

# PHOSPHAGENICS

## NEWSLETTER | DECEMBER 2007

PHOSPHAGENICS LIMITED  
ABN: 32 056 482 403

## r & d update



**Dr Esra Ogru,**  
Executive Vice  
President of Research  
& Development

Dear Shareholders,

As Executive Vice President of Research & Development, it is my pleasure to update you on our research activities so far for 2007.

As we have advised throughout the year, our technologies have brought about significant opportunities in the pharmaceutical market, which is what this newsletter focuses on.

At present we have three clinical trials in progress: a Phase 2a transdermal insulin trial, a Phase 1 transdermal oxycodone trial and an oral Phospha E<sup>®</sup> Phase 2 trial – refer to pipeline on page 3.

During the year, with the recruitment of additional scientists, we accelerated our Research & Development (R&D) program, resulting in the achievement of several major milestones, particularly with our TPM technology for both transdermal (through the skin and into the bloodstream) and local topical applications.

On page 5, I introduce and welcome our new appointments to the R&D team. These scientists will play a major role in reaching our objectives.

### TPM Technology

Phosphagenics' delivery technology, TPM, involves the creation of vesicles - or "bubble" like particles - that can entrap compounds within their core.

Due to the unique properties of our technology, i.e. the softness and malleability of the vesicles, the vesicles are able to pass through the upper layers of the skin and penetrate into the deeper layers.

By manipulating the size and characteristics of the vesicles, the vesicles rate of passage through the skin and depth of penetration can be controlled. Therefore, Phosphagenics can either localise delivery of compounds to the dermis (dermal delivery) or deliver drugs to the systemic circulation (transdermal delivery) – refer to figure 1.

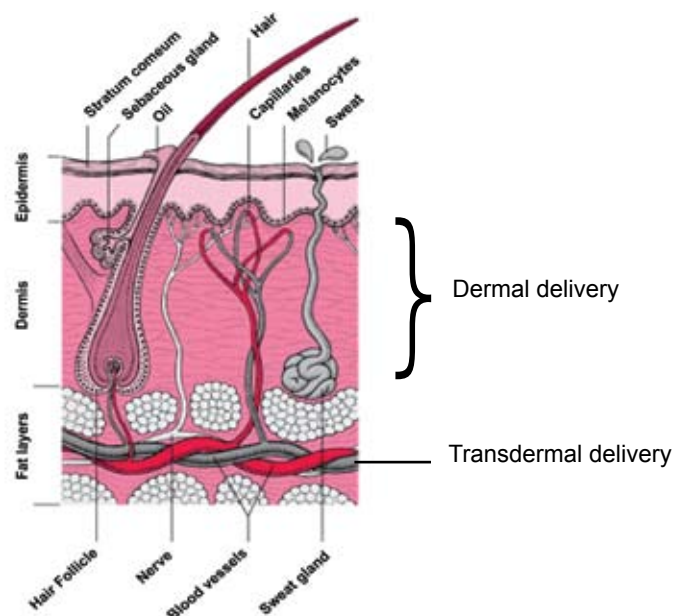
We believe this ability to target the delivery of actives makes our TPM technology unique in the global market.

With the increased number of formulation scientists at Phosphagenics, there have been a number of major breakthroughs in our ability to:

- Formulate a greater number of compounds;
- Administer formulations in gels, liquids, sprays and patch development is underway; and
- Precisely control the size of our vesicles.

*The ability to control vesicle size will play a major role in the extension of our TPM topical strategy as we plan several new clinical trials in 2008.*

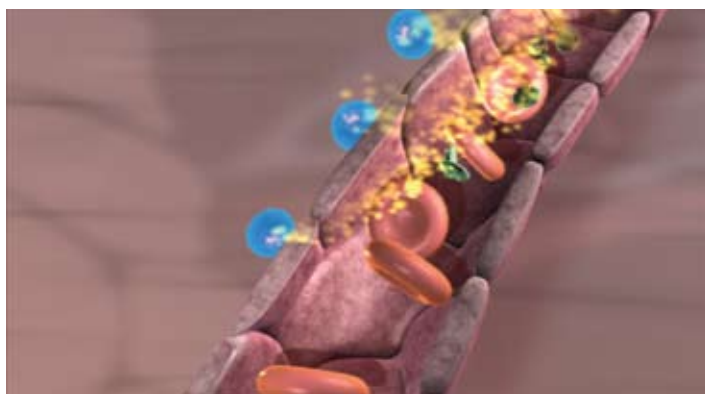
Figure 1 - Skin Diagram



## INSULIN

With the number of people with diabetes forecast to increase from 200 million today to 370 million by 2030, our transdermal technology, TPM, has the potential to transform the US\$7 billion insulin market by providing insulin-dependent diabetics with a non-invasive, effective transdermal alternative to the age old and invasive treatment of insulin injections.

