SUMMARY

Title: New era of *in vivo* molecular imaging and targeted medical care: Antibody-based theranostics

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Abstract: "Theranostics" represents a ground-breaking concept of medical modality featuring a hybrid of therapeutic and diagnostic systems, and has currently undertaken a progressive development into the pre-clinical stage.

We have recently fabricated a 25 kDa single chain variable fragment (scFv), which is essentially a humanized and shortened variant of IgG to establish clinically-applicable theranostics in oncology and cardiovascular medicine, respectively. One of the target molecules of our scFv is mesothelin, a 40 kDa-tumor differentiation-related cell surface glycoprotein antigen, that is frequently expressed by malignant tumors. While another target molecule is an oxidized low-density lipoprotein-β2-glycoprotein I (oxLDL/β2GPI) complex, which is originally known as an autoantigen related to thrombosis and atherosclerosis.

Our theranostics system which comprises of novel and biodegradable ^{89}Zr-radiolabeled nanoparticles conjugated with specific scFv aims to successfully deliver therapeutically effective and apoptosis-inducing small interfering RNA (siRNA) into targeted cells and to offer simultaneous visualization of targets via PET imaging system. The combination of photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) and photo-controlled intracellular siRNA delivery system further offers a promising theranostic-based system, ideally via its targeted apoptosis-inducing feature. Additionally, we are also interested in establishing a simple *in vivo* imaging system for human diagnosis with our fabricated scFv.

Such novel system ultimately gratifies a significant development in the clinical application, whilst offering impactful benefits created from academia-derived basic sciences to clinically applicable interventions, in joint-efforts to define a spot-on disease-risk stratification and a therapeutic regimen.

Key Words: Theranostics (Therapeutic and diagnostic technology), Antibody variant (Single chain variable fragment, scFv), Drug delivery system (DDS, Nano-particle medical device), Photodynamic therapy (PDT), PET imaging

Applications / Indications:

1. scFv-PET imaging
2. Theranostics for cancer and cardiovascular diseases

Advantages:

The humanized and shortened IgG variant, scFv, has rapid *in vivo* clearance due to its low antigenicity. As such, it is a clinically-applicable theranostics as a means of diagnostic (*in vivo* imaging) and therapeutic interventions for cancer or cardiovascular diseases.
The production of scFv by CHO cells is cost-efficient, stable and reproducible.

A patent related to the scFv materials, inclusive of its full amino acid and nucleotide sequence, has been filed.

Market Overview:

The exact market size cannot be estimated forthwith; however, it is expected to be large. When the scFv is applied just for cancer (or cardiovascular diseases) diagnosis, its market size is expected to be relatively similar to that of the FDG-PET imaging in the oncology field. Once the development of the said theranostics technology is fully complete, its market ought to expand extensively.

Stage of Development:

We have completed the fabrication of scFv antibody and the evaluation of its applicability via PET imaging (*in vivo* animal studies). Presently, we endeavor to form partnerships with relevant companies to advance our study at the preclinical stage.
Theranostics technologies involving other technical elements, i.e., drug delivery system (DDS) and RNAi, are currently under development at the basic science stage.

Patent Information & Publication:

<u>Oncology:</u>

[Patent]

<u>Matsuura E</u>, Kobayashi K, Takenaka F; DNA, Polypeptides, Anti-mesothelin antibody, anti-tumor imaging agent and complexes thereof.
JP Application No. 2017-210508

[Publication]

In preparation

Cardiovascular Medicine:

[Patent]

Matsuura E, Kojima K; Antibody against oxidized LDL/β2GPI complex and use of the same.
PCT/JP2009/054473, JP5616592, US8575314B2, EP23198693, CN102124030B

[Publication]

Sasaki T, Kobayashi K, Kita S, Kojima K, Hirano H, Shen L, Takenaka, F, Kumon H, Matsuura E. *In vivo* distribution of single chain variable fragment (scFv) against atherothrombotic oxidized LDL/β2-glycoprotein I complexes into atherosclerotic plaques of WHHL rabbits: Implication for clinical PET imaging.
Autoimmun Rev. 16:159-167, 2017.

Business Opportunity:

1. Collaborative opportunity for development of scFv-PET for cancer and/or cardiovascular diseases diagnosis: once a partner is identified, preclinical POC study will be initiated.
2. Collaborative opportunity for development of theranostics prototype using not only the fabricated scFv but also DDS system and RNAi technologies.

