



Review

# Melanocortin 1 Receptor (MC1R): Pharmacological and Therapeutic Aspects

Yoonwoo Mun <sup>1,†</sup>, Woohyun Kim <sup>1,†</sup> and Dongyun Shin <sup>1,2,\*</sup>

<sup>1</sup> College of Pharmacy, Gachon University, 191 Hambakmoe-ro, Yeonsu-gu, Incheon 21936, Republic of Korea; ansqosdl@naver.com (Y.M.); kimwoohyun132@gmail.com (W.K.)

<sup>2</sup> Gachon Pharmaceutical Research Institute, Gachon University, 191 Hambakmoe-ro, Yeonsu-gu, Incheon 21936, Republic of Korea

\* Correspondence: dyshin@gachon.ac.kr

† These authors contributed equally to this work.

**Abstract:** Melanocortins play crucial roles in regulating the stress response, inflammation, and skin pigmentation. In this review, we focus on the melanocortin 1 receptor (MC1R), a G protein-coupled receptor primarily known for regulating skin pigmentation and exhibiting anti-inflammatory effects. First, we provide an overview of the structure, signaling pathways, and related diseases of MC1R. Next, we discuss the potential therapeutic use of synthetic peptides and small molecule modulators of MC1R, highlighting the development of various drugs that enhance stability through amino acid sequence modifications and small molecule drugs to overcome limitations associated with peptide characteristics. Notably, MC1R-targeted drugs have applications beyond skin pigmentation-related diseases, which predominantly affect MC1R in melanocytes. These drugs can also be useful in treating inflammatory diseases with MC1R expression present in various cells. Our review underscores the potential of MC1R-targeted drugs to treat a wide range of diseases and encourages further research in this area.

**Keywords:** melanocortin; receptor; peptide; modulator; disease



**Citation:** Mun, Y.; Kim, W.; Shin, D. Melanocortin 1 Receptor (MC1R): Pharmacological and Therapeutic Aspects. *Int. J. Mol. Sci.* **2023**, *24*, 12152. <https://doi.org/10.3390/ijms241512152>

Academic Editors: Tae-Kang Kim, István Zupkó and Andrzej Slominski

Received: 21 May 2023

Revised: 22 June 2023

Accepted: 27 July 2023

Published: 29 July 2023



**Copyright:** © 2023 by the authors. Licensee 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/>).

## 1. Introduction

Melanocortins are a group of hormones that play crucial roles in regulating various physiological processes, including stress response, inflammation, and skin pigmentation. These hormones are polypeptides derived from pro-opiomelanocortin (POMC) and include adrenocorticotropin hormone (ACTH),  $\alpha$ -,  $\beta$ -, and  $\gamma$ -melanocyte stimulating hormone ( $\alpha$ -,  $\beta$ -, and  $\gamma$ -MSH) [1,2]. While the functions of ACTH [3] and  $\alpha$ -MSH are well-established in skin pigmentation [4], anti-inflammatory [5], and microbicidal characteristics [6], the role of  $\beta$ -MSH and  $\gamma$ -MSH are less well understood. Some studies suggested that they possess anti-inflammatory properties [7–10].

The functions of melanocortin peptides are mediated by G protein-coupled receptors (GPCRs), primarily the stimulatory G protein (Gs) [11]. The melanocortin receptor family is the smallest member of class A, a rhodopsin-like family of GPCRs, and consists of five isoforms (MC1R, MC2R, MC3R, MC4R, and MC5R) with varied tissue expression and functions [12]. MC1R, mainly expressed in both melanocytes and leukocytes, enhances UV resistance and anti-inflammatory signaling when activated. MC2R is found in the adrenal cortex, and both MC3R and MC4R, which are reported to control food intake and sexual function, are largely present in the CNS. MC5R, located in the brain and skeletal muscle, has an exocrine role. The low sequence homology (40–60%) among the five receptors explains the lack of ligand selectivity [13–16].

The MC1R is a well-known receptor for  $\alpha$ -MSH expressed in the skin and hair follicles, where it controls pigmentation. However, recent studies have revealed that MC1R is also expressed in various other cell types that are susceptible to the anti-inflammatory effects

of melanocortins [17,18]. Thus, understanding the regulation of MC1R could potentially lead to the development of novel therapeutic strategies. This review article provides a brief overview of the structure, signaling pathway, and related diseases associated with MC1R and discusses the potential of synthetic peptide modulators and small molecule modulators of MC1R as therapeutic agents. Through a detailed examination of MC1R and its modulators, this review aims to provide insights into the potential clinical implications of modulating MC1R activity.

## 2. Melanocortin 1 Receptor (MC1R)

### 2.1. Structure

The human MC1R is primarily found on melanocytes and malignant melanoma cells and consists of 317 amino acids [19–21]. While the normal expression of MC1R protein is low, melanocytes express approximately 700 protein units, with slightly higher amounts found on melanoma cells [22,23]. MC1R is a GPCR with seven  $\alpha$ -helical transmembrane (TM) domains, an N-linked glycosylation site at the external N-terminus, a palmitoylation site at the intracellular C-terminus, and a DRY motif at the junction of the third TM domain. Unlike other GPCRs, the first and second extracellular domains of the MC receptor subfamily lack one or two cysteines, while the fourth and fifth TM domains lack proline. The intracellular and transmembrane domains of MC1R regulate adenylyl cyclase connections and signaling, while the extracellular and transmembrane domains interact with MC1R ligands.

The extracellular N-terminal tail serves as a signal anchor and plays a crucial role in ligand affinity. A conserved cysteine residue at the intersection of the N-terminus and the first TM domain is crucial for receptor function [24–28]. The C-terminus is involved in receptor interactions with the G protein at the plasma membrane, as well as protein trafficking from the endoplasmic reticulum to the plasma membrane. Also, C-terminus affects desensitization, internalization, and the plasma membrane location of the receptor [29–33].

The intracellular and extracellular loops (ils and els, respectively) lie between the transmembrane domains of the melanocortin 1 receptor. These loops share conserved sequences with other MC receptors. Despite being smaller than most GPCRs, MC1R els are essential for constitutive basal signaling activity. Mutations in this area affect binding affinity, as the els of the MC1R interact with ligands. Due to conserved proline and cysteine residues, els appear to be essential for melanocortin affinity. Similarly, MC1R ils play a crucial role in Gs protein binding and have phosphorylation sites that impact signal modulation, internalization, and receptor cycling [25,27,28,31,34].

Recently, the Cryo-electron microscopy (Cryo-EM) structure of MC1R and the MC1R–Gs complexes bound to the endogenous hormone  $\alpha$ -MSH, the marketed drug afamelanotide, and a synthetic agonist called SHU9119 were determined [35]. These findings may pave the way for resolving the lack of selectivity in MC drug discovery.

### 2.2. Signaling Pathway

The melanocortin 1 receptor (MC1R) is a receptor that forms a complex with heterotrimeric G proteins. When agonistic ligands bind to MC1R, the G $\alpha$ s protein is separated, and MC1R activates adenylyl cyclase, which leads to the production of cAMP, a crucial second messenger that regulates many cellular processes. In melanocytes, cAMP activates protein kinase A (PKA) and triggers downstream signaling pathways that activate different effector pathways, including the CREB and MITF networks. These pathways lead to the increased expression of tyrosinase and dopachrome tautomerase, two enzymes that are involved in melanin synthesis, resulting in the production of melanin. The melanin produced is then transmitted to nearby keratinocytes, creating a protective layer that improves the skin's ability to prevent further UV damage. Moreover, the increase in cAMP levels in melanocytes enhances antioxidant defenses and accelerates nucleotide excision repair (NER), which is vital for safeguarding the skin from UV damage (Figure 1) [36–43].

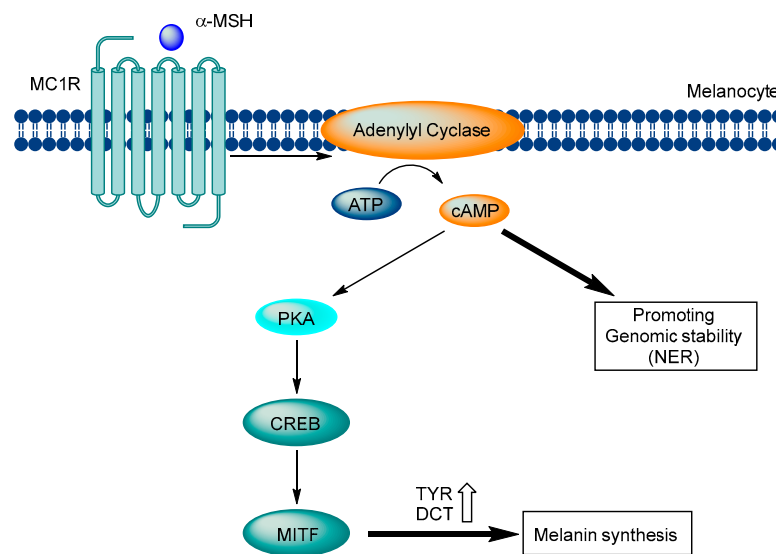


Figure 1. Signaling pathway of MC1R in melanocytes.

Moreover, it is also reported that there is a cAMP-independent pathway mediated by cKIT, which is not discussed in this review. This pathway activates the extracellular signal-regulated protein kinases 1 and 2 (ERK 1/2) by triggering the NRAS-BRAF-MEK-ERK cascade and active ERKs can phosphorylate MITF. Furthermore, it has been suggested that the activation of AKT downstream of  $\alpha$ -MSH may also occur via cKIT [44].

Furthermore, the MC1R signaling axis has an anti-inflammatory effect through downstream pathways. When  $\alpha$ -MSH binds to MC1R, it triggers the production of intracellular cAMP, which activates protein kinases C and A, leading to the activation of the MAPK and JAK-STAT pathways. These pathways prevent I $\kappa$ B degradation and activate CREB, a transcription factor that regulates anti-inflammatory mediators such as IB and IL-10. In addition, protein kinase activation enhances the levels of cytoplasmic I $\kappa$ B, inhibiting the expression of downstream pro-inflammatory genes, including IL-1, TNF- $\alpha$ , IL-6, IL-8, and IL-12, iNOS, and adhesion molecules (ICAM-1, VCAM-1, and MMPs) (Figure 2) [45–60].

