CC/NUMBERS 51-52
DECEMBER 19-26, 1988

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Bollag W. Prophylaxis of chemically induced benign and malignant epithelial tumors by vitamin A acid (retinoic acid). *Eur. J. Cancer* 8:689-93, 1972.
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Retinoic acid showed a preventive effect on the development of chemically induced mouse skin tumors. Papillomas and carcinomas were induced by topical application of dimethylbenzanthracene and croton oil. Retinoic acid delayed the appearance and reduced the incidence of benign papillomas as well as of malignant squamous cell carcinomas of the skin. [The *SCI*® indicates that this paper has been cited in over 285 publications, making it this journal's most-cited paper.]

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August 22, 1988

I became interested in the relationship between vitamin A and cancer after intense literature studies, prompted by an article by U. Saffiotti *et al.* in 1967 on inhibition of tracheobronchial carcinogenesis by vitamin A.[1] In the laboratories of Hoffmann-La Roche I observed that vitamin A exerted not only preventive but also therapeutic effects on chemically induced skin tumors of mice. The limitation for clinical use of vitamin A rested with its toxic side effects, known as hypervitaminosis A. Therefore, my working hypothesis was as follows: By chemical manipulation of the vitamin A molecule, derivatives might be found, still possessing the desired preventive or therapeutic effect, but inducing fewer side effects.

The first compound tested was the synthesized all-trans retinoic acid. Although this analog showed a better therapeutic index, this was far from satisfactory. By performing a large synthetic program, my goal was to find analogs with a much more favorable ratio between tumor effect and toxicity. The Roche chemists, experienced in vitamin A chemistry, were in favor of the project. However, the vitamin biologists argued: "During millions of years of evolution, nature has developed the best substance; looking for a better one would be hopeless." In reply, I discussed with them the analogy to the field of steroids, where synthetic compounds had been found that displayed more selective therapeutic activity than the parent physiological substance. Eventually, Hoffmann-La Roche's management decided in favor of the retinoid project.

I believe that the reason my paper on vitamin A acid (1972) and subsequently those on cancer chemoprevention and therapy with an aromatic retinoic acid analog[2,3] have been cited so frequently was succinctly expressed in 1976 by M.B. Sporn *et al.*: "The first successful efforts which have demonstrated that synthetic retinoids can be more potent and less toxic than natural retinoids for prevention of cancer have very recently been made by Bollag."[4] In fact, this paper opened up the new concept of chemoprevention of cancer by synthetic retinoids. At that time, in 1972, we had already synthesized, biologically tested, and patented hundreds of new retinoids, mainly for prevention and therapy of tumors, but also for dermatological diseases.

My dream was to eliminate as many side effects as possible by changing the various building blocks of the vitamin A molecule and by finding compounds with highly selective effects on proliferation, differentiation, prevention and therapy of premalignant and malignant lesions (including organ site affinity), keratinization, sebum production, inflammation, and immune reactions. Parts of my dream have been fulfilled, since each newly discovered retinoid possessed its own unique spectrum of therapeutic properties and side effects. In the field of dermatology, clinically useful compounds have been detected, including isotretinoin for the treatment of severe cystic acne and etretinate and acitretin for treatment of diseases of keratinization. These retinoids also proved to be active to a certain degree in the prevention and therapy of premalignant and malignant lesions of skin and mucous membranes. New compounds inducing only minor side effects and exerting highly selective activity, for example, in the prevention and therapy of mammary cancer, have been discovered.[5] Innumerable publications confirm the enormous interest in basic and applied, experimental and clinical retinoid research with respect to oncology[6,7] and to other disciplines of medicine, such as dermatology, rheumatology, and immunology.

Honors received for the discovery and development of synthetic retinoids include a cancer research award (Switzerland, 1971), a cancer research award from the American Academy of Dermatology (1982), a psoriasis research award (US, 1982), the Prix Galien (France, 1984), and an honorary doctorate (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. **Bollag W.** Therapeutic effects of an aromatic retinoic acid analog on chemically induced skin papillomas and carcinomas of mice. *Eur. J. Cancer* 10:731-7, 1974. (Cited 205 times.)
3. ————. Prophylaxis of chemically induced epithelial tumors with an aromatic retinoic acid analog (Ro 10-9359). *Eur. J. Cancer* 11:721-4, 1975. (Cited 110 times.)
4. **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.)
5. **Bollag W.** Inhibition of rat mammary carcinogenesis by an arotinoid without a polar end group (Ro 15-0778). *Eur. J. Cancer Clin. Oncol.* 23:131-5, 1987.
6. **Lippman S M, Kessler J F & Meyskens F L.** Retinoids as preventive and therapeutic anticancer agents (part I). *Cancer Treat. Rep.* 71:391-405, 1987.
7. ————. Retinoids as preventive and therapeutic anticancer agents (part II). *Cancer Treat. Rep.* 71:493-515, 1987.

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