Aging as a phenomenon of a protected environment is accompanied by typical diseases of the aging body as neurodegeneration, cardiovascular disease or cancer. To study the underlying pathomechanisms and to foster healthy aging you can either analyse centenarians, humans that display decelerated aging, or children suffering from accelerated aging in so-called premature aging syndroms, progerias. These syndroms display signs of aging like cardiovascular disease or neurodegeneration and cachexia already at childhood. We are interested in two related childhood progerias, Cockayne syndrome and trichothiodystrophy that are characterized by neurological degeneration, retarded growth and cachexia, eventually leading to childhood death. The genes that are mutated in these progerias are all involved in transcription of the ribosomal DNA by RNA polymerase I. As the products of rDNA transcription, the mature rRNAs, are the structural and functional backbones of the ribosome, we are investigating the cellular and organismal consequences of a failure in ribosomal biogenesis. We hypothesize that a disturbed RNA polymerase I transcription is followed by a reduced translational fidelity of the ribosomes. This could lead to an accumulation of misfolded proteins that provoke endoplasmic reticulum stress and an unfolded protein response. The unfolded protein response in turn represses translation and ribosomal biogenesis and thus creates a circulus vitiosus. This circulus vitiosus can be disrupted by the addition of pharmacological chaperones. This hypothesis will be investigated with cells from affected individuals and mouse models of the diseases. The mice that are displaying the symptoms of progeria will be treated with pharmacological chaperones, moreover in tissues and cells from affected mice we will investigate if we find a loss of proteostasis due to a failure in ribosomal biogenesis. Our hypothesis will also be examined with cells and tissues of young and old human donors to prove if loss of proteostasis due to a reduced transcriptional fidelity is a general aging mechanism.