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## **Sementis Allergies:** A solution to food allergies

**Finally a potential quick and safe CURE for peanut  
allergy and other food allergies**



**sementis™**

# Disclaimer

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# Executive Summary



- Sementis is developing a safe vaccine that it believes could be a permanent **cure** for peanut allergy.
- There are estimated to be over 7 million peanut sufferers in the major markets of the U.S., Europe and Japan. This figure is expected to rise to well over 8 million by 2025. One third of these are estimated to have severe peanut allergy. <sup>(a)</sup>
- Delveinsight estimates that, for those major markets, the total cumulative market size of a successful peanut treatment over the seven years from 2018 to 2025 to be over \$US 65 billion. The 2025 yearly “run rate” is estimated to be over \$US 11 billion and rising thereafter. <sup>(a)</sup>
- The prevalence of food allergy in children in the emerging Asian economies (including China) has been rising and it is estimated that it is now comparable to that in Europe. <sup>(b)</sup>
- Sementis estimates that the worldwide estimate for a one off cure is a minimum of \$US 10 billion but likely close to the Delveinsight forecast. As Sementis’ solution is a cure and not a tolerising treatment course, a direct like-for-like comparison is not possible. <sup>(c)</sup>
- The science of a desensitizing cure is comparable for all other food allergies thus opening up the possibility of a vaccine cure for other food allergies. Other food allergies in terms of numbers and potential revenues are estimated to be around twice the size of the peanut allergy market. <sup>(d)</sup>

(a) Delveinsight, “Peanut Allergy – Competitive Landscape, market Insights, Epidemiology and Market Forecast – 2025. These numbers relate only to the U.S., U.K, Germany, France, Italy, Spain and Japan.

(b) World Allergy Organisation Journal 20136:21, “A global survey of changing patterns of food allergy burden in children”

(c) See Appendix 5

(d) JAMA Pediatrics 2013; 167(11):1026-1031.doic:10.1001/jamapediatrics.2013.2376

# Executive Summary Continued



- The potential cure is expected to be only a two or three step process (i.e. injections) over a few months. After that, the **cure** should be permanent and fortified by consuming peanuts at will.
- Theoretically, the **cure** should work in nearly all peanut allergic people. Proof of concept results are highly encouraging with results soon to be published in a peer reviewed science journal. Results from studies using immune cells isolated from blood of peanut allergic individuals (ex vivo) strongly suggest that the Sementis vaccine could be a **cure** in all allergic individuals barring a few that may not be responsive to vaccines in general. This is also confirmed in mice studies.
- It is expected that human trials will begin within the next 12 to 18 months.
- The Sementis solution is expected to be far superior to other processes in that it is designed to be a potential cure and not a tolerizing process.
- The tolerization processes can have relatively low rates of success compared with the expected results of the Sementis vaccine which is aimed at re-educating the immune system to be non-responsive to peanuts rather inducing transient tolerance to peanuts. The current method of toleration can take 18 to 24 months to complete and involves frequent clinical consultations and tests. The treatment is therefore expensive, can cause a lot of discomfort, time consuming and in some cases dangerous. Above all, the tolerization treatments are not a proven long time cure.

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# Sementis

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The Global Allergy Problem and Potential Revenue

# The Size of the Food Allergy Problem



## Houston – We have a problem!

When considering the U.S. alone <sup>(a)</sup>:

- Approximately 15 million people have food allergies of which over 3 million suffer from peanut allergy. 8 per cent of children suffer from food allergies and 30 percent of those suffer from multiple food allergies<sup>(a)</sup>.
- Food allergy prevalence among children increased by an incredible 50 percent between 1997-1999 and 2009-2011. The prevalence of peanut and tree nut allergy have more than tripled between 1997 and 2008 <sup>(a)</sup>.
- JAMA Pediatrics has estimated that caregivers would be willing to pay \$U.S. 20.8 billion annually (\$3504 per year per child) for food allergy treatment. Peanut was the most common allergy (28.7%). They concluded that “research to develop an effective food allergy treatment and cure is critically needed” <sup>(b)</sup>
- Every three minutes a food allergy reaction sends someone to the emergency room. Each year 200,000 in the United States alone people require emergency medical care for allergic reactions to food <sup>(a)</sup>. Adjustment to the way of life for affected children are particularly severe.

(a) Numbers taken from FARE Food Allergy Research and Education: Food Allergy Facts and Statistics for the U.S.

(b) JAMA Pediatrics 2013; 167(11):1026-1031.doi:10.1001/jamapediatrics.2013.2376

# The Size of the Food Allergy Problem



## The problem is global

- The problem is just as serious in Western Europe with an estimated 17 million suffering from food allergy.<sup>(a)</sup>
- Delveinsight estimates that for the seven markets of U.S, U.K. Germany, France, Italy, Spain and Japan there are around 7 million peanut allergy suffers in 2018 which is expected to grow to well over 8 million by 2025. Around one third of these have server peanut allergy.<sup>(b)</sup>
- Furthermore, the World Allergy Organization (WAO) reports that “In large and rapidly emerging societies of Asia, such as China,...the prevalence of OFC <sup>(a)</sup> -proven food allergy is now around 7 percent in preschoolers, comparable to the reported prevalence in European regions.” “Food allergy appears to be increasing in both developed and developing countries in the last 10-15 years” <sup>(c)</sup>
- Globally it has been estimated that there may be between 220 -250 million people that could be suffering from food allergy.<sup>(d)</sup> Peanut has been estimated to be around one third of total food allergies.<sup>(e)</sup> Unlike other food allergies, peanut allergy does not decline significantly with age.<sup>(f)</sup>

(a) European Academy of Allergy and Clinical immunology (EAACI), press release 13 October 2013  
(b) Delveinsight, “Peanut Allergy – Competitive Landscape, market Insights, Epidemiology and Market Forecast – 2025.  
(c) World Allergy organization Journal 20136:21, “A global survey of changing patterns of food allergy burden in children  
(d) World Allergy Organization, World Allergy Week 2013, 8-14 April 2013  
(e) JAMA Pediatrics 2013; 167(11):1026-1031.doic:10.1001/jamapediatrics.2013.2376  
(f) Elucidare, Food Allergies Worldwide, A population review, January 2011



# Potential Revenue



01

Delveinsight estimates that, for the major markets (U.S., U.K., Germany, France, Italy, Spain and Japan), the total cumulative market size of a successful peanut treatment over the seven years from 2018 to 2025 to be over \$US 65 billion. The 2025 yearly “run rate” is estimated to be over \$US 11 billion and rising thereafter.<sup>(a)</sup>

02

Sementis extremely conservative estimate of the worldwide market for a one off CURE is a minimum \$U.S. 10 billion (but likely to be close to the Delveinsight forecast). If most allergy sufferers take up the expected Sementis CURE as opposed to continual treatment with other solutions then the total market may be similar to the Delveinsight estimate.

03

Revenues for cures for other food allergies would be expected to be around twice that for the peanut market both in terms of the total market for a one of cure and new case per year.

04

The bottom line is that the size of the market for a simple one payment, two to three injection, permanent cure is in the 10s billions of dollars and would eclipse all the other complex, very expensive, time consuming, sometimes dangerous, often uncomfortable and certainly not totally effective partial solutions which likely will not last in the long term.

Appendix 5 outlines further detail on the revenue estimates.

(a) Delveinsight, “Peanut Allergy – Competitive Landscape, market Insights, Epidemiology and Market Forecast – 2025.



01

Aimmune has a market capitalization of \$U.S. 1.8 billion\*. It's product is in Phase 3 clinical trial and involves a long and potentially expensive treatment.

02

DBV has a market capitalization of \$U.S. 1.1 billion\*. They have just released Phase 3 trial results which did not meet expectations. It's product is also a long and potentially expensive treatment.

03

Astellas paid \$U.S. 300 million (January 2015) for the license for a DNA vaccine technology for human allergic diseases including Japanese Red Cedar pollen and peanut allergy.

04

AnaptysBio has a market capitalisation of \$ U.S. 2.2 billion

\* As of 18 December 2017.

(a) These companies are at different stages of development of their products, have different cash positions and some have other non peanut aspects of their business which make them not totally comparable on a like for like basis. Sementis for instance has an infectious disease aspect of its business.



# Sementis

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## The Science behind the problem and the solution

***Disclaimer:** the science behind the mechanism of allergy and desensitization is quite complex and involved but for the purpose of greater understanding by a reader with no scientific background it has been simplified to help deliver key take home messages.*

# The Science behind Allergies



1

The immune system of all healthy individuals reacts to food intake in a benign way that goes totally unnoticed in the vast majority of individuals. The normal type of the immune response that react to food is called a “Th1” response and is benign and harmless. The immune system has evolved this way because after all, food is a foreign “invader” and the immune system always react to invaders and evolution has made sure this response is harmless – otherwise we wouldn’t be here.

