A Novel Brain-Permeant Chemotherapeutic Agent for the Treatment of Brain Metastasis in Triple-Negative Breast Cancer

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Development of metastases to central nervous system (CNS) is an increasing clinical issue following the diagnosis of advanced breast cancer. The propensity to metastasize to CNS varies by breast cancer subtype. Of the four breast cancer subtypes, triple-negative breast cancers (TNBC) have the highest rates of both parenchymal brain metastasis and leptomeningeal metastasis (LM). LM is rapidly fatal due to poor detection and limited therapeutic options. Therapy of TNBC brain metastasis and LM is challenged by multifocal brain metastasis and diffuse spread of LM, and must balance brain penetration, tumor cytotoxicity, and the avoidance of neurotoxicity. Thus, there is an urgent need for novel therapeutic options in TNBCs CNS metastasis. QBS10072S is a novel chemotherapeutic that leverages TNBC-specific defects in DNA repair and LAT1 (L-amino acid transporter type 1)-dependent transport into the brain. In our study, activity of QBS10072S was investigated in vitro with various cell lines including the human TNBC cell line MDA-MB-231 and its brain-tropic derivative MDA-MB-231-BR3. QBS10072S was preferentially toxic to TNBC cells. The efficacy of QBS10072S against brain metastasis and LM was tested using a model of brain metastasis based on the internal carotid injection of luciferase-expressing tumor cells into NuNu mice. The compound was well tolerated, delayed tumor growth and reduced leptomeningeal dissemination, resulting in significant extension of survival. Given that current treatments for LM are palliative with only few studies reporting a survival benefit, QBS10072S is planned to be investigated in clinical trials as a therapeutic for TNBC LM.

Significance: TNBC brain metastasis often involves dissemination into leptomeninges. Treatment options for TNBC leptomeningeal metastasis are limited and are mostly palliative. Our study demonstrates significant efficacy of the brain-penetrating agent QBS10072S against TNBC brain metastasis and leptomeningeal spread.

Introduction

Central nervous system (CNS) metastasis is a major clinical challenge in the management of patients with metastatic breast cancer. CNS spread is a poor prognostic sign, leading to drastic reductions in survival and frequent deterioration of patients’ physical function, quality of life, independence, personality and self-awareness. Parenchymal brain metastases represent the majority of CNS metastases, and have been more extensively studied compared with leptomeningeal metastases (LM; ref. 1). LM, characterized by tumor cell spread in brain leptomeninges, settling on and invading into the brain, spinal cord, and cranial and spinal nerves, is associated with considerably worse prognosis than parenchymal brain metastasis (2, 3). LM can present with a range of symptoms, and currently available diagnostic means are insensitive (4). Among breast cancer subtypes, triple-negative breast cancers (TNBC) have the highest propensity for brain metastasis and LM (4–6). The prognosis of patients with TNBC with symptomatic, untreated LM is dismal, with a median overall survival of approximately 4 weeks (2, 3). Unfortunately, most standard treatments, including radiotherapy, intrathecal chemotherapy, and surgery have limited efficacy, are mostly palliative, and associated with considerable morbidity (7).
Chemotherapy is the only modality besides cranio-spinal radiation that allows simultaneous treatment of the entire neuraxis (7). Systemic chemotherapy may address the treatment of multifocal brain metastasis, leptomeningeal spread, and active disease outside the CNS. However, the development of successful systemic treatments for brain metastasis has been hampered by low permeability of drugs across the blood–brain barrier (BBB). The tight junctions between the astrocytes of the BBB protect the brain from accidental toxins, but in doing so also shield the brain from intentional toxins, like chemotherapy (8).

The large amino transporter type 1 (LAT1, also known as SLC7A5) is expressed on both the luminal and abluminal membranes of endothelial cells of the BBB, and is responsible for the delivery of large amino acids (e.g., leucine, phenylalanine) as well as amino acid-based drugs (e.g., L-DOPA, gabapentin) to the brain (9). Although LAT1 is expressed at very low levels in normal tissues, including brain parenchyma, its expression is highly upregulated in most tumor tissues, providing the amino acids necessary for the rapid cell proliferation (9). LAT1 is highly expressed in human TNBC, suggesting a targeted therapy providing the amino acids necessary for the rapid cell proliferation (9). LAT1 is highly expressed in human TNBC, suggesting a targeted therapy for this aggressive breast cancer subtype (10). Moreover, LAT1 overexpression is a shared feature of brain metastasis, and overexpression is specific to brain metastasis compared with healthy brain (11).

