出國報告（出國類別：進修）

低分次放射治療應用於非小細胞肺癌之轉譯醫學與臨床試驗整合性研究

服務機關：國立台灣大學醫學院附設醫院腫瘤醫學部

姓名職稱：許峯銘/主治醫師

派赴國家：美國/德州大學西南醫學中心（University of Texas Southwestern Medical Center）

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單位主管核章：

摘要

During my sabbatical research from December 15 2010 to December 14 2011, I spent full time at both labs and clinics in the department of radiation oncology, UT southwestern medical center, Dallas, Texas. At labs of molecular radiation oncology, I worked with the principle investigator and postdoctoral research fellows studying the radio-sensitizing and chemo-sensitizing effect of certain novel drugs targeting DNA-dependent protein kinase (DNA-PK), cyclin-dependent kinase, and EML4-ALK fusion protein in non-small cell lung cancer cell lines. I learned the translation research platform to investigate the therapeutic potential for combined treatment from in vitro cell line study to in vivo animal study. Our work showed that DNA-PK inhibitor is a potent radio-sensitizer in lung cancer cell lines and presents active therapeutic effect in xenograft animal model. It would allow me to build our own platform back to National Taiwan University Hospital for future translational research and development of clinical trial for multi-modality cancer therapy. At clinics of radiation oncology, I attended the stereotactic body radiotherapy (SBRT) training program and followed radiation oncologists in clinical activities. I learned the entire SBRT platform from simulation, treatment planning, quality assurance, and treatment delivery. It would allow me to implement our own SBRT platform in Nation al Taiwan University Hospital to improve our treatment outcome for cancer patients.

目次

目的

Lung cancer is the leading cause of death in cancer patients for consecutive eleven years in Taiwan. Radiation therapy is an important treatment modality for stage I to III non-small cell lung cancer (NSCLC) patients who surgically or medically inoperable. Recent clinical trials showed that concurrent chemoradiation improves the survival for patients with stage III NSCLC and results in similar median survival as compared to treatment of neoadjuvant chemotherapy followed by surgery. However, locoregional failure remains high despite of radiation dose escalation. Therefore, a novel strategy combined radiation with a non-toxic radio-sensitizer or target agents is mandatory to improve the outcome for stage III NSCLC. On the other hand, for patients with stage I-II NSCLC, recent trials showed that stereotactic body radiotherapy (SBRT) significantly improves local control in comparison to the conventional fractionated radiotherapy. The local control rate is more than 80% and is considered as the treatment of choice for patients who are not eligible for surgery due to underlying medical problems.

Despite of we have both the required facility and equipment including radiation biology lab and high technology linear accelerators (Elekta Synergy with onboard cone-beam kilovoltage CT, Tomotherapy with fan-beam megavoltage CT, Cyberknife with real-time tacking orthogonal roentgenography), we are relatively lack of formal

training and experience in theses frontier fields. Therefore, the purposes of my sabbatical research are to learn and be trained for translational research in radio-sensitization and SBRT to build our own platform for National Taiwan University Hospital.

過程

The UT Southwestern (UTSW) medical center is located at Dallas, Texas, which is the ninth largest city in United States and the Dallas-Fort Worth Metroplex is the fourth largest metropolitan are in United States. UTSW is the is ranked the first as 1st in the world for published research in clinical medicine, 1st in biology & biochemistry, 2nd in neurobiology/behavior, and 3rd in molecular biology/genetics when quantifies citations-per-paper for work published between 2005–2009. In additional to the clinical division, the department of radiation oncology of UTSWMC also includes division of molecular radiation oncology, and division of medical physics and engineering. The research in division of molecular radiation oncology covers radiation resistance & sensitization, DNA double strand break repair, prognostic biomarkers for therapeutic outcomes, biology of SBRT, and space radiation biology. Though the cancer center of UTSW medical center is not high ranked in United States, Dr. Robert D. Timmerman is the pioneer in the field of SBRT and is the principle investigator on several clinical trials designed to evaluate the efficacy and toxicity of SBRT.

