別紙２

Results report

１．Title of Research and Development： Identification of biomarkers for infection-induced reactive arthritis based on the inflammation amplifier

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４．Results of Research and Development:

Reactive arthritis (ReA) is a sterile inflammation of joints, triggered by infection at a distant site i.e. gastro-intestinal tract with *Salmonella*, *Yersenia*, *Shigella*, or *Campylobacter*. It is a major health problem causing acute and chronic arthritis in adolescent and young adults. Since *Salmonella typhimurium* is one of the commonest causes of bacterial diarrhea in India, therefore incidence rate of occurring ReA is expected to be high. Indeed, in sporadic ReA, the Misra laboratory has reported that *Salmonella typhimurium* accounts for one-third of cases in our community, in contrast to *Yersinia* and *Chlamydia* in Western countries. However, there are challenges in this disease, as there are no diagnostic tests as well as diagnostic biomarker for prognistification. One factor limiting the development of specific biomarker and therapy of ReA is the absence of a good animal model for the study of the molecular mechanisms involved.

The Murakami laboratory has discovered a chronic inflammation inducing machinery “inflammation amplifier” in local tissues. The inflammation amplifier induces excessive productions of inflammatory chemokines and growth factors in non-immune cells including endothelial cells, fibroblasts, glia cells, and epithelial cells, which is activated by the simultaneous activation of NFκB and STATs in response to cytokines such as interleukin (IL)-17A and IL-6. Dr Misra has found that presence of these cytokines in large quantities in synovial fluids of ReA patients. Therefore, the Japan-India collaboration by these laboratories will lead to establish a ReA animal model to study ReA pathogenesis and develop a biomarker and therapeutic strategy to ReA.

Dr Murakami already established a ReA mouse model using F759 knock-in mice infected with *Salmonella* in Osaka University. After moving his laboratory to Hokkaido University, the Murakami group improved the ReA model by injecting serum components derived from *Salmonella*-infected mice at the ankle joints of mice during the fiscal year of 2015. This phenomenon can explain joint inflammation by infection at the distant site (i.e. gastro-intestinal tract). Therefore, the pathogenesis of the serum component-induced arthritis will be extensively studied next year. In addition, the evidence of the amplifier activation in ReA patient was further supported by the observation that the amplifier-target soluble factors were elevated in sera of the patients in India.

In this fiscal year, a young researcher from the Indian side joined in the Murakami laboratory and learned experimental techniques to induce the ReA mouse model and analyze it. He will continue to stay in Japan next year to study the mechanism of disease induction by the serum components. In February 2015, Dr Misra visited the Murakami laboratory to discuss the Japan-India collaborative project for the fiscal year of 2016.