SELECTED OPPORTUNITY IN ONCOLOGY

Compounds targeting HSP110 protein for cancer treatment (BIO18040)

COMPOUNDS TARGETING HSP110 PROTEIN FOR CANCER TREATMENT (BIO18040)

Product factsheet

PoC in vivo

- **Target:**
  - Heat shock protein 110 (HSP110, HSP105)
- **Product:**
  - Small molecule
- **Application:**
  - HSP110-associated cancer (colorectal cancer, lymphoma…)
- **Rational / POC:**
  - Identification of 2 inhibitors of HSP110:STAT3 interaction by screening a foldamers library
  - HSP110:STAT3 disruption by foldamers induces inhibition of CRC cells proliferation *in vitro*
  - *In vivo*, HSP110 inhibitors reduce tumor volume
  - Inhibitors of HSP110 abrogate the HSP110/MyD88 interaction observed in diffuse large B cell lymphoma cells lines
- **Patent and publication:**
  - EP19305094: Compounds targeting HSP110 protein for cancer treatment

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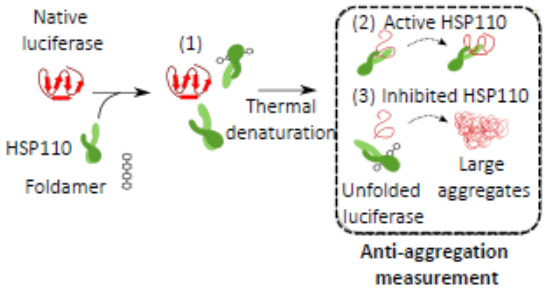
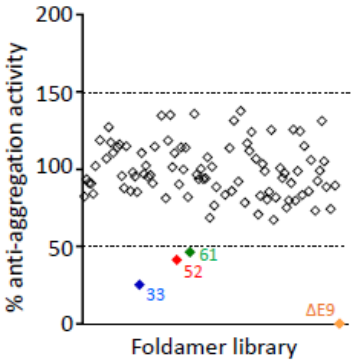
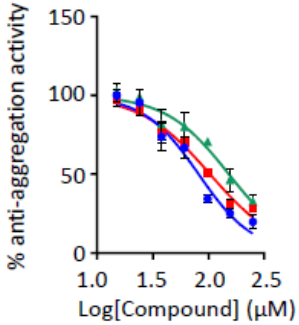
Screening of a foldamers library to disrupt HSP110:STAT3 interaction



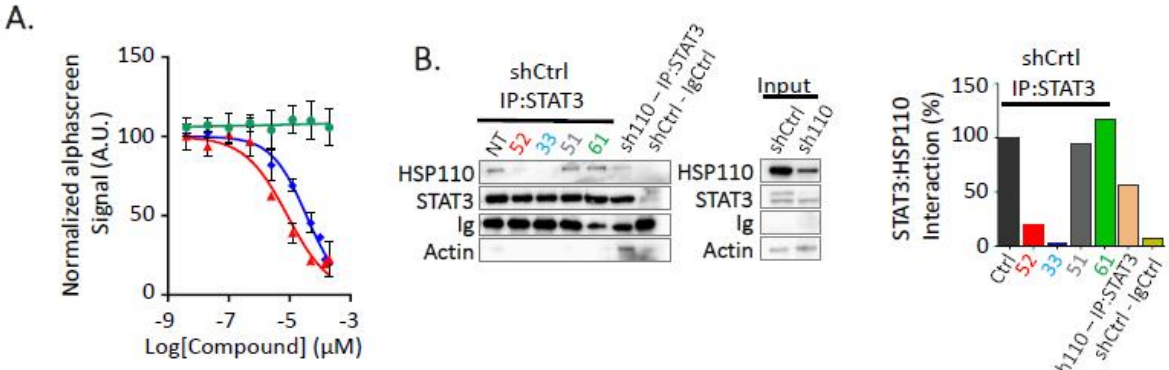
Scheme of HSP110 anti-aggregation test



Screening of foldamers



Dose response curves of hits' antiaggregating activity (33: IC50 = 58.3 ± 1.7 µM, 52: IC50 = 86.0 ± 1.5 µM, 61: R2=0.97, IC50 = 227.5 ± 1.9 µM).



