



Protocol

Vaccine Adjuvants

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Syntheses of Human TLR8-Specific Small-Molecule Agonists

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Abstract

Human toll-like receptor (hTLR)-8 is expressed in myeloid dendritic cells, monocytes, and monocyte-derived dendritic cells. Engagement by TLR8 agonists evokes a distinct cytokine profile which favors the development of type 1 helper T cells. Focused exploration of structure-activity relationships in the imidazoquinolines has led to the identification of several novel human TLR8-specific agonists. The synthetic procedures for best-in-class analogues encompassing four chemotypes are described.

Key words

TLR8 TLR8 agonists Vaccine adjuvants Innate immunity

References

1. Glenny AT, Pope CG, Waddington H, Wallace V (1926) The antigenic value of toxoid precipitated by potassium-alum. *J Pathol Bacteriol* 29:38–45
2. Gupta RK, Siber GR (1995) Adjuvants for human vaccines—current status, problems and future prospects. *Vaccine* 13:1263–1276
CrossRef ([http://dx.doi.org/10.1016/0264-410X\(95\)00011-O](http://dx.doi.org/10.1016/0264-410X(95)00011-O)) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=8585280)
3. Gupta RK (1998) Aluminum compounds as vaccine adjuvants. *Adv Drug Deliv Rev* 32:155–172
CrossRef ([http://dx.doi.org/10.1016/S0169-409X\(98\)00008-8](http://dx.doi.org/10.1016/S0169-409X(98)00008-8)) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=10837642)
4. Sheridan SL, Frith K, Snelling TL, Grimwood K, McIntyre PB, Lambert SB (2014) Waning vaccine immunity in teenagers primed with whole cell and acellular pertussis vaccine: recent epidemiology. *Expert Rev Vaccines* 13:1081–1106
CrossRef (<http://dx.doi.org/10.1586/14760584.2014.944167>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=25093268)
5. Lavine JS, Bjornstad ON, de Blasio BF, Storsaeter J (2012) Short-lived immunity against pertussis, age-specific routes of transmission, and the utility of a teenage booster vaccine. *Vaccine* 30:544–551
CrossRef (<http://dx.doi.org/10.1016/j.vaccine.2011.11.065>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22119924)
6. Suryadevara M, Domachowske JB (2015) Prevention of pertussis through adult vaccination. *Hum Vaccin Immunother* 11:1744–1747
CrossRef (<http://dx.doi.org/10.1080/21645515.2015.1038442>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=25912733) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4517454>)
7. Clark TA (2014) Changing pertussis epidemiology: everything old is new again. *J Infect Dis* 209:978–981
CrossRef (<http://dx.doi.org/10.1093/infdis/jiu001>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=24626532)
8. Cherry JD (2012) Epidemic pertussis in 2012—the resurgence of a vaccine-preventable disease. *New Engl J Med* 367:785–787
CrossRef (<http://dx.doi.org/10.1056/NEJMp1209051>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22894554)
9. Zepp F, Heininger U, Mertsola J, Bernatowska E, Guiso N, Roord J, Tozzi AE, Van Damme P (2011) Rationale for pertussis booster vaccination throughout life in Europe. *Lancet Infect Dis* 11:557–570

CrossRef ([http://dx.doi.org/10.1016/S1473-3099\(11\)70007-X](http://dx.doi.org/10.1016/S1473-3099(11)70007-X)) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21600850)

10. Hara M, Fukuoka M, Tashiro K, Ozaki I, Ohfuji S, Okada K, Nakano T, Fukushima W, Hirota Y (2015) Pertussis outbreak in university students and evaluation of acellular pertussis vaccine effectiveness in Japan. *BMC Infect Dis* 15:45

CrossRef (<http://dx.doi.org/10.1186/s12879-015-0777-3>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=25656486) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4323135>)

11. Dresser DW (1962) Specific inhibition of antibody production. II. Paralysis induced in adult mice by small quantities of protein antigen. *Immunology* 5:378–388

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=13887798) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1424098>)

12. Dresser DW (1968) An assay for adjuvanticity. *Clin Exp Immunol* 3:877–888

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=4179956) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1579011>)

13. Johnson AJ, Gaines S, Landy M (1956) Studies on the O antigen of *Salmonella typhosa*. V. Enhancement of the antibody response to protein antigens by the purified lipopolysaccharide. *J Exp Med* 103:225–233

