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Hutchinson-Gilford progeria syndrome: Rejuvenating old drugs to fight accelerated ageing

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ABSTRACT

What if the next generation of successful treatments was hidden in the current pharmacopoeia? Identifying new indications for existing drugs, also called the drug repurposing or drug rediscovery process, is a highly efficient and low-cost strategy. First reported almost a century ago, drug repurposing has emerged as a valuable therapeutic option for diseases that do not have specific treatments and rare diseases, in particular. This review focuses on Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder that induces accelerated and precocious aging, for which drug repurposing has led to the discovery of several potential treatments over the past decade.

1. Hutchinson-Gilford progeria syndrome

1.1. A premature aging disease

With a prevalence of 1 in 20 million births, Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare and consistently fatal genetic disorder characterized by accelerated aging. Clinical symptoms usually appear in the first 18 months after birth, and include growth retardation, facial dysmorphic changes (long narrow nose, prominent outer ears, wrinkled skin), alopecia, loss of subcutaneous fat, bone and joint abnormalities and cardiovascular pathology. Death occurs at a median age of 14.6 years, mainly due to atherosclerosis, cardiovascular failure and stroke [1,2] (Fig. 1).

The genetic origin of HGPS was identified in 2003 by two independent research groups led by Nicolas Lévy and Francis S. Collins, respectively [3,4]. This autosomal dominant disease is caused by a *de novo* mutation in the LMNA gene which encodes A-type lamins, inner nuclear membrane proteins represented mainly by lamins A and C. A-type lamins play crucial roles in nuclear structure and shape, as well as in chromatin organization, nuclear pore and cytoskeleton organization [5], and mutations in *LMNA* were reported to cause various genetic disorders known as laminopathies. They include a wide spectrum of diseases, with or without overlapping symptoms, such as lipodystrophies, Emery-Dreifuss muscular dystrophy, Charcot-Marie-Tooth disease, dilated cardiomyopathies and progeroid syndromes, including HGPS [6].

Over the past decade, several groups have explored the molecular causes of HGPS, ultimately leading to the identification of the first therapeutic strategies. In physiological conditions, lamin A is produced from its prelamin A precursor, which undergoes complex post-translational modifications (Fig. 2). A cysteine in the C-terminal of prelamin A is first farnesylated, cleaved and finally carboxymethylated by the metalloprotease STE24 (ZMPSTE24) and isoprenylcysteine carboxytransferase (ICTM). The farnesyl group is then removed through cleavage of the 15C-terminal amino acids, leading to the production of the mature lamin A. The most common mutation in HGPS (c.1824C > T), although apparently silent (*LMNA* p.G608G), activates an alternative splice site, leading to the deletion of 150 nucleotides at the end of exon 11, which encode the endoprotease cleavage site. As a result, a prelamin A variant lacking 50 aa residues is produced in a permanently

Abbreviations: HGPS, Hutchinson-Gilford progeria syndrome; ZMPSTE24, metalloprotease STE24; ICTM, isoprenylcysteine carboxytransferase; hES, human embryonic stem cells; IPS, induced-pluripotent stem cells; MSC, mesenchymal stem cell; VSMC, vascular smooth muscle cell; miRNA, micro ribonucleic acid; DNA, Deoxyribonucleic acid; mRNA, messenger ribonucleic acid; FTI, farnesyl-transferase inhibitor; NPY, Neuropeptide Y; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SRFS1, splicing factor serine/arginine-rich splicing factor 1; ROS, reactive oxygen species; SIRT1, NAD^+-dependent sirtuin 1; HSP, heat shock protein; NAC, N-acetyl cysteine drug; HTS, high throughput screening; AON, antisense oligonucleotide; Mono-AP, mono-aminopyrimidine; FPPS, farnesyl pyrophosphate synthase; FT, farnesyl-transferase

