

# Company Update

MAY 2007



The Board of the Directors is pleased to provide an update on the exciting developments in drug discovery and product development that have been ongoing for the last year.

The view of the Company over this period was to focus on building solid scientific foundations that would support and enable a firm commercial move forward during 2007. Recent acceptance of three scientific presentations by the Scientific Board of the World Congress on Inflammation is testament to the validity and importance of the Group's recent work.

The Company through its Australian subsidiary Molecular Pharmacology Limited and its principle shareholder, Pharmanet Group Limited (which is referred to in this document as 'MPL Group' or 'the Group'), conducts a drug discovery and product development program.

We can now state with confidence that the MPL Group is an independent drug discovery entity, utilising a proven and approved anti-cytokine product platform in the creation of multi-level product pipelines focused on diseases and conditions involving inflammation, pain and secondary injury cascades.

This statement encapsulates almost 3 years of intensive scientific vigor and explains where the Group is and where it is heading. The Group is focused on an area of pharmacology dedicated to managing inflammation, pain and the body's reaction to injury, which in the view of the Group are key commercial development fields.

Over the last year the Group has worked with the Australian regulators to bring current production methods to full international GMP standards prior to reintroducing ThermaLife to the market and then expanding those markets into Asia, Europe and the USA. The Group is in discussion with Asian distributors and has engaged regulatory consultants to assist in gaining European and later USA product registration.

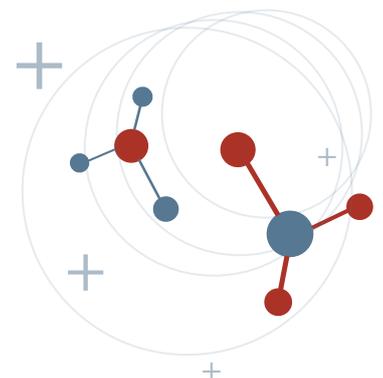
The MPL Group has been working on a new, more refined product with the trademark of SAVANTAC™, which is a more potent and effective formulation. This will enter the regulatory approval process in 2007.

In addition to the product push, the Group has been active in both Europe and USA in the field of new indications, with special focus on the cosmetic and non-therapeutic fields. These areas offer considerable business potential due to the ease with which market approvals can be established.

The MPL Group has achieved success in the fractionation of the parent compound. Discussions are on-going with a number of major US and European pharmaceutical companies, interest has been expressed, and discussions are progressing for the rights to licence the single identifiable molecules that are responsible for highly effective biological activity.

Finally, we are pleased to be able to provide shareholders with a summary of the non-confidential scientific file describing the recent scientific accomplishments achieved by the MPL Group in human medicine.

Jeffrey Edwards  
Director



# The MPL Group has focused on growing its strength in 5 strategic fields:

## Safety and Efficacy

The MPL Group's technology platform has in excess of 18 years unblemished safety and efficacy record. Safety and efficacy are the two most critical aspects in mediating risks in new drug discoveries.

## Molecular Size

The MPL Group is focused on building upon its small antibody-like fragment platform in all its proprietary drug and product portfolio developments. Working in the small molecule field provides the key benefits for rapid action, localized effect and allows the MPL Group to target opportunities in the Prescription (Rx), OTC and Cosmetic/Aesthetics markets.

## Pharmaceutical Pipeline

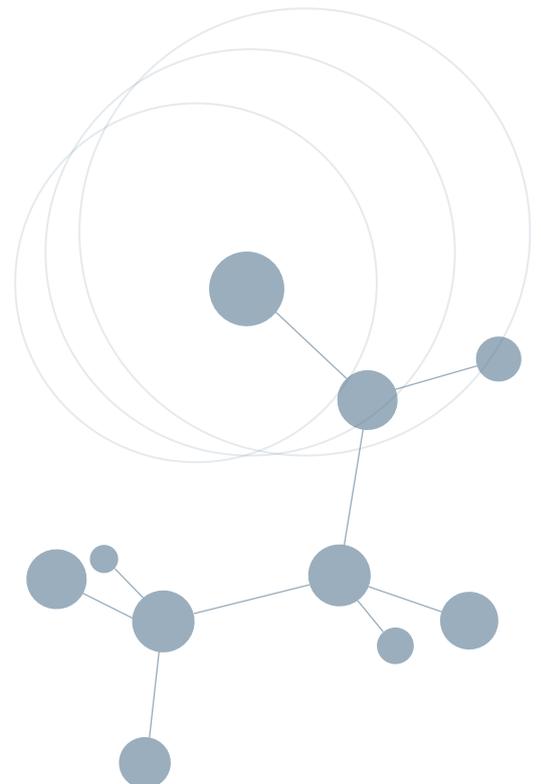
The MPL Group's drug discovery pipeline continues to expand as refinements in production processing, expansion in intellectual property and increased sophistication in testing and isolation grows the pharmaceutical ingredient and product pipelines.

## Cosmetic Pipeline

Developing specialized extracts for cosmetic and aesthetics markets has allowed the MPL Group to create a new and distinct cosmetic pipeline with multiple biological benefits. These actions provide a wider range of consumer-focused benefits ranging from anti-photo-aging, post-resurfacing treatments and post sun products, all with global market potential and low regulatory hurdles.

