ISID 1116

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Innovation · New Therapeutics

ISID 2023 TOKYO

# Novel androgen receptor degrader for Androgenetic alopecia (AGA) application

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## ABSTRACT

Androgenetic alopecia (AGA) is the most common form of hair loss disorder in men and women of all races worldwide. Loss of scalp hair is a distressing condition that dampens patient's self-esteem and lowers the quality of patient's life, but the options for effective and safe treatment are still limited. In patients with AGA, the level of dihydrotestosterone (DHT) and androgen receptor (AR) protein is increased, and excessive DHT-AR signaling plays an essential role in the development and progression of AGA. In this study, we design and synthesize a series of novel protein degraders that can specifically degrade AR protein for AGA treatment. The activity of AR protein degrader (AR-degrader) was evaluated in LNCaP cells and demonstrated a low nanomolar range of $DC_{50}$. Then a DHT-induced hair regrowth inhibition mouse model which simulates AGA was established to evaluate the efficacy of AR-degrader *in vivo*. After daily administration of AR-degrader topically, the DHT-induced delay of hair regrowth was reversed as compared to vehicle control. In addition, the detected amount of AR-PROTAC in the serum was close to the lower limit of quantification, suggesting only a very limited amount of topically administered AR-degrader enters circulation. This could greatly reduce the potential of adverse side effects observed in finasteride, an oral antiandrogen drug in AGA treatment. Collectively, the topically administered AR-degrader provides a novel, efficient, and safe treatment strategy with great therapeutic potential for treating AGA.

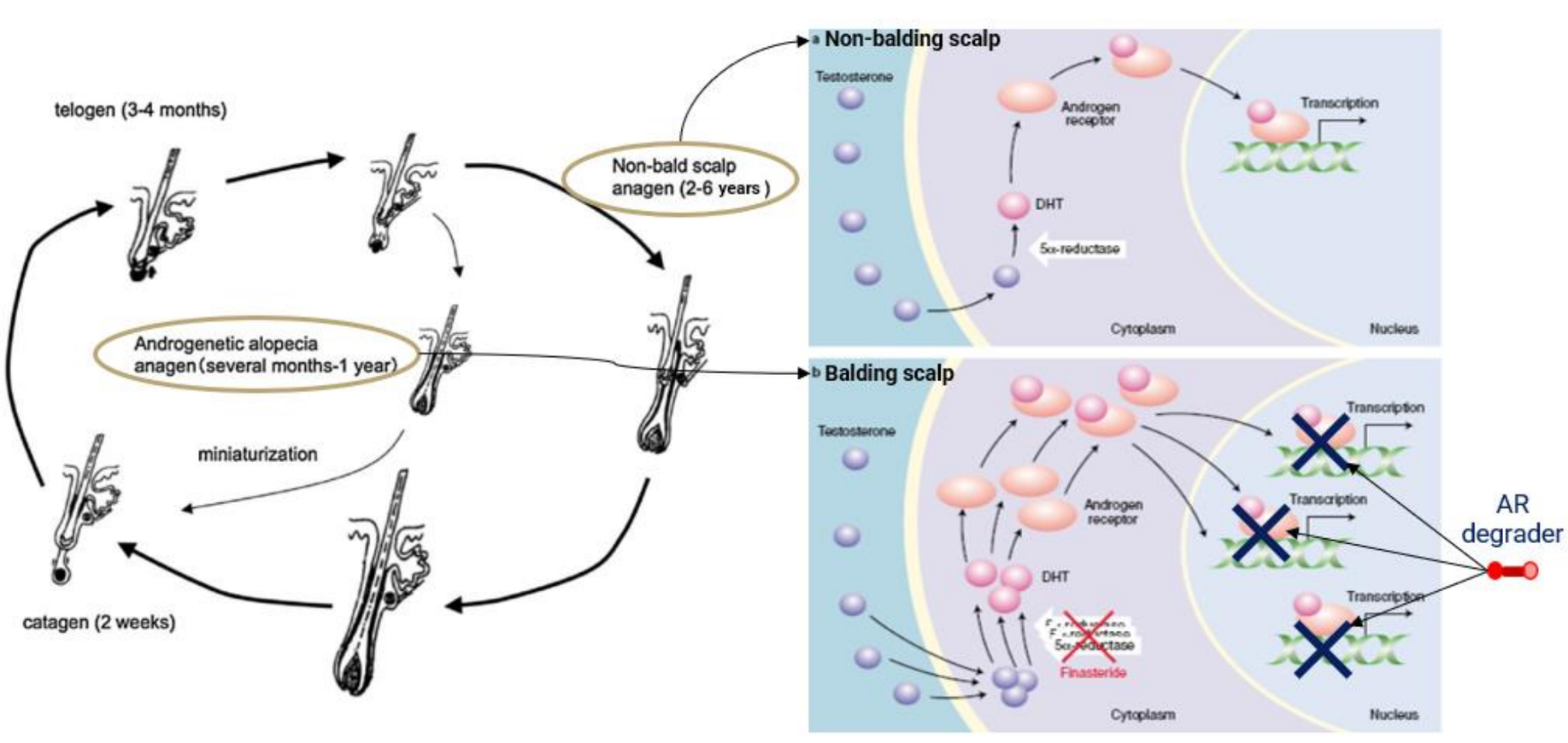



**Figure 1.** Schematic diagram of hair cycle and androgen receptor signaling axis in non-balding and balding scalp in androgenetic alopecia patients. (Reference: 10.1017/S1462399402005112, 10.1016/s0531-5565(02)00093-1)

