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## C-C Chemokine Receptor Seven (CCR7): Coming of Age In Vaccines

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In casual conversation with non-medical individuals, it is common for them to ask: why do we not have a cure for cancer or vaccinations for all diseases? It seems somewhat logical to assume that after so many years of research that cures should be readily available, diseases in general should simply require a pill or jab and that somehow, if scientists are not deliberately hiding these cures, then they must be asleep at the wheel. A typical response to such questions focuses on the complexity of the different cancers/diseases and that there will be no “one cure fits all”. When it comes to vaccinations, there is absolutely no doubt that many vaccines are extremely effective and a multitude of publications can attest to this and cite how many lives have been saved because of our vaccination programs; indeed, vaccinations typically pop up on a list of reasons why humans today are living substantially longer than at any previous time in history.<sup>1–3</sup> Nevertheless, there is always an overriding and to some extent embarrassing realization that despite the relative success of vaccines we still do not, for the most part, know how to make consistently effective vaccines and that often it boils down to a trial and error procedure to establish the best vaccine for a given target.

While vaccine design incorporates a multitude of factors, one way to boost the effectiveness of a given vaccine is to enhance the secondary immune response to provide a more robust production of long-lasting antibodies, primarily IgG’s. Although a discussion of the secondary immune response could take up a substantial review, in this short commentary as an example of one way to potentially boost antibody production, we will focus on a single chemokine receptor, C-C Chemokine Receptor Seven (CCR7). CCR7 is expressed on a number of cells, in particular cells of the immune system including naïve and central memory T-cells, activated B-cells, monocytes, neutrophils and mature dendritic cells.<sup>4–6</sup> CCR7 has two chemokine ligands, CCL19 and CCL21 that are primarily expressed in secondary lymphoid organs and plays a vital role in the chemotactic migration of CCR7 expressing immune cells to the secondary lymphoid tissues.<sup>7</sup> It was reported in CCR7<sup>-/-</sup>

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**CONFLICTS OF INTEREST:** None.

BALB/c mice that the migration of B-cells, T-cells and mature dendritic cells was severely compromised and that the architecture of the secondary lymphoid organs was significantly altered when compared to the wild-type strain.<sup>5</sup> Furthermore, 10 days after exposure to the T-dependent antigen, DNP-KLH, wild-type mice produced a robust primary immune response, in contrast CCR7<sup>-/-</sup> mice had a significantly compromised humoral response; however, after a further 10 days production of IgG1, IgG2a, IgG2b and IgG3 was similar for both the wild-type and CCR7<sup>-/-</sup> mice.<sup>5</sup> Fourteen days after a booster immunization the CCR7<sup>-/-</sup> mice showed an elevated IgG2a and IgG2b titer compared to wild-type mice,<sup>5</sup> (our own unpublished studies using CCR7<sup>-/-</sup> C57BL/6 mice). These studies demonstrated that CCR7 deficient mice have a pronounced delay, but eventual enhancement in IgG isotype switching.

A subsequent study used the paucity of lymph node T-cells (plt) mice, in which a spontaneous mutation resulted in a loss of expression of CCL19 and CCL21 in secondary lymphoid organs and a defect in homing of naive T-cells to these tissues.<sup>8</sup> The plt mice also demonstrated a striking attenuation in the migration of activated dendritic cells to the T-cell zones of spleen and lymph nodes.<sup>7,8</sup> In general abnormalities in leukocyte migration were more severe in CCR7<sup>-/-</sup> mice compared to the plt mice suggesting that there are functional immune differences between the plt and CCR7<sup>-/-</sup> mice. After immunization of plt mice, T-cells and dendritic cells mislocalized in the lymph nodes and spleen compared to wild-type mice; however, similar to the results for the CCR7<sup>-/-</sup> mice plt mice mounted an enhanced, but delayed T-cell related humoral response.<sup>8</sup> Interestingly, CCR7<sup>-/-</sup> mice have an increased polarization of CD4<sup>+</sup> T-cells towards a TH2 phenotype and B-cell activation exemplified by an upregulation of MHC class II surface molecules, which points at a potential humoral response target.<sup>9</sup>

A primary question is whether T-cell dependent activation is required to elicit a delayed and enhanced antibody production in mice with a compromised CCR7 pathway and evidence suggests that this is the case. Thymus-independent type 2 (TI-2), are repetitive antigens, which elicit antibody production by B-cells without T-cell involvement.<sup>10,11</sup> Immunization of CCR7<sup>-/-</sup> mice with TI-2 antigens resulted in an increased number of germinal centers in the spleen that persisted for longer periods when compared to wild-type mice, although there was no increase in germinal centers of the lymph nodes in TI-2 treated CCR7<sup>-/-</sup> mice.<sup>12</sup> The persistence of germinal centers in the spleens of CCR7<sup>-/-</sup> mice was not associated with elevated secondary antibody responses, isotype switching, affinity maturation or memory B-cell generation.<sup>12</sup>

Considering that CCR7 is often discussed in the context of homing T-cells, B-cells and mature dendritic cells to the secondary lymphoid organs, it is empirically surprising that a robust T-cell response has been observed upon loss of the functional chemokine receptor or loss of both activating ligands, albeit that there are not completely overlapping immune manifestations. These responses occur in the absence of normal T-cell distributions and normal secondary lymphoid organ structures.<sup>5,6,8</sup> Along with other laboratories, we have demonstrated both shared and distinct biased signaling pathways in immune cells upon binding of either CCL19 or CCL21 to CCR7<sup>13-15</sup> recent review by Hauser and Legler.<sup>16</sup> It is unclear what individual effects CCL19 or CCL21 plays in modulating

the secondary immune response and it will be interesting to determine what overlaying and distinct responses each chemokine contributes. Enhancing the secondary immune response in a typical boost schedule of vaccinations is an attractive target for research and this commentary touches on one chemokine in a complex wheel of factors involved in controlling the level and longevity of actions of specific antibodies. We still have a lot to learn, but the future is bright and we anticipate that this new journal will provide an avenue for novel and exciting work in the field.

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