Title: DNA Repair Defects in Xeroderma Pigmentosum Result in Senescence and Premature Aging

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Background: Xeroderma pigmentosum (XP) is a rare genetic disease characterized by

extreme sensitivity to UV light, predisposition to skin cancer, and in some cases, neurological defects. XP patients have mutations in nucleotide excision repair (NER), the DNA repair pathway responsible for repairing bulky DNA lesions caused by UV radiation. XP patients often have skin cancer in childhood, approximately 50 years earlier than the general population. There is no cure for XP, therefore patients must avoid sunlight, wear protective clothing, and manage symptoms including skin cancer, ocular degeneration, and neurodegeneration. We sought to investigate the NER defects, senescence burden, and premature aging in XP patient samples.

Methods: The study included 14 XP patients from 5 complementation groups (XPA, XPC, XPD, XPF and XPG) and 26 unaffected first-degree relatives. Participants completed a survey and donated blood and skin biopsies. An NER assay developed by our laboratory was used to evaluate the NER capacity in both blood cells and fibroblast derived from the skin biopsies. With the PBMCs, we used a targeted genotyping panel to confirm the NER gene mutations and used methylation array data to evaluate the samples with multiple DNA methylation aging clocks. We measured the expression of senescence associated markers in the fibroblasts by qPCR and measured NAD levels in the blood.

Results: We confirmed the XP mutations in the patients and identified three siblings as carriers. We found that both fibroblast and PBMCs from the XP patients were deficient in NER and that XP patients have increased age acceleration compared to unaffected relatives. XP patients also had increased expression of p16 INK4a , indicating increased senescence.

Conclusions: We identified increased senescence as a potential driver of premature aging in

XP patients, therefore senotherapeutics are a possible therapy for XP patients.