We have designed an amino acid–based small-molecule nitrogen mustard compound (QBS10072S) that is transported by LAT1 across the BBB and preferentially enters tumor cells. QBS10072S significantly and consistently slowed TNBC growth both in vitro and in vivo. QBS10072S demonstrated therapeutic benefit in a human-in-mouse model of TNBC brain metastasis, reduced LM spread, and thus may represent an effective treatment option for patients with TNBC with CNS metastasis.

Materials and Methods

Cell culture and drug treatment

MDA-MB-231-BR3 cells were a kind gift from Dr. J.E. Price (M.D. Anderson Cancer Center, Houston, TX) and were authenticated and Mycoplasma negative at passages 4 and 14. Cells were authenticated by STR profiling (PowerPlex 16HS + ONE Mouse marker) and proved to be Mycoplasma negative by real-time qPCR Mycoplasma contamination detection test (as of April 26, 2021 by Labcorp.; www.celllineauthentication.com). MDA-MB-231-BR3 is a derivative of the MDA-MB-231 cells selected for their ability to metastasize into the brain. To monitor brain metastases in situ by in vivo bioluminescence imaging (BLI), the MDA-MB-231-BR3 cells were transduced with a lentivirus containing synthetic firefly luciferase gene. Cells were cultured in DMEM supplemented with 10% FBS and maintained in a humidified incubator with 5% CO2 at 37°C. QBS10072S (PubChem SID: 441332443, PubChem CID: 118276683) was synthesized and provided by Quadriga BioSciences, Inc. For in vitro studies, QBS10072S was dissolved in tissue culture-grade dimethyl sulfoxide and diluted into PBS. For in vivo studies, a lyophilized mixture of QBS10072S and Captisol (R) (SBECD) was reconstituted in 0.9% saline prior to use. Detailed QBS10072S information is provided in the Supplementary Materials and Supplementary Tables S1–S5.

Efficacy study

For subcutaneous model, 1 × 106 MDA-MB-231 cells in 100 μL Matrigel/100 μL PBS were inoculated in the lower left abdominal flanks of female NuNu mice (Charles Rivers Laboratories). Tumor volumes were quantitated [volume = (length × width × height)/2] and QBS10072S treatment began once tumors reached a volume of 200 mm3. For brain metastasis model, 2 × 106 MDA-MB-231-BR3 cells were injected in a volume of 20 μL of PBS using a catheter into the left internal carotid artery. Mice were allowed to recover and transcranial BLI measurements were taken to visualize the tumors in the brain. Animals with tumors outside the brain were excluded from the study. BLI imaging was performed using the IVIS Spectrum system (Xenogen Corporation). QBS10072S treatment started when tumors reached a bioluminescence signal of (0.2–0.5) × 106 photons/s. Additional details on internal carotid injection are provided in the Supplementary Materials.

LAT1 expression in breast cancer brain metastasis patient samples

After obtaining Institutional Review Board approval, the Stanford STRIDE database was queried for patients with brain metastases from primary breast cancer, seen at Stanford Hospitals and Clinics (SHC) between 2008 and 2018. Patient charts were individually reviewed to confirm radiographic evidence of brain metastasis (12), as well as molecular subtype [based on hormone receptor (ER/PR) and HER2 overexpression statuses]. Formalin-fixed paraffin-embedded (FFPE) tissue samples for corresponding patients were obtained from Stanford Pathology. De-identified patient FFPE blocks that contained adjacent normal brain, together with brain metastasis, tissues were included in IHC analysis. We confirm that written informed consent was obtained from the patients, and that the studies were conducted in accordance with the Declaration of Helsinki ethical guidelines.

LAT1 expression analysis of publicly available datasets

LAT1 expression in breast cancer cell lines was quantitated using gene expression data from Klijn and colleagues (13). LAT1 expression in matching primary breast tumors and brain metastases was quantitated using gene expression data from Iwamoto and colleagues (14).

