Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

A REVIEW OF XERODERMA PIGMENTOSUM AND ITS MEDICAL IMPLICATIONS

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DOI:https://doi.org/10.5281/zenodo.20770837

Keywords

Xeroderma pigmentosum, nucleotide excision repair, DNA repair disorders, afamelanotide, skin cancer prevention, gene therapy, neurodegenerative diseases, photoprotection.

Article History

Received: 07 April 2026
Accepted: 19 May 2026
Published: 16 June 2026

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Abstract

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease due to impaired nucleotide excision repair (NER) that results in severe sun sensitivity, a 10,000-fold risk of developing skin cancers, and - in 25-30% of cases - central nervous system degeneration. This review offers a thorough assessment of the molecular mechanism of XP, its multi-organ clinical symptoms, and critically reviews emerging and clinically tested therapeutic approaches, such as gene therapy, topical DNA repair enzymes and the new melanocortin agonist afamelanotide. We reviewed the literature for clinical trials, randomized controlled trials, and studies into the molecular mechanisms from 2000 to 2025. The results of this review show that while rigorous sun protection is the mainstay of treatment, new phase II clinical trials have shown that afamelanotide reduces the formation of cyclobutane pyrimidine dimers and could reduce the development of skin cancer. Topical T4N5 endonuclease (Dimericine) was promising but further efficacy studies were halted due to lack of long term efficacy. Gene therapy using XPA-corrected autologous keratinocytes and HVJ liposome to deliver XPA have demonstrated proof-of-concept in mice, but have yet to be translated to humans. Neuro complications lack disease-modifying therapies, and are an unmet need. Overall, XP remains a fatal disease, but there are promising new therapies that target disease-causing pathways with the first reported clinical reduction in DNA damage. Multimodal strategies to treat both skin and neurological aspects are required.

INTRODUCTION

1.1 Historical Context and Disease

Xeroderma pigmentosum (XP) was first described at the end of the 19th century, thanks to the pioneering efforts of Moriz Kaposi and Ferdinand von Hebra. In 1870, these Austrian dermatologists described a new devastating disorder with extreme sun sensitivity of the skin. They coined the eponym "xeroderma pigmentosum" (Greek and Latin for "dry pigmented skin"), describing the two most striking symptoms exhibited by their patients: dryness and pigmentation of the skin(A. R. Lehmann, McGibbon, & Stefanini, 2011). Their observations provided the fundamental insights into XP as a unique photodermatosis, well before the molecular diagnosis of XP as a DNA repair disease was made more than 100 years later. The recognition of XP's classical features of dryness, freckle-like hyperpigmentation and skin cancers at an early age continues to be vital for its diagnosis(Black, 2016).

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1.2 Epidemiology and Geographic Distribution

Geographical and ethnic differences play a key role in the epidemiology of xeroderma pigmentosum (XP). The incidence is estimated to be 2.3 per million live births in Western Europe; high rates are found in Japan (1 in 40,000) and North Africa (founder effects). This variation is thought to be due to increased consanguinity, which greatly affects the incidence of disorders such as XP, due to its autosomal recessive mode of inheritance(Kraemer & Slor, 1985). Higher frequencies have been reported in population with high rates of parental consanguinity, such as in Tunisia, Morocco, Algeria, Egypt, Turkey, Israel, and among the Kanuri in Nigeria. Carrier rates in some parts of North Africa may be as high as 1:30. Rates of this disorder in these geographic areas and demographic groups need to be considered in genetic counselling, early diagnosis and prevention(DiGiovanna & Kraemer, 2012).

1.3 Scope and Objectives

This review focuses on clinically effective therapeutic advances in xeroderma pigmentosum (XP) between 2019 and 2025, which differ from previous reviews in their focus on Phase II and Phase III trial data, rather than preclinical studies and anecdotal reports. While previous comprehensive reviews have focused on the molecular basis of the nucleotide excision repair (NER) defects and the natural history of XP, there is a need to assess systematically the therapeutic strategies that have shown statistically significant improvement in controlled human studies(Leung, Barankin, Lam, Leong, & Hon, 2022). As such, the current review focuses on novel strategies with advanced clinical trial data including afamelanotide, topical DNA repair enzymes and gene therapies. Another important unmet need, neurological complications which do not have disease modifying therapies, are also reviewed. Through limiting the papers included to high quality clinical evidence published in the last six years, the present review seeks to offer clinicians and researchers a current perspective on which emerging therapies should be adopted and/or further studied for use in XP(S. Moriwaki et al., 2017).

2. Molecular Pathophysiology

2.1 The Nucleotide Excision Repair (NER) Pathway

The Nucleotide Excision Repair (NER) pathway is an important mechanism of DNA repair that excises large, helix-distorting damage, such as that induced by ultraviolet (UV) light and carcinogens. NER is a complex, multi-step process that differs from base excision repair in that it excises bulky DNA lesions as a short, single-stranded oligonucleotide (about 24-32 nucleotides) containing the damage. This repair pathway involves several proteins such as XPC, XPA and the transcription factor TFIIH, which unwind the DNA and check the damage(Piccione et al., 2021). After two incisions are made on the damaged strand, the gap is repaired by DNA polymerases δ or ε using the undamaged complementary strand as a template and the remaining nick is repaired by DNA ligase. Mutations in NER genes cause devastating autosomal recessive diseases including xeroderma pigmentosum (XP), Cockayne syndrome and trichothiodystrophy (TTD), which are all highly sensitive to sunlight and (in XP) prone to develop skin cancers. Therefore, NER is essential for preventing mutagenesis and genomic instability as a result of exposure to environmental genotoxins(J. Lehmann, Seebode, Martens, & Emmert, 2018).

2.1.1 Global Genome NER (GG-NER) vs. Transcription-Coupled NER (TC-NER)

Global Genome NER (GG-NER) and Transcription-Coupled NER (TC-NER), which have different lesion recognition mechanisms. GG-NER scans the whole genome for helix-distorting lesions, with the XPC-RAD23B complex recognizing lesions throughout the genome, even if not transcribed. TC-NER, on the other hand, is activated by stalling of RNA polymerase at a lesion on the transcribed strand, bypassing the need for XPC-RAD23B. Subsequent excision and resynthesis steps are common to both sub pathways(Kraemer, Lee, & Scotto, 1987). Mutations in NER components define eight complementation groups (XPA, XPB, XPC, XPD, XPE, XPF, XPG, XPV), reflecting the different proteins that are deficient, and XPV, for a

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ISSN: (e) 3007-1607 (p) 3007-1593

translesion polymerase. Defects in these groups result in diseases such as xeroderma pigmentosum, with patient severity varying according to the sub pathway. Knowing the recognition differences is important to predict cancer risk and neurological manifestations in NER patients(Gratchev, Strein, Utikal, & Goerdt, 2003).

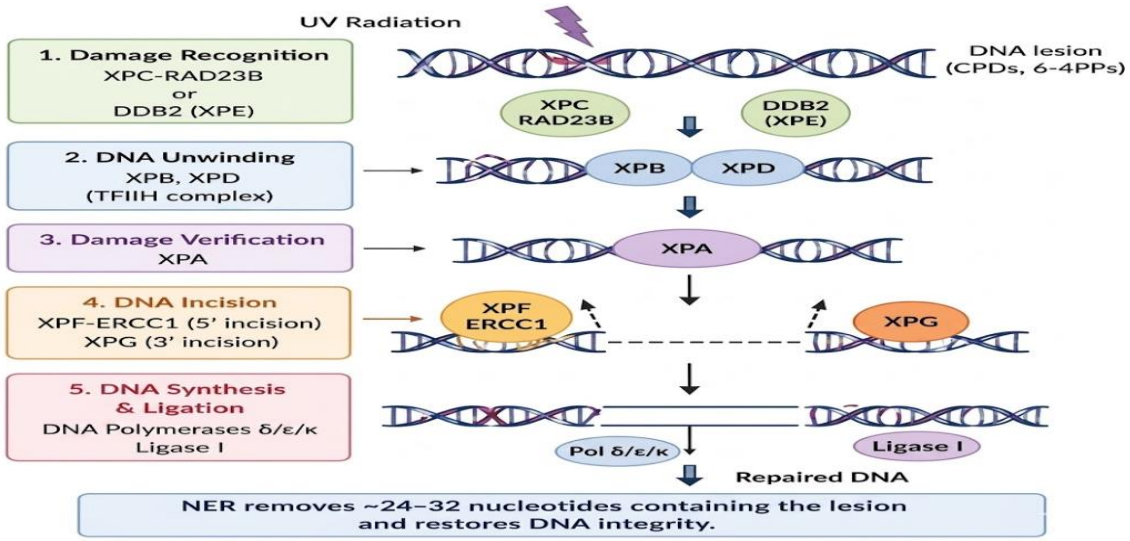


Figure 1: Nucleotide Excision Repair (NER) Pathway and Sites of Action of XP Proteins

