**Objectives**: Triazole resistance in *A. fumigatus* is a growing clinical challenge. We, and others, recently identified mutations in the sterol sensing domain (SSD) of the HMG-CoA reductase enzyme, Hmg1, as significant contributors to triazole resistance. Through exploration of this mechanism, our previous studies suggested that triazole-induced accumulation of the ergosterol intermediates, lanosterol and/or eburicol, are likely to be cellular signals downregulating Hmg1 through their interactions with the SSD. As this mechanism exists to reduce ergosterol pathway activity when cellular sterol intermediates are high, we have proposed that induciton of this feedback is a novel secondary mecahanism of action essential for triaozle susceptibility in *A. fumigatus*. Our objective here was to further these initial discoveries by uncovering the specific molecular mechanism driving Hmg1 downregulation in response to triazole stress.

**Materials & Methods:** All studies were carried out in the wild type *A. fumigatus* labortaory strain, CEA10. Gene deletion was performed using CRISPR/Cas9 genome editing. Gene expression analyses were completed employing standard RT-qPCR approaches. Protein abundance of Hmg1 was assessed through cyclohexamide chase assays employing strains of *A. fumigatus* expressing Hmg1-HiBit or Hmg1-S305P-HiBit (an SSD mutant causing triaozle resistance). The resulting protein membranes were visualized using the HiBit detection assay kit (Promega).

**Results**: In mammals, accumulated sterols are sensed through interactions with the HMGCR SSD and an ER-resdient protein called INSIG. The INSIG protein then promotes the degradation of HMGCR through a ubiquitin-mediated process requiring the ubiquitin ligase, HRD1. Therefore, we sought to test if accelerated degradation is the underlying mechanism of Hmg1 dowregulation in resposne to traizole stress in *A. fumigatus* and to see if the conserved InsA (INSIG ortholog) and HrdA (HRD1 ortholog) proteins are invovled. Targeted protein abundance studies employing lysates from cultures lacking voriconazole revealed that both Hmg1 and Hmg1-S305P proteins exhibited a nine-hour half life. However, when cultured in 0.5 X MIC voriconazole stress, the half life of the Hmg1 wild type reduced significantly to less than three hours whereas the Hmg1-S305P mutant remained stable. These results support accelerated degradation of Hmg1 as the conserved underlying feedback mechanism and suggest that SSD mutation at least partially blocks this feedback. MIC analyses revealed that deletion of *hrdA* or *insA* resulted in triazole resistance, suggesting that each could play a conserved role in the feedback process. However, again employing HiBit-based protien abundance stuides, we surprisingly uncovered that *hrdA* or *insA* gene deletion did not impede the accelerated degradation of Hmg1 in resposne to voriconazole stress. Therefore, additional as yet unidentified component are essential to this feedback system.

**Conclusions**: Taken together, our data point to a complex and poorly conserved mechanism of action underpinning this essential negative feedback loop. Future work is focused on identifying the cellular components required for degradation of Hmg1 in response to triazole stress as pharmalogically inducing this feedback could overcome antifungal resistance and/or improve triazole activity against pathogenic fungi.