

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 1997. 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 in the sap, and at the Queensland Institute of Medical Research (now QIMR Berghofer) at night, testing the separated chemicals for anti-melanoma activity in collaboration with a research team 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.



Euphorbia peplus (petty spurge, radium weed, cancer weed, or milkweed) is a species of Euphorbia, native to most of Europe, northern Africa, and western Asia, where it typically grows in cultivated arable land. Outside of its native range it grows widely, including in Australia, New Zealand, North America and other temperate and sub-tropical regions.

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:

- Prof Andreas Suhrbier, Research Fellowships, 2004 onwards; currently an NHMRC Principal Research Fellow
- Dr Steven Ogbourne, Industry Research Fellowship, 2002-2005
- Dr Sarah-Jane Cozzi, Industry Fellowship, 2007-2011.

Other grants and Investments

- Commonwealth Government AusIndustry START grants, 1999 & 2001
- Queensland Government ISUS grant, 2000
- Commonwealth Government COMET grant, 2000
- 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 \$130 million.

Commercialisation Journey

In 1998, Aylward's company, Peplin Biotech Pty Ltd, secured private investors via angel seed funding, then via venture capital funding in 1999.

Peplin listed on the Australian Stock Exchange in 2000. In 2004, Peplin submitted two Investigational New Drug Applications to the US Food and Drug Administration (FDA).

Danish company LEO Pharma acquired Peplin for A\$348.4 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 world-wide distribution. Since the start of sales of Picato®, at least 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 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.

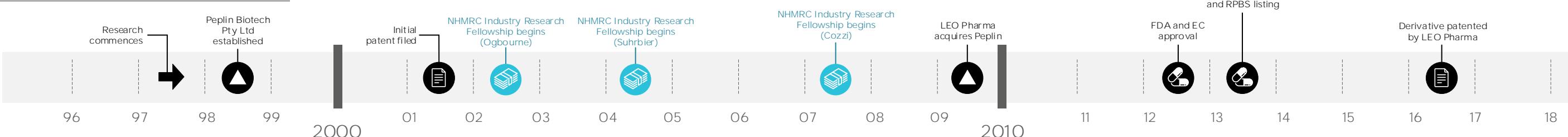
Further safety and efficacy tests were commissioned by Peplin to progress the development of a medication. These tests had to be done offshore and were expensive, depleting investment funds. Some of Aylward's team's research was restricted during this time due to funding gaps.

After a number of years of waiting to secure 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 Therapeutic Goods Administration (TGA) in 2013. In Australia, Picato® is available under the Repatriation Pharmaceutical Benefits Scheme (RPBS) or as a private script.

There is an expectation that treatment of actinic keratoses (sunspots) and field treatment (treating 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.



Dr Jim Aylward

Dr Aylward holds a PhD in Biochemistry from Monash University and worked in medical research labs in the US before joining CSIRO in 1998. He founded Peplin Biotech Pty Ltd in 1998, based on his own IP, which led to the development of Picato® gel. Dr Aylward has continued to help small tech startups in a mentoring capacity through iLab in Toowong (2004-2010) and the Mentoring for Growth program (Queensland Government). Dr Aylward was joint winner of the 2012 LSO Excellence award, in recognition of his contribution to the life sciences industry, and he was awarded the Clunies Ross Innovation Award in 2018. He is an inventor on seven US patents, four as Aylward et al.

Professor Peter Parsons

Professor Parsons holds a PhD in Organic Chemistry. He is the Group Leader of the Drug Discovery Group at QIMR Berghofer, and Honorary Professor, School of Medicine, University of Queensland. Professor Parsons has extensive knowledge and experience in preclinical drug development. His main research focus is prognostic markers in tumours, and on novel therapies for melanoma and other tumours. He has been a member and Deputy Chair of a national cancer grant review panel, and is a reviewer for a number of relevant journals. Professor Parsons now works with the QBiotics Group in research and development in the areas of oncology and wound healing.

Professor Andreas Suhrbier

Professor Suhrbier is Group Leader of the Inflammation Biology Group at QIMR Berghofer. He is a Principal Research Fellow with NHMRC and Adjunct Professor at Griffith University, James Cook University, and the University of Queensland. He has over 160 publications in the fields of virology, immunology and cancer therapeutics. Professor Suhrbier is an inventor on 18 patents: 12 have been commercialised; and seven cover various aspects and uses of Picato®. Professor Suhrbier has been a consultant for, and conducted collaborative R&D with, a number of local and international biotech and pharma companies, including Peplin (from 1999 to 2009) and LEO Pharma (from 2011 to 2012).

Dr Steven Ogbourne

Dr Steven Ogbourne is a Senior Research Fellow of Plant Biotechnology, University of the Sunshine Coast, with a background in plant science and molecular biology. Biodiscovery is his current research focus following his move into the field of drug discovery as a post-doctoral researcher at QIMR Berghofer and drug development and commercialisation as an employee of Peplin and LEO Pharma. Dr Ogbourne's research at QIMR Berghofer culminated with the identification of the natural product ingenol mebutate as the anti-cancer constituent in *E. peplus*. Dr Ogbourne now works closely with the Australian companies EcoBiotics and QBiotics, assisting with their discovery, development and commercialisation pipelines.

Dr Sarah-Jane Cozzi

Dr Sarah-Jane Cozzi is the Medical Scientific Liaison for Merck Sharp & Dohme (MSD) Australia. She holds a PhD in Pharmacology and a Master in Intellectual Property Law. Dr Cozzi's main research focus has been on the mechanism of action of PEP005, which has been published in several peer reviewed scientific journals and has led to the filing of a patent. Her commercialisation experience spans managing R&D projects at Peplin through to developing medical strategies for the launch of Picato® in Australia and New Zealand following the acquisition of Peplin by LEO Pharma. Prior to joining MSD, Dr Cozzi also worked in the Business Development team at QIMR Berghofer.