2.1.2 Substrate Specificities

The preference of the Nucleotide Excision Repair (NER) pathway for its substrates demonstrates the astonishing capacity of this pathway to identify and repair a variety of large DNA lesions. Perhaps the best known substrates are the ultraviolet (UV) photoproducts, cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs)(Feller et al., 2010). CPDs, which arise from the joining of two pyrimidines, are more frequent but less distorting lesions, and are repaired more slowly. 6-4PPs, which induce a greater distortion of the double helix, are less frequent and repaired more efficiently, sometimes as soon as hours after UV exposure. In addition to these external damages, NER repairs some endogenous oxidative DNA lesions, such as 8,5- cyclopurine deoxynucleotides (cyPu). These damages result from attack by reactive oxygen species on the purine ring, forming a covalent linkage between the C8 and C5 atoms of the purine(Johnson, Kondratick, Prakash, & Prakash, 1999). The formation of the cyclopurine structure creates a rigid structure and distortion of the DNA helix, making cyPu unique substrates for NER that are not efficiently repaired by base excision repair (BER). This has clinical implications since defective NER allows cyPu to accumulate, leading to neurodegenerative symptoms in conditions such as xeroderma pigmentosum. Therefore, the wide but specific substrate recognition capacity of NER (UV dimers, oxidative lesions) highlights its crucial function in genome stability(JE Cleaver, 1969).

2.2 Genetic Basis and Complementation Groups

The Nucleotide Excision Repair (NER) pathway is genetically defined by a range of complementation groups, largely discovered through the study of the autosomal recessive disease xeroderma pigmentosum (XP). These - XPA to XPG (XPA, XPB, XPC, XPD, XPE, XPF, XPG) - correspond to different genetic loci whose mutations affect various NER processes(Anttinen et al., 2008). Each complementation group represents a distinct protein deficiency: XPC is involved in lesion recognition in global genome repair, whereas XPB and XPD are helicase components of the transcription factor TFIIH needed to unwind the DNA. XPA serves as a scaffold protein for damage verification, XPG and XPF-ERCC1 cut 3' and 5' of the lesion, respectively, and XPE (DDB2) assists in the recognition of UV-induced photoproducts. A

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further group, XPV, is the translesion synthesis DNA polymerase eta, which replicates over unrepaired photoproducts. XPV patients show hypermutability but no repair deficiency, as a result of defective replication(J. E. Cleaver, 2005). The complementation groups were initially established through cell fusion analysis, in which XP fibroblasts were fused to determine if DNA repair synthesis was restored; groups that didn't complement had the same underlying mutation. In clinical practice, XPA, XPB, XPD and XPG mutations frequently result in severe neurological symptoms, while XPC and XPE patients are at risk of skin cancer only. The genetic basis of NER uncovered by these complementation groups not only revealed repair mechanisms but also allowed for prenatal diagnosis and genetic advice for XP families(Norgauer, Idzko, Panther, Hellstern, & Herouy, 2003).

XP Group	Gene	Protein Function	NER Role	Neurological Involvement	Cancer Risk
XPA	XPA	Damage verification protein	Stabilizes & verifies damaged DNA	Severe (70–80%)	Very High
XPB	ERCC3	Helicase (TFIIH)	DNA unwinding	Moderate	High
XPC	XPC	Damage recognition protein	Recognizes DNA lesions	None	Very High
XPD	ERCC2	Helicase (TFIIH)	DNA unwinding	Moderate–Severe	High
XPE	DDB2	Damage recognition protein	UV lesion detection	None	Moderate
XPF	ERCC4	Endonuclease	5' incision	Mild–Moderate	High
XPG	ERCC5	Endonuclease	3' incision	Moderate	High
XPV	POLH	Translesion synthesis polymerase η	Bypasses lesions during replication	None	Moderate (melanoma ↑)

Figure 2: Genetic Basis of Xeroderma Pigmentosum (Complementation Groups and Clinical Features)

2.3 Emerging Concepts: Mitochondrial Pathophysiology

Recent developments in the field of Nucleotide Excision Repair (NER) point to a key role for NER defects in causing mitochondrial dysfunction, especially in neurodegenerative forms of xeroderma pigmentosum (XP) and Cockayne syndrome. Growing evidence shows that mutations in NER genes, particularly XPA, XPB, XPD and XPG, result in defective mitochondria, with defects in oxidative phosphorylation, loss of mitochondrial membrane potential and changes in organelle shape(S. I. Moriwaki & Kraemer, 2001). The key to this mechanism lies in the persistence of endogenous DNA lesions, such as oxidative base damage and cyclopurine nucleotides, in nuclear and mitochondrial DNA in NER-deficient cells. This leads to sustained activation of poly(ADP-ribose) polymerase (PARP), which causes a loss of cellular NAD+ and ATP, and increased reactive oxygen species (ROS) production. The ensuing oxidative stress leads to a ROS-driven vicious cycle, with further damage to DNA and mitochondrial components, which hastens neuronal cell death in the cerebellum and cortex(J. E. Cleaver & Bootsma, 1974). These findings have implications for therapeutic strategies. Strategies being explored include NAD+ replacement to improve energy production, mitochondrial-specific antioxidants to disrupt the ROS cycle and small molecules to boost remaining NER capacity or to inhibit other repair pathways. So, insights into NER's mitochondrial function highlight new opportunities for therapies against neurodegeneration(Zghal, Fazaa, Abdelhak, & Mokni, 2018).

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2.4 XP-Cockayne Syndrome Complex

The XP-Cockayne syndrome (XP-CS) complex is a rare, severe overlap syndrome with the skin lesions of xeroderma pigmentosum (XP) and systemic and neurological symptoms of Cockayne syndrome (CS). These individuals have XP-like severe light-sensitivity and early onset skin tumors, as well as CS-like severe growth retardation and progressive neurological deterioration, microcephaly and cachectic dwarfism. This dual phenotype results from mutations in the NER genes that have dual functions: XPB, XPD (helicase subunits of TFIIH) and XPG (structure-specific endonuclease)(Sun & Cui, 2008). Whereas classical XP patients have normal transcription, XP-CS mutations disrupt transcription coupled repair and disrupt basal transcription recovery after oxidative stress or UV damage. This results in stalled transcription and subsequent cell death and poor gene expression, accelerating neurodegeneration and developmental abnormalities seen in XP-CS. Therefore, XP-CS reveals the contribution of transcription dysfunction, rather than unrepaired DNA damage, to severe neuro-degeneration(Inui et al., 2008).

3. Clinical Manifestations

3.1 Cutaneous Manifestations

Skin manifestations of xeroderma pigmentosum (XP) are the initial symptoms and are caused by impaired nucleotide excision repair (NER) of UV DNA damage. Patients demonstrate profound sun-sensitivity with 40% experiencing severe sunburn following low exposure to sunlight. One of its characteristic features is freckling at an early age (usually by two years) on sun-exposed skin(Reed, Landing, Sugarman, Cleaver, & Melnyk, 1969). Skin damage from sun exposure progresses to poikiloderma (atrophy, telangiectasias and dyspigmentation) followed by actinic keratosis in childhood or adolescence. Eventually, patients are at a 10,000-fold risk of non-melanoma skin cancers and 2,000-fold risk of melanoma with a median age at first cancer of eight to 10 years(Kraemer, DiGiovanna, Moshell, Tarone, & Peck, 1988).

