ASX / MEDIA RELEASE **28th November 2016**

Sirtex Medical Research & Development Briefing

Sydney, Australia; 28th November 2016 – Sirtex Medical Limited (ASX:SRX) today is hosting analysts and investors at the Sofitel Sydney Wentworth for a Research and Development (R&D) briefing. Attached is a copy of the management and invited speaker presentations to be given this morning.

Furthermore, a live webcast of the R&D briefing, commencing at 8:30 a.m., can be viewed by clicking on the following link or pasting it into your browser:
http://webcast.openbriefing.com/3086/

A recording of the webcast and slide presentation will be made available in the 'Investors' section of the Company website following the conclusion of the briefing at:
http://www.sirtex.com/au/investors/

Investor/Media Enquiries:

Dr Tom Duthy
Global Investor Relations Manager
Sirtex Medical Limited
Phone: +61 (0)2 9964 8427
Email: tduthy@sirtex.com

Sirtex Medical Limited

Investor Research and Development (R&D) Briefing

Mr Gilman Wong, CEO

Dr Steve Jones, Global Head of R&D

Sydney, Australia

28th November 2016

Introduction

- Inaugural investor R&D briefing that aims to educate analysts and investors on the Sirtex R&D technology platforms, as they relate to the science, the opportunity and the strategy to deliver value
- The commercial exploitation of SIR-Spheres® Y-90 microspheres to expand our ~2% penetration to date remains a priority
- SIR-Spheres® evolution will not be discussed today
- Three existing technology platforms will be discussed in detail: Radioprotector (RP), Carbon-Cage Nanoparticles (CCN) and Polymer Coated Nanoparticles (PCN)
- Additionally, Sirtex will be introducing a brand new platform, denoted the Histone Inhibition Program (HIP), which is moving rapidly to first-in-man clinical studies

Introduction (cont.)

- Our platforms have been independently critiqued and assessed by PharmaVentures who have been retained as a technology consultant to Sirtex to provide ongoing advice on commercial opportunities and evaluate strategic options for the R&D portfolio
- Expert presentations by our technology consultant, Dr Fintan Walton at PharmaVentures and a globally recognised leader in the field of sepsis, our initial area of focus for the Histone Inhibition Program, by Professor Rinaldo Bellomo
- Dr Steve Jones, Global Head of R&D from Sirtex will present on the science
- Scientific collaborators from our programs will also present today and are able to answer specific questions on the science during the Q&A sessions
- An expert clinician briefing to follow in 1Q CY17, prior to the expected results from SARAH, SIR*ve*NIB and SIRFLOX/FOXFIRE/FOXFIRE Global studies – details to be announced in due course

Agenda

Introduction and Overall R&D Strategy	Mr Gilman Wong
Scientific Perspectives	Dr Steve Jones
Radioprotector (RP)	
Carbon-Cage Nanoparticles (CCN)	
Polymer Coated Nanoparticles (PCN)	
Commercial Opportunity - RP, CCN, PCN	Dr Fintan Walton
Sirtex Strategy - RP, CCN, PCN	Mr Gilman Wong
Q&A	
Scientific Perspectives – Histone Inhibition Program (HIP)	Dr Steve Jones
Medical Perspectives – Application of HIP in Sepsis	Professor Rinaldo Bellomo
Commercial Opportunity - HIP	Dr Fintan Walton
Sirtex Strategy - HIP	Mr Gilman Wong
Q&A	
Summary & Review	Mr Gilman Wong

Overall R&D strategy

2020Vision

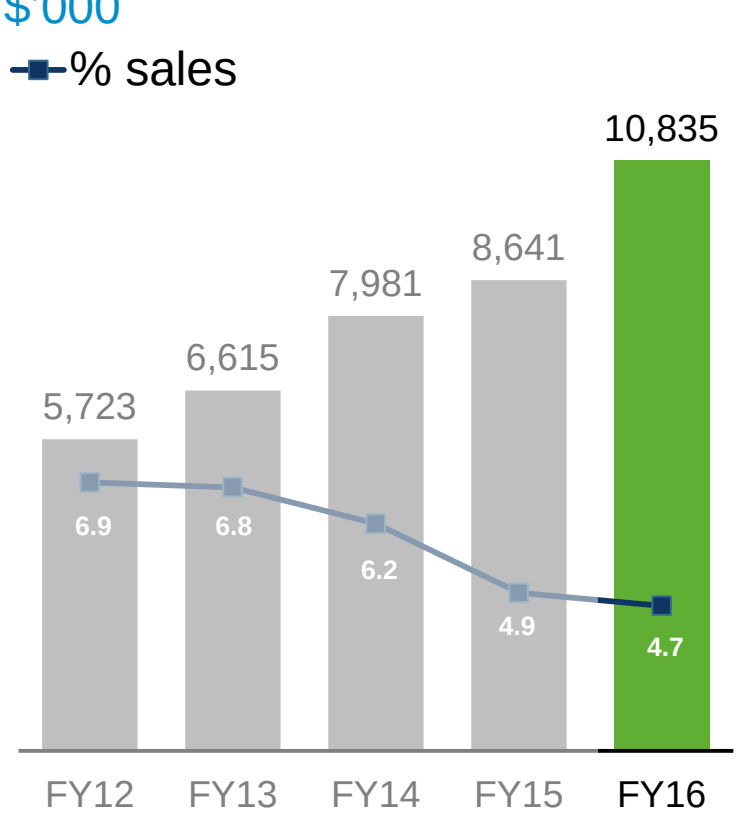
Four key technology platforms

- Radioprotector (RP)
- Carbon-Cage Nanoparticles (CCN)
- Polymer Coated Nanoparticles (PCN)
- Histone Inhibition Program (HIP)

Total R&D investment

- Measured spend across four key technology platforms, and improvements to SIR-Spheres Y-90 resin microspheres
- Key Pillar of *2020Vision* Strategy
- FY16 growth of 25.4%
- 5 year CAGR of 14.0%
- 5 year average spend of 5.9% of sales

Total R&D investment *



** Includes both capitalised and expensed items*

Leading academic collaborators

Leading academic collaborators are the centres of excellence through which the Intellectual Property (IP) rights have been secured by Sirtex and an R&D investment made

Radioprotector (RP)

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Carbon-Cage Nanoparticles (CCN)

ANU
THE AUSTRALIAN NATIONAL UNIVERSITY

Polymer Coated Nanoparticles (PCN)

THE UNIVERSITY OF SYDNEY

Histone Inhibition Program (HIP)

ANU
THE AUSTRALIAN NATIONAL UNIVERSITY

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Prestigious associated collaborators (all R&D)

National Cancer Centre Singapore
SingHealth

THE UNIVERSITY OF MELBOURNE

Royal North Shore Hospital

TetraQ
Integrated Drug Development

Chris O'Brien Lifehouse

Singapore General Hospital
SingHealth

KOLLING INSTITUTE

Michigan Technological University
1885

Griffith UNIVERSITY

bio21 institute

CSIRO

UNSW
THE UNIVERSITY OF NEW SOUTH WALES

Biomodels
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Scientific perspectives

Dr Steve Jones
Global Head of R&D

Radioprotector - Science

- Key collaborator **Professor Roger Martin**, Molecular Radiation Biology Lab, Peter MacCallum Cancer Centre
- A new DNA binding anti-oxidant for the protection of normal tissue during radiotherapy, with a unique mode of action
- Initially being developed as a topically applied drug for prevention of Oral Mucositis (OM) in Head & Neck Cancer (HNC) patients
- Other potential applications in radiotherapy include protection of other mucosal tissue, e.g. rectal (prostate cancer), oesophageal (lung cancer) or even hair follicles
- Possible applications for systemic administration, e.g. in diagnostic radiology and in non-medical military and civilian scenarios

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Radioprotector – Science (cont.)

Radioprotector for Oral Mucositis (OM) - a debilitating side-effect of radiotherapy

- OM is a common and debilitating side effect of radiation treatment for HNC
- Severe OM, defined by the World Health Organization as Grade 3 or 4 occurs in 60% to 80% of patients
- Severe OM may result in interruptions in radiation treatment, which can compromise the otherwise good prognosis for tumour control in many of these patients
- Patients suffer significant pain, may develop serious infections, and may be unable to eat solid food or even drink liquids

Radioprotector – Science (cont.)

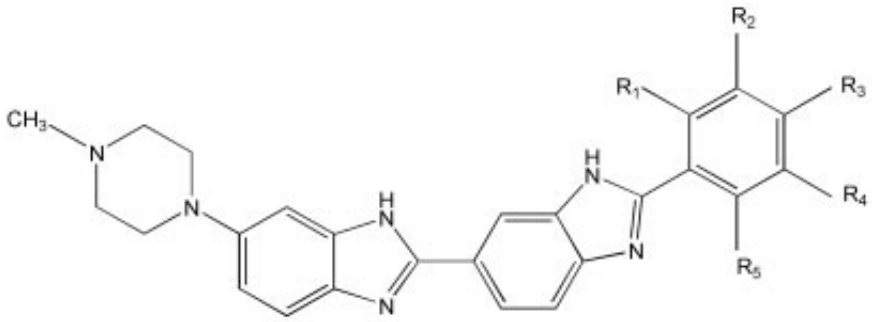
What makes a good Radioprotector?

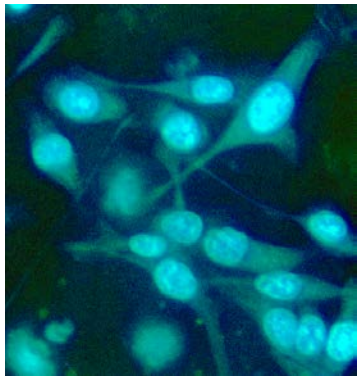
Addressed by topical application

- Does not compromise effect of radiation on tumour killing
- Low toxicity without undesirable secondary effects
- Convenient dose administration appropriate to a fractionated Radiotherapy (RT) regime
- Improves the therapeutic ratio; i.e. has a good Dose Modification Factor (DMF)
- Reasonable cost effectiveness /economically viable
- Improvement in both acute side effects of radiation and long term quality of life

Radioprotector – Science (cont.)

