京都大学若手人材海外派遣事業　ジョン万プログラム
研究者派遣プログラム

英文報告書

提出日：平成 26 年 2 月 28 日

１．渡航者　（日本語）			
氏　　名	村井　純子	採択年度	平成２５年度
部　　局	医学研究科	電　話	
職　　名	助教	メール	
研究課題名	**Mechanistic Insights into the Anticancer Effect of PARP Inhibitors Based on the PARP-DNA Trapping**		
海外渡航期間	平成 25 年 11 月 17 日～　平成 26 年 2 月 17 日		
渡航先 （英語表記）	国名：United States of America 大学等研究機関名：National Institutes of Health 研究室名等：Laboratory of Molecular Pharmacology, NCI 受入研究者名：Dr. Yves Pommier		

２．渡航の報告　（英文）

渡航先の研究環境、研究者との交流、研究発表の状況等、渡航中の滞在経験について英語(500～1000語)で記述して下さい。受入研究者と撮影した写真や研究発表で用いた図等について、可能な範囲で別添として提出して下さい。ページ数については増加してもかまいません。

この報告は、ジョン万プログラムの成果として、京都大学ホームページ（英文）などに掲載されることがあります。

Receiving the fellowship from the John Mung project, I worked at Dr. Pommier's laboratory for 3 months where I had worked as a postdoc from 2010 to 2012. During the former visiting period, I investigated mechanisms of action of PARP inhibitors belonging to a new class of anti-cancer drugs and obtained several interesting results. Although, I published one of the results in 2012 (Murai et al., Cancer Res.), I was not able to finish other projects. It was not impossible but not so easy for me to pursue the projects once I left NIH for a new laboratory in Japan since the frequency to contact with the boss and the motivation of mine to pursue the projects was decreased. I believe that face-to-face discussion with coauthors should be a critical action when preparing manuscripts. Therefore, the three months gifted by the John Mung project was a precious opportunity for me because I was able to devote all of my time to experiments, discussion, and preparation of manuscripts to complete the suspended projects. Taking this opportunity, I would like to introduce Poly(ADP-ribose)polymerase (PARP) inhibitors that I have worked on for these years.

1) A novel mechanism of action of PARP inhibitors. PARP inhibitors are anti-cancer drugs under clinical trials for breast, ovarian and other cancers in USA and European countries. They were initially developed as catalytic inhibitors to block the repair of DNA single-strand breaks. We recently reported that several PARP inhibitors have an additional cytotoxic mechanism by trapping PARP-DNA complexes, and act as PARP poisons at pharmacological concentrations. Our recent reports revealed ~1,000-fold different potency at trapping PARP among five clinical PARP inhibitors, while they are nearly equivalent at catalytic inhibition. Therefore, we have proposed that PARP inhibitors should be evaluated based both on catalytic PARP inhibition and PARP-DNA trapping. The manuscript titled "Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib" was recently published in *Molecular Cancer Therapeutics.*

2) Rationale for PARP inhibitors in combination therapy. Various kinds of combination therapy with PARP inhibitors are ongoing. We examined the rational use of PARP inhibitors with combination drugs based on PARP trapping and PARP catalytic inhibition. We evaluated the combination of PAPR inhibitors with different PARP trapping potencies with therapeutically relevant topoisomerase I inhibitors (camptothecins), alkylating agents (temozolomide), cross-linking agents (cisplatin) or topoisomerase II inhibitors (etoposide) at the cellular and molecular levels. We revealed that catalytic PARP inhibitors are highly effective in combination with camptothecins, whereas PARP inhibitors capable of PARP trapping are more effective with temozolomide. Our study provides new insights in combination treatment strategies of different PARP inhibitors. I recently submitted the manuscript titled "Rationale for PARP inhibitors in combination therapy with camptothecins or temozolomide based on PARP trapping versus catalytic inhibition", and it is now under the second review.

PARP inhibitors will be introduced into Japan in near future. I believe that our works would contribute to the anti-cancer treatment in Japan. In the end, I appreciate Dr. Takeda, Dr. Pommier, and the John Mung project to giving me the precious opportunity to work on PARP inhibitors at NIH.