3.1.1 Acute Photosensitivity

Xeroderma pigmentosum (XP) acute photosensitivity is highly variable among individuals, due to the diversity of NER gene mutations. Around 40% of XP patients have a severe sunburn response to low levels of sun exposure, with intense redness, blistering and inflammation that can persist for weeks. This reaction usually appears in the first two years of life, and is often the first clinical sign. The other 60% of patients do not present with abnormal sunburns, but rather have a more subtle onset of skin lesions(Lucero & Horowitz, 2023). While these patients do not have acute photosensitivity, they all have a pathognomonic sign: early freckling, which occurs at a mean age of two years, most commonly on sun-exposed sites, including the face, neck and dorsal hands. These XP lentigines, in contrast to common freckling, are persistent and progressive, and often progress to poikiloderma. This unique pattern of early freckling, often in the absence of sunburn, highlights the need to consider non-burning forms of XP. This can lead to a delay in diagnosis in patients without acute photosensitivity, suggesting that suspicion of XP should be based on freckle appearance even in the absence of acute sunburns(Li, Bales, Peterson, & Legerski, 1993).

Table 1: Clinical manifestations across organ system

System	Manifestations	Key Features	Clinical Impact
Skin	Freckling, poikiloderma, cancers	Early onset (age <2)	10,000× ↑ cancer risk
Eyes	Photophobia, keratitis	UV sensitivity	Vision impairment
Oral	SCC (tongue/lips)	Early malignancy	High morbidity
Nervous system	Hearing loss, ataxia	Progressive	Reduced lifespan
Systemic	Premature aging, malignancies	Rare	Multi-organ involvement

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3.1.2 Progressive Solar Damage

Progressive sun damage in xeroderma pigmentosum (XP) is an accelerating form of sun damage, starting in early childhood, and progressing rapidly in the absence of appropriate DNA repair. Poikiloderma, a triad of skin atrophy (thinning and wrinkling), telangiectasias (fine red patches of dilated superficial blood vessels(Natale & Raquer, 2017). This poikilodermatous transformation usually occurs on chronically sun exposed sites such as the face, neck and extensor arms, frequently at an early age (first five years). Over time actinic keratosis (AKs) develop in mid to late childhood or adolescence, as opposed to the sixth or seventh decade of life in the general population. These are rough, sandpaper-like intraepidermal keratinocyte dysplasia that are precursors of squamous cell carcinoma(Paszkowska-Szczur et al., 2013). AKs are often numerous, confluent and recurrent in XP patients, necessitating repeated cryotherapy and/or topical medications (such as 5-fluorouracil). Early onset of poikiloderma and actinic keratosis highlight the important role of NER in restraining UV-induced clonal expansion of keratinocytes harboring mutations. In the absence of strict sun protection, frequent dermatological monitoring and management, these progressive changes inevitably lead to invasive skin cancers(A. R. Lehmann, 2001).

3.1.3 Skin Cancer Profile

The array of skin cancers in xeroderma pigmentosum (XP) demonstrates one of the most striking susceptibility to malignant disease in man, as a result of impaired nucleotide excision repair and subsequent accumulation of UV damage. The risk of nonmelanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) is increased 10,000-fold and the risk of cutaneous melanoma 2,000-fold(Sugasawa, 2008). Most remarkable of all, XP patients experience a remarkably young age of cancer onset: the median age of the first skin cancer is 8-10 years (compared to more than 60 years in the general population). XP children often present with their first skin cancer before age 10, and even without scrupulous sun protection, some develop their first skin cancers at the tender age of two. Further, the number of primary cancers is highly unusual; each patient can develop tens or even hundreds of primary cancers throughout their lifetime, which must be removed by surgery and monitored by dermatologists(Lambert, Kuo, & Lambert, 1995). In addition, these tumors are often aggressively invasive, with greater local invasion, recurrence and metastatic potential than their sporadic histologically comparable counterparts. The eye surface is also at risk; with a similarly 2,000- fold increased risk of melanoma in the conjunctiva and uveal tract. This remarkable cancer burden is a consequence of the spectrum of unrepaired UV photoproducts (especially cyclobutane pyrimidine dimers) that result in diagnostic mutations in key tumor suppressor genes such as p53 and PTCH. Therefore, XP provides a model to study UV carcinogenesis and the role of NER in preventing it(Fassihi, 2013).

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

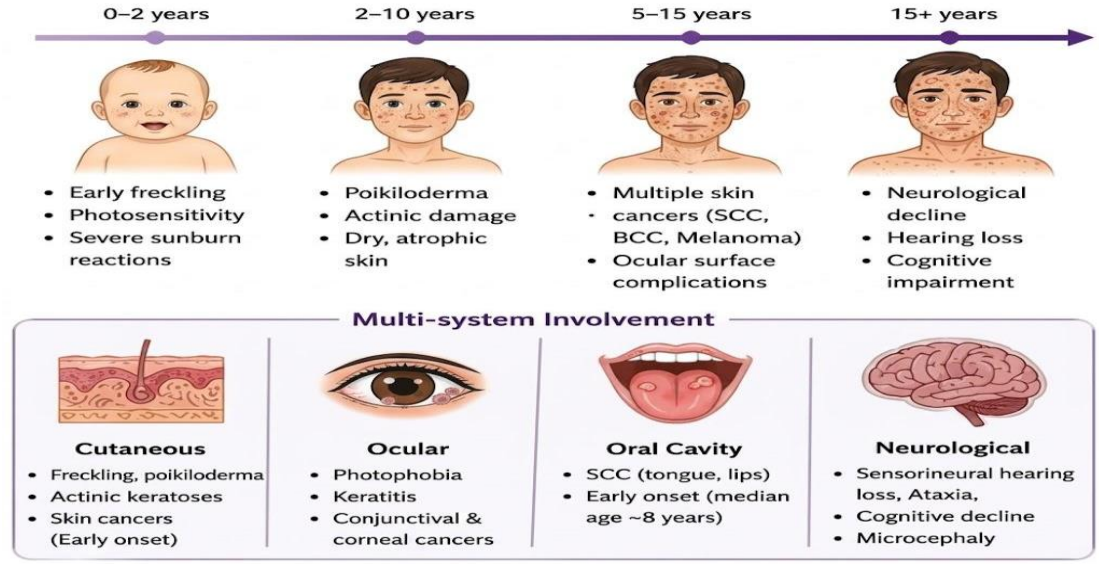


Figure 3: Clinical Manifestations and Disease Progression in XP

3.2 Ocular Manifestations

Almost all patients with xeroderma pigmentosum (XP) have some type of ocular involvement, due to the same dysfunction of nucleotide excision repair (NER) as that seen in the skin, which renders UV-exposed eye tissues susceptible to DNA damage. Nearly all XP patients experience photophobia (excessive, painful light sensitivity) which often develops in early childhood and has a major impact on quality of life. This is a consequence of conjunctival and corneal changes, including dry eye, recurrent conjunctival hyperemia, corneal clouding, pterygium-like growths and limbal stem cell deficiency(Brambullo et al., 2022). These degenerative changes may result in vascularization, scarring and permanent blind. In addition to benign findings, XP patients are at high risk of eye cancer. Conjunctival squamous cell carcinoma (SCC) is common, sometimes at a young age, and can be multifocal and/or aggressive. Conjunctival melanoma is less frequent, but similarly increased in incidence as cutaneous melanoma. Both tumors are treated with excision but recur frequently due to the field defect of the entire ocular surface. Early diagnosis and prevention through regular eye examination starting in infancy, intensive UV protection including sunglasses with wrap around lenses and early treatment of suspicious lesions is crucial to maintain vision and prevent metastatic disease(Copeland, Hanke, & Michalak, 1997).