CrossRef (<http://dx.doi.org/10.1084/jem.103.2.225>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=13286429) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2136584>)

14. Beutler B (2000) Tlr4: central component of the sole mammalian LPS sensor. *Curr Opin Immunol* 12:20–26

CrossRef ([http://dx.doi.org/10.1016/S0952-7915\(99\)00046-1](http://dx.doi.org/10.1016/S0952-7915(99)00046-1)) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=10679411)

15. Beutler B, Poltorak A (2001) The sole gateway to endotoxin response: how *LPS* was identified as *TLR4*, and its role in innate immunity. *Drug Metab Dispos* 29:474–478

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=11259335)

16. Hoffmann J, Akira S (2013) Innate immunity. *Curr Opin Immunol* 25:1–3

CrossRef (<http://dx.doi.org/10.1016/j.coi.2013.01.008>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23452839)

17. Kumagai Y, Akira S (2010) Identification and functions of pattern-recognition receptors. *J Allergy Clin Immunol* 125:985–992

CrossRef (<http://dx.doi.org/10.1016/j.jaci.2010.01.058>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20392481)

18. Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol* 11:373–384

CrossRef (<http://dx.doi.org/10.1038/ni.1863>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20404851)

19. Loo YM, Gale M Jr (2011) Immune signaling by RIG-I-like receptors. *Immunity* 34:680–692
[CrossRef](http://dx.doi.org/10.1016/j.immuni.2011.05.003) (<http://dx.doi.org/10.1016/j.immuni.2011.05.003>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21616437) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21616437) [PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3177755) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3177755>)
20. Kersse K, Bertrand MJ, Lamkanfi M, Vandenabeele P (2011) NOD-like receptors and the innate immune system: coping with danger, damage and death. *Cytokine Growth Factor Rev* 22:257–276
[CrossRef](http://dx.doi.org/10.1016/j.cytogfr.2011.09.003) (<http://dx.doi.org/10.1016/j.cytogfr.2011.09.003>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21996492) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21996492)
21. Clarke TB, Weiser JN (2011) Intracellular sensors of extracellular bacteria. *Immunol Rev* 243:9–25
[CrossRef](http://dx.doi.org/10.1111/j.1600-065X.2011.01039.x) (<http://dx.doi.org/10.1111/j.1600-065X.2011.01039.x>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21884164) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21884164)
22. Salunke DB, Shukla NM, Yoo E, Crall BM, Balakrishna R, Malladi SS, David SA (2012) Structure-activity relationships in human Toll-like receptor 2-specific monoacyl lipopeptides. *J Med Chem* 55:3353–3363
[CrossRef](http://dx.doi.org/10.1021/jm3000533) (<http://dx.doi.org/10.1021/jm3000533>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22385476) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22385476) [PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325328) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325328>)
23. Salunke DB, Connelly SW, Shukla NM, Hermanson AR, Fox LM, David SA (2013) Design and development of stable, water-soluble, human Toll-like receptor 2 specific monoacyl lipopeptides as candidate vaccine adjuvants. *J Med Chem* 56:5885–5900
[CrossRef](http://dx.doi.org/10.1021/jm400620g) (<http://dx.doi.org/10.1021/jm400620g>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23795818) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23795818)
24. Wu W, Li R, Malladi SS, Warshakoon HJ, Kimbrell MR, Amolins MW, Ukani R, Datta A, David SA (2010) Structure-activity relationships in toll-like receptor-2 agonistic diacylthioglycerol lipopeptides. *J Med Chem* 53:3198–3213
[CrossRef](http://dx.doi.org/10.1021/jm901839g) (<http://dx.doi.org/10.1021/jm901839g>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20302301) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20302301) [PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859677) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859677>)
25. Shukla NM, Kimbrell MR, Malladi SS, David SA (2009) Regioisomerism-dependent TLR7 agonism and antagonism in an imidazoquinoline. *Bioorg Med Chem Lett* 19:2211–2214
[CrossRef](http://dx.doi.org/10.1016/j.bmcl.2009.02.100) (<http://dx.doi.org/10.1016/j.bmcl.2009.02.100>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=19285861) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=19285861)
26. Shukla NM, Malladi SS, Mutz CA, Balakrishna R, David SA (2010) Structure-activity relationships in human toll-like receptor 7-active imidazoquinoline analogues. *J Med Chem* 53:4450–4465
[CrossRef](http://dx.doi.org/10.1021/jm100358c) (<http://dx.doi.org/10.1021/jm100358c>) [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20481492) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20481492) [PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2895411) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2895411>)
27. Shukla NM, Mutz CA, Ukani R, Warshakoon HJ, Moore DS, David SA (2010) Syntheses of fluorescent imidazoquinoline conjugates as probes of Toll-like receptor 7. *Bioorg Med Chem Lett* 20:6384–6386

