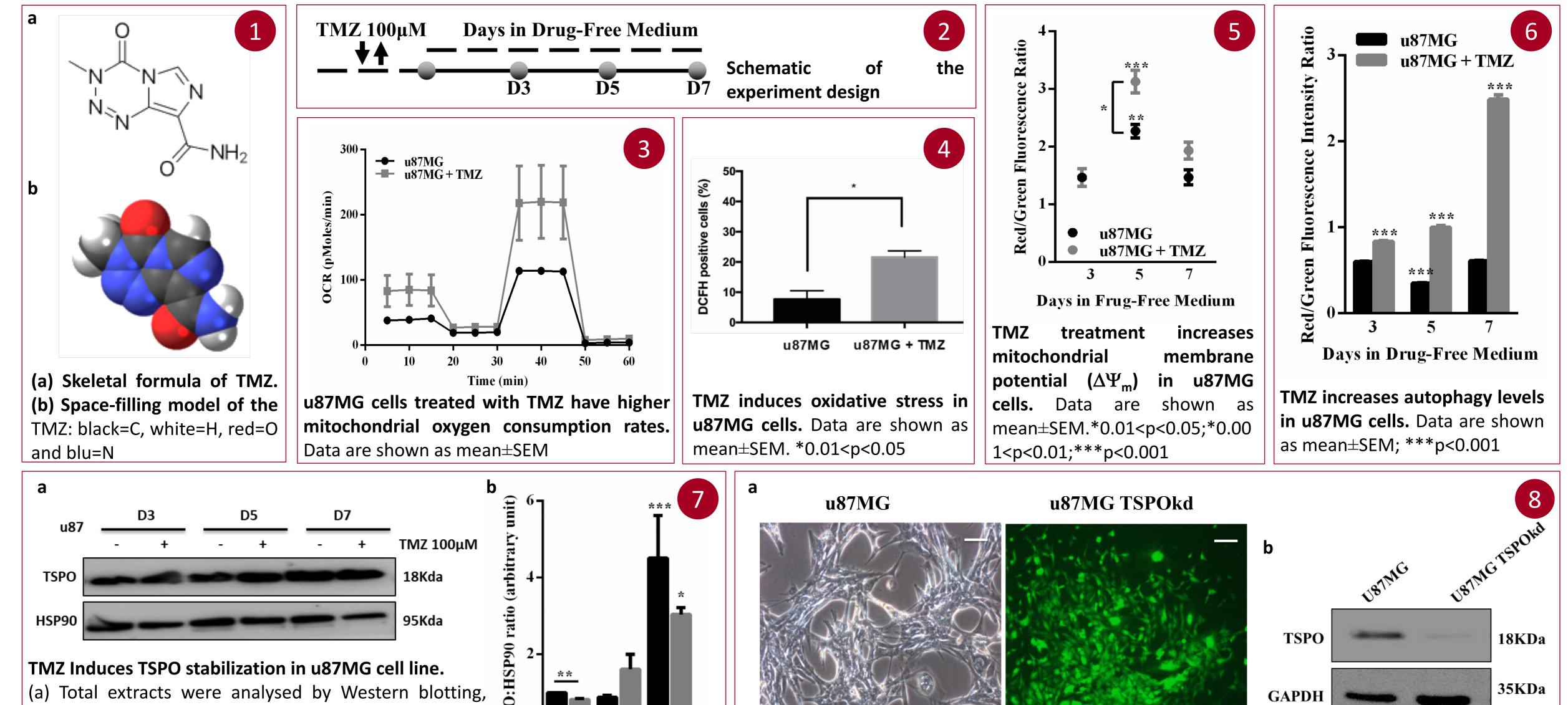
## Impaired mitochondrial quality control induces temozoloide treatment resistance through the 18kDa protein TSPO

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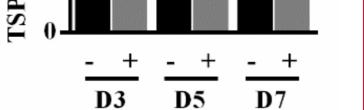
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**ABSTRACT**: Glioblastoma multiform (GBM) is the most malignant form of primary brain tumour in adults. It is highly aggressive and currently incurable. Although the notable advancements made in the past 30 years, the median survival of 12-15 months has not been appreciably improved. Temozolomide (TMZ) is the first-line chemotherapeutic agent for GBM but is compromised in its function by resistance phenomena whose underlying mechanisms remain elusive. Here we describe that TMZ drives the metabolic re-programming of GBM cells and associates with an increment of mitochondrial membrane potential ( $\Delta\Psi_m$ ) (i), autophagy (ii) and establishment of a more oxidative state (iii). We uncovered that TMZ leads to stabilization of the antimitophagy 18kDa protein TSPO which acts as stress response mechanism for the mitochondrion fuelling cell resiliency and reprogramming to resistance. TSPO, which positively associates with the progression of the disease, represses mitochondrial quality control (via mitophagy) and rewires the metabolism of cholesterol to establish a feed-back loop with the nucleus via inter-organelles proximity. GBM cells treated with TSPO ligands and cholesterol lowering drugs regain susceptibility to chemotherapy induced cell death as well as to TMZ treatment. This work sheds new light on the cellular mechanisms of adaptation to chemotoxicity in rapidly evolving resistance and acknowledges the TSPO pathway both as a prognostic and target to inform clinical decisions.