Isolated foldamers were able to disrupt HSP110:STAT3 interaction. A . Dose response curves of dissociation HSP110-STAT3 by alphascreen (Compound 52 : R2= 0.90 ; IC50 = 8.5 ± 1.3 µM and compound 33 : R2 = 0.94 ; IC50 = 35.9 ± 1.1µM). B. Left panels, immunoprecipitation of STAT3 (IP : STAT3) or non-relevant antibody (IP : Ctrl) in SW480 cells treated with indicated compounds at 10 µM for 48 h, was followed by western blot of HSP110. Right panel, quantification of HSP110:STAT3 disruption considering the total amount of HSP110 normalized by Ig

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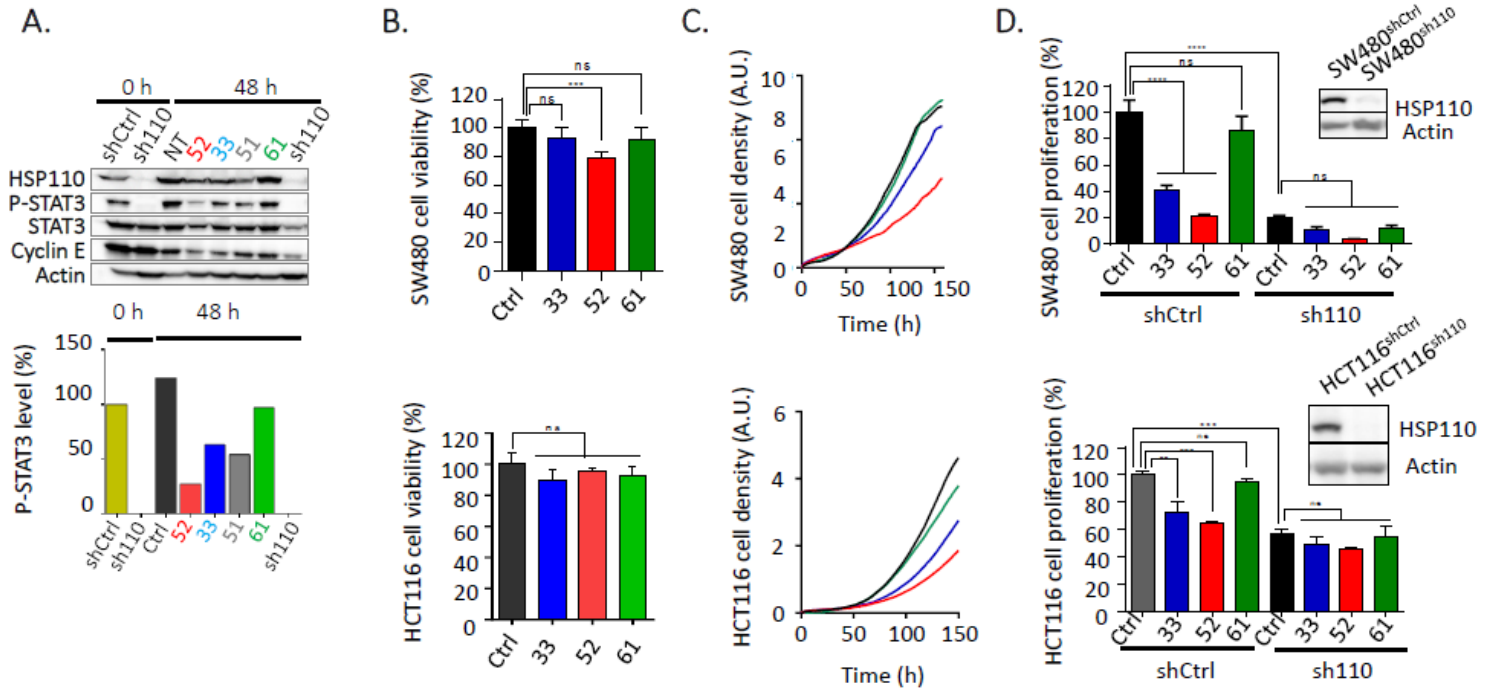
Proof of concept