Sirtex DNA-binding Radioprotector compounds

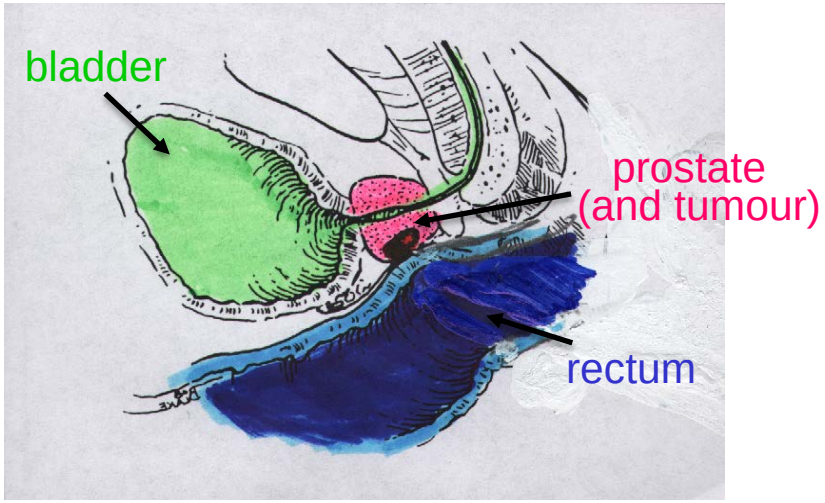




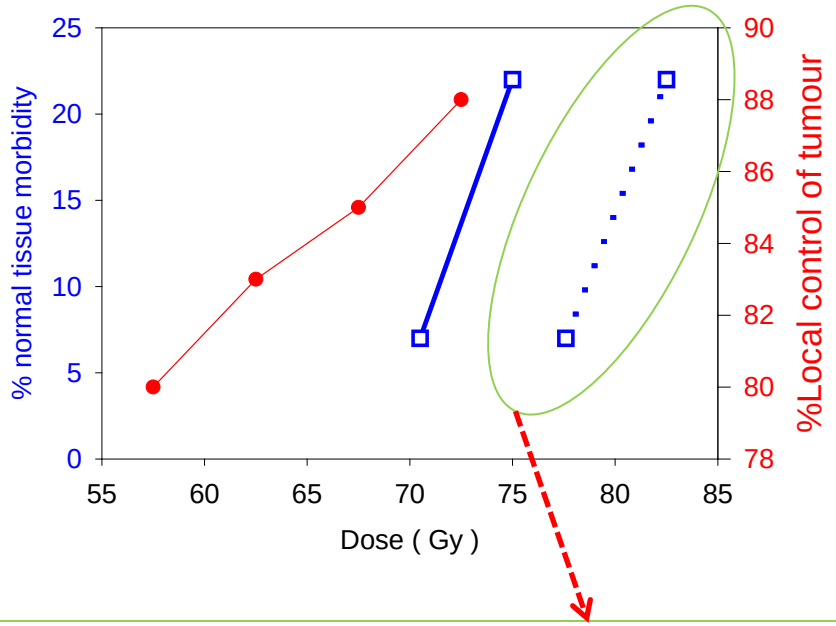
- Based on Hoechst DNA-staining compound scaffolds
- Fluorescent (i.e. drug delivery is imagable under the microscope)
- Bind in the minor groove of DNA, with high affinity
- Patents (granted and filed) to cover 1st, 2nd Gen. compounds; coverage to 2030. New IP for 3rd Gen. compounds to be filed soon.

Radioprotector – Science (cont.)

The concept of Dose Modification Factor (DMF)



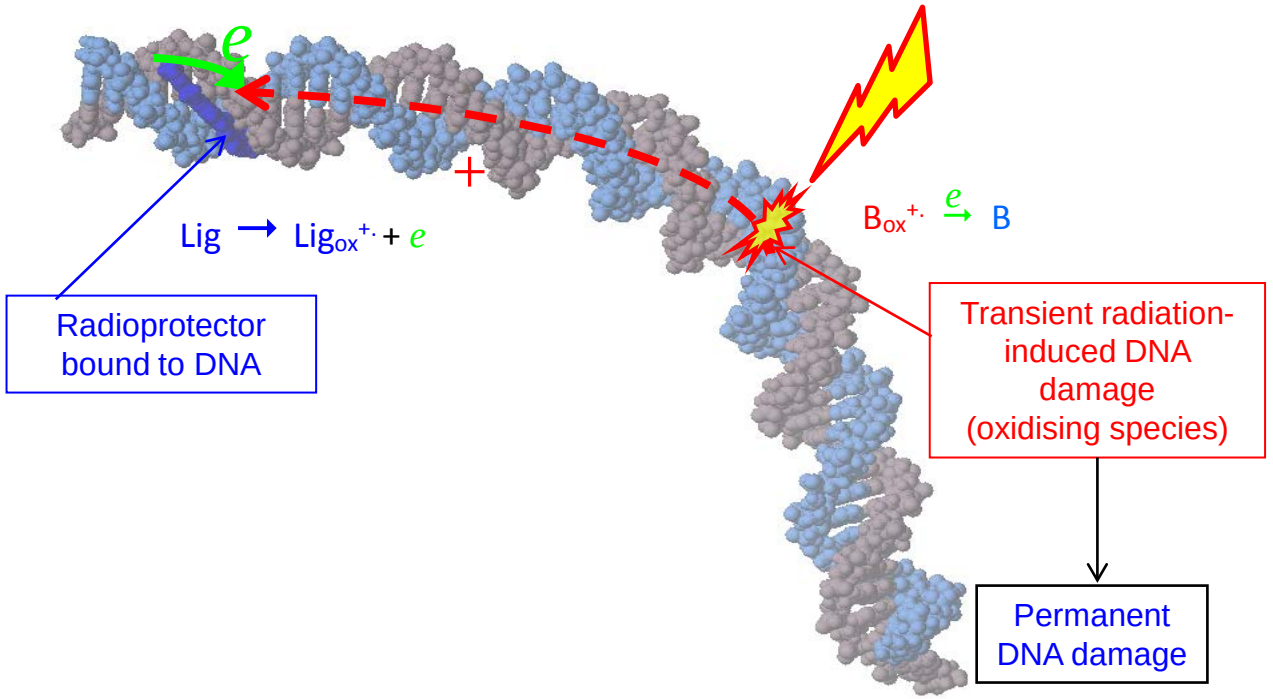
Dose-response relationships in RT of prostate cancer



A small improvement in therapeutic ratio (10%, i.e. DMF ~ 1.1) can have significant positive consequences on treatment outcomes

Radioprotector – Science (cont.)

Mechanism of Action (MOA)



- Novel MOA – electron donation to repair damaged DNA lesions
- Synergistic activity with other agents with unrelated MOA (e.g. Amifostine)

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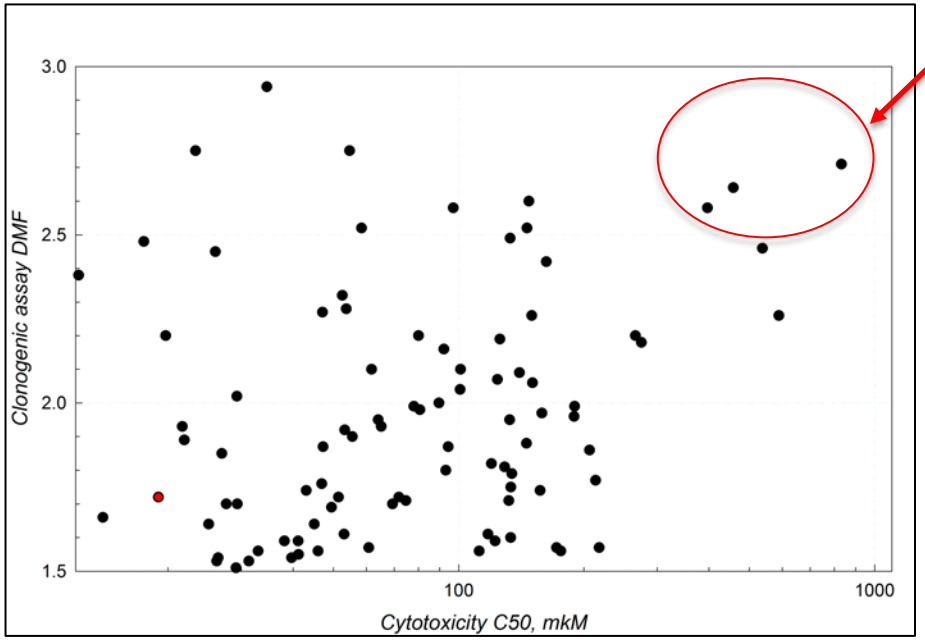
Radioprotector – Science (cont.)

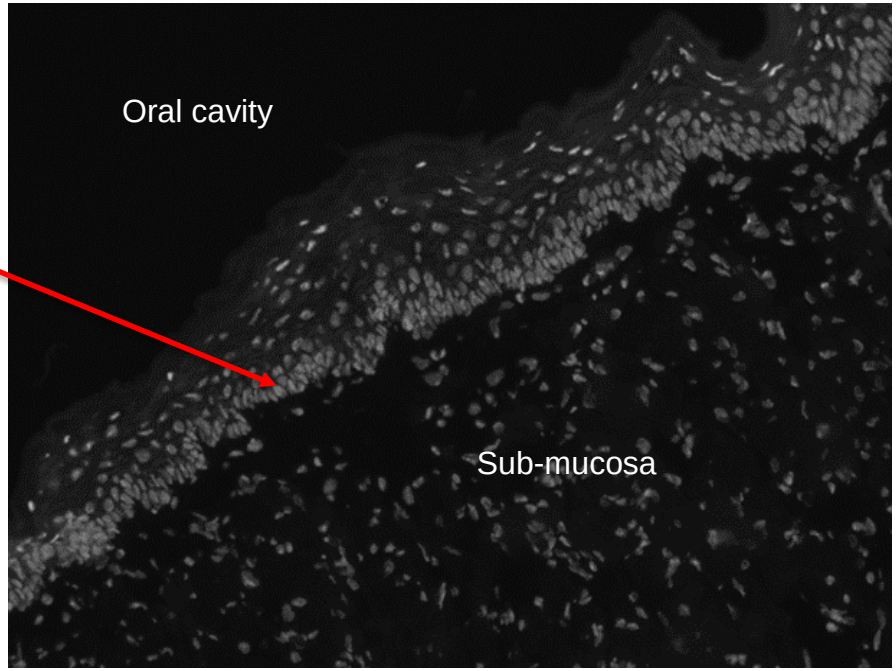
- More than 250 compounds synthesised and tested to date
- Lead optimisation – to improve DMF and reduce cytotoxicity
- 2-3 lead candidates identified to date



Radioprotector – Science (cont.)

- Delivery of drug to target cells *in vivo* has been a challenge
- Several strategies have been attempted
- A prodrug strategy appears to have overcome the obstacles

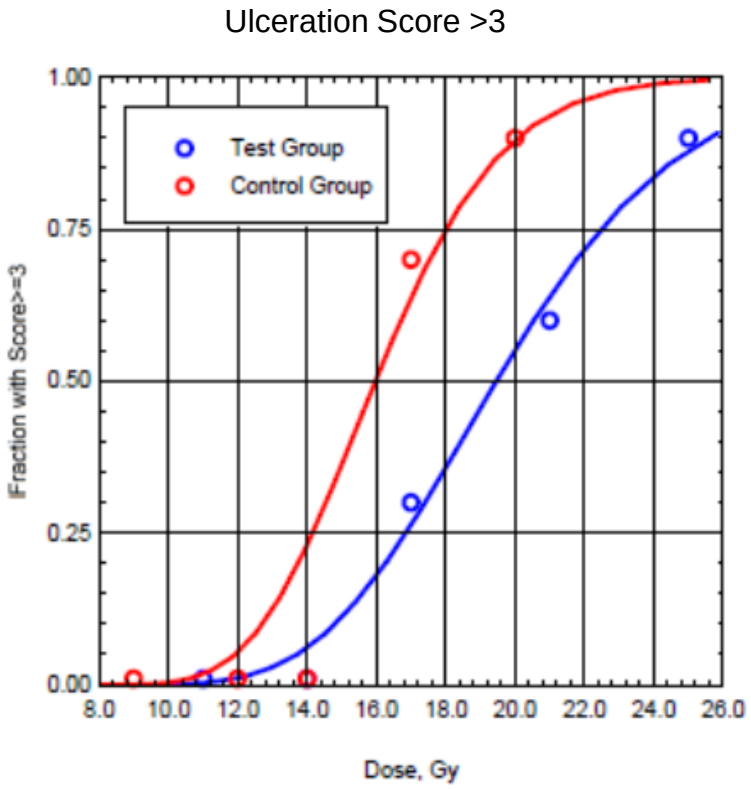
Target for radioprotector delivery is nuclei of basal cells, which include stem cells



Fluorescent Microscope image of mucosal tissue section taken from oral cavity after topical administration of radioprotector

Radioprotector – Science (cont.)