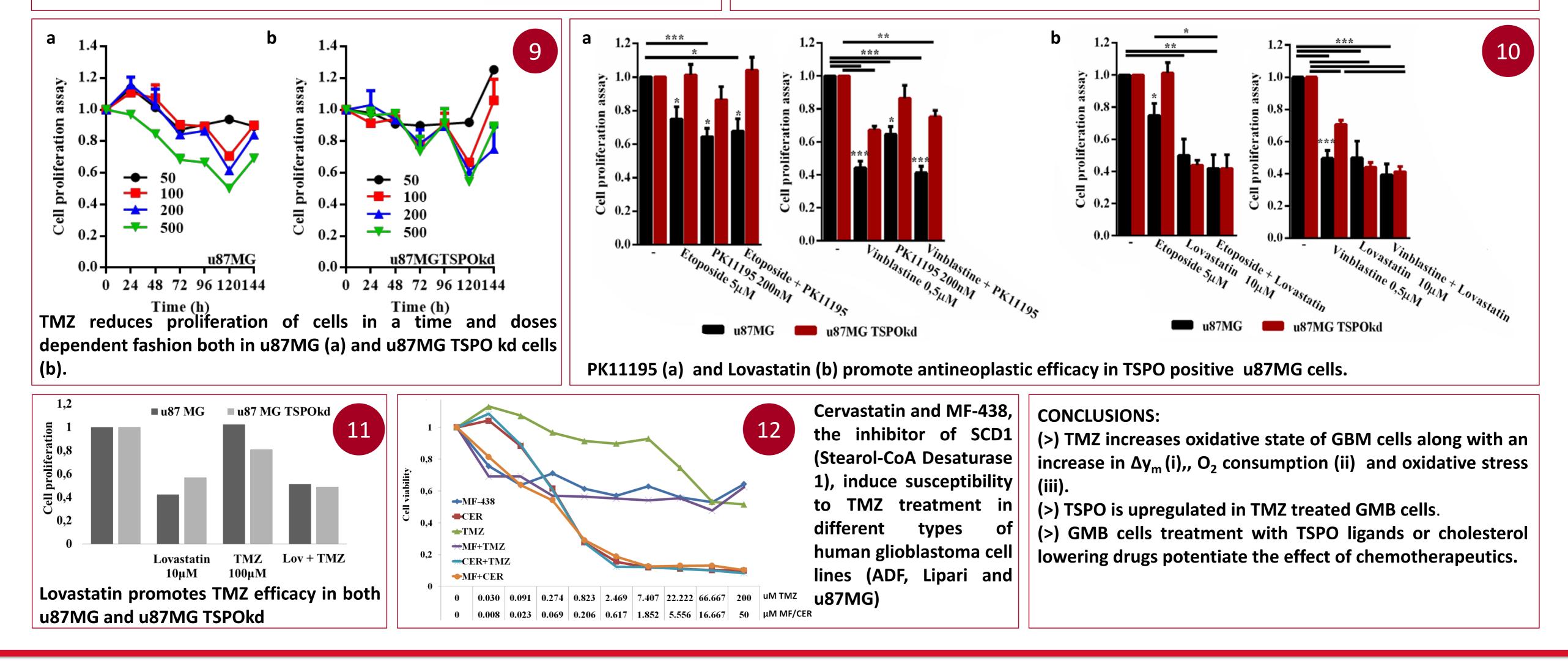
## **RESULTS:**



and data normalized on the basis of HSP90 levels and quantified in (b). Data are shown as mean±SEM. \*0.01<p<0.05; \*0.001<p<0.01;\*\*\*p<0.001



**Generation of a u87MG cell line stably downregulated for TSPO (u87MGTSPOKd)** labelled with pGIPz tGFP lvector (a) and confirmed by Western blotting analysis (b).









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