In commemoration of the 2018 Mataro Nagayo Prize: A road to early diagnosis and monitoring of asbestos-related mesothelioma

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1 | INTRODUCTION

Mesothelioma is a highly aggressive tumor. It is estimated that as many as 43,000 individuals worldwide die annually from this disease.1 The suggestion that mesothelioma results from occupational exposure to asbestos was first made by Gloyne in Britain in 1935.2 Since that time, research on mesothelioma and its causal agents has progressed. IARC (International Agency for Research on Cancer) evaluated asbestos and pointed out its carcinogenic risk to humans in 1977. Subsequently, Hodgson and Darnton quantitatively presented the risks of mesothelioma (and lung cancer) in relation to asbestos exposure in 2000.3

Although incidence has primarily been reported from developed countries, these reports are expected to increase significantly in developing countries where asbestos, the major causal agent of mesothelioma, is still broadly produced and used. In Japan alone, more than 10,900 people exposed to asbestos who developed mesothelioma, lung cancer, asbestosis, or diffuse pleural thickening (DPT) have been recognized and compensated through 2015 (Ministry of the Environment).4 Among these patients, the majority had experience working in factories producing asbestos-related goods.

Because the latency period of mesothelioma is as long as 20-40 years after initial exposure to asbestos, and the cancer initially progresses mainly along the surfaces of pleura or peritoneum without forming masses. As symptoms do not develop until late stages, it has been challenging to diagnose this disease in its early stages and to carry out complete surgical removal. In responding to Japan's asbestos crisis in the mid-2000s, we have developed and improved ERC/MSLN-based serum and radiological markers and pioneered the use of an N-ERC ELISA kit for screening populations at risk for asbestos exposure. In the present article, we review our research toward early diagnosis of asbestos-related mesothelioma before symptoms develop and share our clinical experience of screening, diagnosing and monitoring of this disease. This paper is dedicated to the author (Dr Okio Hino) to commemorate the honor bestowed upon him as the recipient of the Mataro Nagayo Prize in 2018.

KEYWORDS
asbestos, early diagnosis, ERC, mesothelioma, occupational disease
without forming masses, it has been challenging to diagnose this disease in its early stages and to carry out complete surgical removal. Median survival time after diagnosis is 12 months.\(^5\)

In this paper, we present our research on the ERC gene, the ERC-based serum biomarker (N-terminal ERC ELISA system) development, its clinical application in the process of screening and early diagnosis of mesothelioma in humans, and our research regarding pinpointing the location of mesothelioma tumors and treating the cancer by intratumoral injection of an anti-C-terminal ERC mAb in an animal model. Figure 1 shows our methodology considering early diagnosis of mesothelioma from a high-risk population with exposure to asbestos and leading to effective treatment in the future.

### 2 | RESEARCH HISTORY AND RESULTS

#### 2.1 | Brief history of research on the ERC/MSLN gene and its products

The ERC gene, originally discovered as the Erc (expressed in renal carcinoma) gene in the study of the Eker (Tsc2 mutant) rat model,\(^6\) is the name given to its human homolog gene, which was later identified as the MSLN gene.\(^7\) (The Eker rat is a rat model that is predisposed to develop hereditary renal carcinomas as a result of two hit mutations of the tumor suppressor gene, Tsc2.\(^8\)) The Eker rat strain was originally developed by R. Eker, a Norwegian pathologist. Dr Knudson later introduced the Eker rat to the USA for hereditary cancer studies and maintained the mutation by breeding the rats on a normal Long-Evans strain background.\(^9\)

In the study of Eker rat renal carcinogenesis, Hino et al\(^8\) found that the following four genes were highly involved in renal carcinogenesis: the third component of complement (C3) gene, the fos-related antigen 1 (fra-1) gene, the calpactin I heavy-chain (annexin II) gene, and an unknown gene, which was later named the Erc gene.\(^8\)

In 2000, Yamashita et al\(^10\) determined the full sequence of the Erc gene cDNA and its exon-intron structure; also, the Erc locus and the locus of the putative human homologue were mapped in the respective chromosomes by FISH. Results indicated that the rat Erc gene is located in rat chromosomal region 10q12-q21, whereas its human homolog ERC gene is located in chromosomal region 16p13.3. At the nucleotide sequence level, the rat Erc gene showed 67.6% identity with human ERC cDNA.\(^10\) Discovered through mesothelin protein research, the MSLN gene was also found to be located in the same region.\(^7\)

