Review
Zebrafish Syndromic Albinism Models as Tools for Understanding and Treating Pigment Cell Disease in Humans

Sam J. Neuffer and Cynthia D. Cooper *

School of Molecular Biosciences, Washington State University Vancouver, Vancouver, WA 98686, USA; samantha.neuffer@wsu.edu
* Correspondence: cdcouper@wsu.edu

Citation: Neuffer, S.J.; Cooper, C.D. Zebrafish Syndromic Albinism Models as Tools for Understanding and Treating Pigment Cell Disease in Humans. Cancers 2022, 14, 1752. https://doi.org/10.3390/cancers14071752

Academic Editor: Suzie Chen
Received: 8 February 2022
Accepted: 26 March 2022
Published: 30 March 2022

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. License MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Simple Summary: Zebrafish (Danio rerio) is an emerging model for studying many diseases, including disorders originating in black pigment cells, melanocytes. In this review of the melanocyte literature, we discuss the current knowledge of melanocyte biology relevant to understanding different forms of albinism and the potential of the zebrafish model system for finding novel mechanisms and treatments.

Abstract: Melanin is the pigment that protects DNA from ultraviolet (UV) damage by absorbing excess energy. Melanin is produced in a process called melanogenesis. When melanogenesis is altered, diseases such as albinism result. Albinism can result in an increased skin cancer risk. Conversely, black pigment cell (melanocyte) development pathways can be misregulated, causing excessive melanocyte growth that leads to melanoma (cancer of melanocytes). Zebrafish is an emerging model organism used to study pigment disorders due to their high fecundity, visible melanin development in melanophores (melanocytes in mammals) from 24 h post-fertilization, and conserved melanogenesis pathways. Here, we reviewed the conserved developmental pathways in zebrafish melanophores and mammalian melanocytes. Additionally, we summarized the progress made in understanding pigment cell disease and evidence supporting the strong potential for using zebrafish to find novel treatment options for albinism.

Keywords: melanocytes; melanin synthesis; Hermansky–Pudlak Syndrome; albinism; zebrafish

1. Introduction

Melanin is a category of pigments that range in color from yellow-red (pheomelanin) to brown and black (eumelanin), and they are produced by enzymes in a process called melanogenesis [1]. The diverse variety of organisms that produce melanin are adapted to reduce the consequences of ultraviolet (UV) radiation and DNA damage, including altered development, cancer, skin damage, immunosuppression, increased mortality, and reduced quality of life [2–5]. In animals exposed to UV radiation from the sun, melanin protects DNA from mutations by absorbing UV light and free radicals [6]. After UV exposure, additional skin cells (keratinocytes) respond to UV stress by synthesizing and secreting the melanocortin stimulating hormone (MSH) [7,8]. MSH then interacts with melanocortin receptor 1 (MCRI) on the surface of melanocytes (melanin producing cells) to activate a signaling cascade that directs melanocyte specific organelles, melanosomes, to synthesize, store, and transport melanin within pigment cells [9]. Additional signaling pathways, including the endothelin and kit signaling pathways, are involved in promoting melanogenesis and normal melanocyte function. As a result of these signals, the increase in melanin is responsible for tanning and UV protection in humans [8].

Melanogenesis occurs in melanosomes, members of a category of lysosome-related organelles (LROs). LROs are a group of cell specific specialized trafficking and/or secretory compartments that use similar but incompletely understood mechanisms for their
synthesis and function ([10] and more recently reviewed by Delevoye, Marks, and Raposo [11]). Relatedly, defects in proteins important for melanogenesis enzyme transport are correlated with transport defects in other LROs. For example, cytotoxic T lymphocytes generate LROs, lytic granules, using the similar intracellular transportation systems that melanocytes use to traffic melanin [12,13]. The content in lytic granules kills bacteria and cancerous cells [14,15]. When lytic granule generation is perturbed, Hermansky-Pudlak Syndrome (HPS; a form of albinism) patients are more susceptible to infection [13]. Without understanding the genetics of albinism, developing treatments for albinism may be inappropriately targeted to treating albinism symptoms without targeting the immune system malfunctions. Animal models, including zebrafish, are an excellent resource for developing specific treatment options for pigmentation disorders, including melanoma and albinism, due to the ability to characterize conserved melanogenesis and melanogenesis enzyme trafficking pathways [13]. This review will consider conserved mechanisms underlying pigment biology in mammals and zebrafish (Danio rerio), while highlighting gaps in knowledge regarding albinism biology. Additionally, we will discuss how zebrafish can fill those gaps and be used to better understand and treat albinism.

2. Advantages of Using Zebrafish to Study Albinism

House mice (Mus musculus) are traditionally used to study pigment diseases such as albinism because mice are mammals and share many of the genes and processes involved in pigment cell development pathways and melanin synthesis pathways misregulated in human albinism [16,17]. However, zebrafish offer some advantages to studying pigment development and how it is altered in albinism. First, many of the genes that control pigment development and melanocyte function in humans and mice are conserved in zebrafish as well as other chordates [18–20]. Some examples of conserved melanocyte genes controlling the analogous zebrafish cell type, melanophores, include microphthalmia-associated transcription factor (indicated as MITF in humans, Mitf in mice, and mitf in zebrafish), dopachrome tautomerase (DCT), tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1), and oculocutaneous albinism 2 (OCA2) [21,22]. Because melanophores are present in see through skin (in larvae and in casper adults [23]), melanophore development can be observed in live samples in real time. Relatedly, several zebrafish mutants with defects in genes that regulate the master melanophore specification gene, mitfa, have been isolated, uncovering new regulatory roles for foxd3, tfap2a, and colgate/hdac1 during melanophore specification from neural crest cells [24–28]. Additionally, zebrafish mutants with defects in melanophore differentiation and survival are clarifying novel roles for cathepsin protease, non-coding RNAs, and adhesion protein Jam3 during later stages of melanophore development [29–31]. Thus, zebrafish mutants are already providing insight to melanophore/melanocyte development mechanisms.

Second, zebrafish have a higher fecundity than mice. Pregnant female mice are sacrificed to collect approximately 6–10 embryos per mouse to study early pigment development, while zebrafish parents can be returned to their housing after collecting up to 200 eggs from a single spawning pair every 10 days [32–35]. Therefore, zebrafish larvae are highly amendable to large scale drug treatments. This approach can be used with zebrafish disease models to quickly find novel treatment options for albinism. In addition, genetic modification experiments to test the genetic mechanisms underlying pigmentation diseases can be quickly performed on more individuals.

Third, zebrafish are already providing mechanistic insight into albinism biology. Reduction of zebrafish biogenesis of lysosome-related organelles complex 1 (BLOC1) S5 gene (using morpholino knockdown techniques) recapitulates human syndromic albinism, Hermansky-Pudlak Syndrome (HPS) 11 phenotypes including a reduction in eye pigmentation, and cardiovascular defects. Signaling pathways, altered as a consequence of BLOC1S5 reduction, included delta/notch and vascular integrity signaling [36]. HPS genes 1, 3, 4, and 5 zebrafish models present with kidney tissue impairment and illustrate a previously underappreciated impact of HPS gene loss of function–renal disease [37]. Additionally, sev-
eral genomic mutants (discussed below) with HPS phenotypes are available to further our understanding of HPS models and to find novel specific treatments using the advantages of the zebrafish model.

3. Mechanisms Underlying Zebrafish and Mammalian Pigment Cell Biology

3.1. Black Pigment Cell Anatomy and Function

Melanocytes and melanophores are both specialized cells that produce melanin. In mammals, melanocytes reside in the basal layer of the epidermis [38]. In fish, melanophores are located in both the epidermis and the hypodermis on top of muscle [39]. Melanocytes/melanophores consist of a central cell body and dendrites that project outwards. Melanosomes traffic pigment throughout the cell in both melanocytes and melanophores, and they are transferred to neighboring cells in human skin. Though still under debate as to how melanosome transfer to surrounding skin cells occurs, progress has been made thanks to new technologies and approaches for understanding this process [40]. As a result, several models for melanosome transfer have been proposed, including exo/phagocytosis and membrane fusion [41]. In contrast, melanophores retain their pigment within the melanophore [39]. Because zebrafish melanophore biology is very similar to mammal melanocyte biology, we intertwine discussion of developmental mechanisms in both cell types below.

Melanogenesis is the production of melanin by melanin-producing cells and a reduction in melanogenesis underlies all forms of albinism [1]. Melanogenesis requires the expression of genes that code for the proteins that directly synthesize melanin, as well as the genes necessary for trafficking pigment-producing enzymes into the melanosomes and promoting the correct function of those enzymes after their arrival [42–44]. Failure in any of these processes can cause pigment loss resulting in albinism. However, the specific mechanisms working to promote healthy LROs and to prevent albinism symptoms are poorly understood.

