

My Views and Thoughts on Translational Medicine

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Abstract

There are three important factors for translational medicine; vision, environment and idea. We must know what we want to do, why we want to do, and for whom we want to do. In Kyushu island of Japan, I saw many human T-leukemia virus type 1 (HTLV-1)-infected carriers and adult T-cell leukemia (ATL) patients. This is the reason why I decided to do something to help them. We can meet with the best colleagues and important themes of our work in a certain place. Good collaborators could help us to achieve our projects. Such a good relationship activates our performance. Only a few HTLV-1 carriers develop to ATL after a long latent period. It is suggested that there is unique oncogenic mechanism in human, especially immune system in elderly. We have a responsibility to find out important elements composing diseases *in vivo*.

Keywords: Human T-cell leukemia virus type 1 (HTLV-1); Adult T-cell leukemia/lymphoma (ATL); Allogeneic hematopoietic stem cell transplantation (HSCT); Transplantation-related mortality (TRM)

Introduction

If we want to success in our life, we have to consider how to organize our work efficiently. There are three important factors for translational medicine; vision, environment and idea. Our vision is the most important and required for the accomplishment of our objectives. The environment is also important factor for our success and collaboration activates our works. Finally, our idea is a key factor to open our own way.

Adult T-cell leukemia (ATL) is a mature T-cell lymphoma which was identified as the first human disease associated with retrovirus, human T-leukemia virus type 1 (HTLV-1) in Japan [1,2]. The patients show lymphadenopathy, cutaneous lesion, pulmonary infiltration, and hepatosplenomegaly [3]. Lobulated nuclear is a feature of ATL tumor cell as we call flower cell [1,3]. In spite of conventional chemotherapy, the median survival time of ATL patients is about 1 year [4]. Recently, only selected patients underwent allogeneic hematopoietic stem cell transplantation (HSCT) survived more than 3 years [5]. Not only chemotherapy resistance but also transplantation-related mortality (TRM) is a big issue of treatment for ATL patients.

Vision

We must know what we want to do, why we want to do, and for whom we want to do. In Kyushu island of Japan, I saw many HTLV-1-infected carriers and ATL patients. This is the reason why I decided to do something to help them. One issue for HTLV-1 carriers is a long latency from the initial infection (more than 50 or 60 years) and a low frequency of ATL development among them (less than 5%) in their lives. Once they know their status of HTLV-1 infection, they always worry about the development of ATL. As another issue, ATL remains incurable disease and a thousand of ATL patients die every year [6]. Although HSCT is more effective therapy, more than a half of younger patients underwent HSCT died within a few years. Especially high rate of TRM must be reduced for saving their lives.

ATL patient's issues are multi faced and conventional research methods and the duplication may not provide the optimum results. Therefore, we do not used to follow the same methodologies instead we should work together or think differently. If we were doing the same work with others, we'll lose another opportunity.

Environment

We can meet with the best colleagues and important themes of our

work in a certain place. Good collaborators could help us to achieve our projects. Such a good relationship activates our performance.

Under Professor Kiyoshi Takatsuki who found ATL [1], I learned the issue of HTLV-1-career and the treatment of ATL from Dr. Hiroyuki Tsuda (present Chief Medical Director of Kumamoto Civic Hospital) during doctor training at the Second Department of Internal Medicine, Kumamoto University School of Medicine. In 1992, I started my life as a researcher at Kumamoto University Graduate School of Medicine, enrolled in, at first, amylase producing myeloma research. However, I had a duty to take care of a patient with primary ATL of bone and began seeking ways to diagnose using DNA extracted from paraffin embedded tissue of ATL [7]. Fortunately, Dr. Masao Matsuoka (present President of Virus Research Institute, Kyoto University), who returned Kumamoto from the United States, taught me and blessed with the opportunity to establish a new diagnostic method of ATL using inverse PCR [8].

In those days, it came as a complete surprise that only a few percent of ATL cells expressed Tax, HTLV-1 protein and viral and cellular transducer, *in vivo*. In addition, I noticed the gap between cellular genetic abnormalities and clinical pathology in ATL. This is the reason why I decided to analyze abnormal protein levels in patients with ATL. In 1996, I moved to National Cancer Institute/National Institutes of Health (NCI/NIH) in United States of America. In the Dr. Genoveffa Franchini's Laboratory, I investigated the constitutive activation status of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) downstream of cytokine receptors [9] and the dysfunction of tumor suppressor protein p53 using proteins isolated from ATL cells [10].

After three and a half years working as a Visiting Fellow at NCI/NIH, I came back to Japan and worked at the Department of Hematology and Pulmonary Diseases, Kochi Medical School, with Professor Hirokuni Taguchi. We separated HTLV-1-infected cells