Once I arrived and settled down in Dallas, My mentor and instructor, Professor David J. Chen, assigned me to Professor Benjamin C. Chen's lab, where is specialized in studying DNA-dependent protein kinase (DNA-PK) and DNA repair and Professor

Debabrata Saha, where is specialized in translation research in radiation resistance and sensitization, and animal model for radiotherapy. Though I completed my BCT lab course in National Taiwan University, I can not perform biology experiments independently and had to learn from the beginning. Therefore, I spent my first two months in the lab and learned the basic knowledge and techniques required for bench work, including cell culture, cell counting, cell survival assay (Colony formation assay and MTT cell proliferation assay), immunofluorescence, flowcytometry for DNA analysis (cell cycle) and M phase analysis, protein extraction and western blot, preparation of reagents, autoclave of experiment equipments, and trashing laboratory wastes. Then, I studied the radio-sensitization effect selective DNA-PK inhibitors, NU7441 and KU0060648 (water-soluble DNA-PK inhibitor) in non-small cell lung cancer cell lines, H460 and A549. My initial work showed that NU7441 is a potent radio-sensitizer with sub-lethal dose. The radiation dose enhancement ratio is about 1.45 for H450 and 2.27 for A549 with 1 μM NU7441. My further experiments showed that NU7441 prolonged irradiation induced G2M block and impaired DNA damage repair. I also worked with other postdoctoral research fellows investigating its radio-sensitization effect in prostate cancer and other candidate drugs such as cyclin-dependent kinase inhibitor and ALK inhibitor in lung cancer cell lines. Besides radio-sensitization, I also worked on the project evaluating whether DNA-PK

inhibitor could sensitize the cytotoxic effect of cisplatin, a DNA crosslinking agent and developed a platform to analyze drug-drug interaction systematically.

With the initial progress in cell line studies, I start to learn more laboratory techniques such as comet assay, apoptosis assay by Annexin-V/7-AAD using 2 color flow cytometry, and senescence-associated galactosidase assay in order to find out the underlying mechanisms of radio-sensitization. Unlike other techniques which I was taught or instructed by my colleagues, I did these assays by reading the protocols with some modification accordingly. After several months training in lab, I can perform these experiments independently and learn the new techniques from published protocols. We also started to do xenograft animal models to evaluate the efficacy and toxicity of DNA-PK inhibitor. Therefore, I learned how to performed tumor growth delay experiments in detail, which is the classical method evaluating the efficacy of anti-tumor therapy. In summary, I was trained for both the in vitro and in vivo experiments to study the therapeutic effect of combined treatments such as radiation plus drug or combination of two drugs.

During my stay in lab, I also attend their meetings including seminar, journal club, and work in progress and got a chance to present my work in progress in English in front of my colleagues and answer questions from audience.

As I mentioned above, the other purpose of my sabbatical research in training in

SBRT. Therefore, I attended the training program of SBRT in UTSW medical center directed by Dr. Timmerman. The program summarize how to implement SBRT into radiation oncology site and detailed the associated processes including patient simulation, treatment planning skills, notes of quality assurance, and treatment delivery. In additional to the training course, I also followed Dr. Timmerman to visit his patients in the clinics for simulation, treatment and follow-up. The department of radiation oncology includes physicians and allied health professionals such as radiotherapists, medical physicists, dosimetrists, licensed practical nurses, registered nurses, and administraitves. The dosimetrist is specialized in radiotherapy treatment planning and the medical physicist is responsible for machinery maintenance, quality assurance, development of innovation treatment technologies, and research. In our hospital, there is no specialized position for dosimetrist and the treatment planning is done by medical physicist. The UTSW medical center department of radiation oncology is equipped with a variety of novel treatment technologies including Cyberknife, Gammaknife, Tomotherapy, Vero, Elekta Synergy linear accelerators, Vairan Trilogy linear accelerators, and Varian Truebeam linear accelerators. The administrator of UTSW medical center support the department acquiring new technologies if the financial balance is achieved. There is no "perfect" treatment technology and each technology has its PROS and CONS. Dr. Timmerman thinks it's

good to have all the technologies in their department so that he can choose the right one which it the most suitable for individual patients. I also attend their weekly chart round and learned how they practice clinically. There are two major differences between the practice in our hospital and UTSW medical center. The first one is that they are capable of doing 3D treatment planning for brachytherapy and can perform brachytherapy for a variety of disease site other than gynecological cancers. The second one is there is a greater proportion of patients enrolled in clinical trials, either by RTOG protocol or house protocol developed by their own radiation oncologist (most are SBRT trials). The purpose of clinical trial is not for research or academic credit, but is about to improve medicine. Well-designed clinical trial can help the physicians to make progress in medicine. Dr. Timmerman told me that he thinks only Phase 1 and Phase 3 trials are of value because the results will extend our knowledge in medicine. This is the field that we should work harder to generate good clinical trials help solving clinical problems.