There are multiple types of melanin, but eumelanin is the primary pigment altered in albinism [45]. Eumelanin is a polymer that consists of repeating units of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) [1]. It strongly absorbs UV light, which gives melanin its photoprotective properties [46]. Eumelanin is synthesized in stages by one to three different enzymes. Tyrosine is converted into dopaquinone by tyrosinase. Dopaquinone is spontaneously converted into dopachrome, from which point it can be converted into eumelanin by tyrosinase (TYR) after losing the carboxyl group (COO), or it can be converted into DHICA by dopachrome tautomerase (DCT) and then into eumelanin by tyrosinase-related protein 1 (TYRP1) [47].

3.2. Regulation of Melanogenesis—Some Remaining Questions

The primary point of the transcriptional control of melanogenesis is MITF. As a transcription factor, MITF controls the expression of tyrosinase, dopachrome tautomerase, and tyrosinase-related protein 1—enzymes critical to the production of melanin in melanosomes. MITF is regulated via several pathways, some of which include: (1) the MC1R (melanocortin 1 receptor) pathway, (2) the wingless/integrated (WNT) pathway, (3) the c-KIT pathway, and (4) the endothelin B receptor (ETBR) pathway. Together, these conserved, well-studied signaling pathways regulate the development of melanin-producing cells in both mammalian and zebrafish skin [48–65].

Conversely, the processes that control the transport of melanogenesis enzymes and the trafficking of melanosomes are incompletely understood (recently reviewed in Ohbayashi and Fukuda, 2020). Melanosomes are trafficked along microtubule and actin filaments [66]. Melanosomes mature in four stages. Stage one consists of premelanosomes, which lack pigment. Striations form inside the melanosome at stage two to support the deposition of melanin produced in stage three, when melanin synthesis proteins, such as TYRP1, DCT, and TYR, are trafficked to the melanosome. The melanosome becomes darkly pigmented during stage four, when they are considered mature [66,67]. The protein, PMEL, promotes
the formation of striations within stage one of maturing melanosomes. The striations are
responsible for the oblong shape of the melanosome and provide space for the deposition
of pigment; however, PMEL is not absolutely required for pigment formation [67–69].
PMEL must be proteolytically cleaved to form fibrils. HPS1 and HPS4 mutant cells do
not efficiently cleave PMEL, suggesting that they are required for the efficient processing
of PMEL [70].

The melanogenesis enzymes TYRP1, DCT, and TYR are all synthesized in the endo-
plasmic reticulum (ER) and are sorted from the trans-Golgi network. TYR and TYRP1
are trafficked to the early endosome, while DCT is trafficked via the secretory pathway
from the Golgi directly towards the melanosome [66]. TYRP1 requires the biogenesis of
lysosome-related organelle complex 1 (BLOC1) and BLOC2 to sort to melanosomes [71,72].
BLOC1 is a multi-subunit complex that includes the protein gene products of Pallidin,
Muted, Cappucino, Dysbindin, Snapin, Blos1, Blos2, and Blos3 [73]. It works with KIF13A
and actin to elongate endosomal tubules for the transport of TYRP1, while BLOC2 works
to target TYRP1 to the stage two melanosome [66,72,74]. BLOC2 is also a multi-subunit
complex composed of proteins coded by HPS3, HPS5, and HPS6 genes [66]. Different
mouse disease models for many of the subunits in both BLOC1 and BLOC2 exist ([75–80],
while there is limited availability of zebrafish models for the same subunits. Snow white is
the only currently available HPS zebrafish model with defects in BLOC2. Snow white is
a substitution mutation in HPS5, enabling researchers to study the biology of this novel
HPS-causing mutation when the protein is expressed [81].

In a separate, incompletely understood pathway, the adaptor protein 3 (AP3) complex
interacts with the cytoplasmic tail of tyrosinase to pinch off some of the early endosome
(vesicle budding) and traffic tyrosinase to a stage two melanosome [66,82–84]. The BLOC1
complex interacts with AP3 to traffic tyrosinase, though this is not required [71,72,77].
The adaptor protein 1 (AP1) complex can also sort tyrosinase, though it does so weakly and only
when AP3 cannot [84–86]. Therefore, the delivery of tyrosinase to the melanosomes can
occur through functionally-redundant pathways [84]. Fusion of the AP3/tyrosinase vesicles
to target organelles may be mediated by the HOPS complex. In yeast, the expression of
Vps41 on mitochondrial membranes redirected AP3 to the mitochondria [87]. Mutations in
vps41 CRISPR knockouts cause pigmentation and neurological defects [88]. Mutations in
the AP3 complex, such as in the cases of HPS2 and HPS10, result in syndromic albinism [13,89].
Notably, people with Hermansky–Pudlak Syndrome type 10 have symptoms of hypotonia
(decreased muscle tone), which is also present in people with mutations in VPS41 [13].
Whether AP3, VPS41, and/or BLOC1 work collaboratively to promote tyrosinase sorting
is unclear.

The mechanisms for trafficking DCT are even less understood. DCT is trafficked
from the Golgi to the stage two melanosome. Rab6 and ELKS facilitate the docking
of Dct to the melanosome [66,90]. Dct, as well as TYR and TYRP1, requires Rab32/Rab38
for trafficking [91]. Rab32/Rab38 are proteins that exchange GDP for GTP, and they are
called small GTPases. Rab32/Rab38 are involved in the specific targeting of protein cargo through
interactions with other trafficking proteins such as BLOCs or motor proteins required for
trafficking melanosomes along microtubules [66]. Chocolate mice (Rab38) are models for
HPS due to defects in lung surfactant secretion [92,93], but no specific type of HPS in
humans or zebrafish is associated with Rab38.

Once melanogenesis enzymes are in the melanosome, they can produce melanin.
However, these enzymes require the proper environment to function correctly. Tyrosinase,
tyrosinase-related protein 1, and dopachrome tautomerase require a specific pH inside the
melanosome to allow the binding of copper, iron, and zinc cofactors, respectively [94,95].
The pH of the melanosome is regulated by proton pumps [91]. Some of the proteins
thought to regulate melanosomal pH are MATP and OCA2, and mutations in these genes
are associated with albinism [21,96,97]. Treatment of oca2 mutant zebrafish with vacuolar
ATPase (V-ATPase) inhibitor, bafilomycin 1A, rescues melanin synthesis, suggesting that
melanosomal pH is regulated by V-ATPase [21]. An additional regulator of melanosome
pH is the Oca2 protein itself. Acting as an anion channel in melanosomes, Oca2 may also regulate melanosome pH. Whether these proteins function together to control melanosome pH is unclear.

In summary, several questions concerning melanosome generation, trafficking, and pH balance exist. Existing zebrafish mutants, and zebrafish single or double mutants that can be quickly generated using ENU mutagenesis, can be used to understand the cell biology underlying aberrant pigmentation phenotypes. The ability to readily introduce additional HPS mutations using CRISPR and the high fecundity of zebrafish allows for large populations of genetically-modified zebrafish to be produced quickly, and it is advantageous for studying gene interactions in vivo [32–34,98]. Furthermore, the injected zebrafish embryos can then be grown into adults to start a new HPS model. Effects can be observed in injected embryos within days of injection. Although some mutations may ultimately be lethal, knowledge can be gained in mutants and CRISPR knockouts during larval stages, as performed in vacuolar protein sorting (Vps) 11 syndromic albinism models [29,99]. Furthermore, mutations can be introduced to specific regions of a gene in already existing HPS5 models such as snow white, which could provide valuable information on the function of specific protein domain interactions with existing mutations.

4. Diseases Involving Changes to Pigment Cell Development and Function

Changes to melanogenesis and to the growth and development of melanocytes/melanophores can cause disease. The mechanisms causing pigment diseases are varied. Some examples of pigment diseases and their mechanisms are: (1) melanoma resulting from the uncontrolled growth of melanocytes, and (2) albinism caused by altered melanogenesis. Certain diseases associated with pigmentation defects have systemic effects on the body due to the shared cellular machinery used during pigment trafficking and the excretion of cytotoxic granules in the immune system, neurotransmitters in the nervous system, and deposition of surfactants, which are a lipid secreted over alveola cells that help with alveolar expansion by lowering surface tension [13,100].

4.1. Melanoma

Melanoma is caused by the uncontrolled growth of melanocytes [101]. Melanoma cases are increasing in the United States, and if caught early enough, prognosis is good, but it declines with advancing stages [102,103]. In many ways, melanoma is a disease of pigment cell development. The processes that govern pigment cell development to specify, differentiate, and proliferate melanocytes are altered with deadly consequences in melanoma. For example, activation of the WNT pathway is important for the specification of melanoblasts, as it drives neural crests cells to a melanoblast fate instead of a neuron precursor fate [104]. Increased activation of the WNT/MITF pathways is associated with proliferative melanoma [105,106].

Melanoma can occur in the skin, on mucosal membranes, and in the eyes. The least understood melanomas are those of the mucosal membrane and eyes [101]. The mutational causes of these melanomas are less characterized, as opposed to melanoma of the skin. Mucosal melanomas tend to have increased copy numbers of genes critical for pigment development, such as MITF, which, when mutated, can make cancers resistant to treatment [107]. Furthermore, predictions of outcomes for patients requires a better understanding of the biomarkers that predict melanoma outcomes, which requires more research [101]. These biomarkers are genes that play a crucial role in normal pigment cell development such as MITF [101]. Therefore, understanding the development of pigment cells using cell models and animal models, such as zebrafish and mice, is crucial for developing treatments to melanoma (recently reviewed by Patton and colleagues [108]).