- Pre-clinical *in vivo* model of unfractionated RT (i.e. single doses), measures induced ulceration
- Administration via topical application
- A DMF of 1.2 obtained
  - minimal requirement for clinical impact
- More testing required in fractionated-model of RT



Radioprotector – Status of development

- Lead candidate identification from *in vitro* screening
- Optimise formulation for topical delivery
- Development of fractionated RT protocol for *in vivo* screening of lead candidates

Radioprotector – Next steps

- **Key Milestone**: demonstrate topical radioprotection efficacy in fractionated RT protocol 1Q CY17
- Select final lead during 1H CY17
- Move to formal pre-clinical toxicology during CY17
- Anticipate commencement of human clinical studies during CY18

Carbon-Cage Nanoparticles (CCN)

Key Collaborators

- **Prof Ross Stephens,** The Sirtex Chair, Research School of Physics and Engineering, Australian National University
- **Prof Tim Senden**, Director, Research School of Physics and Engineering, Australian National University

Carbon-Cage Nanoparticles – Science

A unique nanoparticle platform technology applicable to a diverse range of medical applications, such as:

- Diagnostic imaging of blood clots (e.g. Deep Vein Thrombosis or DVT)
- Blood perfusion imaging for diagnosis of Pulmonary Emboli (PE)
- Image guided surgery for liver cancer
- Radiolabelling medical devices/implants, e.g. microspheres, stents
- Targeted therapy of tumours
- Screening drug candidates for treatment of lung conditions

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Carbon-Cage Nanoparticles – Science (cont.)

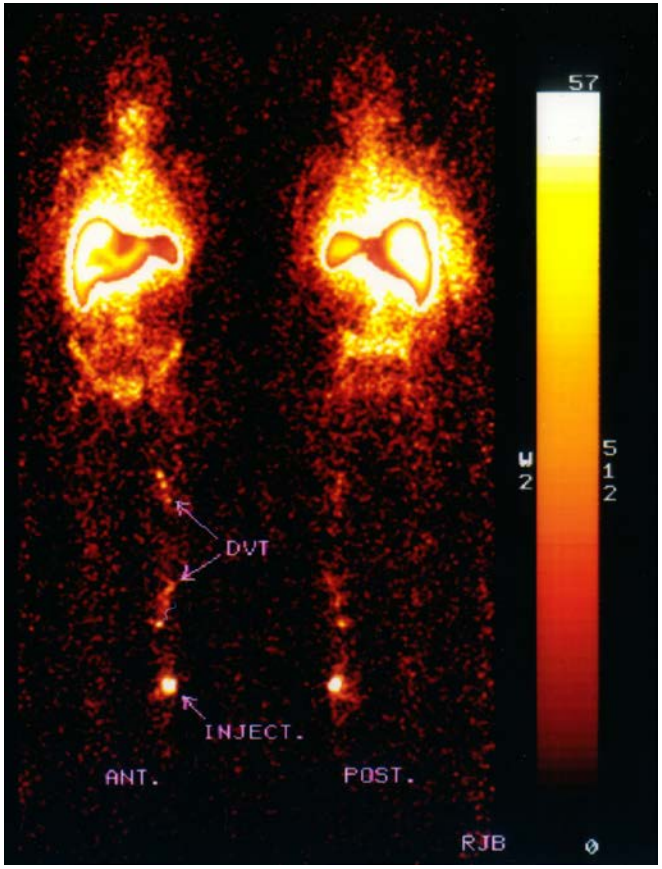
What are Carbon-Cage Nanoparticles?

- CCN consists of nanoparticles of a metallic radioisotope encapsulated in graphitic carbon
- The isotope is held tightly in a carbon cage, and chemically shielded by carbon
- Only graphitic carbon is “seen” by its environment
- A range metallic isotopes can be encapsulated to suit the desired application, e.g. $Tc^{99}m$ for imaging, Y^{90} for therapy or Lu^{177} for both
- Enables very high specific activities (e.g. 20 GBq/mg)
- Provides a stable label without complex chemistry
- Patent coverage until at least 2028

Carbon-Cage Nanoparticles – Science (cont.)

CCN for the diagnosis of blood clots

- CCN has been shown to bind to fibrin in blood clots
- Confirms potential application in DVT imaging diagnosis
- Similar diagnostic potential anywhere pro-coagulant activity is depositing fibrin
- When a graphite surface is exposed to blood it very rapidly acquires a protein coat of classical adhesion proteins including fibrinogen[1]
- The fibrinogen coated nanoparticles are then rapidly incorporated into actively growing fibrin clots

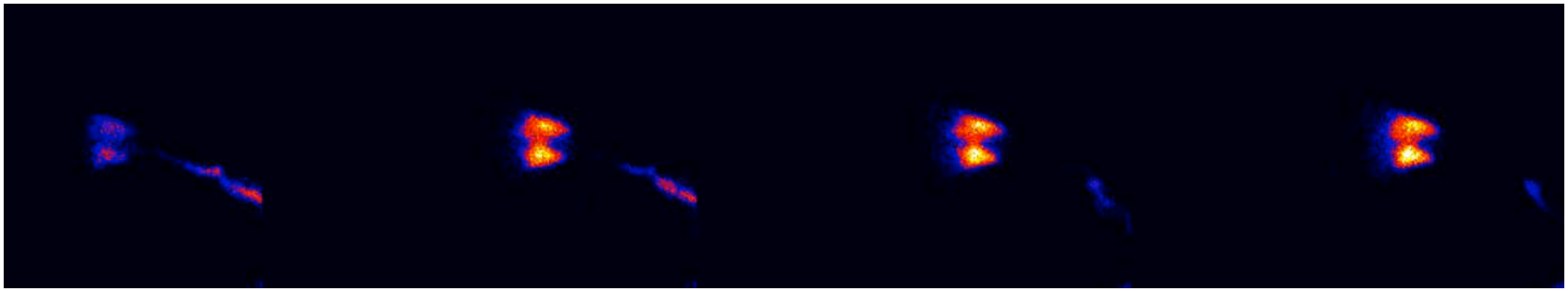


[1] *Source: Eriksson & Nygren (1997) J Biomed Mater Res 37:130-136*

Carbon-Cage Nanoparticles – Science (cont.)

CCN as replacement for MAA[1] in lung perfusion imaging

e.g. potential application in V/Q scanning for diagnosis of pulmonary emboli



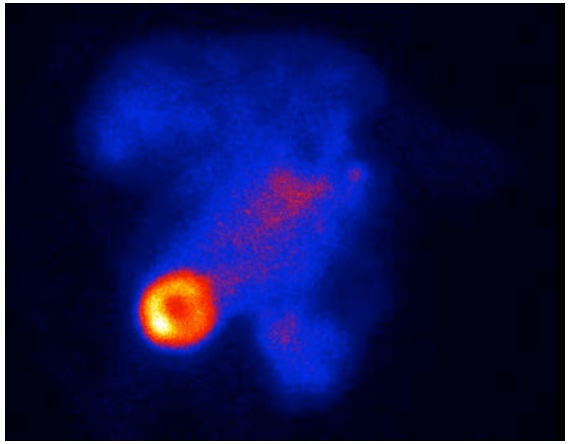
Sequence of gamma images following i.v. injection of poly-lysine coated CCN-Tc99m in a pre-clinical model clearly shows accumulation in the lung (images 30 seconds apart)

[1]*MAA : Macro Aggregated Albumin*

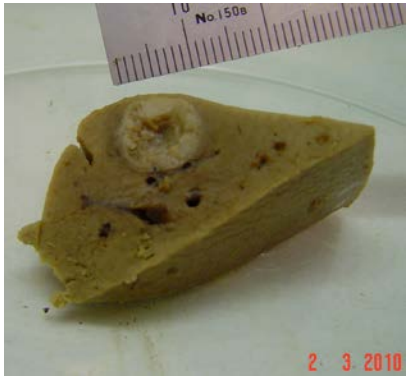
Carbon-Cage Nanoparticles – Science (cont.)

CTH[1] coated CCN accumulate at tumour sites

- Administration of CTH/CCN containing Tc99m via the hepatic artery
- Enables regional imaging of tumour stroma
- May be used to assess staging of tumours & impact of anti-angiogenic therapy
- Potential to be used to target therapy or during image guided surgery



Gamma camera image showing accumulation of CTH/CCN containing Tc99m in liver tumour in a pre-clinical model

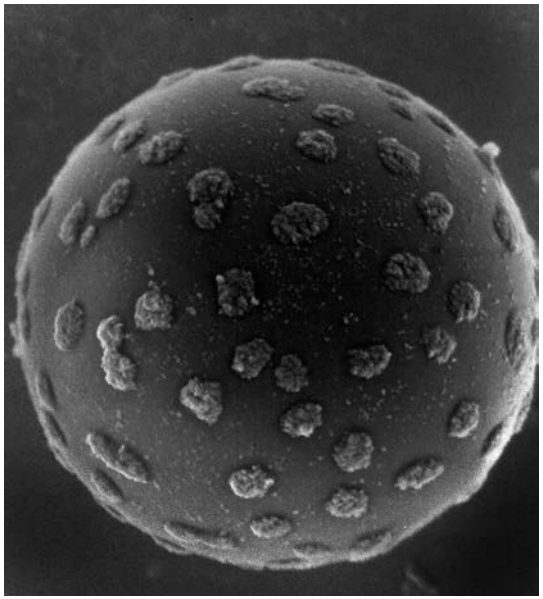


Fixed liver tissue containing tumour

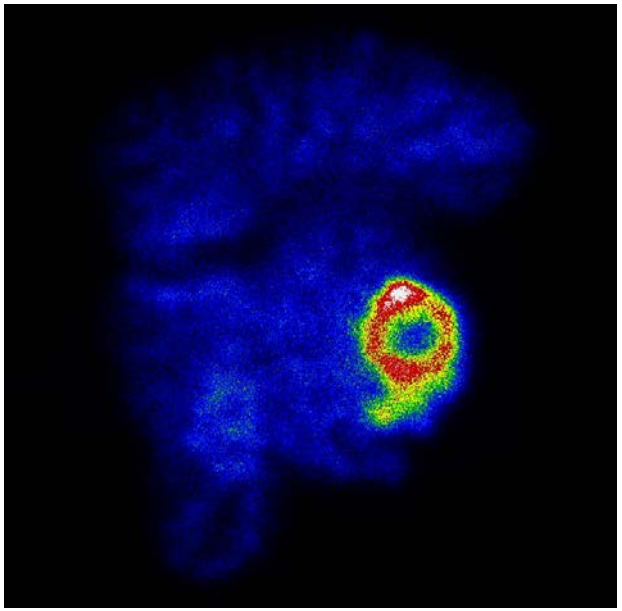
[1]CTH : Calf Thymus Histone; Source: Stephens et al Biomaterials 2015;39:218-224

Carbon-Cage Nanoparticles – Science (cont.)

