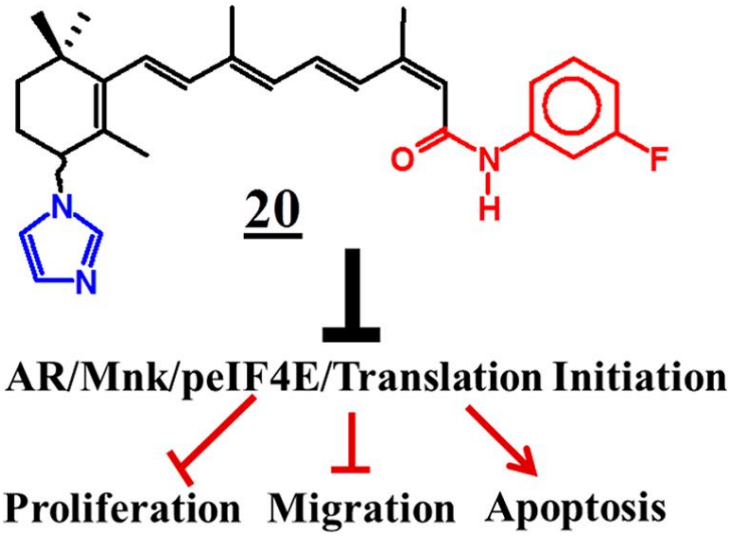
TECHNOLOGY

Novel Retinamides for Treatment of Cancer and Dermatological Diseases

OVERVIEW

Retinoic acid metabolism blocking agents (RAMBAs) inhibit the cellular enzyme that metabolizes all-trans retinoic acid (ATRA), which actively directs cells to mature in a controlled manner to ensure normal growth. However, the beneficial effects of ATRA are limited due to its rapid cellular conversion into inactive metabolites. Researchers at UMB discovered novel retinamide RAMBAs and validated their therapeutic utility in animal models of breast and prostate cancer. In addition to enhancing the beneficial effects of ATRA, the mechanism of action for these RAMBAs has been shown to involve degradation of Mnk1/2, suppesssion of the oncogenic eIF4E pathway, as well as modulating the action of the androgen receptor (full-length & splice variants). Importantly, these anti-oncogenic effects were more potent than those observed for currently approved therapies (i.e., clinically relevant retinoids, established MNK inhibitors, etc.; *see Ramamurthy et al., 2015*). For potential use in treating dermatological conditions, UMB researchers obtained promising early results demonstrating that lead retinamide RAMBAs have equal or superior effects over approved retinoids (ATRA and 13-CRA) to inhibit proliferation of normal human adult keratinocytes and sebocytes, and antikeratinizing effects in reconstructed human epidermis. Initial toxicity profiles for a panel of RAMBAs [*Njar et al., 2006*] also showed good indications for safe therapeutic use.



APPLICATIONS

These novel RAMBAs block the normal metabolism of endogenous ATRA in cells, increasing the beneficial effects of ATRA. They provide a unique approach to achieve the therapeutic benefit of retinoid therapy while potentially circumventing the adverse events associated with it, a very important property for application to dermatology therapy. ATRA deficiencies are associated with dermatological diseases (acne and psoriasis), and retinoid derivatives have been one of the mainstay therapies for acne. Liarozole is in clinical use for the treatment of psoriasis and ichthyosis. Dermatological retinoid deficiencies are characterized by hyperkeratinization and desquamation and include diseases such as acne, eczema, psoriasis, cold sores, wounds, burns, sunburn, ichthyosis, skin cancer, and Kaposi's Sarcoma, all of which are plausible targets for retinamide RAMBA therapy.

ADVANTAGES

Lead compounds show potent *in vivo* anti-cancer activity

Lead compounds show promise *in vitro* for treating dermatology conditions

Good oral bioavailability and safety profile

STAGE OF DEVELOPMENT

Oncology: Lead retinamide RAMBA compounds demonstate potent tumor inhibition in mouse xenograft models of human triple-negative breast cancer and castration-resistant prostate cancer [*see Refs 2014 - 2015*].

Dermatology: Lead retinamide RAMBAs demonstrate antikeratinization & sebosuppressive effects *in vitro* and in reconstructed human epidermis, with equal or superior effects to currently marketed retinoids, 13-CRA and ATRA [*unpublished data*].

(As of 6/9/2017)- NC

R&D REQUIRED

Targeted clinical development for application of interest.

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PATENT STATUS

US Patent 9,156,792 (issued 10/13/2015) WO 2016/081589 (published 5/26/2016) Other patents pending

LICENSE STATUS

Partnered

CATEGORIES

- Therapeutics
- Biologics

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ATTACHMENTS

- Download SUMMARY VN Retinamides DERM 6-9-17 FINAL.pdf

EXTERNAL RESOURCES

- Novel C-4 heteroaryl 13-cis-retinamide Mnk/AR degrading agents inhibit cell proliferation and migration...
- Simultaneous targeting of AR and MNKs by novel retinamides inhibits growth of human prostate cancer cell lines
- Retinoic acid metabolism blocking agents (RAMBAs) for treatment of cancer and dermatological diseases.

- First MNKs degrading agents block phosphorylation of eIF4E, induce apoptosis, inhibit cell growth, migration and invasion...

DOCKET CODE

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