***In vivo* reduction of tumor volume using the abiotic foldamer 33.**



***A**. Immunoblot analysis of HSP110, P-STAT3, STAT3 and Cyclin E in SW480 cells treated with indicated compounds at 10 µM for 48 h (upper figure). Quantification of P-STAT3 normalized by actin (lower figure). **B.** Quantification of cell viability in both SW480 (upper panel) and HCT116 cells (lower panel) after treatment with the foldamer (10 µM of during 48h) using flow cytometry Annexin V and 7AAD labelling. **C.** Real-time cell proliferation of SW480 (upper figure) and HCT116 cells (lower figure) treated with the indicated foldamers at 10 µM. **D.** Relative quantification of cell proliferation in SW480 (upper figures) and HCT116 cells (lower figure) transfected with shRNA for HSP110- silencing (sh110) or shRNA control (shCtrl) treated with the indicated foldamers at 10 µM for 96 h. Insert, western blot of HSP110 in the shRNA-silenced and control cells.*

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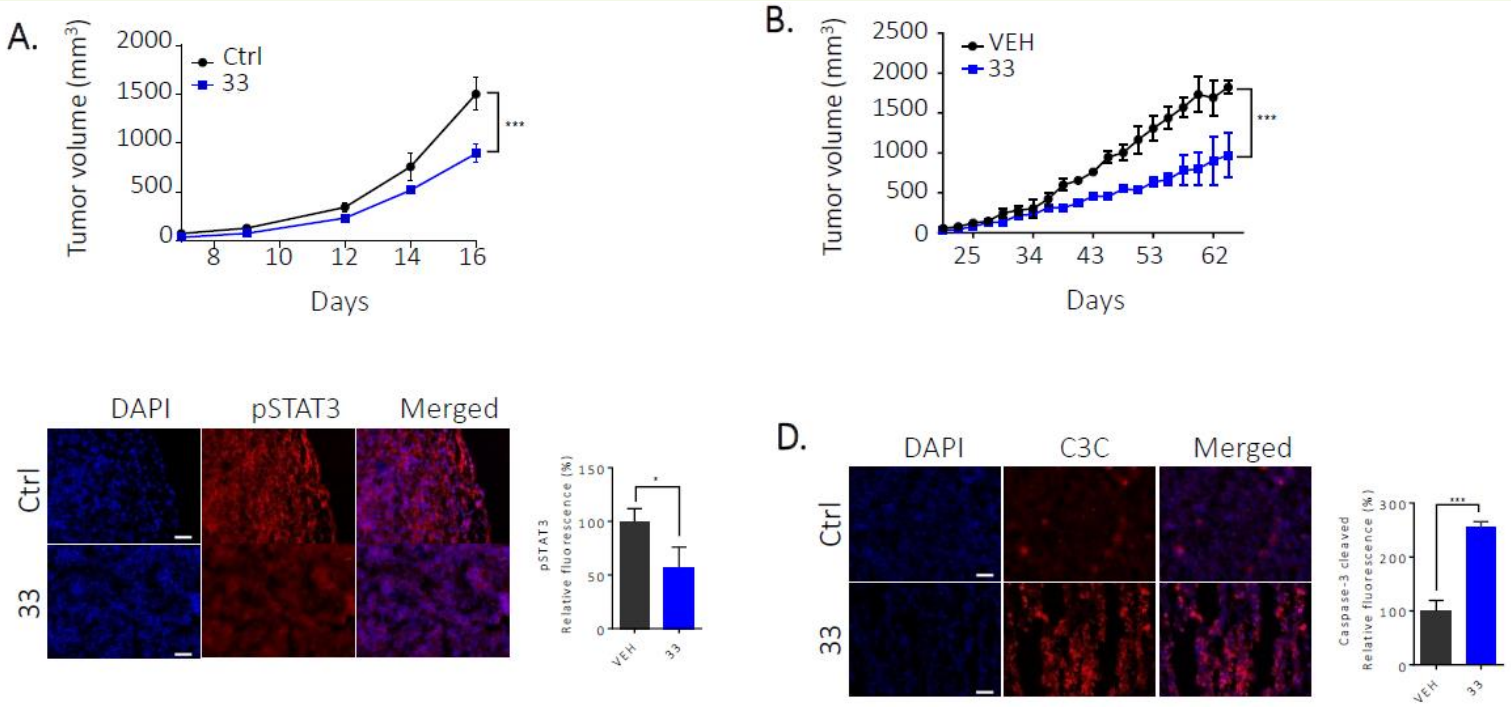