CCN can be used to radiolabel synthetic polymers



SEM image of CCN-Tc99m labelled microsphere



Gamma image of the liver after IHA instillation of CCN-Tc99m-microspheres in preclinical model of liver cancer, shows accumulation around the tumour

Carbon-Cage Nanoparticles – Key features

- Diverse range of possible applications
- Low production cost by benchtop machine
- Long track record of safety (extensive clinical use already in certain configurations)
- High stability, can be autoclaved
- Non-biologic
- High specific activities (e.g. 20 GBq/mg)
- Stable label without complex chemistry

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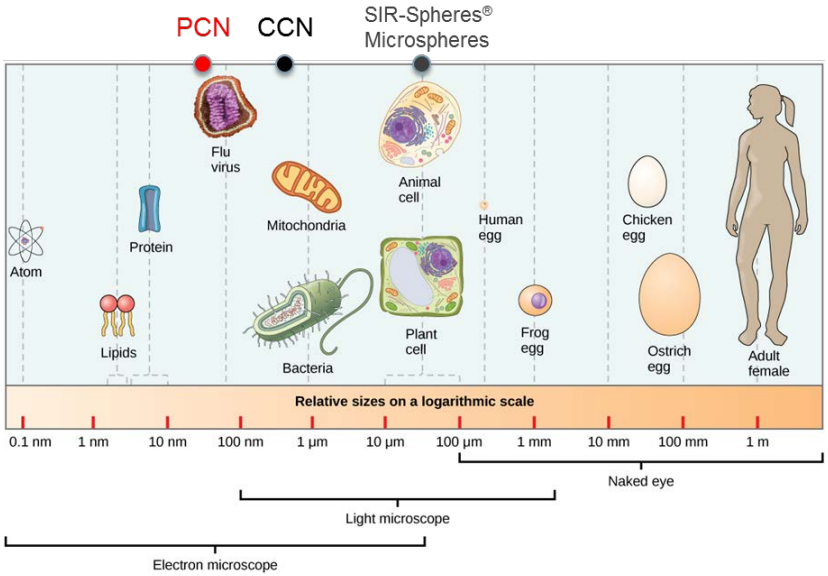
Carbon-Cage Nanoparticles – Next Steps

- Ascertain optimal regulatory pathway (device or drug)
- Complete pre-clinical development of CCN for DVT/PE imaging during CY17
- *In vivo* – studies in pre-clinical models to further test toxicity, safety and efficacy, pharmacokinetics, biodistribution, intracellular fate of CCN when administered intravenously
- Targeting the commencement of clinical studies during CY18

Polymer Coated Nanoparticles (PCN) – Science

- Key Major Collaborator **Professor Brian Hawkett**, Key Centre for Polymers and Colloids, University of Sydney
- Nanoparticles have unique properties that could be exploited in many medical applications
- They are neither molecules nor a bulk solid like a microparticle
- Ideally, they would be invisible ('stealth like') as they circulate through the body with their payload, looking for their target



Polymer Coated Nanoparticles – Science (cont.)

- If such behaviour in biological systems can be achieved by nanoparticles then there are many areas of unmet need that could be satisfied

Imaging	improved MRI contrast agents multimodal PET/MRI agents for improved diagnosis of disease
Drug Delivery	better targeting of existing drugs, genes or biological agents for improved therapeutic effect and reduced toxicity
Cell Separation/ Cell Therapy	tumour cell detection, monitoring of diseases, e.g. stroke, MS, cancer
Other	hyperthermia, enhancing external beam RT, ‘lab on a chip’ diagnostic technologies, transfection of DNA and RNA, cosmetics

- Unfortunately, with current technologies, the nanoparticle ‘dream’ remains elusive

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Polymer Coated Nanoparticles – Science (cont.)

Existing technologies have failed

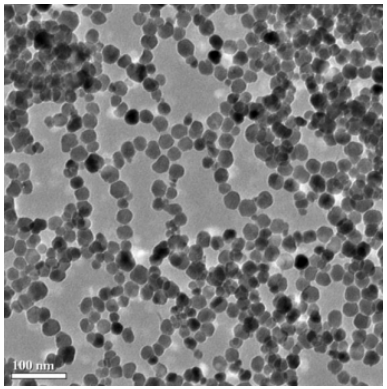
Sirtex PCN are suitable for widespread use

**The Sirtex PCN technology platform has patent coverage beyond 2031 in all major markets*

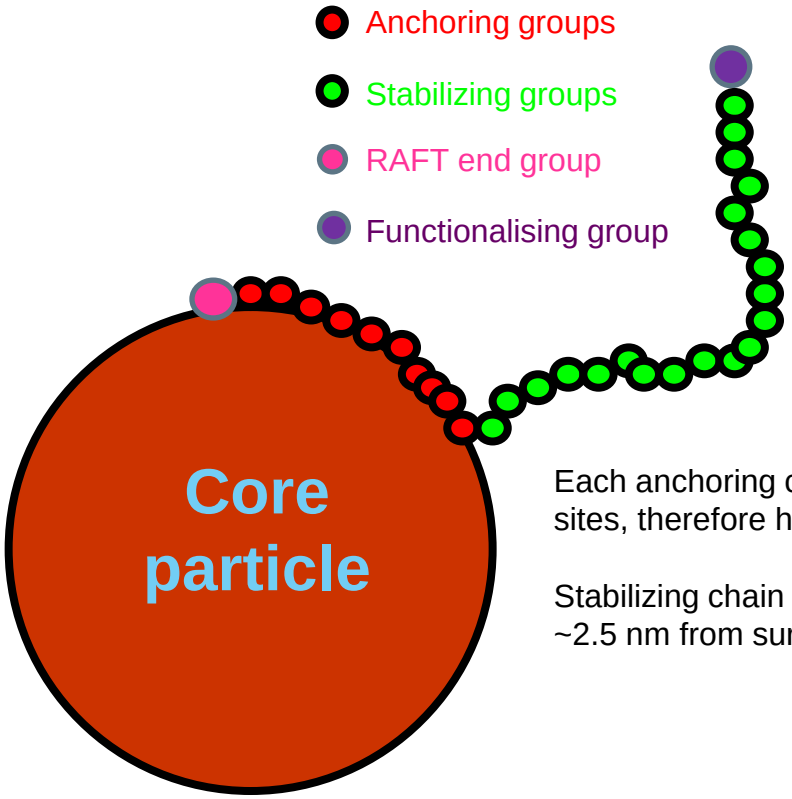
Polymer Coated Nanoparticles – Science (cont.)

Two advanced technologies combined to form one novel platform

1. Sirtex Iron Oxide Nanoparticles (25nm diameter)
2. Polymer coating technology for steric stabilisation based on Reversible Addition Fragmentation chain Transfer (*RAFT*); licensed from CSIRO



Electron micrograph showing 25nm Sirtex Iron Oxide Nanoparticle cores



Each anchoring chain has many anchoring sites, therefore hard to displace

Stabilizing chain can extend from as little as ~2.5 nm from surface

Polymer Coated Nanoparticles – What is RAFT?

- Invented by CSIRO and developed in partnership with DuPont
- RAFT technology provides control over the formation of polymer structures and offers the ability to tailor these materials for different applications and is scalable
- Enables the synthesis of polymers that were impossible pre-RAFT
- RAFT is a form of controlled free radical polymerisation that enables design of polymers with enhanced properties. RAFT can be used with a wide range of monomers and reaction conditions and gives unprecedented control over polymer size, composition and architecture.
- Some of the companies that already use RAFT in their commercial products include: LUBRIZOL – lubricants; DUPONT - Photoresist Polymers; MIRUS BIO – Biopolymers
- Also used in industrial coatings, personal care products and industrial polymers

Source: http://www.csiro.au/en/Research/MF/Areas/Chemicals-and-fibres/Chemistry-and-biotechnology/RAFT

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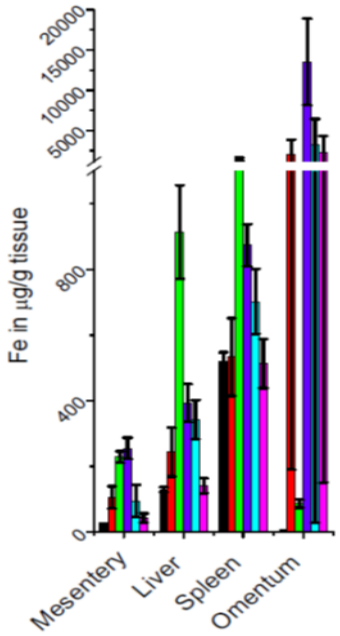
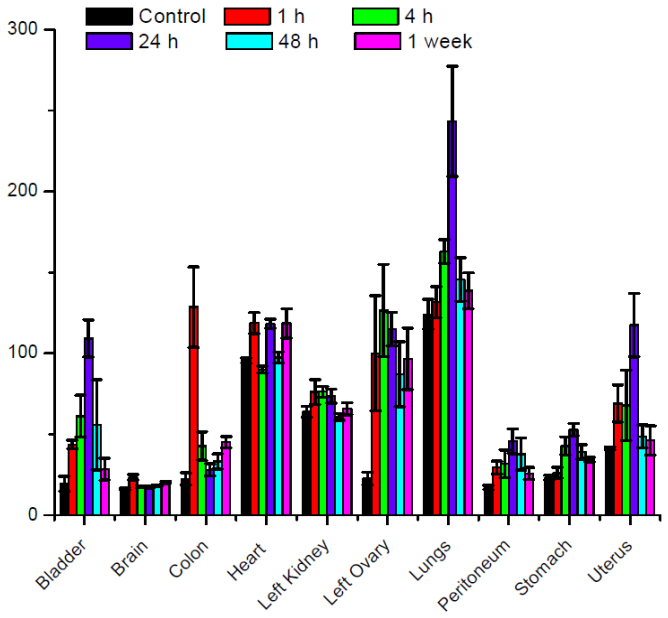
Polymer Coated Nanoparticles – Biodistribution

- Our results demonstrate single IP administration of PCN is non-toxic and biodistribution is broad but transient – PCN cleared from all tissues within one week
- The main clearance mechanisms of PCN appear to be via macrophages & faecal excretion
- Such advantageous biodistribution characteristics underpin a number of *in vivo* applications



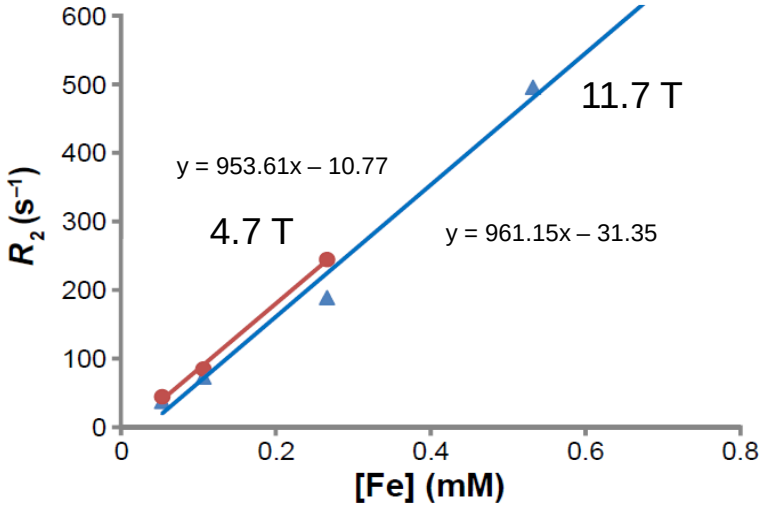
High accumulation in the omentum, a common metastatic site in ovarian cancer, may prove beneficial for PCN-mediated cancer therapy



Source: Bill Walsh Translational Cancer Research, Kolling Institute of Medical Research

Polymer Coated Nanoparticles – MRI Contrast

- PCN have excellent R_2 relaxivities for T2 weighted MRI imaging
- Approx. 10 times better than published result for commercial sample (Ferridex)



R_2 = 956 $mM^{-1}sec^{-1}$

- Currently pursuing further studies of PCN potential as MRI contrast agent *in vivo*

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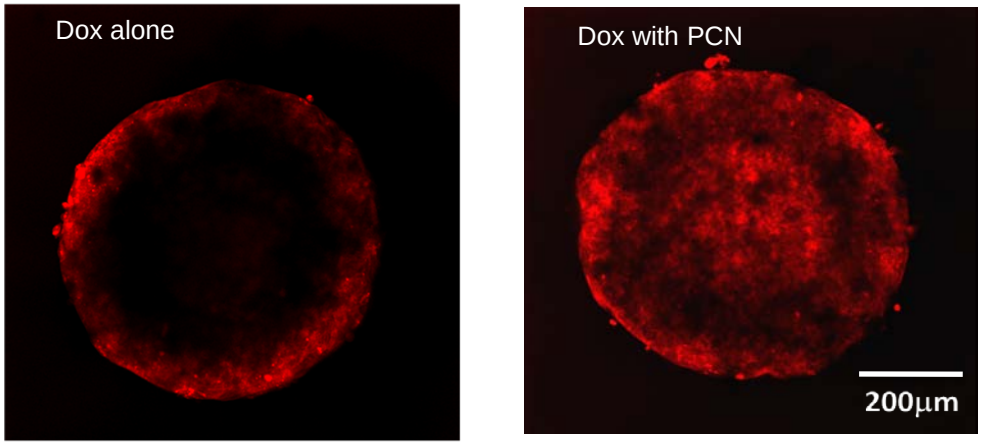
Polymer Coated Nanoparticles – Cancer Therapy