4.2. Albinism

Albinism is defined by the reduction or absence of melanin. Albinism can be broadly categorized into three types: (1) syndromic albinism due to mutations affecting lysosome-
related organelles (LROs) and different systems in the body that rely on the proper bio-
genesis and function of LROs; (2) nonsyndromic albinism with symptoms confined to
pigment loss and defects that arise from pigment loss; (3) albinism-associated disorders
resulting from the loss of pigment-producing genes due to large chromosomal deletions,
as is the case with Prader-Willi Syndrome and Angelman Syndrome. Only 1% of people
with Prader-Willi Syndrome and Angelman Syndrome present with albinism, as their
pigment-producing genes may escape deletion [109,110].

4.2.1. Syndromic Albinism

The main forms of syndromic albinism are Chediak–Higashi Syndrome (CHS) and
Hermansky–Pudlak Syndrome (HPS). CHS is an extremely rare disease, as less than
500 cases have been reported. The disease is characterized by reduced amounts of neu-
rophils, natural killer cell defects, albinism, and platelet deficiency. Therefore, patients
often die from infection when they are children, and treatments, such as a bone marrow
transplant, are not always effective [111–113]. CHS is caused by loss-of-function muta-
tions in the lysosomal trafficking regulator (indicated as LYST in human and as Lyst in
mouse) [114,115]. Loss-of-function mutations in LYST cause large, malformed melanosomes
that are not evenly dispersed [116]. This effect is due to melanosomes fusing with each
other, and LYST is likely involved in the correct localization of lysosome-related organelles
and exocytosis, though its functions are still being determined [117–119].

Currently, there are 11 recognized types of Hermansky–Pudlak Syndrome (HPS) [42].
HPS shares some symptoms with CHS because both diseases are the result of defective
intracellular trafficking. Patients with HPS have seizures, show increased inflammation,
increased risk of skin cancer, pulmonary fibrosis (lung scarring), varying degrees of albi-



| Table 1. Types of albinism disorders with some relevant mouse and zebrafish models. |
|---------------------------------|--------------------|------------------|-----------------|-----------------|-----------------|
| Albinism Type                  | Human Disease     | Human Gene        | Protein          | Mouse Model (Gene) | Zebrafish Model (Gene) |
|-----------------|-----------------|-----------------|-----------------|-------------------|-------------------|
| Syndromic      |                 |                 |                 |                   |                   |
| CHS            | LYST            | LYST            | Beige           | beige/            | lyseps207         |
| HPS1           | RAB38           | RAB38           | Chocolate       | Pale ear           | Not available     |
| HPS2           | AP3B1           | AP3B1           | Pale ear        | Not available     |                   |
| HPS3           | HPS3            | BLOC2, SUBUNIT 1 | Cocoa           | Not available     |                   |
| HPS4           | HPS4            | BLOC2, SUBUNIT 2 | Light ear       | Not available     |                   |
| HPS5           | HPS5            | BLOC2, SUBUNIT 3 | Ruby-eye 2      | snow white (hps5) |                   |
| HPS6           | HPS6            | BLOC1, SUBUNIT 8 | Sandy           | Not available     |                   |
| HPS8           | DTPARP1         | BLOC1, SUBUNIT 3 | Reduced pigmentation | Not available |                   |
| HPS9           | BLOC1S5         | BLOC1, SUBUNIT 6 | Fimbrin         | Not available     |                   |
| HPS10          | AP3D1           | AP3D1           | Mocha           | Not available     |                   |
| HPS11          | BLOC1S5         | BLOC1, SUBUNIT 5 | Muted           | Not available     |                   |
| HPS            |                 |                 |                 |                   |                   |
| Nonsyndromic   |                 |                 |                 |                   |                   |
| OA1            | GPI143          |                 |                 | Bloc1s1 /– /– [126] | Bloc1s1 /– /– [127] |
| OCA1           | TYR1            |                 |                 | Oa- /y [128]     | sandy (hps)       |
| OCA2           | OCA2            |                 |                 |                   | oca2 [22]         |
| OCA3           | TYR3            |                 |                 |                   |                   |
| OCA4           | SLC45A2         |                 |                 |                   |                   |
| OCA5           | 4q24            |                 |                 |                   |                   |
| OCA6           | SLC34A5         |                 |                 |                   |                   |
| OCA7           | C10orf11        |                 |                 |                   |                   |
| OCA8           | DCT             |                 |                 |                   |                   |
| Albinism-associated |                 |                 |                 |                   |                   |
| PWS            |                  |                 |                 | PWYSial [129]     | Not available     |
| AS             |                  |                 |                 | Ubc3a /– /– /– [130] | Not available     |

* Neuffer et al., under revision.
4.2.2. Nonsyndromic Albinism

Ocular albinism (OA), albinism of the eyes, and oculocutaneous albinism (OCA), albinism of the eyes and skin, are the main forms of nonsyndromic albinism. The diseases are characterized by a reduction in pigmentation, vision defects, and susceptibility to cancer [131]. These diseases are caused by mutations in the enzymes that create melanin (as is the case with OCA1 caused by mutations in TYR) or alter the melanosome environment required for proper melanogenesis enzyme function (as is the case with OCA2 caused by a mutation in the P-protein coded by OCA2) [131]. There are currently eight different types of oculocutaneous albinism and one type of ocular albinism [10]. OCA1 accounts for half of all albinism cases, while OCA2 accounts for 30% of cases, and zebrafish models exist for both of these conditions (Table 1) [21,132,133]. Patients with OCA1 and OA1 can be treated with a few drugs to stimulate melanogenesis [132]. The other diseases are managed by avoiding sun exposure, excision of cancerous lesions, and corrective lenses [45]. There is no cure for oculocutaneous albinism.

4.2.3. Albinism Associated Disorders

Prader-Willi Syndrome (PWS) patients have sleep abnormalities, cognitive delay, abnormal differences in body structure, and obesity. PWS is caused by large chromosomal deletions on chromosome 15. The region that is deleted contains OCA2 and HERC2, two genes involved in pigmentation with HERC2 regulating the expression of OCA2 [134,135]. Without these genes, patients present with albinism along with PWS, but deletion of these genes is rare [109]. Angelman Syndrome (AS) patients present with developmental delay and seizures and such as PWS, results from deletions or changes in imprinting of chromosome 15. Albinism occurs from the deletion of OCA2, but albinism is not present in all cases [136].

5. Future Perspectives

5.1. The Genetics Underlying Pigmentation Disease Is Still Unfolding

It was found that, for 28% of patients with albinism, there were no mutations in known albinism-causing genes [137]. Therefore, we do not fully understand all the genes that cause albinism [138]. Indeed, new disease-causing mutations are being discovered as recently as 2020 [139,140]. Some mutations in pigment are first discovered in animal models before being described in humans, as is the case with the Mocha mouse, which was determined to have a defect in Ap3d1 in 1998 [141]. Hermansky–Pudlak Syndrome type 10, which is caused by a mutation in AP3D1, was described in 2016, and it is rare [13,137,142]. While mouse models for HPS10 have been used to understand the role of the AP3 complex, there is a paucity of information on HPS10. Furthermore, by studying zebrafish albinism models that are not yet implicated in human albinism, we will gain a head start on clarifying the function of genes potentially underlying human albinism disorders. For example, the fadeout zebrafish mutation maps to chromosome 2 [143]. None of the genes currently implicated in human HPS have homologs on zebrafish chromosome 2. Therefore, if the fadeout gene was identified, we could screen people with suspected HPS for the mutation in the fadeout gene.

Because the different types of albinism can present in similar ways clinically, it is crucial to understand the genetics and cell biology of such patients [121]. Even conditions that, in theory, should be similar, may have slight differences. For example, HPS2 occurs when one subunit of the AP3 complex, AP3B1, is mutated. HPS10 is caused by mutations in AP3D1—another subunit of the AP3 complex. Patients with HPS2 tend to bleed excessively, which is not the case for patients with HPS10. Additionally, patients with HPS10 have severe neurological defects that are not characteristic of HPS2 [142]. Treatment strategies may differ for these patients, and correct diagnosis is crucial for alleviating symptoms. Furthermore, when studying each condition, one protein in a complex may function slightly differently than the other. It is best to have models for all proteins in a complex to obtain
the clearest picture of their true function. Because zebrafish can be rapidly screened for gene function using CRISPR, they are excellent models for albinism gene discovery.

There is currently no cure for albinism at this time. However, there are possible therapeutic approaches for preventing albinism. While not available to everyone, in vitro fertilization (IVF) allows for the screening of embryos for genetic mutations that cause albinism before implantation is possible [144]. Knowing which genes and which mutations to screen for is therefore critical for this approach, and new gene editing technologies may allow for the treatment of these diseases before they develop.

