【Grant-in-Aid for Scientific Research (S)】

Broad Section E

Title of Project：　Comprehensive search of cancer specific enzymatic activities and creation of innovative neutron capture therapy probe

URANO, Yasuteru
(The University of Tokyo, Graduate School of Pharmaceutical Sciences, Professor)

Research Project Number：19H05632　Researcher Number：20292956
Keyword：Fluorogenic probes, BNCT, Quantum chemical calculation, Cancer, Biomarker

【Purpose and Background of the Research】

The establishment of a treatment for refractory diseases such as cancer is an extremely important issue in present-day Japan, and various basic analysis techniques including imaging are developed worldwide. Under these circumstances, this research representatives have developed a completely new diagnostic and therapeutic technology based on "live imaging of clinical specimens" using the "chemical fluorogenic probes" to realize the advanced precision fluorescence guided surgery etc.

On the other hand, there are still many types of cancer that cannot be visualized by the probes developed so far, and optical methods cannot be applied to deep imaging and treatment. Therefore, in order to solve these problems, in the present application we will carry out the projects listed in the next section to find out specific biomarker enzymes of cancer types that cannot be visualized using conventional methods, to achieve rapid fluorescence imaging, and to develop innovative Boron Neutron Capture Therapy (BNCT) probes for treatment and discovery of deeply located cancer.

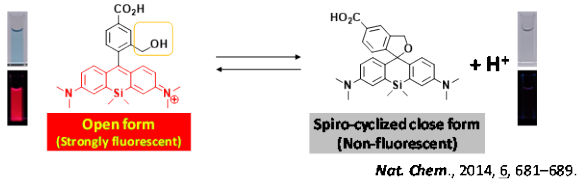
This research subject was carried out with the participation of clinical surgeons and neutron beam irradiation equipment development researchers as research co-workers, centering on the research representative who had advanced probe development technology.

【Research Methods】

The research method of this subject is as follows.

(1) Logical design of fluorogenic probes based on quantum chemical calculation, finding out novel biomarkers, and developing new intraoperative rapid imaging technology

Using quantum chemical calculation, we aim to establish a system that accurately predicts the equilibrium constant of intramolecular spiro-cyclization equilibrium (see below), which is a fluorescence ON / OFF control mechanism that has been uniquely established by the research representative, to realize the development of novel probes for oxidases and reductases. By applying these probes to various cancer clinical specimens, new biomarker enzymatic activities are discovered, and new intraoperative imaging techniques are established.

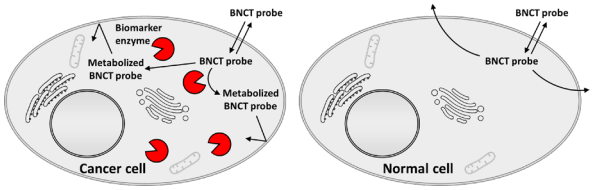


Nat. Chem., 2014, 6, 681–689.

(2) Development and verification of BNCT probes for treatment and visualization of deeply located microtumors

BNCT is a therapeutic method for killing cancer cells using α particles and Li ions generated by the nuclear reaction of boron (^{10}B) and neutrons, and has attracted great attention as an innovative therapeutic method with less damage to normal cells. In this research, we aim to develop BNCT probes based on a new principle by utilizing specific biomarker enzymatic activity of cancer cells. Specifically, we develop probes that turn into highly retained products due to specific enzyme activity of cancer cells, but quickly leaks from normal cells, to realize BNCT treatment with a high T/N ratio. (Below)

【Expected Research Achievements and Scientific Significance】



The establishment of a method to design and develop highly practical fluorescent probes using quantum chemical calculation non-empirically is the world's first achievement, which provides breakthrough benefits to live cell and clinical imaging. Furthermore, a novel BNCT probe that utilizes biomarker enzymatic activity is a novel cancer medical technology that realizes selective treatment and detection of deeply located microtumors whose social significance is extremely high.

【Publications Relevant to the Project】

・Uno S, et al., ***Nat. Chem.*** 2014, 6, 681-689.
・Umezawa K, et al., ***Nat. Chem.*** 2017, 9, 279-286.

【Term of Project】 FY2019-2023

【Budget Allocation】 154,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~taisha
http://cbmi.m.u-tokyo.ac.jp
uranokun@m.u-tokyo.ac.jp