- Enhanced penetration of chemotherapy drugs into solid tumour spheroids when co-administered with PCN
- Likely applications in drug delivery and improved therapy of poorly vascularised solid cancers



Red fluorescence shows penetration of Doxorubicin (Dox) into tumour spheroid - clearly enhanced penetration when Dox co-administered with PCN

- Currently investigating therapeutic efficacy of PCN combined with chemotherapy in pre-clinical models of metastatic ovarian cancer

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Polymer Coated Nanoparticles – Features and benefits

KEY FEATURES & BENEFITS

Novel nanoparticle stabilization system that can work on diverse nanoparticles such as Fe_2O_3, silica and gold	**Improved stability under diverse environments** ▪ at physiological conditions ▪ after autoclaving ▪ after multiple freeze-thaw cycles
Good safety profile	**Clearance without toxicity**
Diverse biodistribution profile	**High accumulation in omentum** **Low accumulation in brain, heart, bladder, lungs, uterus, stomach and kidney**
Potential to improve negative contrast in MRI	**Increase R_2 relaxivity- up to 1000$mM^{-1}s^{-1}$**
Proprietary nanoparticle production capability	**Efficient manufacture at low production cost** ▪ potential for scale up ▪ high degree of size and quality consistency achievable

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Polymer Coated Nanoparticles – Next Steps

- *In vitro* – toxicity studies including degradation of PCN compared to other reference products
- *In vivo* – studies in pre-clinical models to further test toxicity, safety and efficacy, pharmacokinetics, biodistribution, intracellular fate of PCN when administered intravenously
- Pre-clinical MRI imaging data demonstrating the equivalence/superiority of Sirtex PCN compared to currently available contrast agents expect to complete in 1H CY17
- Complete proof of concept drug delivery studies in metastatic ovarian cancer model in 1H CY17

Thank you

Commercial Opportunities

Dr Fintan Walton
CEO & Founder
PharmaVentures

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About

- Consultant to Sirtex Medical, engaged to:
  - Assess the four platform technologies discussed today
  - Ascertain the commercial opportunity
  - Evaluate strategic options
- Our mission is to serve and support all life science corporations, regardless of size, in successful deal making
- More than 700 assignments including pharma M&A, Licensing, Strategy, Valuation and Expert Services

PharmaVentures
Experts in deals and alliances

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Overview of program potential

- The Radioprotector (RP), Carbon-Cage Nanoparticles (CCN) and Polymer-Coated Nanoparticles (PCN) technologies have applications in both moderately sized markets and large sizeable markets

Radioprotector	CCN	PCN
▪ Oral Mucositis	▪ DVT Imaging Agent	▪ MRI Imaging Agent
▪ Radiation Induced Proctitis	▪ Perfusion Imaging Agent	

Applications in moderately sized markets or market share

Reasonably Advanced

Further R&D Required

▪ Targeted Therapies	▪ Drug Delivery
	▪ Cell Separation/Therapy

Sizeable Markets (i.e. US$500m plus)

Source: PharmaVentures, Sirtex Medical

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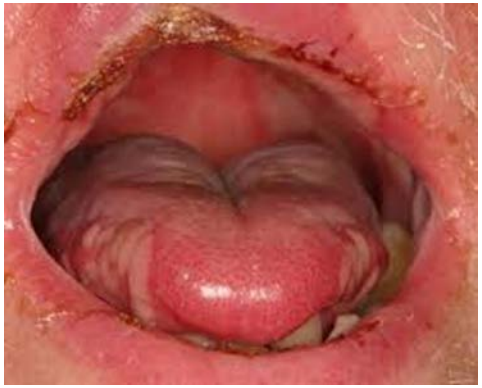
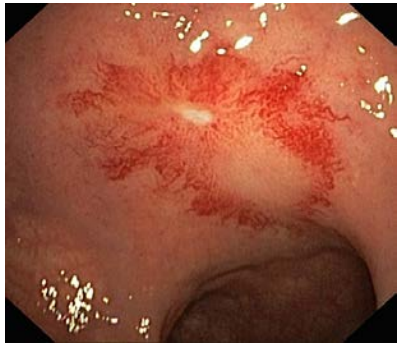
Radioprotector – Clinical indications

- **Oral Mucositis (OM):** debilitating side-effect of radiotherapy and chemotherapy treatments
  - Severe OM (grade 3 and 4) occurs in up to 80% of head and neck cancer (HNC) patients treated with radiotherapy[1]
  - Annual incidence of HNC in Northern America, Europe and AU/NZ approx. 200,000 p.a.[2] with ~75% patients treated with radiotherapy



- **Radiation proctitis:** radiation induced damage to the small bowel
  - Acute form occurs in ~75% of patients receiving pelvic radiotherapy for prostate, bladder, cervix, uterus, rectal and anal cancers[3] (US incidence alone ~500,000 cases p.a.[2]) Chronic form occurs in 2-20% of patients
  - ~50% will receive radiotherapy treatment[4]



Sources: [1] Elting, L. S., et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy . Cancer, 113: 2704–2713. doi: 10.1002/cncr.23898; [2] GLOBOCAN, PharmaVentures; [3]Grodsky MB, Sidani SM. Radiation Proctopathy. Clinics in Colon and Rectal Surgery. 2015;28(2):103-111. doi:10.1055/s-0035-1547337; [4]Chamie K, Williams SB, Hu JC. Population-Based Assessment of Determining Treatments for Prostate Cancer. JAMA Oncol. 2015;1(1):60-67. doi:10.1001/jamaoncol.2014.192.

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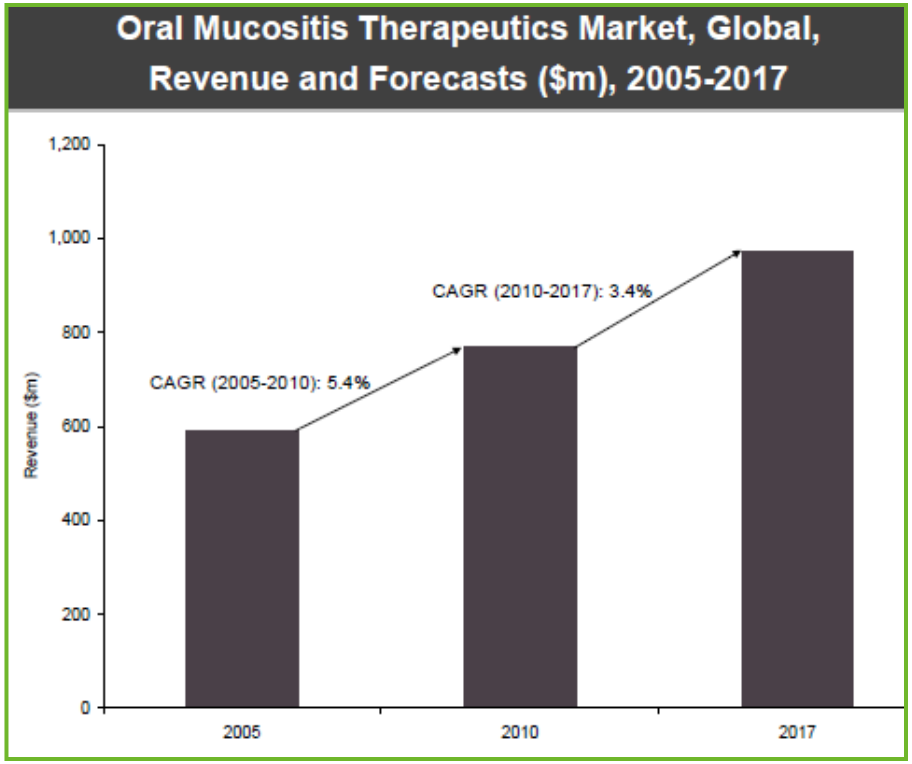
Radioprotector – Oral Mucositis

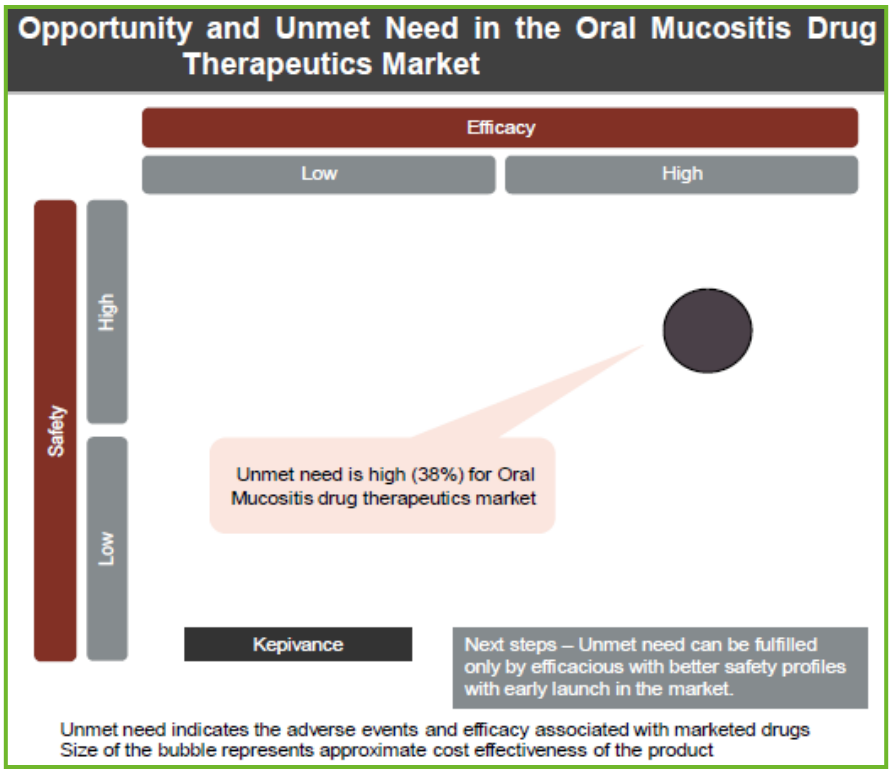
- Market size forecast to reach US$974m by 2017[1]
- Approx. 600,000 new cases globally each year
- One approved therapeutic agent – Kepivance® (palifermin), indicated for severe OM in bone marrow cancers
- Other treatments involve mouth washes/oral rinses and over-the-counter products