2

For whatever reason, in some individuals, particularly children, the immune system responds to the food “invader” in a different way. It “thinks” the food invader is a parasite. The immune system’s typical response to invasive parasites is to release biological chemicals in the vicinity of the parasite with the intention to kill by causing the parasite to go into anaphylactic shock.

3

These biological chemicals include histamines and with no actual parasite to kill, these chemicals turn back on the body end up causing an allergic reaction at low concentration and at high concentrations anaphylactic shock resulting in possible death.

4

This “parasite immune reaction” is known as a “Th2” immune response. This is a needed immune response when there is an actual parasite in the body but potentially disastrous when it reacts to proteins derived from food where these proteins that stimulate an allergic reaction are known as allergens.

5

It is not known for certain what causes the immune system to respond in this way or why the prevalence has been increasing over the past few decades. One popular theory is that it has to do with the developed world’s increasingly hygienic lifestyle.

# The Science behind the Solution



The Holy Grail for the desensitization to food allergens is to get the immune system to revert to the harmless Th1 response to food as it does in the vast majority of individuals.

As it happens, science has proven that the immune system responds to a live virus by initiating a Th1 response and where a Th1 immune response can tell a Th2 immune response to “stand down”. Th1 immune responses initiated by viruses will set up long lasting Th1 memory so that it is ready for when the virus re-infects. This is how regular vaccines work, such as measles, mump and rubella vaccines, by establishing long lasting Th1 memory to give you life long immunity to these diseases.

Using this proven knowledge, Sementis has inserted genes that make peanut allergens (i.e. peanut protein molecules) into its proprietary non-replicating (i.e. perfectly safe<sup>1</sup>) platform vector virus called SCV.

<sup>1</sup>So far only tested in animals with no antiviral immune response but the expectations are that it will be completely safe in humans with an uncompromised immune response and should be safe in humans with deficient immune responses.



# The Science behind the Solution



Sementis' peanut allergy vaccine has been designed so that upon vaccination the immune system will see not only the SCV-viral vector but also the peanut proteins made by the SCV and in doing so should create a Th1 immune response to both SCV and peanut protein made by SCV.

This induction of a peanut-specific Th1 immune response will tell a peanut-specific Th2 immune response to permanently "stand down" thus curing the vaccinated individual of peanut allergy and rebalance his or her immune response to appropriately respond to peanut proteins in a normal Th1 manner. Because there is memory associated with Th1 response this cure should last a lifetime where eating peanuts will actually fortify this memory response.

In effect, Sementis' peanut allergy vaccine should permanently "flip the switch" from a harmful Th2 to a non harmful Th1 response that is the norm for all non-allergic individuals. This is expected to work in every individual that has a functional Th1-based immune system, that is effectively anyone that can respond to regular vaccinations.

# Does Sementis' cure work?



Surprisingly, with the current scientific knowledge of how to create a cure to food allergies, no one has attempted to use viral vector vaccines as a solution to create a cure for food allergies, especially knowing that viral vectors are potent stimulators of the Th1 immune response.



Sementis' peanut allergy vaccine proof-of-concept studies use immune cells isolated from blood donated by peanut allergic individuals. They have shown that in every case, i.e., all samples taken from all the peanut allergic individuals that participated in this study, the vaccine is more than capable of “flicking the switch” from a peanut-specific Th2 to Th1 – no exceptions! These results are further backed up by studies in peanut-sensitized mice.



It is quite clear that the results from our peanut allergy vaccine studies, as expected, conform to the theory of desensitization to food allergens and thus may be used as a long term cure for peanut allergy.



Inserting genes in viral vectors in order for them to make proteins upon vaccination is not a new concept and has been around for 30 years now. The best example being the vaccinia based rabies vaccines where the smallpox vaccine was used as a vector for making a rabies protein upon vaccination. This vaccine was so successful it was used to eradicate rabies from the red fox population in the forests of Central and Northern Europe.

# Is it safe?




Sementis viral vector platform is a non-replicating virus, a genetically modified variation to the very same smallpox vaccine used to eradicate rabies in Europe. Being non-replicating, it is expected to be extremely safe and can cause no harm by repeated vaccinations (backed up by our safety studies in mice<sup>1</sup>).



The SCV peanut allergy vaccine cannot itself cause an allergic reaction as repeated vaccination of sensitized mice has shown. This is because the immune system will always default to a non harmful peanut-specific Th1 immune response when exposed to a virus even when given to an individual already allergic to peanuts.



Treatment with the Sementis vaccine should only take a couple of vaccinations until a clear cut peanut-specific Th1 immune response can be measured from blood samples. Thus, individuals who do not respond to the vaccine can be advised to keep avoiding peanuts as usual or the vaccination dose can be increased until they show a response to the vaccine. Once a treated individual shows a response to the vaccine then they should be able to safely eat peanuts at will without fear of allergy reaction or anaphylaxis.



The Sementis vaccination solution to curing allergies will be highly cost effective compared with the current tolerization methods that require 18-24 month treatment course and regular visits to the allergy clinic.

<sup>1</sup> So far only tested in animals with no antiviral immune response but the expectations are that it will be completely safe in humans with an uncompromised immune response and should be safe in humans with deficient immune responses.



# Sementis

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Competing Solutions

# Competing Solutions - Sementis is Unique



There are many other competing solutions but **Sementis is one of two companies developing a true vaccine that will potentially result in a life long cure with a vast majority of the sufferers expected to be cured<sup>1</sup>**



**Avoidance and Epinephrine Auto Injectors** are a common practice but these are not cures or even temporary cures



**Desensitization Therapy** is one of the most common approaches being investigated by companies. Sementis is of the view that these approaches are lengthy, costly, high maintenance, have safety issues and most important of all, are not a long term solution.



**DNA Vaccines** are similar to the Sementis approach but Sementis believes that they are not very immunological and therefore are unlikely to work.



**Nanoparticles** are still in early stages but mainly aimed at reducing the risk of severe reactions as opposed to a cure



**Monoclonal Antibodies** treatment is aimed at preventing the severity of a reaction and is not a cure

Appendix 2 details the competing solutions

<sup>1</sup> As far as we know. The other approach is a DNA vaccine strategy.





01

There are a number of competitors using the various methods described. Some are at more advanced stages than Sementis

02

There are no known competitors using a live, but safe, virus to permanently switch the immune response.

03

That is, Sementis is the only company which may have a permanent cure which is easily and quickly administered.

04

Therefore even if others come up with some sort of temporary solution earlier than Sementis' cure, the Sementis potentially permanent cure should surpass all competitors

Appendix 3 outlines the competitors



# Sementis

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Looking Ahead

# The Next Steps for Sementis



Sementis' immediate goal is to prove the effectiveness of its peanut allergy vaccine by testing the vaccine in a Phase I clinical trial in peanut allergic volunteers. The aim of this study will be to test how much peanut a vaccinated volunteer can ingest after vaccination. Before starting a clinical trial the following will have to be performed:

- Manufacture a clinical batch of vaccine. First the manufacturing process will need to be developed and then validated before clinical batches can be made.
- Perform a toxicology study to demonstrate our vaccine will be safe to give to human volunteers (standard practice for all vaccines and drugs in development).
- Obtain ethical approval for the clinical trial protocol (standard practice for vaccines and drugs in development)

Trials will last for approximately 1 year, allowing for regular follow ups to demonstrate the long lasting effect of the vaccine. However conclusive results will be forthcoming shortly after vaccination by the first signs of no restriction on eating a full diet of peanuts.

Fundraising for the toxicology and clinical trial will be undertaken late next year on the success of the development of the manufacturing process. In the meantime it is intended to open discussions with other Pharmaceutical companies in order to ascertain whether partnerships are possible that will help fund clinical development activities.

It is possible that there will be a liquidity event following positive outcomes of the clinical trial.

A vaccine for cat allergy is also being developed and tested in preclinical proof-of-concept studies. It is possible that trials for this vaccine will also begin late next year.



# Sementis People

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Board, Collaborators & Advisors

## Paul Howley PhD

*CEO, Chief Scientist, Board Director, Co-Founder  
and Inventor*

Paul's scientific background is in the field of molecular virology, specialising in viral vector systems and vaccinology. Paul is the inventor of the Sementis SCV platform vaccine delivery technology and the vaccines in development. He directs and manages the vaccine development programs for Sementis, utilising his extensive knowledge, experience and networks in the areas of antigen design and discovery, proof of concept studies in animal models, GLP preclinical and toxicology studies, process development and cGMP manufacturing, regulatory affairs and first in man studies concerning live viral vectored vaccines.