Histology and IHC

LAT1 IHC was performed on frozen and paraffin-embedded tumor sections. Frozen sections (10 μm) were dried, fixed in 4% paraformaldehyde, quenched in 50 mmol/L NH4Cl, and permeabilized by 0.5% Triton X-100. FFPE sections were deparaffinized, rehydrated, and heat-induced antigen retrieval was performed using citrate buffer (pH 6.0). LAT1 was detected using mouse anti-mouse/human LAT1 (Santa Cruz Biotechnology, sc-374232) or rabbit anti-human LAT1 (Abcam, ab208776). Endothelial cells were detected using rat anti-mouse CD31 (BD Pharmingen, 550274) and mouse anti-human CD31 (Abcam, 187377) antibodies. MDA-MB-231-BR3 cancer cells were detected using anti-vimentin (Millipore, CBL202 or sc-6260, Santa Cruz Biotechnology) or with anti-human nuclei (Millipore, MAB1281) antibodies. Primary antibodies were detected using secondary antibodies labeled with fluorochromes Alexa Fluor 488, Alexa Fluor 594, Alexa Fluor 659. Molecular Probes). Cell nuclei were detected with DAPI. Alexa Fluor 488 anti-mouse Fc-gamma subclass 2a specific (Jackson ImmunoResearch Laboratories, 115–545–206) was used as a secondary antibody for detection of human vimentin (Millipore, CBL202). Whole skulls were fixed in a combined fixation/ decalcification solution (Cal-Ex II, Fisher Scientific, CS511–1D) for 72 hours, sectioned, and stained with hematoxylin and eosin.

Study approval

All animal procedures were approved by Stanford University’s Administrative Panel on Laboratory Animal Care (APLAC). Research involving human subjects was approved by Stanford Institutional Review Board.
Statistical analysis
Specific details of statistical tests, numbers of samples, and experimental replicates are included in figure legends. A Student t test was used for comparing two groups of parametric data. Kaplan–Meier survival curves were analyzed for statistical differences between groups using the log-rank Mantel-Cox test. The treatment groups were compared across time (at each time point and post hoc, pairwise comparisons were done with a Tukey adjustment). All tests were 2-sided with an α level of 0.05. All tests were performed in Prism (GraphPad Software). A P value less than 0.05 was considered significant.

Results
QBS10072S is effective against TNBC
QBS10072S is a non-cleavable molecule that combines a nitrogen mustard group and an amino acid moiety recognized by an amino acid transporter LAT1 (Fig. 1A). Thus, QBS10072S can selectively target TNBC cells which have high expression of LAT1 (Supplementary Fig. S1; ref. 10) and are known to have defects in DNA repair (15–18). Specifically, approximately 70% of TNBCs are deficient in homologous recombination (17, 18), and thus are likely to be especially vulnerable to DNA interstrand crosslink-inducing nitrogen mustards (19, 20). Formulation of QBS10072S and experiments testing QBS10072S selectivity toward LAT1-expressing cells, low toxicity to normal brain cells, ability to cross BBB, and QBS10072S distribution in normal and tumor tissue are described previously in detail in refs. (21, 22).

Compared with melphalan, a structurally related nitrogen mustard compound, QBS10072S displayed 25-fold higher specificity for LAT1 and 2- to 5-fold lower cytotoxicity toward normal cells (astrocytes, fibroblasts, and bone marrow progenitors; ref. 22). Consistent with robust LAT1 expression and a DNA repair deficiency phenotype, TNBC cells displayed high sensitivity to QBS10072S in vitro (Fig. 1B). Of note, the assessment of LAT1 gene expression in cell lines revealed high LAT1 expression in all breast cancer subtypes (Supplementary Fig. S1A; ref. 13). This contrasted the finding of higher protein LAT1 in TNBC patient tumor samples (10), but may be explained by different regulation of LAT1 expression in cell lines under in vitro conditions and in tissues. LAT1 expression was uniformly high in the TNBC cell lines used in our study (Supplementary Fig. S1B), suggesting that LAT1 was not responsible for variations in sensitivity to QBS10072S within these cells. Rather, given the significant variation in DNA repair capacity among TNBC cell lines (23), it is more likely that sensitivity to QBS10072S is determined by each cell’s DNA repair proficiency, with increased sensitivity in cell lines unable to resolve DNA interstrand crosslinks.

QBS10072S effectively slowed down growth of a triple-negative MDA-MB-231 cell lines both in vitro (Fig. 1C) and in vivo (Fig. 1D) in a subcutaneous xenograft model at 10 mg/kg without obvious toxicity.

