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Bollag W. Vitamin A and vitamin A acid in the prophylaxis and therapy of epithelial tumours. *Int. Z. Vitaminforsch.* 40:299-314, 1970.
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The paper included a review of the literature and some of my own research work dealing with the relationship between vitamin A and tumors. In animal experiments and in clinical investigations vitamin A and vitamin A acid had shown a preventive effect on the development of tumors as well as a therapeutic effect on certain established premalignant and malignant epithelial lesions. [The *SCI*® indicates that this paper has been cited in over 105 publications.]

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When I started research on vitamin A in 1967, I had already spent 10 years with Hoffmann-La Roche as head of cancer research. My task was the search for new cytotoxic agents. In spite of the successes with fluoropyrimidines and methylhydrazines I felt unhappy with this approach to cancer chemotherapy because of the limitations imposed by severe side effects, such as bone marrow depression. In 1967 I read the paper by U. Saffiotti and colleagues[1] on the experimental prevention of tracheobronchial metaplasia and squamous cell tumors by high doses of vitamin A. I was immediately thrilled by this article, since vitamins could not be regarded as cytotoxic agents. I pursued all the existing literature on the biological effects of vitamin A. From these, it was evident that vitamin A could be of preventive or therapeutic value in the fields of oncology and dermatology. Vitamin A had indeed been investigated clinically in the treatment of precancerous and cancerous conditions as well as of acne, psoriasis, and other keratinizing dermatoses. However, only moderate therapeutic effects had been achieved, and, moreover, vitamin A therapy was associated with the intolerable side effects known as hypervitaminosis A syndrome.

My working hypothesis was, therefore, would it be possible to synthesize analogs of vitamin A that would exhibit a more favorable dissociation between preventive or therapeutic effect and side effects? I proposed to our vitamin A chemists a synthetic program consisting of the chemical manipulation of the vitamin A molecule. This project was started in 1968 and proved to be a very fruitful one.

I believe that the reason the article has been so highly cited is as follows: it proved by literature review and by my own investigations that vitamin A had not only the character of a vitamin, but had other properties with a particular relationship to oncology (and to dermatology). I was able to demonstrate the therapeutic effect of vitamin A acid—a vitamin A analog—experimentally on chemically induced mouse skin papillomas and clinically on premalignant actinic keratoses and basal cell carcinomas of the skin. This paper was the starting point of the development of further analogs structurally related to vitamin A (later termed retinoids by M.B. Sporn *et al.*[2]). It incited innumerable investigations on retinoids in basic and applied research.[3-6] In fact, at the time of the publication of the article in 1970, we had already synthesized and biologically tested, by means of our new screening model system of the carcinogen-induced mouse skin papilloma, a large series of retinoids possessing properties different from vitamin A, with a better therapeutic margin. Up to this time more than 2,500 retinoids have been evaluated in our laboratories. Some, like 13-cis retinoic acid, etretinate, and etretin, have proven to be clinically useful in oncological and dermatological diseases. An intensive search for better compounds still continues.

Honors received for the discovery and development of synthetic retinoids include a cancer research award in Switzerland (1971); a cancer research award from the American Academy of Dermatology (1982); an award for psoriasis research, US (1982); the Prix Galien, Paris (1984); and an honorary doctorate from the University of Basel, Switzerland (1987).

1. **Saffiotti U, Montesano R, Sellakumar A R & Borg S A.** Experimental cancer of the lung. Inhibition by vitamin A of the induction of tracheobronchial squamous metaplasia and squamous cell tumors. *Cancer* 20:857-64, 1967. (Cited 325 times.)
2. **Sporn M B, Dunlop N M, Newton D L &'Smith J M.** Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *Fed. Proc.* 35:1332-8, 1976. (Cited 575 times.)
3. **Bollag W.** The development of retinoids in experimental and clinical oncology and dermatology. *J. Amer. Acad. Dermatol.* 9:797-805, 1983. (Cited 20 times.)
4. **Bollag W & Hartmann H R.** Prevention and therapy of cancer with retinoids in animals and man. *Cancer Surv.* 2:293-314, 1983. (Cited 25 times.)
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6. ———. Retinoids as preventive and therapeutic anticancer agents (part II). *Cancer Treat. Rep.* 71:493-515, 1987.

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