## Maurice O'Shannassy B.Sc. MEc (Prelim)

*Non-Executive Chairman*

Maurice spent 25 years in the financial services industry in Australia and overseas. He held a number of CEO and CIO roles around the world for BlackRock and its antecedents prior to becoming CEO of BlackRock Australia. He currently holds a number of directorships in a variety of industries and not for profit organisations.



## Peter Wulff MSc

*Retired European Patent Attorney  
Non-Executive Director*

Peter has over 30 years experience in the biotech and pharma industry, especially vaccines and patents. Peter co-founded Bavarian Nordic, a biotechnology company listed on the Copenhagen Stock Exchange, developing vaccines for infectious diseases and cancer. He served as president and CEO from 1994 until the company had secured a large supply contract with the U.S. government for its MVA smallpox vaccine, Immvamune, in 2007. Peter has participated in several private placements, two IPOs, and a number of follow-on offerings. He also has extensive experience with investor relations and government relations in Europe, Asia, and North America. He is currently an Independent Consultant to the Biotech industry.

## Dr Glen Burgess MB BS FRACS

*Non-Executive Chairman*

Glen is an Otolaryngologist , Head and Neck surgeon. He is based in Melbourne Victoria where he is principal of Southern ENT, and Director of Monash Health, Snoring and Sleep Apnoea Clinic. He is a lecturer (adj) at Monash University Dpt of Surgery. He graduated from Monash University in 1988 and completed his FRACS - ENT Head and Neck surgery in 2000. He worked at Stanford University medical school before completing consecutive fellowships in Head and Neck Surgery at St Georges Hospital, London and Queens University Hospital Nottingham. He has been a medical consultant for the medical industry including time with Arthrocare , Smith and Nephew and Phonak. He is currently a director of Victorian Hearing. He has published papers on airway management, sleep apnoea and hearing loss. He is currently engaged in research in assessment and treatment of sleep apnoea.

## Michael Hickinbotham BEc LLB

*Non-Executive Chairman*

Michael is the Managing Director of the Hickinbotham Group which is the largest and longest established building and development group in South Australia and has been awarded a Centenary Medal for service to the Australian Building industry and community. He has a strong interest in entrepreneurial ventures that create value as well as innovation, education, and community building having established Australia's, and one of the world's, first joint ecumenical Anglican Catholic Schools at Andrews Farm in the north of Adelaide. He also funds educational scholarships for children from high needs families, and supports many cultural, sporting and community groups and charities. Prior to joining the Hickinbotham Group, Michael was a solicitor at the Melbourne office of national law firm Black Dawson (now Ashurst) and he holds a degree in Economics from the university of Adelaide and an Honours degree in Law From University College London.

University  
South  
Australia  
(UniSA)



Sementis has a long standing relationship with UniSA where it uses the labs and pays for a number of scientists to undertake research and animal trials under the guidance of our Chief Scientific Officer, Paul Howley.



Science and Industry Endowment Fund STEM+ Business Industrial Research Fellowship Award: for a 3 year period; Post-Doc salary and consumable costs

Department  
of  
Clinical Immunology  
and allergy



Dr Willian Smith, Clinical immunologist: provided blood samples from his peanut allergic patients for *Ex Vivo* testing by Sementis and expert opinion

Royal Adelaide Hospital

## Prof. John Hayball

Immunologist at University of South Australia. Heads the Experimental Therapeutics Laboratory (ETL) at the University of South Australia. Professor Hayball has an interest in understanding the fundamental mechanisms involved in controlling the mammalian immune response, particularly those involved in the development of an early innate immune response. He is using this information in rational approaches to develop new therapeutics for the prevention and treatment of diseases such as cancer, infection and wound healing. Sementis (with Ass. Prof. Hayball's oversight) conducts all preclinical immunological research and testing the efficacy of its new vaccines at ETL.

## Prof. Andreas Suhrbier

Immunologist at QIMR Berghofer Medical Research Institute, Queensland, Australia. Prof Suhrbier is a world leader in infectious diseases particularly Chikungunya and Zika virus. He is a member of Global Virus Networks and Chikungunya Working Party. He has developed an internationally accepted mouse model for studying Chikungunya infection. Using his model, he has tested our Chikungunya and Zika virus vaccine and has shown that Sementis vaccine can protect mice from a virulent Chikungunya and a virulent Zika virus challenge.

## Jim Ackland PHD

Regulatory Affairs Consultant, Jim has over 30 years experience in the manufacture, quality control, development and international regulatory requirements for biopharmaceutical products. He has provided regulatory and product development advice and assistance to large and small companies. Prior to establishing Global Bioscience Solutions, Jim was employed at CSL Limited as Head of Regulatory Affairs.





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**Allergen** – A substance that causes an allergic reaction

**Antigen** - A foreign protein substance that induces an immune response in the body

**Attenuation** – Reduced or weakened virulence

**Bioreactor** – A vessel that grows cells as a suspension in a liquid volume

**Desensitization** – A process that makes the body less sensitive to an allergen

**Genes** – DNA that codes for the production of proteins such as antigens and allergens

**Immunity** – resistances to infection mediated by the immune system

**Immunogenic** - relating to or denoting substances able to produce an immune response

**Pathogen** – A bacteria, virus or other microorganism that can cause disease

**Platform** - A live virus (sometimes called a vector) that acts as a carrying vehicle for antigens (proteins) from diseases

**Replicating (or multiplying)** – Replication causes safety issues with vaccines, i.e. sickness

**SCV** - The Sementis platform, Sementis Copenhagen Vector

**TH1 Response** – TH1 cells are the body's immune cells, responsible for defense against viruses and bacteria

**TH2 Response** – TH2 cells are responsible for defence against parasite infections

**Tolerization** – Be capable of a continued subjection to an allergen without adverse reaction

**Vaccine** –Antigenic material used to stimulate an individual's immune system to develop an adaptive immunity to a pathogen

**Virus** - An extremely small piece of organic material that causes disease

**Vaccinia Virus** - The smallpox vaccine, which originated from the cowpox virus

**Vector** – an entity for delivering antigens to the immune system with the aim to stimulate an immune response to said antigens



## Live attenuated vaccine (e.g., smallpox, measles, rubella)

These vaccines are made by weakening and crippling the disease causing virus so that it no longer causes the disease but is still recognized by the immune system to stimulate life long immunity. Drawback is the possibility of reverse to virulence!



## Inactivated (polio, flu, etc.)

To overcome the drawback to reversion to virulence, the original disease causing virus is inactivated (killed) but still recognized by the immune system. The disadvantages of these vaccines are lack of ability to stimulate potent immunity responses. There is also a risk the inactivation step has not killed all the virus in the batch of vaccine!



## Subunits (HBV, etc.)

To maintain the safety of the inactivated vaccines and reduce the risk of incomplete inactivation, only parts of the disease causing virus are used in the vaccines, e.g., viral coat proteins that by themselves are non-infectious and non-virulent. However, they are unable to stimulate a potent immune response and need multiple vaccinations and regular boosting vaccination every 5 to 10 years.



## VLPs (HPV)

Overcomes the drawback of subunit vaccine by increasing the potency of immunity but still require multiple vaccinations and regular boosting. The manufacturing process is more complicated than with attenuated, inactivated and subunit vaccines.



## DNA vaccines (none)

New approach of addressing safety and long term immunity. However, to date, this technology developed in the 1980s has not proven effective in humans.



## Vectored (Adv and MVA under advance development)

New technology that combines the advances of attenuated vaccine in terms of long lasting potent immune response to the safety of inactivated and subunit vaccines.



# Appendices

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# Appendix 1: Sementis Revolutionary Platform Technology



The Sementis platform is called Sementis Copenhagen Vector (SCV), which is a delivery mechanism for antigens (proteins) from diseases/food to initiate an immune response to the disease/food in question as well as a non consequential immune response to the vector. The idea is to get the immune system to undertake what is known as a Th1 immune response to the food/disease.



THE SCV IS ESSENTIALLY THE OLD SMALLPOX VACCINE, WHICH WAS USED TO ERADICATE SMALLPOX GLOBALLY AND AS A VECTORED VACCINE FOR RABIES FROM CENTRAL AND NORTHERN EUROPE. HOWEVER, IT HAS BEEN GENETICALLY ALTERED TO BE:

- **Perfectly safe<sup>1</sup>** - it doesn't multiply to give side effects that were seen during the mass smallpox vaccination campaigns of 1950s, 60s & 70s.
- **More immunogenic<sup>2</sup>** – it makes it more visible to the immune system, thereby making it more active, which increases the effectiveness of the vaccine.