The ERC/MSLN gene encodes several proteins and its primary product is a full-length 71-kDa precursor protein, which is cleaved physiologically by a furin-like protease into a 31-kDa N-terminal fragment (N-ERC) that is secreted into the blood and a 40-kDa C-terminal fragment (C-ERC) that remains membrane-bound. N-ERC, also known as megakaryocyte potentiating factor (MPF), is a soluble protein released into the extracellular space.\(^11\) C-ERC, also known as mesothelin—first recognized by the monoclonal antibody K1 in human mesotheliomas and ovarian cancers—is a glycoprotein tethered to the cell surface by a glycosyl phosphatidyl inositol anchor.

#### 2.2 | Research targeting N-ERC

##### 2.2.1 | Development of a series of N-ERC ELISA systems as diagnostic biomarkers of mesothelioma

ERC-based ELISA development targeted the 31-kDa N-terminal (N-ERC). Shiomi et al\(^13\) used a mouse monoclonal anti-ERC antibody MoAb 7E7 and a rabbit anti-ERC antibody PoAb-282 to develop an ELISA system for detecting N-ERC in sera of mesothelioma patients (Figure 2). Epitope mapping showed that the epitope of MoAb 7E7 was in amino acids 134-139 of N-ERC and that PoAb-282 recognized amino acids 282-295.\(^14\)

Shiomi et al\(^14\) continued searching for other antibody clones to improve ERC-based ELISA sensitivity and established a novel sandwich ELISA system by using MoAb 7E7 and a rabbit anti-ERC antibody PoAb-282 to develop a new ELISA system for detecting N-ERC in sera of mesothelioma patients (Figure 2). Epitope mapping showed that the epitope of MoAb 7E7 was in amino acids 134-139 of N-ERC and that PoAb-282 recognized amino acids 282-295.\(^14\)

In a study of 53 patients referred to Juntendo University Hospital from June 2005 to March 2013, the 7-20 ELISA system showed improved sensitivity and specificity compared with the previous 7-16 ELISA system.
ELISA system. Regarding the epithelioid type in particular, AUC (area under the curve) was 0.91, sensitivity was 0.95, and specificity was 0.76 in plasma. Although the number of patients enrolled was small, the 7-20 ELISA system was clinically proven useful for precise diagnosis of the epithelioid type of pleural mesothelioma.

In addition, Human N-ERC/Mesothelin Assay Kit – IBL was commercialized by Immuno-Biological Laboratories Co. Ltd (IBL, Fujikoshi, Gumma, Japan) in 2013. The Assay Kit has been used as a tool, combined with positron-emission tomography/computed tomography (PET/CT) scans and biopsy, to diagnose mesothelioma at clinical practices in Japan.

### 2.2.2 N-ERC as diagnostic marker:

#### Large-scale screening of construction workers for early diagnosis of asbestos-related mesothelioma by N-ERC ELISA in Japan

A 5-year large-scale screening of Japanese construction workers who were or had been at risk of asbestos exposure was started in February 2007. As of March 2012, approximately 40,000 participants were enrolled in this research study and a total of 179,201 blood samples from 85 research sites across Japan were collected and analyzed for N-ERC levels by 7-16 ELISA. Samples with N-ERC levels above 8 ng/mL were sent to Juntendo Medical School for a second 7-16 ELISA test, along with the HAMA (human antimouse immunoglobulin antibody) test. Approximately 900 subjects (~2000 blood samples) were recommended for examinations, including CT scans, at hospitals. One hundred and ninety subjects followed the advice and had further examinations for diagnosis of mesothelioma and other asbestos-related diseases.

Hirohashi et al. reported that, overall, 62 participants were ultimately identified as the “high-risk” population and referred to have further assessment. “High-risk” was defined as the following: (i) HAMA not detected; (ii) age ≥35 years; and (iii) detection of abnormal values (>8.0 ng/mL) of N-ERC on more than two occasions during the annual assessments.