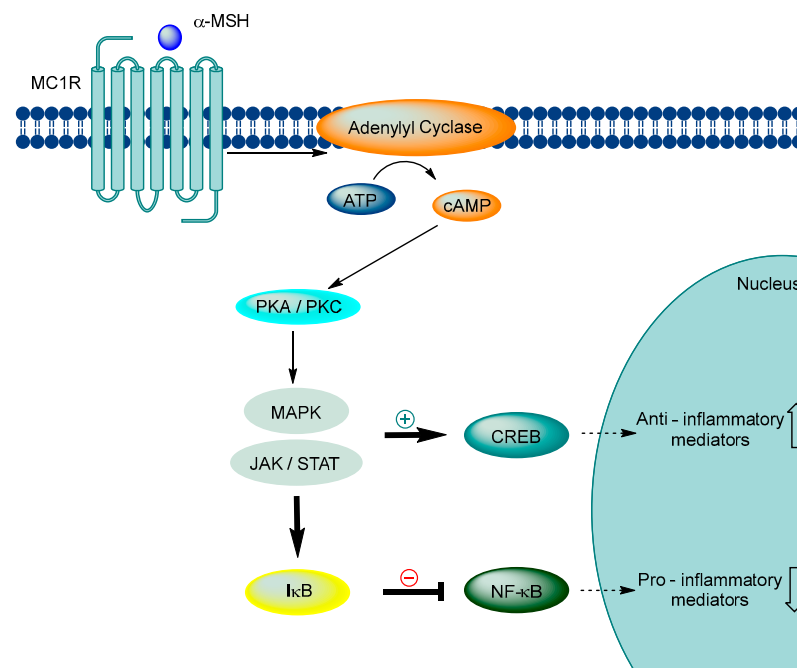


Figure 2. The role of MC1R signaling in anti-inflammatory effects.

### 3. MC1R-Related Diseases

#### 3.1. Melanoma

Melanoma is a highly aggressive and resistant cancer that results from the malignant progression of melanocytes, which are pigment cells located in the skin's epidermis [61]. The traditional chemotherapy treatments have demonstrated limited efficacy in treating melanoma, which highlights the need for innovative therapeutic approaches that can take advantage of the distinctive features of these tumors [62]. One such characteristic is the overexpression of the MC1R cell surface endocytic receptor on the surface of human melanomas, which makes it a crucial tumor marker [63,64]. The activation of MC1R is necessary to regulate melanocyte cell division and melanin production, which provides the skin with protection from UV radiation. Additionally, MC1R has potential applications in diagnostics and targeted drug delivery [65,66]. Innovative treatment approaches are currently being developed based on MC1R for melanoma. MC1R expression is frequently elevated in both melanoma cell lines and melanomas, and contrary to earlier claims that MC1R activation could cause melanoma, recent scientific evidence demonstrates that this receptor not only does not cause melanoma but that its activation can actually stimulate DNA repair processes that have the potential to prevent the disease [67–69]. In addition, the MC1R is also implicated in vitiligo, a pigmentation disorder characterized by the loss or destruction of melanocytes in the skin and hair follicles. This results in the inability to produce melanin, which is necessary for normal pigmentation. Thus, MC1R emerges as a potential therapeutic target for vitiligo since MC1R plays a crucial role in regulating skin pigmentation. Recently, a novel MC1R peptide agonist is reported, and we will introduce it in the synthetic peptide modulators section [70].

#### 3.2. Systemic Sclerosis

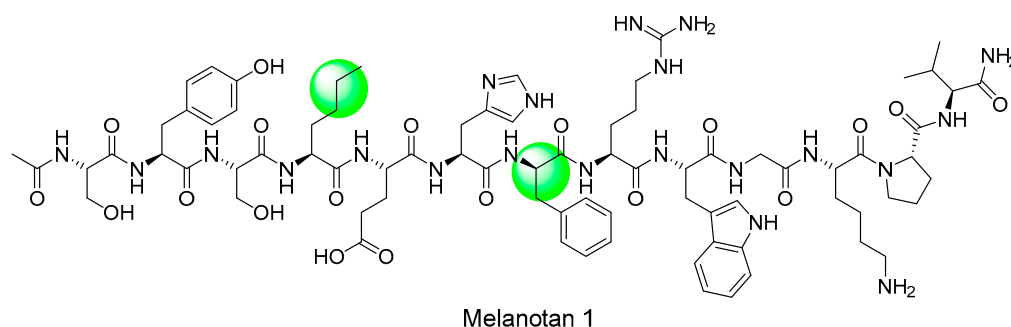
Systemic sclerosis (SSc), or scleroderma, is an autoimmune disorder characterized by dysregulation of the immune system and inflammation, microvascular dysfunction, and widespread fibrosis in various organs [71]. While no approved medications exist for SSc apart from those for SSc-associated ILD (interstitial lung disease), there is a pressing need for innovative treatments that can effectively target fibrosis in multiple organs, including the skin [72–74]. Activating the melanocortin 1 receptor has been shown to have broad anti-inflammatory and antifibrotic effects. Thus, a recent study investigated the potential of a novel oral MC1R agonist, dersimelagon (MT-7117), as a treatment for SSc. In preclinical SSc models, MT-7117 exhibited disease-modifying effects. Target expression analysis and research into its mode of action indicated that MT-7117 has a favorable effect on inflammation, vascular dysfunction, and fibrosis, all of which are key pathologies in SSc. These findings suggest that MT-7117 may have potential as a treatment for SSc. A phase 2 clinical trial is currently underway to evaluate the efficacy and tolerability of MT-7117 in patients with early, progressive diffuse cutaneous SSc [74]. More information about dersimelagon will be discussed in the section on small molecule modulators.

#### 3.3. Neuroinflammation

Neuroinflammation is a critical factor in the progression of neurological damage caused by hypoxic-ischemic (HI) events, and microglia play a significant role in this process [75,76]. In various neurological disorders, MC1R activation has been shown to have anti-inflammatory and neuroprotective effects [77,78]. Recently, researchers investigated the potential of MC1R activation to mitigate neuroinflammation and repair neurological impairments in neonatal rats with hypoxic-ischemic neurological damage [79]. The results showed that BMS-470539, an MC1R activator, reduced neuroinflammation and repaired neurological impairments in these rats. The study also revealed that the anti-inflammatory and neuroprotective effects of MC1R activation were mediated through the MC1R/cAMP/PKA/Nurr1 signaling pathway. The findings suggest that MC1R activation could be a promising therapeutic target for the treatment of hypoxic-ischemic encephalopa-



receptor, such as PL-8177 [67]. Among them, we would like to introduce melanotan I and II, which are key substances in the development of peptide drugs (Figure 4).



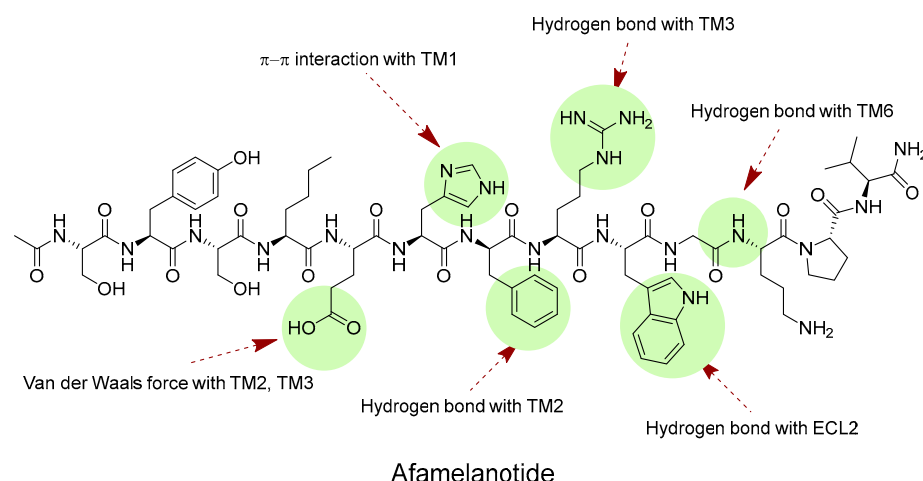
**Figure 4.** Structure of melanotan I.

#### 4.2.1. Melanotan I (MT-I)

Melanotan I is an early analog of  $\alpha$ -MSH that acts as a non-selective agonist of melanocortin receptors and stimulates melanin production. During the development of peptide-based drugs, researchers focused on the common sequence of MSH, namely His6-Phe-Arg-Trp9, and further studies were conducted on this sequence (Figure 4) [98]. Eventually, in the frog skin bioassay, it was observed that Ac(Acetyl)- $\alpha$ -MSH7-10-NH<sub>2</sub> and Ac- $\alpha$ -MSH6-8-NH<sub>2</sub> had no activity, while Ac- $\alpha$ -MSH6-9-NH<sub>2</sub> did. This led to the discovery that the minimal sequence required for the biological activity of  $\alpha$ -MSH is His6-Phe-Arg-Trp9 [99]. Furthermore, to increase the stability of the initial  $\alpha$ -MSH analog, Sawyer et al. replaced Phe at position 7 with D-Phe and Methionine at position 4 with the amino acid norleucine to prevent oxidation of methionine, as highlighted in green ball. These changes resulted in the production of [Nle4, D-Phe7]- $\alpha$ -MSH (NDP-MSH, melanotan I), a peptide with higher potency and stability than  $\alpha$ -MSH [100].

When melanotan I activates MC1R, cAMP is produced, and it activates microphthalmia transcription factor (MITF) expression, which induces the expression of enzymes for eumelanin production. This process increases the production of eumelanin in melanocytes. In addition, melanotan I activates tyrosinase and induces an increase in eumelanin content in melanocytes [103–105].

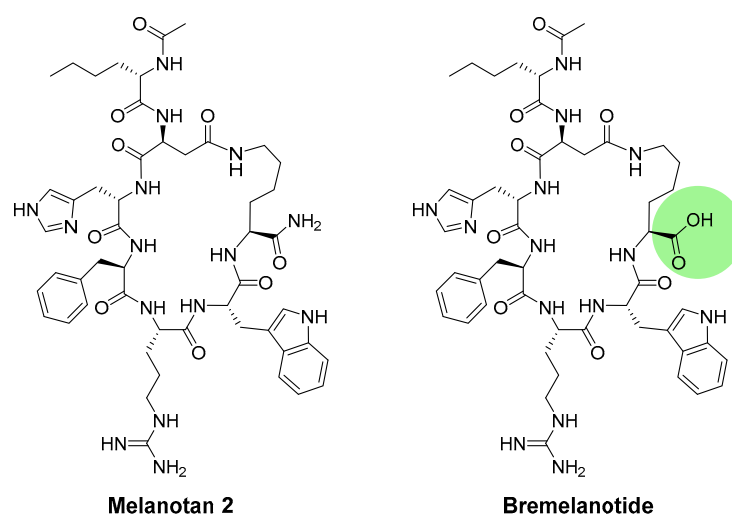
Afamelanotide, well-known as the international nonproprietary name of melanotan I, has been used in patients with erythropoietic protoporphyria (EPP) since 2019. EPP is a disease that causes abnormal hemoglobin synthesis in red blood cells, which can cause skin damage even with a little sunlight. When afamelanotide binds to MC1R, it activates melanocytes and stimulates eumelanin synthesis. Eumelanin protects against UV light by absorbing and scattering it, scavenging free radicals and reactive oxygen species, and acting as a neutral density filter capable of decreasing transmission of all wavelengths of light [106,107]. Recent studies have shed light on the binding structure of MC1R and ligands, while no information has yet been disclosed about the binding structure of receptors and peptides. Afamelanotide, the compound that was switched from Phe7 to D-Phe7 in  $\alpha$ -MSH, has an extra hydrogen bond with the TM2 domain in D-Phe7. It has been demonstrated that afamelanotide has a higher affinity for receptors than  $\alpha$ -MSH, as evidenced by its capacity to make cAMP, which is superior to  $\alpha$ -MSH, as determined by various mutants (Figure 5) [35].