## Approvals

Existing product approvals in Australia allow the Group to manufacture and distribute high value added products in Australia and in near-Asian neighbors, as soon as novel packaging and labeling is completed. In addition, these existing approvals provide regulatory pathway short-cuts for opportunities in new therapeutic fields and indications Furthermore, the current approvals allow for rapid clinical trialing for new commercial opportunities in Europe and the USA avoiding the need for additional pre-clinical programs.



# A new generation of low cost, topically deliverable antibody-like therapeutic products

Antibodies have been the focus of medical and pharmaceutical research for several decades because they are part of the body's natural defense mechanisms and are highly specific in their actions. However, manufacturing antibodies for drug use is a complex and costly process, which has resulted in the current round of antibody-based drugs being amongst the most expensive medicines known to date.

Apart from cost, the other great challenge facing developers of antibody-based drugs has been deliverability. Antibodies are large and complex proteins, which can only be administered by slow infusion directly into the bloodstream. This dramatically increases both cost and risk of administration and can result in large amounts of regular unproductive time.

The protein-protein interaction between antibodies and their targets are not restricted to just diseases. Molecules which bind to multiple targets are in constant use to shuttle molecules around the body via the bloodstream. These binding proteins have the potential to be harnessed in exactly the same way as antibodies, as a treatment for a broad range of diseases and disease-causing molecules.

The MPL Group has focused on antibody-like protein fragments for some time and has developed a novel drug development platform and pipeline based on these proteins.

In order to overcome the delivery problems usually associated with

Adaptation of antibody-like protein fragments into drug formulations has enormous clinical and commercial potential.

large and complex antibodies, the scientific team focused on a range of topically deliverable protein fragments with specific biological activities.

The Group creates its antibody-like fragments by specifically cleaving well established food-chain plasma proteins using a proprietary and patented process that provides both high yields and low production costs.

The antibody-like fragments have now been studied for their specific biological activities and have yielded an impressive range of cytokine-specific Intellectual Property (IP).

- TNF- $\alpha$  antagonism

Some 40 different receptors and enzymes mediation properties have been identified to date, including, but not limited to:

- Inhibition of TACE
- Caspase inhibition
- Cox-1 and Cox-2 inhibition
- Bradykinin antagonism
- Cannabinoid receptors
- Chemokine CCR receptors



These same biological mechanisms are associated with a number of commercially important sectors in which the topical delivery route of active ingredients derived from the platform provide a sustainable competitive advantage.

- Arthritis and Joint Degeneration
- Inflammatory Skin Disease
- Cosmetic and Aesthetic Surgery
- Musculo-skeletal Pain and Inflammation
- Photo-damage and Photoaging
- Peripheral Neuropathies

## Deliverability

While antibodies usually face challenges of high manufacturing cost and patient unfriendly delivery routes due to their complexity and molecular size, the antibody-like fragments of the MPL Group are relatively small and stable molecules that can be manufactured using standard pharmaceutical processing techniques.

Our small antibody-like fragments are applicable to a wider than usual application base that includes through-the-skin delivery, local targeting, non-systemic applications as well as potential applications in oral and subcutaneous administration.

The potential of transdermally delivered antibody-like protein fragments creates a broad range of therapeutic and commercial possibilities in the over-the counter treatments across the cosmetic as well as therapeutic markets.

## Safety

A number of years ago, the Group made the decision to utilize plasma proteins that were an established part of the normal human food chain. This was a critical decision, as it implies a high level of intrinsic compatibility and safety in humans.

However, the most compelling evidence of long term safety and efficacy in humans come from the very first product, which has now been successfully marketed as a pharmaceutical product in Australia for over 18 years. This topically applied OTC product is approved for the temporary relief of arthritic and muscular pain and inflammation and has an unblemished safety and efficacy record. As the antibody-like fragments are extracted and refined from the same protein source, the Group has good reason to have a high level of confidence that clinical safety and efficacy will emerge as one of the primary benefits of all products and processes of the MPL Group.

## The Future

Globally, billions of dollars have been expended in the research of antibodies and means of production and delivery. A number of highly successful drugs have emerged over recent years which has made antibody-type drug discovery an attractive space for product research and development.

The MPL Group is determined to lead the development of high volume, medium value drug products targeting global and expanding unmet medical needs with a family of antibody-like fragment therapeutics. The MPL Group has the technology, the intellectual property, the scientific lead and the ambition to make this a reality.

# TRIPEPTOFEN SCIENTIFIC FILE

The MPL Group is utilising a market proven and registered over-the-counter product as a low risk development platform for the creation of a multi-level product pipeline focused on diseases and conditions involving inflammation, pain and the secondary injury cascade. When originally conceived some 18 years ago, the then current scientific view was that the original topical analgesic and anti-inflammatory product provided relief from arthritic and muscular pain due to the rare elements used in its production. With the benefit of modern science, we now understand that the biological interactions that underpin the efficacy of the original product are far more complex than envisaged and from this knowledge has evolved new and exciting anti-cytokine and secondary injury mediation processes.