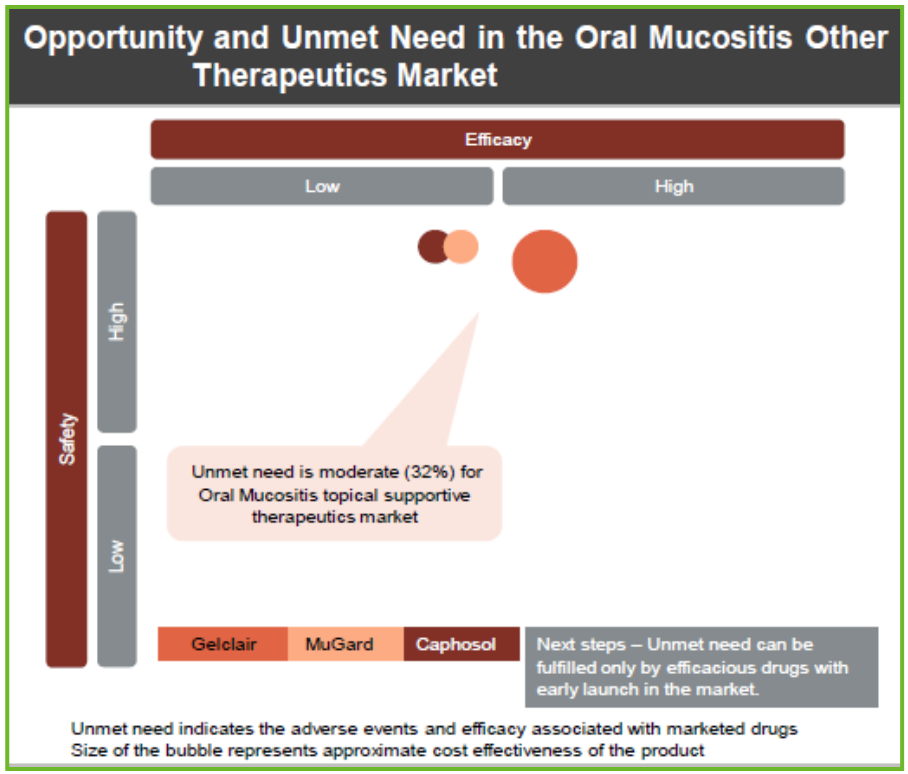
[1] *Oral Mucositis Therapeutics - Pipeline Assessment and Market Forecasts to 2017. Source: GlobalData*

Radioprotector – Oral Mucositis

- Significant unmet need for new effective agents to treat OM
- No drug currently approved to treat severe OM in head and neck cancer



Source: GlobalData



Source: GlobalData

Radioprotector – Radiation Proctitis

- There are no effective therapeutics to prevent the development of CRP. Drugs such as amifostine, sucralfate, or sulphasalazine have shown limited benefit and are not widely used[1]
- Potential addressable market size of US$205m[2] by 2028 in prostate cancer alone

	Cancer Incidence[3]					
Region	Prostate	Bladder	Cervix	Uterus	Colorectum	**TOTAL**
USA	233,159	68,639	12,966	49,645	134,349	498,758
European Union (EU-28)	345,195	124,188	33,679	64,929	345,346	789,149
Australia	21,966	3,489	793	2,268	15,869	44,385
New Zealand	3,330	266	145	492	3,018	7,251
Japan	55,970	22,042	9,390	11,449	112,675	211,526
ROW	435,296	335,357	470,651	190,822	749,345	2,181,471
TOTAL (WORLD)	**1,094,916**	**429,793**	**527,624**	**319,605**	**1,360,602**	**3,732,540**

[1]Source: Vanneste BGL, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: tricks to prevent and treat. International Journal of Colorectal Disease. 2015;30:1293-1303. doi:10.1007/s00384-015-2289-4. [2]Source: PharmaVentures , [3]Source: GLOBOCAN

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Carbon-Cage Nanoparticles – Options

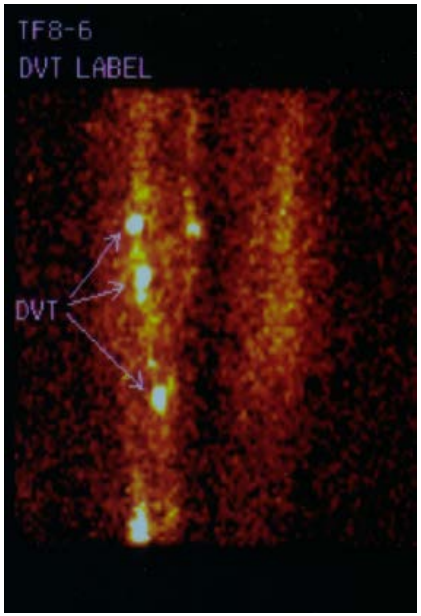
Multiple applications to consider, focus on more advanced opportunities first

DVT/PE Imaging	Perfusion Imaging	Liver Tumour Imaging	Microspheres/ Labelling	Targeted Therapy
▪ Use of CCNs as an imaging agent for DVT diagnosis ▪ Potentially application closest to clinical development ▪ Potentially to be regulated as a medical device ▪ Development timelines of potentially 2-4 years (CE Mark)	▪ CCN as an agent for lung perfusion imaging ▪ Proof of concept in pre-clinical models ▪ Potentially drug regulatory pathway	▪ Use of histone coated CCN as imaging agent for liver tumours ▪ So far some pre-clinical studies have been done ▪ Could be a drug regulatory pathway ▪ Potential need to address safety of use of histone	▪ Use of CCN to labelled Y-90 microspheres for improving dosimetry of Sirtex liver cancer therapy ▪ Potentially has other applications in dosimetry of other nano or microparticle based therapies ▪ Early stage research	▪ Use of histone coated CCN for targeted cancer therapy using ability to localise in angiogenic zone of tumours ▪ Early stage research

Carbon-Cage Nanoparticles – DVT/PE Imaging

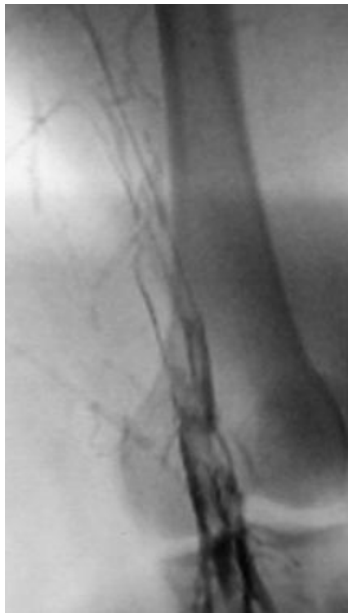
- Worldwide imaging agent market anticipated to reach US$10.7 billion by 2022[1]
- Imaging agents, applicable for CCN have 44% share
  - 48% of global demand from the U.S, 23% Japan and 19% Europe
- CCN may be regulated as medical device, which could see expedited development pathway towards a CE Mark

DVT - CCN



Source: ANU

DVT – Venography



Source: Medscape

Source: Lantheus Medical Imaging S1 June 2015 except (1) which is from Global Industry Analysts ,Sept. 2016

Carbon-Cage Nanoparticles – Imaging and Radiopharma Players

- Characterised by a small number of especially large players globally
- Concentrated distribution
- Many smaller market participants

Selected Larger Players

- Bayer
- GE Healthcare
- Cardinal Health
- Mallinckrodt
- Bracco
- Advanced Accelerator Applications
- Eckert & Ziegler Strahlen- und Medizintechnik AG
- IBA Molecular North America (now Zevacor Pharma)
- Jubilant Life Sciences (Draximage)
- Lantheus
- FUJIFILM RI Pharma

Selected Smaller Players

- COMECER
- DuChemBio
- Eczacibasi
- Erigal
- Samyoung Unitech
- Pharmalucence
- Sanochemia
- VisEn Medical
- Spago Nanomedical
- Progenics
- Macrocylics
- ABT Molecular Imaging

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Selected M&A Deals – Imaging agents

					Enterprise Value to	
Date	Target Business	Target	Acquiror	100% Value	Revenue	EBITDA
Jun 16 (pending)	Fluorine based imaging agent solutions for PET	Ground Fluor Pharmaceuticals (US)	FluoroPharma Medical (US)	n.a.	n.a.	n.a.
Jul 15	Contrast media and delivery systems ('CMDS') business	CMDS business of Mallinckrodt (UK)	Guerbet (FR)	$270m	0.7 x	n.a.
Sep 14	FDG-PET imaging agent business in Italy	FDG-PET imaging agent business of GE Healthcare Srl (IT)	Advanced Accelerator Applications (FR)	€0.7m	n.a.	n.a.
Nov 10	Molecular imaging agents for chronic human diseases	Avid Radiopharmaceuticals (US)	Eli Lilly (FR)	$300m plus $500m contingent	n.a.	n.a.
Aug 10	Fluorescence in vivo imaging agent technology platforms	VizEn Medical (US)	PerkinElmer (US)	$23m	n.m.	n.a.
Nov 09	Contrast agents for MRI and CT	Insight Agents (DE)	Agfa (BE)	€10m	3.6 x	n.a.
Feb 08	Imaging agents	Imaging agents business of Bristol-Myers Squibb (US)	Avista Capital (US)	$525m	n.a.	n.a.
Oct 07	Contrast agents for GI radiology	E-Z-EM (US)	Bracco (IT)	$200m	1.4 x	14.5 x

Source: PharmaVentures, Sirtex Medical

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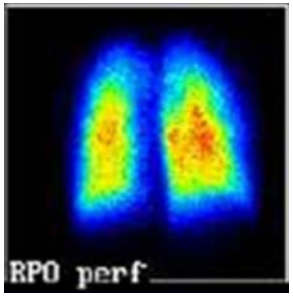
Carbon-Cage Nanoparticles – Perfusion

- Standard of care is intravenous injection of radioactive technetium macro aggregated albumin (Tc99m-MAA) for lung perfusion
- Attractive market attributes
  - Increasing costs of MAA, lack of competition
- Potential market size of US$90 million in Western markets[1]



CCN	MAA
▪ Does not aggregate	▪ Well recognised but has limitations
▪ Smaller amount of material used	▪ Blood product with potential biological hazards (prions, HIV, HCV, and HPV)
▪ Binding is to heparan sulfate in capillary endothelium	▪ Apparent quality control issues
▪ Not biological	▪ Polydispersion
▪ Clear lung specificity	▪ Variations in size
▪ Potential cheap to produce compared to MAA (on site)	▪ Mechanically arrested at limiting diameters of the capillary bed

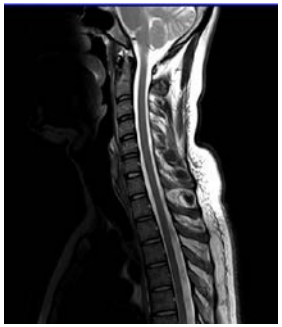
[1] *Source: PharmaVentures*

Polymer Coated Nanoparticles – Options

PCNs have applicability across a wide range of applications

Imaging

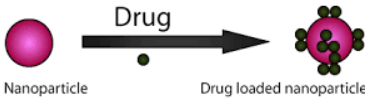
- PCN contrast agent for Magnetic Resonance Imaging (MRI)
- Unmet need for contrast agent which does not cause nephrotoxicity Radioisotope doped PCN shows potential in imaging
- Applicable in multimodal imaging technologies such as PET/MRI which is increasing in popularity
- Growing market segment in diagnostic imaging



MRI NECK AXIAL T2 IMAGE

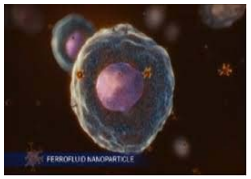
Drug Delivery

- Potential to deliver diverse moieties such as drugs, and genes
- Potential to deliver drugs to target different tissues
- Radioisotope doped PCN shows potential in radiotherapy
- Topical delivery of drugs



Cell Separation/ Cell Therapy

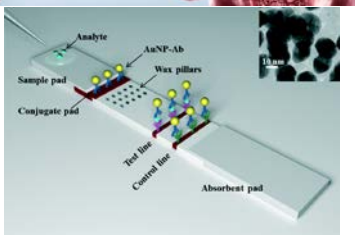
- Tumour cell detection
- Growing market for cell separation technologies
- Effective monitoring of cells in indications such as Ischemic Stroke, Multiple sclerosis, Cancer, Vascular disease
- Magnetically targeted cell delivery



