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Review Articles

Astellas' Drug Discovery Strategy: Focus on Oncology

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Based on the goal of delivering innovative and reliable pharmaceutical products to cancer patients for whom no effective treatments exist, Astellas is focusing its efforts on a strategy of precision medicine in its drug discovery which is carried out at three research sites with diversity in their research platforms and research styles.

Key words: Astellas – oncology – drug – discovery – strategy

INTRODUCTION

Astellas Pharma Inc. was formed in April 2005 by the merger of two research and development (R&D)-driven companies, namely Yamanouchi Pharmaceutical Co., Ltd, and Fujisawa Pharmaceutical Co., Ltd. 'Astellas' expresses the idea of 'aspired stars' and 'advanced stars' based on the Latin 'stella', Greek 'aster' and English 'stellar', which all refer to 'stars'. 'Astellas' also sounds like the Japanese phrase 'a-su wo te-ra-su' which means 'to shine on tomorrow' (1).

In this paper, we describe our drug discovery strategy in view of our guiding principles, current research activities and future perspectives, with a particular focus on oncology.

OUR GUIDING PRINCIPLES: PHILOSOPHY, MESSAGE AND VISION

At our very start, we clarified our guiding principles as our philosophy, corporate message and vision. Our philosophy is to contribute toward improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. Our corporate message is that we will be the 'Leading Light for Life' to deliver world-class state-of-the-art pharmaceuticals that promise people from around the world a healthier life (2). For patients and their families and for ourselves, we have further condensed our message into the phrase 'Changing tomorrow' (3).

We went on to decide 'VISION 2015' as our management vision in order to show how Astellas must look in the year 2015. In this vision, we constructed our business model, a 'Global Category Leader' (GCL). A GCL shows high competitiveness by providing value-added products globally in several categories where high unmet medical needs exist and a high degree of expertise is required, and thereby takes a leading position in such 'categories'. At the same time, we established our important R&D categories including urology, immunology including transplantation and infectious diseases, neuroscience, diabetes mellitus complications and metabolic diseases, and oncology (4).

OUR RESEARCH PLATFORM

We strongly believe that we need to reinforce our research capabilities by approaching new technologies and new research areas in a timely manner in order to create innovative drugs (5). In 2009, we started operation of an X-ray beam line at the Photon Factory of the High Energy Accelerator Research Organization, Tsukuba, purposely built for efficient elucidation of protein structures for use by Astellas and academic institutions (6) (Fig. 1). We also created the