The Group has spent the last 3 years researching these underlying biological mechanisms, designing novel extracts to produce the same biological activities, and devising strategies for widening the therapeutic applications of current products. These activities have resulted in a broad IP platform, suitable for protecting the current advanced pipeline, as well as the novel active ingredient projects.

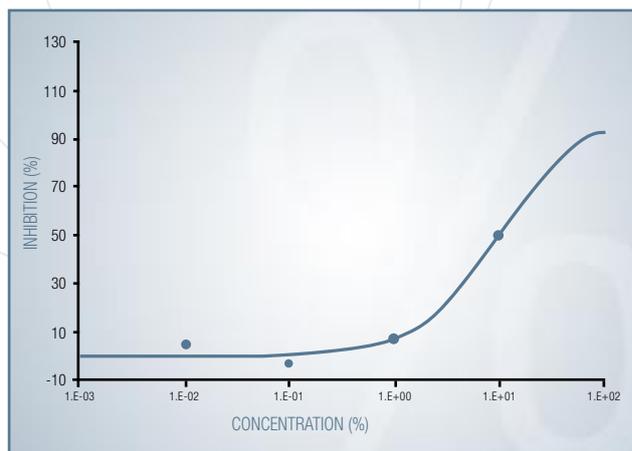
## TNF- $\alpha$ - antagonism

### Summary

TNF- $\alpha$  - Tumor Necrosis Factor alpha is one of the most commercially significant targets in the management of inflammation and inflammatory disease. The scientific data, provided by internationally respected research organisations, have shown that the drug development platform of the Group inhibits the binding of TNF- $\alpha$  at very low concentrations, which makes it an ideal candidate for products and new molecular entities targeted at rheumatoid arthritis, lupus, inflammatory bowel disease, and inflammatory skin diseases.

Antibody-like agents, such as MPL-104, can reduce the levels of this pro-inflammatory cytokine and subsequently the production of IL-1b (interleukin-1b) in rheumatoid synovial cultures along with many others. As TNF- $\alpha$  is known to stimulate apoptosis (programmed cell death) agents such as MPL-104 provide the pharmaceutical industry with a highly localised and high value anti-apoptotic agent.

The development of topically deliverable and locally acting antagonists of TNF- $\alpha$  represents an important strategy for the MPL Group. Applications are currently being researched in the areas of rheumatoid arthritis, lupus, inflammatory bowel disease, psoriasis and other inflammatory skin diseases.



## Background

The parent formulation from which the new molecular products are being derived is known as Thermalife. Thermalife has been on the Australian market as an over-the-counter medication for the topical and temporary relief of arthritic and muscular pain for more than 18 years. Its primary competitors are topical NSAID's, which account for sales of approximately US\$1 billion per annum worldwide.

Thermalife's safety and efficacy has been established in several open and controlled clinical studies, animal as well as human safety studies, spontaneous consumer reports and a near total absence of recorded adverse side effects. The safety plus efficacy of Thermalife provides a solid basis for a new drug development platform.

## Activity

The results set out below, represent an executive summary of some of the biological activities that have been modulated by candidates from the antibody-like protein fragments.



## Inhibition of TACE

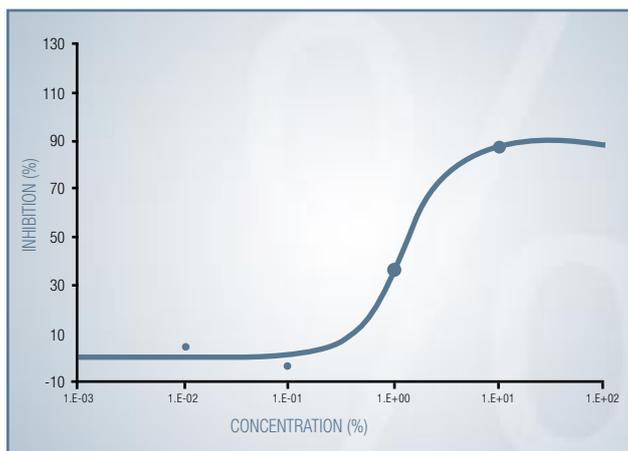
### Summary

TACE is a converting enzyme necessary for the release of pro inflammatory components. The ability to inhibit TACE at concentrations as low as 1.3% makes the specific development candidate a potentially important new topically deliverable mediator for inflammatory and post-injury processes in both the therapeutic and cosmetic applications.