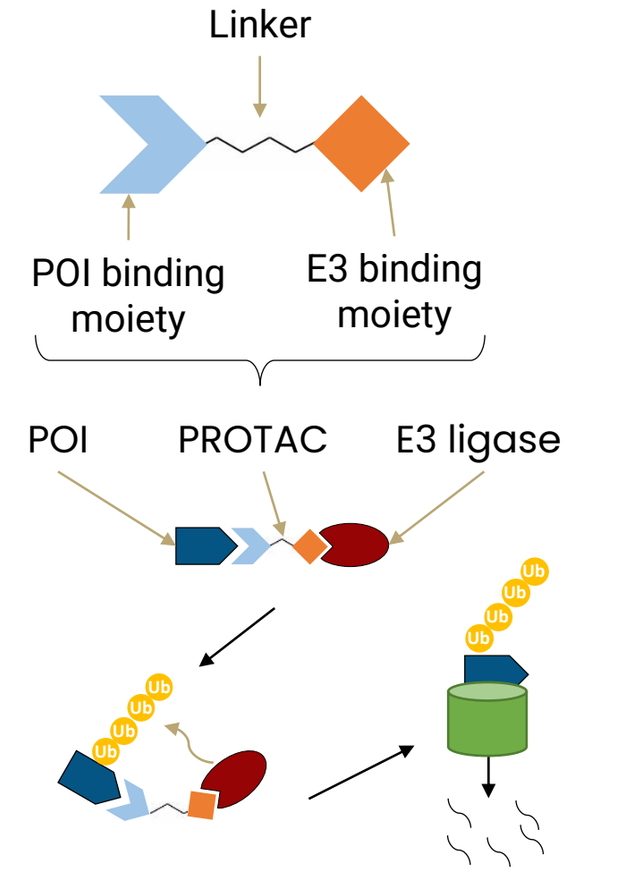



**Figure 2.** Key components of a PROTAC molecule and illustration of its mechanism of action.

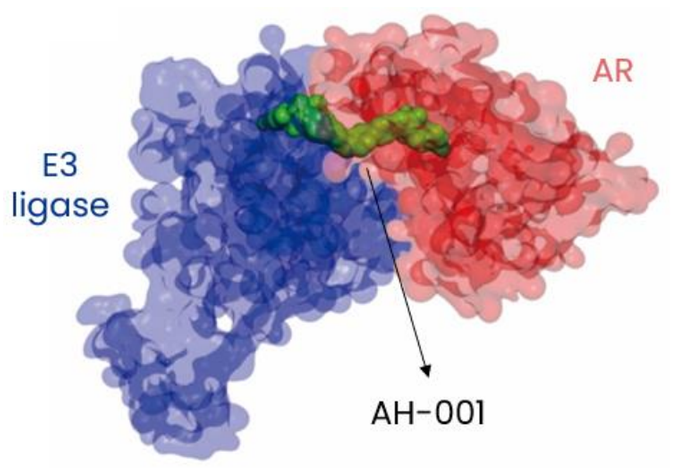
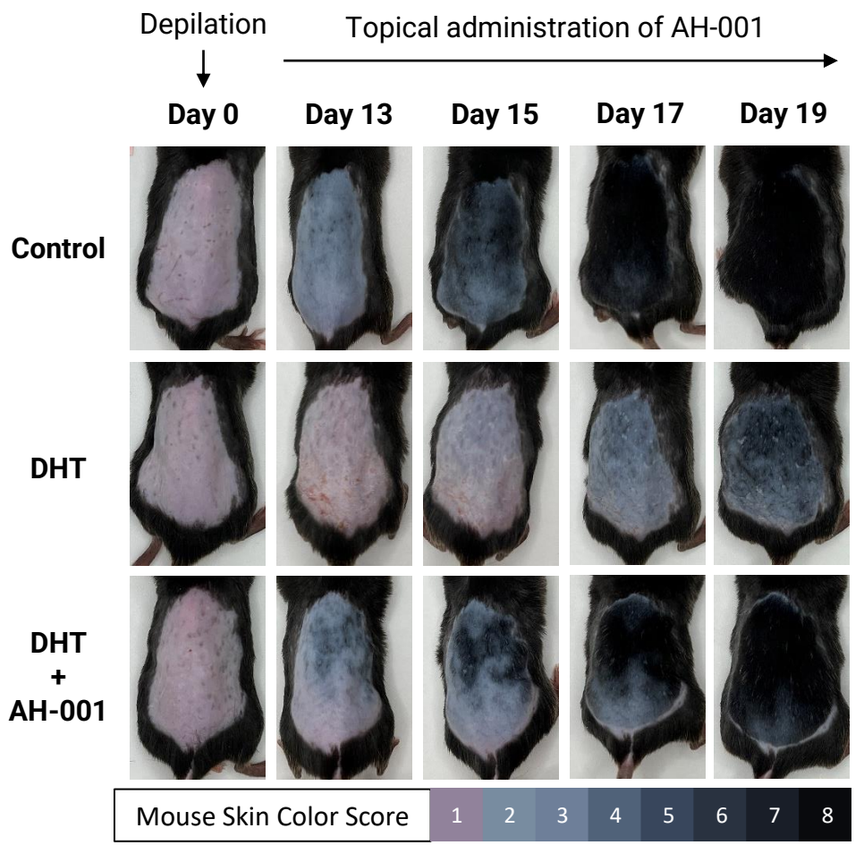



