Cytotoxic Activity Of Schweinfurthin Analogue TTI-3114 In Multiple Myeloma Cells
Multiple myeloma and bone marrow niche

- Second most frequent hematological cancer
- The incidence of new cases -35,000/yearly (USA)- is rising ( -> aging)
- Male to female ratio is approximately 1.54 to 1
- Current treatments have prolonged survival BUT MM IS CURRENTLY INCURABLE

Experimental design

Three human derived cell lines to study multiple myeloma:

- RPMI-8226
- H-929
- MM.1s

Picture available at: ATCC.ORG
Hypothesis

Schweinfurthin-induced myeloma cell cytotoxicity arises from the inhibition of multiple signaling pathways that stem from PI3K/Akt.

Aim 1. To establish the mechanism of schweinfurthin-induced toxicity in malignant plasma cells (cell survival and cycle progression)

Cell survival (growth and viability)
1. Trypan blue assay
2. Mitochondrial activity (MTT)
3. Apoptosis (flow cytometry)

Cell cycle
1. Cell cycle phases (flow cytometry)

Signaling pathway PI3K/AKT
1. AKT activation (WB)
TTI-3114 decreases cell viability and mitochondrial activity

Statistics: two-way ANOVA and Dunnett's multiple comparisons. n.s. not significative, * p<0.05; ** p<0.01, *** p< 0.001
TTI-3114 increases cell death by time and concentration dependence

Figure 2

Statistics: two-way ANOVA and Dunnett's multiple comparisons. * p<0.05; ** p<0.01, *** p<0.001, # p<0.0001

TTI-3114 increases cell death by time and concentration dependence.
TTI-3114 increases cell population in G2/M phase of the cell cycle

Cell cycle modeling: ModFit software.

Statistics: two-way ANOVA and Dunnett’s multiple comparisons. * p<0.05; ** p<0.01, *** p< 0.001
TTI-3114 decreases Akt activation

Statistics: one-way ANOVA and Dunnett’s multiple comparisons. * p<0.05; *** p< 0.001
Conclusions

In all of three multiple myeloma cell lines, schweinfurthin TTI-3114:
• exerts a cytotoxic activity, causing cell death
• reduces the mitochondrial activity

In RPMI-8226 and MM.1s cell lines, schweinfurthin TTI-3114:
• Increases cell cycle arrest in G2 or M phase in dose-dependent manner
• reduces Akt activation

Our data support the study of TTI-3114 in vivo, in a murine animal model of induced MM, as a next step towards translation of this compound into eventual human testing. The impact of such a successful outcome can provide an alternative treatment for refractory MM sub-clones. It is also possible that this compound could be used to prevent progression of smoldering disease.