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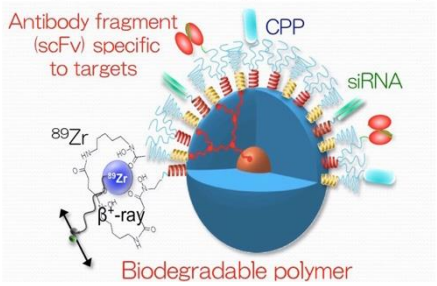
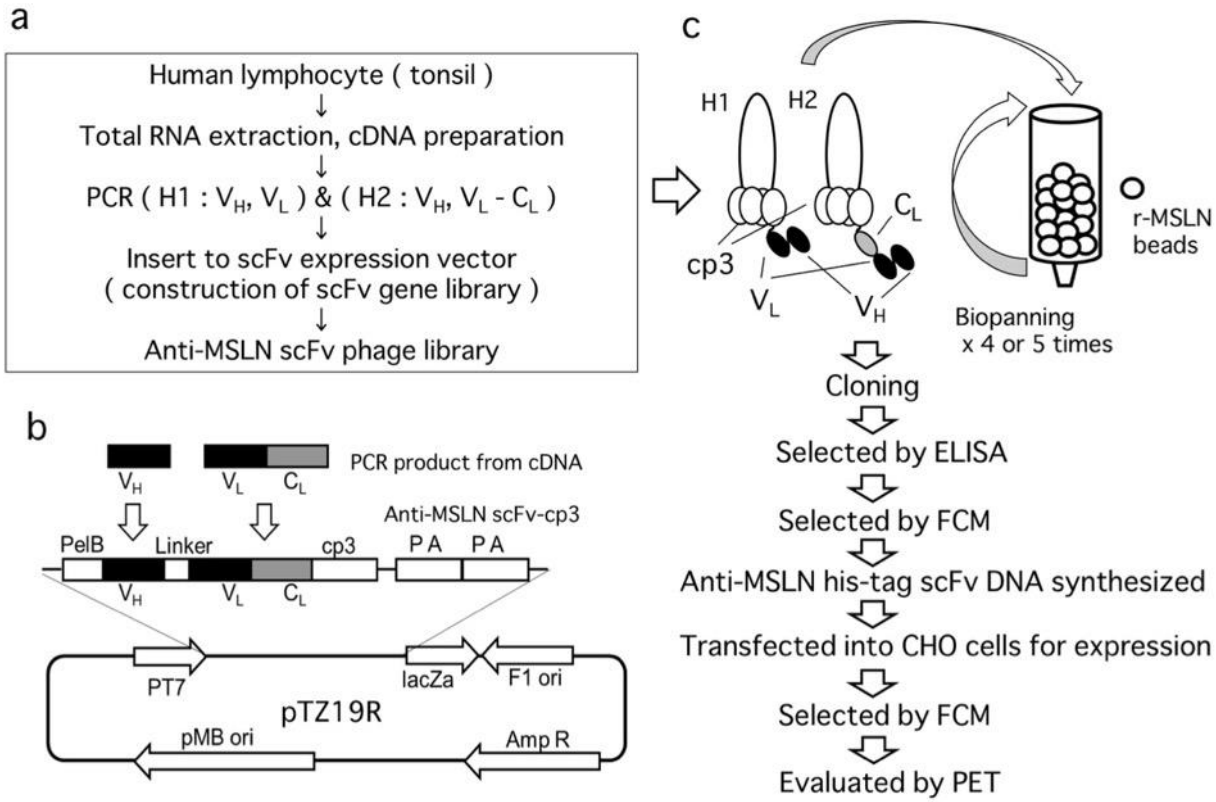
Appendix

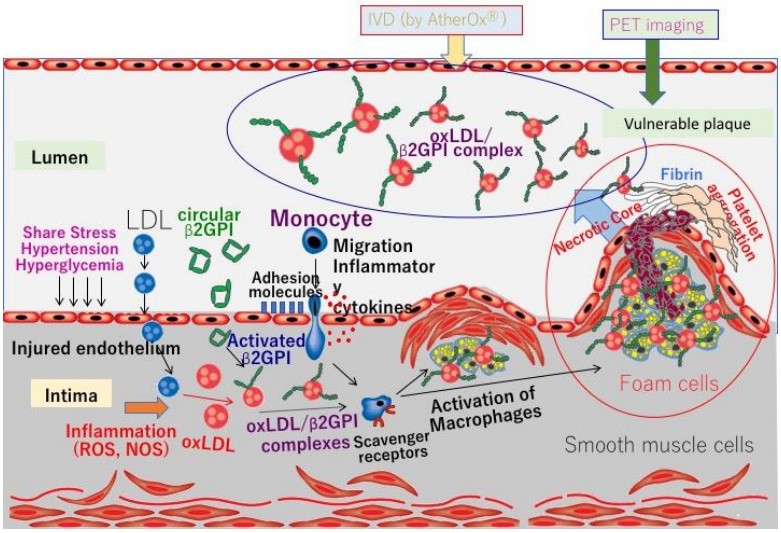
Concept of “Theranostics”
(A novel technology offering simultaneous diagnosis and therapy interventions)



Schematic diagrams of the preparation and structure of the anti-MSLN scFv



Paradigm of vulnerable plaque diagnosis



Summary of PET imaging of atherosclerotic plaques in the WHHL rabbits