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IUIS VIC and EVIG Travel Award Report

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First of all, I would like to express my sincere gratitude to The International Union of Immunological Societies (IUIS) Veterinary Immunology Committee (VIC) and the European Veterinary Immunology Group (EVIG) for giving me the invaluable opportunity to attend the IVIS 2016, a well-organized and high-level meeting on any fields of veterinary immunology. With this support, I traveled to Gold Coast, where I learned a lot on the topics of my interest, got interested in topics I previously was not, and met many participants who may be future collaborators for my studies. I was really honored to be selected as an oral presenter in this IVIS and to present my own study in front of the sophisticated attendees of the symposium.

I am studying on canine cancer immunology and immunotherapy as a theme of my PhD thesis in Hokkaido University, Japan. Especially, I am interested in cytotoxic $CD8^+$ T cell responses against tumor cells and immune escape mechanisms of cancer or so called cancer immunoediting. Cellular immunity is considered a main part of anti-tumor immunity, but cancers can evade the CTL response for some reasons, resulting in the persistence of cancer cells in the body. Immune surveillance itself, in most cases, is effective to fight against cancer: by stopping the immune evasion, cancers should be spontaneously eliminated. Considering the great potential of immunity, it is obvious that targeting the mechanisms of cancer immune escape is a fascinating strategy to develop new options for cancer treatment. Indeed, in humans, such strategies have been taken and some of them are already in the clinical use. For example, immunoinhibitory receptors on T cells, such as PD-1 and CTLA-4, also known as immune checkpoint molecules, are promising targets to potentiate the immune surveillance against cancers. They are negative feedback systems of T cell activation and has an important role in immune homeostasis; however, in cancers this mechanism is

known to be associated with the immune evasion. Recently, antibody drugs which bind and block these inhibitory receptors have been developed and they showed exciting anti-tumor effect on several types of malignant cancers in humans. These findings have completely altered the situations of cancer treatment in humans; until then, immunotherapy had not been recognized as effective and attractive options in clinical settings. One of the top journals, Science, chose the cancer immunotherapy as the "breakthrough of the year" in 2013, taking the success of anti-PD-1 antibody drug into consideration. Although antibody drugs, including the immune checkpoint inhibitors, and other biological drugs are getting common in humans, there are not so many studies on biological drugs, especially antibody drugs, in veterinary medicine at present time. Thus, I am interested in the application of this kind of strategy to canine cancer treatment, and the goal of my current study is to develop an antibody drug targeting the PD-1 pathway in dogs.

In Japan, there are not so many researchers working on the clinical immunology in veterinary medicine and studies on cancer immunotherapy in dogs are substantially limited. For this reason, IVIS was a good opportunity for me to learn the leading researches on any kinds of clinical immunology. Especially, in this IVIS, we had an "Antibody Therapy" session (Plenary 5). I think the development of antibody drug for the treatment of animal diseases is a growing field of research, and I am sure more researchers will work on this topic in next 10 years particularly for the treatment of companion animals. Therefore, I was so lucky to know the latest achievements of this developing and promising field of research at this time point, so that I can improve my own study, and I hope my study would be one of the leading models for the development of antibody therapy in veterinary science.

Dr. David Gearing from Nexvet Biopharma kindly introduced their strategy to develop antibody drugs for animal use, so called "PETization". Converting the antibody framework to reduce the immunogenicity of antibody protein is so important to make it effective *in vivo*, and they have developed a unique technique to make species-specific antibodies. In humans, chimerized (variable region grafted), humanized (complementarity determining region (CDR) grafted) or fully-humanized (established in a genetically modified mouse which has segments of human immunoglobulin loci) antibodies are used for the clinical application. Fully animalized antibody is difficult to develop because specialized transgenic mice for each animal are needed. Dr. Gearing and his team overcame this problem by substituting the amino acids of original antibody using a special algorithm to make 100% animalized antibody. This technique can acceralate the development of antibody drug in veterinary field because the amino acid sequence of certain antibody is the only required information to be PETized. Dr. Gearing also showed us the updated achievement of anti-NGF antibody for the control of pain in dogs. The team conducted a large-scaled clinical trial that included more

than 250 dog patients to show the clinical benefit of anti-NGF antibody drug. That was a placebo-controlled study, in which 1/3 of the patients had received the placebo instead of the antibody drug. The evaluation of the clinical benefit of a new drug is difficult for some reasons, and sometimes placebo-control is needed. This clinical trial may be a leading case of the evaluation of antibody drug in veterinary medicine, and I would like to follow it when I perform the clinical trial of antibody drug of my interest in the future.

Dr. Serge Muyldermans gave us a talk regarding his outstanding findings on camelid antibody, or heavy chain antibody. He introduced the amazing and unique characteristics of camelid antibody and I learned it from the discovery to research/clinical applications. Simply because of the low-molecular weight, single domain antibody (sdAb) or VHH (Nanobody) can be used for various purposes including tissue-infiltrating antibody drug and diagnostic antibody with its specific binding. This kind of new tool can be introduced into veterinary science, and I think animals including dogs could be a good animal model for the evaluation of new reagents before applying to humans. I am interested in "antibody engineering", and the talk was really exciting and informative for me.

Because the immune response comes up as the result of complicated interaction among the various immune cells and the target cells, understanding the roles of each participants is important to elicit a favorable response. Dr. Isabelle Schwartz explained about the functions of dendritic cell (DC) subsets in animal species and new strategies to target appropriate DC subsets to get a maximum vaccine benefits. This kind of information can be applied to cancer vaccination, although the DC subsets in dogs have not been studied intensely until now. I also found interesting studies on macrophages, NK cells, gamma delta T cells, regulatory subsets of immune cells and more in this IVIS, which all could be utilized in cancer vaccination strategy. Although the antibody drugs targeting the PD-1/PD-L1 pathway showed promising clinical benefits on advanced cancer patients in humans, the objective response had been observed only in around 20-30% of the patients. In order to improve the response rate, additional immune modulating therapies are needed, including adoptive transfer of T cells/antigen-loaded DCs, cancer vaccination, and/or other molecular-targeted drugs. In humans, researchers are trying to find the best combination therapy which can be used along with PD-1 therapy. I think dogs could serve as an efficient animal model for this kind of clinical researches if we have an antibody drug targeting PD-1/PD-L1, because, compared to humans, it's relatively easier to conduct clinical trials in dogs. It was nice for me to learn various strategies to improve the vaccine efficacy and to elicit strong immune response against pathogens because after finishing my current work, I would like to seek the combination therapy for dog cancers, and I hope my study would also work as a pre-clinical study for the development of combination therapies for humans, which has a high impact

not only on veterinary medicine, but also on human medicine.

I enjoyed all the programs provided by IVIS 2016 so much, including my own oral presentation entitled “Expression of canine immune checkpoint molecules PD-1/PD-L1 and the therapeutic potential of anti-PD-L1 antibody in canine malignant cancers” in the Companion Animals/horses session (Concurrent Session 3 on the last day). That was an invaluable opportunity for me to be known by the other researchers and after my talk, I got great feedbacks from the participants, including scientific discussions and possible collaborations in the future. Communicating with people was really stimulating and inspiring, and I think it’s that important for my future studies and career path, so I would like to thank this opportunity so much.

Again, I would like to express my deepest gratitude to IUIS/VIC and EVIG for giving me an invaluable and fruitful opportunity to attend IVIS 2016. Without this support, I would not be able to attend this meeting because the budget for my PhD research is limited. I am sure I will be better with this experience. Thank you so much.

Sincerely,

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