**Figure 5.** Interactions of afamelanotide (melanotan I) with MC1R domains.

#### 4.2.2. Melanotan II (MT-II)

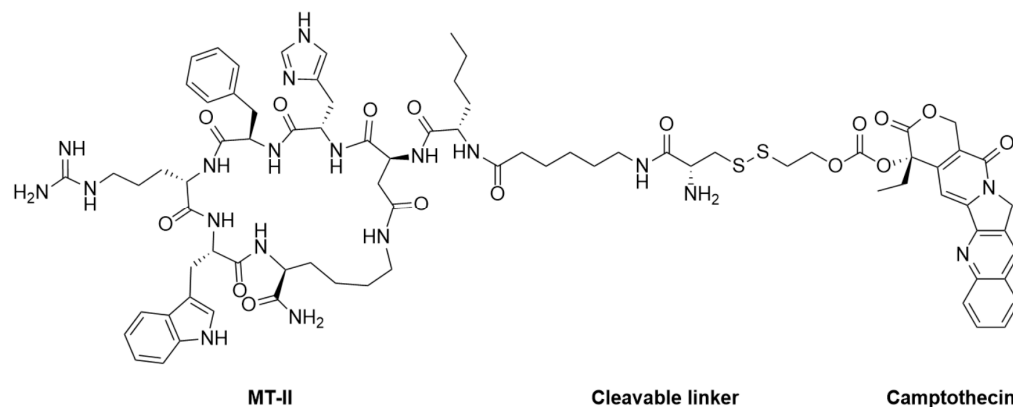
Melanotan II is a cyclic peptide that is derived from melanotan I (Figure 6). In particular, the peptide is modified by replacing Glu5 with Asp and Gly10 with Lys. Previous studies by Obeidi and Hadley have demonstrated that cyclic peptides are more stable and potent than linear peptides. Their research investigated the efficacy and stability of a linear form of Ac-[Nle4, D-Phe7, Lys10]- $\alpha$ -MSH4-10-NH<sub>2</sub> and a cyclic form, in which Asp5 and Lys10 were linked. The findings of their bioassay demonstrated that cyclic peptides exhibited greater potency and stability than linear peptides [101,102]. Melanotan II has been shown to activate melanocytes as an MC1R agonist, but it is weaker than melanotan I. However, melanotan II was proven to have a stronger sexual effect [108]. It has been reported to induce penile erections in male rats and sexual inspiration [109,110] and increases the sexual activities of female rats [111]. Bremelanotide (PT-141), an acid derivative of melanotan II, acts as an agonist of the MC1R and MC4R and has been demonstrated to increase erectile function and sexual desire (Figure 6) [112,113].



**Figure 6.** Structure of melanotan II and bremelanotide.

In 2020, Zhou et al. reported an attractive study in which melanotan II was utilized as a probe for selective drug delivery [114,115]. The authors synthesized and designed ligand-drug conjugates with the melanocortin 1 receptor (MC1R) agonist melanotan-II (MT-II) to couple a cytotoxic drug, camptothecin with low cancer resistance (Figure 7). The drug-MT-II conjugates efficiently bound to MC1R and selectively delivered drugs to A375 melanoma cells in vitro. Camptothecin-MT-II was used to study the inhibitory

activity on A375 melanoma cells and yielded an IC<sub>50</sub> of 16 nM. This approach of drug-MT-II conjugates offers more options in cytotoxic drug selection and is noteworthy for potentially overcoming the cancer-resistant problem of melanoma.

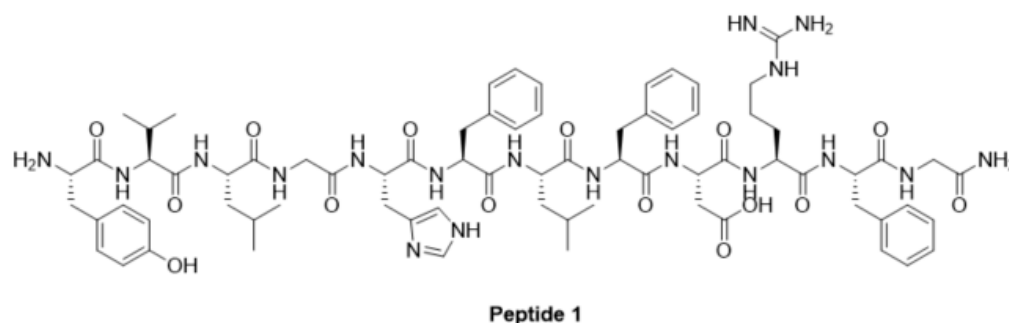


**Figure 7.** Structure of Camptothecin-MT-II conjugate.

#### 4.2.3. Peptide Agonist for Vitiligo Treatment

As a key regulator of skin pigmentation, MC1R may be an effective therapeutic target for vitiligo. However,  $\alpha$ -MSH not only binds to MC1R but also other melanocortin receptors. This leads to diverse physiological changes including sexual function and immunomodulation. Furthermore, the short half-life of peptide drugs has been suggested as a major obstacle. This emphasizes the need for potent and highly selective MC1R agonists, distinct from  $\alpha$ -MSH, to effectively treat vitiligo.

In 2023, Zhu et al. introduced a novel MC1R agonist capable of self-assembling into nanofibrils (Figure 8). This peptide, known as Peptide 1, forms a hydrogel that exhibits enhanced stability compared to free peptides. Notably, this hydrogel demonstrates resistance to enzymatic proteolysis. In vitro and ex vivo experiments have convincingly shown that Peptide 1 stimulates MC1R and enhances melanin production by activating tyrosinase and tyrosinase-related protein. Researchers propose that these findings support the MC1R agonist hydrogel as a promising treatment for vitiligo. Moreover, the peptide hydrogel shows potential for preventing UV-induced melanoma and other skin cancers. Consequently, Zhu et al. suggest that this selective and potent MC1R agonist hydrogel presents an alternative for the treatment or prevention of skin pigmentation disorders such as EPP and melanoma [70].



**Figure 8.** Structure of Peptide 1.

#### 4.3. Small Molecule Modulators

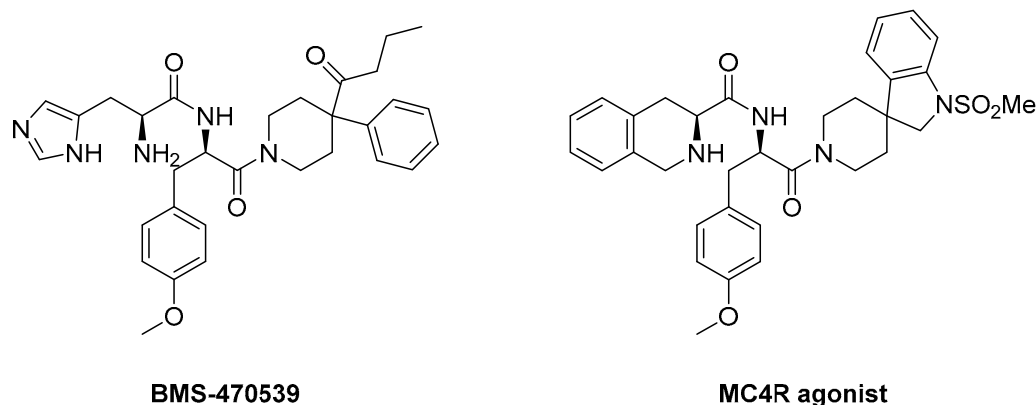
During the development of peptide-based drugs, challenges such as low stability of enzymes and selectivity for receptors were encountered. For example, the peptide agent, melanotan I (afamelanotide) is a non-selective agonist of melanocortin receptors except for MC2R [116]. To address the limitations of peptide-based therapeutics, small



molecule development has been rapidly evolving, utilizing peptides as starting scaffolds and screening compound libraries [117]. As a result, BMS-470539, derived from an MC4R agonist, has been developed [118]. Additionally, various agonists, including AP1189 and CD08108, are under development [119,120]. Recently, dersimelagon (MT-7117), which selectively acts on MC1R, has been approved in Europe for the treatment of EPP and also has an anti-inflammatory effect [74,116]. Furthermore, JNJ-10229570, an antagonist of the melanocortin 1, 5 receptors, has been developed, and it has been reported to affect sebaceous lipid production [121].

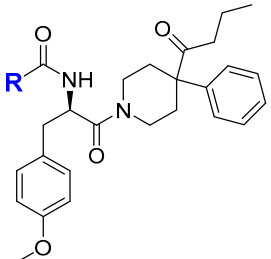
#### 4.3.1. BMS-470539

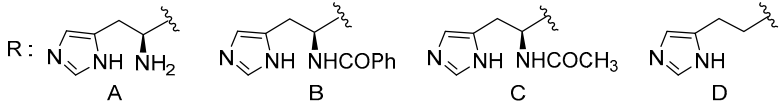
BMS-470539 is a small molecule agonist selective for MC1R, which was synthesized by modifying the structure of a known MC4R agonist (Figure 9). In a study conducted by Timothy et al., the selectivity for receptors of several compounds was measured by comparing their activity using EC<sub>50</sub> values of other isotypes. The EC<sub>50</sub> (nM) value for MC1R of Compound A (BMS-470539) was  $28 \pm 12$  nM, which was higher than Compound B, Compound C, and Compound D, indicating relatively low activity compared to other compounds (Table 1). However, when expanded to other receptors, it was found that Compound 1 did not activate MC3R, and the selectivity for MC4R and MC5R was significantly lower than that of MC1R. Also, the other compounds had receptors with relatively similar efficacy to MC1R and had relatively high intrinsic activity (IA) for all receptors. This suggests that other compounds may have higher activity but lower selectivity than compound 1 [118]. Therefore, Compound 1, known as BMS-470539, was identified as having much better selectivity than other compounds (Table 1).



**Figure 9.** Structure of BMS-470539 and MC4R agonist.

BMS-470539 is also known for its anti-inflammatory effects. BMS-470539 was administered to mice in which an immune response was induced by LPS, and the amount of TNF- $\alpha$ , an inflammatory factor, was measured. The results showed a rapid decrease of up to 92 percent at 100  $\mu$ mol/kg of BMS-470539 [118]. Kang et al. investigated the activity of NF- $\kappa$ B associated with inflammation to prove the anti-inflammatory effect of BMS-470539 and found a noticeable decrease in the activity of NF- $\kappa$ B. Moreover, it induced a decrease in the infiltration of white blood cells in the lungs of mice by LPS [78]. Recently, BMS-470539 was found to decrease the phosphorylation of p38, ERK1/2, and JNK involved in the MAPK pathway associated with inflammation in neutrophils stimulated by LPS [122].