The study showed that: (i) mean N-ERC level of the high-risk population was similar to that of mesothelioma patients; and (ii) for the high-risk population, annual N-ERC level increased significantly at ~2.0 points annually. During the 5-year study period, two patients in the high-risk population developed mesothelioma, and two other patients developed lung and appendiceal cancer. Others in the high-risk population were encouraged to have annual check-ups.

### 2.2.3 N-ERC Index as a monitoring and prognostic marker for pleural mesothelioma

Between June 2005 and June 2010, 26 inoperable patients with histologically confirmed pleural mesothelioma (21 epithelial type, 4 sarcomatoid type, and 1 biphasic type) were recruited for chemotherapy treatment at Juntendo University Hospital of Japan. The most frequently used regimen was pemetrexed + cisplatin. Overall response rate was 19.2% with five partial responses (PR), 10 patients with stable disease (SD) and 11 patients with progressive disease (PD).

Blood samples were measured for N-ERC levels twice using the sandwich ELISA kit (by IBL): first before giving chemotherapy and the second time after complete recovery from the adverse effects of two courses of chemotherapy. N-ERC Index was defined as log₂ (N-ERC value after two courses of chemotherapy/N-ERC value prior to chemotherapy).

In this study, Mori et al. found that: (i) median N-ERC Index in patients with PR was significantly lower than that in patients with SD/PD; (ii) average survival time in the high-level group (with N-ERC Index above median) was 10.3 months (5.8-14.1 months), much lower than that in the low-level group (with N-ERC Index below median), which was 26.6 months (15.9-37.2 months).

Mori et al. acknowledged that the study had limitations—including only 26 patients with a variety of stages and chemotherapeutic regimens—and reported that the study could not lead to any definitive conclusions; further validation would be required to establish the N-ERC Index as a valid monitoring and prognostic marker for pleural mesothelioma.
2.3 | Research targeting C-ERC

2.3.1 | Development of C-ERC radiological marker for locating mesothelioma tumor

To further improve the accuracy of early diagnosis by imaging-guided biopsy, in 2010 Yoshida et al. developed a radiological marker by using $^{64}$Cu-labeled Fab to monitor in-vivo distribution through PET imaging of human mesothelioma xenografts in a mouse model.

After conducting cell-binding assays, Yoshida et al. found that the binding of $^{64}$Cu-DOTA-Fab to H226 (human mesothelioma cell line) cells (80.3% at $5 \times 10^6$ H226 cells) was greater than that of $^{111}$In-labeled or $^{125}$I-labeled Fabs, and an immunoreactive fraction of $^{64}$Cu-DOTA-Fab was estimated to be 98%.

In the biodistribution study, Yoshida et al. carried out serial PET imaging in a mouse bearing the H226 tumor at 1, 6, and 16 hours after injection of 4 MBq of $^{64}$Cu-DOTA-Fab. The C-ERC-expressing xenografted tumor could be clearly visualized as in Figure 3, which suggests that C-ERC-specific imaging using a positron-emitting radiopharmaceutical $^{64}$Cu-DOTA-Fab could be used to facilitate the diagnosis of patients with early-stage mesothelioma.

2.3.2 | Investigating antitumor activity of 22A31: Anti-C-ERC mAb in vivo

In 2010, in the study of antitumor activity of an anti-C-ERC mAb 22A31—the C-ERC-specific mouse mAb derived from a mesothelioma cell line—Inami et al. found that when conducting intratumoral injection of 22A31 into mice bearing ACC-MESO-4 (derived from human mesothelioma, provided by RIKEN) tumors, it induced antibody-dependent cell mediated cytotoxicity (ADCC) with natural killer (NK) cells. The study showed that 22A31 consistently exerted an antitumor effect in vivo, and the effect was shown to occur in a dose-dependent way.

Although 22A31 did not notably inhibit tumor growth when i.p. injected into ACC-MESO-4 tumor-bearing mice, it did induce ADCC with NK cells through intratumoral injection. The result suggested that 22A31 is a possible therapeutic tool for C-ERC-expressing mesothelioma.

3 | DISCUSSION

Usually diagnosed at late stages, mesothelioma is rapidly progressive and invariably fatal. Chemotherapy has only a modest impact on survival—adding approximately 2-3 months to overall survival and reducing time to progression. Currently, the most effective treatment in practice is removal of the tumor at early stages. Biomarker development, therefore, is critical for high-risk population screening and early diagnosis of asbestos-mesothelioma.

