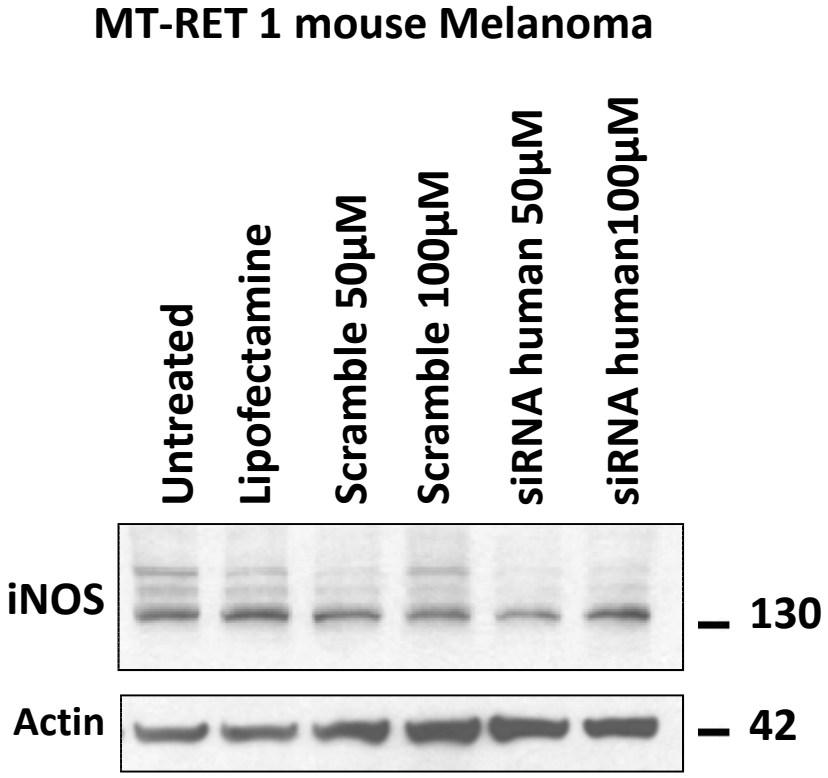Supplementary S2