

Editorial

US-Japan collaboration: Collaboration across international boundary

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The United States and Japan through their respecting funding agencies, the National Cancer Institute (NCI) and the Japan Agency for Medical Research and Development (AMED; www.amed.go.jp) have been conducting meetings each year to enhance collaboration across the Pacific since 2012. The NCI's Early Detection Research Network-(www.edrn.nci.nih.gov) and AMED-funded investigators and their program leaders have been jointly developing the program agenda to share, exchange, and collaborate on specific research topics related to the early detection of cancer. The most recent workshop was held in Tokyo in 2020 at the prestigious campus of the University of Tokyo (Fig. 1). The meeting was attended by the US and Japanese grantees along with participants from across Japan. The highlights of this meeting included the early-stage investigators from both countries who presented their research and orally and in posters for in-depth discussions.

A primary cause of poor survivability is that many cancers are detected late, often after metastasizing to distant sites. Once cancer has spread, it is more difficult to eradicate it. Successful prevention depends on the accurate evaluation of risk for many cancers, and successful treatment depends on early detection. For example, the five-year survival for colorectal cancer is more than 91% if it is detected while still localized, 66% if detected with lymph node involvement, and only 9% if it has metastasized to distant sites. Consequently, many oncologists and cancer biologists are working to develop methods to detect cancers at their early stages of development. Over 7000 research papers are published each year on potential early detection biomarkers, yet the FDA approves only approximately one marker every

other year. The reason for such a wide gap between the development of potential biomarkers and the conversion of the beneficial ones into approval is the lack of clinical validation toward a specific condition or indication.

Early detection of cancer faces challenges in finding the early indicators of disease because it is like finding the needle in the haystack. At an early stage of cancer, there are fewer abnormal cells among millions of normal cells. The research on biomarkers has faced similar challenges where various technologies are used to discover biomarkers, but the developed biomarkers cannot provide the required sensitivity and specificity for early-stage disease. New molecular technologies, such as Next Generation Sequencing (NGS), proteomics, genomics, and metabolomics, are paving the path for more sensitive detection that is promising, but also generating many false positives contributing to overdiagnosis and unnecessary invasive diagnostic workups. Leveraging data and findings from US and Japan in handling a vast amount of data using computational tools is valuable for combining clinical information with biological markers to provide robust and accurate detection. This may help address unmet clinical needs, including differentiating lethal cancers from non-lethal disease, reducing overdiagnosis, lowering the number of false-positive and false-negative test results, and developing more accurate tests to detect and assess breast, prostate, ovarian, pancreas, esophageal, lung, and other cancers.

The development of biomarkers requires sizeable investment and infrastructure-related resources and takes several years to bring biomarkers to clinical use. In addition, both private sectors and government institutions face several regulatory hurdles. The purpose of

the special issue of *Cancer Biomarkers* is to discuss and share views on multi-institutional collaboration involving multiple intellectual property issues and regulatory requirements from international researchers' viewpoints. It is hoped that the discussion will lead to an effective, streamlined, collaborative process that is equitable to the interests of investigators across the international boundary. However, the culture of successful collaboration remains elusive because our funding mechanism emphasizes individual achievement and competitive funding success over cross-disciplinary collaboration. As a result, investigators view collaboration as a "funding source" for their research and are hesitant to participate in collaborative research. Now many funding agencies promote and support transdisciplinary, multi-institute collaborative research. This has motivated investigators to realize the fruits of a collaborative environment and are increasingly contributing their resources and expertise to the common goals. For example, research on cancer biomarkers is increasingly becoming a collaborative enterprise that provides cohesive, interactive, and mutually supportive platforms to evolve into a highly translational and inclusive environment.

The US-Japan partnership will strengthen collaborations by creating a vehicle for each country to interact with and co-fund the development of the required infrastructure. Japan will benefit by having the opportunity to leverage its investments in infrastructure by contributing to a greater resource base, having access to new resources, expertise, databases, and reagents that result from each other's infrastructure investments. NCI's established the Early Detection Research Network (EDRN) a *vertically integrated* environment with its mission to *discover* and *validate biomarkers* for both the early detection of cancer and cancer risk assessment. Since its introduction, many have regarded EDRN as a model system for translational research. Japan's AMED-supported biomarker research for early detection and risk assessment shares a common goal with EDRN on reducing the burden of cancer by early detection. There is an urgent need to discover and validate biomarkers for less common cancers and the collaboration between the US and Japan could enhance the discovery process by:

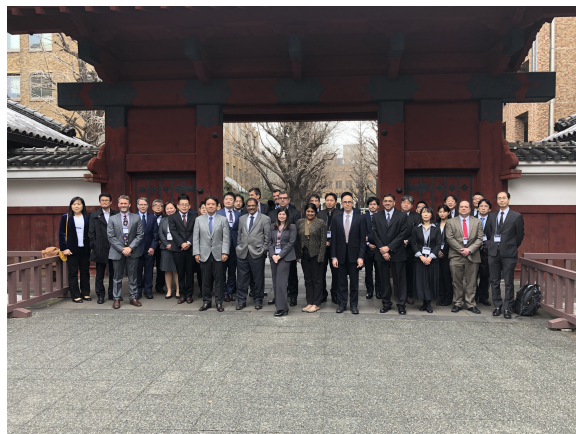


Fig. 1. Attendees of the US-Japan meeting held in Tokyo, 2020.

- Moving biomarkers from discovery (technologically based discovery research) to validation research.
- Enforcing milestones to achieve research goals in a timely fashion.
- Dealing with barriers to technology transfer. The review and approval processes at institutions take place at a "snail's pace" and cause major delays in collaboration, work completion, and realization of scientific achievements.
- Continuing a concentration on breast, colon, prostate, and lung cancers.
- Advancing biomarker discovery on less common tumors, such as stomach, nasopharyngeal, and head and neck cancers. A major infusion of expertise in leadership, validation, and discovery is needed in this area.

In this special issue of the journal, investigators from the US and Japan have discussed various approaches from capillary micro-sampling for single-cell metabolomics, to radiomics for measuring doubling time to risk stratification based on blood-based biomarkers including proteomics and circulating miRNA. In the spirit of collaboration between two countries, it is hoped that such sharing of data and knowledge will continue to help tackle the complex issues surrounding biomarkers for early detection. Finally, the editor would like to thank Japan's AMED for their generous hospitality and support for travel to Japan by the US investigators.