Targeting the Glioblastoma Master Regulator C/EBPβ– a Pharmacokinetic and Pharmacodynamic Neoadjuvant Study of ST101

P11.82.A

Fabio Massaiti Iwamoto[1], Robin Arthur Buerki[2], Nicholas A. Butowski[3], Katherine B. Peters[4], Robert Michel[5], Stephen Kaesshaefer[5], Gina Capiaux[5], Jim Rotolo[5], Erol Wiegert[5], Alicia Bargo[1], Danielle Pitchon[1], Kriti Manjrekar[1], Alice Susannah Bexon[5]

Contact information: Abi Vainstein, MD[5] : abi@sapiencetherapeutics.com

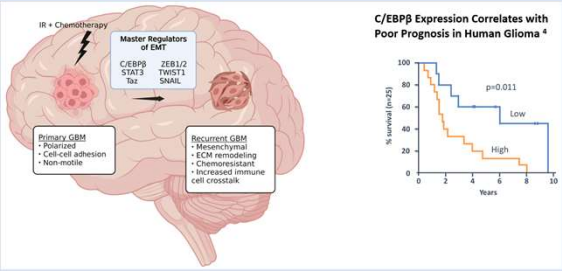
Sapience Therapeutics is a clinical stage biotechnology company forging a new class of peptide-based cancer therapeutics. Our drug candidates are uniquely designed to target transcription factors known to drive oncogenesis and immune suppression in patients with high mortality cancers.

ST101 is a peptide antagonist of the oncogenic transcription factor CCAAT/Enhancer Binding Protein Beta (C/EBPβ). ST101 is currently being evaluated in a Phase 1/2 clinical study in patients with advanced unresectable and metastatic solid tumors, with expansion cohorts in cutaneous melanoma, glioblastoma, hormone receptor positive breast cancer and castrate-resistant prostate cancer.

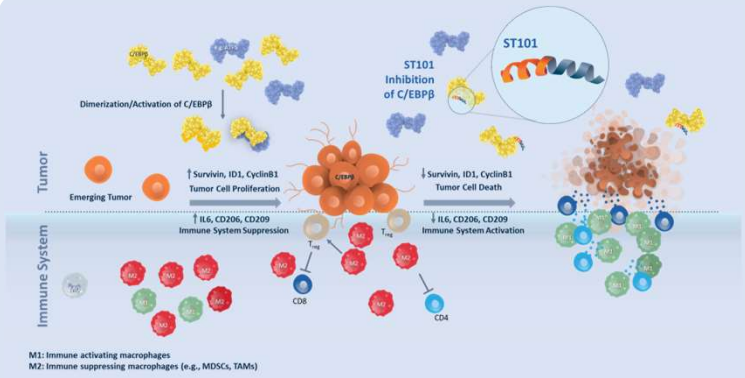
Background

- CCAAT/enhancer-binding protein β (C/EBPβ) is an oncogenic transcription factor that promotes cell proliferation, survival, and differentiation [1]
- C/EBPβ regulates polarization toward immunosuppressive M2 phenotype in activated macrophage [2,3]
- C/EBPβ expression increases with tumor grade[3] and is inversely correlated with overall survival rates and disease-free survival in GBM [4,5]
- ST101, a cell-penetrating peptide, disrupts C/EBPβ homo- and hetero-dimerization to inhibit DNA binding and reduce the expression of selective oncogenes [6]
- In vitro data demonstrates ST101 targeted killing of tumor cells, across multiple cancers, while preserving normal cells [6]

C/EBPβ is a Master Regulator of Mesenchymal Transition in GBM



(Left) Figure adapted from (Carro et al, Nature 2010) indicates that C/EBPβ is one of six transcription factors that control the mesenchymal signature of high-grade glioma, as identified by ARACNe. The mesenchyma cell state in glioblastoma is associated with resistance to chemoradiation and associated with increased recurrence. (Right) TCGA datasets and studies such as Homma et al, Oncology Reports 2006[4] indicate that C/EBPβ expression inversely correlates with responses in glioma patients.