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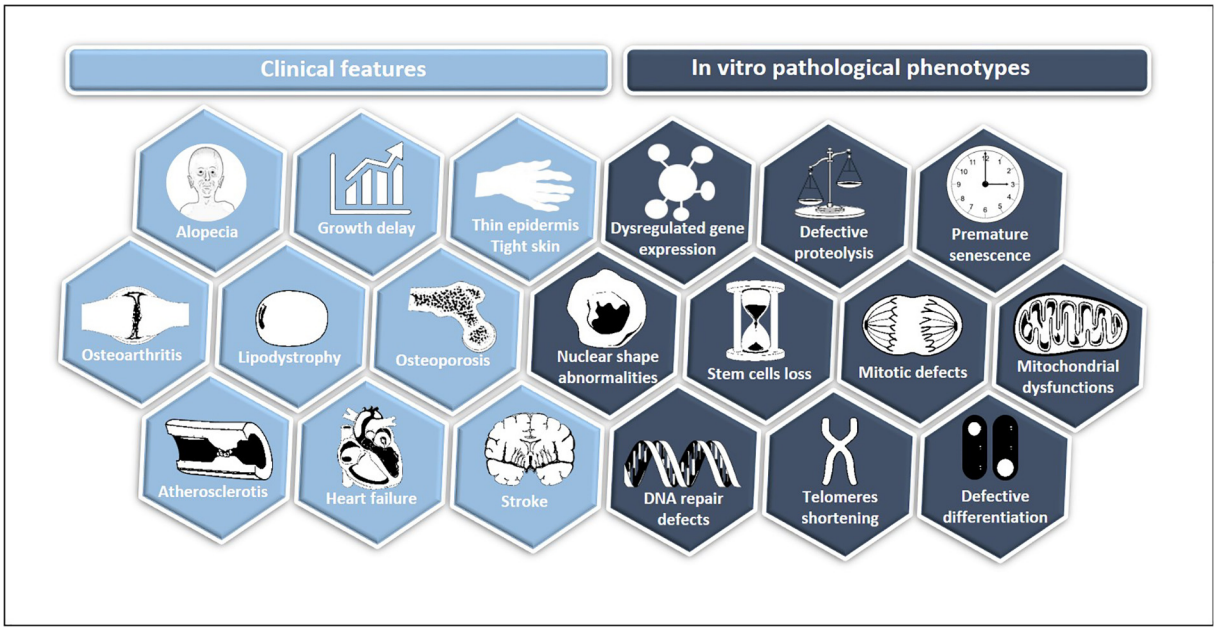

Fig. 1. Hallmarks of HGPS. In light blue, the principal clinical features of HGPS are recapitulated whereas in dark blue, the major *in vitro* pathological phenotypes are represented.

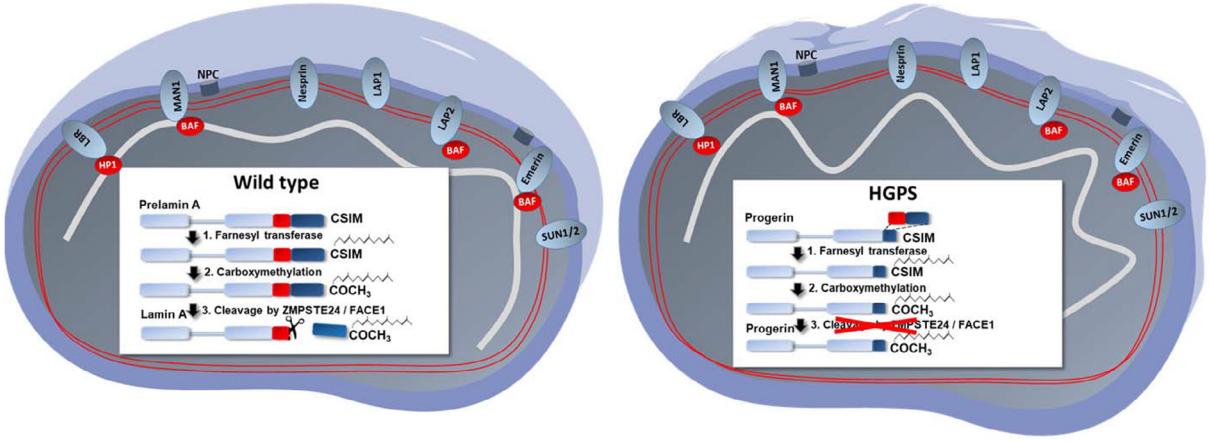

Fig. 2. Defective processing of prelamin A in HGPS and associated nuclear shape disorganization. Lamin A protein is obtained after several post-translational modifications, including the addition of a farnesyl group at the C-terminal and further cleavage by ZMPSTE24 endonuclease. The mutation on the LMNA gene that causes HGPS is responsible for the activation of an alternative splicing site that results in the deletion of 50 amino acids from a lamin A protein, including the cleavage site for ZMPSTE24. Consequently, the resulting mutant protein, called progerin, remains permanently farnesylated and thus induces nuclear shape abnormalities and disorganization.

farnesylated form, and the resultant protein, called progerin, exerts toxic effects in HGPS cells [7,8].

1.2. Phenotypic characteristics of HGPS

Due to the structural role of lamins in the nucleus, accumulation of progerin is accompanied by dramatic changes in nuclear structure and function (Fig. 1). In contrast to the mature lamin A, progerin remains anchored to the inner nuclear membrane, leading to shape abnormalities with the appearance of “blebs”, disorganization of the heterochromatin (e.g. tri-methylation on lysine 47 of histone (H3K27)) [7–9], as well as abnormal chromosome segregation and telomere degradation [10–12]. Among the cellular phenotypes reported in HGPS, premature senescence as a result of genomic instability [10,13,14] and accumulation of DNA double-strand breaks, notably through the decrease in recruitment of major DNA repair factors [7,15–17], have been widely described. Cells expressing progerin also exhibit mitochondrial defects [18], increased oxidative stress [19–21], decreased stress tolerance [9], stem cell exhaustion [22], alteration of proteolysis [23–25] and inflammation [26,27]. Since these phenotypes are commonly observed in physiological ageing [28], HGPS is considered a genetically induced model of accelerated ageing. First evidence came from the observation that progerin was expressed at low levels in physiologically aged-cells [29–32], but its possible role in tissue dysfunction during physiological aging has not been demonstrated and its role or its contribution toward tissue dysfunction remains unanswered.