Genes for antigens from food/diseases are inserted into the SCV platform thus making a vaccine (i.e. Th1 response) against both smallpox and that food/disease.

In principle there are literally dozens of food/diseases that the platform could accommodate to create a vaccine for these conditions/diseases.

<sup>1</sup> So far only tested in animals with no antiviral immune response but the expectations are that it will be completely safe in humans with an uncompromised immune response and should be safe in humans with deficient immune responses

<sup>2</sup> Based on animal preclinical proof-of-concept studies

# Appendix 1 (cont.): Does the SCV platform work and is it safe?



The SCV platform has already been proven to work as there is extensive proof of its effectiveness dating back to the rabies eradication campaign. In addition, Sementis' extensive proof-of-concept studies confirms the effectiveness as a viral vaccine vector in animals.

*Sementis has also proven the complete safety of the SCV platform by showing it doesn't multiply upon vaccination<sup>2</sup>.*

A peer reviewed publication describes in detail the results of SCV's proof of concept trials, as a true non replicating platform<sup>1</sup>.



Sementis proof-of-concept trials<sup>2</sup> have also confirmed the powerful immunogenic properties of the SCV platform, which only requires a single shot vaccination strategy, where most vaccines require priming and boosting strategies. **This is extremely important as many vaccines have questionable consistency and efficacy.**



Trials in humans are the next step but as the vaccinia virus has been used in humans as a **smallpox vaccine for over 200 years, its effectiveness and properties are well understood.**



With SCV, we will have eliminated the side affects that were seen with the original smallpox vaccine. **Hence there are high expectations that human trials will simply confirm its previous success.**

<sup>1</sup> So far only tested in animals with no antiviral immune response but the expectations are that it will be completely safe in humans with an uncompromised immune response and should be safe in humans with deficient immune responses.

<sup>2</sup> Yet to be confirmed in human clinical trials. Due to the nature of the proof-of-concept studies, the expectation is that the proof-of-concept will translate to humans.



# Appendix 2: Other Potential Solutions

## Avoidance:

Currently the only way to prevent allergic and anaphylactic reactions is to avoid the source of the food allergen. This is practically difficult if public places serving food such as restaurants, schools and airplane flights etc can not be avoided as allergic reaction can be set off by trace amount of food left on surfaces or occur as dust in the air.

## Epinephrine Auto injectors:

These expensive devices (\$U.S. 300-500 for 1 shot) contain a needle that injects a single dose of medication. They do not prevent an attack and are not a cure, and is basically the first line of defense against anaphylactic shock.

## Desensitization Therapy:

- ☑ There are numerous organizations participating in this space (see appendix (3)). The basic concept is giving the patient increasing doses of peanut over time often with some “adjuvant” to help restrain the harmful Th2 response.
- ☑ Basically, these therapies are trying to tone down the Th2 response by getting the immune system to block the creation of those troublesome Th2 cells which cause all the problems – a process referred to as tolerization. Constant exposure to small amounts of peanut apparently can do this in some allergic individuals but not all and the ones that become tolerant to peanut allergen will eventually return to being allergic to peanut again and will have to repeat this therapy maybe every 5 to 10 years.
- ☑ One of the problems with this therapy there is little or no immune memory associated with this approach so that as soon as the individuals stops consuming peanuts for a period they become sensitized again.
- ☑ The “theory” behind this therapeutic approach is not well understood as opposed to the Sementis vaccination approach which is well understood and supported by scientific data that has accumulated over many decades.
- ☑ In summary the tolerization therapy approaches suffer from some or all of the following:
  - they are intense and costly to administer
  - require high maintenance – a missed treatment step can render the treatment up to that stage useless, i.e., 1 year of treatment maybe lost if the subsequent ongoing treatment is interrupted.
  - not a long term solution., i.e. the “cure” is short lived.
  - the treatments have safety concerns, exposure to the small tolerating doses can inadvertently set off an allergic reaction.
  - because the process is lengthy (i.e. around 18 months) compliance is low, i.e. occasional treatment interruptions.
  - In the early stages of the treatment most patients will feel ill, i.e. nauseous and sometime vomiting, hence high rates of drop outs from the treatment course are often observed.

# Appendix 2: Other Potential Solutions Cont.

## DNA Vaccines :

These are alternative vector platforms to viral vector platforms like SCV. DNA vaccine and viral vector vaccines are classed as genetic vaccines in that they contain the gene that then make the target protein upon vaccination. Because the vector is making the protein/allergen as opposed to the allergen being ingested, the immune response defaults to Th1 and being superior to a Th2 immune response will shut down the target allergen-specific Th2 immune response indefinitely. The advantages of DNA vaccines over viral vector vaccine is that DNA vaccine are considered safer. However, the main drawback with DNA vaccines, even though they work well in mice vaccination studies they have not worked so well in humans and have been often be referred to as being as immunologically potent as water! The Sementis SCV-peanut allergy vaccine is as safe as DNA vaccine but as the SCV vector is derived from a smallpox vaccine it is very much more immunological potent as testified by its effective use to globally eradicate smallpox.

## Nanoparticles :

This is still in very early experimental research phase in mice and consists of food allergen bound to biodegradable nanoparticles. When injected they seem to stop amplification of Th2 immune response to ingested allergen but does not seem to remove the pre-existing food-allergen-specific Th2 immune response. The use of such therapy while not curing food allergy will reduce the risk of severe or fatal anaphylactic shocks upon accidental exposure to food allergens. It is not known if the therapeutic properties seen in mice will translate into humans.

## Monoclonal Antibodies :

An allergic reaction is caused by food allergens binding to IgE antibodies that are bound to the surfaces of Mast Cells. When allergens bind to these IgE antibodies a signaling reaction takes place that causes the Master Cells to release histamine and leukotriene that then trigger allergic reactions and in large quantities trigger anaphylaxis. Anti-IgE antibodies have been developed to bind to the IgE antibodies on the surfaces of Mast Cells to block allergen binding and thus prevent the release of histamine and leukotrienes. This treatment is aimed at preventing anaphylaxis once a individual starts to shown sign of an allergic reaction and to be used if an allergic individual is at risk of being accidentally exposed to aerosolize allergens such as pollen, food dust allergens, pet danders etc. This treatment is not a cure but rather a symptom modulator by reducing the risk of anaphylaxis during an allergic reaction.

# Appendix 3: Competitors



## Aravax

Australian unlisted company. The company uses peptides that represent selected fragments of peanut proteins to switch off allergic reactions to peanuts. The peptides do not contain the parts of the peanut proteins that cause life threatening anaphylactic reactions. The company claims that when peptides interact with immune cells in the absence of simultaneous inflammation the immune cells that casual allergy can be reprogrammed to become tolerant. The company is developing a product called PVX108 which is a monthly intra-dermal injection to induce tolerance to peanuts and reduce the risk of allergic reactions upon accidental exposure. Aravax is beginning phase 1 human trials.



## DBV Technologies

Listed on Paris stock exchange (market capitalization of \$U.S. 1.1 (18 December 2017) and the NASDAQ. It has a partnership with Nestle. It is developing solutions for peanut, milk and egg allergy. It is in stage 3 trials for its peanut product.

Their technology platform is called Viaskin and is based on an electrostatic patch which administers the allergen directly on the skin. Once administered the allergen concentrate in the superficial layers of the skin where it activates the immune system by specifically targeting antigen presenting cells without passage into the blood stream. DBV Technologies calls this epicutaneous immunotherapy or EPIT

The claim is that EPIT induces a decrease of allergen specific responses (i.e. decrease of allergen-specific IgE, decrease of TH2 cytokine production, and decrease of local and systemic response after exposure to allergen) and increase of regulatory responses (i.e. increase of allergen-specific IgG2a or IgG4, increase of regulatory T cells (Tregs).

The effect of EPIT is mediated by the induction of Foxp3+ Tregs. EPIT appears to induce a large repertoire of homing receptors on Tregs, allowing migration toward different organs. The company believes the Tregs, induced by EPIT maintain suppressive activity for a long period of time after discontinuation of the treatment. Their research has shown that EPIT induces a sustained modulation effect of immune responses by generating particular Tregs that maintain for long term, and by deeply decreasing the TH2 responses.

It recently announced the results of a Phase 3 trial where the results whilst statistically significant did not align with the primary endpoint. The company remains positive of the potential for their therapy.



## Aimmune

Listed on NASDAQ (market capitalization \$U.S. 1.8 billion (18 December 2017). Its AR101 peanut product is in phase 3 trials. It also has an egg product. In November 2016 Nestle Health Science made a \$U.S. 145 million equity investment in Aimmune which corresponded to 15% of the company.