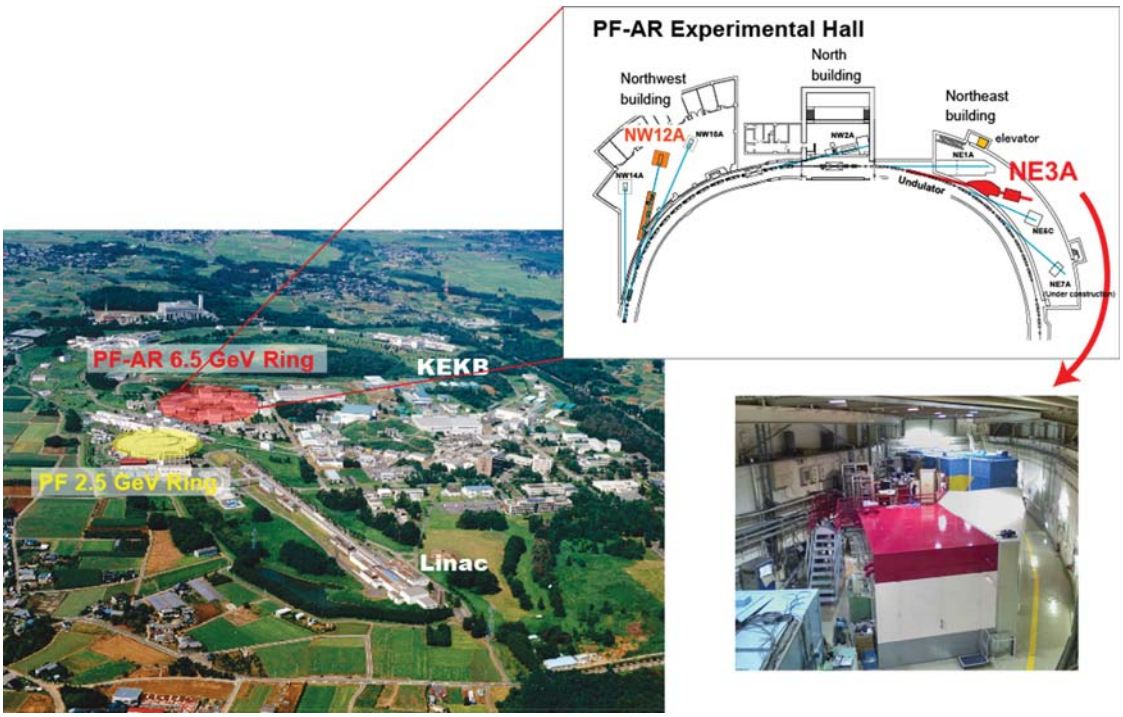

Figure 1. Astellas beamline at the High Energy Accelerator Research Organization (KEK). Left: Aerial view of the KEK campus located 9 km north of the Astellas Tsukuba Research Center. Top right: The plan of the PF-AR experimental hall. Astellas beam line (red color) is placed in the NE3 section. Bottom right: The NE-3A deck for X-ray diffraction experiments colored in Red and Gray (Astellas Corporate Brand Color). AR-NE3A, an X-ray beamline with a beam energy of 6.5 GeV ring, is designed for high-throughput macromolecular crystallography which is applied in a structure-based drug design (SBDD). KEK and Astellas jointly developed a fully automated data collection and processing system inside the NE-3A deck. This system can collect X-ray diffraction data sets from more than 200 samples per day by optimizing the schedules of sample exchange, centering, data collection and data processing.

Figure 2. Astellas' Bioimaging Research Laboratories (BIRL). Upper left: Building of BIRL at Astellas Tsukuba Research Center. Upper right: Automated system for PET tracers developed in-house. Lower left: Positron emission tomography (PET)/computed tomography scanner for small animal studies (Inveon, Siemens). Lower right: PET scanner for large animal studies (SHR-17000, co-developed with Hamamatsu Photonics K.K.).

Bioimaging Research Laboratories at our Tsukuba Research Center in order to enhance our capability in drug discovery and translational sciences (7) (Fig. 2). In addition, we are keen to strengthen our capability in other important technology platforms including proteomics (8) and bioinformatics (9,10).

In view of treatment modality, Astellas had specialized primarily in small molecules, including natural products. Therefore, we in-licensed VelocImmune technology from Regeneron Pharmaceuticals, Inc., in order to efficiently generate fully human monoclonal antibodies (11) and acquired Agensys, Inc., in order to strengthen our drug discovery of antibodies in cancer (12).

OUR RESEARCH APPROACH

Based on our in-house research and introduction from other companies in the past few years, our current oncology R&D programs consist of the following three approaches (13):

(i) Precision medicine
(ii) Mechanisms of action with application across multiple tumor types
(iii) Leveraging Astellas' current capabilities in urology and other therapeutic area

In the past, we took the second and third approaches in our drug discovery. From the second approach, we created YM155, a selective survivin suppressant for multiple tumors (14,15). From the third approach, we created potential treatments for hormone-dependent cancers including YM511, an aromatase inhibitor (16), and YM580, a non-steroidal androgen receptor antagonist (17). Through our experience in these drug discovery programs and subsequent clinical trials, we had fostered the notion that we must deliver novel therapies for improving the health of well-defined populations of patients suffering from a number of cancers.

The establishment of our principles on top of the above-mentioned mindset naturally shifted our research approach in a direction in which we can offer highly effective therapeutic options for precisely defined patient populations based on molecular targeting and precise diagnosis. We call it the precision medicine approach (5,13,18) (Fig. 3).

Precision medicine is becoming a treatment option for certain cancers. In July 2011, the US Food and Drug Administration (FDA) published the draft guidance for *in vitro* companion diagnostic devices (19). In August 2011, the FDA approved Zelboraf™ (vemurafenib), a kinase inhibitor, for the treatment of patients with unresectable or metastatic melanoma whose tumors express a gene mutation called BRAF V600E together with a diagnostic test to detect such mutation in patients' melanoma cells (20). The FDA also approved Xalkori® (crizotinib), a kinase inhibitor, for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who express the abnormal anaplastic lymphoma kinase (ALK) gene together with a diagnostic test to detect such abnormal gene (21)

Figure 3. Astellas' precision medicine approach. Astellas would like to realize 'right drug for right patients' by offering medicines targeting pathogenic molecules (we call it Precision Medicine) combined with companion diagnostic tests fitting to such medicines.

