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Editorial

Robert M. Brosh Jr. [Senior Investigator and Chief, Section on DNA Helicases]

Laboratory of Molecular Gerontology, National Institute on Aging, National Institutes of Health,
NIH Biomedical Research Center, 251 Bayview Blvd, Baltimore, MD 21224 USA

Monogenic accelerated ageing disorders are frequently characterized by genomic instability and defects in DNA repair or the DNA damage response. This special issue of *Ageing Research Reviews* is comprised of a series of review articles by leaders in the field who address molecular and cellular defects characteristic of such disorders and their underlying mechanisms. A unique feature of the compilation is the attention toward preclinical and clinical aspects of the premature ageing disorders, and potential therapeutic options. We begin with analyses of three RecQ helicase disorders, namely Werner syndrome (WS), Bloom's syndrome (BS), and Rothmund-Thomson syndrome (RTS), which are discussed in separate review articles by outstanding experts in the field. WS, a segmental progeroid disorder, is considered by many to be a disease most resembling normal ageing only at an accelerated pace. In a *tour du force*, University of Washington Investigators Drs. Oshima, Sidorova and Monnat discuss the clinical features, pathogenesis, and potential therapeutic interventions for WS (Oshima et al., 2017). A strong argument is made that the underlying basis for the molecular, cellular and organismal phenotypes of WS and other diseases of premature ageing is genomic instability, which also undermines the disease processes associated with normal ageing. A unique aspect of this article in this special issue of *Ageing Research Reviews* is the exploration of potential therapeutic approaches to treat individuals with WS including compounds that act to modulate stress-signaling pathways or human induced pluripotent cells to promote genome stabilization and possibly healing of WS-associated maladies.

Dr. Ellis (University of Arizona Cancer Center), one of the original members of the team that discovered the genetic linkage of BS to mutations in the *BLM* gene, and his colleagues deliver a unique perspective of the profound cancer susceptibility and distinctive clinical features of the disease (de Renty and Ellis, 2017). *BLM* encodes a DNA helicase with sequence similarity within the helicase domain to the WRN protein defective in WS. While BS is not considered to be a prototypic accelerated aging disorder, the predisposition to a wide spectrum of cancers observed in the normal ageing population prompts interest from gerontologists and cancer biologists alike. Provided in the review is a useful discussion of the potential molecular and cellular deficiencies underlying BS which include unusual chromosomal instability features and aberrant regulation of gene expression. Given that cancer is one of the greatest risk factors for ageing, the Ellis review on BS is a must-read. Rounding up the RecQ helicase disorder diseases, Dr. Wang from the Baylor College of Medicine contributes a review which discusses the ageing features characteristic of RTS and the related RECQL4 disorders Baller-Gerold syndrome (BGS) and RAPADILINO syndrome (Lu et al., 2017). All three diseases arise from autosomal recessive mutations in the *RECQL4* helicase gene, and the features of these *RECQL4* diseases are compared to WS

and BS. Relationships between RECQL4 deficiency and cellular senescence or mitochondrial dysfunction are discussed by Lu et al. (Lu et al., 2017).

I was highly pleased that Dr. Shiloh of Tel Aviv University and his colleague Dr. Lederman of the Johns Hopkins Medical Institutions agreed to participate in this special issue of *Ageing Research Reviews* by writing on the disease Ataxia-telangiectasia (A-T) (Shiloh and Lederman, 2017). In their review, they focus on describing the premature ageing aspects of A-T which include immune system phenotypes, endocrine abnormalities, cancer predisposition, decline of brain functionality, and neurodegeneration. Genomic instability and a defective DNA damage response arising from autosomal recessive mutations in the *ATM* gene encoding a multi-functional protein kinase is likely to underlie the cellular senescence characteristic of A-T, and the authors discuss published work which suggests that A-T carriers may display enhanced morbidity.

Molecular defects in the nuclear lamina have been associated with a number of genetic diseases including the premature ageing disorder Hutchinson-Gilford Progeria syndrome (HGPS). Dr. Gonzalo of Saint Louis University School of Medicine and her colleagues focus their article for the special issue of *Ageing Research Reviews* on the molecular mechanisms responsible for the cellular decline in HGPS which arise from a defective *LMNA* gene resulting in expression of a mutant progerin protein (Gonzalo et al., 2017). Gonzalo et al. (Gonzalo et al., 2017) discuss the pathophysiology of HGPS and offer a strong rationale for the importance of understanding the disease to create insights into the normal ageing process. The authors also present a narrative on emerging therapies in preclinical stages for treating individuals with HGPS.