To achieve this, we completed pre-clinical studies and conducted a Phase 1a clinical trial in 2006 that confirmed the safety and tolerability of our TPM and insulin formulation in delivering insulin into the bloodstream without adverse effects.



**A representation of three TPM insulin vesicles delivering insulin over a sustained period into the bloodstream.**

In May this year, we completed a Phase 1b double-blinded trial in 45 volunteers with an improved TPM formulation at the Royal Adelaide Hospital in South Australia. The results of this trial demonstrated a greater sustained effect in the reduction of all the parameters tested being blood sugar levels, endogenous insulin and C-peptide and also greater statistical significance than the Phase 1a trial – see results on page 3.

As mentioned, we recently began treating diabetic patients with our transdermal insulin formulation in a Phase 2a trial, which is scheduled to be completed during the first half of next year.

We are preparing an Investigational New Drug Application for the US Food and Drug Administration (FDA), which will enable us to continue clinical development in the US after the completion of our Australian trial.

We continue to collaborate closely with our medical advisers, Assistant Professor William Hsu from the Joslin Diabetes Center, Harvard Medical School, Texas, US, and Professor Thomas Rades from the University of Otago, New Zealand, to develop our insulin formulation and program.

## OXYCODONE

We recently commenced a Phase 1 clinical trial of our TPM oxycodone formulation. Oxycodone is a leading pain-management drug with worldwide annual sales of more than \$US1 billion. It is similar to, but more potent than, morphine and has less adverse effects. However, it is currently only administered as a tablet or injection.

This trial is expected to be completed during the first quarter, 2008.

Our aim is to become the first company to commercialise a sustained-release oxycodone patch for chronic pain sufferers.

## RETINOIC ACID

Pre-clinical studies have shown that our TPM technology can increase the penetration of retinoic acid, a leading anti-aging and acne treatment compound, into the dermis layer of the skin – refer to figure 1.

These studies showed that formulating retinoic acid with TPM achieved a three-fold increase in the level of retinoic acid delivered into the dermis, compared to retinoic acid alone. Additionally, studies have shown a reduction of skin irritation with TPM.

The aim and challenge of most dermatological and cosmetic products is to deliver an active ingredient, such as retinoic acid, past the upper skin layer, which is made up of dead skin cells, and into the active skin layer, the dermis, without the active entering the bloodstream.

These studies again highlighted TPM's adaptability to be formulated with many compounds to improve skin penetration and increase effectiveness.

We are now preparing a clinical program for retinoic acid, which is expected to commence in early 2008.

## PHOSPHA E®

Phosphagenics and Nestlé Nutrition (Nestlé) undertook two pre-clinical studies in 2006, which showed that Phosphagenics' Phospha E®, when given orally, significantly reduced many of the key biomarkers associated with metabolic syndrome.

Metabolic syndrome is characterised by a group of risk factors that increase the threat of diabetes, coronary heart disease and other diseases associated with plaque build up in artery walls, such as stroke.

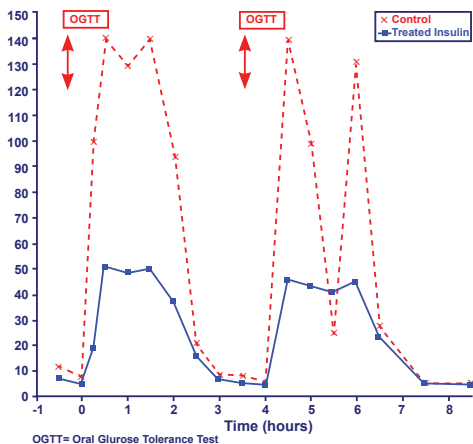
Based on these positive pre-clinical results, Nestlé is currently funding a Phase 2 clinical trial to establish the efficacy of Phosphagenics' Phospha E® in the management of metabolic syndrome.

## R & D PIPELINE

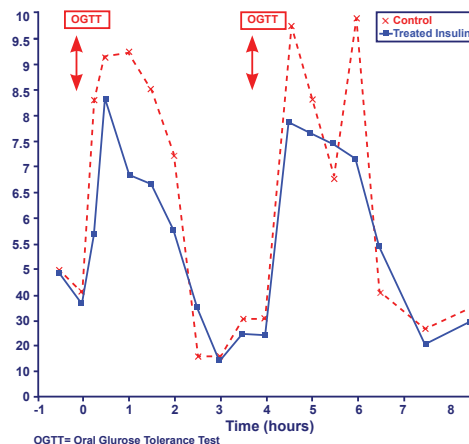
	Discovery & Research	Pre-clinical	Phase 1	Phase 2	Target Application
<b>Transdermal</b>					
Insulin	[Progress bar]				Diabetes
Morphine	[Progress bar]				Pain Management
Oxycodone	[Progress bar]				Pain Management
<b>Dermal</b>					
Retinoic Acid	[Progress bar]				Acne
<b>Oral</b>					
Phospha E®	[Progress bar]				Metabolic Syndrome
APA-01 + Statin	[Progress bar]				Atherosclerosis
GTP-0805	[Progress bar]				Cancer

The above table provides a summary of Phosphagenics' current R&D pipeline.