With new genetic editing tools such as the CRISPR-Cas9 system, it is now possible to edit DNA in a specific manner. Theoretically, CRISPR-Cas9 could be used to edit out deleterious mutations in whole embryos. Alternatively, CRISPR-Cas9 could be used to repair mutations in melanocyte stem cells for implantation into the skin. Cell suspensions injected into the skin are capable of repigmenting skin in patients with vitiligo. This method requires taking cultured melanocytes from the patient and transplanting them elsewhere [145]. However, in patients with albinism without any pigmented skin, genetically-modified melanocytes derived from induced pluripotent stem cells or altered follicular melanocyte stem cells might offer an avenue for repigmentation [146]. A similar method has been used to correct mutations in alveolar cells from patients with HPS2 [147]. However, CRISPR modification comes with a risk of off-target effects, and the technology will have to be further developed to be used in gene therapy [148]. Zebrafish could be utilized to study these methods more in depth, as cells can be genetically modified in embryos, then transplanted into unedited mutant fish to test if genetic correction was successful.

5.2. The Role of Zebrafish Syndromic Albinism Models to Study and Find New Treatments for Pigment Disease

Certain albinism disorders are lethal to patients, as is the case with HPS10 [13,142]. The short lifespan of these patients means that there is very little time to better understand the disease to improve treatment options. Animal models provide the means to study disease progression and outcomes for rare diseases. For example, crasher homozygous recessive zebrafish carry mutations in ap3d1 (hps10), and fish do not survive past two weeks of life (Neuffer et al., submitted). This is somewhat different than Mocha mice, with most surviving to adulthood even as homozygotes [141,149]. Furthermore, research in zebrafish may complement research in mice. For example, new albinism genes can be quickly discovered in zebrafish because of the rate at which gene knockouts can be performed in large numbers. Then, promising genes can be more closely studied in a mouse model. Additionally, biomarkers of disease outcomes may help monitor disease progression, but the available biomarkers to predict mortality in HPS are limited. Zebrafish models are better models to study premature death in patients with HPS, and they will be helpful in developing these biomarkers [120,150].

Additionally, albino zebrafish may also be used to study melanoma. At first glance, using an albino animal to study melanoma seems counterintuitive because people with albinism do not generate pigment, and therefore they would not generate pigmented lesions. However, if some pigment production is possible, then melanoma can result. In HPS1 caused by mutations in the biogenesis of lysosome-related organelle complex-3 (BLOC3) subunit 1, pigmented nevi (moles) are common and can develop into melanoma [122,151]. Previously, our lab utilized several zebrafish albinism models to understand chemotherapeutic resistance in melanoma [147]. These models and their corresponding albinism disorder were mitfα (Waardenburg Syndrome type 2), vps11 (general syndromic albinism), and oca2 (Oculocutaneous albinism 2) [19,29,152,153]. The chemotherapeutic drug, cisplatin, induces DNA damage and triggers apoptosis in melanoma cells [154]. However, melanoma cells can become resistant to cisplatin over time. A potential mechanism suggested by multiple groups underlying resistance include sequestration in mature melanosomes [155,156]. All of the albinism models we used to study resistance to cisplatin had defects in melanosome function, and melanophores from melanosome mutants were
more sensitive to cisplatin-induced melanophore loss [153]. HPS zebrafish models have not been used to study chemoresistance. It could be expected that melanophores in current HPS zebrafish models could have increased sensitivity to cisplatin due to melanosome dysfunction, and therefore these zebrafish lines could serve as additional models for better understanding chemotherapeutic resistance in melanocytes.

6. Conclusions

The genetic similarity of melanogenesis and melanophore development genes, the availability of current zebrafish OCA and HPS models, and the ability to generate new ones through genetic engineering make zebrafish with albinism attractive models to understand not only albinism disorders but other skin pigmentation disorders.

Author Contributions: Conceptualization, S.J.N.; resources, S.J.N. and C.D.C.; original draft preparation, S.J.N.; writing—review and editing, S.J.N. and C.D.C.; supervision, C.D.C.; funding acquisition, S.J.N. and C.D.C. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported (in part) by the Poncin Scholarship Fund (awarded to S.J.N), Washington State University (WSU) Vancouver (awarded to C.D.C.), WSU College of Veterinary Medicine Intramural Funding Program (awarded to C.D.C), WSU College of Arts and Sciences (awarded to S.J.N.) and National Institutes of Health Grant HD103609 (awarded to C.D.C.).

Acknowledgments: The authors wish to thank dissertation committee members to S.J.N. for their feedback on this document.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Pralea, I.E.; Moldovan, R.C.; Petrache, A.M.; Ilies, M.; Hegeš, S.C.; Ielciu, I.; Nicoară, R.; Moldovan, M.; Ene, M.; Radu, M.; et al. From Extraction to Advanced Analytical Methods: The Challenges of Melanin Analysis. Int. J. Mol. Sci. 2019, 20, 3943. [CrossRef] [PubMed]
2. Wang, Y.; Casadevall, A. Decreased susceptibility of melanized Cryptococcus neoformans to UV light. Appl. Environ. Microbiol. 1994, 60, 3864–3866. [CrossRef]
3. Saxena, D.; Ben-Dov, E.; Manasherob, R.; Barak, Z.; Boussiba, S.; Zaritsky, A. A UV tolerant mutant of Bacillus thuringiensis subsp. kurstaki producing melanin. Curr. Microbiol. 2002, 44, 25–30. [CrossRef] [PubMed]
4. Brenner, M.; Hearing, V.J. The protective role of melanin against UV damage in human skin. Photochem. Photobiol. 2008, 84, 539–549. [CrossRef] [PubMed]
5. Alves, R.N.; Agustí, S. Effect of ultraviolet radiation (UVR) on the life stages of fish. Rev. Fish Biol. Fish. 2020, 30, 335–372. [CrossRef]
6. Cordero, R.J.; Casadevall, A. Functions of fungal melanin beyond virulence. Fungal Biol. Rev. 2017, 31, 99–112. [CrossRef]
7. Chakraborty, A.K.; Funasaka, Y.; Slominski, A.; Ermark, G.; Hwang, J.; Pawelek, J.M.; Ichihashi, M. Production and release of proopiomelanocortin (POMC) derived peptides by human melanocytes and keratinocytes in culture: Regulation by ultraviolet B. Biochim. Biophys. Acta 1996, 1313, 130–138. [CrossRef]
8. Cui, R.; Widlund, H.R.; Feige, E.; Lin, J.Y.; Wilensky, D.L.; Igura, V.E.; D’Orazio, J.; Fung, C.Y.; Schanbacher, C.F.; Grantor, S.R.; et al. Central role of p53 in the suntan response and pathologic hyperpigmentation. Cell 2007, 128, 853–864. [CrossRef]
9. Suzuki, I.; Cone, R.D.; Im, S.; Nordlund, J.; Abdel-Malek, Z.A. Binding of melanotropic hormones to the melanocortin receptor MC1R on human melanocytes stimulates proliferation and melanogenesis. Endocrinology 1996, 137, 1627–1633. [CrossRef]
10. Marks, M.S.; Heijnen, H.F.; Raposo, G. Lysosome-related organelles: Unusual compartments become mainstream. Curr. Opin. Cell Biol. 2013, 25, 495–505. [CrossRef]
11. Delevoye, C.; Marks, M.S.; Raposo, G. Lysosome-related organelles as functional adaptations of the endolysosomal system. Curr. Opin. Cell Biol. 2019, 59, 147–158. [CrossRef] [PubMed]
12. Clark, R.H.; Stinchcombe, J.C.; Day, A.; Blott, E.; Booth, S.; Bossi, G.; Hamblin, T.; Davies, E.G.; Griffiths, G.M. Adaptor protein 3-dependent microtubule-mediated movement of lytic granules to the immunological synapse. Nat. Immunol. 2003, 4, 1111–1120. [CrossRef] [PubMed]
13. Ammann, S.; Schulz, A.; Krägeloh-Mann, I.; Dieckmann, N.M.; Niethammer, K.; Fuchs, S.; Eckl, K.M.; Plank, R.; Werner, R.; Altmüller, J.; et al. Mutations in AP3D1 associated with immunodeficiency and seizures define a new type of Hermansky-Pudlak syndrome. Blood 2016, 127, 997–1006. [CrossRef] [PubMed]
14. Janeway, C.; Walport, M.; Travers, P. Immunobiology: The Immune System in Health and Disease, 5th ed.; Garland Science: New York, NY, USA, 2011.
15. Oykhman, P.; Mody, C.H. Direct microbial activity of cytotoxic T-lymphocytes. *J. Biomed Biotechnol.* 2010, 2010, 249482. [CrossRef] [PubMed]

16. Feldman, H.W. Linkage of Albino Allelomorphs in Rats and Mice. *Genetics* 1924, 9, 487–492. [CrossRef] [PubMed]

17. Jackson, I.J. Homologous pigmentation mutations in human, mouse and other model organisms. *Hum. Mol. Genet.* 1997, 6, 1613–1624. [CrossRef]