Quadrupole Magnetic cell Sorter- Ikotech

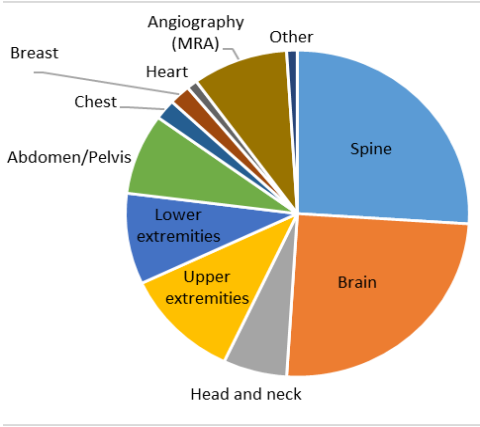
Other Applications

- Hyperthermia therapy
- External beam radiotherapy
- Transfection of DNA and RNA
- Cosmetics – targeting the growing anti-aging market
- Lateral flow immunoassay- to target the increasing demand for fast diagnostic kits
- Hemodialysis - It is proposed that in the presence of iron-oxide nanoparticles ('IONPs') or Gold nanoparticles, hemodialysis efficiency can be increased by improving the rate of osmosis



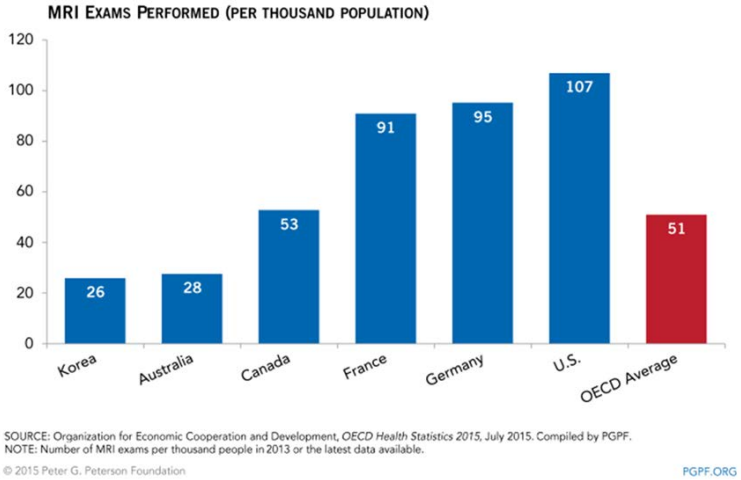
Polymer Coated Nanoparticles – Imaging

- Majority of MRIs are for brain and spine scans
- Market need for low toxicity associated with contrast agents driving development; clinical studies required
- Gadolinium (Gd) contrast used in ~25% of the ~30 million contrast-enhanced MRI procedures conducted worldwide[1]
- Gadavist® sales of US$322 million in 2015[2], the current market leader



Tissue distribution of MR examinations globally.

Magnetic resonance in medicine. 9th edition 2016



[1] *Source: Bayer Healthcare,* [2] *Source: EvaluatePharma*

Polymer Coated Nanoparticles – Drug Delivery

- The global advanced drug delivery market is forecast to grow from c. US$179 billion in 2015 to c. US$227 billion by 2020, a compound annual growth rate (CAGR) of 4.9%[1]

- PCN flexibility to use diverse functional groups for targeting opens the opportunity to develop a drug delivery vehicle that could be loaded with appropriate drug moieties to target different tissues

- Formulation of PCN with doxorubicin aimed at lowering toxicity, lower dose and prolongation of benefit

- Doxorubicin sales of US$376 million in 2015 and expected to grow to US$695 million in 2022[2]

[1] Source: BCC Research, [2] Source: EvaluatePharma

Thank you

Sirtex Strategy – Radioprotector, Carbon-Cage Nanoparticles & Polymer Coated Nanoparticles

Gilman Wong
CEO

Strategy

- The recently concluded report from PharmaVentures has outlined a number of strategies to realise value from our core Radioprotector, Carbon-Cage Nanoparticles and Polymer Coated Nanoparticles technologies

- Progressing discussions with PharmaVentures to develop the optimal commercial pathway forward for each, with the overall objective of implementing an out-licensing strategy

- Each of our programs have defined pre-clinical milestones to achieve

- If the various programs are unable to reach specific pre-clinical milestones in preparation for clinical studies where value realisation is more likely, Sirtex will carefully assess continued funding

Strategy – (cont.)

- For Radioprotector, there is significant potential in:
  - Oral mucositis
  - Radiation proctitis
- For Carbon-Cage Nanoparticles, there is significant potential in:
  - DVT imaging
  - Perfusion imaging
- For Polymer Coated Nanoparticles, there is significant potential in:
  - MRI imaging
  - Drug delivery
- For these three platforms, the overall aim would be to secure a licensing partner prior to the commencement of major clinical studies

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Q&A

Questions

Histone Inhibition Program (HIP) – Scientific perspectives

Dr Steve Jones
Global Head of R&D

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Histone Inhibition Program – Collaborators

Three of Australia's premier scientists are collaborating on HIP

- **Professor Chris Parish**, John Curtin School of Medical Research, Australian National University
- **Professor Ross Stephens**, Research School of Physics and Engineering, Australian National University
- **Professor Mark von Itzstein**, Institute for Glycomics, Griffith University

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About sepsis

- Severe sepsis is a life threatening inflammatory response to infection that has spread throughout the body
- In the US alone, upwards of 750,000 cases of severe sepsis every year, resulting in 215,000 deaths[1]
- Sepsis is the single most expensive condition treated in US hospitals
- **Extracellular Histones** – scientifically validated as major mediators of hyper-inflammatory response in sepsis
- The Histone Inhibition Program (HIP) is developing novel compounds specifically targeting extracellular histones in the treatment of sepsis

[1] *Source: Angus et al, Crit Care Med **29,** 1303-1310 (2001)*

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Sepsis awareness is growing

Muhammad Ali's Death Could Raise Awareness About Sepsis With The Announcement Of His Cause of Death, “Muhammad Ali Has Likely Saved Countless Lives.”

(Huffington Post, 7/6/2016)

Patty Duke Died From Sepsis, The Common Killer You’ve Never Heard Of

Sepsis killed legendary actress Patty Duke earlier this week, but experts say it's not just a disease for the elderly—and it's more common than you think

(Huffington Post, 31/3/2016)

Histone Inhibition Program – Science

What are Histones?

- Proteins with high net positive charge
- Exist in the nucleus of cells
- Primary role to package DNA
- Released by dying/dead cells
- Maintain positive charge
- Toxic when circulating outside of cells

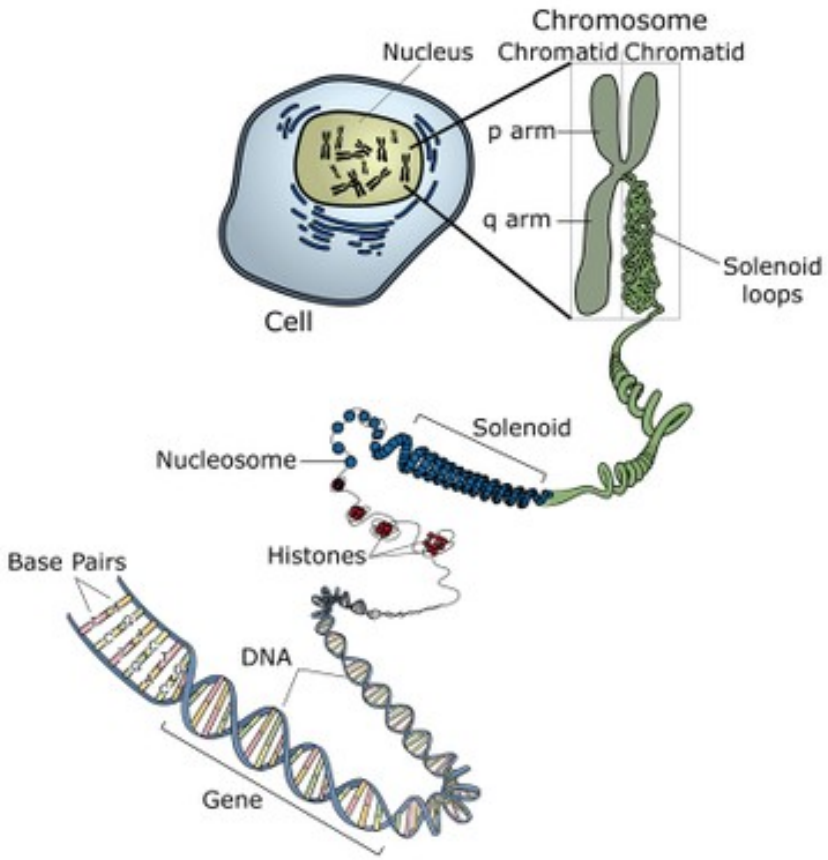
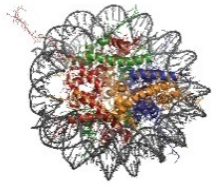


Image adapted from: National Human Genome Research Institute.

Histone Inhibition Program – Science (cont.)

Histones in the cell nucleus
Sustains nucleosomes and chromosomal stability



Histones released into extracellular fluid from dying cells as a result of stress (e.g. infection, trauma, ischemia)

INHIBITOR OF EXTRACELLULAR HISTONES
Early intervention in the hyper-inflammatory damage cascade

Free histones circulating in the extracellular fluid

Focus of HIP

Death of endothelial cells lining blood vessels

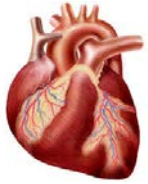
Impaired blood perfusion

Coagulation and thrombosis

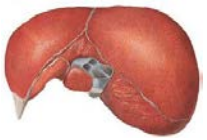
ORGAN DAMAGE

LUNG

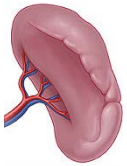
CARDIAC



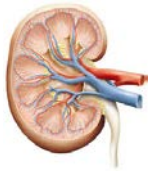
LIVER



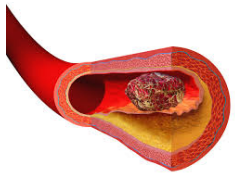
SPLEEN



KIDNEY



COAGULATION



POTENTIALLY LEADINGTO DEATH

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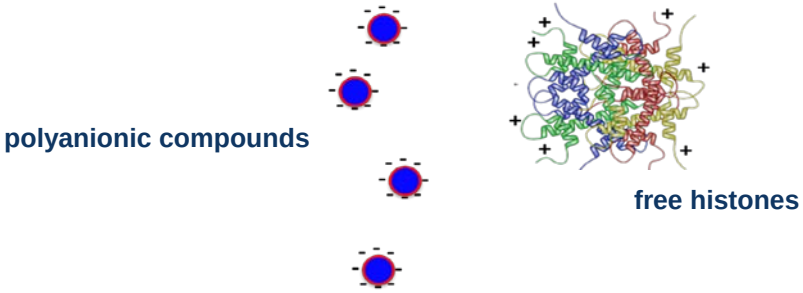
Histone Inhibition Program – Science (cont.)

- ANU has developed certain **polyanionic** molecules, a new class of compounds for inhibiting extracellular histones
- ANU working with the Glycomics Institute at Griffith University to further develop the Intellectual Property (IP)
- Patent coverage to 2030 and beyond
- Sirtex has secured the rights to all IP and is supporting the development program

Histone Inhibition Program – Science (cont.)

