Hot Topics in Pharmacognosy: Serendipity and the Attuned Mind

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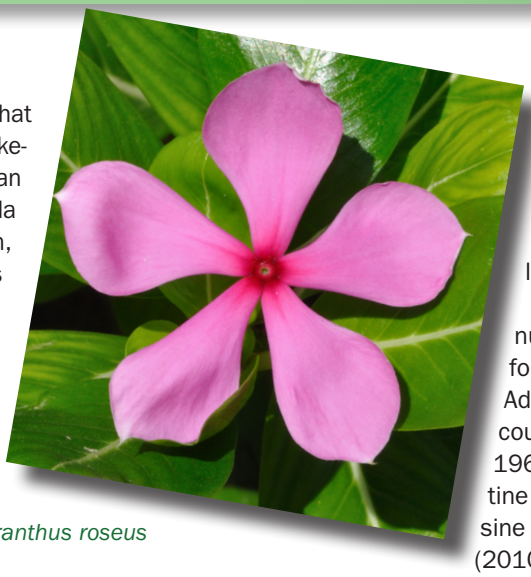

Catharanthus roseus

Experiments leading to a drug series that changed the diagnosis of childhood leukemia from a death sentence to better than 80% survival started in 1949 in Canada at the University of Western Ontario (London, Ontario). Researchers were intrigued by reports from Jamaica that extracts of the rosy periwinkle (*Catharanthus roseus*, then *Vinca rosea*) were used as a tea to control diabetes. Oral administration experiments on diabetic and normal rats and rabbits showed no effect on either blood sugar levels or glucagon, but a proprietary formulation known as Vinculin had been marketed in the United Kingdom as a treatment for diabetes.

However, when dosed intravenously, the rats succumbed within a week and on necropsy, showed signs of septicemia (blood poisoning) although the injected fluid was sterile. Analyzing blood counts and blood chemistries, it became obvious that the white blood cells were being significantly depressed; this was performed over 60 years ago without the knowledge or techniques now available.

In 1955, the laboratory commenced a more thorough investigation using a bioactivity linked isolation and finally using gradient elution on Woehlm alumina (which took the writer back to his days as a technician in the same time period), followed by crystallization of the sulfate salt. This resulted in "vinleukoblastine" (VLB, now known as vinblastine). The enriched crude fractions gave activity (carcinostatic) against a transplantable sarcoma in rats and against a mammary carcinoma in DBA/JAX mice.[1]

Just to show that Mother Nature has a sense of humor, an independent study by Svoboda et al. at the Lilly Company was started because of the company's insulin franchise and evidence from ethnobotanical reports of the use of *C. roseus* extracts in Indonesia during World War II as a treatment for diabetes. [2,3] Continued studies by the Lilly group demonstrated the cytotoxic activity of the extract against lipocytes, and they reported the alkaloids leurosine and VLB approximately a year after Noble et al.[2,3] Interestingly for a paper in 1959, there is mention of the use of nuclear magnetic resonance (NMR) as part of the analytical techniques used. These papers were closely followed by another in 1960 demonstrating the in vivo activity of both leurosine and VLB in a mouse model of acute lymphocytic leukemia in DBA/2 mice.[4]

Since these original publications, the number of approved (meaning launched following approval by the Food and Drug Administration or its equivalent in other countries) derivatives of VLB (launched in 1963 or 1965; sources differ) and vincristine (launched in 1963) has risen to vindesine (1979), vinorelbine (1989), vinflunine (2010), and a recent liposomal formulation of vincristine (2013), 50 years after the base compound was approved in the United States.

Currently there are three variations on the vincas at varying stages of clinical development. The liposomal variation of vinorelbine is in Phase I with Tekmira Pharmaceutical Company, 12'methylthiovinblastine is also in Phase I against solid tumors with Albany Molecular Research, Inc. and Bessor Pharma, LLC, and the most advanced is Vintafolide, a conjugate of desacetylvinblastine hydrazide-folate (see structure) from Endocyte, Inc., now licensed to Merck and with a Phase III trial currently recruiting against platinum resistant ovarian cancer (NCT01170650).

Thus, 50 years after the first approval of the base compounds, these very active natural products are still being used as the basis for novel antitumor drugs, and in addition to these approved and clinical trials candidates, there are 12 preclinical candidates shown in the Integrity™ database as of February 2014; of these, perhaps 6 to 7 are still viable.

For people who wish to read further on the subject, a recent review article by Christian Bailly[5] from Pierre Fabre should be consulted, as this company has devoted very significant resources to the vinca alkaloid based drugs in more recent times. In addition, work up through 2009 was covered extensively by Roussi et al.,[6] and their review is also worth reading. ■

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2. Neuss, N., Gorman, M., Svoboda, G. H., Maciak, C. T. and Beer, C. T. Vinca Alkaloids III. Characterization of Leurosine and Vincaleukoblastine, New Alkaloids from *Vinca Rosea* Linn, *J. Amer. Chem. Soc.,* **1959,** 4754-4755.

3. Gorman, M., Neuss, N. and Svoboda, G. H.; Vinca Alkaloids IV. Structural Features of Leurosine and Vincaleukoblastine, Representatives of a new type of Indole-Indoline Alkaloids, *J Amer Chem Soc.* **1959**, 81, 4745-4746.

4. Johnson, I. S., Wright, H. F., Svoboda, G. H. and Vlantis, J., Antitumor Principles Derived from *Vinca rosea* Linn, *Cancer Res.*, **1960**, 20, 1016-1022.

5. Bailly, C., Cell-targeted cytotoxics: a new generation of cytotoxic agents for cancer treatment, *Phytochem Rev.,* **2014**, 13, 171-181.

6. Roussi, F., Gueritte, F. and Fahy, J. The Vinca Alkaloids, in Anticancer Agents from Natural Products, Eds., Cragg, G. M., Kingston, D. G. I. and Newman, D. J., Taylor and Francis, Boca Raton, FL, 2nd Edition, pp. 177-198, **2012**.