LAT1 is overexpressed in TNBC brain metastases
LAT1 is overexpressed in primary TNBC (10), but LAT1 expression in brain metastasis from TNBC has not been investigated in detail. The studies of brain metastasis from other primary tumors in the flank of nude mice have revealed that LAT1 overexpression is common for brain metastasis (11). Consistent with this, gene expression analysis of primary breast cancers and matched brain metastases suggests that LAT1 expression is equally high in brain metastases and primary breast tumors (Supplementary Fig. S1C and S1D). IHC analysis of patient samples revealed high LAT1 expression in TNBC brain metastases (Fig. 2A–D; Supplementary Table S6; Supplementary Fig. S2). Importantly, LAT1 levels in the brain metastases were higher than in adjacent non-malignant brain, where most LAT1 signal was associated with blood vessels (Fig. 2B–D; Supplementary Fig. S2A and S2B). Among breast cancer subtypes, LAT1 expression in brain metastases mirrored reported LAT1 expression in primary breast tumors (10), with TNBC having the highest LAT1 (Supplementary Table S6) and luminal A cancers having notably low LAT1 levels. Thus, QBS10072S has the potential to serve as a selective therapy for TNBC brain metastasis.

QBS10072S is an effective treatment for TNBC brain metastasis and leptomeningeal disease
To produce brain metastases, MDA-MB-231-BR3 cells (a brain-tropic variant of the MDA-MB-231 cell line) were injected into nude mice, and treatment started after tumors reached the volume of 200 mm³. Mice were treated with 10 mg/kg QBS10072S or vehicle (n = 10 animals/group), given intravenously once a week for 8 weeks. Left, change in body weight of treated animals over the course of the study. Tumors sizes were measured 2–3 × per week. Data are mean ± SD. **, P < 0.0001; QBS, QBS10072S.
mice through the internal carotid artery (ICA; Supplementary Fig. S3 and Supplementary Methods). Like other TNBC cell lines (i.e., 4T1, MMTV-PyMT, MDA-MB-435, MDA-MB-231, CN34 and brain-tropic derivatives of the MDA-MB-231 cells; refs. 24–27), MDA-MB-231-BR3 cells have been reported to form metastases both in the parenchyma and leptomeninges upon injection into arterial circulation. Consistent with those observations, we observed leptomeningeal spread in brain metastasis formed by MDA-MB-231-BR3 cells (Fig. 2E) and by brain-naive TNBC cell line HCC1806 (Fig. 2F).

These data substantiate both clinical and preclinical observations of LM from TNBCs. The ICA method was chosen for this study because it allows one to differentiate the effects of CNS-specific metastatic spread from that of the systemic disease (systemic disease being more prominent in the intra-cardiac injection method), and thus is critical for the development of CNS-directed therapy.

Similar to observations in patient samples (Fig. 2A–D), metastases formed by MDA-MB-231-BR3 cells in NuNu mice expressed high levels of LAT1, whereas minimal LAT1 expression was observed in surrounding normal brain, with the exception of blood vessels (Fig. 2G). MDA-MB-231-BR3 cells formed morphologically distinct groups of metastases, including large dense bulky metastases in leptomeningeal space, smaller clusters of 30–100 cells and single-cell dissemination throughout the brain (Fig. 3). In contrast with the large bulky metastases, which contained large blood vessels (Fig. 3A), the small metastatic clusters and single-cell spread had no obvious association with brain vasculature. Both large bulky metastases and...

Figure 2.
Breast cancer brain metastases overexpress LAT1 both in patient samples and in an in vivo mouse model. A–D, Patient samples of breast cancer brain metastases show higher LAT1 levels compared with normal brain. A, TNBC brain metastasis displays characteristic membrane staining of LAT1. B, LAT1 signal in normal brain tissue is associated with blood vessels. C and D, Representative images of LAT1 staining in TNBC brain metastases with adjacent normal brain; scale bars, 200 µmol/L (A–C), 400 µmol/L (D). E and F, Representative images of LAT1 staining in mouse brain metastases formed after ICA injection of TNBC cells. E, Brain metastases formed after ICA injection of MDA-MB-231-BR3 cells. Left, bulky metastasis located in the brain parenchyma (arrowhead) and in the meninges (arrows). Right, Metastatic spread in the meninges. H&E staining shows MDA-MB-231-BR3 tumor cells in the leptomeningeal space between the brain and the skull. Arrows point to metastases; scale bar, 1,000 µmol/L. Inset, Empty space between metastasis and the brain is due to a common artefact of whole-skull fixation. F, Leptomeningeal metastases formed after ICA injection of HCC1806 cells; scale bar, 400 µmol/L. G, LAT1 expression in metastases formed after ICA injection of MDA-MB-231-BR3 is higher than in normal brain; scale bars left to right, 200, 400, and 200 µmol/L. Right, Average LAT1 antibody fluorescence intensity quantification based on 3–4 metastases (10–30 fields per metastasis and adjacent brain) from n = 3 mice. Data are mean ± SD. ***, P < 0.0001; NB, normal brain.
small clusters/single cells expressed comparably high levels of LAT1 (Fig. 3B).