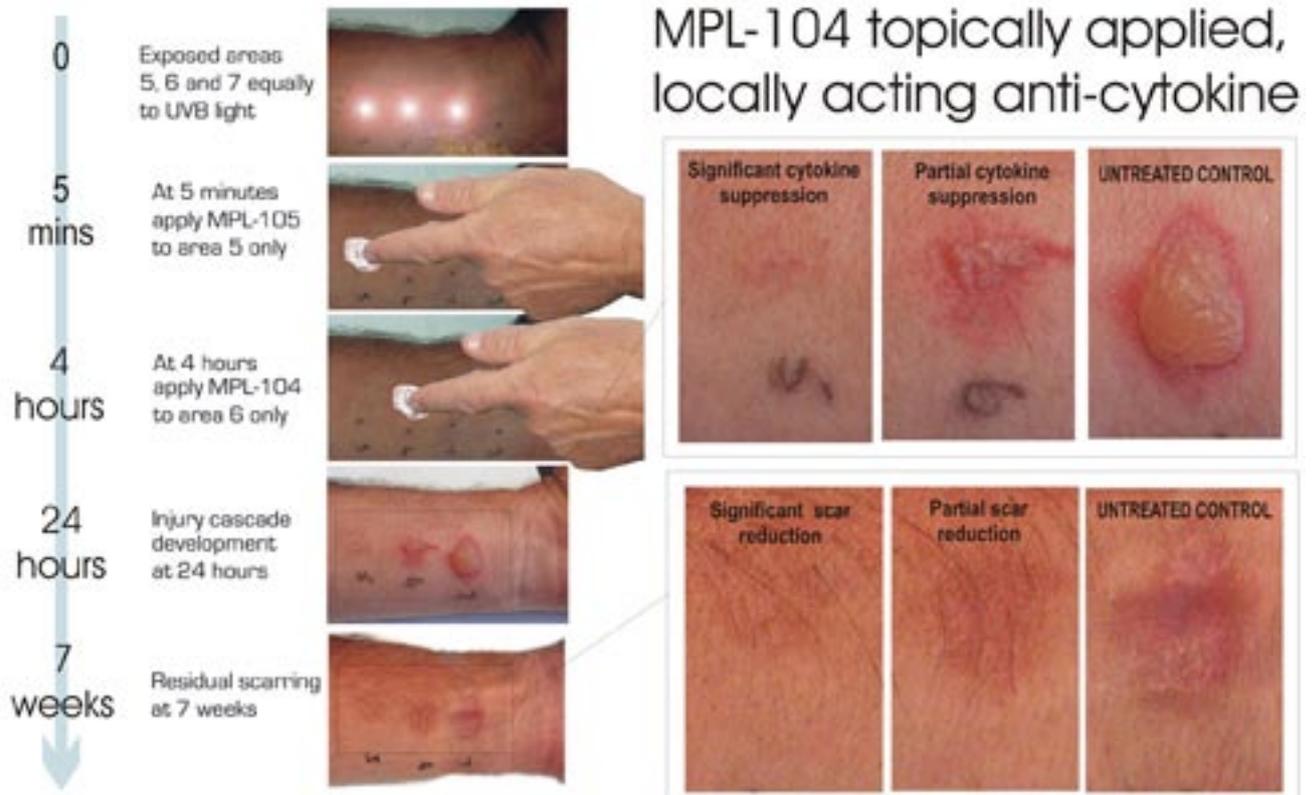
TACE, or TNF- $\alpha$  converting enzyme, belongs to the family of metallo-protease disintegrins (also known as ADAM or MDC family), essential for the release of membrane-bound pro-TNF- $\alpha$ .

TACE is also required for the activation of the receptor for the epidermal growth factor (EGFR) in vivo and for the development of tumors in nude mice, indicating a crucial role of TACE in tumorigenesis.

A direct measurement of human TACE activity in human recombinant insect Sf21 cells revealed inhibition of TACE activity with an IC50 of 1.3.



One candidate from the MPL Group drug delivery platform was found to inhibit binding of TNF- $\alpha$  to its receptor as assessed with human U937 cells. For those technically minded, the Ki is 7.2% (IC50: 10%).



## Caspase inhibition

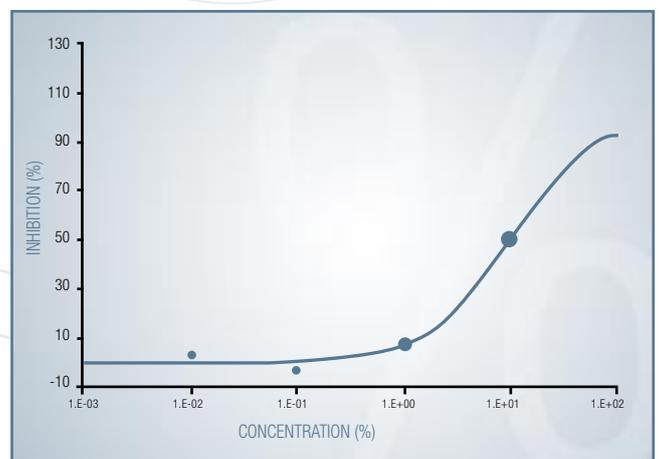
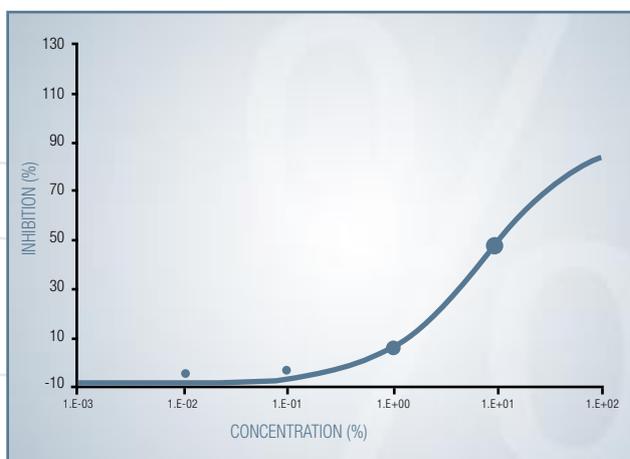
### Summary

CASPASES are a family of enzymes implicated in the destruction of otherwise healthy cells surrounding an injury. Apoptosis as this is referred to, is an important area for the Group, especially in applications such as photo-aging and post-injury therapeutics.