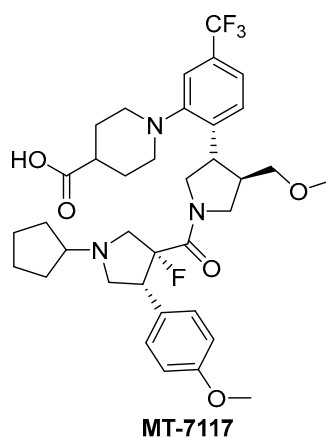
**Table 1.** SAR of side chain of BMS-470539.


R: 

|          | MC1R                  | MC3R                  | MC4R                  | MC5R                  |
|----------|-----------------------|-----------------------|-----------------------|-----------------------|
| Compound | EC <sub>50</sub> (nM) | EC <sub>50</sub> (nM) | EC <sub>50</sub> (nM) | EC <sub>50</sub> (nM) |
| A        | 28 ± 12               | NA                    | 2600 ± 200            | 4400 ± 1300           |
| B        | 0.19 ± 0.02           | 250 ± 170             | 2.9 ± 0.04            | 2100 ± 400            |
| C        | 0.35 ± 0.07           | 2200 ± 1000           | 23 ± 12               | 3900 ± 900            |
| D        | 2.5 ± 1.3             | 7000 ± 1700           | 840 ± 150             | 9400 ± 200            |

#### 4.3.2. MT-7117 (Dersimelagon)

MT-7117, or dersimelagon, is a selective agonist of MC1R that has been found to have a much higher selectivity for MC1R than NDP-MSH (afamelanotide), a peptide effective in treating erythropoietic protoporphyria (EPP). In binding affinity and agonistic activity measurement experiments conducted by Suzuki et al., MT-7117 was demonstrated to have a  $K_i$  value of 2.26 nM for hMC1R (human MC1R), with much higher selectivity ranging from at least 15 to as much as 700 times compared to other receptors (Figure 10). On the other hand, NDP-MSH showed only a 10-fold difference in selectivity for MC1R compared to other receptors, which suggested that NDP-MSH has lower selectivity than MT-7117 [123]. Due to issues with enzyme stability associated with peptide drugs and higher selectivity for MC1R, MT-7117 has been recently approved in Europe as an alternative treatment for EPP [116].



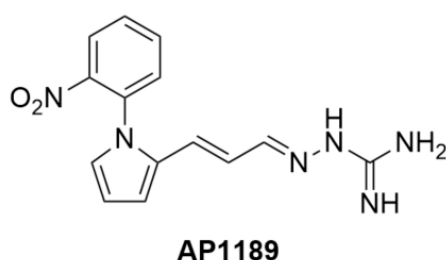
|            | hMC1R | hMC2R | hMC3R | hMC4R |
|------------|-------|-------|-------|-------|
| $K_i$ (nM) | 2.26  | 1420  | 32.9  | 486   |

**Figure 10.** Binding affinities ( $K_i$ ) of MT-7117 (dersimelagon).

A recent study revealed that MT-7117 exhibits anti-inflammatory effects [74]. The study showed that daily oral administration of MT-7117 to rats with fibrosis induced by bleomycin significantly delayed skin fibrosis and lung inflammation. In addition, it was found to significantly reduce the expression of ACTA2 ( $\alpha$ -smooth muscle actin) mRNA in human skin fibroblasts that had been increased by TGF- $\beta$ . This effect was attributed to the inhibition of inflammatory signaling pathways such as IL-6 signaling. Based on these effects, a clinical trial is currently underway to investigate the association of MT-7117 with SSc patients.

#### 4.3.3. AP1189 (Resomelagon)

A series of pyrrole aminoguanidine derivatives were investigated as ligands in the melanocortin receptors by Lundstedt et al. In order to assess the activity of melanocortin receptors, researchers measured the binding affinities ( $K_i$ ) of pyrrole aminoguanidine derivatives for MC1R, MC3R, MC4R, and MC5R. While most of the compounds did not display significant activity or selectivity, the phenylpyrrole allylidene derivatives exhibited enhanced binding affinities towards MC1R and therefore, meaningful selectivities. The phenyl group was found to be particularly important for binding to MC1R. AP1189 ([1-(4-chlorophenyl)-1H-pyrrol-2-yl-allylideneamino]guanidinium acetate) was identified as an agonist for melanocortin receptors MC1R and MC3R. (Figure 11) [119,124].



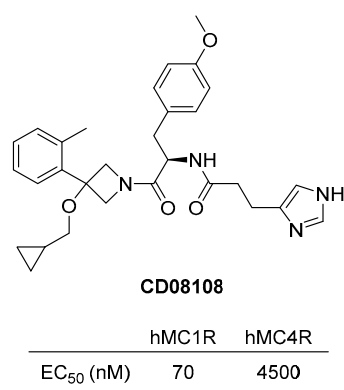
|            | MC1R | MC3R  | MC4R  | MC5R  |
|------------|------|-------|-------|-------|
| $K_i$ (nM) | 360  | >1000 | >1000 | >1000 |

**Figure 11.** Structure and binding affinity of AP1189.

AP1189 has a unique mechanism that distinguishes it from other compounds. It does not stimulate cAMP production and is not involved in melanogenesis. Instead, it induces phosphorylation of ERK1/2, resulting in a decrease in cytokine levels in macrophages. This may help resolve acute inflammation and potentially alleviate arthritis in mice [125]. Based on these findings, AP1189 is currently being evaluated in clinical trials for the treatment of rheumatoid arthritis and idiopathic membranous nephropathy [67].

#### 4.3.4. CD08108

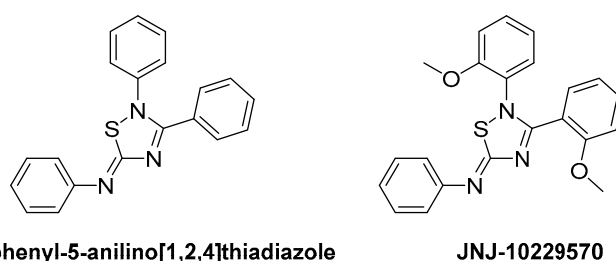
Selective novel MC1R agonists were discovered by the research group in GALDERMA research and development in 2013 [120]. Imidazolyl-linked azetidine derivatives were synthesized and evaluated for activity for human melanocortin receptors. Among them, CD08108 exhibited a significant hMC1R agonistic activity with EC<sub>50</sub> of 70 nM and showed the selectivity of MC1R over MC4R up to 64 times (Figure 12). In 2015, Boiteau et al. reported an efficient synthetic route for CD08108 in a kilogram scale [126]. CD08108 has been implicated in the process of melanogenesis, indicating its potential as a therapeutic target for the treatment of skin conditions such as hypodermic or photosensitive diseases.



**Figure 12.** Structure of CD08108.

#### 4.3.5. JNJ-10229570

2,3-Diphenyl-5-anilino [1,2,4]thiadiazole has been confirmed to act as an agonist for MC4R, thereby inhibiting food intake and affecting eating behavior in mice. JNJ-10229570 is a compound with 2,3-(2-methoxyphenyl) at 2,3-Diaryl and reported to function as an antagonist for MC1R and MC5R, which are melanocortin receptors expressed in sebocytes (Figure 13). Melanocortin receptors in sebocytes are known to play a crucial role in producing sebaceous lipids. Studies on the relationship between MC5R activation and sebocytes indicate that the activation of MC5R increases the production of cAMP, inducing the production of sebaceous lipids [127–129]. Sebaceous lipids are essential for skin integrity and inflammatory processes. However, excessive sebum production is shown to be a significant contributor to the pathophysiology of Acne vulgaris [130–132]. Eisinger et al. demonstrated that JNJ-10229570 acts as an antagonist for MC1R and MC5R present in human sebaceous cells, inhibiting sebaceous secretion and reducing sebaceous gland size [121]. The IC<sub>50</sub> measurements for MC1R and MC5R, using 125I-NDP- $\alpha$ -MSH, were found to be 270  $\pm$  120 and 200  $\pm$  50 nM (Mean  $\pm$  S.D.), respectively, indicating that JNJ-10229570 binds to both receptors. Furthermore, the reduction in the amount of cAMP, elevated by NDP-MSH after the sebocyte was exposed to 0.6 nM of JNJ-10229570, suggests that this compound acts as an antagonist for MC1R and MC5R. In addition, human skin transplanted into SCID mice and treated with JNJ-10229570 showed a decrease in squalene, wax esters, and triglyceride, suggesting new information about the effect of JNJ-10229570 on surface lipid secretion in vivo.



**Figure 13.** Structures of 2,3-Diphenyl-5-anilino [1,2,4]thiadiazole and JNJ-10229570.

## 5. Conclusions

The discovery of the melanocortin 1 receptor several decades ago has led to extensive research into its potential as a therapeutic target. Studies have revealed that the MC1R signaling pathway is crucial in treating melanoma, as it affects various physiological changes in melanocytes. However, recent research has also shown a growing interest in investigating the molecular mechanisms responsible for the non-pigmentary effects of MC1R, particularly in the treatment of inflammatory diseases. Ongoing investigations suggest that drugs targeting MC1R may hold promise in treating patients with high-need

conditions such as systemic sclerosis, neuroinflammation, rheumatoid arthritis, fibrosis, and others. With numerous innovative molecules and clinical trials currently underway, it is possible that these drugs may soon improve the quality of life for those with chronic inflammatory conditions. Furthermore, the development of MC1R ligands using multiple chemistry approaches and knowledge of the receptor's crystal structure may lead to the creation of additional drugs to treat new conditions in the future.