The company uses a characterized oral desensitization immunotherapy (CODIT) approach. It is commonly referred to as oral immunotherapy (OIT). The product is called AR101 and is an oral biological drug product containing the protein profile found in peanuts. It involves an up dosing desensitization regimen over approximately a 20 week period. The patient assessment and all up dosings are scheduled to take place every two weeks at an allergist's office with steady level daily home dosing in between visits. Following completion of the up dosing protocol; patients continue to take an ongoing daily maintenance dose of AR101 at a set amount. Patients ingest their daily dose of AR101 mixed with a matrix of food. Hence the patient needs to continue to take maintenance doses in order to maintain desensitization. The company is undertaking a Phase 3 trial of its peanut allergy treatment.

# Appendix 3: Competitors



## Murdoch Children's Research Institute (MCRI)/Prota Therapeutics

Prota Therapeutics (a private company) was spun out of the MCRI and involves a probiotic peanut desensitizing solution. It involves mixing peanut flour with a probiotic bacterium. Probiotics are thought to help reduce harmful inflammatory responses in the gut and so, when mixed with peanut protein, the probiotic a long and involved process to achieve desensitization with daily treatments and fortnightly visits to the allergist for adjustments, for 18 months. The company has recently announced results of trials that show that for just over half of a small number of people (12) tolerance seems to be maintained for those that kept eating peanuts for 4 years after treatment and then abstained for 8 weeks. This is thought to be unique.



## Hal Allergy Group

Hal is a Dutch company specializing in the diagnostic and treatment of allergies and on contract manufacturing with a specialization on the pharmaceutical development and production of batches for preclinical and clinical studies. It is a subsidiary of the family owned Droege Group AG. The company has a number of products for grasses, trees, bees, wasps with trials for mites. Its peanut product has successfully completed a phase 1 trial with it subcutaneous immunotherapy (SCIT) product called HAL-MPE1. It is a chemically modified aluminum hydroxide peanut extract for subcutaneous administration.



## Immunomic /Astellas Pharma Inc.

Immunomic is a private company that uses its LAMP-based nucleic acid immunotherapy platform for cancer and animal health. It has out licensed the use of its platform to Astellas Pharma Inc. to explore the use of Lamp-Vax for allergy treatment. The Lamp-Vax platform is thought to work by encoding the Lysosomal Associated Membrane Protein, an endogenous protein in humans. The company claims that in this way DNA or RNA vaccines have the potential to utilize the body's natural biochemistry to develop a broad immune response including antibody production, cytokine release and critical immunological memory.

Astellas Pharma is a major Japanese pharmaceutical company listed on the Japanese stock exchange. It has received U.S. Food and Drug Administration Fast Track designation for the drug candidate ASP0892 which is a peanut allergy DNA vaccine using the Lamp-Vax technology. A phase 1 trial has begun.

# Appendix 3: Competitors



## ASIT biotech

ASIT biotech is listed on the Brussels stock exchange (market capitalization €46.5 million (18th December 2017)). The company is in phase three trials for grass pollen rhinitis and discovery for peanut allergy. Their technology called Pnut-ASIT+ (Peanut-Allergen-Specific Immunotherapy) product is based on highly purified peanut allergen fragments obtained from natural sources. As a result of their high purity and broad epitope composition, ASIT fragments serve as candidates for combination with adjuvants to provide immunotherapy product that is administered sublingually.

Upon administration, the outer layer of mucosa absorbs the peanut fragment/adjuvant complex. The complex is then engulfed by the Langerhans cells (LC), which in turn migrate to the lymph node where they activate the proper immune response. This activation is based on triggering the development of TREG (T lymphocyte Regulator) which in turn inhibits T helper (TH2,0 and 1), mast, basophil, and B-lymphocytes immune cells that are involved in activation of anaphylactic shock. Once these cells are suppressed downstream events of proper immune response take place.



## Novartis

Novartis is a global healthcare company based in Switzerland. QGE031 (Ligelizumab) developed by Novartis is a humanized IgG1 monoclonal antibody that binds to the C@3 domain of IgE thus achieving its suppression. There are phase 2 trials for the treatment of allergic asthma, bullous pemphigoid and urticaria. There doesn't seem to be any development on food allergies.



## Virtici\*

Founded in 2011, Virtici is a privately held product-development company headquartered in Seattle, Washington. Virtici's is primarily developing products to treat cancer, autoimmunity, and cardiovascular/metabolic diseases.

Virtici is developing VTC-064, an orally administered novel tolerance-inducing therapeutic for the treatment of Peanut Allergy. It is a recombinant protein composed of the reovirus head protein, ps1, fused to the peanut allergen (PNA), ara h 2. Ara h 2 is a dominant peanut allergen that is recognized by human immunoglobulin E in more than 90% of the patients who have peanut allergy. Reoviruses are segmented, double-stranded RNA viruses that infect humans via mucosal surfaces.

Microfold cells (M cells) play a crucial role in the generation of tolerance to a given antigen. These M cells are present at epithelial layer that covers Gut Associated Lymphoid Tissue (GALT) and Nasopharyngeal Associated Lymphoid Tissue (NALT) regions. These cells are specialized to environmental antigens and present them to the adjacent immune cells. Reoviruses bind to the M cells surface via ps 1, and thus company has designed VTC-064 to use ps1 to target ara h 2 antigens specifically to M cells. ps1-mediated tolerance in antigen-sensitized mice, by both oral and intranasal routes of administration, is due to the induction of anti-inflammatory cytokines and an increase in suppressive regulatory T-Cells (Tregs). VTC- 064 is expected to rapidly induce long-term tolerance to major peanut allergens in allergic patients following short-term treatment.

# Appendix 3: Competitors



## AnaptyBio\*

AnaptyBio (listed on the NASDAQ market capitalisation of \$US 2.1 Billion (12/012/2017)) is a clinical-stage biotechnology company developing first-in-class antibody product candidates focused on unmet medical needs in inflammation. The company's proprietary anti-inflammatory pipeline includes its anti-IL-33 antibody (ANB020) for the treatment of moderate-to-severe adult atopic dermatitis, severe adult peanut allergy and severe adult eosinophilic asthma; its anti-IL-36R antibody (ANB019) for the treatment of rare inflammatory diseases, including generalized pustular psoriasis and palmo-plantar pustular psoriasis; and a portfolio of checkpoint receptor agonist antibodies for the treatment of certain autoimmune diseases where immune checkpoint receptors are insufficiently activated, which have demonstrated efficacy in an animal model of graft-versus-host disease. AnaptyBio's antibody pipeline has been developed using its proprietary somatic hypermutation (SHM) platform, which uses *in vitro* SHM for antibody discovery and is designed to replicate key features of the human immune system to overcome the limitations of competing antibody discovery technologies. AnaptyBio has also developed multiple therapeutic antibodies in an immuno-oncology partnership with TESARO and an inflammation partnership with Celgene, including an anti-PD-1 antagonist antibody (TSR-042), an anti-TIM-3 antagonist antibody (TSR-022) and an anti-LAG-3 antagonist antibody (TSR-033), which are currently under clinical development with TESARO, and an anti-PD-1 checkpoint agonist antibody (CC-90006) currently in the clinic with Celgene.



## Genentech\*

Omalizumab is a recombinant humanized monoclonal antibody which specifically binds to the C epsilon3 domain of immunoglobulin (Ig) E. It inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils which in turn limits the degree of release of mediators of the allergic response. Omalizumab is approved under the brand name Xolair, for the treatment of Asthma and Chronic Idiopathic Urticaria.

Currently Omalizumab is in Phase II clinical studies for treatment of Peanut Allergy. The company had initiated development of Omalizumab for Peanut allergy back in 2004, however the development was halted due to safety concerns raised during human experiments in 2006. It was re-initiated after evaluation of a recently conducted clinical study demonstrating the positive outcome of Omalizumab in desensitization of Peanut allergy patients. This study was funded by Food Allergy Research & Education (FARE), the Bunning Food Allergy Project, and Genentech.



## Allergy Therapeutics\*

Allergy Therapeutics (listed in London – market capitalisation £166 million sterling (18/12/2017)) is developing a vaccine candidate Polyvac Peanut using its licensed Virus-Like-Particles (VLP) technology. This vaccine is focused on a subcutaneous application of recombinant peanut allergen coupled with VLP adjuvant to increase the safety and efficacy profile. This approach aims at inducing protective immunity, enabling shorter therapy duration and an enhanced safety profile. Company believes that this approach will have significant implications for peanut allergy therapy with the potential to redefine the market for food allergy products. While most of the peanut vaccines in development often require repeated and long-lasting exposure transdermally or orally, this therapy will offer shorter therapy duration.