18. Braasch, I.; Scharl, M.; Volff, J.N. Evolution of pigment synthesis pathways by gene and genome duplication in fish. *BMC Ecol. Biol.* 2007, 7, 74. [CrossRef]

19. Esposito, R.; D’Aniello, S.; Squarzon, P.; Pezzotti, M.R.; Ristoratore, F.; Spagnuolo, A. New insights into the evolution of metazoan tyrosinase gene family. *PLoS ONE* 2012, 7, e35731. [CrossRef]

20. Howe, K.; Clark, M.D.; Torroja, C.F.; Torrance, J.; Berthelot, C.; Muffato, M.; Collins, J.E.; Humphray, S.; McLaren, K.; Matthews, L.; et al. The zebrafish reference genome sequence and its relationship to the human genome. *Nature* 2013, 496, 498–503. [CrossRef]

21. Beirl, A.J.; Linbo, T.H.; Cobb, M.J.; Cooper, C.D. *oca2* Regulation of chromatophore differentiation and number is cell type specific in zebrafish. *Pigment Cell Melanoma Res.* 2014, 27, 178–189. [CrossRef]

22. Cooper, C.D.; Raible, D.W. Mechanisms for reaching the differentiated state: Insights from neural crest-derived melanocytes. *Semin. Cell Dev. Biol.* 2009, 20, 105–110. [CrossRef] [PubMed]

23. D’Agati, G.; Belte, R.; Sessa, A.; Burger, A.; Zhou, Y.; Mosimann, C.; White, R.M. A defect in the mitochondrial protein Mpv17 underlies the transparent casper zebrafish. *Dev. Biol.* 2017, 430, 11–17. [CrossRef] [PubMed]

24. Lister, J.A.; Cooper, C.; Nguyen, K.; Modrell, M.; Grant, K.; Raible, D.W. Zebrafish Foxd3 is required for development of a subset of neural crest derivatives. *Dev. Biol.* 2006, 290, 92–104. [CrossRef] [PubMed]

25. Ignatius, M.S.; Moose, H.E.; El-Hodiri, H.M.; Henion, P.D. colgate/hdac1 Repression of foxd3 expression is required to permit mitfa-dependent melanogenesis. *Dev. Biol.* 2008, 313, 568–583. [CrossRef]

26. Curran, K.; Raible, D.W.; Lister, J.A. Foxd3 controls melanophore specification in the zebrafish neural crest by regulation of Mitf. *Dev. Biol.* 2009, 332, 408–417. [CrossRef]

27. Curran, K.; Lister, J.A.; Kunkel, G.R.; Prendergast, A.; Parichy, D.M.; Raible, D.W. Interplay between Foxd3 and Mitf regulates cell fate plasticity in the zebrafish neural crest. *Dev. Biol.* 2010, 344, 107–118. [CrossRef]

28. Van Otterloo, E.; Li, W.; Bonde, G.; Day, K.M.; Hsu, M.Y.; Cornell, R.A. Differentiation of zebrafish melanophores depends on transcription factors AP2 alpha and AP2 epsilon. *PLoS Genet.* 2010, 6, e1001122. [CrossRef]

29. Clancey, L.F.; Beirl, A.J.; Linbo, T.H.; Cooper, C.D. Maintenance of melanophore morphology and survival is cathepsin and vps11 dependent in zebrafish. *PLoS ONE* 2013, 8, e65096. [CrossRef]

30. Serre, C.; Busuttil, V.; Botto, J.M. Intrinsic and extrinsic regulation of human skin melanogenesis and pigmentation. *Int. J. Cosmet. Sci.* 2018, 40, 328–347. [CrossRef]

31. Eom, D.S.; Patterson, L.B.; Bostic, R.R.; Parichy, D.M. Immunoglobulin superfamily receptor function in zebrafish (Jam3) requirement for melanophore survival and patterning during formation of zebrafish stripes. *Dev. Biol.* 2021, 476, 314–327. [CrossRef]

32. Lawrence, C. The husbandry of zebrafish (Danio rerio): A review. *Aquaculture* 2007, 269, 1–20. [CrossRef]

33. Skinner, A.M.J.; Watt, P.J. Strategic egg allocation in the zebrafish, Danio rerio. *Behav. Ecol. Sociobiol.* 2007, 18, 900–905. [CrossRef]

34. Uusi-Heikkilä, S.; Böckenhoff, L.; Wolter, C.; Arlinghaus, R. Differential allocation by female zebrafish (Danio rerio) to different-sized males—an example in a fish species lacking parental care. *PLoS ONE* 2012, 7, e48317. [CrossRef] [PubMed]

35. Durkin, M.E.; Qian, X.; Popescu, N.C.; Lowy, D.R. Isolation of Mouse Embryo Fibroblasts. *Bio. Protoc.* 2013, 3, e908. [CrossRef] [PubMed]

36. Zhong, Z.; Wu, Z.; Zhang, J.; Chen, J. A novel BLOC1S5-related HPS-11 patient and zebrafish with blos1s5 disruption. *Pigment Cell Melanoma Res.* 2021, 34, 1112–1119. [CrossRef] [PubMed]

37. Schenk, H.; Müller-Deile, J.; Schroder, P.; Bolaños-Palmieri, P.; Beverly-Staggs, L.; White, R.; Bräs, J.H.; Haller, H.; Schiffer, M. Characterizing renal involvement in Hermansky-Pudlak Syndrome in a zebrafish model. *Sci. Rep.* 2019, 9, 17718. [CrossRef]

38. Birlea, S.A.; Costin, G.E.; Roop, D.R.; Norris, D.A. Trends in Regenerative Medicine: Repigmentation in Vitiligo Through Melanocyte Stem Cell Mobilization. *Med. Res. Rev.* 2017, 37, 907–935. [CrossRef]

39. Hirata, M.; Nakamura, K.; Kanemaru, T.; Shibata, Y.; Kondo, S. Pigment cell organization in the hypodermis of zebrafish. *Dev. Dyn.* 2003, 227, 497–503. [CrossRef]

40. Tadokoro, R.; Takahashi, Y. Intercellular transfer of organelles during body pigmentation. *Curr. Opin. Genet. Dev.* 2017, 45, 132–138. [CrossRef]

41. Moreiras, H.; Seabra, M.C.; Barral, D.C. Melanin Transfer in the Epidermis: The Pursuit of Skin Pigmentation Control Mechanisms. *Int. J. Mol. Sci.* 2021, 22, 4466. [CrossRef]

42. Garrido, G.; Fernández, A.; Montoliu, L. HPS11 and OCA8: Two new types of albinism associated with mutations in BLOC1S and DCT genes. *Pigment Cell Melanoma Res.* 2021, 34, 10–12. [CrossRef] [PubMed]

43. Bellono, N.W.; Escobar, I.E.; Lefkovith, A.J.; Marks, M.S.; Oancea, E. An intracellular anion channel critical for pigmentation. *Elife* 2014, 3, e04543. [CrossRef] [PubMed]
44. Le, L.; Escobar, I.E.; Ho, T.; Lefkovith, A.J.; Latteri, E.; Haltaufderhyde, K.D.; Dennis, M.K.; Plowright, L.; Sviderskaya, E.V.; Bennett, D.C.; et al. SLC45A2 protein stability and regulation of melanosomal pH determine melanocyte pigmentation. *Mol. Biol. Cell* **2020**, *31*, 2687–2702. [CrossRef] [PubMed]

45. Marçon, C.R.; Maia, M. Albinism: Epidemiology, genetics, cutaneous characterization, psychosocial factors. *An. Bras. Dermatol.* **2019**, *94*, 503–520. [CrossRef]

46. Meredith, P.; Sarna, T. The physical and chemical properties of eumelanin. *Pigment Cell Res.* **2006**, *19*, 572–594. [CrossRef]

47. Pillaiyar, T.; Manickam, M.; Namasiyavam, V. Skin whitening agents: Medicinal chemistry perspective of tyrosinase inhibitors. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 403–425. [CrossRef]

48. Chhatani, V.; Wikberg, J.E. Molecular cloning and expression of the human melanocyte stimulating hormone receptor cDNA. *FEMS Lett.* **1992**, *309*, 417–420. [CrossRef]

49. Selz, Y.; Braasch, I.; Hoffmann, C.; Schmidt, C.; Schultheis, C.; Volff, J.N. Evolution of melanocortin receptors in teleost fish: The melanocortin type 1 receptor. *Gene* **2007**, *401*, 114–122. [CrossRef]

50. Herraz, C.; Garcia-Borron, J.C.; Jiménez-Cervantes, C.; Olivares, C. MC1R signaling. Intracellular partners and pathophysiological implications. *Biochem. Biophys. Acta Mol. Basis. Dis.* **2017**, *1863*, 2448–2461. [CrossRef]

51. Cal, L.; Suarez-Bregua, P.; Braasch, I.; Irión, U.; Kelsch, R.; Cerdá-Reverter, J.M.; Rotllant, J. Loss-of-function mutations in the melanocortin 1 receptor cause disruption of dorso-ventral countershading in teleost fish. *Pigment Cell Melanoma Res.* **2019**, *32*, 817–828. [CrossRef]