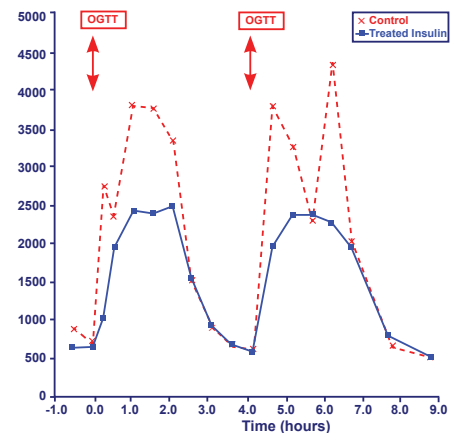
## KEY RESULTS: PHASE 1B INSULIN TRIAL



Mean Blood Endogenous Insulin Concentration vs Time



Mean Blood Glucose Concentration vs Time



Mean Blood C-peptide Concentration vs Time

## INTERVIEW WITH ASSISTANT PROFESSOR WILLIAM HSU

William C. Hsu, M.D., is a Diabetologist, a Clinical Investigator, an Assistant Professor of medicine at Harvard Medical School, the Director of the Asian Clinic and the Co-Director for the Asian American Diabetes Initiative at Joslin Diabetes Center, Harvard Medical School, Boston, US. His research interests focus on developing and applying novel medical technologies for the treatment of diabetes.

Dr Hsu's role on Phosphagenics' advisory board is to advise and assist with the development of our clinical trial programs in Australia and in the US.

**Q: What stage of development is Phosphagenics' TPM insulin at?**

**A:** Phosphagenics has completed Phase 1a and 1b clinical trials with its TPM technology, which showed that TPM can deliver insulin through the skin and into the bloodstream without causing skin disruption. Phase 2 clinical trials are currently underway.

**Q: Why was diabetes called a "Western epidemic" and what are the future trends for this disease?**

**A:** Diabetes used to be called a Western epidemic because the rise in new cases used to only occur in industrialised nations. Today, it is becoming a global epidemic.

It is estimated that more than 370 million people will have diabetes worldwide by 2030 and more than half of the new cases will come from the Asian region, especially India and China.

**Q: What are the current trends in delivering insulin to diabetics and where might a transdermal product like Phosphagenics' TPM insulin be appropriate?**

**A:** Insulin deficiency is a major defect in both type 1 and type 2 diabetes. While type 1 is a state of absolute insulin deficiency, those with type 2 can't make enough to keep up with the body's increased demand for more insulin. This condition is also known as relative insulin deficiency. If a person has type 2 diabetes long enough, he/she is likely to need insulin replacement.

One of the major barriers to starting insulin is the invasive nature of the delivery route. A transdermal insulin platform

will eliminate this major obstacle to insulin adoption, leading to better diabetes control and ultimately less diabetes related complications.

**Q: What do patients have to look forward to?**

**A:** Insulin will continue to serve important clinical needs and the market demands a non-invasive system that is safe, reliable and affordable, therefore, I believe the transdermal delivery of insulin is uniquely positioned as the next breakthrough.

## Sky News Interview



Dr Esra Ogru was interviewed by Sky News, covering Phosphagenics' development in the non-invasive delivery of insulin and pain-relief drugs through the skin.

## GOVERNMENT GRANTS

Phosphagenics' patented world-class technologies address areas of medical need, such as diabetes, metabolic syndrome and chronic pain.

*The Australian government awarded Phosphagenics a \$2.1 million AusIndustry Commercial Ready grant for its insulin program and a \$3.2 million Pharmaceuticals Partnerships Program (P3) grant in May and June 2007 respectively.*

## R & D TEAM: new member profiles

In the last 12 months, we have recruited five highly qualified and respected scientists to our R&D team to support our exciting R&D program and increased clinical activity, with three concurrent clinical programs currently underway.

Phosphagenics would like to introduce and welcome them to the team.

### **Dr Esther Apos - Pre-clinical Project Manager (Pharmaceutical) BSc, PhD**

Dr Apos has significant industry experience having worked as a senior Technical Quality Associate at CSL Ltd and as a Scientific Documentation Coordinator for Meditech Research Ltd.