ACTIVITIES IN OUR RESEARCH SITES

Astellas has three sites for oncology drug discovery, namely Astellas Pharma Inc. Tsukuba Research Center at Tsukuba, Ibaraki, Japan, OSI Pharmaceuticals, LLC at Farmingdale, NY, USA, and Agensys, Inc. at Santa Monica, CA, USA. The three research sites pursue precision medicine in a diverse manner based on the research platform and research strategy of each site.

Tsukuba Research Center focuses on the creation of small molecules that inhibit the function of molecules which are essential for the survival or growth of tumor cells as a result of either genetic or epigenetic alterations to the drug target molecules themselves or in the presence of certain genetic or epigenetic contexts. In order to create drugs to well-defined patient populations, Tsukuba Research Center is placing significant emphasis on efforts to identify and validate novel molecular targets based on in-house research and external collaborations. It should be noted that these 'target discovery' efforts also form the basis of translational research for determination of the right patients. Based on this research style, we created ASP3026, an inhibitor of ALK tyrosine kinase (22,23).

OSI joined Astellas in 2010 (24), and it is pursuing small molecule drug discovery with a different style using different precision medicine strategies. During the development of erlotinib, an inhibitor of epidermal growth factor receptor tyrosine kinase, OSI completed much research to better understand which patients optimally benefit from this therapy and which patients would become refractory or resistant (25–27). This research led OSI to focus on drug discovery and translational research related to epithelial–mesenchymal transition (26,28,29) and compensatory activation mechanisms in oncogenic signal transduction (27,30,31) for both publicly known as well as novel oncology targets. In addition, OSI is doing extensive translational research to identity novel biomarkers for patient selection based on the characterization of gene and protein signatures in responsive tumor cells (32).

Agensys joined Astellas in 2007 (12). Agensys specializes in drug discovery of antibodies for cancer therapy, focusing on the creation of novel monoclonal antibodies from two

aspects. First, Agensys invested in identifying novel antigen molecules or epitopes which are selectively expressed on the surface of certain sets of tumor cells. These antigen molecules or epitopes are molecular targets for Agensys' antibodies as well as biomarkers for the selection of the right patients. Agensys is focusing to create antibody–drug conjugates (ADCs, also known as 'immunoconjugates') to these antigens. ADC is an antibody covalently attached to a cytotoxic molecule (such as tubulin inhibitor or DNA minor groove binder) via a linker. Once an ADC binds to the antigen on a tumor cell, it is internalized into the tumor cell and the cytotoxic molecule is released to cause cell death (33). This unique combination of novel molecular targets and ADC technology is expected to provide innovative therapeutic options for precision medicine to the patients for whom no effective drug currently exists. Agensys has put three ADCs into clinical trials so far, with AGS-22M6E (also known as ASG-22ME), an ADC targeting nectin-4, as the latest example (34). Secondly, Agensys is using its panel of patient-derived xenografts (PDX) to validate antibody targets in cancers and develop functional antibodies. The panel of over 60 PDX, representing 14 different indications, provides unique preclinical models and allows preclinical evaluation of targets that are required for tumor growth and survival in a particular microenvironment that may not be found or required for growth of xenografts of conventional cell lines. The anti-prostate stem cell antigen antibody AGS-1C4D4 completing a Phase II study in pancreatic cancer is the most advanced example of this approach (35,36).

The chemical compounds and antibodies created by our three research sites, together with in-licensed compounds, form our oncology development pipeline as shown in Table 1.

