I n 2012, the FDA approved a classical phorbol ester, ingenol 3-angelate (see structure below) known as Picato™ for the treatment of actinic keratosis (AK). For those of you who remember the early pharmacology of phorbols, phorbol esters, and the initial reports of the classical protein kinase C (PKC) inhibitor (and sometimes activator) bryostatin 1 and its analogues, this news was quite heartening. Approval in the European Union occurred later in 2012.

There were reports from a variety of sources including a report from Egypt in *Phytochemistry* in 1985 and in 1976, and a report in the *Medical Journal of Australia* on home treatment, that the sap of *Euphorbia peplus* (also known as petty spurge in the United Kingdom and radium weed in Australia) may well be an effective treatment for AK and related “cancers.”

Further literature searching brought up a very interesting reference with a well-known ASP member as one of the authors. In fact it may well be part of Dr. Doug Kinghorn’s Ph.D. doctoral research at the University of London.

It gives an extensive coverage of the diterpenes from *Euphorbia* spp. and *Elaeophorbia* spp. with extensive reports of the occurrence of ingenol or its esters and derivatives.

The compound, effectively the natural product under the original name PEP 005 from the Australian company Peplin, has been in a variety of clinical trials mainly as a treatment for AK; but, there were also reports of Phase II trials against superficial and nodular basal cell carcinoma (results have not yet been published).

A Phase II trial against non-melanoma skin cancer using mainly the sap of *Euphorbia peplus* was reported as being effective by Australian researchers in 2011. Leo Pharma in Denmark purchased Peplin in 2009, and Peplin now operates as a United States subsidiary. Aside from the Australian trials there have been to date, 41 trials are listed in the Clinicaltrials.gov database with Picato.

There are also two other very interesting recent publications related to this compound. In 2013, Xing and Siliciano demonstrate that ingenol will reactivate latent HIV and perhaps more importantly, Baran et al has just published a 14 step stereospecific synthesis of ingenol from the relatively easily available, (+)-3-carene, using synthetic schema that will permit the syntheses of analogues that have not yet been “seen.”

The bottom line however, is that the “folk medicine” originally described and used in Australia (granted an “N” of 1), reported in Hartwell’s compendium, has now become an approved drug as the natural product.

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