腸管免疫を利用した新規経口がんワクチンの開発

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プロジェクト概要

近年、ビフィズス菌と腸管免疫の相互作用について多くの知見が集積されている。ビフィズス菌をマウスに経口投与した場合、菌体が1時間後にパイエル板で、24時間以内に樹状細胞（DC）と共に腸間膜リンパ節（MLN）で検出される。我々は、腸管免疫系への抗原デリバリーシステムとしてビフィズス菌を用いた経口ワクチンプラットフォームを世界で初めて開発し、腫瘍関連抗原として評価の高いWT1タンパクを表層発現するWT1経口癌ワクチンを作製した（Cancer Immunol Immunother 2017：66,p787-）。WT1タンパクを表層発現したビフィズス菌が（図1）、腸管上皮のM細胞を通じてパイエル板のDCに取り込まれ、WT1タンパクを細胞内に取り込んだDCがMLN内で各種リンパ球に作用し、強力なWT1特異的細胞性免疫を誘導する（図2）。現在までに、WT1発現ビフィズス菌の抗腫瘍効果と抗PD-1抗体との併用効果をマウス前立腺癌TRAMP-C2および膀胱癌MBT-2モデルで確認している（Molecular Therapy -Oncolytics 2021: 22, p593-, 図3. B. longum 2021:WT1非発現ビフィズス菌（コントロール）、B. longum 420:マウスWT1発現ビフィズス菌、B440：ヒトWT1発現ビフィズス菌死菌凍結乾燥粉末（原薬））。

注：ヒトWTI発現ビフィズス菌を製剤化した原薬B440（死菌凍結乾燥粉末）の薬効も動物実験で確認し、2023年1月より尿路上皮癌を対象とした医師主導治験を開始した。

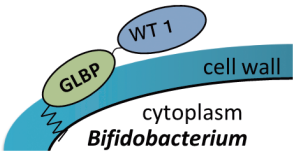

図１、WT1表層発現ビフィズス菌

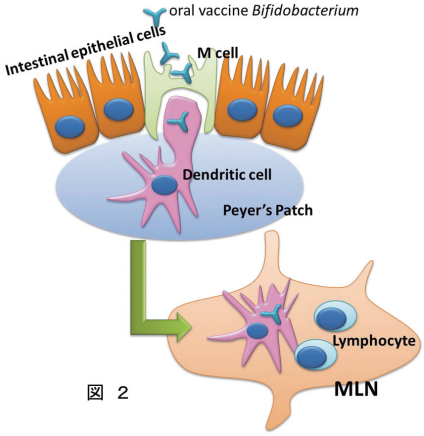

図 2

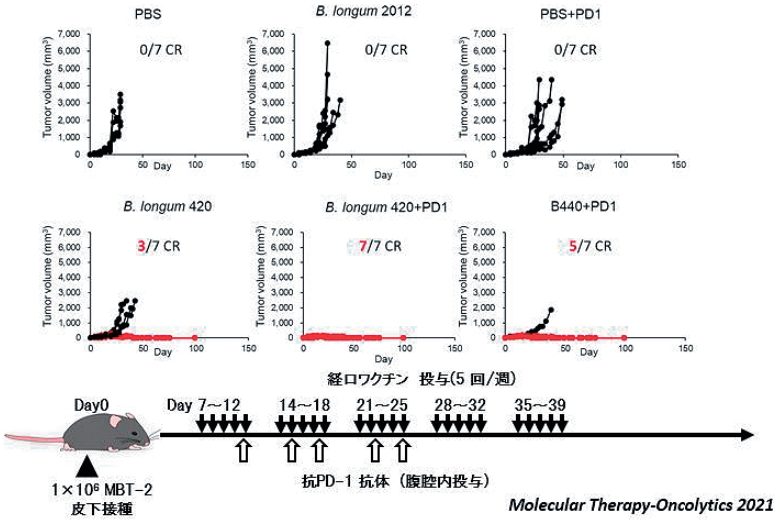

図３、マウス膀胱癌MBT-2モデルの腫瘍増殖曲線

【開発のロードマップ】

現在、非臨床POCおよびCMC開発を全て確立し、2023年1月に医師主導治験を開始した。 第2相の医師主導治験の終了後、大手製薬企業へのLicensing導出を実施し、その後は企業主導で治験を進めていき、2028年までの薬事承認を目指す。

【知財権の状況】

Ⅰ．基盤技術特許「ビフィズス菌表層提示融合タンパク質発現遺伝子」神戸大学、森下仁丹㈱、
日本特許5561681号、米国8,354,113、（出願　2010年9月17日）

Ⅱ．開発物質特許「経口腫瘍ワクチン」神戸大学、大阪大学、日本特許6770269号、
米国10,695,385（出願　2016年5月30日）

Ⅲ．用途特許「経口腫瘍ワクチンと免疫抑制阻害剤との併用によるがん治療」神戸大学、大阪大学、
日本特許6810877号（出願　2017年12月8日）

【研究者らの目指すところ】

本経口癌ワクチンは、WT1タンパクほぼ全長をDCに処理させ最適なWT1エピトープを選択提示するので、強力なCTL誘導が可能で、ペプチドワクチンに比較して抗腫瘍効果の劇的な向上を確認している。大量生産・精製も簡便・低コストで経口剤という利便性も有する。WTIを発現する、尿路上皮癌、肺癌、脳腫瘍、前立腺癌等に低副作用で長期薬効が期待でき、抗PD-1抗体等の免疫チェックポイント阻害剤とも併用できる汎用性の高い世界初の経口癌免疫療法（IO）剤の開発を目指す。

Development of new oral cancer vaccine with the use of intestinal tract immunity

Principal Investigator

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Professor Toshiro SHIRAKAWA

Project Outline

In recent years abundant knowledge on the interaction between Bifidobacteria and gut immunity has been accumulated. When Bifidobactera are orally administered to mice, bacterial cells will be detected on a Peyer's patch an hour later, and within 24 hours they will be detected at mesenteric lymph node (MLN) with dendritic cells (DCs).