**Figure 3.** Predicted binding pose of E3-AH-001-AR ternary complex




| Blood Sample | | |
|---|---|---|
| **Drug** | **Treatment Duration** | Blood Concentration (ng/mL) |
| AH-001 (Topical) | 7 day | < 1.0 |
| | 14 days | < 1.0 |
| | 19 days | < 1.0 |

**Table 1.** Detected AH-001 concentration in blood sample after consecutive topical administration

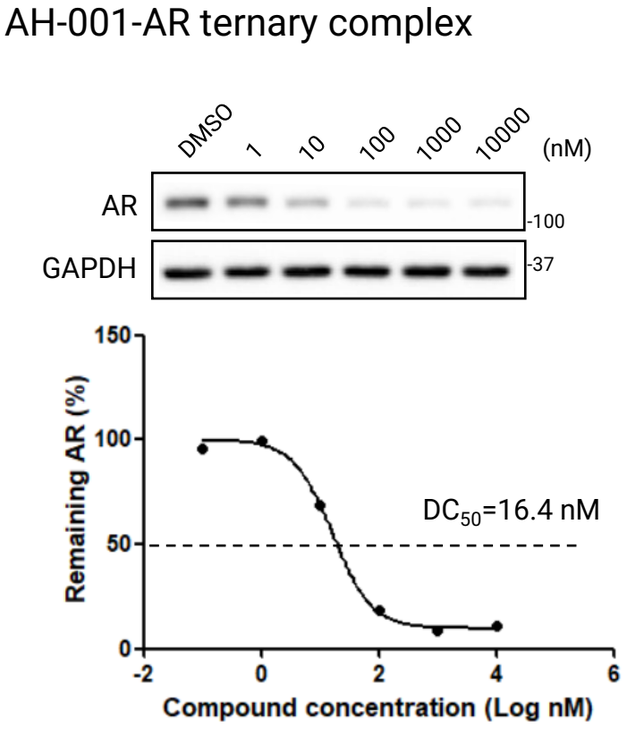



**Figure 4.** AH-001 induced endogenous AR protein degradation in a dose-dependent manner in LNCaP cell

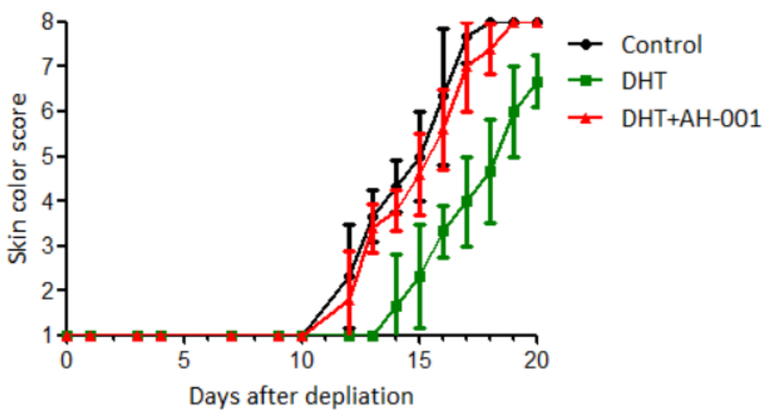



**Figure 5.** Topical administration of AH-001 reverse hair regrowth inhibition induced by DHT in AGA mouse model

## HIGHLIGHTS

- AH-001 efficiently degrades endogenous androgen receptor protein via recruiting E3 ubiquitin ligase.
- AH-001 effectively reverses DHT-induced hair regrowth inhibition in AGA mouse model.
- Topical administration of AH-001 could avoid systematic exposure and reduce potential adverse effects to achieve a better safety profile.

## CONTACT INFORMATION

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