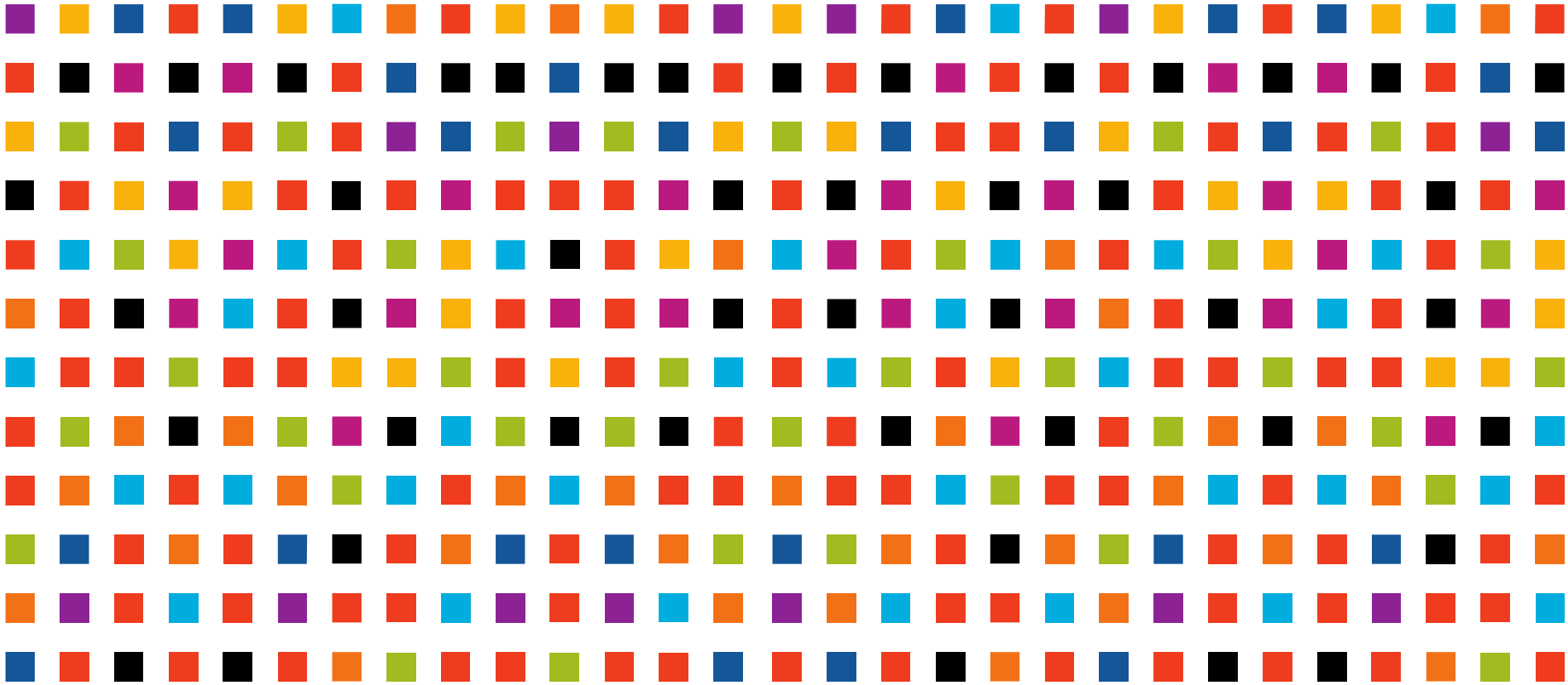
Proof of concept

***In vivo* reduction of tumor volume using the abiotic foldamer 33**



A. *Tumor volume monitoring of CT26 cells in Balb/c mice control-treated (Ctrl – black lines) and treated with the compound 33 (5mg/kg – blue lines). Animals were treated (i.p.) every three days. Mean volume+-SD is represented (n=6) (p=0,0053).* **B.** *Mean Tumoral volume (+-SD) of HCT116 cells grown in NOD/SCID animals either treated with a non-relevant foldamer (control) or the foldamer 33 (5mg/kg, injected i.p. every three days. 6 animals per group. p=0,0053).* **C.D.** *IF assay on dissected syngeneic tumors of pSTAT3 (C) and cleaved caspase-3 (C3C) (D). Scale bar = 50 µm. p=0,0019 and p=0,0003, for pATA3 and C3C, respectively.*



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