
Check for updates

produced by
lenge *in vivo*. This
due to space const
benefits of magn
addressed by us
magnetic fields
periments desc
upon drug del
subsequently
murine panc

2. Materia

This s
descriptio
the expe
The for
magne
non-i
The s
peri
loa
so

2

g,
ous
mol)
rogen
ed pres-
rude pro-
) silica gel
1% yield) as
H), 6.42 (brs,
29 (s, 1H, CH),
82 (m, 1H, CH),
$_2$ X 2), 1.47–1.29
$_2$S, 372.23; found

1-yl) 8,8′-((((2-(5-(2-
entanamido)ethyl)
*)bis(8-oxooctanoate) (**5**)*
(0.5 g, 1.3 mmol) and TEA
DMF was added disuccinimidyl
eaction mixture stirred at room
atmosphere. After completion of
200 mL) was added to the reaction
us obtained was filtered and washed 3
× 3). The crude product was purified
on basic (TEA) silica gel (methanol:
give **5** (0.83 g, 71% yield) as low melting
SO-d_6): δ 7.94 (brs, 2H, NH X 2), 7.67 (brs,
NH), 6.34 (brs, 1H, NH), 4.29 (s, 1H, CH), 4.12
(m, 3H, CH and CH_2), 2.88–2.72 (m, 6H, CH_2 X
, CH_2 X 4), 2.45–2.34 (m, 6H, CH_2 X 3), 2.20–2.06
1.60–1.21 (m, 22H, CH_2 X 11). ^{13}C NMR (DMSO-d_6):
0.7 (C=O), 163.1 (C=O), 162.7 (C=O), 61.4 (CH),
(CH_2), 53.9 (NCH_2), 39.9 (CH_2), 39.8(CH_2), 39.6(CH_2),

was stirred at 22 °C for 24 h under a
mpletion of the reaction, Rose Bengal
according to [22]), (0.43 g, 0.45 mmol)
d TEA (0.5 mL) were added to the reaction
ir for 24 h. Once the reaction was complete,
mL) was added to the solution and stirred for
precipitate thus obtained was triturated with
), ethyl acetate (100 mL), acetone-water mixture
) and finally with ethyl acetate-hexane mixture
L) respectively to afford a pink powder of compound **8**
ld). ^{1}H NMR (DMSO-d_6), Fig. S1: δ 7.95 (brs, 2H, NH_2),

6H, NCH_2 [illegible]),
2.17–2.06 (m, 10H
(DMSO-d_6), (Fig. S
162.7 (C=O), 15
(CH), 131.0 (C),
69.3 (CH), 61.5
(CH_2), 40.2 (C
31.0 (CH_2), 28
(Fig. S3): ca
1925.90 (M

2.3. In vitro
and gemcito

The h
was mai
100 U/m
serum
PaCa-
Medi
100
seru
we
pl
c

m
ure
obles
s then
nsity at
mple for
ration, the
posure were
mber. A 2 MHz
uency from the
and storage onto
alculated for each
quantify cavitation
e) by determining the
es (f_0*(n + 0.5), with
indicative of nonlinear

ontrol device

bed by Barnsley et al. and as-
ly, the magnetic body consisted of
gnet material whose geometry was
agnetic field of 0.2 T at a distance of
edge. An integrated ultrasonic element
10 mm provided a pressure field that
e magnetic field peak, with sufficient am-
avitation of MBs used in this study. An alu-
ne MAD (hereafter referred to as "aMAD") was
n US-only control for *in vitro* and *in vivo* experi-

n the gap between the US element and the delivery
the present work, a coupling cone (Fig. 2) was cast
wax and secured with US gel. The cone material was

chosen
1 MHz
surem
tion v
both

2.1

m
its
) to
wn in
control

lagMB-RB
μM) were
3.5 min, after
ed water. The
and reserved for
e completed in a

ested, with Perspex holder.

Fig. 3. *In vi*
element tu
water bath

Table 1
In vitro

Grou
Un
M
U
M

gel. In
risk, the
material
e transmis-
ved from the
. Using these
Subject weight
first treatment.
eated with gemci-
n the results section

mes in the *in vivo* experi-
value ± one standard devia-
as mean ± standard error on
n tumour volume measurement.
ons were established using an un-
roups and a 1-way ANOVA followed
mparing more than two groups using

*B-gem (**8**) and its efficacy in pancreatic cancer*

the SDT sensitiser RB and antimetabolite Gem to be
e MB surface, MBs were surface functionalised with
podal ligand was designed to have a single biotin anchor

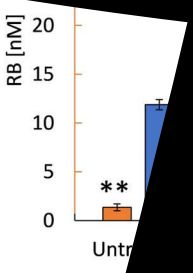
filled circles) (A) BxPC-3 and (B) Mia-PaCa-2 cell lines.

MB concen
1.0
5

Fi
h

from
nt ob-
fficulty
sed. The
US) could
agments, in
nd was found
($p < .01$). In-
milar degree, in
8].

production (orange, $n = 3$)
after US exposure, with asso-
ic emissions from MBs (blue)
inear oscillations. ** = $p < .01$
ugh a 1-way ANOVA with Tukey's
sample was prepared with $\pm 5 \times 10^7$
41 μM biotin-RB, and 1.25 μM SOSG in
PBS. US parameters were 1.17 MHz,
peak negative pressure, 30% duty cycle,
pulse repetition frequency for 3.5 min. (For
retation of the references to colour in this
re legend, the reader is referred to the web ver-
on of this article.)



3.4. *In vi*

To t
combin
with e
tribut
in Fig
trea
wit
wh
u
4

-
ju-
im-
nents
manu-
was also
ibited no
ding of the

0 are encouraging,
to be discussed. First,

s 0, 2, and 5. (B) Comparison of relative tumour volumes at
, MB, and M + U).

[28] E. Stride, C. Port
mediated gene del