There are thirteen members of the human caspase family, with a number being involved or associated with mediating apoptosis.

Apoptosis is a cellular response to an event such as UV light, chemical or physical damage or a viral infection. This insult initiates a cascade of events which lead to the destruction of the surround, but as yet uninjured cells. This excessive cleansing is often called "programmed cell death".

Apoptosis is believed to be an innate response designed to limit the potential for injury transmission into surrounding healthy tissues. Exaggeration of apoptosis causes excessive or unwarranted tissue-damage. Hepatitis, insulinitis, graft-versus-host disease, and allergic encephalitis are all diseases in which excessive apoptosis plays a considerable role.



In vitro studies have shown inhibition of human Caspase 1 at an IC50 of 8.1%. Caspase 3 inhibition was observed at an IC50 of 2.8%. The Caspase 9 was inhibited 57% at 10%.

# Cox-1 and Cox-2 inhibition

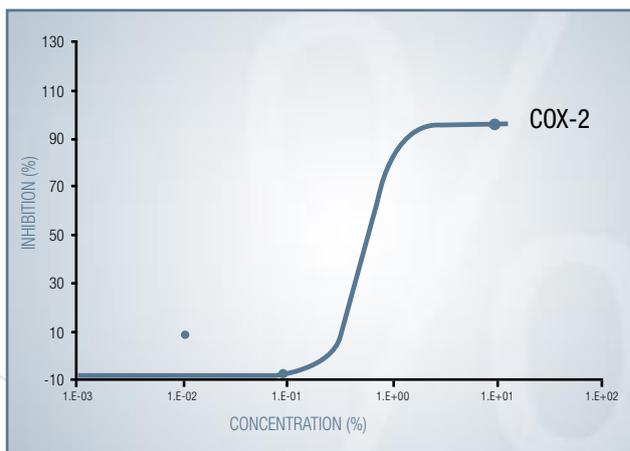
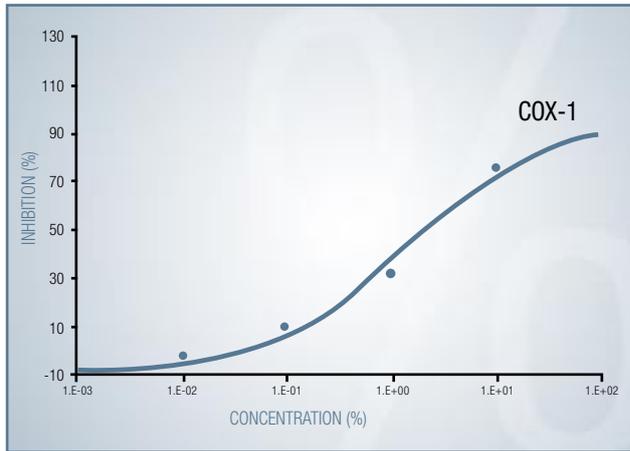
## Summary

COX-1 & 2 inhibition is possibly the best known and effective anti-inflammatory therapy, however, gastrointestinal side effects have seen oral products such as Celebrex and Vioxx, come under considerable safety concerns.

Topically delivered Cox 1 & 2 inhibitors, such as in the Group's platform, are expected to provide unique commercial opportunities.

Cyclooxygenases (Cox-2, Cox-1) inhibitors are amongst the most recognised of all anti-inflammatory agents. Gastrointestinal side effects of Cox inhibitors are blamed for roughly 100,000 hospitalisations and 15,000 deaths each year in the United States alone. Therefore Cox-2 inhibitors, like celebrex and vioxx rapidly overhauled the non-selective Cox-inhibitory, like aspirin. However in late 2004, a major trial on long term treatment found that almost twice the subjects who took vioxx for eighteen months had strokes or heart attacks than subjects on placebo. Vioxx was immediately withdrawn from the market.