**Author Contributions:** Conceptualization, D.S.; methodology, Y.M., W.K. and D.S.; writing—original draft preparation, Y.M. and W.K.; writing—review and editing, D.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the National Research Foundation of Korea (NRF-2020R1A6A1A03043708 and NRF-2021R1A2C1012280).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

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

## References

- Cawley, N.X.; Li, Z.; Loh, Y.P. Biosynthesis, trafficking, and secretion of pro-opiomelanocortin-derived peptides. *J. Mol. Endocrinol.* **2016**, *56*, T77–T97. [[CrossRef](#)] [[PubMed](#)]
- Cone, R.D. Studies on the Physiological Functions of the Melanocortin System. *Endocr. Rev.* **2006**, *27*, 736–749. [[CrossRef](#)]
- Gallo-Payet, N. Adrenal and extra-adrenal functions of ACTH. *J. Mol. Endocrinol.* **2016**, *56*, T135–T156. [[CrossRef](#)] [[PubMed](#)]
- Robbins, L.S.; Nadeau, J.H.; Johnson, K.R.; Kelly, M.A.; Roselli-Rehfuss, L.; Baack, E.; Mountjoy, K.G.; Cone, R.D. Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function. *Cell* **1993**, *72*, 827–834. [[CrossRef](#)] [[PubMed](#)]
- Hiltz, M.E.; Lipton, J.M. Alpha-MSH peptides inhibit acute inflammation and contact sensitivity. *Peptides* **1990**, *11*, 979–982. [[CrossRef](#)]
- Cutuli, M.; Cristiani, S.; Lipton, J.M.; Catania, A. Antimicrobial effects of  $\alpha$ -MSH peptides. *J. Leukoc. Biol.* **2000**, *67*, 233–239. [[CrossRef](#)] [[PubMed](#)]
- Madeira, M.F.; Queiroz-Junior, C.M.; Montero-Melendez, T.; Werneck, S.M.; Correa, J.D.; Soriani, F.M.; Garlet, G.P.; Souza, D.G.; Teixeira, M.M.; Silva, T.A.; et al. Melanocortin agonism as a viable strategy to control alveolar bone loss induced by oral infection. *FASEB J.* **2016**, *30*, 4033–4041. [[CrossRef](#)]
- Gomez-SanMiguel, A.B.; Martin, A.I.; Nieto-Bona, M.P.; Fernandez-Galaz, C.; Villanua, M.A.; Lopez-Calderon, A. The melanocortin receptor type 3 agonist d-Trp(8)- $\gamma$ MSH decreases inflammation and muscle wasting in arthritic rats. *J. Cachexia Sarcopenia Muscle* **2016**, *7*, 79–89. [[CrossRef](#)]
- Gomez-SanMiguel, A.B.; Villanua, M.A.; Martin, A.I.; Lopez-Calderon, A. D-TRP(8)- $\gamma$ MSH Prevents the Effects of Endotoxin in Rat Skeletal Muscle Cells through TNF $\alpha$ /NF-KB Signalling Pathway. *PLoS ONE* **2016**, *11*, e0155645. [[CrossRef](#)]
- Kadiri, J.J.; Thapa, K.; Kaipio, K.; Cai, M.; Hruby, V.J.; Rinne, P. Melanocortin 3 receptor activation with [D-Trp8]- $\gamma$ -MSH suppresses inflammation in apolipoprotein E deficient mice. *Eur. J. Pharmacol.* **2020**, *880*, 173186. [[CrossRef](#)]
- Mountjoy, K.G.; Robbins, L.S.; Mortrud, M.T.; Cone, R.D. The cloning of a family of genes that encode the melanocortin receptors. *Science* **1992**, *257*, 1248–1251. [[CrossRef](#)] [[PubMed](#)]
- Wolf Horrell, E.M.; Boulanger, M.C.; D'Orazio, J.A. Melanocortin 1 Receptor: Structure, Function, and Regulation. *Front. Genet.* **2016**, *7*, 95. [[CrossRef](#)] [[PubMed](#)]
- Gantz, I.; Shimoto, Y.; Konda, Y.; Miwa, H.; Dickinson, C.J.; Yamada, T. Molecular cloning, expression, and characterization of a fifth melanocortin receptor. *Biochem. Biophys. Res. Commun.* **1994**, *200*, 1214–1220. [[CrossRef](#)]
- Gantz, I.; Miwa, H.; Konda, Y.; Shimoto, Y.; Tashiro, T.; Watson, S.J.; DelValle, J.; Yamada, T. Molecular cloning, expression, and gene localization of a fourth melanocortin receptor. *J. Biol. Chem.* **1993**, *268*, 15174–15179. [[CrossRef](#)] [[PubMed](#)]
- Desarnaud, F.; Labbe, O.; Eggerickx, D.; Vassart, G.; Parmentier, M. Molecular cloning, functional expression and pharmacological characterization of a mouse melanocortin receptor gene. *Biochem. J.* **1994**, *299 Pt 2*, 367–373. [[CrossRef](#)] [[PubMed](#)]
- Gantz, I.; Yamada, T.; Tashiro, T.; Konda, Y.; Shimoto, Y.; Miwa, H.; Trent, J.M. Mapping of the gene encoding the melanocortin-1 ( $\alpha$ -melanocyte stimulating hormone) receptor (MC1R) to human chromosome 16q24.3 by Fluorescence in situ hybridization. *Genomics* **1994**, *19*, 394–395. [[CrossRef](#)]
- Schaible, E.V.; Steinstrasser, A.; Jahn-Eimermacher, A.; Luh, C.; Sebastiani, A.; Kornes, F.; Pieter, D.; Schafer, M.K.; Engelhard, K.; Thal, S.C. Single administration of tripeptide  $\alpha$ -MSH(11–13) attenuates brain damage by reduced inflammation and apoptosis after experimental traumatic brain injury in mice. *PLoS ONE* **2013**, *8*, e71056. [[CrossRef](#)]

18. Bhardwaj, R.; Becher, E.; Mahnke, K.; Hartmeyer, M.; Schwarz, T.; Scholzen, T.; Luger, T.A. Evidence for the differential expression of the functional alpha-melanocyte-stimulating hormone receptor MC-1 on human monocytes. *J. Immunol.* **1997**, *158*, 3378–3384. [[CrossRef](#)]
19. Siegrist, W.; Stutz, S.; Eberle, A.N. Homologous and heterologous regulation of alpha-melanocyte-stimulating hormone receptors in human and mouse melanoma cell lines. *Cancer Res.* **1994**, *54*, 2604–2610.
20. Siegrist, W.; Solca, F.; Stutz, S.; Giuffre, L.; Carrel, S.; Girard, J.; Eberle, A.N. Characterization of receptors for alpha-melanocyte-stimulating hormone on human melanoma cells. *Cancer Res.* **1989**, *49*, 6352–6358.
21. Ghanem, G.E.; Comunale, G.; Libert, A.; Vercammen-Grandjean, A.; Lejeune, F.J. Evidence for alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH) receptors on human malignant melanoma cells. *Int. J. Cancer* **1988**, *41*, 248–255. [[CrossRef](#)]
22. Roberts, D.W.; Newton, R.A.; Beaumont, K.A.; Helen Leonard, J.; Sturm, R.A. Quantitative analysis of MC1R gene expression in human skin cell cultures. *Pigment Cell Res.* **2006**, *19*, 76–89. [[CrossRef](#)]
23. Donatien, P.D.; Hunt, G.; Pieron, C.; Lunec, J.; Taieb, A.; Thody, A.J. The expression of functional MSH receptors on cultured human melanocytes. *Arch. Dermatol. Res.* **1992**, *284*, 424–426. [[CrossRef](#)]
24. Sanchez-Laorden, B.L.; Sanchez-Mas, J.; Turpin, M.C.; Garcia-Borrón, J.C.; Jimenez-Cervantes, C. Variant amino acids in different domains of the human melanocortin 1 receptor impair cell surface expression. *Cell. Mol. Biol.* **2006**, *52*, 39–46.
25. Frandberg, P.A.; Doufexis, M.; Kapas, S.; Chhajlani, V. Cysteine residues are involved in structure and function of melanocortin 1 receptor: Substitution of a cysteine residue in transmembrane segment two converts an agonist to antagonist. *Biochem. Biophys. Res. Commun.* **2001**, *281*, 851–857. [[CrossRef](#)]
26. Wallin, E.; von Heijne, G. Properties of N-terminal tails in G-protein coupled receptors: A statistical study. *Protein Eng.* **1995**, *8*, 693–698. [[CrossRef](#)] [[PubMed](#)]
27. Chhajlani, V.; Xu, X.; Blauw, J.; Sudarshi, S. Identification of ligand binding residues in extracellular loops of the melanocortin 1 receptor. *Biochem. Biophys. Res. Commun.* **1996**, *219*, 521–525. [[CrossRef](#)] [[PubMed](#)]
28. Garcia-Borrón, J.C.; Sanchez-Laorden, B.L.; Jimenez-Cervantes, C. Melanocortin-1 receptor structure and functional regulation. *Pigment Cell Res.* **2005**, *18*, 393–410. [[CrossRef](#)]
29. Pitcher, J.A.; Freedman, N.J.; Lefkowitz, R.J. G protein-coupled receptor kinases. *Annu. Rev. Biochem.* **1998**, *67*, 653–692. [[CrossRef](#)] [[PubMed](#)]
30. Luttrell, L.M.; Lefkowitz, R.J. The role of  $\beta$ -arrestins in the termination and transduction of G-protein-coupled receptor signals. *J. Cell Sci.* **2002**, *115*, 455–465. [[CrossRef](#)]
31. Strader, C.D.; Fong, T.M.; Tota, M.R.; Underwood, D.; Dixon, R.A. Structure and function of G protein-coupled receptors. *Annu. Rev. Biochem.* **1994**, *63*, 101–132. [[CrossRef](#)]
32. Qanbar, R.; Bouvier, M. Role of palmitoylation/depalmitoylation reactions in G-protein-coupled receptor function. *Pharmacol. Ther.* **2003**, *97*, 1–33. [[CrossRef](#)]
33. Schulein, R.; Hermosilla, R.; Oksche, A.; Dehe, M.; Wiesner, B.; Krause, G.; Rosenthal, W. A dileucine sequence and an upstream glutamate residue in the intracellular carboxyl terminus of the vasopressin V2 receptor are essential for cell surface transport in COS.M6 cells. *Mol. Pharmacol.* **1998**, *54*, 525–535. [[CrossRef](#)] [[PubMed](#)]
34. Holst, B.; Schwartz, T.W. Molecular mechanism of agonism and inverse agonism in the melanocortin receptors:  $Zn^{2+}$  as a structural and functional probe. *Ann. N. Y. Acad. Sci.* **2003**, *994*, 1–11. [[CrossRef](#)] [[PubMed](#)]
35. Ma, S.; Chen, Y.; Dai, A.; Yin, W.; Guo, J.; Yang, D.; Zhou, F.; Jiang, Y.; Wang, M.W.; Xu, H.E. Structural mechanism of calcium-mediated hormone recognition and G $\beta$  interaction by the human melanocortin-1 receptor. *Cell Res.* **2021**, *31*, 1061–1071. [[CrossRef](#)]
36. Arisi, M.; Rossi, M.; Rovati, C.; Tomasi, C.; Mori, L.; Laini, L.; Calzavara-Pinton, P.G. Clinical and dermoscopic changes of acquired melanocytic nevi of patients treated with afamelanotide. *Photochem. Photobiol. Sci.* **2021**, *20*, 315–320. [[CrossRef](#)]
37. Kadekaro, A.L.; Leachman, S.; Kavanagh, R.J.; Swope, V.; Cassidy, P.; Supp, D.; Sartor, M.; Schwemberger, S.; Babcock, G.; Wakamatsu, K.; et al. Melanocortin 1 receptor genotype: An important determinant of the damage response of melanocytes to ultraviolet radiation. *FASEB J.* **2010**, *24*, 3850–3860. [[CrossRef](#)]
38. Song, X.; Mosby, N.; Yang, J.; Xu, A.; Abdel-Malek, Z.; Kadekaro, A.L.  $\alpha$ -MSH activates immediate defense responses to UV-induced oxidative stress in human melanocytes. *Pigment Cell Melanoma Res.* **2009**, *22*, 809–818. [[CrossRef](#)]
39. Kokot, A.; Metze, D.; Mouchet, N.; Galibert, M.D.; Schiller, M.; Luger, T.A.; Böhm, M.  $\alpha$ -melanocyte-stimulating hormone counteracts the suppressive effect of UVB on Nrf2 and Nrf-dependent gene expression in human skin. *Endocrinology* **2009**, *150*, 3197–3206. [[CrossRef](#)]
40. Abdel-Malek, Z.A.; Swope, V.B.; Starner, R.J.; Koikov, L.; Cassidy, P.; Leachman, S. Melanocortins and the melanocortin 1 receptor, moving translationally towards melanoma prevention. *Arch Biochem. Biophys.* **2014**, *563*, 4–12. [[CrossRef](#)] [[PubMed](#)]
41. Suzuki, I.; Tada, A.; Ollmann, M.M.; Barsh, G.S.; Im, S.; Lamoreux, M.L.; Hearing, V.J.; Nordlund, J.J.; Abdel-Malek, Z.A. Agouti signaling protein inhibits melanogenesis and the response of human melanocytes to  $\alpha$ -melanotropin. *J. Invest. Dermatol.* **1997**, *108*, 838–842. [[CrossRef](#)] [[PubMed](#)]
42. Dorsam, R.T.; Gutkind, J.S. G-protein-coupled receptors and cancer. *Nat. Rev. Cancer* **2007**, *7*, 79–94. [[CrossRef](#)] [[PubMed](#)]
43. Neves, S.R.; Ram, P.T.; Iyengar, R. G protein pathways. *Science* **2002**, *296*, 1636–1639. [[CrossRef](#)]