CrossRef (<http://dx.doi.org/10.1016/j.bmcl.2010.09.093>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20933417) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2957514>).

28. Shukla NM, Lewis TC, Day TP, Mutz CA, Ukani R, Hamilton CD, Balakrishna R, David SA (2011) Toward self-adjuvanting subunit vaccines: model peptide and protein antigens incorporating covalently bound toll-like receptor-7 agonistic imidazoquinolines. *Bioorg Med Chem Lett* 21:3232–3236

CrossRef (<http://dx.doi.org/10.1016/j.bmcl.2011.04.050>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21549593) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3098923>).

29. Shukla NM, Malladi SS, Day V, David SA (2011) Preliminary evaluation of a 3H imidazoquinoline library as dual TLR7/TLR8 antagonists. *Bioorg Med Chem* 19:3801–3811

CrossRef (<http://dx.doi.org/10.1016/j.bmc.2011.04.052>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21620714) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3114175>).

30. Shukla NM, Mutz CA, Malladi SS, Warshakoon HJ, Balakrishna R, David SA (2012) Toll-like receptor (TLR)-7 and -8 modulatory activities of dimeric imidazoquinolines. *J Med Chem* 55:1106–1116

CrossRef (<http://dx.doi.org/10.1021/jm2010207>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22239408) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3276691>).

31. Shukla NM, Salunke DB, Balakrishna R, Mutz CA, Malladi SS, David SA (2012) Potent adjuvant activity of a pure TLR7-agonistic imidazoquinoline dendrimer. *PLoS One* 7, e43612

CrossRef (<http://dx.doi.org/10.1371/journal.pone.0043612>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22952720) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3429503>).

32. Yoo E, Crall BM, Balakrishna R, Malladi SS, Fox LM, Hermanson AR, David SA (2013) Structure-activity relationships in Toll-like receptor 7 agonistic 1*H*-imidazo[4,5-*c*]pyridines. *Org Biomol Chem* 11:6526–6545

CrossRef (<http://dx.doi.org/10.1039/c3ob40816g>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23974333)

33. Yoo E, Salunke DB, Sil D, Guo X, Salyer AC, Hermanson AR, Kumar M, Malladi SS, Balakrishna R, Thompson WH, Tanji H, Ohto U, Shimizu T, David SA (2014) Determinants of activity at human Toll-like receptors 7 and 8: quantitative structure-activity relationship (QSAR) of diverse heterocyclic scaffolds. *J Med Chem* 57:7955–7970

CrossRef (<http://dx.doi.org/10.1021/jm500744f>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=25192394) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4191598>).

34. Salunke DB, Yoo E, Shukla NM, Balakrishna R, Malladi SS, Serafin KJ, Day VW, Wang X, David SA (2012) Structure-activity relationships in human Toll-like receptor 8-active 2,3-diamino-furo[2,3-*c*]pyridines. *J Med Chem* 55:8137–8151

CrossRef (<http://dx.doi.org/10.1021/jm301066h>) PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?>

[cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22924757](#)) [PubMedCentral](#)
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3461104>)

35. Kokatla HP, Yoo E, Salunke DB, Sil D, Ng CF, Balakrishna R, Malladi SS, Fox LM, David SA (2013) Toll-like receptor-8 agonistic activities in C2, C4, and C8 modified thiazolo[4,5-c]quinolines. *Org Biomol Chem* 11:1179–1198

[CrossRef](#) (<http://dx.doi.org/10.1039/c2ob26705e>) [PubMed](#) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23314908) [PubMedCentral](#)
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3577938>)

36. Kokatla HP, Sil D, Malladi SS, Balakrishna R, Hermanson AR, Fox LM, Wang X, Dixit A, David SA (2013) Exquisite selectivity for human toll-like receptor 8 in substituted furo[2,3-c]quinolines. *J Med Chem* 56:6871–6885

