Finding a way to develop resistance survive an unfriendly environment is the fundamental in the evolution of a species in nature. Even as small as a single normal cell, this rule applies. Tumors develop resistance to survive the attacks of a variety of cancer treatment modalities. Glioblastoma (GBM) in particular is one of the most treatment-resistant cancers associated with extremely poor prognosis. The current standard of care includes surgery with or without combined radiation/chemotherapy. Most cancer therapies focus on attacking the biological constituents of tumor cells by using methods that interfere with their gene expression, growth milieu, signaling pathways, matrix and endothelial proteins, growth factor receptors, etc. Strategies to identify highly prevalent targets that constitute the master promoters of oncogenesis in specific tumors seem promising. However, this promoter is often driven by several signaling pathways that are differentially activated or silenced with both parallel and converging complex interactions. It has thus been difficult to both identify prevalent master promoter targets, and address novel agents to treat malignant gliomas. New methods and techniques for the targeted treatment of gliomas such as inactivation of signaling pathways, boron neutron capture therapy, and targeted transport of nanoparticles by biomimetic protein vectors are under investigation. However, the
clinical outcomes it delivered have made little progress in malignant gliomas to date. It is thus necessary to reevaluate current strategies to find alternative approaches to eradicate malignant gliomas, or revisit the fundamental biology to explore the potential cancer resistance mechanisms in GBMs. Also, it implies that the development of cancer resistance may be through certain common signaling pathways that are involved in cell growth and proliferation. With this regard, we hypothesized that by understand the underlying common therapeutic-induced resistance, either chemical or radiation, may help to find the Achilles tendon of GBM.

Glioblastoma (GBM) therapy may be complicated by radiation-induced resistance (RIR). Resistant cells may undergo epithelial mesenchymal transition (EMT). TGF-β promotes EMT and inhibits apoptosis in epithelial and cancer cell lines. TGF-β signaling initiates and maintains via the Smad2/3/4 complex. Cyclin-dependent kinases (Cdns) regulate antiproliferative function of Smad. In the absence of a strong TGF-β signal, Cdk phosphorylation of Smad3 blocks TGF-β activity which results in cell cycle progression. TIAF1 participates in TGF-β signaling and regulates p53, Cip1/p21, and Smad proteins activation. TIAF1 might very likely regulate EMT and cell cycle via TGF-β/Smad pathway in radiation-induced resistance.

We are testing the hypotheses that cell cycle arrest and EMT may be important in the
development of radiation-induced tumor resistance; 2) TGF-β/Smad or TGF-β/TIAF1/Smad signaling pathway might participate in TGF-β-regulated cell cycle and/or EMT in RIR cell. TIAF1 is a TGF-β1-induced antiapoptotic factor.

In the last year, our laboratory had received funding support from NCKU Research and Department to testing our hypotheses and had some encouraging findings. We had used these preliminary findings to apply NSC grand. The proposal was approved for one year by the NSC (102WFA0900822). Currently, we have graduate students continuously working on this project. We believe that with the results of this study can be published by the scientific journal when more data become available. Also, with our interests in glioma resistance, I worked as the first and correspondent author to write a review article about GBM resistance. This review article was published by the journal of Frontiers in Oncology. Sze CI, Su WP, Chiang MF, Lu CY, Chen YA, Chang NS. Assessing current therapeutic approaches to decode potential resistance mechanisms in glioblastomas. Front Oncol. 2013 Mar 19;3:59. doi: 10.3389/fonc.2013.00059. eCollection 2013. The role of TIAF-1 was included in the article content.

The followings are current preliminary data of the study.
Figure 2. The Histograms of CNS-1 and RIR Cell Lines showing Expression of p53 and p21. The p53 expression in general was upregulated in a radiation dose-dependent manner among RIR cells, (n=3 *p < 0.05). However, except in R1 cells, it showed no significant difference in R2 and R3 cells when compared to the CNS-1 cells. The p21 expression showed similar pattern to p53, however, it showed no significant change when compared to CNS-1 cell, (n=3 *p < 0.05).

Figure 3. The Histograms of CNS-1 and RIR Cell Lines Showing Expression of pCdk1, Cdk2, Cdk4 and γ-tubulin. The cell cycle checkpoint mediated proteins, pCdk1, Cdk2 and Cdk4, were up-regulated in R2 cells, then down-regulated in R3 cells. The γ-tubulin was also up-regulated in a radiation dose-dependent manner in RIR cells. n=3, *P < 0.05, **P < 0.01.
Figure 4. The Histograms of CNS-1 and RIR Cell Lines Showing Expression of PLK, Cdk25B and Cdc25C. The G2/M checkpoint mediator proteins, PLK, Cdc25B and Cdc25C, were upregulated in R2 cells, and then down-regulated in R3 cells. *P < 0.05, **P < 0.01.

Figure 5. Flow cytometry analyses showed that R3 cell line (post 120 Gy irradiation) treated with paclitaxel, enters cell cycle G2/M arrest in a time and radiation dosage dependent fashion when compared with controls.