3.3 Oral Mucosal Involvement

Xeroderma pigmentosum (XP) patients are also at high risk of UV-induced oral mucosal lesions due to the high exposure of the lips and anterior tongue to sunlight. The most frequent malignant lesion of the oral cavity is squamous cell carcinoma (SCC) with a striking distribution: 46.2% on the tongue and 36.6% on the lips, due to their direct sun exposure(Kraemer, DiGiovanna, & Peck, 1992). Notably, the median age of oral SCC in XP patients is just 8 years (interquartile range 7), which is significantly younger than the median age of first cutaneous tumors (8-10 years), suggesting that the oral mucosa might be especially susceptible to UV damage, or that the lesions are detected later because of reduced self-examination. This is in contrast to sporadic oral SCC, which occurs after 60 years of age(Bradford et al., 2011). Basal cell carcinomas (BCCs) are restricted to the vermilion borders of the lips (red, hair-bearing border) and spares the non-hair-bearing intraoral mucosal surfaces, an intriguing but consistent finding that reflects the different biology of these different types of epithelia and their different exposure to UV light. Risk factors like these

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ISSN: (e) 3007-1607 (p) 3007-1593

warrant early and frequent oral inspection starting in infancy with inspection of the tongue, lips and vermilion border (with palpation for induration). Suspicious non-healing ulcers, leukoplakia patches and exophytic masses should be biopsied. Preventative interventions include opaque lip products, sun-shielding face masks and dental monitoring(Wang et al., 2009).

3.4 Neurological Manifestations

One of the most severe and intractable features of xeroderma pigmentosum (XP) is the neurological involvement, which affects around 25% of patients, mainly those in complementation groups XPA, XPB, XPD, XPF and XPG. The molecular basis is impaired repair of damaged neurons by nucleotide excision repair (NER) resulting in progressive neurodegenerative changes from an early age. These include sensorineural hearing loss, which can become profound, cerebellar ataxia (gait instability and incoordination), spasticity, dysarthria and dementia. Dysphagia (risk of aspiration) and peripheral neuropathy are also common(Nishigori, Moriwaki, Takebe, Tanaka, & Imamura, 1994). Neurological involvement cannot be cured, as unlike skin cancers, there are no disease-modifying treatments for neurological disease. There is no specific treatment, only supportive management with hearing aids, physical and occupational therapy for ataxia, speech therapy for dysarthria and swallowing evaluations. Innovative research investigates mitochondrial dysfunction and oxidative stress, but is not yet in clinical us(Masutani et al., 1999).

3.4.1 Prevalence and Complementation Group Distribution

Prevalence Neurological involvement in xeroderma pigmentosum (XP) is found in around 25-30% of patients overall, but varies between different complementation groups, which reflect the different functions of various NER proteins in addition to DNA repair. Neurologic deterioration is most frequent in the XPA and XPD groups, which exhibit progressive sensorineural hearing loss, areflexia, ataxia, cognitive dysfunction and peripheral neuropathy, typically during childhood or adolescence(Stary & Sarasin, 2002). By contrast, few if any patients from the XPC, XPE or XPV complementation groups display any signs of neurological involvement despite severe skin photosensitivity and skin cancer predisposition. This phenomenon of a clear discrepancy between the neurological and dermatological XP phenotypes points to the fact that neurodegenerative disorders in XP patients are not simply due to the inability to repair UV-induced DNA damage but more specifically the inability to repair endogenous oxidative damage to DNA such as cyclosporine nucleotides that accumulate in non-dividing neurons. Therefore, the distribution of complementation groups is an important prognostic factor for neurological disease(Van Steeg & Kraemer, 1999).

3.4.2 Progressive Neurodegeneration Pattern

The neurodegenerative course in xeroderma pigmentosum (XP) follows a typical clinical course, mainly in XPA, XPB, XPD and XPG complementation groups, and is the major cause of morbidity and mortality other than skin cancer. Sensorineural hearing loss is generally the first neurological symptom, which usually appears in early to mid-childhood and progresses to complete deafness by adolescence(Weon & Glass, 2019). This is often followed by mental retardation and intellectual deterioration, from mild learning disabilities to global dementia, with the latter typically progressing no further but sometimes stabilizing. Cerebellar ataxia includes gait instability, truncal titubation, and progressive dysarthria (scanning or slurred speech), due to cerebellar atrophy seen on magnetic resonance imaging (MRI). Pyramidal signs include spasticity, hyperreflexia (later becoming areflexia) and extensor plantar responses, while extrapyramidal signs (dystonia, chorea, parkinsonian rigidity) are variable(Redondo et al., 2008). Late, but almost universal, areflexia neuropathy is seen in severely affected patients, with distal sensory and motor deficits, and nerve conduction studies showing axonal degeneration. These symptoms are not detected at birth, but develop insidiously, if at all, after years of normal development. The clinical presentation resembles combined central and

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ISSN: (e) 3007-1607 (p) 3007-1593

peripheral demyelination but pathology shows primary neuronal loss, not demyelination. This degeneration results from the progressive build-up of unrepaired oxidative DNA damage, including cyclosporine nucleotides, in postmitotic neurons, and underscores the importance of NER in sustaining the life of neurons(Abeti et al., 2019).

3.4.3 Prognostic Impact

Neurodegeneration in xeroderma pigmentosum (XP) has a large negative impact on survival, with an average age of death of 29 years for patients who display neurological deterioration, versus 37 years in those without central nervous system involvement. This nine-year gap in life expectancy is due to the devastating effects of ataxia, deafness and dementia, which often culminate in aspiration pneumonia or other complications. Crucially, there are no treatments that alter the course of the neurological disease in xeroderma pigmentosum (XP), with supportive care only in the form of hearing aids, physical therapy and gastrostomy feeding(Patton & Valdez, 1991).

3.5 Other Systemic Involvement

Beyond skin, eye and neurological disease, xeroderma pigmentosum (XP) also has other systemic involvement. A high prevalence of early menopause in women, starting in their twenties, has significant endocrine consequences, such as infertility, and the risk of osteoporosis and need for hormone replacement therapy. Further, patients may have a low risk of internal cancers, particularly brain cancers (including medulloblastoma and glioblastoma) and leukemia, but less common than skin cancers. These cancers usually develop in childhood and adolescence, and should be monitored(Kraemer, Lee, Andrews, & Lambert, 1994).

4. Current Standard of Care Management

4.1 Photo protection Strategies

Preventative measures to avoid photosensitivity can go well beyond the periodic application of sunscreen, especially for those with severe photosensitivity. This includes complete UV protection, including protection against both UVA and UVB light. In extreme cases, this can even include protection from visible light, as some dermatologic disorders (such as erythropoietic protoporphyria) are also sensitive to high-energy visible light. This can be achieved by using protective clothing with a dense weave and sunscreens with a high sun protection factor (SPF) and broad wavelength protection(JE5655953 Cleaver, 1968). UV filters should also be applied to windows in homes, cars and workplaces, as glass blocks UVB, but not UVA light. But, such light avoidance comes at a metabolic cost: vitamin D deficiency. UVB light is needed for skin production of vitamin D, which is removed by these measures. As a consequence, it is mandatory to supplement vitamin D regularly to preserve bone strength and immunity. Most guidelines advocate for serum 25-hydroxyvitamin D levels to be checked and supplement doses of 600-2000 IU per day, to be titrated according to the individual's levels. Failure to supplement patients may lead to secondary osteomalacia, fractures and a reduced benefit from photo protection. Therefore, a comprehensive photo protection strategy needs to combine physical measures, sunscreens, environmental and nutritional interventions to be safe and effective(Sethi, Lehmann, & Fassihi, 2013).