52. Dorsky, R.I.; Raible, D.W.; Moon, R.T. Direct regulation of nacre, a zebrafish MITF homolog required for pigment cell formation, by the Wnt pathway. *Genes Dev.* **2000**, *14*, 158–162. [CrossRef] [PubMed]

53. Takeda, K.; Yasumoto, K.; Takada, R.; Takada, S.; Watanabe, K.; Udono, T.; Saito, H.; Takahashi, K.; Shibahara, S. Induction of melanocyte-specific microphthalmia-associated transcription factor by Wnt-3a. *J. Biol. Chem.* **2000**, *275*, 14013–14016. [CrossRef] [PubMed]

54. Vibert, L.; Aquino, G.; Gehring, I.; Subkankulova, T.; Schilling, T.F.; Rocco, A.; Kelsch, R.N. An ongoing role for Wnt signaling in differentiating melanocytes in vivo. *Pigment Cell Melanoma Res.* **2017**, *30*, 219–232. [CrossRef] [PubMed]

55. Rabbani, P.; Takeo, M.; Chou, W.; Myung, P.; Bosenberg, M.; Chin, L.; Ito, M.; Ito, M. Coordinated activation of Wnt in microphthalmia-associated transcription factor and melanocortin 1 receptor cause disruption of dorso-ventral countershading in teleost fish. *Pigment Cell Melanoma Res.* **2019**, *32*, 817–828. [CrossRef] [PubMed]

56. Lim, X.; Nusse, R. Wnt signaling in skin development, homeostasis, and disease. *Cold Spring Harb. Perspect. Biol.* **2013**, *5*, a008029. [CrossRef] [PubMed]

57. Patton, E.E.; Widlund, H.R.; Kutok, J.L.; Kopani, K.R.; Amatruda, J.F.; Murphey, R.D.; Berghmans, S.; Mayhall, E.A.; Traver, D.; Fletcher, C.D.; et al. BRAF mutations are sufficient to promote nevi formation and cooperate with p53 in the genesis of melanoma. *Curr. Biol.* **2005**, *15*, 249–254. [CrossRef] [PubMed]

58. Cooper, C.D.; Linbo, T.H.; Raible, D.W. Kit and foxd3 genetically interact to regulate melanophore survival in zebrafish. *Dev. Dyn.* **2009**, *238*, 875–886. [CrossRef]

59. Goldinger, S.M.; Murer, C.; Stieger, P.; Dummer, R. Targeted therapy in melanoma—The role of BRAF, RAS and KIT mutations. *EJC Suppl.* **2013**, *11*, 92–96. [CrossRef]

60. Parichy, D.M.; Rawls, J.F.; Pratt, S.J.; Whitfield, T.T.; Johnson, S.L. Zebrafish sparse corresponds to an orthologue of c-kit and is required for the morphogenesis of a subpopulation of melanocytes, but is not essential for hematopoiesis or primordial germ cell development. *Development* **1999**, *126*, 3425–3436. [CrossRef]

61. Parichy, D.M.; Mellgren, E.M.; Rawls, J.F.; Lopes, S.S.; Kelsch, R.N.; Johnson, S.L. Mutational analysis of endothelin receptor b1 (rose) during neural crest and pigment pattern development in the zebrafish *Danio rerio*. *Dev. Biol.* **2000**, *227*, 294–306. [CrossRef]

62. Spitaler, M.; Cantrell, D.A. Protein kinase C and beyond. *Nat. Immunol.* **2005**, *5*, 785–790. [CrossRef] [PubMed]

63. Imokawa, G.; Yada, Y.; Kimura, M. Signalling mechanisms of endothelin-inducet mitogenesis and melanogenesis in human melanocytes. *Biochem. J.* **1996**, *314 Pt 1*, 305–312. [CrossRef]

64. D’Mello, S.A.; Finlay, G.J.; Baguley, B.C.; Askanian-Amiri, M.E. Signaling Pathways in Melanogenesis. *Int. J. Mol. Sci.* **2016**, *17*, 1144. [CrossRef]

65. Sato-Jin, K.; Nishimura, E.K.; Akasaka, E.; Huber, W.; Nakano, H.; Miller, A.; Du, J.; Wu, M.; Hanada, K.; Sawamura, D.; et al. Epistatic connections between microphthalmia-associated transcription factor and endothelin signaling in Waardenburg syndrome and other pigmentary disorders. *FASEB J.* **2008**, *22*, 1155–1168. [CrossRef]

66. Ohbayashi, N.; Fukuda, M. Recent advances in understanding the molecular basis of melanogenesis in melanocytes. *F1000Research* **2020**, *9*, 608. [CrossRef] [PubMed]

67. Wasmeyer, C.; Hume, A.N.; Bolasco, G.; Seabra, M.C. Melanosomes at a glance. *J. Cell Sci.* **2008**, *121*, 3995–3999. [CrossRef] [PubMed]

68. Hellström, A.R.; Watt, B.; Fard, S.S.; Tenza, D.; Mannström, P.; Narfström, K.; Ekestun, B.; Ito, S.; Wakamatsu, K.; Larsson, J.; et al. Inactivation of Pmel alters melanosome shape but has only a subtle effect on visible pigmentation. *PLoS Genet.* **2011**, *7*, e1002285. [CrossRef] [PubMed]

69. Hee, J.S.; Mitchell, S.M.; Liu, X.; Leonhardt, R.M. Melanosomal formation of PMEL core amyloid is driven by aromatic residues. *Sci. Rep.* **2017**, *7*, 44064. [CrossRef]

70. Gerondopoulos, A.; Langemeyer, L.; Liang, J.R.; Linford, A.; Barr, F.A. BLOC-3 mutated in Hermansky-Pudlak syndrome is a Rab32/38 guanine nucleotide exchange factor. *Curr. Biol.* **2012**, *22*, 2135–2139. [CrossRef]
71. Setty, S.R.; Tenza, D.; Truschel, S.T.; Chou, E.; Sviderskaya, E.V.; Theos, A.C.; Lamoureux, M.L.; Di Pietro, S.M.; Starcevic, M.; Bennett, D.C.; et al. BLOC-1 is required for cargo-specific sorting from vacuolar early endosomes toward lysosome-related organelles. *Mol. Biol. Cell* 2007, 18, 768–780. [CrossRef]

72. Dennis, M.K.; Mantegazza, A.R.; Snir, O.L.; Tenza, D.; Acosta-Ruiz, A.; Delevoye, C.; Zorger, R.; Sitaram, A.; de Jesus-Rojas, W.; Ravichandran, K.; et al. BLOC-2 targets recycling endosomal tubules to melanosomes for cargo delivery. *J. Cell Biol.* 2015, 209, 563–577. [CrossRef]

73. Lee, H.H.; Nemecek, D.; Schindler, C.; Smith, W.J.; Ghirlando, R.; Steven, A.C.; Bonifacino, J.S.; Hurley, J.H. Assembly and architecture of biogenesis of lysosome-related organelles complex-1 (BLOC-1). *J. Biol. Chem.* 2012, 287, 5882–5890. [CrossRef] [PubMed]

74. Delevoye, C.; Heiligenstein, X.; Ripoll, L.; Gilles-Marsens, F.; Dennis, M.K.; Linares, R.A.; Derman, L.; Gokhale, A.; Morel, E.; Faundez, V.; et al. BLOC-1 Brings Together the Actin and Microtubule Cytoskeletons to Generate Recycling Endosomes. *Curr. Biol.* 2016, 26, 1–13. [CrossRef] [PubMed]

75. Talbot, K. The sandy (sdy) mouse: A dysbindin-1 mutant relevant to schizophrenia research. *Prog. Brain Res.* 2009, 179, 87–94. [CrossRef] [PubMed]

76. Gwynn, B.; Martina, J.A.; Bonifacino, J.S.; Sviderskaya, E.V.; Lamoreux, M.L.; Bennett, D.C.; Moriyama, K.; Huizing, M.; Helip-Wooley, A.; Gahl, W.A.; et al. Reduced pigmentation (rp), a mouse model of Hermansky-Pudlak syndrome, encodes a novel component of the BLOC-1 complex. *Blood* 2004, 104, 3181–3189. [CrossRef]

77. Falcón-Pérez, J.M.; Starcevic, M.; Gautam, R.; Dell’Angelica, E.C. BLOC-1, a novel complex containing the pallidin and mutated proteins involved in the biogenesis of melanosomes and platelet-dense granules. *J. Biol. Chem.* 2002, 277, 28191–28199. [CrossRef]

78. Hirobe, T.; Yoshihara, C.; Takeuchi, S.; Wakamatsu, K.; Ito, S.; Abe, H.; KawA, Y.; Soma, Y. A novel deletion mutation of mouse ruby-eye 2 named ru2(d)/HpsR(ru2-d) inhibits melanocyte differentiation and its impaired differentiation is rescued by L-tyrosine. *Zool. Sci.* 2011, 28, 790–801. [CrossRef]

79. Hirobe, T. How are protein sorting and differentiation of melanocytes regulated? *Pigment Cell Melanoma Res.* 2011, 24, 462–478. [CrossRef]

