The First International Seminar on Immunology and Cancer in Okayama / 13th URA International Symposium

Date: October 31, 2018
Time: From 14:00 to 16:30
Place: Muscat Hall at Okayama University Shikata-campus
Entry Fee: Free

14:00~15:00 Special Lecture:
Session Chair: Prof. Heiichiro UDONO (Department of Immunology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences)

Prof. Sylviane MULLER (CNRS, UMR Biotechnology and Cell Signaling, Strasbourg University, France)
Lecture Title: LUPUS: a challenging world-wide disease II – Autophagy Process, a new target to treat autoinflammatory disease.

15:00~16:30 Symposium: Molecular Basis for Cancer Immunity and Metastasis
1. Prof. Heiichiro UDONO (Department of Immunology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences)
Lecture Title: Metabolic competition between tumor infiltrating CD8T lymphocytes and tumor cells determines the growth of the tumor.
2. Dr. Mikako NISHIDA (Department of Immunology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences)
Lecture Title: Molecular basis for metformin and anti-PD-1 Ab combination therapy against solid tumors.
3. Prof. Masakiyo SAKAGUCHI (Department of Cell Biology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences)
Lecture Title: Development of novel biologics to prevent lung tropic cancer metastasis.
ABSTRACT
Nowadays, pharmacologic treatments of inflammatory and autoimmune diseases are largely palliative rather than curative. Most of them result in non-specific immunosuppression, which can be associated with disruption of natural and induced immunity with significant, sometimes dramatic, adverse effects. Among the novel strategies that are under development, tools that modulate the immune system to restore normal tolerance mechanisms, are central. In these approaches, peptide therapeutics constitute a class of agents that display many physicochemical advantages.

Within this class of potent drugs, the phosphopeptide P140 is very promising for treating patients with SLE, and likely also patients with other chronic inflammatory diseases. In a multicenter, randomized, placebo-controlled phase-IIb study for lupus, P140/Lupuzor™ was found to be safe and met its primary efficacy end points, confirming pre-clinical data generated in MRL/lpr lupus-prone mice. Lupuzor is currently evaluated in phase-III clinical trials in the US, Europe and Mauritius. We discovered that P140 targets autophagy, a finely orchestrated catabolic process, involved in the regulation of inflammation and in the biology of immune cells. P140 acts directly on a particular form of autophagy called chaperone-mediated autophagy, which is hyperactivated in lupus in certain subsets of lymphocytes. The “correcting” effect of P140 on autophagy results in a weaker signaling of autoreactive T cells, leading to a significant improvement of physiopathological states of treated mice. These findings open novel avenues of therapeutic intervention in other pathological conditions in which reduction of autophagy activity would be desired. New data will be presented in the context of neurological autoinflammatory diseases.
Metabolic competition between tumor infiltrating CD8T lymphocytes and tumor cells determines the growth of the tumor

Prof. Heiichiro Udomo¹, Dr. Mikako Nishida¹, Dr. Shingo Eikawa¹, Dr. Yuki Kunisada², Dr. Takenori Uehara³
¹Department of Immunology, ²Department of Oral and Maxillofacial Surgery, ³Department of Orthopedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

ABSTRACT
In the tumor microenvironment, large amount of glucose is consumed by tumors and not by immune cells, which allows tumors to grow. Effector memory CD8T lymphocytes (CD8TEM) requires glucose to fight against tumors, but in the absence of glucose, rapidly differentiates into central memory type (CD8TCM) whose ability of multiple cytokine production is hampered. In addition, absence of glucose allows for expansion of Treg, MDSC and M2-like macrophages in the tumors, leading to strong inhibition of T cell-mediated anti-tumor immunity. Therefore, to overcome this metabolic imbalance between tumors and immune effector cells is one of the target we need to focus on for the therapeutic intervention in cancers. In fact, PD-1-PD-L1 blockade has been shown to downregulate glycolysis of tumors, while in contrast, it results in the elevation of CD8T lymphocytes.