We have developed the world's first oral vaccine platform using *Bifidobacterium* as an antigen delivery system to the gut immune system. We have also developed WT1 oral cancer vaccine that expresses WT1 protein, which is highly ranked as a tumor-associated antigen *(Cancer Immunol Immunother2017: 66, p787-)*. The *Bifidobacterium* displaying WT1 protein (Fig.1) is incorporated into DC in the Peyer's patch through M cells of the intestinal epithelial cells, and then DC containing WT1 protein acts on lymphocytes in MLN, thus inducing powerful WT1 specific cellular immunity (Fig. 2).

Up until now, we have verified antitumor effect of *Bifidobacterium* displaying murine WT1 (B.longum420) as well as the synergistic effect of combination with anti-PD-1 antibody in the mouse prostate cancer tumor model (Molecular Therapy-Oncolytics 2021: 22, p593-, Fig.3. B. longum 2021:WT1 non-expressing Bifidobacterium (Mock control), B. longum 420: mouse WT1-expressing Bifidobacterium, B440: human WT1 expressing Bifidobacterium (Drug Substance)).

Note : B.longum 2012 is *Bifidobacterium* not expressing WT1. Efficacy of B440 formulated from *Bifidobacterium* displaying human WT1 (freeze-dried killed bacteria powder) has already been verified by an animal testing and a P1 clinical trial for advanced urothelial cancer has been started from January, 2023.

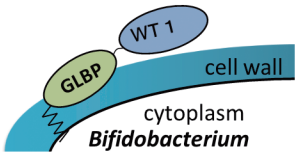

Figure 1:
Bifidobacterium displaying WT1 protein

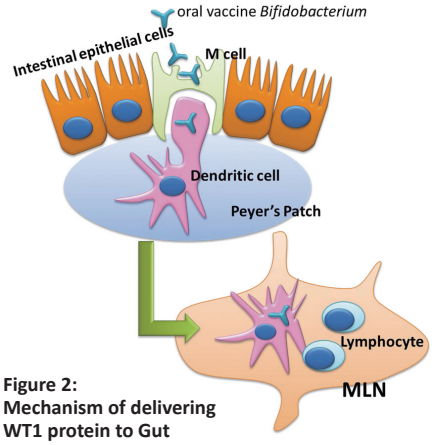

Figure 2:
Mechanism of delivering WT1 protein to Gut immune system

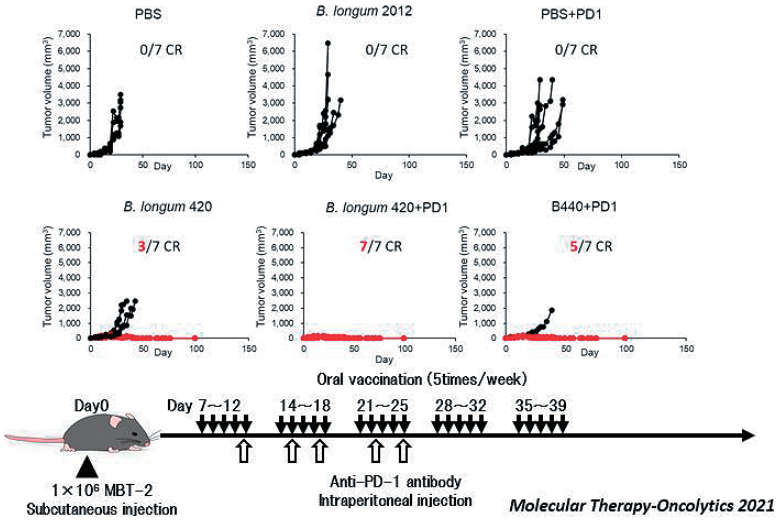

Fig.3 Tumor growth curves in Urinary bladder cancer MBT-2 model with mice

[Roadmap of the development]

Up to now, we established all non-clinical POC and CMC, and then started an investigator initiated clinical trial from Jan, 2023. After a Phase II clinical trial is completed, we will seek for an alliance with a major pharmaceutical companies will derive licensing, and then sponsor initiated clinical trial will be pursued to obtain a pharmaceutical approval by 2028.

[Current status of intellectual property rights]

I. Core technology patent "Bifidobacteriumdisplaying protein on cell surface gene" Kobe university, Morishita Jintan Co., Ltd. Japanese Patent No.5561681, the US No.8,354,113.
II. Developed substance patent. "Oral cancer vaccine" Kobe university, Osaka university, JP6770269,US10695385
III. Use patent Cancer therapy by concomitant use of oral tumor vaccine with immunosuppressant inhibitor" Kobe university, Osaka university, JP6810877

[Researchers' goal]

This oral cancer vaccine allows DCs to process almost whole length of WT1 protein and select/present the optimal WT1 epitope. Therefore, it is capable of inducing CTL powerfully with various types of HLA. We have verified that it has dramatically improved anti-cancer effect as compared with conventional peptide vaccine. It suits for mass production and purification is possible at low cost, beside it has a great convenience as a oral preparation. We can expect that it has long-lasting efficacy to WT1 expressing cancers such as prostatic cancer, Gastrointestinal cancer and lung cancer, and its has only mild side effects. Our goal is to develop the world's first Immunotherapy by oral that allows a combined use with immune check point inhibitors such as anti-PD-1 antibody.