80. Zhang, Q.; Zhao, B.; Li, W.; Oiso, N.; Novak, E.K.; Rusiniak, M.E.; Gautam, R.; Chintala, S.; O’Brien, E.P.; Zhang, Y.; et al. Ru2 and Ru encode mouse orthologs of the genes mutated in human Hermansky-Pudlak syndrome types 5 and 6. *Nat. Genet.* 2003, 33, 145–153. [CrossRef]

81. Daly, C.M.; Willer, J.; Gregg, R.; Gross, J.M. Snow white, a zebrafish model of Hermansky-Pudlak Syndrome type 5. *Genetics* 2013, 195, 481–494. [CrossRef]

82. Höning, S.; Sandoval, I.V.; von Figura, K. A di-leucine-based motif in the cytoplasmic tail of LIM-II and tyrosinase mediates selective binding of AP-3. *EMBO J.* 1998, 17, 1304–1314. [CrossRef] [PubMed]

83. Huizing, M.; Sarangarajan, R.; Strovel, E.; Zhao, Y.; Gahl, W.A.; Boissy, R.E. AP-3 mediates tyrosinase but not TRP-1 trafficking in melanocytes. *J. Biol. Chem.* 2020, 295, 3181–3189. [CrossRef] [PubMed]

84. Theos, A.C.; Tenza, D.; Martina, J.A.; Hurban, I.; Peden, A.A.; Sviderskaya, E.V.; Stewart, A.; Robinson, M.S.; Bennett, D.C.; Cutler, D.F.; et al. Functions of adaptor protein (AP)-3 and AP-1 in tyrosinase sorting from endosomes to melanosomes. *Mol. Biol. Cell* 2015, 26, 5356–5372. [CrossRef] [PubMed]

85. Di Pietro, S.M.; Falcón-Pérez, J.M.; Tenza, D.; Setty, S.R.; Marks, M.S.; Raposo, G.; Dell’Angelica, E.C. BLOC-1 interacts with BLOC-2 and the AP-3 complex to facilitate protein trafficking on endosomes. *Mol. Biol. Cell* 2006, 17, 4027–4038. [CrossRef] [PubMed]

86. Delevoye, C.; Hurban, I.; Tenza, D.; Sibarita, J.B.; Uzan-Gafsiou, S.; Ohno, H.; Geerts, W.J.; Verkleij, A.J.; Salamero, J.; Marks, M.S.; et al. AP-1 and KIF13A coordinate endosomal sorting and positioning during melanosome biogenesis. *J. Biol. Chem.* 2009, 284, 247–264. [CrossRef]

87. Schoppe, J.; Mari, M.; Yavavli, E.; Auffarth, K.; Cabrera, M.; Walter, S.; Fröhlich, F.; Ungermann, C. AP-3 vesicle uncoating occurs after HOPS-dependent vacuole tethering. *EMBO J.* 2020, 39, e105117. [CrossRef]

88. Sanderson, L.E.; Lanko, K.; Alsagob, M.; Almass, R.; Al-Ahmadi, N.; Najafi, M.; Al-Muhaizea, M.A.; Alzaidan, H.; AlDhaalan, H.; Perenthaler, E.; et al. Bi-allelic variants in HOPS complex subunit VPS41 cause cerebellar ataxia and abnormal membrane trafficking. *Brain* 2021, 144, 769–780. [CrossRef]

89. Jung, J.; Bohn, G.; Allroth, A.; Boztug, K.; Brandes, G.; Sandrock, I.; Schäffer, A.A.; Rathinam, C.; Köllner, I.; Beger, C.; et al. Identification of a homozygous deletion in the AP3B1 gene causing Hermansky-Pudlak syndrome, type 2. *Blood* 2006, 108, 362–369. [CrossRef]

90. Patwardhan, A.; Bardin, S.; Miserey-Lenkei, S.; Larue, L.; Goud, B.; Raposo, G.; Delevoye, C. Routing of the Rab6 secretory pathway towards the lysosome related organelle of melanocytes. *Nat. Commun.* 2017, 8, 15835. [CrossRef]

91. Marubashi, S.; Shimada, H.; Fukuda, M.; Ohbayashi, N. RUTBC1 Functions as a GTPase-activating Protein for Rab32/38 and Regulates Melanogenic Enzyme Trafficking in Melanocytes. *J. Biol. Chem.* 2016, 291, 1427–1440. [CrossRef]

92. Osanai, K.; Oikawa, R.; Higuchi, J.; Kobayashi, M.; Tsuchihara, K.; Iguchi, M.; Jongshu, H.; Toga, H.; Voelker, D.R. A mutation in Rab38 small GTPase causes abnormal lung surfactant homeostasis and aberrant alveolar structure in mice. *Am. J. Pathol.* 2008, 173, 1265–1274. [CrossRef] [PubMed]
116. Trantow, C.M.; Mao, M.; Petersen, G.E.; Alward, E.M.; Alward, W.L.; Fingert, J.H.; Anderson, M.G. Lyst mutation in mice recapitulates iris defects of human exfoliation syndrome. *Investig. Ophthal. Vis. Sci.* **2009**, *50*, 1205–1214. [CrossRef] [PubMed]

117. Sepulveda, F.E.; Burgess, A.; Heiligenstein, X.; Goudin, N.; Ménager, M.M.; Romao, M.; Côte, M.; Mahlaoui, N.; Fischer, A.; Raposo, G.; et al. LYST controls the biogenesis of the endosomal compartment required for secreted lysosome function. *Traffic* **2015**, *16*, 191–203. [PubMed]

118. Westphal, A.; Cheng, W.; Yu, J.; Grassl, G.; Krautkrämer, M.; Holst, O.; Förger, N.; Lee, K.H. Lysosomal trafficking regulator Lyst links membrane trafficking to toll-like receptor-mediated inflammatory responses. *J. Exp. Med.* **2017**, *214*, 227–244. [CrossRef]

119. Ullate-Agote, A.; Burgelin, I.; Debry, A.; Langrez, C.; Montange, F.; Peraldi, R.; Daraspe, J.; Kaessmann, H.; Milinkovitch, M.C.; Tzika, A.C. Genome mapping of a LYST mutation in corn snakes indicates that vertebrate chromatophore vesicles are lysosome-related organelles. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 26307–26317. [CrossRef]

120. El-Chemaly, S.; Young, L.R. Hermansky-Pudlak Syndrome. *Clin. Chest. Med.* **2016**, *37*, 505–511. [CrossRef]

121. Power, B.; Ferreira, C.R.; Chen, D.; Zein, W.M.; O’Brien, K.J.; Introne, W.J.; Stephen, J.; Gahl, W.A.; Huizing, M.; Malicdan, M.C.V.; et al. Hermansky-Pudlak syndrome and oculocutaneous albinism in Chinese children with pigmentation defects and easy bruising. *Orphanet. J. Rare Dis.* **2019**, *14*, 52. [CrossRef]

122. Huizing, M.; Malicdan, M.C.V.; Wang, J.A.; Pri-Chen, H.; Hess, R.A.; Fischer, R.; O’Brien, K.J.; Merideth, M.A.; Gahl, W.A.; Gochuico, B.R. Hermansky-Pudlak syndrome: Mutation update. *Hum. Mutat.* **2020**, *41*, 543–580. [CrossRef]

123. Huizing, M.; Malicdan, M.C.V.; Gochuico, B.R.; Gahl, W.A. Hermansky-Pudlak Syndrome. In *GeneReviews [Internet]*; University of Washington: Seattle, WA, USA, 2000. Available online: https://www.ncbi.nlm.nih.gov/books/NBK1287/ (accessed on 8 February 2022).

124. Evstratova, A.; Chamberland, S.; Faundez, V.; Tóth, K. Vesicles derived via AP-3-dependent recycling contribute to asynchronous release and influence information transfer. *Nat. Commun.* **2014**, *5*, 5530. [CrossRef]

125. Vicary, G.W.; Vergne, Y.; Santiago-Cornier, A.; Young, L.R.; Roman, J. Pulmonary Fibrosis in Hermansky-Pudlak Syndrome. *Ann. Am. Thorac. Soc.* **2016**, *13*, 1839–1846. [CrossRef] [PubMed]

126. Zhang, A.; He, X.; Zhang, L.; Yang, L.; Woodman, P.; Li, W. Biogenesis of lysosome-related organelles complex-1 subunit 1 (BLOS1) interacts with sorting nexin 2 and the endosomal sorting complex required for transport-I (ESCRT-I) component TSG101 to mediate the sorting of epidermal growth factor receptor into endosomal compartments. *J. Biol. Chem.* **2014**, *289*, 29180–29194. [CrossRef] [PubMed]

127. Chen, T.; Song, G.; Yang, H.; Mao, L.; Cui, Z.; Huang, K. Development of the Swinbladder Surfactant System and Biogenesis of Lysosome-Related Organelles Is Regulated by BLOS1 in Zebrafish. *Genetics* **2018**, *208*, 1131–1146. [CrossRef] [PubMed]