1.3. In vitro models to study HGPS

For almost a decade, the main biological material available for the *in vitro* study of HGPS were fibroblasts isolated from skin biopsies or generated following progerin overexpression [7,29,33,34]. Even though skin fibroblasts were useful to assess pathological phenotypes, their limited proliferation capacities and lack of clinical relevance have

delayed the identification of the tissue-specific mechanism of action and specific treatments. The discovery of human embryonic stem cells (hES) and, more recently, the possibility of reprogramming somatic cells into pluripotent stem cells (iPS) [35], have opened up the possibility of studying some of the phenotypes associated with diseases *"in a dish"*. Pluripotent stem cells have the unique properties of being able to self-renew and to differentiate into any cell type, allowing the production of an "unlimited" quantity of cells for disease modeling and drug screening [36]. In 2011, the groups led by J.C Belmonte and A. Colman pioneerly reported the derivation of the first HGPS iPS cell lines [15,37]. Interestingly, in agreement with previous studies conducted with human embryonic stem cells [38], these two groups reported that neither lamin A nor progerin were expressed in undifferentiated HGPS iPS cells, making it possible to expand and differentiate these cells with no bias relating to the disease. Through a mechanism that remains unknown, these two groups have also reported that lamin A and progerin were re-expressed upon differentiation into different cell types, inducing pathological features such as nuclear abnormalities, reduced telomere length and premature senescence [15,37]. In addition to these findings, Zhang et al. also demonstrated that progerin was mainly expressed in mesenchymal stem cells (MSC) and vascular smooth muscle cells (VSMC), two cell types of particular relevance for the disease, but was absent in neuronal cells [37]. In 2012, our group discovered the origin of this specificity, identifying that miR-9, a miRNA predominantly expressed in neural cells, was capable to target the 3'UTR of progerin and decrease its expression in neurons [39]. Later, several other studies have subsequently elucidated some pathological mechanisms occurring in progerin-expressing cells in different cell types using iPS cells [15,17,27,37,40,41]. For example, Zhang et al. proposed in 2014 that the loss of proliferation in VSMCs could be attributed to a decrease in PARP-1 expression through an increase in chromosomal aberrations [17] and Xiong et al. demonstrated in 2013 a role of progerin in the deregulation of PPARγ2 and C/EBPα expression, two factors implicated in the differentiation in adipocytes [41].

1.4. In vivo models of HGPS

Several animal models have been developed to elucidate the pathological mechanisms of HGPS and to evaluate potential therapeutic strategies. The first living HGPS model was developed in 2002 through the depletion of *ZMPSTE24* (FACE-1), which encodes the enzyme responsible for the cleavage of the prelamin A farnesylated residue. *Zmpste24*$^{-/-}$ mice display several progeroid features, such as growth retardation, alopecia, cardiomyopathy, lipodystrophy, muscular dystrophy and premature death [42,43]. This model was used as the gold standard for HGPS and related disorders for almost a decade, demonstrating that the accumulation of the farnesylated protein induces nuclear abnormalities in vascular and osteogenic tissues, as well as p53 hyperactivation, defective DNA repair, cellular senescence and stem cell dysfunction [14,16,44]. Since this model expresses the full-length version of farnesylated prelamin A, 2nd generation models were based on the knock-in of a mutant allele of *LMNA* using selective or ubiquitous promoters, leading to the specific expression of progerin with or without lamin A and C [45,46]. More recently, Osorio et al. generated a knock-in mouse strain carrying the HGPS mutation in *LMNA*. This mouse model produces progerin through aberrant splicing of its endogenous *LMNA* mRNA and recapitulates the main features of HGPS disease at both molecular and clinical levels, including reduced lifespan, as well as vascular calcification, and cardiovascular and bone defects [47,48]. Even though mouse models are essential and widely used to depict molecular mechanisms of the disease and to test different therapeutic strategies, some key differences remain between these models and humans. To bridge the gap between mice and humans, and thanks to new gene editing methodologies, the group led by Vicente Andrès has recently reported the generation of a minipig model of HGPS carrying, by knock-in, the heterozygous *LMNA* c1824C > T mutation. This model has the advantage of having a cardiovascular system with strong similarities to that in humans and is therefore particularly relevant to HGPS [49].

