Potent anti-tumor activity of a Lead-212 labelled MT1-MMP targeting Bicycle Radionuclide ConjugateTM

Abstract

212Pb-BCY20603 is a Bicycle Radionuclide ConjugateTM (BRC™), which comprises a bicyclic peptide that binds with high affinity to the tumor antigen MT1-MMP and a chelate of Lead-212, a potent alpha particle emitting radionuclide. 212Pb-BCY20603 shows tumor targeting in rodent tumor xenograft studies, with radioactivity levels of >45% injected dose per gram (ID/g) 24 hours post injection. It is well tolerated and in relevant efficacy studies, shows potent anti-tumor activity after a single dose of 5 μCi. Complete tumor regressions were seen after 3 dosing cycles of 10 μCi, two weeks apart, with no tumor regrowth at the end of the 100-day study.

Introduction

Targeted alpha therapy (TAT) allows selective delivery of potent, alpha particle emitting radioisotopes to tumors through conjugation of the payload to a tumor antigen targeting molecule. Bicyclic peptides (Bicycles) are an ideal modality for radiolabeling due to their short circulating half-lives. Lead-212 is an ideal alpha particle emitting radionuclide for selective radioisotope delivery. It is a natural nucleus that decays through a single alpha particle emission and has a decay half-life of 10.6 hours, which is well suited for small molecules and peptides that have short circulating half-lives.

Bicycle Radionuclide Conjugate™ (BRC™) 212Pb-BCY20603

(A) MT1-MMP targeting Bicycle
High affinity (5 nM) binding to tumor antigen MT1-MMP
Allows precision targeting of BCR/2 to tumor cells

(B) Lead-212
Potent radioisotope payload that causes double strand DNA breaks through a single alpha particle emission

(C) Half-life extending moiety
Reversibly albumin binding motif
Prolongs circulating half-life of conjugate

Bicycles and analogs containing a peptide sequence that binds to MT1-MMP were identified and evaluated for their potential to deliver alpha particle therapy. 212Pb-BCY20603 was developed as a potent alpha emitter conjugate with tumor targeting properties. MT1-MMP is a cell surface metalloproteinase that is overexpressed in a variety of cancer types, including breast, lung, and gastrointestinal cancers.

Results

212Pb-BCY20603 shows activity levels of >45% ID/g 24 hours post injection

212Pb-BCY20603 is well tolerated up to 40 μCi as a single dose

212Pb-BCY20603 shows potent anti-tumor activity in an MT1-MMP expressing xenograft model

212Pb-BCY20603 shows rapid and homogeneous tumor microdistribution

Adminstration of 212Pb-BCY20603 led to increased survival at all doses tested

In vivo biodistribution of 212Pb-BCY20603 in athymic nude female mice carrying subcutaneous HT1080 tumors: 10 μCi of drug was administered and organs were collected from 5 mice per timepoint: 1 hour, 4 hours and 24 hours post injection. The tissue uptake is expressed as %ID/g per gram (mL). %ID/g was calculated for each organ collected. In an in vivo efficacy study in mice, 212Pb-BCY20603 showed potent anti-tumor activity. Tumor shrinkage was seen in groups treated with 212Pb-BCY20603 at 1x5 μCi, 1x10 μCi, and 3x10 μCi (2-week dosing intervals). Animals dosed with 3x10 μCi showed complete tumor regressions and 6/10 animals were tumor free or regressing at the end of the 100-day study.

Conclusions

212Pb-BCY20603 binds to MT1-MMP with high affinity
Tumor targeting of 212Pb-BCY20603 has been demonstrated in mice, with activity levels >45% ID/g after 24 hours and a tumor to kidney ratio of 1:1.
212Pb-BCY20603 is well tolerated up to 40 μCi in single dose mouse DRF studies and shows potent anti-tumor activity
Complete tumor regressions were seen in mouse xenograft groups dosed with 3x10 μCi, dosing every 2 weeks
To our knowledge, this is the first example of anti-tumor activity demonstrated with an MT1-MMP targeting radio conjugate

We believe these data indicate that Bicycles are well suited for selective delivery of radionuclides to payloads of interest.

References


Bicycle Therapeutics, Inc. 35 Cambridgepark Drive Cambridge, MA 02140 Suite 350

BicycleTx Limited Portway Building Ganta Park Cambridge, CB21 0DS UK

Bicycle Therapeutics, Inc. 35 Cambridgepark Drive Cambridge, MA 02140

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