44. Herraiz, C.; Journé, F.; Abdel-Malek, Z.; Ghanem, G.; Jiménez-Cervantes, C.; García-Borrón, J.C. Signaling from the human melanocortin 1 receptor to ERK1 and ERK2 mitogen-activated protein kinases involves transactivation of cKIT. *Mol. Endocrinol.* **2011**, *25*, 138–156. [[CrossRef](#)]
45. Bohm, M.; Schulte, U.; Kalden, H.; Luger, T.A. Alpha-melanocyte-stimulating hormone modulates activation of NF- $\kappa$ B and AP-1 and secretion of interleukin-8 in human dermal fibroblasts. *Ann. N. Y. Acad. Sci.* **1999**, *885*, 277–286. [[CrossRef](#)] [[PubMed](#)]
46. Tanaka, T.; Narazaki, M.; Kishimoto, T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb. Perspect. Biol.* **2014**, *6*, a016295. [[CrossRef](#)] [[PubMed](#)]
47. Bonfiglio, V.; Camillieri, G.; Avitabile, T.; Leggio, G.M.; Drago, F. Effects of the COOH-terminal tripeptide  $\alpha$ -MSH(11–13) on corneal epithelial wound healing: Role of nitric oxide. *Exp. Eye Res.* **2006**, *83*, 1366–1372. [[CrossRef](#)]
48. Becher, E.; Mahnke, K.; Brzoska, T.; Kalden, D.H.; Grabbe, S.; Luger, T.A. Human peripheral blood-derived dendritic cells express functional melanocortin receptor MC-1R. *Ann. N. Y. Acad. Sci.* **1999**, *885*, 188–195. [[CrossRef](#)]
49. Scholzen, T.E.; Sunderkotter, C.; Kalden, D.H.; Brzoska, T.; Fastrich, M.; Fisbeck, T.; Armstrong, C.A.; Ansel, J.C.; Luger, T.A.  $\alpha$ -melanocyte stimulating hormone prevents lipopolysaccharide-induced vasculitis by down-regulating endothelial cell adhesion molecule expression. *Endocrinology* **2003**, *144*, 360–370. [[CrossRef](#)]
50. Kalden, D.H.; Scholzen, T.; Brzoska, T.; Luger, T.A. Mechanisms of the antiinflammatory effects of  $\alpha$ -MSH. Role of transcription factor NF- $\kappa$ B and adhesion molecule expression. *Ann. N. Y. Acad. Sci.* **1999**, *885*, 254–261. [[CrossRef](#)]
51. Zhang, L.; Dong, L.; Liu, X.; Jiang, Y.; Zhang, L.; Zhang, X.; Li, X.; Zhang, Y.  $\alpha$ -Melanocyte-stimulating hormone protects retinal vascular endothelial cells from oxidative stress and apoptosis in a rat model of diabetes. *PLoS ONE* **2014**, *9*, e93433. [[CrossRef](#)] [[PubMed](#)]
52. Galimberti, D.; Baron, P.; Meda, L.; Prat, E.; Scarpini, E.; Delgado, R.; Catania, A.; Lipton, J.M.; Scarlato, G.  $\alpha$ -MSH peptides inhibit production of nitric oxide and tumor necrosis factor- $\alpha$  by microglial cells activated with  $\beta$ -amyloid and interferon  $\gamma$ . *Biochem. Biophys. Res. Commun.* **1999**, *263*, 251–256. [[CrossRef](#)] [[PubMed](#)]
53. Delgado, R.; Carlin, A.; Airaghi, L.; Demitri, M.T.; Meda, L.; Galimberti, D.; Baron, P.; Lipton, J.M.; Catania, A. Melanocortin peptides inhibit production of proinflammatory cytokines and nitric oxide by activated microglia. *J. Leukoc. Biol.* **1998**, *63*, 740–745. [[CrossRef](#)] [[PubMed](#)]
54. Taherzadeh, S.; Sharma, S.; Chhajlani, V.; Gantz, I.; Rajora, N.; Demitri, M.T.; Kelly, L.; Zhao, H.; Ichiyama, T.; Catania, A.; et al.  $\alpha$ -MSH and its receptors in regulation of tumor necrosis factor- $\alpha$  production by human monocyte/macrophages. *Am. J. Physiol.* **1999**, *276*, R1289–R1294. [[CrossRef](#)]
55. Ottani, A.; Giuliani, D.; Neri, L.; Calevro, A.; Canalini, F.; Vandini, E.; Cainazzo, M.M.; Ruberto, I.A.; Barbieri, A.; Rossi, R.; et al. NDP- $\alpha$ -MSH attenuates heart and liver responses to myocardial reperfusion via the vagus nerve and JAK/ERK/STAT signaling. *Eur. J. Pharmacol.* **2015**, *769*, 22–32. [[CrossRef](#)]
56. Buggy, J.J. Binding of  $\alpha$ -melanocyte-stimulating hormone to its G-protein-coupled receptor on B-lymphocytes activates the Jak/STAT pathway. *Biochem. J.* **1998**, *331 Pt 1*, 211–216. [[CrossRef](#)]
57. Mandriks, I.; Muceniece, R.; Wikberg, J.E. Effects of melanocortin peptides on lipopolysaccharide/interferon-gamma-induced NF-kappaB DNA binding and nitric oxide production in macrophage-like RAW 264.7 cells: Evidence for dual mechanisms of action. *Biochem. Pharmacol.* **2001**, *61*, 613–621. [[CrossRef](#)]
58. Gerlo, S.; Kooijman, R.; Beck, I.M.; Kolmus, K.; Spooren, A.; Haegeman, G. Cyclic AMP: A selective modulator of NF- $\kappa$ B action. *Cell. Mol. Life Sci.* **2011**, *68*, 3823–3841. [[CrossRef](#)]
59. Manna, S.K.; Aggarwal, B.B. Alpha-melanocyte-stimulating hormone inhibits the nuclear transcription factor NF-kappa B activation induced by various inflammatory agents. *J. Immunol.* **1998**, *161*, 2873–2880. [[CrossRef](#)]
60. Wang, W.; Guo, D.Y.; Lin, Y.J.; Tao, Y.X. Melanocortin Regulation of Inflammation. *Front. Endocrinol.* **2019**, *10*, 683. [[CrossRef](#)]
61. Lo, J.A.; Fisher, D.E. The melanoma revolution: From UV carcinogenesis to a new era in therapeutics. *Science* **2014**, *346*, 945–949. [[CrossRef](#)]
62. Rosenkranz, A.A.; Slastnikova, T.A.; Durymanov, M.O.; Sobolev, A.S. Malignant melanoma and melanocortin 1 receptor. *Biochemistry* **2013**, *78*, 1228–1237. [[CrossRef](#)] [[PubMed](#)]
63. Salazar-Onfray, F.; Lopez, M.; Lundqvist, A.; Aguirre, A.; Escobar, A.; Serrano, A.; Korenblit, C.; Petersson, M.; Chhajlani, V.; Larsson, O.; et al. Tissue distribution and differential expression of melanocortin 1 receptor, a malignant melanoma marker. *Br. J. Cancer* **2002**, *87*, 414–422. [[CrossRef](#)]
64. Ogbah, Z.; Puig-Butille, J.A.; Simonetta, F.; Badenas, C.; Cervera, R.; Mila, J.; Benitez, D.; Malveyh, J.; Vilella, R.; Puig, S. Molecular characterization of human cutaneous melanoma-derived cell lines. *Anticancer. Res.* **2012**, *32*, 1245–1251. [[PubMed](#)]
65. Eggermont, A.M. Advances in systemic treatment of melanoma. *Ann. Oncol.* **2010**, *21* (Suppl. S7), vii339–vii344. [[CrossRef](#)]
66. Iriyama, N.; Yoshino, Y.; Yuan, B.; Horikoshi, A.; Hirabayashi, Y.; Hatta, Y.; Toyoda, H.; Takeuchi, J. Speciation of arsenic trioxide metabolites in peripheral blood and bone marrow from an acute promyelocytic leukemia patient. *J. Hematol. Oncol.* **2012**, *5*, 1. [[CrossRef](#)] [[PubMed](#)]
67. Montero-Melendez, T.; Boesen, T.; Jonassen, T.E.N. Translational advances of melanocortin drugs: Integrating biology, chemistry and genetics. *Semin. Immunol.* **2022**, *59*, 101603. [[CrossRef](#)]
68. Chen, S.; Zhu, B.; Yin, C.; Liu, W.; Han, C.; Chen, B.; Liu, T.; Li, X.; Chen, X.; Li, C.; et al. Palmitoylation-dependent activation of MC1R prevents melanomagenesis. *Nature* **2017**, *549*, 399–403. [[CrossRef](#)]