2. Repurposing of old drugs for HGPS

2.1. Why we should consider repositioning drugs for ultra-rare diseases

HGPS is one of the rare or orphan diseases, defined as disorders affecting less than 5/100,000 people in Europe or fewer than 200,000 Americans at any point in time (around 650 in 1 million people). Mostly genetic in origin, more than 7,000 disorders were classified as rare, with no available treatment for most of them. In this context, "drug repurposing" represents a valuable strategy for bridging the gap between the need for treatment for patients with HGPS and the limited profits expected by pharmaceutical companies from developing new chemical entities. Drug repurposing – also called repositioning - consists of identifying new indications for existing or abandoned pharmacological drugs. This strategy takes advantage of previous data collected for a compound during clinical trials, notably on its bioavailability and safety, thus reducing the risks linked to the development of an entirely new product, which consequently accelerates access to the market. While these strategies present clear advantages, some challenges remain. The principle of repurposing depends not only on knowledge of the nature of the drugs, but also on knowledge on the disease, with the latter condition that is not always fulfilled in rare diseases.

2.2. Different strategies for pharmacological repositioning

The principle of drug repurposing is not novel. First successes were historically due to serendipity, as described with sildenafil, that was initially indicated as an anti-hypertensive drug before its successful use in erectile dysfunction, or with thalidomide, initially developed for insomnia or morning sickness treatment and then repurposed for multiple myeloma, other forms of cancer or leprosy [50]. One of the most striking example of successful repurposing based on drugs' side effects observations was recently described when french physicians located in Bordeaux observed the unexpected effect of Propanolol on the hemangioma present in the patient's face [51] whereas it was initially used to treat his heart condition. Ever since, other approaches have led to the development of more systematic strategies of drug repurposing, which can be classified into two groups: experimental and computational approaches. Experimental approaches mainly comprise two kinds of assays, binding assays to identify target interactions (not described here) or assays to rescue a phenotype.

In computational approaches, knowledge about the drug and diseases, and the analysis of data from a variety of origins, form the basis for the discovery of potential new drug-disease associations [52]. First, a "target-centric approach" could be envisaged in repurposing a drug, by focusing on the biological role that a specific component plays in disease. This requires the identification of potential genes implicated in the pathological phenotypes and searching in the pharmacopeia for existing drugs known to target them. Another relevant strategy is "pathway or network mapping", which consists of targeting a pathway upstream or downstream from the causative gene, but with strong relevance for the disease. The identification of such pathways could arise from the study of *in vitro* or *in vivo* models, with the development of "omics" data and transcriptomic analysis, in particular, being of great interest to the discovery of new deregulated genes. Transcriptomic data generated to identify misregulated pathways in the context of disease or drug treatment might also be useful for another approach called "signature mapping". Other methods exist and rely mostly on similarities between drugs to identify new possible indications. For example, a comparable chemical structure in different drugs suggests a shared biological activity and therefore the possibility to be repurposed. The search for similarities in side effects has also been reported as a possible

approach to drug repurposing, based on the hypothesis that similar side effects result from shared target or protein pathways and could thus lead to the discovery of new drug indications. These various strategies are not exhaustive, but reflect the major *in silico* methods that are currently being used in repurposing. Because several of these strategies have been successfully applied to HGPS, we will discuss the main findings of these reports below.

2.3. Repurposing old drugs in HGPS: From the first "success" with farnesylation inhibitors to promising compounds targeting progerin

Farnesylation, and more generally prenylation, is a common cellular mechanism that concerns a large number of proteins, including small GTPases, proteins implicated in the regulation of important cellular events like proliferation or cell motility. Targeting of the farnesylation process, which is required for the malignant activities of the RAS oncogenic family, has led to the development of farnesyl-transferase inhibitors (FTIs) as anti-cancer drugs [53]. Since 2000, several clinical trials using FTIs (lonafarnib, tipifarnib, BMS-214662 and L-778123) have evaluated their toxicity and efficacy in various cancer indications and revealed acceptable tolerance in humans [54–56]. Based on this knowledge, several FTIs were tested *in vitro* for HGPS, where an improvement in the nuclear shape was demonstrated [57–60], and also *in vivo*, revealing an improvement in the symptoms of the disease, in addition to a decrease in nuclear blebbing, [46,61–63] and an extension to lifespan [62] (Figs. 3 and 4).

In 2008, a similar pharmacological approach targeting the entire prenylation pathway was employed in repurposing for HGPS using the combination of zoledronate, a member of the amino-bisphosphonates class mainly used to treat osteoporosis [64], and pravastatin, that belongs to a class of inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) used to reduce cholesterol levels and prevent cardiovascular disease [65]. Treatment of the *Zmpste24*$^{-/-}$ mouse model with this combination led to an improvement in several hallmarks of HGPS, including lifespan [66].