4.2 Regular Surveillance Protocols3

Surveillance guidelines are crucial to detect and manage complications in the photosensitivity disorders or syndromes with a predisposition to skin cancers. The protocols generally include a dermatologic examination, with a thorough skin check every three to six months to screen for actinic keratosis, atypical moles or squamous and basal cell carcinomas(Hwang, Ford, Hanawalt, & Chu, 1999). Likewise, an annual eye examination is essential, as prolonged exposure to low levels of ultraviolet light can hasten the development of cataracts, pterygium or retinal degeneration, especially in patients receiving photosensitizing drugs or with inherited DNA repair defects such as xeroderma pigmentosum. For high-risk populations (such as those with neurologic diseases such as Cockayne syndrome or porphyria), a baseline neurologic examination and annual assessment is advised to detect peripheral

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neuropathy, ataxia or cognitive impairment that may occur in the absence of dermatologic pathology(Chu & Chang, 1988). Finally, a formal oral examination performed by a dentist and dermatologist at the time of diagnosis and annually is required to detect mucosal leukoplakia, squamous cell carcinoma of the lip or pigmented lesions of the gingiva and hard palate, which may be missed in routine dermatologic surveys. These multidisciplinary surveillance plans enhance outcomes with early detection. Overall, such multidisciplinary, time-limited checks convert photo protection from a preventive to a proactive, ongoing medical care program(Kraemer, Lee, & Scotto, 1984).

4.2 Regular Surveillance Protocols

Surgery continues to be the mainstay for most skin cancers, with two main approaches based on the lesion and risk factors. The treatment of choice for primary, well-defined cutaneous cancers is excision with margin control, which involves removal of the lesion with a margin of clinically normal skin (usually 4-6 mm for low-risk basal cell carcinomas, but a larger margin is used for squamous cell carcinomas or melanomas). The tissue is histologically examined to ensure negative margins, thus maximizing the chances of complete excision without sacrificing large amounts of tissue. But for recurrent or facial cancers, Mohs micrographic surgery is the treatment of choice. This unique technique involves the removal and immediate evaluation of thin layers of tissue, which permits mapping of microscopic extensions of the tumor. Mohs surgery has higher cure rates, and allows for optimal preservation of healthy tissue, making it the preferred procedure for cosmetically sensitive areas such as the eyelids, nose, lips and ears(Daya-Grosjean, 2008). However, this group of patients presents unique challenges to surgeons, including the need to address multiple (synchronous or metachronous) tumors, the younger age of some patients (with the need for long-term prevention of recurrence and aesthetic outcomes) and the inherent high risk of recurrence due to aggressive histologic subtypes or failed prior attempts at surgical removal. This requires careful surgical planning, close follow-up and often multiple surgical sessions. In conclusion, the choice between conventional excision and Mohs surgery is based on individual risk factors, tumor site and patient choice in an effort to achieve both good oncologic and aesthetic outcomes(Koch, Simon, Ebert, & Carell, 2016).

5. Clinically Proven Emerging Treatments

5.1 Topical DNA Repair Enzymes

5.1.1 T4N5 Endonuclease (Dimericine)

T4N5 endonuclease (also known as Dimericine) was a potential topical treatment for the repair of cyclobutane pyrimidine dimers (CPDs), the predominant ultraviolet radiation-induced DNA lesions. The drug comprised bacteriophage T4 endonuclease V encapsulated in liposomes to be delivered into the nuclei of skin cells to promote excision repair of CPDs with the possibility of blocking ultraviolet-induced mutagenesis. Supporting this approach, one prospective randomized controlled trial showed topical Dimericine markedly decreased the incidence of new actinic keratosis (AKs) and basal cell carcinomas (BCCs) in xeroderma pigmentosum (XP) patients(Sijbers et al., 1996). However, the results from larger and longer follow-up studies have not shown consistent efficacy and further studies have been terminated prematurely. The causes for this inconsistency are unclear but may relate to poor skin penetration, instability of enzyme or lack of activity in human skin. Today, Dimericine is not available for xeroderma pigmentosum or any other use. Although photo protection and skin cancer prevention by topical application of DNA repair enzymes is an appealing possibility, no such product has so far become approved or accepted for routine use(Goyal, Rao, Srinivasan, & Agrawal, 1994).

5.1.2 Other Topical Approaches

Alternative topical treatments for prevention of photo damage and skin cancer risk in photosensitive patients have been trialled, but little clinical trial evidence exists. A pyrimidine antagonist that inhibits DNA synthesis, 5-fluorouracil (5-FU), has been used off-label for actinic keratosis in diseases like xeroderma

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pigmentosum. But its use is only anecdotal, with no controlled trials to support effective or safe use of this agent in this population(Lim, Sethi, & Morley, 2017). Likewise, imiquimod, a toll like receptor 7 agonist which stimulates local interferon production, has been reported as effective in the treatment of superficial basal cell carcinomas and actinic keratosis in rare cases. Neither has shown a significant effect on the prevention of new tumor development when used in a field effect approach. As such, topical immunomodulators and chemotherapeutics are still used as supplementary or lesion-specific therapies, rather than the default photo protective therapy of choice for genetically at-risk individuals(Mimaki et al., 1986).

5.2 Afamelanotide – The Most Promising Current Therapy

5.2.1 Mechanism of Action

Afamelanotide is the most exciting new photo protective agent for patients with extreme photosensitivity conditions, such as erythropoietic protoporphyria (EPP) and xeroderma pigmentosum. Afamelanotide works in a different way to conventional sunscreens or DNA repair enzymes. Afamelanotide is a synthetic peptide mimicking endogenous α-melanocyte stimulating hormone (α-MSH), and binds to the melanocortin-1 receptor (MC1R) on melanocytes, thus activating the cyclic AMP pathway resulting in continuous eumelanin induction(Kraemer et al., 2007). Importantly, this induction of eumelanin happens without any UV exposure, avoiding the risk posed to photosensitive patients by UVB-induced tanning. The brown-black eumelanin pigment that is produced is distributed throughout the epidermis, resulting in broadband photo protection against ultraviolet and visible light. In contrast to photo protection via DNA repair, afamelanotide primarily provides photo protection through physical and chemical sunscreens, by absorbing and scattering photons, and scavenging reactive oxygen species and photo damaged DNA(Berneburgl & Lehmann, 2001). Critically, the melanogenesis brought about in this manner is not dependent on functional DNA repair, and is therefore of particular benefit to patients with inherited defects in nucleotide excision repair (e.g. xeroderma pigmentosum). By allowing a level of natural protection from light, independent of DNA repair, afamelanotide corrects the fundamental pathophysiological abnormality in these based disorders. Clinical trials have shown substantial reductions in phototoxic reactions, pain episodes and improved quality of life, proving that afamelanotide is a disease-modifying rather than palliative therapy(Rizza et al., 2021).

5.2.2 Clinical Trial Evidence

The clinical trial data for afamelanotide is convincing, especially for the treatment of erythropoietic protoporphyria (EPP) where it is now regarded as standard of care. It has been shown to decrease phototoxic reactions in a pivotal Phase III, multi centre, randomized, placebo controlled trial. This study demonstrated a reduction in the number of days of moderate and severe pain in patients who had afamelanotide implants compared to placebo, as well as increased sun exposure without pain. This led to a recommendation for approval by the European Medicines Agency for the treatment of adult EPP patients in 2014 and approval in the USA (2019) and Australia (2020)(J. Lehmann, Schubert, & Emmert, 2014). An observational study from Germany also provided real-world, long-term evidence of a good safety profile and considerable quality-of-life benefits, with 91% of patients remaining on treatment. Efforts are underway to explore other photosensitivity disorders. A Phase II a proof-of-concept study (CUV156) has been started to assess afamelanotide's effectiveness in Xeroderma Pigmentosum (XP) patients, though is currently listed as terminated. A further study (NCT05370235) to assess its safety (CUV105) are exploring its use in a systemic treatment for vitiligo (depigmentation)(Hengge & Emmert, 2008).