69. Castejon-Grinan, M.; Herraiz, C.; Olivares, C.; Jimenez-Cervantes, C.; Garcia-Borrón, J.C. cAMP-independent non-pigmentary actions of variant melanocortin 1 receptor: AKT-mediated activation of protective responses to oxidative DNA damage. *Oncogene* **2018**, *37*, 3631–3646. [[CrossRef](#)]
70. Zhu, C.; Li, T.; Wang, Z.; Li, Z.; Wei, J.; Han, H.; Yuan, D.; Cai, M.; Shi, J. MC1R Peptide Agonist Self-Assembles into a Hydrogel That Promotes Skin Pigmentation for Treating Vitiligo. *ACS Nano* **2023**, *17*, 8723–8733. [[CrossRef](#)]
71. Bhattacharyya, S.; Wei, J.; Varga, J. Understanding fibrosis in systemic sclerosis: Shifting paradigms, emerging opportunities. *Nat. Rev. Rheumatol.* **2011**, *8*, 42–54. [[CrossRef](#)]
72. Khanna, D.; Lin, C.J.F.; Furst, D.E.; Goldin, J.; Kim, G.; Kuwana, M.; Allanore, Y.; Matucci-Cerinic, M.; Distler, O.; Shima, Y.; et al. Tocilizumab in systemic sclerosis: A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir. Med.* **2020**, *8*, 963–974. [[CrossRef](#)] [[PubMed](#)]
73. Distler, O.; Highland, K.B.; Gahlemann, M.; Azuma, A.; Fischer, A.; Mayes, M.D.; Raghu, G.; Sauter, W.; Girard, M.; Alves, M.; et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N. Engl. J. Med.* **2019**, *380*, 2518–2528. [[CrossRef](#)] [[PubMed](#)]
74. Kondo, M.; Suzuki, T.; Kawano, Y.; Kojima, S.; Miyashiro, M.; Matsumoto, A.; Kania, G.; Blyszczuk, P.; Ross, R.L.; Mulipa, P.; et al. Dersimelagon, a novel oral melanocortin 1 receptor agonist, demonstrates disease-modifying effects in preclinical models of systemic sclerosis. *Arthritis Res. Ther.* **2022**, *24*, 210. [[CrossRef](#)]
75. Pimentel, V.C.; Bellé, L.P.; Pinheiro, F.V.; De Bona, K.S.; Da Luz, S.C.; Moretto, M.B. Adenosine deaminase activity, lipid peroxidation and astrocyte responses in the cerebral cortex of rats after neonatal hypoxia ischemia. *Int. J. Dev. Neurosci.* **2009**, *27*, 857–862. [[CrossRef](#)]
76. McRae, A.; Gilland, E.; Bona, E.; Hagberg, H. Microglia activation after neonatal hypoxic-ischemia. *Brain Res. Dev. Brain Res.* **1995**, *84*, 245–252. [[CrossRef](#)] [[PubMed](#)]
77. Wu, X.; Fu, S.; Liu, Y.; Luo, H.; Li, F.; Wang, Y.; Gao, M.; Cheng, Y.; Xie, Z. NDP-MSH binding melanocortin-1 receptor ameliorates neuroinflammation and BBB disruption through CREB/Nr4a1/NF- $\kappa$ B pathway after intracerebral hemorrhage in mice. *J. Neuroinflamm.* **2019**, *16*, 192. [[CrossRef](#)]
78. Kang, L.; McIntyre, K.W.; Gillooly, K.M.; Yang, Y.; Haycock, J.; Roberts, S.; Khanna, A.; Herpin, T.F.; Yu, G.; Wu, X.; et al. A selective small molecule agonist of the melanocortin-1 receptor inhibits lipopolysaccharide-induced cytokine accumulation and leukocyte infiltration in mice. *J. Leukoc. Biol.* **2006**, *80*, 897–904. [[CrossRef](#)]
79. Yu, S.; Doycheva, D.M.; Gamdzyk, M.; Yang, Y.; Lenahan, C.; Li, G.; Li, D.; Lian, L.; Tang, J.; Lu, J.; et al. Activation of MC1R with BMS-470539 attenuates neuroinflammation via cAMP/PKA/Nurr1 pathway after neonatal hypoxic-ischemic brain injury in rats. *J. Neuroinflamm.* **2021**, *18*, 26. [[CrossRef](#)]
80. Rinne, P.; Rami, M.; Nuutinen, S.; Santovito, D.; van der Vorst, E.P.C.; Guillamat-Prats, R.; Lyytikäinen, L.P.; Raitoharju, E.; Oksala, N.; Ring, L.; et al. Melanocortin 1 Receptor Signaling Regulates Cholesterol Transport in Macrophages. *Circulation* **2017**, *136*, 83–97. [[CrossRef](#)]
81. Catania, A.; Gatti, S.; Colombo, G.; Lipton, J.M. Targeting melanocortin receptors as a novel strategy to control inflammation. *Pharmacol. Rev.* **2004**, *56*, 1–29. [[CrossRef](#)]
82. Rinne, P.; Silvola, J.M.; Hellberg, S.; Stahle, M.; Liljenback, H.; Salomaki, H.; Koskinen, E.; Nuutinen, S.; Saukko, P.; Knuuti, J.; et al. Pharmacological activation of the melanocortin system limits plaque inflammation and ameliorates vascular dysfunction in atherosclerotic mice. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 1346–1354. [[CrossRef](#)]
83. Rinne, P.; Kadiri, J.J.; Velasco-Delgado, M.; Nuutinen, S.; Viitala, M.; Hollmen, M.; Rami, M.; Savontaus, E.; Steffens, S. Melanocortin 1 Receptor Deficiency Promotes Atherosclerosis in Apolipoprotein E<sup>-/-</sup> Mice. *Arterioscler. Thromb. Vasc. Biol.* **2018**, *38*, 313–323. [[CrossRef](#)] [[PubMed](#)]
84. Xu, P.B.; Mao, Y.F.; Meng, H.B.; Tian, Y.P.; Deng, X.M. STY39, a novel alpha-melanocyte-stimulating hormone analogue, attenuates bleomycin-induced pulmonary inflammation and fibrosis in mice. *Shock* **2011**, *35*, 308–314. [[CrossRef](#)]
85. Spana, C.; Taylor, A.W.; Yee, D.G.; Makhlina, M.; Yang, W.; Dodd, J. Probing the Role of Melanocortin Type 1 Receptor Agonists in Diverse Immunological Diseases. *Front. Pharmacol.* **2018**, *9*, 1535. [[CrossRef](#)]
86. Cai, W.; Srivastava, P.; Feng, D.; Lin, Y.; Vanderburg, C.R.; Xu, Y.; McLean, P.; Frosch, M.P.; Fisher, D.E.; Schwarzschild, M.A.; et al. Melanocortin 1 receptor activation protects against alpha-synuclein pathologies in models of Parkinson's disease. *Mol. Neurodegener.* **2022**, *17*, 16. [[CrossRef](#)]
87. Chakraborty, A.K.; Funasaka, Y.; Slominski, A.; Ermak, 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](#)] [[PubMed](#)]
88. Schauer, E.; Trautinger, F.; Kock, A.; Schwarz, A.; Bhardwaj, R.; Simon, M.; Ansel, J.C.; Schwarz, T.; Luger, T.A. Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes. *J. Clin. Investig.* **1994**, *93*, 2258–2262. [[CrossRef](#)] [[PubMed](#)]
89. Abdel-Malek, Z.; Scott, M.C.; Suzuki, I.; Tada, A.; Im, S.; Lamoreux, L.; Ito, S.; Barsh, G.; Hearing, V.J. The melanocortin-1 receptor is a key regulator of human cutaneous pigmentation. *Pigment Cell Res.* **2000**, *13* (Suppl. S8), 156–162. [[CrossRef](#)] [[PubMed](#)]
90. Ollmann, M.M.; Lamoreux, M.L.; Wilson, B.D.; Barsh, G.S. Interaction of Agouti protein with the melanocortin 1 receptor in vitro and in vivo. *Genes Dev.* **1998**, *12*, 316–330. [[CrossRef](#)]



