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Targeting the mevalonate and mammalian target of rapamycin pathways in breast cancer

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Introduction: Breast cancer is the commonest cause of cancer mortality in Maltese females. The availability of eukaryotic translation initiation factor 4E (eIF4E) is reduced by mammalian target of rapamycin (mTOR) inhibitors e.g. rapamycin and metformin. Expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the mevalonate pathway rate limiting enzyme, is regulated by eIF4E. Additionally statins e.g. simvastatin, are HMG-CoA reductase inhibitors.
Aims: Investigating the effect of HMG-CoA inhibitors in breast cancer cells, when used in combination with mTOR inhibitors, as opposed to being used alone.
Methods: Previous results indicate that when Hs 578T, MDA-MB-468 (ER- PR- HER2-), MCF7 (ER+ PR+ HER2-) cells were treated with rapamycin or metformin; sensitisation was reached by MDA-MB-468 and MCF7 with rapamycin. Sensitisation is cell viability decrease, statically maintained through 3 consecutive higher concentrations. Sensitisation concentration (C_s) and time-point (T_s) were determined. Both cell lines were exposed to rapamycin C_s. Following T_s, simvastatin was added as 0, 5, 10, 15, 20, 65, 110, 155, 200μM. After 24 hours an MTT assay was carried out.
Results: For both cell lines C_s and T_s were 35ng/mL and 24 hours respectively. MDA-MB-468 and MCF7 cells did not

reach IC_{50} with simvastatin alone, but when pre-exposed to 35ng/mL rapamycin both attained an IC_{50} at 5.7μM and 134 μM simvastatin respectively.

Conclusion: The results obtained indicate that addition of an mTOR inhibitor decreases the HMG-CoA inhibitor dose required to attain IC_{50}. This depicts that pursuing two different pathways converging on the same target, using the lowest possible drug concentrations, results in an optimum response.