Table 1. Astellas' oncology development pipeline

Code no., generic name	Classification	Therapeutic target	Phase	Origin	Remarks
ASP3550, degarelix	GnRH receptor antagonist	Prostate cancer	Filed	Ferring Pharmaceuticals	
MDV3100	Androgen antagonist	Prostate cancer	III	Medivation	
Erlotinib (Tarceva)	HER1/EGFR tyrosine kinase inhibitor	Non-small cell lung cancer (first line for patients with EGFR mutation, adjuvant), hepatocellular carcinoma	III	In-house (OSI)	New indication
OSI-906	IGF-1R/IR tyrosine kinase inhibitor	Adrenocortical carcinoma (ACC), ovarian cancer, non-small cell lung cancer, hepatocellular carcinoma	III (ACC), II (others)	In-house (OSI)	Ref. (30)
ASP4130, tivozanib	Triple VEGF receptors inhibitor	Renal cell carcinoma (RCC), breast cancer, colorectal cancer	III (RCC), II (others)	AVEO Pharmaceuticals, Inc.	
YM155	Survivin suppressant	Breast cancer, non-Hodgkin's lymphoma	II	In-house (Tsukuba)	Refs (14,15)
AC220	FLT3 kinase inhibitor	Acute myeloid leukemia	II	Ambit Biosciences Corporation	
AGS-1C4D4	Antibody (prostate stem cell antigen)	Pancreatic cancer	II	In-house (Agensys)	Refs (34,35)
OSI-027	mTOR kinase inhibitor	Renal cell carcinoma	II	In-house (OSI)	
AGS-16M8F	Antibody-drug conjugate (ADC)	Cancer	I	In-house (Agensys)	
ASG-5ME	ADC	Cancer	I	In-house (Agensys)	Co-development with Seattle Genetics
ASP1707	Small molecule	Prostate cancer, endometriosis	I	In-house (Tsukuba)	
ASP3026	ALK kinase inhibitor	Cancer	I	In-house (Tsukuba)	Refs (21,22)
ASP9521	Small molecule	Prostate cancer	I	In-house (Tsukuba)	
AGS-22M6E	ADC	Cancer	I	In-house (Agensys)	Ref. (33), Co-development with Seattle Genetics

GnRH, gonadotropin-releasing hormone; HER1, human epidermal growth factor receptor 1; EGFR, epidermal growth factor receptor; IGF-1R, insulin-like growth factor receptor 1; IR, insulin receptor; VEGF, vascular endothelial growth factor; FLT3, fetal liver tyrosine kinase 3.
This table is based on the status of November 2011. Astellas is not developing YM511 or YM580. Astellas has out-licensed FK228 to Gloucester Pharmaceuticals Inc. (currently Celgene Corporation) and YM753 to Oncolys BioPharma Inc.

The three research sites have multiple collaborations that span sites on the basis of research programs as well as platform technologies. The research activities at the sites are coordinated through a team consisting of research leaders, clinical leaders, including medical oncologists, and strategy leaders. This team reviews the research activities of each site and offers ideas for improvement of research programs at each site and to facilitate further collaboration.

In concluding this chapter, we would like to describe how we tackle rapidly progressing fields, taking epigenetics as an example. When molecules involved in epigenetic modification of histone emerged as therapeutic targets, both of our parent companies utilized their natural product technology platform to the discover histone deacetylase inhibitors, namely FK228 and YM753 (37). Since then, a number of epigenetic modification mechanisms have been identified as potential therapeutic targets and biomarkers (38), and we now see this progress as an opportunity for novel drug discovery based on our current mindset and technology platforms.

FUTURE PERSPECTIVES

We have described our research activities with emphasis on what we are doing in our research sites. However, our research activities are already based on a number of external collaborations (39), and we seek further opportunity of such collaborations in order to create and deliver novel treatments to cancer patients. We understand that such opportunity is not only in the accomplishments of basic science, but also in the findings and insights derived from clinical practice. While we understand that the feedback of clinical findings to drug discovery in a timely and appropriate manner is a big challenge, it is our hope that we can take this challenge with the readers of this paper.

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Figure 1 was kindly provided by the High Energy Accelerator Research Organization (KEK). We thank many colleagues in Astellas for their support in preparing the manuscript. This paper is dedicated to the late Dr Teruhisa Noguchi, the pioneer of biotechnology and genomics-based drug discovery in Japan who led drug discovery at the former Yamanouchi Pharmaceutical Inc., one of the parent companies of Astellas, as an Executive Vice President.

Conflict of interest statement

Yutaka Yanagita, PhD, is an employee of Astellas Pharma Inc. Toichi Takenaka, DVM, PhD, is a Senior Scientific Advisor and a former Chairman of the Board of Astellas Pharma Inc.

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