91. Blanchard, S.G.; Harris, C.O.; Ittoop, O.R.; Nichols, J.S.; Parks, D.J.; Truesdale, A.T.; Wilkison, W.O. Agouti antagonism of melanocortin binding and action in the B16F10 murine melanoma cell line. *Biochemistry* **1995**, *34*, 10406–10411. [[CrossRef](#)]
92. Candille, S.I.; Kaelin, C.B.; Cattanaach, B.M.; Yu, B.; Thompson, D.A.; Nix, M.A.; Kerns, J.A.; Schmutz, S.M.; Millhauser, G.L.; Barsh, G.S. A  $\beta$ -defensin mutation causes black coat color in domestic dogs. *Science* **2007**, *318*, 1418–1423. [[CrossRef](#)] [[PubMed](#)]
93. Harder, J.; Bartels, J.; Christophers, E.; Schroder, J.M. Isolation and characterization of human  $\mu$ -defensin-3, a novel human inducible peptide antibiotic. *J. Biol. Chem.* **2001**, *276*, 5707–5713. [[CrossRef](#)] [[PubMed](#)]
94. Wilson, B.D.; Ollmann, M.M.; Kang, L.; Stoffel, M.; Bell, G.I.; Barsh, G.S. Structure and function of ASP, the human homolog of the mouse agouti gene. *Hum. Mol. Genet.* **1995**, *4*, 223–230. [[CrossRef](#)]
95. Lu, D.; Willard, D.; Patel, I.R.; Kadwell, S.; Overton, L.; Kost, T.; Luther, M.; Chen, W.; Woychik, R.P.; Wilkison, W.O.; et al. Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor. *Nature* **1994**, *371*, 799–802. [[CrossRef](#)] [[PubMed](#)]
96. Nix, M.A.; Kaelin, C.B.; Ta, T.; Weis, A.; Morton, G.J.; Barsh, G.S.; Millhauser, G.L. Molecular and functional analysis of human  $\beta$ -defensin 3 action at melanocortin receptors. *Chem. Biol.* **2013**, *20*, 784–795. [[CrossRef](#)]
97. Swope, V.B.; Jameson, J.A.; McFarland, K.L.; Supp, D.M.; Miller, W.E.; McGraw, D.W.; Patel, M.A.; Nix, M.A.; Millhauser, G.L.; Babcock, G.F.; et al. Defining MC1R regulation in human melanocytes by its agonist  $\alpha$ -melanocortin and antagonists agouti signaling protein and  $\beta$ -defensin 3. *J. Invest. Dermatol.* **2012**, *132*, 2255–2262. [[CrossRef](#)]
98. Harris, J.I.; Lerner, A.B. Amino-acid sequence of the  $\alpha$ -melanocyte-stimulating hormone. *Nature* **1957**, *179*, 1346–1347. [[CrossRef](#)]
99. Hruby, V.J.; Wilkes, B.C.; Hadley, M.E.; Al-Obeidi, F.; Sawyer, T.K.; Staples, D.J.; de Vaux, A.E.; Dym, O.; Castrucci, A.M.; Hintz, M.F.; et al. alpha-Melanotropin: The minimal active sequence in the frog skin bioassay. *J. Med. Chem.* **1987**, *30*, 2126–2130. [[CrossRef](#)]
100. Sawyer, T.K.; Sanfilippo, P.J.; Hruby, V.J.; Engel, M.H.; Heward, C.B.; Burnett, J.B.; Hadley, M.E. 4-Norleucine, 7-D-phenylalanine-alpha-melanocyte-stimulating hormone: A highly potent alpha-melanotropin with ultralong biological activity. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 5754–5758. [[CrossRef](#)]
101. Hadley, M.E.; Marwan, M.M.; Al-Obeidi, F.; Hruby, V.J.; Castrucci, A.M. Linear and cyclic  $\alpha$ -melanotropin [4-10]-fragment analogues that exhibit superpotency and residual activity. *Pigment Cell Res.* **1989**, *2*, 478–484. [[CrossRef](#)] [[PubMed](#)]
102. Al-Obeidi, F.; Castrucci, A.M.; Hadley, M.E.; Hruby, V.J. Potent and prolonged acting cyclic lactam analogues of alpha-melanotropin: Design based on molecular dynamics. *J. Med. Chem.* **1989**, *32*, 2555–2561. [[CrossRef](#)] [[PubMed](#)]
103. Hunt, G.; Todd, C.; Cresswell, J.E.; Thody, A.J.  $\alpha$ -melanocyte stimulating hormone and its analogue Nle4DPhe7 alpha-MSH affect morphology, tyrosinase activity and melanogenesis in cultured human melanocytes. *J. Cell Sci.* **1994**, *107 Pt 1*, 205–211. [[CrossRef](#)]
104. Hunt, G.; Kyne, S.; Ito, S.; Wakamatsu, K.; Todd, C.; Thody, A. Eumelanin and pheomelanin contents of human epidermis and cultured melanocytes. *Pigment Cell Res.* **1995**, *8*, 202–208. [[CrossRef](#)]
105. Dorr, R.T.; Dvorakova, K.; Brooks, C.; Lines, R.; Levine, N.; Schram, K.; Miketova, P.; Hruby, V.; Alberts, D.S. Increased eumelanin expression and tanning is induced by a superpotent melanotropin [Nle4-D-Phe7]- $\alpha$ -MSH in humans. *Photochem. Photobiol.* **2000**, *72*, 526–532. [[CrossRef](#)]
106. Langendonk, J.G.; Balwani, M.; Anderson, K.E.; Bonkovsky, H.L.; Anstey, A.V.; Bissell, D.M.; Bloomer, J.; Edwards, C.; Neumann, N.J.; Parker, C.; et al. Afamelanotide for Erythropoietic Protoporphyrria. *N. Engl. J. Med.* **2015**, *373*, 48–59. [[CrossRef](#)]
107. Schiöth, H.B.; Chhajlani, V.; Muceniece, R.; Klusa, V.; Wikberg, J.E.S. Major pharmacological distinction of the ACTH receptor from other melanocortin receptors. *Life Sci.* **1996**, *59*, 797–801. [[CrossRef](#)] [[PubMed](#)]
108. Haskell-Luevano, C.; Nikiforovich, G.; Sharma, S.D.; Yang, Y.-K.; Dickinson, C.; Hruby, V.J.; Gantz, I. Biological and Conformational Examination of Stereochemical Modifications Using the Template Melanotropin Peptide, Ac-Nle-c[Asp-His-Phe-Arg-Trp-Ala-Lys]-NH<sub>2</sub>, on Human Melanocortin Receptors. *J. Med. Chem.* **1997**, *40*, 1738–1748. [[CrossRef](#)]
109. Wessells, H.; Hruby, V.J.; Hackett, J.; Han, G.; Balse-Srinivasan, P.; Vanderah, T.W. Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-NH<sub>2</sub> induces penile erection via brain and spinal melanocortin receptors. *Neuroscience* **2003**, *118*, 755–762. [[CrossRef](#)]
110. Wessells, H.; Levine, N.; Hadley, M.E.; Dorr, R.; Hruby, V. Melanocortin receptor agonists, penile erection, and sexual motivation: Human studies with Melanotan II. *Int. J. Impot. Res.* **2000**, *12* (Suppl. S4), S74–S79. [[CrossRef](#)]
111. Rossler, A.S.; Pfaus, J.G.; Kia, H.K.; Bernabe, J.; Alexandre, L.; Giuliano, F. The melanocortin agonist, melanotan II, enhances proceptive sexual behaviors in the female rat. *Pharmacol. Biochem. Behav.* **2006**, *85*, 514–521. [[CrossRef](#)] [[PubMed](#)]
112. Diamond, L.E.; Earle, D.C.; Garcia, W.D.; Spana, C. Co-administration of low doses of intranasal PT-141, a melanocortin receptor agonist, and sildenafil to men with erectile dysfunction results in an enhanced erectile response. *Urology* **2005**, *65*, 755–759. [[CrossRef](#)] [[PubMed](#)]
113. Molinoff, P.B.; Shadiack, A.M.; Earle, D.; Diamond, L.E.; Quon, C.Y. PT-141: A Melanocortin Agonist for the Treatment of Sexual Dysfunction. *Ann. N. Y. Acad. Sci.* **2003**, *994*, 96–102. [[CrossRef](#)] [[PubMed](#)]
114. Hugo, W.; Zaretsky, J.M.; Sun, L.; Song, C.; Moreno, B.H.; Hu-Lieskovan, S.; Berent-Maoz, B.; Pang, J.; Chmielowski, B.; Cherry, G.; et al. Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma. *Cell* **2016**, *165*, 35–44. [[CrossRef](#)]
115. Zhou, Y.; Mowlazadeh Haghighi, S.; Liu, Z.; Wang, L.; Hruby, V.J.; Cai, M. Development of Ligand-Drug Conjugates Targeting Melanoma through the Overexpressed Melanocortin 1 Receptor. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 921–930. [[CrossRef](#)]
116. Goodwin, R.G.; Kell, W.J.; Laidler, P.; Long, C.C.; Whatley, S.D.; McKinley, M.; Badminton, M.N.; Burnett, A.K.; Williams, G.T.; Elder, G.H. Photosensitivity and acute liver injury in myeloproliferative disorder secondary to late-onset protoporphyria caused by deletion of a ferrochelatase gene in hematopoietic cells. *Blood* **2006**, *107*, 60–62. [[CrossRef](#)]

117. Haskell-Luevano, C.; Rosenquist, A.; Souers, A.; Khong, K.C.; Ellman, J.A.; Cone, R.D. Compounds that activate the mouse melanocortin-1 receptor identified by screening a small molecule library based upon the  $\beta$ -turn. *J. Med. Chem.* **1999**, *42*, 4380–4387. [[CrossRef](#)]
118. Herpin, T.F.; Yu, G.; Carlson, K.E.; Morton, G.C.; Wu, X.; Kang, L.; Tuerdi, H.; Khanna, A.; Tokarski, J.S.; Lawrence, R.M.; et al. Discovery of tyrosine-based potent and selective melanocortin-1 receptor small-molecule agonists with anti-inflammatory properties. *J. Med. Chem.* **2003**, *46*, 1123–1126. [[CrossRef](#)] [[PubMed](#)]
119. Boman, A.; Jonassen, T.E.N.; Lundstedt, T. Phenyl Pyrrole Aminoguanidine Derivatives. U.S. Patent 8,058,306, 15 November 2011.
120. Bouix-Peter, C. Oxazetidine Derivatives, Process for Preparing Them and Use in Human Medicine and in Cosmetics. U.S. Patent 9,353,083, 31 May 2016.
121. Eisinger, M.; Li, W.H.; Anthonavage, M.; Pappas, A.; Zhang, L.; Rossetti, D.; Huang, Q.; Seiberg, M. A melanocortin receptor 1 and 5 antagonist inhibits sebaceous gland differentiation and the production of sebum-specific lipids. *J. Dermatol. Sci.* **2011**, *63*, 23–32. [[CrossRef](#)]
122. Lee, S.; Ju, W.; Tin, T.D.; Kim, J.; Lee, J.S.; Park, C.H.; Kwak, S.H. Effect of BMS-470539 on lipopolysaccharide-induced neutrophil activation. *Korean J. Anesthesiol.* **2020**, *73*, 151–157. [[CrossRef](#)]
123. Suzuki, T.; Kawano, Y.; Matsumoto, A.; Kondo, M.; Funayama, K.; Tanemura, S.; Miyashiro, M.; Nishi, A.; Yamada, K.; Tsuda, M.; et al. Melanogenic effect of dersimelagon (MT-7117), a novel oral melanocortin 1 receptor agonist. *Ski. Health Dis.* **2022**, *2*, e78. [[CrossRef](#)]
124. Lundstedt, T.; Skottner, A.; Boman, A.; Andersson, P.; Seifert, E.; Andrianov, V. N-Phenylpyrrole Guanidine Derivatives as Melanocortin Receptor Ligands. U.S. Patent 7,442,807, 28 October 2008.
125. Montero-Melendez, T.; Gobetti, T.; Cooray, S.N.; Jonassen, T.E.; Perretti, M. Biased agonism as a novel strategy to harness the proresolving properties of melanocortin receptors without eliciting melanogenic effects. *J. Immunol.* **2015**, *194*, 3381–3388. [[CrossRef](#)] [[PubMed](#)]
126. Boiteau, J.G.; Rodeville, N.; Martin, C.; Tabet, S.; Moureou, C.; Muller, F.; Jetha, J.C.; Cardinaud, I. Development of a Kilogram-Scale Synthesis of a Novel MC1R Agonist. *Org. Process Res. Dev.* **2015**, *19*, 646–651. [[CrossRef](#)]
127. Zhang, L.; Li, W.H.; Anthonavage, M.; Eisinger, M. Melanocortin-5 receptor: A marker of human sebocyte differentiation. *Peptides* **2006**, *27*, 413–420. [[CrossRef](#)]
128. Rosenfield, R.L.; Wu, P.P.; Ciletti, N. Sebaceous epithelial cell differentiation requires cyclic adenosine monophosphate generation. *In Vitro Cell. Dev. Biol. Anim.* **2002**, *38*, 54–57. [[CrossRef](#)] [[PubMed](#)]
129. Zhang, L.; Anthonavage, M.; Huang, Q.; Li, W.H.; Eisinger, M. Proopiomelanocortin peptides and sebogenesis. *Ann. N. Y. Acad. Sci.* **2003**, *994*, 154–161. [[CrossRef](#)]
130. Zouboulis, C.C. Acne and sebaceous gland function. *Clin. Dermatol.* **2004**, *22*, 360–366. [[CrossRef](#)]
131. Zouboulis, C.C.; Schagen, S.; Alestas, T. The sebocyte culture: A model to study the pathophysiology of the sebaceous gland in seborrhoea, seborrhoea and acne. *Arch. Dermatol. Res.* **2008**, *300*, 397–413. [[CrossRef](#)]
132. Saint-Leger, D.; Bague, A.; Lefebvre, E.; Cohen, E.; Chivot, M. A possible role for squalene in the pathogenesis of acne. II. In vivo study of squalene oxides in skin surface and intra-comedonal lipids of acne patients. *Br. J. Dermatol.* **1986**, *114*, 543–552. [[CrossRef](#)]

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.