Technology bulletin

CSIR-Indian Institute of Chemical Biology, India

Potent TLR9-selective and TLR9/7 dual antagonists

A series of novel and potent inhibitors of toll-like receptor (TLR) 9 as well as dual antagonists of TLR9 and TLR7, with potential application in autoimmune disease and metabolic syndrome.

- ❑ **Potent (nano to low micromolar IC_{50}) inhibitors of TLR9 and TLR7: 'ABODINIBS' and 'ADADINIBS'**
- ❑ **Demonstrated efficacy in human immune cells and pharmacokinetics in preclinical rodent model**
- ❑ **Demonstrated efficacy in a preclinical model of psoriasis**

Challenge/Application domain

Activation of toll-like receptors (TLRs) on immune cells is one of the critical mechanisms for self-nonself discrimination by the host immune response[1]. Interestingly, aberrant TLR9 activation is implicated in the pathogenesis of a number of autoimmune diseases[2] (viz. psoriasis, systemic lupus, scleroderma, rheumatoid arthritis, type 1 diabetes etc.) as well as in different components of metabolic syndrome[3] (obesity-associated type 2 diabetes, fatty liver disease, atherosclerosis). TLR9 is established as an important therapeutic target in these different clinical contexts. But inhibitors of TLR9 are yet to be available for clinical use.

Technology

The present invention relates to a lead series of small molecule compounds for inhibiting TLR9 or both TLR9 and TLR7[4,5], developed through rational design driven by well characterized SAR in human primary immune cells (Table 1). The lead series includes molecules with oral bioavailability, documented target-binding, favourable pharmacokinetics and in vivo efficacy for TLR9/7 antagonism in preclinical rodent pharmacodynamics studies as well as a preclinical disease model of the autoimmune disease psoriasis (Figure 1).

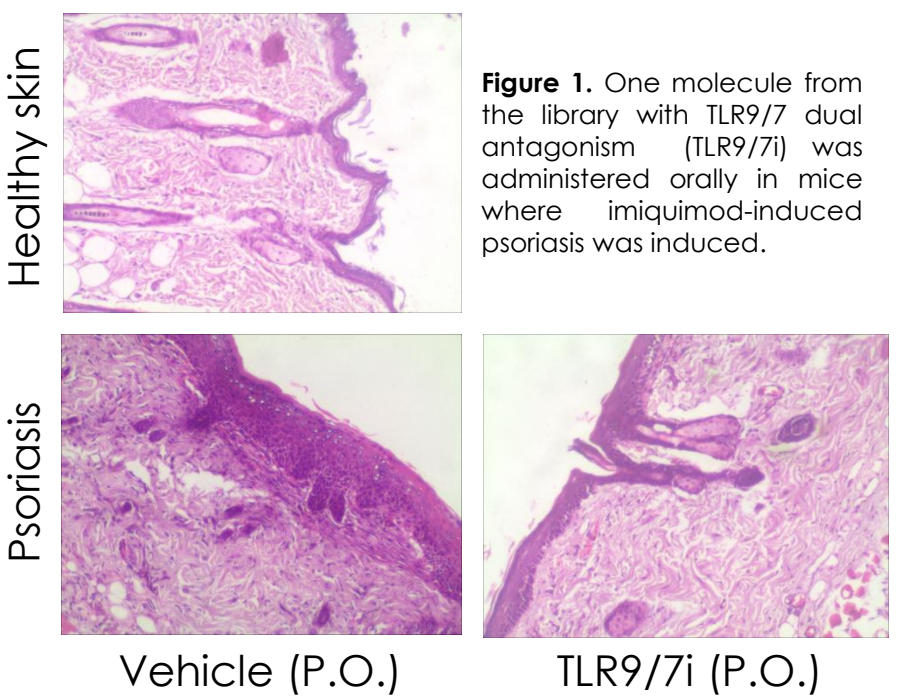

Figure 1. One molecule from the library with TLR9/7 dual antagonism (TLR9/7i) was administered orally in mice where imiquimod-induced psoriasis was induced.

Opportunity

CSIR-Indian Institute of Chemical Biology is seeking to transfer the technology of this advanced lead series of TLR9/7 inhibitors to an pharmaceutical industry entity (with global footprint and past experience with clinical trial for drugs toward global regulatory approval for human use) for further preclinical development and nomination of clinical candidate/s for evaluation in clinical trials.

References/Patents

1. WO/2019/092739, US 2020/034706. (GRANTED)
2. WO2017/163264A1, US10662177B2. (GRANTED)
3. Ganguly D, Trends Immunol, 2018.
4. Roy S et al., Eur J Med Chem, 2017.
5. Mukherjee et al., J Med Chem, 2020, 63, 4776.
6. Kundu B et al., J. Med. Chem. 2021, 64, 13, 9279
7. Paul B et al., Eur J Med Chem, 2018.

Project Investigator
Dr. Arindam Talukdar
CSIR-Indian Institute of Chemical Biology
Email: atalukdar@iicb.res.in
Dr. Dipyaman Ganguly
CSIR-Indian Institute of Chemical Biology
Email: dipyaman@iicb.res.in