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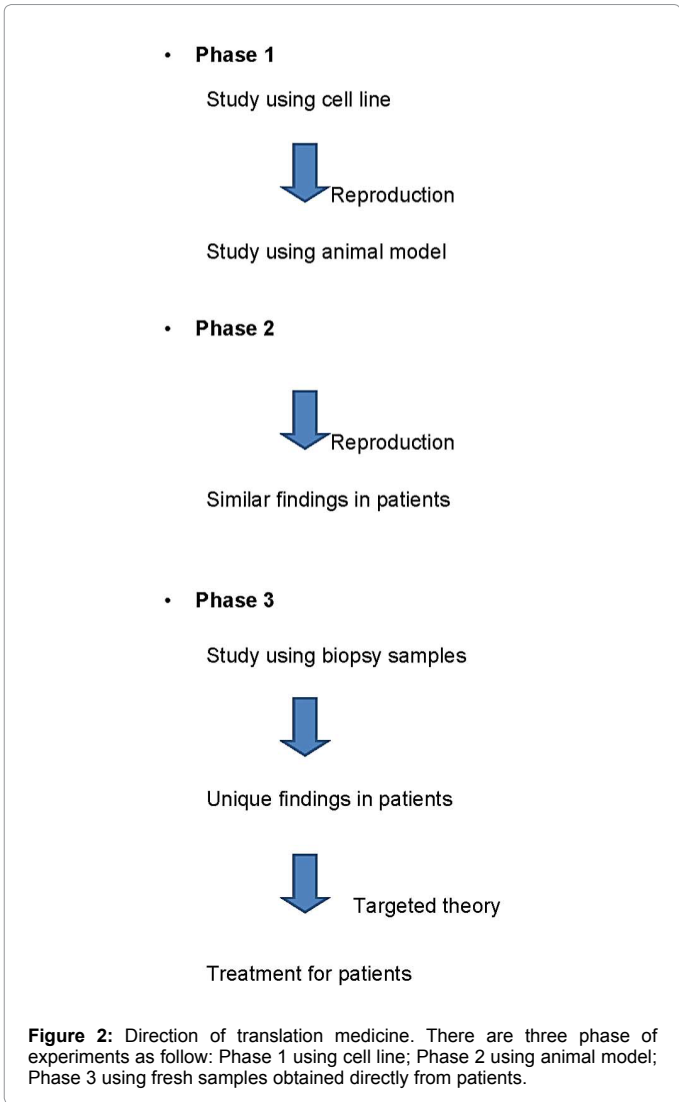
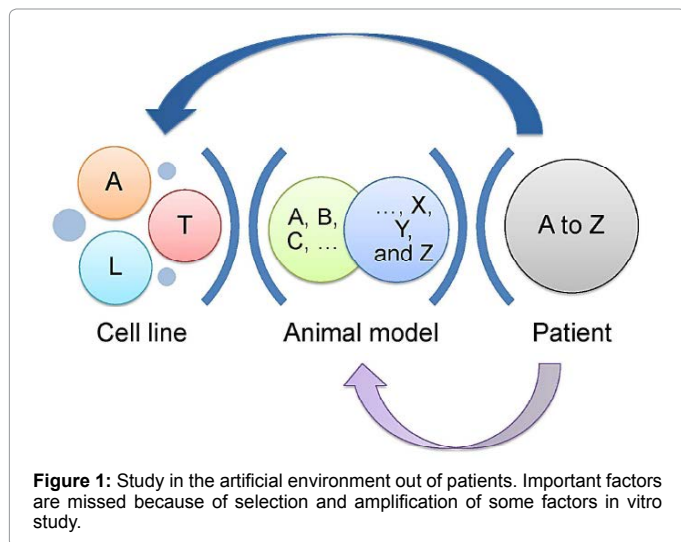
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from peripheral blood of HTLV-1 carriers as well as from patients with ATL and examined cell proliferation with/without T-cell activation. Peripheral blood monocyte-derived dendritic cells were induced and their function was assessed [11]. We tried to apply them to a therapeutic vaccine experiment using HTLV-1-infected rabbit animal model [12]. Interestingly, it seemed that CD30+ cells existed in the initial lesions of ATL. In addition, serum levels of solubleCD30 (sCD30) correlated to the aggressiveness of disease [13].

In 2005, I returned to Kumamoto, devoted myself to the treatment of leukemia patients and lymphoma patients at National Hospital Organization (NHO) Kumamoto Medical Center. I experienced some problems of ATL therapy. One thing is that biomarker had not been established for an evaluation of therapeutic effect and for a prediction of disease recurrence in ATL. Therefore we started comparative study of sCD30 with sIL-2R. In addition, change in the serum levels of the sCD30 in patients with ATL were monitored throughout chemotherapy and HSCT because NHO Kumamoto Medical Center was the representative institute of HSCT in Japan. Recently, we succeeded in demonstrating that serum levels of sCD30 combined with C-reactive protein could predict the TRM before conditioning therapy of HSCT [14]. Now we'll be able to consider additional therapy to improve the pro inflammatory state or select alternative therapy for such a patient.

Idea

Usually, basic research is performed using cell line repeatedly (Figures 1 and 2; Phase 1). Because HTLV-1 endemic areas are restricted in some areas, especially in developing countries, it is hard to see the real diseases and to get tumor samples obtained directly from ATL patients. Most researchers tried to find out oncogene which is responsible for the tumorigenesis and they wanted to reproduce their results using animal model (Figures 1 and 2; Phase 2). They found many interesting results because HTLV-1 is the first discovered human retrovirus and ATL is a rare tumor of mature CD4+ T lymphocyte. However, I think they got those results from the artificial condition in which survived cells are selected and some factors are amplified in vitro. As I mentioned above, only a few HTLV-1 carriers develop to ATL after a long latent period. It is suggested that there is unique oncogenic mechanism in human, especially immune system in elderly. For example, the patterns of JAK/STAT activation are different between *in vivo* and *in vitro* [9]. The formation of microenvironment for ATL stem cell may be the critical process of disease progression [15]. This is



the reason why I've focused on samples freshly isolated from patients. The complex mechanism should be figured out and the practically useful factors must be detected by our hands (Figures 1 and 2; Phase 3).

Conclusion

We eagerly work for anybody who requires our help. We should look for the best environment where we can work well. We need collaborators who have mutual interests. In post era of experiments using cell lines and animal models, we have a responsibility to find out important elements composing diseases *in vivo*. Specially, we are studying to identify the high risk group from HTLV-1 carrier to ATL development and another group from indolent ATL to aggressive ATL now.

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