Cockayne syndrome (CS), long considered a DNA repair and transcription disorder, is characterized by a number of features that resemble those found in normal ageing. Dr. Bohr of the National Institute on Aging and his colleagues describe in valuable detail the clinical features of CS, including diagnosis criteria, and present current models for the molecular mechanisms that underlie the cellular defects characteristic of the disorder (Karikkineth et al., 2017). In their review, Karikkineth et al. (Karikkineth et al., 2017) provide insightful commentary on the hypothesis that mitochondrial dysfunction may contribute significantly to CS pathologies. I expect that this article of the special *Ageing Research Reviews* issue on monogenic accelerated ageing disorders will gather tremendous interest from the ageing, DNA repair/transcription, and mitochondria communities.

While Fanconi Anemia (FA) is perhaps best known clinically as a disease of progressive bone marrow failure, it also displays a number of clinical features (*e.g.*, endocrine dysfunction, osteoporosis, sarcopenia, immune deficiency, myelodysplastic syndromes, cancer) that are symptomatic of accelerated aging. Drs. Brosh and Seidman, together with their colleagues Drs. Bellani and Liu of the National Institute on Aging, review the literature and offer a global perspective of FA as a disease caused by DNA repair defects, oxidative stress and inflammation, which together are responsible for the accelerated decline of hematopoietic stem cells and bone marrow failure in FA (Brosh et al., 2017). They present a model which incorporates this theme as well as the roles of a persistent DNA damage response and senescence associated secretory phenotype which perpetuates a vicious cycle

prevalent in FA. This model may also provide insights for processes that undermine healthy aging. healthy aging.

The special issue of *Ageing Research Reviews* also includes two articles which address from a larger perspective the important roles of a chromosomal DNA structure (telomere) (Opresko and Shay, 2017) and an organelle (mitochondrion) (DeBalsi et al., 2017) in age-related genetic diseases. A number of monogenic telomeropathies that arise from defects in chromosome end maintenance machinery display features of premature aging, leading researchers to focus their energies on understanding the molecular and cellular mechanisms underlying their tissue specificity and age of onset. Dr. Opresko (University of Pittsburgh) and Dr. Shay (University of Texas Southwestern Medical Center) tackle the complexity of telomere-associated aging disorders with a refreshing and comprehensive outlook that will be highly valuable to experts and novices alike (Opresko and Shay, 2017). They provide captivating perspectives on hot topics including the distinctions between primary and secondary telomere-associated aging disorders, genetic anticipation as it relates to generation-dependent severity of the symptoms identified in telomeropathies, and the role of environment in telomere length changes. Switching gears, Dr. Copeland and his colleagues at NIEHS assess the role of mitochondrial DNA replication machinery in mitochondrial DNA mutagenesis, ageing, and age-related diseases (DeBalsi et al., 2017). They also discuss interventions such as caloric restriction and exercise training to ameliorate mitochondrial dysfunction as potential avenues to attenuate the symptoms of aging.

Altogether, the nine articles assembled for this special issue of *Ageing Research Reviews* on monogenic accelerated ageing disorders comprise a significant and unique collection that should be a valued treasure to the ageing community and related groups. I look forward to the spirited discussions these *Ageing Research Reviews* articles will elicit and hopefully new advances to promote healthy ageing based on the topics addressed. I wish to thank K.C. Alexander (*Ageing Research Reviews* Editorial Assistant) and Dr. Mark Mattson (*Ageing Research Reviews* Editor-in-Chief) as well as Nithya Sathishkumar (*Elsevier* Publishing Content Specialist) and Dr. Shamus O'Reilly (*Elsevier* Senior Publisher) for their guidance and assistance to make this project possible. I am also very grateful to the contributing authors from their respective laboratories for their diligent efforts. I would especially like to acknowledge my parents Joanne and Robert Brosh, Sr. for their unwavering support which enabled me to pursue science and life's challenges with passion and determination.

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