We recently observed that metformin, an anti-diabetic drug, as well as anti-PD-1 mAb activates CD8T lymphocytes (CD8TILs) to produce multiple cytokines, in a glucose transporter, Glut-1 dependent manner. We will present evidence of how metformin-induced metabolic change can influence on population of CD8TILs, Treg, MDSCs and M1/M2-like macrophages in the tumor microenvironment. We propose that the metabolic reprogramming of tumor microenvironment converts immune tolerance to activation, leading to regression of solid tumors.
Molecular basis for metformin and anti-PD-1 Ab combination therapy

Dr. Mikako Nishida, Prof. Heiichiro Udono
Department of Immunology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University

ABSTRACT
We previously reported that combination with metformin and anti-PD-1-Ab conferred better therapeutic effect than either mono-therapy alone against growth of tumors. Antioxidant, N-acetyl cysteine (NAC) canceled the effect of metformin but not of anti-PD-1-Ab. The results indicate that metformin induced anti-tumor immunity requires reactive oxygen species (ROS). At present study, we have examined the relationship between ROS production and glycolysis of CD8 TIL of mice that received metformin.

Tumor (Meth A) bearing mice were treated with metformin along with or without NAC. Three days later, CD8 TILs were examined by FACS for their cytokine production. Also, expressions of Glut-1, mitochondrial ROS, pS6, Ki67, Nrf2 and Heme oxygenase-1(HO-1), a downstream molecule of Nrf2, were investigated. pS6, Ki67, IFN γ, Nrf2 and HO-1 were the highest in their expressions in ROS (-) Glut-1(+) and second in ROS (+) Glut-1(+), third in ROS (+) Glut-1(-) populations. All expressions were canceled by NAC administration or by in vitro GSH or Nrf2 inhibitor treatment of TILs. Interestingly, we found that combination with metformin and glucose showed better effect than either alone against the growth of tumor. The results indicate metformin-induced ROS initiates both glycolysis and Nrf2 activation, leading to the cytokine production, mTORC1 activation and the T cell proliferation in the tumor microenvironment.
Development of novel biologics to prevent lung tropic cancer metastasis.

Prof. Masakiyo Sakaguchi
Department of Cell Biology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

ABSTRACT
Cancer metastasis is the main cause of cancer death and an understanding of metastasis at molecular levels is therefore important. S100A8/A9, a heterodimer complex of S100A8 and S100A9, is an attractive molecule that is involved in cancer metastasis. This protein has an interesting feature of abundant secretion in the lung. Even for melanoma that is present at place far from the lung, the secreted S100A8/A9 attracts the melanoma from the original skin lesion to the metastatic site in the lung. What receptor(s) does cancer use to sense the S100A8/A9 signal? TLR4 (Hiratsuka et al., Nature Cell Biol 2006 & 2008) and RAGE (Saha et al., J Biol Chem 2010) have been shown to be S100A8/A9 receptors. However, the expression of these receptors is not commonly detected in either metastatic melanoma or other metastatic cancers.

Our endeavors have resulted in identification of other important receptors: EMMPRIN (Hibino et al., Cancer Res 2013), NPTNα and NPTNβ (Sakaguchi et al., J Invest Dermatol 2016), and MCAM and ALCAM (Ruma et al., Clin Exp Metastasis 2016; Sumardika et al., Oncol Res 2017). These novel receptors are expressed in a wide range of cancer species at different levels. Their expression levels tend to be increased following cancer malignancy and they have functions similar to those TLR4 and RAGE in cancer metastasis. Thus, these receptors may work as a compensatory receptor each other that may also work together to reinforce the metastatic signal(s) in response to S100A8/A9 in cancer cells. This idea spurred us to develop receptor-based decoys and S100A8/A9 antibody that are expected to cut the linkage between S100A8/A9 from a pre-metastatic organ and the intrinsic receptors at the cancer side, eventually leading to prevention of S100A8/A9-mediated cancer lung metastasis. In this presentation, I hence introduce our newly produced biologics to aim at effective prevention of the lung tropic cancer metastasis.