[CrossRef](#) (<http://dx.doi.org/10.1021/jm400694d>) [PubMed](#) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23899291) [PubMedCentral](#)
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3790333>)

37. Kokatla HP, Sil D, Tanji H, Ohto U, Malladi SS, Fox LM, Shimizu T, David SA (2014) Structure-based design of novel human Toll-like receptor 8 agonists. *ChemMedChem* 9:719–723

[CrossRef](#) (<http://dx.doi.org/10.1002/cmdc.201300573>) [PubMed](#) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=24474703) [PubMedCentral](#)
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105021>)

38. Beesu M, Malladi SS, Fox LM, Jones CD, Dixit A, David SA (2014) Human Toll-like receptor 8-selective agonistic activities in 1-alkyl-1*H*-benzimidazol-2-amines. *J Med Chem* 57:7325–7341

[CrossRef](#) (<http://dx.doi.org/10.1021/jm500701q>) [PubMed](#) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=25102141) [PubMedCentral](#)
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161153>)

39. Agnihotri G, Ukani R, Malladi SS, Warshakoon HJ, Balakrishna R, Wang X, David SA (2011) Structure-activity relationships in nucleotide oligomerization domain 1 (Nod1) agonistic gamma-glutamyl diaminopimelic acid derivatives. *J Med Chem* 54:1490–1510

[CrossRef](#) (<http://dx.doi.org/10.1021/jm101535e>) [PubMed](#) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21299227) [PubMedCentral](#)
(<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3076632>)

40. Ukani R, Lewis TC, Day TP, Wu W, Malladi SS, Warshakoon HJ, David SA (2012) Potent adjuvant activity of a CCR1-agonistic bis-quinoline. *Bioorg Med Chem Lett* 22:293–295

[CrossRef](#) (<http://dx.doi.org/10.1016/j.bmcl.2011.11.014>) [PubMed](#) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22104149)

41. Bekeredjian-Ding I, Roth SI, Gilles S, Giese T, Ablasser A, Hornung V, Endres S, Hartmann G (2006) T cell-independent, TLR-induced IL-12p70 production in primary human monocytes. *J Immunol* 176:7438–7446

[CrossRef](#) (<http://dx.doi.org/10.4049/jimmunol.176.12.7438>) [PubMed](#) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=16751389)

42. Warshakoon HJ, Hood JD, Kimbrell MR, Malladi S, Wu WY, Shukla NM, Agnihotri G, Sil D, David SA (2009) Potential

adjuvant properties of innate immune stimuli. *Hum Vaccin* 5:381–394

CrossRef (<http://dx.doi.org/10.4161/hv.5.6.8175>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=19270494)

43. Bohnenkamp HR, Papazisis KT, Burchell JM, Taylor-Papadimitriou J (2007) Synergism of Toll-like receptor-induced interleukin-12p70 secretion by monocyte-derived dendritic cells is mediated through p38 MAPK and lowers the threshold of T-helper cell type 1 responses. *Cell Immunol* 247:72–84

CrossRef (<http://dx.doi.org/10.1016/j.cellimm.2007.07.008>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=17927969)

44. Philbin VJ, Levy O (2007) Immunostimulatory activity of Toll-like receptor 8 agonists towards human leucocytes: basic mechanisms and translational opportunities. *Biochem Soc Trans* 35:1485–1491

CrossRef (<http://dx.doi.org/10.1042/BSTO351485>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=18031250)

45. Saruta M, Michelsen KS, Thomas LS, Yu QT, Landers CJ, Targan SR (2009) TLR8-mediated activation of human monocytes inhibits TL1A expression. *Eur J Immunol* 39:2195–2202

CrossRef (<http://dx.doi.org/10.1002/eji.200939216>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=19637197) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2839407>)

46. Beesu M, Caruso G, Salyer AC, Khetani KK, Sil D, Weerasinghe M, Tanji H, Ohto U, Shimizu T, David SA (2015) Structure-based design of human TLR8-specific agonists with augmented potency and adjuvant activity. *J Med Chem* 58:7833–7849

CrossRef (<http://dx.doi.org/10.1021/acs.jmedchem.5b01087>) PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=26351878) PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4601487>)

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