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Table 2: Afamelanotide clinical trials in XP

Trial ID	Phase	Population	Status	Key Outcomes
CUV151	IIa	XP-C, XP-V	Completed	↓CPDs, ↓p53 & γH2AX
CUV152	II	XP-C, XP-V	Ongoing (2025)	Safety+ efficacy
CUV156	IIa	Mixed XP groups	Terminated	Proof-of-concept only
Observational Studies	NA	Small cohorts	Completed	Improved UV tolerance

5.2.3 Clinical outcomes

Afamelanotide's therapeutic effects include not only subjective improvements in symptoms, but also objective decreases in biomarkers of DNA damage. In xeroderma pigmentosum (XP), treatment has decreased the presence of cyclobutane pyrimidine dimers (CPDs), especially in the deeper layers of the epidermis and dermis where melanin stimulated by afamelanotide can accumulate. In controlled ultraviolet light exposure, treated patients have reduced sunburn, in line with the photo protective effects of eumelanin. Crucially, biomarkers of DNA damage such as p53 accumulation and γH2AX foci formation (both indicative of genotoxic stress) on the skin of treated patients show beneficial effects(Bootsma, 1978). These results demonstrate the effectiveness of afamelanotide as the first treatment with objective biomarker outcomes in XP patients, compared to subjective measures such as pain or quality of life. The improvement in these surrogate outcomes provides evidence for a potential mechanism of cancer risk reduction with prolonged therapy but requires long-term follow-up to demonstrate a reduction in tumors. However, the capacity to reduce UV-induced DNA damage on a molecular level is an important milestone in the treatment of disorders with defective nucleotide excision repair(Naegeli & Sugasawa, 2011).

5.2.4 Safety Profile and Limitations

Afamelanotide has a good safety profile, although there are some caveats. It is delivered as a 16 mg implant, subcutaneously every two months (usually in the upper arm or abdominal wall) under local anesthesia. Clinical trials of afamelanotide in patients with erythropoietic protoporphyria (EPP) and xeroderma pigmentosum (XP) have demonstrated good tolerability, with mostly mild to moderate local reactions at the site of implantation (such as erythema, pruritus or nodule formation) that are usually managed without intervention. Significantly, there have been no severe or life-threatening adverse events in XP studies and the drug is not genotoxic or carcinogenic. But afamelanotide does not address the underlying nucleotide excision repair deficiency present with XP, and will not remove the susceptibility to UV-induced mutagenesis(Baykal, Atcı, Yılmaz, & Büyükbabani, 2021). As such, patients receiving the drug still need to use photo protection measures such as clothing, sunscreens and avoidance of sunlight. Finally, afamelanotide is not yet approved for the treatment of XP. Although it has been approved for EPP in Europe, the US (2019) and Australia, it is not yet approved for XP or only available in clinical trials. The absence of specific Phase III studies in XP means that there are currently no data on the long-term efficacy of the drug on tumor prevention and it remains unclear whether it will be reimbursed. Moreover, the procedure for implanting the device needs specialist training, and it may not be financially feasible. So, while support for the use of afamelanotide comes from biomarker studies, it remains an investigational, adjunct treatment for XP(Dorn, 1959).

5.2.5 Future Directions

The potential use of afamelanotide is not limited to the current indications but could be used in combination with other agents and in other populations. An exciting possibility is the potential combination of afamelanotide with topical DNA repair enzymes, such as T4N5 endonuclease, that can provide synergistic photo protection through melanin-induced photo protection from afamelanotide, as well as increased excision repair of residual cyclobutane pyrimidine dimers. This combination potentially

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leads to a greater reduction in ultraviolet-induced mutagenesis than either treatment alone, especially in xeroderma pigmentosum with a defective repair mechanism(Garcia-Moreno et al., 2023). Moreover, afamelanotide could be beneficial to immunosuppressed individuals, such as solid organ transplant recipients, who are at high risk of developing cutaneous squamous cell carcinoma from chronic immunosuppression and UV exposure. Afamelanotide may restore pigmentation to the epidermis without UVB exposure and thus offer a protective effect regardless of immune status. Other high-risk populations include those with multiple actinic keratosis, field cancerization or rare skin diseases such as trichothiodystrophy or Bloom syndrome. But it has yet to be tested in immunosuppressed patients, and its interaction with calcineurin inhibitors and mTOR inhibitors has not been tested. Current and future clinical trials will help determine the risk-to-benefit ratio of afamelanotide's photo protective effect in these new populations(Rapin, Lindenbaum, Dickson, Kraemer, & Robbins, 2000).

5.3 Gene Therapy Approaches

5.3.1 Preclinical Evidence:

XPA Murine Models Preclinical studies of gene therapy for xeroderma pigmentosum (XP) have been successful, with studies mostly conducted in XPA knockout mice that model human DNA repair deficiency. These studies used hemagglutinating virus of Japan (HVJ)- liposome complexes to introduce XPA cDNA into mice with the skin disease. After topical or intradermal treatment, animals showed restoration of unscheduled DNA synthesis (UDS) - a measure of nucleotide excision repair - showing that the disease-correcting gene was successfully transferred and expressed(Brooks et al., 2013). Moreover, the functional activity was confirmed by immunohistochemical detection of decreased levels of cyclobutane pyrimidine dimers (CPDs) and pyrimidine-(6-4)- pyrimidone photoproducts (6-4PPs) following ultraviolet B (UVB) exposure in the gene-corrected skin compared to non-corrected skin. This study offers proof of concept for the transient correction of repair capacity, and reduction of UV-induced DNA damage following somatic gene delivery. But this approach has only been preclinical. The main issues are achieving long-term expression without triggering immune responses, efficient delivery to keratinocytes and melanocytes, and delivering vector to a large area of skin. No clinical trials have been launched and there are concerns about insertional mutagenesis and off-target effects(de Andrade, de Oliveira Cavalcanti, Isoldi, & Ferreira, 2021).

5.3.2 Ex Vivo Keratinocyte Correction

Ex vivo gene therapy for xeroderma pigmentosum (XP) is technically more challenging but potentially long-lived alternative approach to in vivo gene delivery. In this approach, patient-derived keratinocytes are obtained by skin biopsy, genetically corrected in the lab by transducing the cells with retroviral or lentiviral vectors encoding the gene of interest for XP (XPA, XPC or XPD). The modified cells are then cultured and used to generate cultured skin equivalents - three dimensional epidermal and dermal grafts(Fassihi et al., 2016). These equivalents are then grafted back into the patient (usually following excision of actinic damage or premalignant skin). Animal studies have shown normalization of nucleotide excision repair, unscheduled DNA synthesis and retention of cyclobutane pyrimidine dimers in the corrected keratinocytes. But this remains experimental, and has no clinical use. Technical hurdles include complete safety regarding insertional mutagenesis (activation of oncogenes), long-term engraftment with non-clonal dominance of corrected cells and scaling up production for large surface areas. In addition, the cost of manufacturing, regulatory issues with viral vectors and the need for multiple interventions in a progressive condition such as XP limit the usefulness of this approach. Ex vivo correction is a beautiful concept, but still limited to proof-of-concept studies, with residual issues of potential immunogenicity to viral vector elements or correction proteins(Martens, Emmert, & Boeckmann, 2020).

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5.3.3 Challenges for Clinical Translation

The translation of gene therapy into the clinic for xeroderma pigmentosum (XP) presents unique challenges, in addition to those that apply for all rare diseases. First and foremost is the size of the therapeutic genes. Although XPA (at 1.5kilobases) can easily be accommodated within the adeno-associated virus (AAV) vectors that have been used successfully in other gene therapies, XPC (4.4 kilobases) is too large to be carried by AAV and exceeds the limits of many retroviral vectors(Kraemer, Levy, et al., 1994). This necessitates either multiple vector approaches or alternative viral vectors, with consequent regulatory and safety challenges. More importantly, therapy requires systemic, not local, correction, and for life. XP patients not only suffer from hypersensitivity to sunlight, but also have a higher risk of progressive neurodegenerative disease due to a lack of DNA repair in neurons. Thus, any effective treatment must provide long-term gene expression in the central nervous system, which will require traversing the blood-brain barrier or direct delivery into the brain - both formidable barriers(Khan et al., 2000). Concerns for immunogenicity also pose a challenge, with pre-existing or induced neutralizing antibodies to the capsids of viral vectors abolishing efficacy with subsequent administration. Moreover, the extremely low incidence of XP (estimated 1 in 1,000,000) is unviable for commercial development without considerable philanthropic or government support. The challenges of producing clinical-grade viral vectors, conducting pivotal studies and creating registries for follow-up of a minute number of patients also pose problems(Satokata et al., 1990).