128. Incerti, B.; Cortese, K.; Pizzigoni, A.; Surace, E.M.; Coppola, M.; Jeffery, G.; Seeliger, M.; Jaisle, G.; Bennett, D.C.; et al. Oa1 knock-out: New insights on the pathogenesis of ocular albinism type 1. *Hum. Mol. Genet.* **2000**, *9*, 2781–2788. [CrossRef]

129. Davies, J.R.; Wilkinson, L.S.; Isles, A.R.; Humby, T. Prader-Willi syndrome imprinting centre deletion mice have impaired baseline and 5-HT2CR-mediated response inhibition. *Hum. Mol. Genet.* **2019**, *28*, 3013–3023. [CrossRef]

130. Spikol, E.D.; Laverriere, C.E.; Robnett, M.; Carter, G.; Wolfe, E.M.; Glasgow, E. Zebrafish Models of Prader-Willi Syndrome: Fast Track to Pharmacotherapeutics. *Diseases* **2016**, *4*, 13. [CrossRef]

131. Grønskov, K.; Ek, J.; Brondum-Nielsen, K. Oculocutaneous albinism. *Orphanet J. Rare Dis.* **2007**, *2*, 43. [CrossRef]

132. Kamaraj, B.; Purohit, R. Mutational analysis of oculocutaneous albinism: A compact review. *Biomed. Res. Int.* **2014**, *2014*, 905472. [CrossRef]

133. Neuhauss, S.C.; Biehlmaier, O.; Seeliger, M.W.; Das, T.; Kohler, K.; Harris, W.A.; Baier, H. Genetic disorders of vision revealed by a behavioral screen of 400 essential loci in zebrafish. *J. Neurosci.* **1999**, *19*, 8603–8615. [CrossRef]

134. Jin, D.K. Systematic review of the clinical and genetic aspects of Prader-Willi syndrome. *Korean J. Pediatr.* **2011**, *54*, 55–63. [CrossRef] [PubMed]

135. Visser, M.; Kayser, M.; Palstra, R.J. HERC2 rs12913832 modulates human pigmentation by attenuating chromatin-loop formation between a long-range enhancer and the OCA2 promoter. *Genome Res.* **2012**, *22*, 446–455. [CrossRef] [PubMed]

136. Bird, L.M. Angelman syndrome: Review of clinical and molecular aspects. *Appl. Clin. Genet.* **2014**, *7*, 93–104. [CrossRef] [PubMed]

137. Lasseaux, E.; Plaisant, C.; Michaud, V.; Pennamen, P.; Trumouille, A.; Gaston, L.; Monfermé, S.; Lacombe, D.; Rooryck, C.; Morice-Picard, F.; et al. Molecular characterization of a series of 990 index patients with albinism. *Pigment Cell Melanoma Res.* **2015**, *28*, 26307–26317. [CrossRef]

138. Bowman, S.L.; Bi-Karchin, J.; Le, L.; Marks, M.S. The road to LROs: Insights into lysosome-related organelles from Hermansky-Pudlak syndrome and other rare diseases. *Traffic* **2019**, *20*, 404–435. [CrossRef] [PubMed]

139. Pennamen, P.; Le, L.; Tingaud-Sequeira, A.; Fiore, M.; Bauters, A.; Van Duong Béatrice, N.; Coste, V.; Bordet, J.C.; Plaisant, C.; Diallo, M.; et al. BLOC1S5 pathogenic variants cause a new type of Hermansky-Pudlak syndrome. *Genet. Med.* **2020**, *22*, 1613–1622. [CrossRef] [PubMed]

140. Pennamen, P.; Tingaud-Sequeira, A.; Gazova, I.; Keighren, M.; McKie, L.; Marlin, S.; Gherbi Halem, S.; Kaplan, J.; Delevoye, C.; Lacombe, D.; et al. Dopa-chrome tautomerase variants in patients with oculocutaneous albinism. *Genet. Med.* **2021**, *23*, 479–487. [CrossRef]

141. Kantheti, P.; Qiao, X.; Diaz, M.E.; Peden, A.A.; Meyer, G.E.; Carskadon, S.L.; Kapfhammer, D.; Sufalko, D.; Robinson, M.S.; Noebels, J.L.; et al. Mutation in AP-3 delta in the mocha mouse links endosomal transport to storage deficiency in platelets, melanosomes, and synaptic vesicles. *Neuron* **1998**, *19*, 111–122. [CrossRef]
142. Mohammed, M.; Al-Hashmi, N.; Al-Rashdi, S.; Al-Sukaiti, N.; Al-Adawi, K.; Al-Riyami, M.; Al-Maawali, A. Biallelic mutations in AP3D1 cause Hermansky-Pudlak syndrome type 10 associated with immunodeficiency and seizure disorder. *Eur. J. Med. Genet.* 2019, 62, 103583. [CrossRef]

143. Bahadori, R.; Rinner, O.; Schonthaler, H.B.; Biehlmaier, O.; Makhankov, Y.V.; Rao, P.; Jagadeeswaran, P.; Neuhauss, S.C. The Zebrafish fade out mutant: A novel genetic model for Hermansky-Pudlak syndrome. *Investig. Ophthalmol. Vis. Sci.* 2006, 47, 4523–4531. [CrossRef]

144. Patel, N.; Bhadarka, H.K.; Vaniawala, S.; Patel, A. A Successful Case for Deselection of Albino Embryo and Live Birth of Albinism-Free Healthy Baby Followed by PGT-M. *J. Hum. Reprod. Sci.* 2020, 13, 245–248. [CrossRef]

145. Orouji, Z.; Bajouri, A.; Ghasemi, M.; Mohammadi, P.; Fallah, N.; Shahbazi, A.; rezvani, M.; Vaezirad, F.; Khalajasadi, Z.; Alizadeh, A.; et al. A single-arm open-label clinical trial of autologous epidermal cell transplantation for stable vitiligo: A 30-month follow-up. *J. Dermatol. Sci.* 2018, 89, 52–59. [CrossRef] [PubMed]

146. Lei, T.C.; Hearing, V.J. Deciphering skin re-pigmentation patterns in vitiligo: An update on the cellular and molecular events involved. *Chin. Med. J.* 2020, 133, 1231–1238. [CrossRef] [PubMed]

147. Korogi, Y.; Gotoh, S.; Ikeo, S.; Yamamoto, Y.; Sone, N.; Tamai, K.; Konishi, S.; Nagasaki, T.; Matsumoto, H.; Ito, I.; et al. In Vitro Disease Modeling of Hermansky-Pudlak Syndrome Type 2 Using Human Induced Pluripotent Stem Cell-Derived Alveolar Organoids. *Stem. Cell Rep.* 2019, 13, 235. [CrossRef] [PubMed]

148. Papasavva, P.; Kleanthous, M.; Lederer, C.W. Rare Opportunities: CRISPR/Cas-Based Therapy Development for Rare Genetic Diseases. *Mol. Diagn. Ther.* 2019, 23, 201–222. [CrossRef]

149. Lane, P.W.; Deol, M.S. Mocha, a new coat color and behavior mutation on chromosome 10 of the mouse. *J. Hered.* 1974, 65, 362–364. [CrossRef]

150. Zhou, Y.; He, C.H.; Herzog, E.L.; Peng, X.; Lee, C.M.; Nguyen, T.H.; Gulati, M.; Gochuico, B.R.; Gahl, W.A.; Slade, M.L.; et al. Chitinase 3-like-1 and its receptors in Hermansky-Pudlak syndrome-associated lung disease. *J. Clin. Investig.* 2015, 125, 3178–3192. [CrossRef]

151. Toro, J.; Turner, M.; Gahl, W.A. Dermatologic manifestations of Hermansky-Pudlak syndrome in patients with and without a 16-base pair duplication in the HPS1 gene. *Arch Dermatol.* 1999, 135, 774–780. [CrossRef]

152. Johnson, S.L.; Nguyen, A.N.; Lister, J.A. mitfA is required at multiple stages of melanocyte differentiation but not to establish the melanocyte stem cell. *Dev. Biol.* 2011, 350, 405–413. [CrossRef]

153. Peterson, K.A.; Neuffer, S.; Bean, M.E.; New, L.; Coffin, A.B.; Cooper, C.D. Melanosome maturation proteins Oca2, MitfA and Vps11 are differentially required for cisplatin resistance in zebrafish melanocytes. *Exp. Dermatol.* 2019, 28, 795–800. [CrossRef]

154. Siddik, Z.H. Cisplatin: Mode of cytotoxic action and molecular basis of resistance. *Oncogene* 2003, 22, 7265–7279. [CrossRef]

155. Weng, C.H.; Wu, C.S.; Wu, J.C.; Kung, M.L.; Wu, M.H.; Tai, M.H. Cisplatin-Induced Giant Cells Formation Is Involved in Chemoresistance of Melanoma Cells. *Int. J. Mol. Sci.* 2020, 21, 7892. [CrossRef] [PubMed]

156. Cooper, C.D. Insights from zebrafish on human pigment cell disease and treatment. *Dev. Dyn.* 2017, 246, 889–896. [CrossRef] [PubMed]