Inhibition was found in human platelet cyclooxygenase-1 (Cox-1) with an IC50 of 1.4% and the cyclooxygenase-2 (Cox-2) at 0.68% concentration

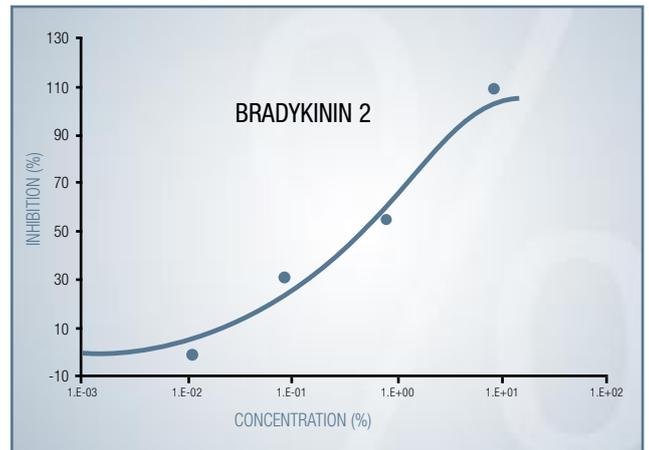
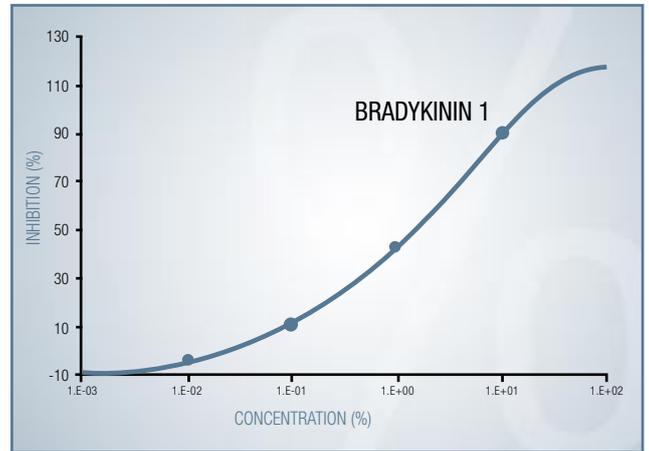


Potent COX inhibition offers the promise of reduced side-effects, local activity and an avoidance of systemic action.

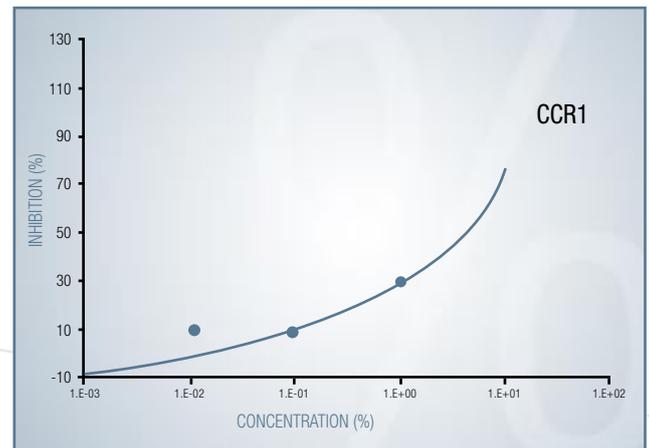
# Bradykinin antagonism

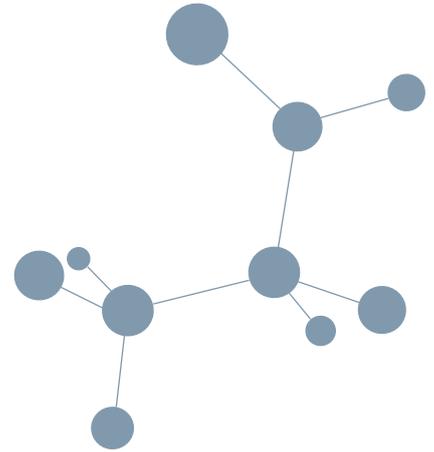
## Summary

Bradykinins are proinflammatory peptides involved in numerous vascular and pain responses following injury. It is this activity when combined with other non-diclofenac activities, that is believed to provide much of the fast acting analgesic properties. Commercial applications include local neurological and pain responses, blunt trauma, neurological deficit and in inflammation-induced secondary damage.



Binding to the human bradykinin 1 receptor was analysed by competition with binding which was found with a  $K_i$  of 0.22% (IC50: 0.85%). Binding to the human bradykinin 2 receptor was a  $K_i$  of 0.41% (IC50= 0.69%).





## Other Studies

Other studies including Free Radical Scavenging are of particular relevance to the Group's cosmetic interests. The use of small molecular structure with local deliverability provides significant competitive advantage in the cosmetic and non-regulated anti-aging markets.

A 94% free radical scavenging activity was observed in ABTS-H2O2-Peroxidase system generation (inhibition), which is encouraging to the cosmetic and aesthetics development activities.

## MULTIPLE BIO-TARGETS IN COSMETICS

The Group has been active in developing a novel 3-way TNF – TACE - MMP inhibitor for treating aging and photodamage within the cosmetic and aesthetic industries.

The Group's scientific team is especially excited about recent developments that showed that combinatorial inhibition of TNF- $\alpha$ , TACE and MMP creates considerable promise and potential within the cosmetic sector.

TNF- $\alpha$  and TACE inhibition can reduce inflammation, erythema (redness) and block the accumulation of extracellular fluids. MMP or matrix metallo-proteinases are a family of enzymes that are responsible for the breakdown of extracellular matrix components such as collagen, laminin and the structural and elastic components of the skin. Collagen destruction and degraded proteoglycans are features of multiple aging processes. By combining these biological effects in one product, a new active cosmetic ingredient is created well suited to the serum, cream and foam markets.