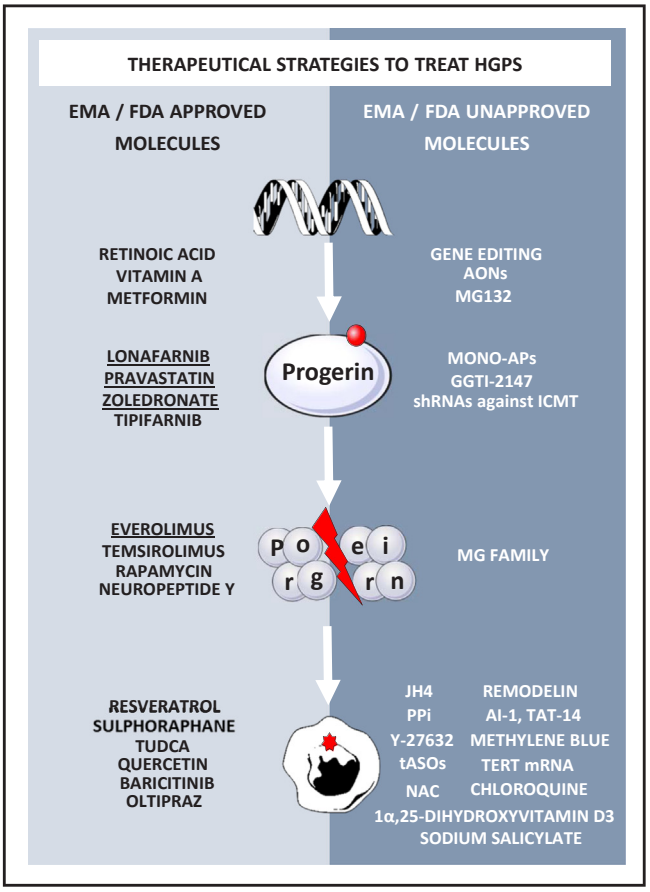

Fig. 3. Therapeutic strategies in HGPS. Several therapeutic strategies to treat HGPS has been proposed targeting either the production of the mutant protein progerin, its degradation or its pathological consequences. Here are represented all the therapeutical strategies, FDA or EMA approved or not, that have been investigated for the treatment of HGPS. The underlined compounds have been clinically tested.

These pioneering preclinical studies have successfully led to the design of several clinical trials, highlighting the efficiency of the repurposing of these drugs. The first ever clinical trial was launched in 2007 (ClinicalTrials.gov, NCT00425607) using the FTI lonafarnib on a cohort of 25 patients for a minimum period of 2 years, showing encouraging results with an improvement in weight gain, vascular stiffness and bone density [67]. In 2008, following the identification of the zoledronate and pravastatin effect, a second clinical trial was initiated using these two drugs in 12 patients (ClinicalTrials.gov, NCT00731016) followed by a tri-therapy clinical trial combining lonafarnib, zoledronate and pravastatin in 37 patients (ClinicalTrials.gov, NCT00879034). Results of this last clinical trial was reported describing no additional improvement of the tri-therapy as compared to lonafarnib alone [68]. More recently, in late 2015, another phase I/II clinical trial combining the existing drugs lonafarnib and everolimus (ClinicalTrials.gov, NCT02579044) was started in 60 patients, for which results are expected in October 2020 (https://www.progeriaresearch.org/clinical-trials/). Everolimus is an analog of the antibiotic macrolide drug rapamycin, an mTOR inhibitor, already used against cancer or for immunosuppression and implicated in the regulation of several cellular functions such as cell proliferation, protein synthesis, transcription, cytoskeleton rearrangement and autophagy [69]. Previous studies had suggested that rapamycin improved lifespan, notably in aged mice, through activation of autophagy, a process that is down-regulated during ageing [70–74]. This led to the hypothesis that autophagy induction could decrease the accumulation of the toxic progerin through a complementary mechanism to lonafarnib and improve cell phenotypes in progeria. Indeed, in HGPS fibroblasts treated with rapamycin or with temsirolimus, a decrease was observed in progerin through autophagy activation, accompanied by an improvement in abnormal nuclear shape, a decrease in senescence [75] and a reduction in DNA damage [76]. More recently, Neuropeptide Y (NPY), a neuronal peptide evaluated in Humans to treat feeding difficulties, acute stress disorders or posttraumatic stress disorders, was also shown to decrease progerin expression and alleviate several *in vitro* hallmarks of HGPS through autophagy induction [77]. In parallel to the evaluation of autophagy activators, several other studies have investigated the possibility to induce progerin clearance by modulating other degradation processes. To date, the most advanced and promising strategy to target this process is the use of proteasome inhibition. First evidence was described in 2017 by the group led by Nicolas Lévy, showing that MG132 treatment could lead to progerin clearance by an indirect induction of autophagy [78]. Finally, modulating alternative splicing regulation was also described to be a valuable strategy to target progerin content. Successfully applied to HGPS, the main target of these studies is the splicing factor serine/arginine-rich splicing factor 1 (SRFS1), previously shown to enhance the aberrant splicing of lamin A pre-mRNA involved in the production of progerin [79]. The first results were reported in 2016, when our group demonstrated that treatment with metformin, an antidiabetic drug with a good safety profile, could lead to a decrease in SRSF1 and progerin in both iPS cell-derived MSCs and HGPS fibroblasts. In this study, we also reported that metformin treatment was associated with a reduction in several defects, such as a decrease in nuclear shape abnormalities, in premature osteoblastic differentiation and in DNA damage [80]. Interestingly, MG-132 was also reported to induce the downregulation of SRSF1, suggesting a second additive level of regulation of progerin expression [78].