5.4 Neurological Symptom Management

Despite the success of photo protection and surgical treatment of skin cancers, there are few treatment options to reduce neurological symptoms in xeroderma pigmentosum (XP). Unfortunately, there are no therapies available to arrest the progressive neurodegenerative process that occurs in about 25% of XP patients, especially those from complementation groups XPA, XPB, XPD and XPG. As such, treatment is currently only supportive and palliative, emphasizing preservation of functional independence and quality of life(JE Cleaver, Greene, Coriell, & Mulivor, 1981). Approaches to sensorineural hearing loss, which often starts in childhood and advances to profound hearing loss, include the use of standard hearing aids, but may involve cochlear implant in some patients. Ataxia, due to cerebellar degeneration and dorsal column pathology, is treated with physical therapy to maintain ambulation, balance retraining and mobility devices, while occupational therapy is beneficial for fine motor coordination for everyday activities. Dysarthria, which can be seen in bulbar involvement, is treated with speech therapy, such as articulatory training, augmentative and alternative communication (AAC) systems and family communication training. Further, patients often develop dysphagia, with modification of diet and speech pathology evaluation to avoid aspiration pneumonia(Ramkumar et al., 2011). Potential new treatment targets include two interrelated mechanisms: mitochondrial dysfunction, as the impaired nucleotide excision repair results in mitochondrial DNA damage and defects in oxidative phosphorylation, and chronic oxidative stress, which hastens neuron degeneration. Animal models are investigating the use of N-acetyl cysteine, coenzyme Q10 and mitochondrially targeted antioxidants to provide neuroprotection. But these have yet to be tested in clinical trials. While waiting for gene therapy or small molecule therapies, multidisciplinary supportive care is the mainstay of care for neurological involvement in XP(Setlow, Regan, German, & Carrier, 1969).

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ISSN: (e) 3007-1607 (p) 3007-1593

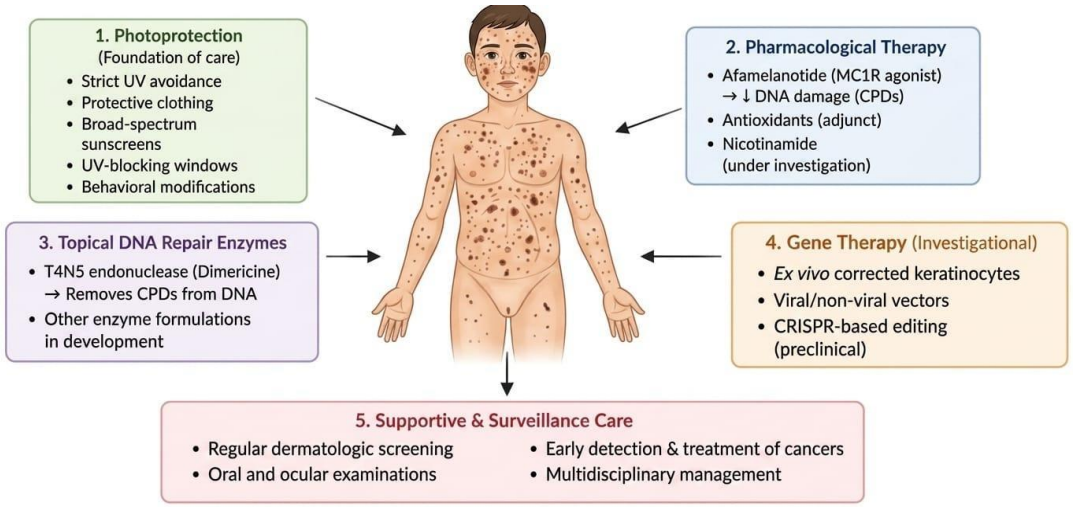


Figure 4: Current and Emerging Therapeutic Strategies in XP

6. Toward a Cure – Future Directions and Unmet Needs

6.1 Critical Unmet Needs

The path to treating xeroderma pigmentosum (XP) is a daunting one, with key gaps in basic science, clinical practice and therapeutic development. First, there is no disease modifying therapy for the rapidly progressive neurodegenerative disease that affects 25-30% of XP patients. The lack of therapies to reverse or halt neurodegenerative disease is the highest priority unmet need, given that neurodegeneration is the cause of early death and severe disability(Sugasawa, Shimizu, Iwai, & Hanaoka, 2002). Second, there are no effective systemic treatments to reduce the thousands-fold-increased risk of skin cancer. The only available strategies are ultra-high protection from sunlight and repeated surgery, which are onerous, disfiguring and, ultimately, ineffective due to the ever-escalating number of primary tumors. Third, effective markers that predict disease progression, including which complementation groups will get neurological type disease and when, are lacking, making it difficult to plan interventions. Fourth, genetic testing and newborn screening for XP are largely unavailable, resulting in a delay in diagnosis and accumulation of irreversible UV damage in early life(Broughton et al., 2002). Fifth, no topical compounds are available to activate residual NER or provide pharmacological photo protection (other than physical sunscreens). Sixth, XP's rarity (estimated 1 in 1 million in most populations) presents challenges for clinical trials, such as participant recruitment, absence of natural history data and the lack of commercial incentive to develop orphan drugs. Finally, there are often no seamless transitions between pediatric and adult care, and limited dedicated, multidisciplinary XP clinics worldwide. To overcome these challenges, international consortia, registries, novel clinical trial designs such as n-of-1 trials, and research into gene therapy, small molecule read through agents and neuroprotective interventions (to combat oxidative stress and PARP hyper activation) are needed(Sugasawa et al., 1998).

Table 3: Current gaps vs future therapeutic opportunities

Area	Current Status	Gap	Future Direction
Skin cancer prevention	Photo protection+ surgery	Not sufficient	Biomarkers-based therapies
Neurological disease	Supportive only	No cure	Mitochondrial therapy
Gene Therapy	Preclinical	No human trials	CRISPR, viral vectors
Drugs trials	Small sample sizes	Lack of RCTs	Global registries

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Biomarkers	Limited	Not validated	Molecular endpoints

6.2 Emerging Research Frontiers

The cutting edge in xeroderma pigmentosum (XP) research is exploring a range of molecular mechanisms beyond sun-avoidance. One of these is the creation of mitochondria targeted antioxidants, such as Mito Q and SS-31 that target the ongoing oxidative stress and dysfunction that results from the DNA damage. compounds are currently only in the preclinical stage, but have been successful in XPA mice. compounds have been shown to have a neuroprotective effect in XPA mice. For patients with nonsense mutations, read-through drugs such as geneticin and ataluren are being tested to enable the read-through of premature stop codons and thus generate full-length protein(Kraemer & DiGiovanna, 2015). More definitively, CRISPR Cas9 stem cells (iPS) cells, resulting in correction of mutations in XPA, XPC and XPD with little to no off-target activity. stem cells, to correct mutations in the genes XPA, XPC and XPD with minimal off-target effects. Likewise, antisense oligonucleotide repair of splicing mutations have normalized mRNA in XP cells. Finally, delivery nanoparticles like lipid nanoparticles and polymers, are being optimized for topical delivery to correct the gene, promising a non-invasive approach to treat skin lesions. These systems are still mostly in the research but combined they provide a array of tools to move from palliative to corrective therapies(Mareddy, Reddy, Babu, & Balan, 2013).

6.3 The Role of Patient Registries and Natural History Studies

Registries and natural history studies are essential for development of therapies designs are often impossible for the ultra-rare disease xeroderma pigmentosum (XP). designs are often infeasible. Multinational collaborations (XP Family Support Group and the National Institutes of Health XP clinic registry have amassed data on phenotypes, complications and consequences of the disease. These resources enable natural history studies that inform clinical end points in treatment studies and facilitate patient interventional studies. Further, post market surveillance of existing therapies such as afamelanotide - which is licensed for erythropoietic protoporphyria, but used off label for XP relies heavily on registry data for monitoring long term safety, adverse effect and efficacy. effectiveness. Without this, new and potentially effective therapies may not be approved for XP, and patients could miss out on potential therapies. approval for XP and patients may miss out on therapies(Khatri, Bemghazil, Shafi, & Machina, 1999).