To test the efficacy of QBS10072S against TNBC brain metastasis, QBS10072S was administered at 8 mg/kg either intravenously once a week for 9 weeks or intraperitoneally twice a week for 9 weeks. Both dosing regimens resulted in equivalent exposure to QBS10072S (Supplementary Fig. S4). Treatment with QBS10072S via intraperitoneal and intravenous resulted in significant reduction in intracranial tumor growth (Fig. 4A), an increase in overall survival (Fig. 4B) and no obvious toxicity (Fig. 4C) compared with vehicle controls. Proliferation (as measured by the Ki-67 expression) was reduced at the end of QBS10072S treatment, but these changes were observed only in small metastases (Supplementary Fig. S5A). No difference in Ki-67-positive cell fractions between vehicle control and QBS10072S were observed in large bulky metastases, possibly reflecting reduced accessibility to the drug in large tumors (Supplementary Fig. S5B and S5C). Although QBS10072S concentration in CSF was lower than in blood (Supplementary Table S7), the drug was consistently effective against disseminated leptomeningeal metastases, as we observed significantly reduced numbers of small clusters and single cancer cells in the QBS10072S-treated group (Fig. 4D, Supplementary Fig. S6). Thus, high tumor specificity, low normal tissue toxicity, as well as its ability to control disseminated metastasis, suggest a potential benefit of QBS10072S for patients with brain metastasis and LM.

Discussion

In this study, we investigated the potential of a novel brain-permeant chemotherapeutic agent, QBS10072S, as a single-agent treatment option for parenchymal brain metastasis and LM in patients with TNBC. Both types of CNS metastasis bear a dismal prognosis, with LM presenting additional challenges due to difficulties in detection and paucity of therapeutic options outside of palliation. Treatment of LM is complicated by its diffuse spread via cerebrospinal fluid (CSF) and within the meningeal layers of the brain and spine (2, 3).

As such, current treatments (e.g., intra-CSF chemotherapy, systemic therapy, craniospinal and whole-brain radiotherapy) are individualized due to no generally accepted standard of care in the treatment of breast cancer LM (4). Optimally, treatment of LM should cover the entire CSF space and prevent the re-seeding of the leptomeninges by systemic metastatic disease. Hence, systemic chemotherapy, which can simultaneously treat brain metastasis, LM, and systemic disease, is regaining interest as an effective therapy for TNBC CNS metastasis (4, 28).

We demonstrated that systemic administration of QBS10072S delayed tumor growth and extended survival in the animal model of TNBC CNS metastasis. Consistently, we observed a significant reduction in the numbers of small tumor clusters and scattered single tumor cells in the QBS10072S-treated animals, suggesting that QBS10072S holds great potential to prevent implantation and metastatic dissemination in breast cancer LM. The ability of QBS10072S to target scattered micro-metastases and single-cell spread is particularly exciting in light of the inability of current methods to detect and thus treat these metastases, which are the likely candidates for propagation of LM. A Phase I clinical trial is currently underway to determine the MTD of QBS10072S; (ClinicalTrials.gov, NCT04430842). A phase IIa clinical trial is planned to open in 2021 at Stanford for patients with TNBC and brain metastasis.

Successful treatment of CNS metastases requires both selective tumor-targeting and the ability to penetrate the BBB and blood-tumor barrier (8). The brain permeant compound QBS10072S functions as a bifunctional agent that contains a nitrogen mustard (to which the majority of TNBC is particularly sensitive due to defects in DNA repair) and targets LAT1-expressing cells (LAT1 is high in TNBC metastases). Although we focused our study on TNBC, defining patient populations who may benefit from the drug may require stratification based on LAT1 expression and homologous recombination (HR) deficiency (HRD) score rather than breast cancer subtype. Although majority of TNBCs are HR-deficient, 30% of them have...
groups had n = 4 mice per group, 4 sections per mouse and 30–40 fields per section. Data are mean ± SD. **, P < 0.01; ***; P < 0.0001; QBS, QSBI0072S.

normal HR (17, 18). In addition, the HRD phenotype (also known as BRCAlessness) is not unique to TNBC, with reported majority (83%) of breast tumors with BRCA2 germline mutations being of luminal subtype (29). In our study, LAT1 levels in brain metastasis were high in luminal B and HER2+ breast cancer subtypes, thus providing a potential to extend the application of the drug to treatment of brain metastasis and LM in those breast cancers.