Since the discovery of the ERC/MSLN gene in 1994, we have developed a MoAb 7E7-PoAb 282 ELISA system (2006) to detect N-ERC in sera and plasma. Subsequently, the 7-16 ELISA system and the 7-20 ELISA system were developed in 2008 and 2014, respectively, to improve the sensitivity and specificity of diagnosing mesothelioma. For the epithelioid type of pleural mesothelioma, in
particular, our most advanced 7-20 ELISA system has achieved 95% sensitivity and 76% specificity in plasma.\(^1\)

N-ERC is secreted from normal mesothelial cells and the volume increases along with the progress of mesothelioma. It is a candidate to become a clinically useful biomarker for early diagnosis and screening (Figure 4, area A). By using N-ERC 7-16 ELISA, we conducted a large-scale screening research study from February 2007 to March 2012; two subjects with abnormal N-ERC values did eventually develop mesothelioma, and one subject developed lung cancer and was surgically treated. Notably, the screening project was designed for all participants of Tokyo General Construction Workers Union and the Tokyo Doken National Health Insurance Association. To further improve the overall cost-effectiveness of such studies, criteria including determination of a minimum age, gender, length of exposure to asbestos etc. may need to be added.

In addition, N-ERC has been combined with PET-CT scans and biopsy to diagnose mesothelioma. It has also been clinically used as a monitoring biomarker to measure therapeutic responses and as a prognostic biomarker to predict survival time for advanced mesothelioma patients in Japan (Figure 4, area B). Yet, there remain several problems, as our current N-ERC ELISA systems are more useful for epithelioid type than sarcomatoid and biphasic types; our research on 22A31 (an anti-C-ERC mAb) and \(^{64}\)Cu-DOTA-Fab for treatment of mesothelioma are still at the level of the animal model.

Among non-invasive biomarkers, mesothelin (also known as SMRP, soluble mesothelin-related peptides), high mobility group box 1 (HMGB1), fibulin-3, and osteopontin (OPN) have been researched worldwide.\(^2\) As described earlier in “Brief history of research on the ERC/MSLN gene and its products,” mesothelin is a membrane-bound 70-kDa precursor protein that can be cleaved to yield a 31-kDa peptide known as megakaryocyte-potentiating factor (MPF or N-ERC/mesothelin) and a membrane-bound, 40-kDa protein (C-ERC/mesothelin). HMGB1 is a member of the high mobility group-box superfamily, playing an important role in a variety of biological processes such as transcription, DNA repair, proliferation, and inflammation.\(^2\) Fibulin-3 is an extracellular glycoprotein generally expressed in most tissues in the early embryonic stage, whereas OPN is encoded by the SPP1 gene (secreted phosphoprotein 1), which mediates cell-matrix interaction and cell signaling through interaction with integrin and CD44 receptors.\(^2\) Table 1 shows representative studies of these biomarkers and their results.

Mesothelin is one of the most extensively studied mesothelioma biomarkers and is the only blood-based biomarker approved by FDA in mesothelioma diagnosis. However, studies showed that although it is characterized by good specificity, it has low sensitivity, especially for non-epithelioid mesothelioma. Serum HMGB1 can be considered a prognostic marker, rather than a diagnostic marker, for MPM. Regarding fibulin-3, studies do not show consistent results. However, some studies are investigating the hypothesis that fibulin-3 may be responsible for the malignant transformation of mesothelial cells after exposure to asbestos and/or asbestos-like fibers.\(^2\) Concerning OPN, the results obtained by Pass et al (see Table 1) were not confirmed by other
research groups. Whether OPN is a biomarker of mesothelioma is still under discussion.