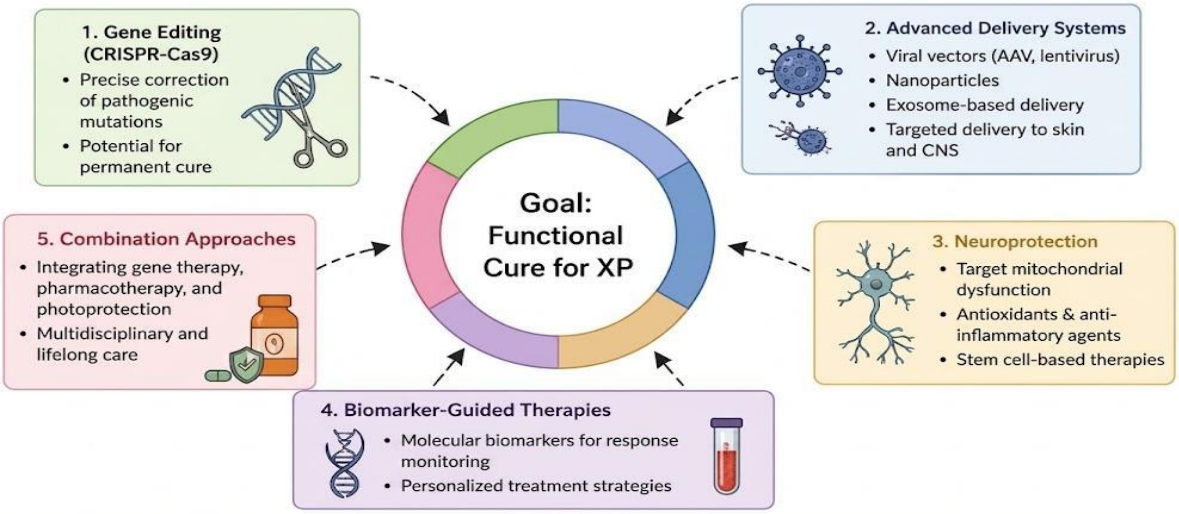


Figure 5: Future Directions: Toward a Potential Cure for XP

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7. Clinical Practice Guidelines Summary

7.1 Diagnosis

Xeroderma pigmentosum (XP) is diagnosed by first suspecting the condition by presenting features: severe sunburn (photosensitivity) with little UV light exposure, and an unusual freckling of sun-exposed skin at an early age (usually before two years). Confirmatory testing can be either molecular or functional. measurement in fibroblasts is the gold-standard functional test, and quantifies residual nucleotide excision repair measurement is the most sensitive functional assay, measuring residual nucleotide excision repair activity; levels less than 20% of normal are highly indicative of XP(JE Cleaver, 1972). Additional mutation analysis reveals mutations in any of the eight XP complementation genes (XPA, XPC, XPD, XPE, XPF, XPG, XPB and XPV), allowing accurate classification and correlation of genotype and phenotype. Crucially, there is a test for prenatal for families with mutations identified, via chorionic villus sampling or amniocentesis with UDS or direct DNA sequencing. The earlier the diagnosis, the better in order to start photo protection skin and eye damage, which has newborn screening as a topic of current debate(Robbins, 1988).

7.2 Multidisciplinary Care Team

Ideal care for xeroderma pigmentosum (XP) includes a multidisciplinary care team, led by dermatologists as the most affected system is the skin manifestations. Ophthalmology offers yearly screening for and treats corneal opacities, pterygia and eyelid tumors. Neurology is critical for patient in complementation groups A, B, D, F and G due to the increased risk of debilitating degeneration; it is recommended to have baseline and annual neurologic examinations. Dentistry and oral manages actinic damage and squamous cell carcinoma of the oral mucosa, lips and tongue. Psychology and psychiatry help with the considerable psychosocial problems, such as anxiety, and depression from avoiding the sun. Finally, genetic counseling explains to families about the genetic inheritance (autosomal recessive), risk of recurrence and prenatal diagnosis provides optimal, proactive care of all affected systems(Soufir et al., 2010).

7.3 Monitoring Schedule (Evidence-Based Recommendation)

Protocols for early intervention are key in xeroderma pigmentosum (XP). Skin check is recommended every three months from diagnosis as there are rapid onset of actinic keratosis and cancers in childhood. Biannual or annual exam (every six to 12 months) is recommended to diagnose corneal neovascularization, conjunctival melanomas and eyelid carcinomas prior to sight loss. For central nervous system involvement, patients in groups at risk of developing the disease (XPA, XPB, XPD, XPF, XPG) should have an initial assessment at the time of diagnosis, as well as yearly cognitive and motor function(Ahmad & Hanaoka, 2008). Lastly, oral examination with particular attention to the lower lip, tongue and buccal mucosa where squamous cell carcinomas of the oral cavity arise is advised every six months from diagnosis, including the lower lip, tongue and buccal mucosa, sites for squamous cell carcinoma development. This frequent surveillance is backed up by prospective cohort studies showing that surveillance decreases the size of the tumor at excision(Rademakers et al., 2003).

8. Conclusion

Continual skin cancer development persists in patients with xeroderma pigmentosum (XP) despite life-changing photoprotection strategies, including strict avoidance of natural and artificial UV light, sunprotective apparel, high Sun Protection Factor (SPF) sunscreens and mandatory vitamin D supplementations. The current treatment strategy for XP patients is to excise cancers every three to six months, which may include specialized surgical methods such as Mohs micrographic surgery for facial cancers or recurrent cancers. This ongoing challenge highlights the need for a more efficient physical and/or topical barrier to protect against skin cancer in the absence of functional nucleotide excision repair.

The most recent molecular approach is the analogue of the α-melanocyte stimulating

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hormone, afamelanotide. It activates eumelanin synthesis independent of UV exposure, and offers photo protection that is independent of the patient's capacity for DNA repair. This has been shown to significantly reduce cyclobutane pyrimidine dimers, the number of sunburn reactions, and to have a positive influence on the DNA damage markers p53 and γH2AX in clinical trials. But there are major drawbacks. Afamelanotide is not approved for use in XP, doesn't prevent the need for ongoing photo protection, or resolve the underlying DNA repair deficiency. Thus, it is beneficial but not a cure. Topical agents (5-fluorouracil and imiquimod) are based solely on case reports and there is no good evidence for their use. T4N5 endonuclease (Dimericine) had some initial success in reducing UV damage but has yet to proceed to new trials. These treatments are only adjunctive.

The ideal treatment is to correct the genetic defect. Preclinical exploration of in vivo gene correction of keratinocytes, CRISPR-Cas9 technology and nanoparticles as delivery vectors are ongoing. This is hampered by a number of significant challenges: the size of several XP genes, potential immunogenicity of vectors and need for systemic and lifelong genetic correction (to treat neurodegeneration) - in particular in complementation groups A, B, D, F and G. To date, there is no sustained genetic therapy.

Patients with neurological complications (groups A, B, D, F, and G) do not have any beneficial interventions to ameliorate or reverse the neurodegenerative process. Treatment is symptomatic, with hearing aids for hearing loss, physical therapy for ataxia and speech therapy for dysarthria. This sobering fact underlines the difference between dermatologic and disease-modifying therapies. The gap from alleviation to cure can be closed by large-scale efforts. The next steps include: Multicentre registries to collect data and natural history. Natural history cohorts to establish natural history and biomarkers. Multidisciplinary approaches incorporating dermatology, ophthalmology, neurology, oral medicine and psychology. Only with such global, multi-disciplinary and evidence-based strategies can we move from treating complications to effective cure of this cruel disease.

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