Although assessment of LAT1 levels is straightforward (and in the absence of brain metastasis samples could be done by extrapolating LAT1 values from the primary tumor samples, see Supplementary Fig. S1), the assessment of HRD is challenging by the lack of a single HRD biomarker (30). BRCA1 and BRCA2 germline mutations predict HRD and sensitivity to chemotherapy, but they account only for 10–20% of TNBC and 5%–7% of all breast cancer cases (29, 31). Moreover, even BRCA1 mutant tumors are not uniformly HR-deficient, as high genomic instability pushes for an adaptation to the loss of BRCA function. BRCA1mt tumors rewire HR by multiple mechanisms, including compensatory overexpression of RAD51, upregulation of alternative pathways of HR, or as in the case of HCC1937 cell line—by concurrent loss of function of BRCA1 and PTEN (32, 33). Novel, more comprehensive, biomarkers that combine high-throughput genomic profiling techniques (including array-based comparative genomic hybridization, SNP genotyping, and next-generation sequencing) may help to identify future patients who will receive greater benefit from QSBI0072S (18, 29–31, 33, 34).

In summary, QSBI0072S showed high efficacy as a single agent in the TNBC brain metastasis and LM animal model, significantly reducing tumor burden and improving survival. Therefore, further validation of QSBI0072S in clinical trials is planned in patients with TNBC LM.

Authors’ Disclosures

S.B. Chernikova reports grants from Quadriga during the conduct of the study; and other support from Quadriga Biosciences Inc. outside the submitted work; as well as a patent for US10,246,406 issued, US10,017,459 issued, US9,878,487 issued, US10,034,847 issued, US9,861,599 issued, and US9,394,237 issued. W.N. Fischer reports grants from NIH/NCI and NIH/NCI during the conduct of the study; other support from Quadriga Biosciences, Inc. outside the submitted work; a patent for US10,246,406 issued, US10,017,459 issued, US9,878,487 issued, US10,034,847 issued, US9,861,599 issued, and US9,394,237 issued. K.J. Koller reports grants from NIH/NCI and NIH/NCI during the conduct of the study; other support from Quadriga Biosciences, Inc. outside the submitted work; has a patent for US10,246,406 issued, US10,017,459 issued, US9,878,487 issued, US10,034,847 issued, US9,861,599 issued, and US9,394,237 issued. B.O. Jandelet reports grants from NIH/NCI and NIH/NCI during the conduct of the study; and other support from Quadriga Biosciences, Inc. outside the submitted work; as well as a patent for US10,246,406 issued, US10,017,459 issued, US9,878,487 issued, US10,034,847 issued, US9,861,599 issued, and US9,394,237 issued. G.M. Ringold reports grants from NIH/NCI and grants from NIH/NCI during the conduct of the study; and personal fees from Quadriga Biosciences outside the submitted work; and a patent for US10,246,406 issued, US10,017,459 issued, US9,878,487 issued, US10,034,847 issued, US9,861,599 issued, and US9,394,237 issued. M.H. Gephardt reports grants from Quadriga, NIH, California Breast Cancer Research Program, and Metavivor during the conduct of the study. No disclosures were reported by the other authors.

Authors’ Contributions

J. Deng: Data curation, formal analysis, validation, investigation, writing—original draft. S.B. Chernikova: Conceptualization, resources, data curation, formal analysis, supervision, validation, investigation, visualization, methodology, writing—original draft, project administration, writing—review and editing. Y. Wang: Data curation, data analysis, validation, investigation, visualization, writing—review and editing. M.L. Rodriguez: Formal analysis, validation, investigation. S.S. Ahmadian: Conceptualization, resources, data curation, formal analysis, validation, investigation, visualization, writing—review and editing. B. Jandeleit: Conceptualization, resources, formal analysis, funding acquisition, investigation, methodology, writing—review and editing. K.J. Koller: Conceptualization, resources, data curation, formal analysis, funding acquisition, validation, investigation, methodology, writing—review and editing. B. Jandeleit: Conceptualization, resources, formal analysis, funding acquisition, methodology, project administration, writing—review and editing. G.M. Ringold: Conceptualization, resources, funding...
acquisition. M.H. Gephart: Conceptualization, supervision, funding acquisition, investigation, project administration, writing-review and editing.

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