In February 2017, Allergy Therapeutics announced positive results from preclinical research into its unique therapeutic peanut allergy vaccine. Pre-clinical finding demonstrated that a single dose of the Company's virus-like-particles (VLP) adjuvant combined with recombinant peanut allergen successfully protected against anaphylaxis when challenged with peanut. Additionally, those vaccinated with Polyvac Peanut exhibited no symptoms compared to placebo when challenged with peanut. The vaccine itself did not trigger any unwanted symptoms when injected subcutaneously as designed. Furthermore, in peanut-sensitized subjects, the vaccine itself did not induce anaphylaxis even with intravenous injection demonstrating excellent safety in the model. Having delivered these positive preclinical Proof of Concept results, this vaccine can now progress Phase I development.

# Appendix 3: Competitors



## Sanofi\*

Sanofi is developing SAR-439794, a Toll-like receptor 4 (TLR4) agonist in collaboration with Immune Design. The therapeutic product is an immune therapy developed using Immune Design's GLASS Platform. Under collaborative research arrangement, both the companies has generated significant preclinical data demonstrating that certain formulations of Glucopyranosyl Lipid Adjuvant (GLA), core of the GLAAS platform, when given prophylactically or therapeutically, can shift the immune responses in a way that may result in significant protection and reduction from allergy symptoms. Currently Sanofi is conducting Phase I study for Peanut Allergy.

In August 2014, Sanofi and Immune Design entered into a license agreement to use Immune Design's GLAAS discovery platform to develop therapeutic agents to treat peanut food allergy. Sanofi obtained to discover, develop and commercialize products. Immune Design has received an undisclosed upfront payment and will be eligible to receive development and commercialization milestones totaling USD 168 million, as well as tiered royalties on sales of approved products. In September 2016, use Immune Design received an undisclosed milestone payment for the start of the Phase I trial of the first clinical application of GLAAS discovery platform.

Immune Design has licensed GLASS platform from Infectious Disease Research Institute (IDRI).

GLA selectively binds to the TLR4 receptor and causes potent activation of dendritic cells (DCs) leading to the production of cytokines and chemokines that drive a Th1-type immune response. This GLA is accompanied by an antigen and injected into a patient, this combination is taken up by DCs and leads to the production and expansion of immune cells called CD4 T helper lymphocytes with a Th1 phenotype. These CD4 T cells play a key role in boosting pre-existing CTLs that are specific to the same antigen and thus providing help to other immune cells, including B lymphocytes that are the precursor to antibodies and natural killer cells that are also important in the overall immune response. GLAAS product candidates have the potential to target multiple types of cancer, as well as infectious, allergic and autoimmune diseases and have now been evaluated in over 1000 subjects in Phase I and Phase II trials demonstrating an acceptable safety profile and efficacy.



## Selecta Biosciences\*

Selecta biosciences (listed on the NASDAQ –market capitalization \$US 223.4 million (18/12/2017)) is developing a vaccine, SVP-CPE + SVP-Resiquimod under its Peanut Allergy Research Program using Synthetic Vaccine Particle (SVP) Technology. Company believes that this product will be different from other therapies in development due to its use of active immunomodulators, uniquely enabled by SVP technology, that appear to trigger a lasting immune switch away from allergy-inducing IgE following a limited number of treatments. Company's SVP technology is designed to program the immune system to elicit tolerance to a specific antigen without impacting the rest of the immune system. Selecta believes that this novel approach could be applied to other food allergies as well. The drug is in pre-clinical stage. Selecta plans to evaluate strategic opportunities to continue advancing this non-core program.

SVP tolerance programs utilize SVP Rapamycin, the company's biodegradable nanoparticle encapsulating the immunomodulator rapamycin. SVP Rapamycin is co administered at the beginning of therapy with a biologic drug to mitigate the formation of ADAs without altering the drug or its dose regimen. Pairing of SVP Rapamycin with a biologic drug offers the potential for a new proprietary product candidate that can be separately patented, approved and marketed.



# Appendix 3: Competitors



## BioLingus\*

BioLingus is developing Interleukin-2 biobetter, a low dose IL-2 immunotherapy for the treatment of Peanut Allergy. Interleukin-2 (IL-2) is a type of cytokine signaling molecule that regulates the activities of white blood cells whose role has been implicated in some disease including arthritis, psoriasis, diabetes type 1, peanut allergy and cancer. Company has significant data supporting IL-2 immunotherapy effect in these indication. The therapeutic effect of IL-2 immunotherapy is may be due to altering the balance of Tregs. This immune therapy has been developed using company's proprietary Sublingual Immunotherapy (SLIT) technology. Company claims that sublingual administration can increase efficacy and/or reduce side-effects compared to administration of IL-2 by injection. BioLingus is seeking partnerships with other pharmaceutical companies in order to unlock the potential of the BioLingus Technology.

Company has validated the low dose IL-2 efficacy in an experiment of Peanut Allergy model. The data from this experiment demonstrated that sublingual administration is as effective as injected IL-2, but at a dose which is 500 times lower. Sublingual low dose IL-2 was able to achieve good efficacy in Peanut Allergy model in comparison to injectable dose. Company believes that the reason behind this positive results was their SLIT technology which brings the molecules effectively in the lymphatic system, which is the heart of the immune system.



## Laboratorios LETI\*

Laboratorios LETI is developing a Depigmented-Polymerized Peanut Allergenic Extract for the treatment of Peanut Allergy. This extract has been prepared by polymerizing Peanut native extract (NE) with glutaraldehyde. NE is first manufactured after the extraction of the protein fraction from roasted peanuts. This fraction was dialyzed and freeze-dried. Afterwards, the NE was purified (mild acid treatment) to remove low MW substances (depigmentation) and finally polymerized with glutaraldehyde (PE).



## Adverum\*

Adverum (listed on NASDAQ - market capitalization \$US 144.1 million (18/12/2017)) is developing ANN-004, an AAVrh.10anti-hIgE gene therapy for the treatment of severe allergies such as multiple food allergies or severe Peanut Allergy. This gene therapy is designed to allow the endogenous production of anti-IgE antibodies in severely allergic patients. The goal is to provide continuous levels of anti-IgE antibody to prevent severe reaction when a patient is exposed to allergen(s). The therapeutic product is currently undergoing pre-clinical studies.

A pre-clinical study has been done for Anti-hIgE gene therapy in a humanized murine model of peanut allergy. A novel humanized murine model of peanut allergy has been developed that recapitulates the human anaphylactic response to peanuts in NOD-scid IL2R $\gamma$ manull mice transferred with blood mononuclear cells from donors with peanut allergy and then sensitized with peanut extract. AAVrh.10anti-hIgE gene therapy is an adeno-associated rh.10 serotype vector coding for a full-length, high-affinity, anti-hIgE antibody derived from the Fab fragment of the anti-hIgE mAb omalizumab. During the study peanut sensitization and hypersensitivity was induced in reconstituted mice peanut-specific IgE and reactions were provoked by feeding peanuts to mice with symptoms similar to those of human subjects with peanut allergy.

Data from this study demonstrated that a single administration of AAVrh.10anti-hIgE vector expressed persistent levels of anti-hIgE. The anti-hIgE vector, administered either before sensitization or after peanut sensitization and manifestation of the peanut-induced phenotype, blocked IgE-mediated alterations in peanut-induced histamine release, anaphylaxis scores, locomotor activity, and free IgE levels and protected animals from death caused by anaphylaxis. If this degree of persistent efficacy translates to human subjects, this therapy has potential to be an effective 1-time preventative therapy for peanut allergy and possibly other severe, IgE-mediated allergies. .

# Appendix 3: Competitors



## Intrimmune Therapeutics\*

INT-301 is a transmucosally administered drug candidate which is being developed for the treatment of peanut allergies. INT-301 leverages the novel oral mucosal immunotherapy (OMIT) platform to integrate peanut allergy desensitization therapy into a patient's everyday tooth brushing routine. Intrimmune Therapeutics is developing INT-301 and is currently in Pre-clinical stage of development for the treatment of Peanut Allergy. The company is still planning if the human trials will be a Phase I/II trial or a Phase IIa/IIb trial and is expected to complete it by 2018.

The core technology, oral mucosal immunotherapy (OMIT), is a novel platform that delivers allergy immunotherapy while a user brushes their teeth. Oral mucosal immunotherapy (OMIT) is administered via a specially formulated toothpaste that incorporates and stabilizes therapeutic agents (allergens). Allergens are applied to antigen presenting cells in the oral mucosa with every tooth brushing, integrating administration into a patient's daily routine.