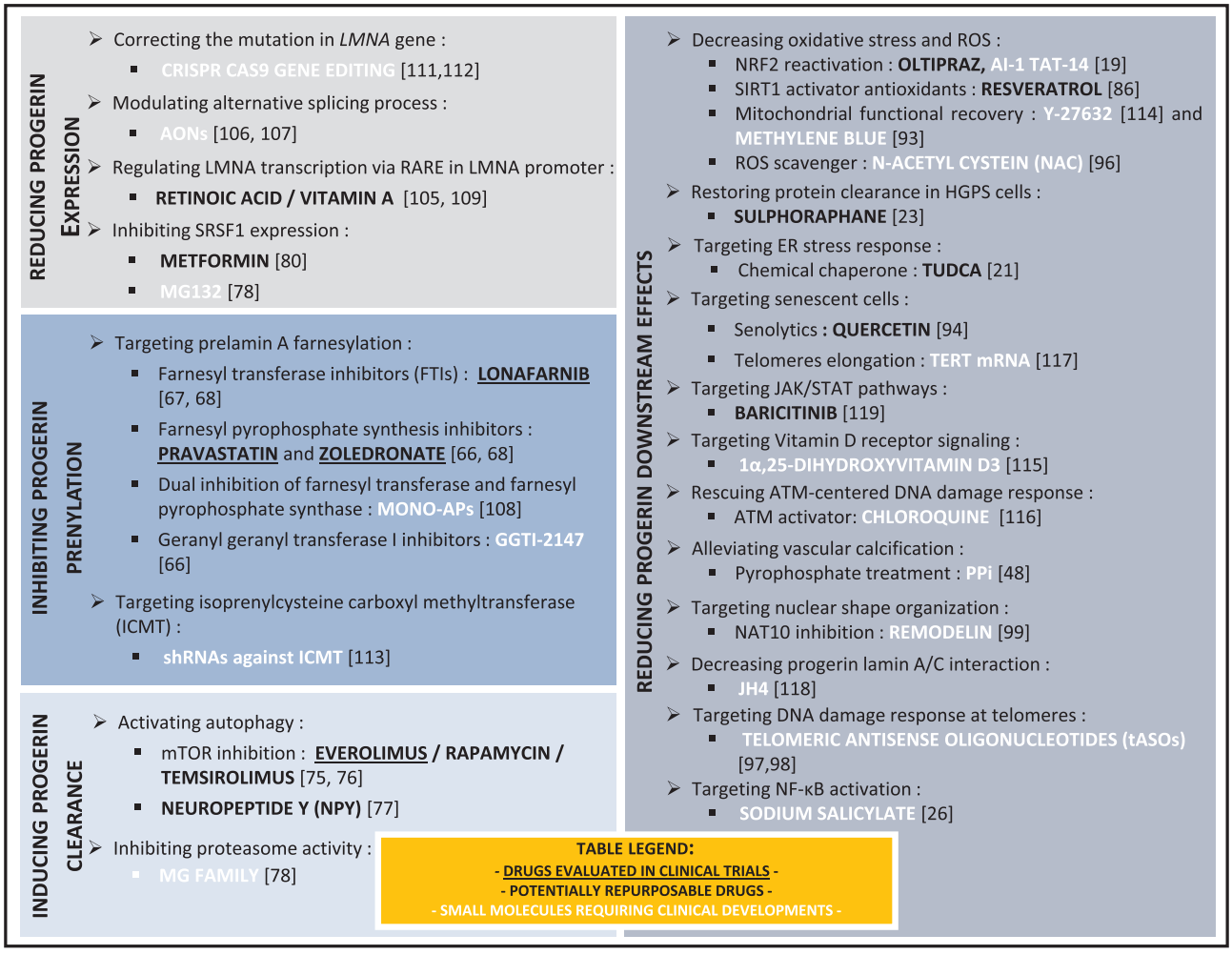

Fig. 4. Recapitulation of the therapeutic compounds described in HGPS. This scheme recapitulates the therapeutic approaches for the treatment of HGPS depending on their target. Non-repurposable strategies are represented in white, whereas repurposable drugs are highlighted in **bold** or underlined for the one used in clinical trials for HGPS. Progerin expression was decreased directly at gene level through gene therapy (CRISPR Cas 9 and AON) or through small molecules like retinoids and metformin. Strategies targeting progerin at a protein level or its prenylation have also been evaluated, among them small molecules that have reached the clinic, such as FTIs like lonafarnib, and rapamycin analogs like everolimus. Finally, targeting the downstream effects of progerin has been described as a valuable strategy for HGPS, with some repurposable drugs that have proven effective in correcting the disease-associated phenotypes in cellular and/or animal models. (See above-mentioned references for further information.)

