氏　　名	東川　桂
授与した学位	博　　士
専攻分野の名称	薬　科　学
学位記授与番号	博甲第 5139 号
学位授与の日付	平成 27 年 3 月 25 日
学位授与の要件	医歯薬学総合研究科　薬科学専攻 （学位規則第５条第１項該当）
学位論文の題目	Development of novel nuclear medical imaging methods for multiple diagnoses of disease-related molecules (疾患関連分子の複合画像診断を行うための新規核医学診断法の開発)
論 文 審 査 委 員	教　授　須藤　雄気（主査） 教　授　狩野　光伸　　准教授　大河原　賢一

学　位　論　文　内　容　の　要　旨

Inflammatory bowel disease (IBD) and cancer are intractable diseases that cause great mental and financial stresses on patients. These diseases involve multiple and complex molecular interactions, and the methods for curing these diseases remain largely undeveloped. Thus, for improving the therapeutic benefits, it is necessary to develop noninvasive methods providing the necessary information on multiple disease-related molecular species, and to establish the systems combining molecular diagnostics and therapy. Therefore, this study aimed at exploring the target molecules for nuclear medical imaging of IBD (Chapter 1), developing a novel imaging probe targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), which is a target molecule for cancer immunotherapy (Chapter 2), and developing a method for simultaneous imaging of multiple disease-related molecular species by using Gamma-Ray Emission Imaging (GREI) (Chapter 3). Developing the methods for noninvasive probing of the presence of multiple pathogenic molecular species is expected to assist in developing personalized therapies.

Chapter 1: Time-dependent changes in the expression levels of cytokines (interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, S100A8) and cytokine receptors (IL-6Rα, IL-1R type 1, Toll-like receptor-4) in the inflamed areas of dextran sulfate sodium- and indomethacin-induced IBD mouse models were analyzed by RT-PCR. These results suggested that IL-6, IL-1β, and S100A8 were particularly promising target molecules for IBD imaging because the expression levels of these

molecules are altered early during the inflammation and depend on the extent of inflammation. Hence, utilization of nuclear medical imaging probes targeting these inflammation-related molecules would be helpful for grasping in greater detail the inflammatory conditions of IBD early on, which would eventually lead to the development of evidence-based therapy methods.

Chapter 2: ^{64}Cu-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-anti-CTLA-4 monoclonal antibody (mAb) was synthesized for the first time. The usefulness of this probe in PET and ex vivo biodistribution analysis in CTLA-4-positive CT26-bearing mice was evaluated. As a result, although ^{64}Cu-DOTA-Control IgG (isotype control) exhibited slight accumulation in the CT26 tumor tissues likely owing to enhanced permeability and retention (EPR) effects, the accumulation of ^{64}Cu-DOTA-anti-CTLA-4 mAb was more pronounced. These results suggest that ^{64}Cu-DOTA-anti-CTLA-4 mAb is useful for evaluating the CTLA-4 expression in tumors.

Chapter 3: Imaging experiments by GREI were conducted using ^{89}Zr-deferoxamine (DFO)-anti-epidermal growth factor receptor (EGFR) mAb and ^{111}In-DOTA-anti-human epidermal growth factor receptor 2 (HER2) mAb. The GREI experiments suggested that although the quality of ^{111}In-labeled probe data remains to be improved, GREI can be used for noninvasively visualizing multiple disease-related molecular species (EGFR and HER2) in tumors.

As mentioned above, these studies provide the fundamental information necessary for developing the methods for evaluating the expression of multiple disease-related molecular species relevant to IBD and cancer, which would lead to the establishment of personalized therapies.

論 文 審 査 結 果 の 要 旨

本研究は，炎症性腸疾患（IBD）やがんの診断に利用できる核医学イメージング法の開発を目的としている。疾病の効率的な診断・治療の実現を目指した各種イメージング法の開発が世界各国で行われているが，疾患関連分子を標的とするものは少なく，また「複数」の分子種を「同時」に画像化する方法は確立されていない。これらの課題に対し，本学位論文では，ボトムアップ的アプローチを取った。すなわち，(1)イメージングプローブの標的分子の探索・選定，(2)プローブの開発，(3)画像化技術の開発を行い，それぞれ，1)複数の標的候補分子の発見，(2)がん診断標的分子のプローブ開発，(3)GREI（Gamma-Ray emission imaging）による複数種分子の同時可視化の可能性提示を達成した。これらの一部は，二報の査読付き原著論文としても報告されている。このように，「診断に利用できるプローブの開発とイメージング法の確立」という目的に対し，適切なアプローチが取られており，得られた結果は，学術上の高い新規性・進歩性を有する。また，予備審査および第一回審査会で指摘されたデータの取り扱い・提示および議論の内容についても適切に修正されている。従って，本審査委員会は本論文が博士の授与に値すると全員一致で判断した。