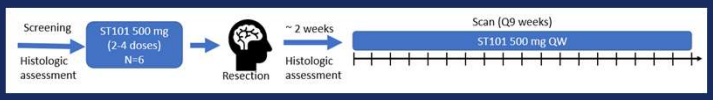


ST101 Anti-tumor Activity Enhanced by Immune Activation. *Top*, C/EBPβ overactivation in many cancer drives tumor cell proliferation, survival and inhibits differentiation. ST101 disrupts C/EBPβ dimerization, preventing C/EBPβ mediated transcription and enhancing proteasomal degradation [4]. The result is antagonism of oncogenic gene transactivation leading to selective tumor cell death. *Bottom,* M2-like TAMs suppress immune response to the tumor by impairing T cell activation. ST101 shifts the TAM program toward the immune active M1-like state, leading to activation of cytotoxic T cells and a potent anti-tumor immune response.

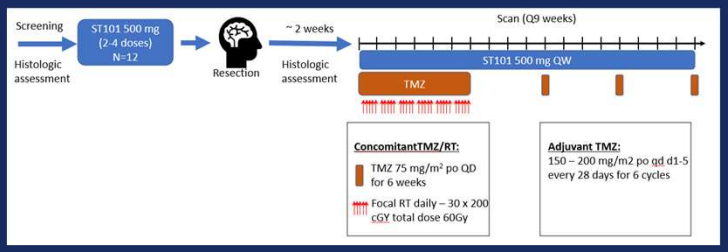
Study Design

- Sample size: 6 recurrent GBM patients and 12 newly diagnosed
- Treatment: 2-4 doses of ST101 (500 mg, IV infusion) pre-surgery followed by weekly dosing
  - Newly diagnosed will receive standard-of-care treatment with radiation/temozolomide following surgery in combination with weekly ST101
- Pharmacokinetics analysis:
  - ST101 plasma concentration will be correlated with ST101 drug levels in MRI-enhancing and non-enhancing tumor tissue of patients
- Pharmacodynamic analysis:
  - Evaluation of molecular changes in the post-treatment tissue will be conducted through deep bulk whole-exome sequencing, mRNAseq, and single nucleus RNAseq against the patient's baseline tissue
  - Analysis of tissue will include ST101-responsive genes such as BCL2, cyclins, and cyclin-dependent kinases and investigate the impact of ST101 on IL-6 signaling, macrophage polarization, and immune infiltration.

Recurrent GBM



Newly Diagnosed GBM



References

1. Van de Vijveret et al., NEJM 2002
2. Woboda et al., Oncogene 2020
3. Lei et al., Redox Biology (2020), Vol 34
4. Homma et al., Oncology Reports (2006), Vol 15.
5. Califano et al. Nature Reviews Cancer 2017, vol. 17
6. Carro et al. Nature 2010, vol. 463
7. Neftel et al. Cell 2019, vol. 178

Affiliations

1. Columbia University Irving Medical Center, New York, NY; 2. Northwestern Medicine, Neuro-oncology, Chicago, IL; 3. University of California, Brain Tumor Center, San Francisco, CA; 4. Sapience Therapeutics Inc., Harrison, NY.

Abbreviations

ARACNe – Algorithm for the Reconstruction of Gene Regulatory Networks, BCL2 – Bcell lymphoma 2 gene, C/EBPß - CCAAT/Enhancer Binding Protein Beta, GBM – glioblastoma, IV – intravenous, IL-6 – interleukin 6, MDSCs – myeloid-derived suppressor cell, MRI – magnetic resonance imaging, PO – oral, Q9 – every 9 weeks, RT – radiotherapy, TAM – tumor-associated macrophage, TCGA – The cancer genome atlas, TMZ – temozolomide, QD – daily

www.Sapiencetherapeutics.com