## ImmusanT\*

ImmusanT has developed its proprietary Epitope-Specific Immuno-Therapy (ESIT) Platform Technology to translate basic science to precision clinical therapeutics and diagnostics to address unmet medical needs. This technology is initially being utilized to develop a novel therapy and diagnostic for celiac disease. It also has potential value-generating opportunities in other indications including type 1 diabetes, thyroid autoimmunity, autoimmune liver diseases, and rheumatoid arthritis.

Company's epitope screening approach further enables development of treatments for allergies with defined peptides for Peanut Allergy. Currently company is primarily focusing on Celiac Disease.

The drug discovery platform was initially developed by Nexpep. In March 2011, ImmusanT acquired discovery platform for targeted immunotherapies from Nexpep. .



## Northwestern University

Is investigating AHG-2, peanut allergen IgG construct Ara h2-Fc gamma, which blocks basophil and mast cell degranulation, for the potential treatment of peanut allergies. Through the inhibitory receptor FcγRII, AHG2 partially inhibited the Whole Peanut extract induced acute anaphylactic reaction.



## Cour Pharmaceuticals

Cour are a group venture comprising partners from Stanford Medicine, Harvard medical School, Northwestern Medicine, Takeda, Cooley, The University of Sydney and Biomedical Engineering – University of Michigan. Cour uses two nanoparticle platforms with highly specific capability. They are in the final preclinical stages of allergy and celiac treatments. 1) Immune Modifying Nanoparticles (IMP). This starts with an FDA approved co-polymer (PLGA). The particles target/bind inflammatory cells (monocytes) and eliminate them through normal metabolism. Hence reduction in circulating monocytes prevents tissue damage. 2) Tolerizing Immune Modifying Nanoparticles (TIMP). This is used for autoimmune conditions.



## McMaster University

Is investigating Ara h 1 peptides as an immunotherapy for the potential treatment of peanut allergy. While no platform is set yet they identify HLA-degenerate CD4+ T cell epitope based peptides of the major peanut allergen Ara h 1 as candidates for peanut specific immunotherapy. These peptides target allergen specific T cells without causing IgE mediated inflammatory cell activation.



## SCV Cell Substrate for manufacturing:

- Viral Vector Manufacturing.  
Inventor: Paul Howley and Liang Liu. International Application Number: PCT/AU2014/050330 (International publication number: WO 2015/061858)
- National phase examinations: AU, NZ, CA, CN, EP, IL, JP, MY, KR, RU, ZA, US, IN, HK
- Granted: SG



## SCV Peanut Allergy Vaccine:

- Immune Modulation, Inventor: Paul Howley. International Application Number: PCT/AU2014/000286 (International Publication Number: WO 2014/138824A1)
- *National phase examinations:* AU, US, EP, RU, ZA, CN, KR, IL, MY, JP, CA, HK
- *Granted:* NZ, SG



## SCV dual Zika/Chikungunya vaccine:

Viral Vaccines, Inventor: Paul Howley. International Application Number: PCT/AU2017/050879

# Appendix 5: Potential Revenue



- The U.S. numbers for **children only** suggest that caregivers would spend around \$U.S. 7 billion **per year** on peanut allergy treatment <sup>(a)</sup>. It would therefore seem reasonable to assume that the total world one off revenue for a cure would be in excess of \$U.S. 10 billion.
- Alternatively, assume that say half of the estimated 3 million U.S. citizens suffering from peanut allergy (i.e. both adult and children) would pay (or their government or insurance company would pay) a once off \$U.S. 3,000 for a permanent solution, that would be revenue of \$U.S. 4.5 billion from the U.S. alone. This would be a very conservative figure given that the cost of EpiPen alone in the U.S. is between \$U.S. 300 and \$U.S. 500. Given they need to be replaced every 18 months, the lifetime cost would be around \$U.S. 16,000. This does not include visits to the doctor and other associated costs etc. Western Europe appears to have a similar peanut allergy problem to the U.S. and Asia is even bigger in total numbers but may be lower in terms of total revenue. Again, the total figure of \$U.S. 10 billion in market size would seem conservative especially considering that this is the estimated total one-off market and not a per year figure.
- It has been reported that two listed companies offering a desensitization process intend charging \$U.S. 5,500 and \$U.S. 6,500 for one year's supply! Analysts have forecast peak annual U.S. sales of \$U.S. 1.33 and \$U.S. 2 billion for the each company <sup>(b)</sup>. These are yearly and U.S. only estimates and for a treatment that may need to be taken for years!
- Clearly the \$U.S. 10 billion estimated total market for a one off payment for a two to three injection permanent peanut cure is conservative and that relates to existing sufferers. It has been estimated that there are 100,000 new cases annually in the U.K. and U.S. <sup>(c)</sup>. Assuming that only half take up the treatment at \$U.S. 3,000 that would equate to \$U.S. 150 million in new revenue. Assuming the rest of the world was as large again that would equate to \$U.S. 300 million in new revenue per year.
- The market for a one off payment for a permanent cure to other food allergies is most likely two to three times that size as would be recurring revenue from new sufferers.
- The bottom line is that the size of the market for a simple one payment for two to three injection permanent cure is in the billions of dollars and would eclipse all the other complex, very expensive, time consuming, sometimes dangerous, often uncomfortable and certainly not totally effective partial solutions which likely will not last in the long term.

(a) JAMA Pediatrics, 2013; 167(11): 1026-103. doi:10.100/jamapediatrics2013.2376

(b) <http://www.reuters.com/article/us-biotech-peanuts/biotech-companies-chase-elusive-peanut-allergy-treatment-idUSKCN0SL2LK20151027>

(c) Allergy UK, Allergy Prevalence: useful facts and figure ([https://www.allergyuk.org/assets/000/001/369/Stats\\_for\\_Website\\_original.pdf?1505209830](https://www.allergyuk.org/assets/000/001/369/Stats_for_Website_original.pdf?1505209830))

# Appendix 5 Continued: reconciliation of different estimates of market size



- Given the estimated cost **per year** of Epipen and the proposed treatment estimates of the desensitization treatments (i.e. around \$US5,500 to \$U.S. 6,500 **per year**) it would not be unreasonable to assume that the \$20,000 could be charged for a one off lifetime cure rather than the Sementis assumptions on the previous page.
- Given that one third of sufferers have severe peanut allergy then assuming they pay (or the insurance company or government subsidizes) the \$20,000 fee then the seven major markets alone would bring in \$US 50 billion (2.5 million sufferers (one third of the estimated 7.5 million sufferers in 2021 times \$US 20,000)).
- If there were 200,000 new sufferers each year and the one third ratio applies then that would be \$US 1.3 billion in new revenue each year.
- These figures do not include non-Japan Asia despite that fact that food allergy amongst children in these countries is thought to be at European levels.
- These figures for the total market size are now approaching the DeleInsight estimates for the total size over the seven year period. The DeleInsight which do not take into account the “one off cure” nature of the Sementis solution but include ongoing costs means that a complete reconciliation is not possible. In effect they are different markets.
- Either way Deleinsight assumptions about sufferers readiness to pay for treatment suggest that Sementis’ \$10 billion estimate may only represent about 20 percent of the total size of the market.

# Appendix 6: Competitor Analysis

## Major competitors

Company	Product	Type of Treatment	Delivery Method	Clinical Trials	Strengths	Other considerations
DBV Technologies	Viaskin Peanut	Peanut protein	Epicutaneous Immunotherapy	Phase 3	<ul style="list-style-type: none"> <li>Proprietary, novel technology, safe to use (avoids bloodstream), convenient patch</li> <li>Well-established company, Fast track designation and Breakthrough technology designation from FDA</li> <li>Positive results in Phases 1 and 2, phase 3 ongoing</li> </ul>	<ul style="list-style-type: none"> <li>Long process (3 years)</li> <li>Cost-intensive (Patch supply, regular visits to allergist)</li> <li>30 to 50% still uncured</li> <li>Long-term effects unknown</li> <li>Last Phase 3 trial (PEPITES) results did not meet their Statistical Analysis Plan submitted to the FDA.</li> </ul>
Aimmune Therapeutics	AR101	Peanut protein	Oral Immunotherapy	Phase 3	<ul style="list-style-type: none"> <li>Quicker than Viaskin patch (6 month vs 3 years)</li> </ul>	<ul style="list-style-type: none"> <li>Requires patient to take maintenance doses to stay desensitized (Lifelong treatment)</li> <li>High cost</li> <li>High chance of adverse reactions, gastrointestinal side effects reported</li> </ul>
HAL Allergy Group	HAL-MPE1	Peanut protein	Subcutaneous Immunotherapy	Phase 1	<ul style="list-style-type: none"> <li>Generally safe and well- tolerated</li> <li>Induced immune response within 5 months</li> <li>Well-established company with a focus on a wide range of treatments, products already registered</li> </ul>	<ul style="list-style-type: none"> <li>Early in development, no significant data on efficacy of treatment</li> </ul>