2.4. Rescue of progerin-downstream pathological phenotypes

Among repurposing strategies, targeting the phenotypic consequences of progerin expression is another possibility that could indirectly reduce the burden caused by the aberrant protein in HGPS cells. The recent development of a mouse model for HGPS and of more relevant cellular models, such as based on iPS-derived cells, has allowed the identification of such pathological phenotypes and pathways and thus led to the identification of other possible drugs for repurposing (Figs. 3, 4).

First evidences came from the identification of the beneficial effect of resveratrol in HGPS, an anti-ageing polyphenol compound reported to have antioxidant properties [81–83]. Resveratrol is an activator of the NAD^+-dependent sirtuin 1 (SIRT1), a histone deacetylase protein with implied involvement in several cell processes, such as antioxidant and stress responses, mitochondrial biogenesis and metabolism [84] that was initially tested for the treatment of cancer, diabetes, obesity, neurological or cardiovascular disorders [85]. Using the *Zmpste24*$^{-/-}$ mouse model treated with resveratrol, Liu et al demonstrated a decrease in the abnormal lamin A-SIRT1 association observed in HGPS, which was thus accompanied by a restoration of HGPS defects, including a decrease in stem cell loss and an extension to lifespan [86]. Whereas the clinical use of resveratrol is currently limited because of its poor bioavailability, a micronized form with a good safety profile was developed (SRT501) [87] opening new perspectives for HGPS.

In 2015, another example was reported by Gabriel et al [23]. With the goal of restoring proteolytic machinery activity in HGPS cells [24,25] and consequently inducing progerin degradation, authors has evaluated the effect of sulforaphane, an antioxidant molecule found in cruciferous vegetables clinically used for its capability to improve symptoms of chronic inflammatory diseases and for the treatment of cancer [88]. Sulforaphane's mechanism of action was reported to be mediated by an improvement in proteostasis, including an increase in heat shock protein (HSP) and components of the proteasome and autophagy machineries [89,90], and through the targeting of Keap1/Nrf2 pathways [91]. As described in this study, treatment of HGPS cells with this compound was accompanied by an increase in proteolytic activity, a reduction in progerin, a decrease in DNA damage, and an increase in cell proliferation, suggesting its possible use as a therapy for HGPS [23,92].

Attempts to target the reactive oxygen species (ROS) accumulation were also made with several compounds, such as methylene blue [93], that improve mitochondrial dysfunction, and oltipraz, an antiparasitic drug that targets the antioxidant Nrf2 pathways and was also evaluated

for its effect against cancer cells [19]. Interestingly, in relation to this second compound, both sulforaphane and resveratrol, mentioned above, also depend at least partially on Nrf2 for their beneficial antioxidant effects, suggesting a common mechanism of action.

Senolytics represents a promising anti-ageing therapeutic strategy that targets senescent cells. Recently, a study performed in the context of Werner syndrome, another premature ageing disease, identified the benefits of quercetin, a polyphenol derived from plants and known for its anti-inflammatory and antioxidant properties. Authors of this study reported that quercetin treatment was able to rescue the replicative senescence in Werner syndrome MSCs through the transcriptional regulation of several cellular processes, such as cell cycle and antioxidation pathways. Interestingly, a similar effect on senescence were observed in HGPS cells, suggesting a common geroprotective effect of quercetin that could be relevant for premature and physiological aging [94].

In the past decade, several other pharmacological compounds have been reported to decrease progerin-induced pathological phenotypes (see review [95]) by several ways, such as a decrease in ROS production through N-acetyl cysteine drugs [96], decreasing vascular calcification through pyrophosphate treatment [48], targeting telomere dysfunction [97,98] or the restoration of nuclear organization through SUN1-associated acetyl transferase protein NAT10 inhibition with Remodelin [99] (Figs. 3 and 4). Recently, a promising strategy was reported by Hamczyk et al [21] showing that the treatment with a chemical chaperone tauroursodeoxycholic acid (TUDCA), successfully used in humans to treat cholestatic liver disease [100–103], was able to alleviate endoplasmic reticulum stress delaying medial VSMC loss and extending lifespan of progeroid mice.

3. Drug repurposing by drug screening

Even if previous research has led to the identification of a large number of potential therapeutic interventions by small molecules to correct HGPS defects, there is still a need for the discovery of new drugs that are suitable for trials in humans. To this end, another approach is to use high throughput screening (HTS) to evaluate the effect of old drugs on new phenotypes. This drug discovery strategy corresponds to the unbiased experimental testing of a compound library in order to find positive “hits” capable of correcting a defective mechanism of action or phenotype. This strategy will be discussed below in the light of three different studies reported in recent years.

