JPS-ASPET Lecture

3 月 14 日（木）15:00～16:00（第 92 回日本薬理学会年会　A 会場）

Combining Pharmacology and Genetics to Study and Treat Human Diseases

Prof. Lorraine J. Gudas

Department of Pharmacology, Weill Cornell Medicine of Cornell University, Weill Cornell Graduate School of Biomedical Sciences, and the Weill Cornell Meyer Cancer Center, New York 10065, USA

日本薬理学会と米国薬理学会（ASPET）の講師交換プログラムは今回３回目となります。Gudas 教授は、プリンストン大学で PhD を取得され、UCSF でのポストドクを経てハーバード大学で PI となり、1991 年にコーネル大学へ異動され、現在は同大学の医学部薬理学教室のチェアマンを務められています。レチノイン酸受容体の機能を様々な疾患モデルマウスを用いて研究し、癌、糖尿病、脂肪肝などの予防に関与することを示し、それを標的とした薬物開発を進めています。ASPET から交換プログラム講師としてご推薦いただき、薬理学会年会にお招きすることになりました。多数の会員のご参加をお願いします。

Members of the nuclear receptor family, the retinoic acid receptors (RARs) alpha, beta, and gamma, regulate aspects of cell differentiation and the epigenetic states of stem and differentiated cells. We have shown that these RARs also play key roles in cancer prevention and in the prevention/inhibition of diabetes and hepatic steatosis, but the complexity of signaling by multiple receptors and the regulated production of active ligands from precursors make it challenging to establish the molecular mechanisms for these effects. To identify new targets and to develop new pharmacological treatments, we have generated unique murine models of both early stage *clear cell renal cell carcinoma (ccRCC)* and *head and neck cancer (HNSCC).* These models reflect molecular and histological changes that take place in human carcinogenesis, providing us with powerful systems in which to test new drugs and increase our understanding of the molecular events in the early stages of carcinogenesis. For example, in our *HNSCC model* we are exploring the role of retinoic acid receptor (RAR) gamma as a tumor suppressor, and we also have shown that a RAR gamma selective agonist can inhibit the development of oral squamous cell carcinoma. Our ccRCC model has allowed us to establish the importance of novel therapeutic targets. Using both dietary (i.e., a high fat diet) and genetic (i.e., db/db mice) models of diabetes and/or hepatic steatosis, we have demonstrated that a RAR beta selective retinoid can prevent/reduce the pathological features of diabetes and hepatic steatosis. Furthermore, we have discovered that this RAR beta selective retinoid is useful in the treatment of diabetic nephropathy and is cardioprotective. Thus, combining pharmacological studies with robust, representative models of disease not only provides important insights into a broad variety of common human diseases (metabolic syndrome, cancer, kidney disease, and heart disease), but also leads to potential therapeutics or lead compounds to improve human health.