# Appendix 6: Competitor Analysis Cont.

## Major competitors

Company	Product	Type of Treatment	Delivery Method	Clinical Trials	Strengths	Other Considerations
Murdoch Research Children's Institute	PPOIT	Peanut protein	Oral Immunotherapy	Phase 3	<ul style="list-style-type: none"> <li>• Novel treatment with 70% success rate</li> <li>• Provides a platform for other allergies</li> </ul>	<ul style="list-style-type: none"> <li>• Long treatment period (1.5 years)</li> <li>• 30% of patients remain uncured</li> <li>• High cost (2 weekly visits)</li> <li>• Long-term effects insignificant as number patients is too small (only 7 out of 12 patients)</li> </ul>
Immunomic/ Astellas Pharma Inc.	ASP0892	DNA Vaccine	Intradermal or intramuscular Administration	Phase 1	<ul style="list-style-type: none"> <li>• Novel platform inducing complete immune response and can potentially be applied to other diseases</li> <li>• Vaccine offers distinct advantages over other immunotherapies (less cost and treatment duration, and long-term cure)</li> <li>• Major company Astellas Pharma will accelerate progress</li> </ul>	<ul style="list-style-type: none"> <li>• Early stages and no significant data available yet (Phase 1, recruiting)</li> <li>• Covers allergens ara h 1- 3, whereas Sementis Ltd covers ara h 1-11.</li> </ul>
Cour Pharmaceuticals	TIMP	Vaccine	Nanoparticles	Preclinical	<ul style="list-style-type: none"> <li>• Novel platform with high specificity to target molecules</li> <li>• Vaccine offers distinct advantages over other immunotherapies (less cost and treatment duration, and long-term cure)</li> </ul>	<ul style="list-style-type: none"> <li>• Early stages and no significant data available yet (Preclinical)</li> </ul>
Aravax Pty Ltd	PVX108	Peanut protein	Intradermal injection	Phase 1	<ul style="list-style-type: none"> <li>• Novel treatment as the protein administered does not contain the harmful parts of the peanut</li> <li>• Potentially safer (no harmful peanut proteins), faster, simpler (monthly injections)</li> </ul>	
Northwestern University	AHG-2	Peanut protein		Discovery	<ul style="list-style-type: none"> <li>• May represent an innovative approach to treat peanut allergy</li> </ul>	<ul style="list-style-type: none"> <li>• At the early stage of discovery, technology is still unclear.</li> </ul>



# Appendix 6: Competitor Analysis Cont.



## Major competitors

Company	Product	Type of Treatment	Delivery Method	Clinical Trials	Strengths	Other Considerations
ASIT Biotech	Pnut-ASIT+	Mixed peptides derived from allergen protein fragmentation	Parenteral administration	Discovery	<ul style="list-style-type: none"> <li>• Peptide fragments binds to IgE already loaded onto Mast Cells but unable to cross link individual IgEs together thus preventing Mast Cell degranulation</li> <li>• Does not require adjuvants</li> </ul>	<ul style="list-style-type: none"> <li>• Cures the symptoms but not the cause</li> </ul>
Novartis	QGE031 (Ligelizumab)	Humanized anti-IgE monoclonal antibody therapy	Inhaler administration	Phase II	<ul style="list-style-type: none"> <li>• High-affinity anti-IgE monoclonal antibody</li> <li>• Treatment for chronic spontaneous urticaria / chronic idiopathic urticaria</li> </ul>	<ul style="list-style-type: none"> <li>• Cures the symptoms but not the cause</li> <li>• In development for the treatment of asthma</li> </ul>
Virtici	VTC-064	Oral desensitization	Ara h2 fusion to reovirus head protein ps1	Pre-clinical	<ul style="list-style-type: none"> <li>• Targets Ara h2 to microfold cells (M cells) in the gut to induce anti-inflammatory cytokines and increase Treg production</li> </ul>	
AnaptysBio	ANB020	Antibody that inhibits the activity of IL33	Parenteral administration	Phase I	<ul style="list-style-type: none"> <li>• High affinity antibody that binds to IL33 and neutralizes its biological activity. IL33</li> </ul>	<ul style="list-style-type: none"> <li>• IL-33 directly mediates release of disease-associated downstream cytokines, which recruit pro-inflammatory cells that mediate atopic disease including atopic dermatitis, food allergies and asthma.</li> </ul>
Genentech	Omalizumab	Humanized anti-IgE monoclonal antibody therapy	Parenteral administration	Phase II	<ul style="list-style-type: none"> <li>• High affinity anti-IgE monoclonal antibody that reduces the reactivity to peanuts</li> </ul>	<ul style="list-style-type: none"> <li>• Cures the symptoms but not the cause</li> </ul>

# Appendix 6: Competitor Analysis Cont.

## Major competitors

Company	Product	Type of Treatment	Delivery Method	Clinical Trials	Strengths	Other Considerations
<b>Allergy Therapeutics</b>	Polyvac Peanut	Recombinant peanut protein combined with VLP adjuvant	Virus-Like-Particle technology	Pre-clinical	<ul style="list-style-type: none"> <li>• Preclinical finding show a single dose protects against anaphylaxis</li> </ul>	<ul style="list-style-type: none"> <li>• No published data to back up claim!</li> </ul>
<b>Sanofi</b>	SAR-439794	TLR4 agonist Th1 Adjuvant technology mixed in with peanut protein		Phase 1	<ul style="list-style-type: none"> <li>• When SAR-439794 binds to TLR4 on dendritic cells in the presence of peanut protein causes the production of Th1 cytokines and activation of peanut-specific Th1 T-cells</li> </ul>	
<b>Selecta Biosciences</b>	SVP-CPE and SVP-Resiquimod	Nanoparticles containing Resiquimod immune modulator and peanut allergens	Injection of nanoparticles called Synthetic Vaccine Particles	Pre-clinical	<ul style="list-style-type: none"> <li>• Inhibits peanut allergen specific IgE and thus prevent systemic anaphylaxis</li> <li>• SVP technology is designed to trigger a lasting immune switch away from allergy-inducing IgE</li> </ul>	
<b>BioLig</b>	Interleukin 2	IL2 immunotherapy	Sublingual	Pre-clinical	<ul style="list-style-type: none"> <li>• Low dose IL2 immunotherapy to activate T-cells</li> </ul>	<ul style="list-style-type: none"> <li>• Risk that IL2 will also amplify Th-2 T-cells</li> </ul>
<b>Laboratorios LETI</b>	Depigmented-Polymerized Peanut Allergenic Extract	Oral desensitization	Oral	Pre-clinical	<ul style="list-style-type: none"> <li>• Hypoallergic peanut extract safe for immunotherapy treatment for toleration to peanuts</li> </ul>	<ul style="list-style-type: none"> <li>• In preclinical studies, treatment reduced sensitivity to peanut</li> </ul>

# Appendix 6: Competitor Analysis Cont.

## Major competitors

Company	Product	Type of Treatment	Delivery Method	Clinical Trials	Strengths	Other Considerations
Adverum	ANN-004	Anti-IgE gene therapy	Adenovirus Associated Virus	Pre-clinical	<ul style="list-style-type: none"> <li>Endogenously produces continuous anti-IgE in severely allergic individuals thus guarding against anaphylaxis upon exposure to allergens</li> </ul>	<ul style="list-style-type: none"> <li>Indiscriminately targets all IgEs and thus leaving the individual vulnerable to conditions where IgE is needed for control</li> </ul>
Intromune Therapeutics	INT-301	Oral mucosal immunotherapy	Toothpaste	Pre-clinical	<ul style="list-style-type: none"> <li>Peanut allergy desensitization therapy from daily routine of cleaning teeth</li> </ul>	<ul style="list-style-type: none"> <li>Another form of incremental dosing increasing allergen immunotherapy</li> </ul>
ImmusanT	TIMP-Allergen	Tolerizing Immune Modifying Particles	Nanoparticle technology	Pre-clinical	<ul style="list-style-type: none"> <li>The Tolerizing Immune Modifying Nanoparticles (TIMP) platform provide a novel and highly specific immune targeting capability to safely apply to allergen tolerization. This technology is programmed to target allergic conditions by introducing disease-specific antigens to reprogram the immune system.</li> </ul>	
McMaster University	Desensitizing Peanut-specific epitope	Peanut Epitope-specific Immuno-Therapy		Discovery	<ul style="list-style-type: none"> <li>Company's epitope screening approach enables development of treatments for allergies</li> </ul>	