6 weeks later) with virulent *Salmonella.* Shown are CFU enumeration from the liver on D5 (taken from ref. 21). Reprinted from Immunity (2019), Disruption of Coronin 1 Signaling in T Cells Promotes Allograft Tolerance while Maintaining Anti-Pathogen Immunity, Jayachandran et al., Vol. 50, pp 152-156 Copyright (2019), with permission from Elsevier.

Figure 2: Model depicting the role of coronin 1 in production of cAMP in T cells. In T cells, as in neurons, coronin 1 modulates cAMP levels, and the absence of coronin 1 results in a reduced cAMP production. However, upon coronin 1 deletion, a compensatory reduction in PDE4-mediated cAMP degradation causes an accumulation of cAMP T cells. This in turns hyperactivates PKA which inhibits Ca^{2+}-dependent activation of CaMKIV by inhibiting CaMKK, thereby resulting in defective CREB phosphorylation and suppression of T cell mediated allograft responses. See text for further details.

Figure 3: Cartoon depicting the allograft-specific tolerance induced by coronin 1 deletion.

Upper panels: following allograft transplantation T cells, will strongly react against either mismatched MHC molecules or allopeptides presented by self-MHC foreign antigens (left side), as well as against infectious microbes whose peptides are presented by self-MHC (right side).

Lower panels: Upon coronin 1 deletion, the increase in cAMP levels renders the T cells suppressive through as-yet-unknown mechanisms. However, following a microbial infection, the costimulatory molecules CD80/86 can induce a strong costimulus through ligation of the T cell coreceptor CD28, thereby overcoming the cAMP-mediated immunosuppression.

Figure 1

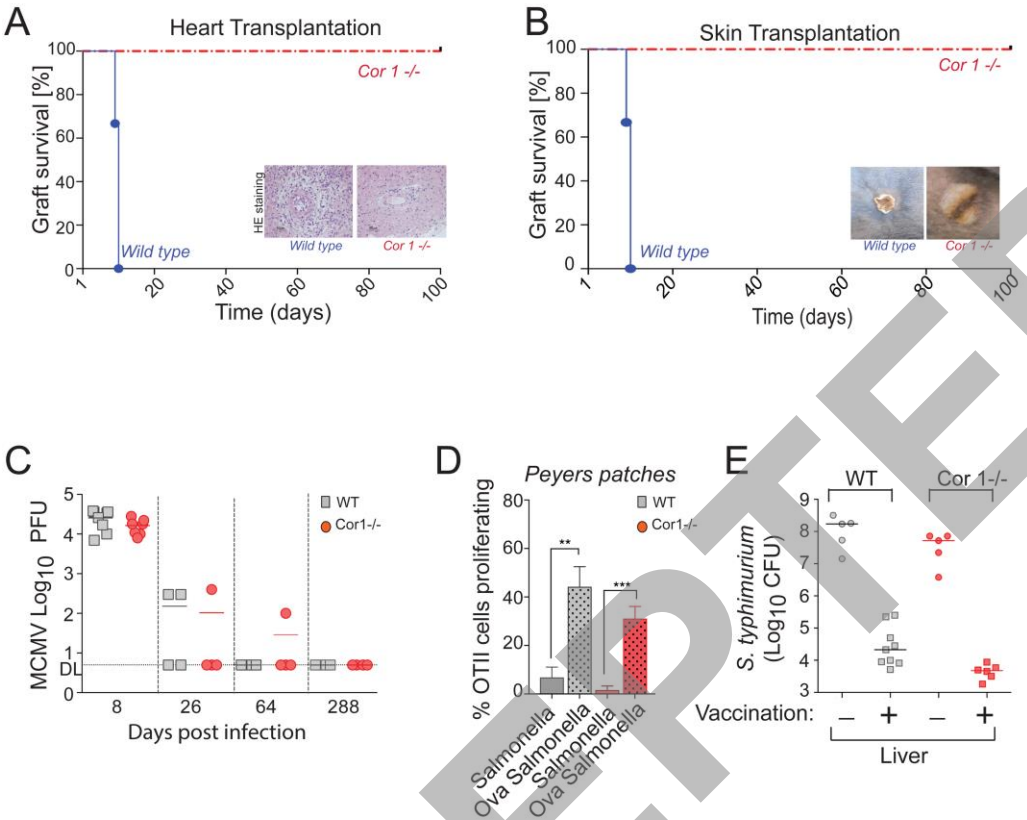

Figure 2

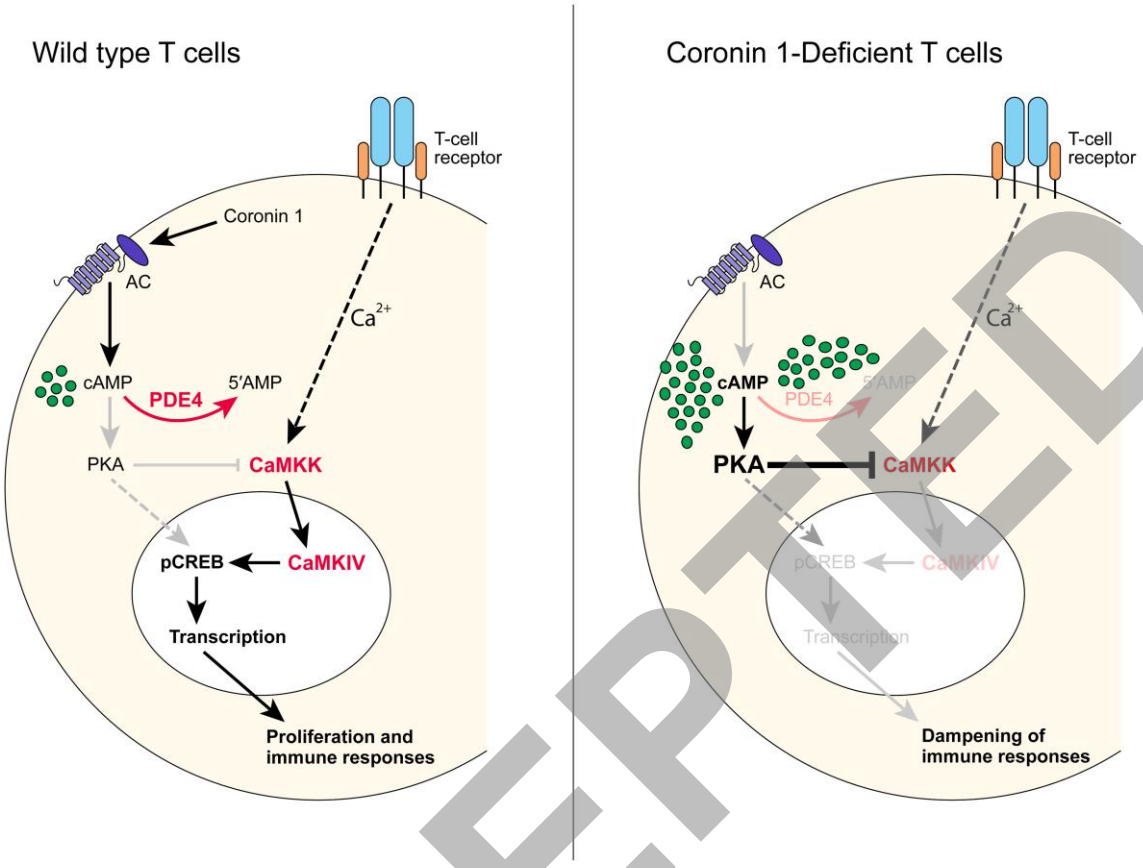

Figure 3