3.1. Challenges in drug screening for HGPS

The first and most obvious challenge in high-throughput drug screening is the need for a robust and relevant assay that can be used to test the compounds. Such strategies could be developed based on several ways, with either “target-based”, also called “mechanism-based”, or “phenotypic-based” screening. A second challenge that has to be taken into consideration in drug screening is the choice of the cellular model. High-throughput screening requires a large quantity of stable cells that are relevant to the disease in order to work in reproducible conditions. In the case of HGPS, the use of primary cells from patients is challenging, firstly, because their growth, and thus the production of large quantities of cells, is limited by premature senescence and, secondly, because they are also associated with a phenotypic heterogeneity that could interfere with the identification of drugs of interest. Consequently, immortalized fibroblasts are generally preferred for HTS to bypass the use of primary cells. However, as it has been demonstrated in HGPS, progerin expression is progressively lost following immortalization, thus limiting its use for pharmacological interventions in HGPS [104]. Alternative strategies have been described to overcome this obstacle, involving inducing progerin in non-HGPS cell lines by overexpression [105] or using antisense oligonucleotides (AON) [106,107]. Finally, in this context, iPS cell derivatives have emerged as a model of choice for drug screening, in addition to their role in disease modeling. Their high capacity for proliferation and the possibility of differentiating iPS cells into different cell types allows the generation of large banks of cells that recapitulate the main phenotypes of HGPS. To date, only three drug screening processes have been performed to identify new drugs using different cell models in the case of HGPS. These are described in more detailed in the following section.

3.2. Use of HTS to repurpose old drugs for HGPS

In 2016, our group reported the first high-throughput screening conducted on HGPS cells using MSCs derived from iPS cells. This screening led to the identification of a new class of compounds that decreases the farnesylation of prelamin A [108]. In this study, HGPS iPS-derived MSCs were used to evaluate the effects of 21,608 compounds on the subcellular localization of prelamin A by immunofluorescence, assuming that this would reflect a decrease in its farnesylation. From an initial list of 59 hits, 11 were ultimately validated regarding their efficacy in relation to increasing prelamin A staining in the nuclear membrane, their safety and the correction of HGPS phenotypic defects, as assessed in a secondary assay. Among these, a statin was identified, which highlights the relevance of screening as this class of compounds was previously shown to target progerin prenylation [66]. Most importantly, a new class of compounds with a common mono-aminopyrimidine group (Mono-AP) was found to improve osteogenic differentiation and nuclear shape organization. Thanks to docking experiments, it was later proposed that Mono-AP decreases farnesylation by simultaneously inhibiting farnesyl pyrophosphate synthase (FPPS) and FTs. Therefore, even if this class of drugs is not directly repurposable, it could represent an advantageous form of treatment for HGPS by targeting farnesylation at different stages.

In 2016, Tom Misteli’s group reported on further high-throughput screening conducted on HGPS, using immortalized skin fibroblasts that overexpressed progerin in an inducible manner [105]. Several phenotypes of HGPS, such as reduced levels of the nuclear protein lamin B1, and LAP2, disorganization of the heterochromatin and an increase in DNA damage, were assessed at different points in time. Detection of lamin B1 and of γH2AX foci, a DNA damage marker, was selected to develop a multi-parametric assay and screen 2,816 FDA-approved drugs and bioactives. Among these, 27 compounds were identified as potential hits, including two members of the retinoids, previously used for the treatment of acne or psoriasis, which exhibited strong and significant effects on all parameters that were tested.

Retinoids were also identified independently by our group in a third high-throughput screening performed on HGPS iPS-derived MSCs [109]. In this study, the premature osteogenic differentiation observed in HGPS iPS-derived MSCs [110] was used as a readout to screen a chemical library of 2800 drugs. 10 compounds were identified and, ultimately, the retinoids emerged as potential drug candidates. Results of this screening also confirmed the anti-progeroid effect of this class of drugs that was previously identified by Kubben et al. using another cellular model [105], also demonstrating its efficiency in reducing other pathological defects in HGPS MSCs. Furthermore, this work has added a proof of concept, showing that drug screening using iPSC-derived cells could be helpful in the discovery of drugs that target cell-types specific to phenotypes in HGPS.

4. Conclusions

Since the discovery of the genetic origin of HGPS in 2003, much progress has been made, leading to greater in-depth knowledge on the disease, its mechanisms of action and the cellular consequences that ultimately drive the disease phenotypes. Given this short period of time, it is very surprising to see that several successful clinical translations of drug repurposing have already been reported, as shown for lonafarnib, zoledronate and pravastatin. Drug repurposing allowed researchers to

progress rapidly to phase II clinical trials and to evaluate the efficacy of a limited number of drugs in a time and cost-effective manner. As discussed in this review, identification of these treatments was mainly based on hypothesis-driven approaches and unbiased high-throughput screening. To date, around 35 molecules have been reported to have a positive effect on HGPS by either limiting progerin expression, modulating alternative splicing, decreasing progerin accumulation or its pathological consequences. This situation is almost unique making impossible to evaluate the clinical benefit of all these individual drugs because of a limited number of patients. In the future, the systematic evaluation of the combination of drugs targeting in one hand progerin and in the other hand its downstream consequences appears to be a valuable strategy to identify an efficient treatment for this disease that remains uncured.

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Appendix A. Supplementary data

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