Picato® (ingenol mebutate) gel: Case Study

Picato® is a prescription gel that treats skin actinic keratosis (potentially pre-cancerous sunspots). The journey to develop this product began in the 1970s when Queensland researcher, Jim Aylward, became interested in a local farming story about the healing properties of the sap of the radium weed Euphorbia peplus (E. peplus) when applied to sunspots on the skin.

**Origin**

Dr Jim Aylward began researching the sap of E. peplus in earnest in 1979. His early studies showed that the sap had a profound effect on melanoma cells in vitro. On this basis, he lodged a provisional patent application and established a company with his CSIRO manager which he named Peplin Biotech Pty Ltd. He had 12 months to find the active principle to complete the patent requirements. He worked at CSIRO labs during the day separating the chemicals for anti-melanoma activity in collaboration with a research program led by Professor Peter Parsons.

In 1998, Aylward managed to extract and purify active compounds in the sap, including acetyl ingenol angelate, and completed the patent in August. His patent subsequently claimed a family of ingenol angelates including PEP005 (ingenol mebutate). Further research in collaboration with another QIMR Berghofer research team, led by Professor Andreas Suhrbier, helped define how PEP005 worked at a cellular level.

**Grants and Investment**

**NHMRC**

NHMRC funding (through Fellowships and equipment grants) has contributed significantly to the research and development of this product, and has built intellectual and technological capacity at QIMR Berghofer that can be accessed for commercial translation and development. QIMR Berghofer has more than 15 research teams working on different aspects of melanoma and skin cancer. Individual researcher funding included:

- **NHMRC Industry Research Fellowship, 1999-2015**
- **Dr Steven Ogbourne, Industry Research Fellowship, 2002-2005**
- **Dr Sarah-Jane Cozzi, Industry Fellowship, 2007-2011**
- **Other grants and investments**
  - Queensland Government USI grant, 2000
  - Queensland Government COMET grant, 2010
  - Commonwealth Government Pharmaceuticals Partnerships Program P3 grant, 2008
  - Private and public (ASX) investments, including from overseas, in Peplin Ltd at various stage of product development up to acquisition, approximately $30 million.

**Commercialisation Journey**


Danish company LEO Pharma acquired Peplin for AS$4.8 million in 2009, with the retention of manufacturing facilities in Australia. By this point, the first FDA-compliant Phase III trials were complete, with others ongoing just prior to this acquisition.

Since the initial patent for ingenol mebutate, Aylward’s new drug has led to more than $4.5 million in research funding to the Parsons and Suhrbier laboratories. E. peplus has been grown for commercial purposes on farms in Queensland. Workers employed at the manufacturing facility at Southport, Queensland (Peplin Operations (Pty) Ltd) extract and purify the Active Pharmaceutical Ingredient, Picato®, for wide-world distribution. Since the start of sales of Picato®, all 100 local jobs have been created. Global sales of Picato® were around US$76 million in 2017.

**Results and Trials**

Parsons and his team established that ingenol mebutate was a potent protein kinase C activator, a key cellular enzyme. Suhrbier and his team illustrated that ingenol mebutate induced necrotic cell death in cancer cells. This research identified ingenol mebutate as a 'first-in-class' drug, which opened the way for a new family of drugs. The combined QIMR Berghofer work resulted in eight additional patents for different applications of the ingenol mebutate, and numerous scientific papers.

Over 290 research articles have now been published on ingenol mebutate around the world (source: PubMed). Parsons continues to research other potential compounds in this class and how they mediate their anticancer activities.

Further safety and efficacy tests were commissioned by Peplin to progress the development of a mediation. These tests had to be done offshore and were expensive, depleting investment funds. Some of Aylward’s team’s research was restricted during this time due to funding gaps.

After a number of years to wait for securing funding, Peplin was able to begin clinical trials in 2004. The first Phase III trials were completed in 2009, just prior to the company’s acquisition by LEO Pharma.

**Health Outcomes**

Picato® was approved by the US FDA and the European Commission (EC) in 2012, and the Australian Therapeutics Goods Administration (TGA) in 2013. In Australia, Picato® is available under the Regeneration Pharmaceuticals Benefits Scheme (RPBS) or as a private script.

There is an expectation that treatment of actinic keratoses (sunspots) and field treatment (treatments of areas of sun-exposed skin with Picato®) will lead to a reduction in skin cancers. Other uses for ingenol mebutate against non-melanoma skin cancers, such as basal cell carcinomas, are now being actively explored.