The exciting potential in the cosmetic and aesthetics fields has already created some commercial interest even though the MPL Group has not actively promoted or presented its new discoveries to the industry. Initial interest has come from USA based cosmetic and product distribution companies and from Europe where interest in licensing the Group's active ingredient has emerged.



## GLOBAL COMMERCIAL STRATEGY

The MPL Group product and technology development programs have moved to a more global footing with activities now in the USA, Germany, Australia, and South East Asia.

The international scientific focus is now supported by an equally important global commercial strategy which has been gaining momentum particularly in Europe under the direction of Dr Lucio van Rooijen.

Dr van Rooijen, who leads van Rooijen & Partners of Munich and London, is a specialist pharmaceutical consulting group and is assisting the Group with its presentations, negotiations, collaborations and potential out-licensing opportunities with a number of major European pharmaceutical companies.

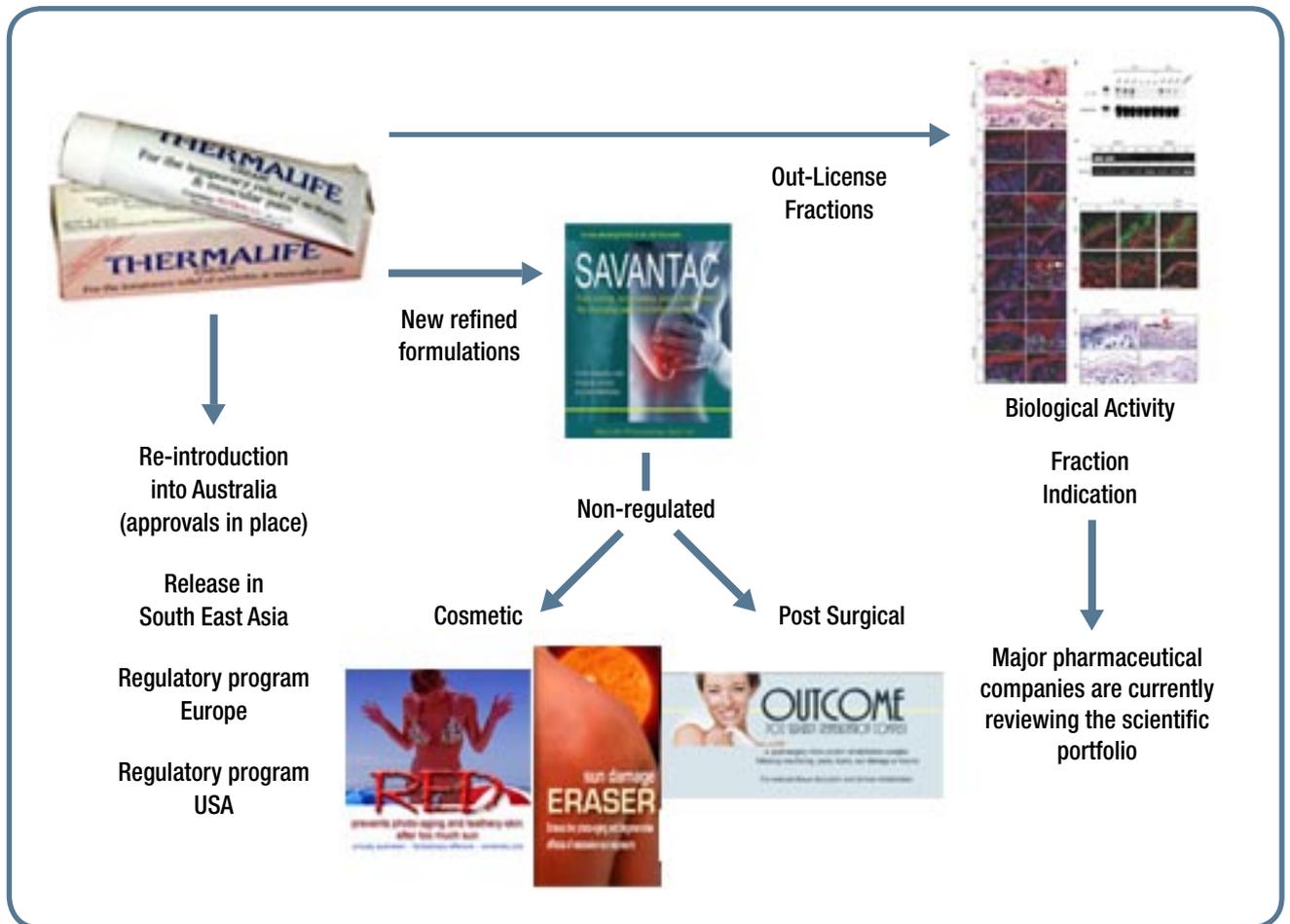
The MPL Group of companies are clearly focused on products, drug development and cosmetic opportunities that target diseases, conditions and processes involving inflammation, pain and secondary injury cascades.