During my stay, I also have a chance to attend the ASTRO annual meeting in Miami, Florida. ASTRO annual meeting is the most important academic meeting for radiation oncology and attendees can get the newest updates in the oncology. The speaker of presidential symposium this year is a physicist from office of physical sciences oncology, NIH. He proposed an interesting theory in cancer progression.

心得

First, I appreciate the support form our division chair, department chair and superintendent for my sabbatical research. It is a priceless experience to live and work in United States for one year. Actually, I think one year is less than enough but I still cherish every moment when I stay in Dallas. I learn a lot from lab and clinics of UTSW medical center and make progress in my abilities of listening, speaking and writing in English. Generally, we are too busy in NTUH for clinical service and administrative work and I only have fragmented time to learn new things, which are not part of my training either in medical school or residency. Therefore, I think sabbatical research is very important for us to innovate in medicine. It is also good to have a family life. Family is an important value and support for individual's success.

In Taiwan, many novel technologies are expensive and are not covered by national health insurance. The extent of coverage is also determined by politics instead of science. It will results in either ineffective or inappropriate use of technology, stratification of medical care, or slow adaptation of technology in the long term. It is true that some technologies are controversial but the bureau of national health insurance should take an active role in investing cost-effective analysis for adaptation of novel technology and determine whether coverage will increase the patient's benefit reasonably.

Thanks for the support from university hospital, the radiation oncology division in NTUH made a lot of progress in past years. Now we are capable of providing high quality and contemporary treatments for our cancer patients in most fields but we are still several miles away from the top in this specialty among the world, especially in the development of innovative treatment. In the future, I wish our young generations will join the sabbatical research project and make contribution to advance our service and research.

建議事項

I was planned to start my research on 1st December 2011 but was forced the delay my visit because of problems to get my J1 visa approved. The AIT acquired additional administrative process for application of biomedical research regardless the applicant is a physician, scientist, or student. During the waiting period, I am very anxious about my flight and timeline because it happened to be a hot season. Though I myself must take the responsibility because I should apply the visa earlier but I heard that I am not the only or first one encountered this problem. I wish my bad experiences can become a know-how or faq for others so that they will never get delayed and sometimes into trouble.

The longest stay for sabbatical research is one year at present. Though the applicants are allowed to propose a two-year plan but there is no financial support for the second year stay. However, the first month and last month should be subtracted because you can almost do nothing but settling down and preparing movement at that time. When you get used to the life and get some initial results from your research, it is almost about the time to return. I think that the university hospital should support one or two applicants per year to have a two-year sabbatical research and allow the applicants to complete for the chance. A two-year training should be more complete and worth the investment if there is a good proposal.

The health insurance is one of the major problems for visiting researchers in Unites States. We are not employee so that the cost is high if we want to join a good health insurance plan. The cost is even higher if we bring family with us. There are some insurance companies providing cheaper policy but they may provide inferior coverage. Most important, we do not have adequate information about how to choose the suitable policy during our stay. This is the greatest risk for sabbatical research and I wish the ministry of education and national science council can work together to help solve this issue since lots of people get supplementary financial support from them to visit United States yearly.

Biological research nowadays requires lots of statistical analysis. Unfortunately, our university and university hospital did not help the researchers to get the required commercial software. In UTSW, they have site license for sigmaplot and graphpad prism, which are popular easy-to-use statistical, curve-fitting, and scientific graphing softwares. If the researchers need some advanced software such as SPSS or Matlab, the university can help the investigators to get it with an affordable price. Otherwise, the UTSW library provides computers installed with licensed software for users to run. The medical library and department of research should help investigators get licensed software instead of risk them violating the copyright law.