# Ivy Foundation

## Therapeutic Targeting of the STAT3 Pathway

## PRINCIPAL INVESTIGATORS

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## OBJECTIVES

- The signal transducer and activator of transcription 3 (STAT3) is over expressed in the majority of malignancies, but especially within glioblastoma.
- STAT3 is a key driver of gliomas and mediates tumor cell proliferation and survival, migration and invasion, and angiogenesis; is a negative prognostic factor for survival; and is required for the maintenance of cancer stem cells which give rise to recurrence and treatment resistance.
- STAT3 also becomes activated in immune cells in the presence of malignancy which then enhances the expression of immune suppressive cytokines, turns off antigen presenting cells, suppresses macrophage and T cell activation and function, and induces immune suppressive regulatory T cells.
- By only inhibiting STAT3 in the immune cells, marked immune-mediated anti-tumor activity can be achieved in animals.
- Although widely recognized as a highly desirable therapeutic target, prior attempts at therapeutically targeting STAT3 have failed, in part secondary to toxicity issues.
- We have devised a small molecule inhibitor (WP1066) of STAT3 that that is: 1) orally bioavailable; 2) minimal toxic *in vivo;* 3) a potent stimulator of anti-tumor immune responses; 4) efficacious *in vivo* against a wide variety of immune competent murine models of malignancy; 5) has excellent blood brain barrier penetration; and 6) has direct anticancer stem cell activity properties. However, an appropriate human formulation has prevented clinical trial implementation.

## PROGRESS REPORT

- A new formulation of WP1066 has been devised using nanoparticles that markedly increased serum half-life after oral dosing. The IND of WP1066 in almost complete with only chronic toxicity assays pending prior to submission to the FDA.
- The Phase I trial design for WP1066 has been approved by the M.D. Anderson Cancer Center Institutional Review Board.
- STAT3 inhibition used in combination with radiation or with immune activating approaches has demonstrated marked therapeutic synergy in mouse models of established glioblastoma.
- A second therapeutic approach for targeting STAT3 is being developed which includes a blocking microRNA delivered to the immune cells using nanoparticles. This strategy inhibits the STAT3 pathway regardless of how it was turned on, is highly efficacious in gliomas models of glioma, protects from tumor rechallenge by inducing immunological memory, and has minimal toxicity.
- The current state of the art for immunotherapy is confined to targeting cell surface markers; the use of nanoparticles to deliver a payload to inside the immune cell opens a new category of immune modulatory therapeutics.

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