## BUSINESS STRATEGY

- Marketing and sales of current OTC registered product in Australia, expanding into Asian region.
- Short-term market submissions for Europe utilizing existing OTC product approval status in Australia
- Developing new indications for the existing approved product and derivatives in areas of topical inflammation, pain and injury mediation
- Partnering new development opportunities in locally deliverable anti-cytokine compounds, complexes and fractions derived from the parent product
- Out-Licence rights to isolate and patent single molecular entities



# PRODUCT STRATEGY



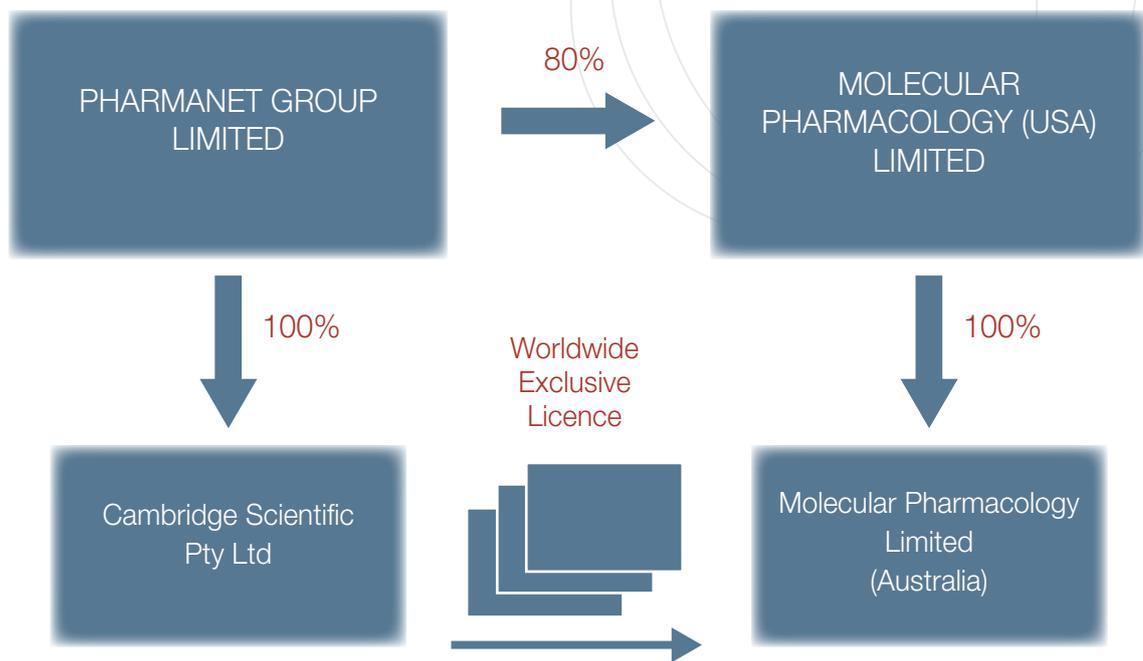
## SUMMARY OF CORPORATE OBJECTIVES

- To utilize existing approvals in Australia and Asia to generate revenues
- To utilize existing approvals and registrations to enable the clinical programs necessary for early entry into the European and US markets
- To utilize existing approvals to expand into new Rx indications
- To develop a range of OTC and professional cosmetic and non-therapeutic products
- To out-licence the fractionation and isolation opportunities for unique patentable entities

# CORPORATE STRUCTURE

Molecular Pharmacology (USA) Limited's wholly owned subsidiary Molecular Pharmacology Limited, Research and Development division is located on the west coast of Australia.

Through its Australian subsidiary, MPL-USA holds a worldwide exclusive licence to develop and commercialize analgesics and anti-inflammatory products for worldwide sale.



This licence was issued by Cambridge Scientific Pty Ltd, a wholly owned subsidiary of PHARMANET Group Limited – Molecular Pharmacology (USA) Limited's largest shareholder.

The close working relationships and their common interests allow for mutual co-operation in ensuring that all necessary steps are in place to achieve commercial success.



# WORLD CONGRESS ON INFLAMMATION

Molecular Pharmacology (USA Limited) announced that progress in its drug discovery program collectively operated by its Australian subsidiary Molecular Pharmacology Limited and its principle shareholder, Pharmanet Group Limited, ("MPL Group") will be presented at the 8th World Congress on Inflammation in Copenhagen in June 2007.

Invitations have been received from the Scientific Committee of the World Congress to present three separate scientific papers on developments of the company's licenced topical anti-cytokine and anti-inflammatory drug developments.

The World Congress on Inflammation is the premier scientific forum for new discoveries in inflammation control and management. To have three papers accepted at such a prestigious forum provides a strong endorsement of the scientific quality of the company's drug discovery program.

The three papers to be presented in Copenhagen in June 2007 cover the management of sun-damage and photo-aging using the Groups topical anti-cytokine complex, the reduction of pro-inflammatory cytokines in human monocytes using the Groups Zn-plasma protein complex and the influence of the Group's patented trace element complex on managing pro-inflammatorily cytokines in arthritis.

The three papers to be presented at the World Congress represent only a small part of the Group's recent progress in the development of its proprietary Tripeptofen drug development platform. The public release of this new data in Copenhagen has only recently been made possible by completion of the company's expanded Intellectual Property program.



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