Other recent studies toward early diagnosis of mesothelioma include research regarding the antibodies YP218 and YP223 and histopathological marker development based on SKM9-2. In 2015, Zhang et al.26 reported the discovery of a new group of high-affinity mAb recognizing non-overlapping epitopes on mesothelin. One pair of antibodies (YP218 and YP223) was reported to be suitable to detect soluble mesothelin in a sandwich ELISA with high sensitivity, bringing the bodies (YP218 and YP223) was reported to be suitable to detect soluble mesothelin lower than that of MESOMARK (Fujirebio Diagnostics Inc., Malvern, PA, USA).26 As for histopathological marker development, it was reported in 2017 that SKM9-2, a mAb against sialylated HEG1, was effective in detecting sarcomatoid (64%) and desmoplastic (50%) pleural mesothelioma (2017).27

Although mesothelioma is considered to be primarily caused by exposure to asbestos, the mechanism of mesothelioma is not fully elucidated. Our ERC/MSLN-based research has been conducted toward early diagnosis and treatment of mesothelioma. To further improve the sensitivity of our biomarkers and to develop treatment methods, differentiation in terms of expressed glycoproteins between normal mesothelial cells and mesothelioma cells is currently being studied in our laboratory.

With a long latency, asbestos-related mesothelioma is expected to peak in the next decade across developed countries, and the world will see a significant increase in the incidence of mesothelioma in developing countries in the coming decades. Japan has experienced a significant increase in mesothelioma incidence from the mid-2000s. In response to this growing crisis, the author (Okio Hino) was instrumental in opening an outpatient clinic for asbestos/mesothelioma; he also identified ERC as a novel serum marker for mesothelioma. We have developed our Juntendo (Tokyo) Model—preliminary N-ERC serum biomarker tests for a population with exposure to asbestos and secondary tests by biomarkers combined with PET-CT and biopsy for subjects of abnormal N-ERC value (cut-off value of 8 ng/mL)—to achieve early diagnosis and early treatment of asbestos-related mesothelioma. By implementing our Juntendo (Tokyo) Model across Japan, more patients could be found at early stages before symptoms develop, therefore early treatment would be possible.

As the winner of the Mataro Nagayo Prize in 2018, the author (Okio Hino) appreciates the opportunity to contribute to the global society by sharing our learned knowledge with other countries experiencing increased incidence of asbestos-related mesothelioma.

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**TABLE 1** Comparison of biomarkers for early diagnosis of mesothelioma (representative studies and corresponding results)

| Biomarker    | Representative study                                                                 | Corresponding results                                                                                                                                 |
|--------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mesothelin (SMRP) | Hollevoet et al (2010) studied a total of 507 individuals (101 healthy control subjects, 89 healthy asbestos-exposed subjects, 123 patients with benign asbestos-related disease, 46 with benign respiratory disease, 63 with lupus cancer and 85 with MPM)26 | The study showed a high specificity of 95%, but a sensitivity of 64% (cut-off = 2.00 nmol/L)28                                                                 |
| HMGB1        | Tabata et al (2013) studied 106 subjects with a history of asbestos exposure. Of them, 61 had confirmed MPM, 26 had pleural plaques and/or asbestososis, and 19 had no asbestos-related lesions despite being exposed to asbestos29 | At the optimal cut-off value of 9.0 ng/mL, diagnostic sensitivity was 34.4% and specificity was 100%                                                   |
| Fibulin-3    | Pass et al (2012) studied a sample of 92 mesothelioma patients and 290 controls (formerly exposed to asbestos, subjects with benign and malignant pleural effusions not from mesothelioma, other tumors, and unexposed healthy subjects)31 | Pass et al showed a high diagnostic accuracy of fibulin-3 (AUC = 0.99) with sensitivity of 97% and specificity of 95%30                  |
|             | Creaney et al (2015) studied a cohort of 153 patients (82 of whom had mesothelioma)21 | Creaney et al reported a sensitivity of 22% and a specificity of 95% for plasma fibulin-3 (cut-off: 52 ng/mL, AUC = 0.671)31                  |
| Osteopontin (OPN) | Pass et al (2005) compared 69 patients with benign asbestos-related lung disease to 45 subjects without exposure to asbestos and 76 pleural mesothelioma surgically treated patients32 | An analysis of serum OPN levels comparing the ROC curve in the group exposed to asbestos with that of the group with mesothelioma had a sensitivity of 77.6% and a specificity of 85.5% at a cut-off value of 48.3 ng OPN/mL32 |

AUC, area under curve; HMGB1, high mobility group box 1; IQR, interquartile range; MPM, malignant pleural mesothelioma; ROC, receiver-operating characteristic.
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CONFLICTS OF INTEREST

Authors declare no conflicts of interest for this article.

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