Dr Apos joined the R&D team at Phosphagenics in November 2006 to formalise documentation systems and quality assurance procedures to enable the company to streamline its documentation practices with FDA guidelines.

In September 2007, Dr Apos was promoted to Pre-clinical Project Manager of the R&D team to help coordinate and project-manage key R&D programs within the pharmaceutical division.

*"I joined Phosphagenics to be part of an exciting and vibrant biotech company".*

### **Dr Sahar Bassal - Senior Regulatory Affairs Associate BSc, PhD**

Dr Bassal has held several senior post-doctoral roles in academia and industry. Her academic experience and training include fellowships at the USA National Institutes of Health, Peter MacCallum Cancer Institute and the Baker Heart Research Institute.

Dr Bassal's industry experience has focused upon the biotechnology sector with positions of responsibility in clinical trial management and regulatory affairs including a senior role with Johnson & Johnson Pharmaceuticals. She has developed a career in regulatory affairs with significant exposure to USA, EU, South African and Australian regulatory agencies.

### **Dr Jeremy Cottrell - Research Fellow BSc, PhD**

Dr Cottrell has extensive experience in the fields of physiology and metabolism having worked at the Victorian Department of Primary Industries as a Research Scientist, investigating the benefits of dietary selenoproteins on aged immune function.

Before this appointment, Dr Cottrell completed his Post-Doctoral Fellowship in 2005 at the Baylor College of Medicine, Houston, Texas, US, where he investigated intestinal adaptation and metabolism in the neonate.

During his time at Baylor, Dr Cottrell was the recipient of the Russell and Virginia McFarland award and the American Society of Nutritional Sciences (ASNS) Energy and Macronutrient Metabolism Post-Doctoral Fellow poster award at Experimental Biology, San Diego, US.

### **Dr Mahmoud El-Tamimy - Research Fellow BSc, MSc, PhD**

Dr El-Tamimy has more than 13 years experience in pharmaceutical research in several countries, specifically in the area of general and transdermal drug delivery.

Prior to joining Phosphagenics, Dr El-Tamimy played a key role at an Australian-based company that provides R&D development services in the area of percutaneous absorption to the pharmaceutical, cosmetic and veterinary industries.

### **Dr Reza Muzafari - Research Fellow BSc, MSc, PhD**

Dr Muzafari has more than 14 years experience in the areas of Nanobiotechnology, Micro- and Nanoencapsulation of bioactive material including peptide and nucleic acid-based drugs, cosmetics, nutraceuticals and controlled release of bioactive agents.

Dr Muzafari has published more than 70 scientific articles, four books, refereed numerous scientific papers and has presented as a key speaker extensively to the international scientific community in the fields of molecular biology, biomedicine, pharmaceuticals, gene/drug delivery and scanning probe microscopy.

# looking ahead



President & CEO - Harry Rosen

As mentioned, our R&D activities over the past year have been extremely exciting with three clinical programs currently underway.

We are now working towards translating these exceptional discoveries into commercial outcomes over the next 12 months, while continuing to explore the opportunities presented by our commercial strategy in the next wave of our R&D programs.

Our TPM technology has shown the ability to deliver drugs systemically (into the bloodstream) and to deliver drugs topically (localised) into specific areas of the body.

With the help of more than 20 scientists at Phosphagenics in Australia and around the world, we intend to continue to develop TPM with insulin and oxycodone as well as expanding our work in the local topical delivery market.

*In 2008, we aim to use the precision and efficiency of TPM to enhance the safe delivery of approved topical drugs to a localised site of action, while minimising exposure of the active to the systemic circulation – similar to our retinoic acid study.*

A number of leading topical products for the treatment of pain and inflammation are currently under investigation as well as products that have not previously been capable of topical delivery for these indications.

This suite of products will build on the impressive dermal delivery capabilities of TPM, which has also demonstrated successful results in the systemic delivery of both small and large molecules, such as insulin and opiates.

Phosphagenics sees that a portfolio of topically delivered products offers a number of advantages, including:

- Faster time to market compared to transdermal products delivering actives into the bloodstream;
- Relatively easier path to regulatory approval;
- A cost effective development program; and
- Significant markets and unmet needs.

In respect to our competitive positioning, the TPM platform offers opportunities to:

- Provide a more effective topical product;
- Reduce systemic exposure of the active;
- Provide a variety of dosage forms including gels, foams or sprays without comprising the effectiveness of the product; and
- Overcome issues of intolerance and dermal reactions presented by many topical therapies.

TPM's unique benefits support strong differentiation opportunities for selected products in their relevant market segments.

We look forward to the challenges and rewards that lie ahead and remain focused on the discovery of new and cost-effective ways to enhance the bioavailability, activity, safety and delivery of proven pharmaceutical and nutraceutical products.