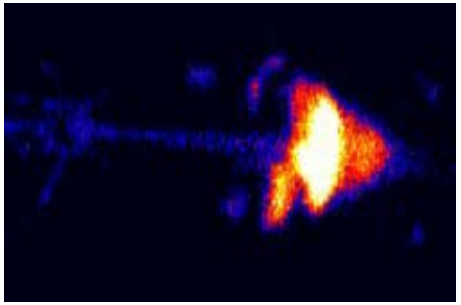
- Histones are polycations (positive charge)
- They rapidly and tightly complex with polyanions (negative charge) to form an inactive neutral complex
- Their natural function depends on this, i.e. binding to DNA (a polyanion) in the nucleus
- The Sirtex development program focussed on screening candidate molecules (polyanions available from ANU and Griffith Uni.) to maximise histone inhibition activity



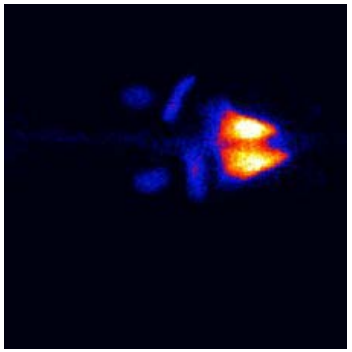
Histone Inhibition Program – Science (cont.)

ANU compounds block the accumulation of radiolabelled histones in lung in a preclinical model

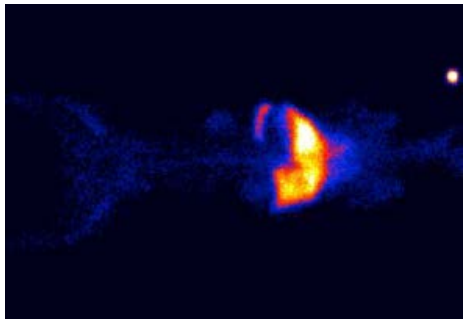
(a) i.v. injection of radiolabelled nanoparticles – mainly end up in the liver



(b) i.v. injection of **histone** coated radiolabelled nanoparticles – target the lung



(c) i.v. injection of histone coated radiolabelled nanoparticles + ANU compound – deposition in lungs is **blocked**

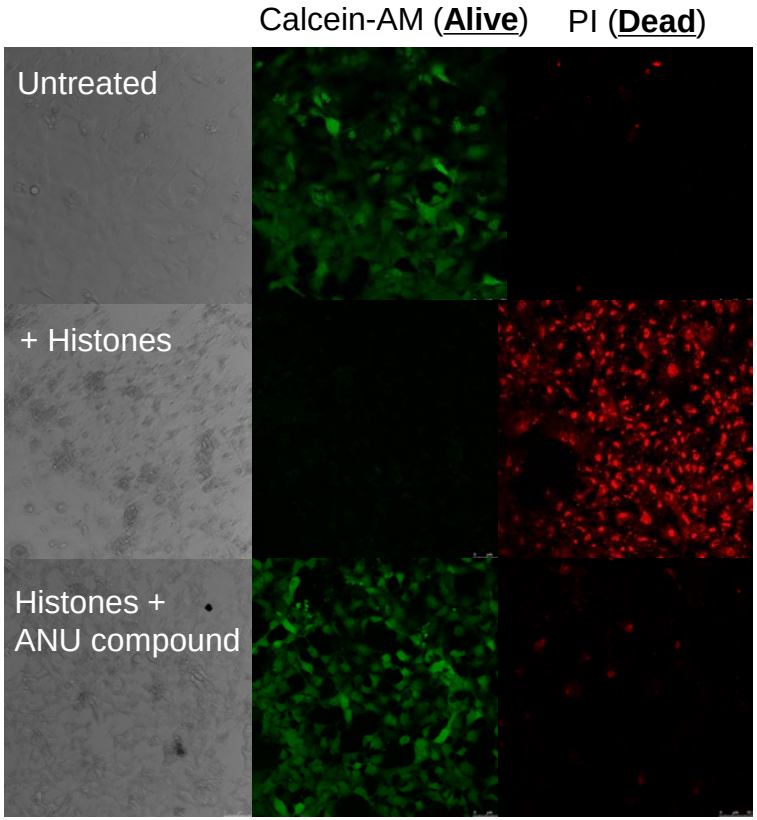


Source: Stephens et al, ANU

Acute lung injury is a common complication of sepsis, confirmed to be histone mediated (*Xu et al 2009*)

Histone Inhibition Program – Science (cont.)

Endothelial cells exposed to histones are protected by ANU compound



Images of Human Microvascular Endothelial Cells (HMEC) obtained with a confocal microscope

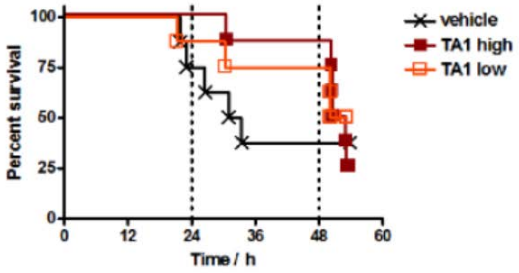
Source: Anna Bezos, ANU

Histone Inhibition Program – Science (cont.)

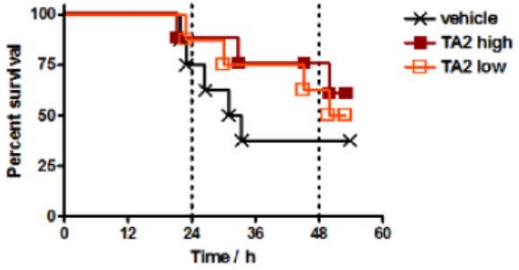
HIP compounds improve survival in pre-clinical model of sepsis

- Test Article (TA) was administered at 0, 24 and 48 hours

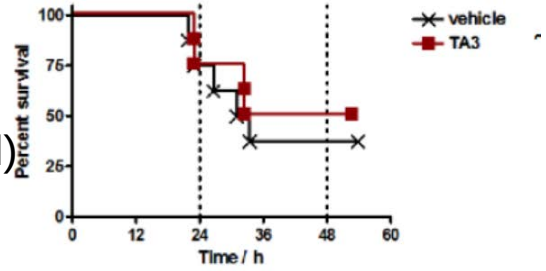
TA1



TA2



TA3 (control)



Histone Inhibition Program – Current status

- Lead compound – **STC314**
- **Pharmacokinetics**
  - Short blood residence time (T½ ~40min -1 hr)
  - Rapidly excreted mainly via urine (>50% within 4 hr) typical of small molecular compounds
  - Steady state plasma levels achieved via continuous infusion and proportional to the dose
- **Toxicology**
  - Not metabolised and low plasma protein binding – consistent with clearance profile
  - 7-day infusion studies at ~3000mg/kg/day showed no obvious signs of toxicity (i.e. via clinical chemistry, hematology and pathology)
  - Standard suite of GLP toxicology are being completed to support Phase 1 trial

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Histone Inhibition Program – Next steps

- STC314 - Early clinical development strategy

- Plan to commence in 1H of CY17
- Subsequent Phase 2 and 3 studies expected to be much shorter duration than trials for oncology drugs

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Thank you

Application of Histone Inhibition Program in Sepsis – Medical perspectives

Prof. Rinaldo Bellomo MBBS MD FRACS

Professor of Intensive Care Medicine

University of Melbourne

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Sepsis - Medical perspectives

Who am I?

- Professor of Intensive Care Medicine, University of Melbourne
- Director of Intensive Care Research and Staff Specialist in Intensive Care at Austin Health
- Co-Director of the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC)
- NHMRC Practitioner Fellow and was Foundation Chair of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG)
- Named one of the world's most influential scientific minds of our time[1]

[1] *Source: Thomson Reuters published "The world's most influential scientific minds 2014"*

Sepsis - Medical perspectives (cont.)

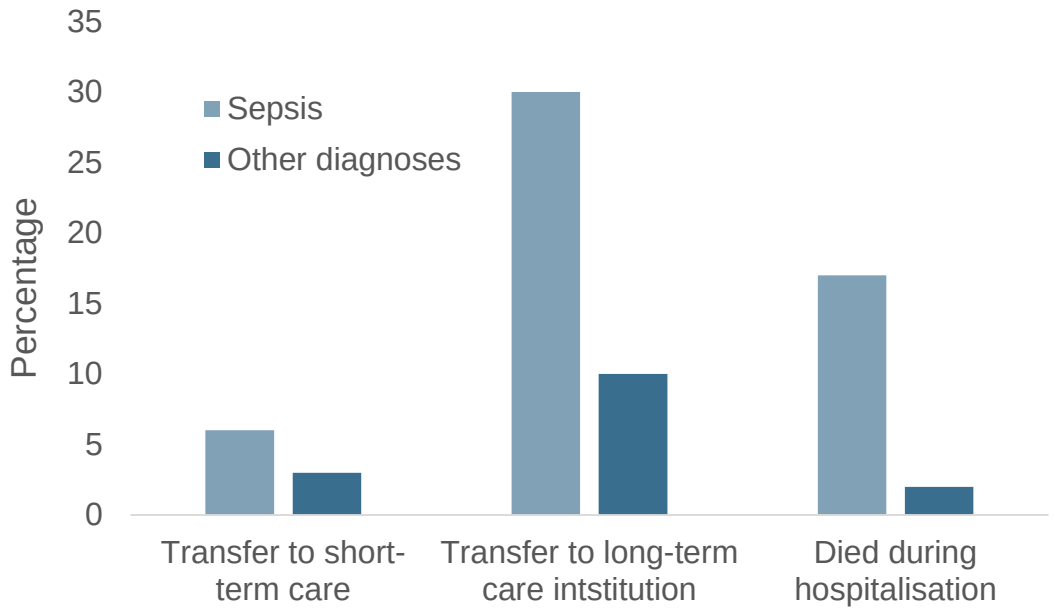
- Sepsis is a leading cause of death in the US and is the single most expensive condition treated in US hospitals[1]
- Sepsis is often fatal. Those who survive severe sepsis are more likely to have permanent organ damage, cognitive impairment and physical disability
- Only 2% of hospitalisations are for sepsis, yet they make up 17% of in-hospital deaths in the US

[1] *Source: Centres for Disease Control and Prevention*

Sepsis - Medical perspectives (cont.)

- Patients hospitalised for sepsis are more than eight times as likely to die during their hospitalisation[1]

- The proportion of hospitalised patients discharged to other short or long term care institutions is much higher for sepsis than for other conditions



[1] *Source: NCHS Data Brief*

Sepsis - Medical perspectives (cont.)

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Just a Cut

A 51-year-old surgeon lacerated his left ring finger near the volar distal interphalangeal joint with a fillet knife while he was cleaning fish after a late summer day of fishing in coastal New England seawaters. After the bleeding was stopped with direct pressure, he washed the wound and applied topical antibiotic ointment. At 4 a.m., 12 hours after the injury, he awoke with throbbing pain in his fingertip and took a dose of cephalexin. By 7 a.m., the pain had markedly increased and was progressively worsening, and the finger was erythematous, with localized edema distal to the distal interphalangeal joint. He presented to his primary care physician for urgent evaluation at 9 a.m. He had been well before this injury. He noted that he had received his last dose of adalimumab (administered every other week for psoriatic arthritis) 6 days before presentation.

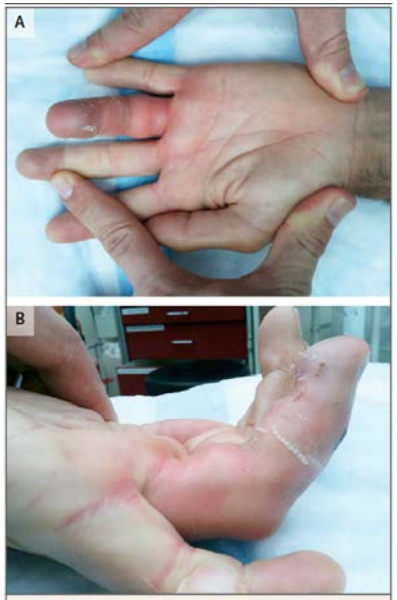


Figure 1. Circumferential Swelling of the Left Ring Finger with Tracking Erythema Extending to the Metacarpophalangeal Joint.

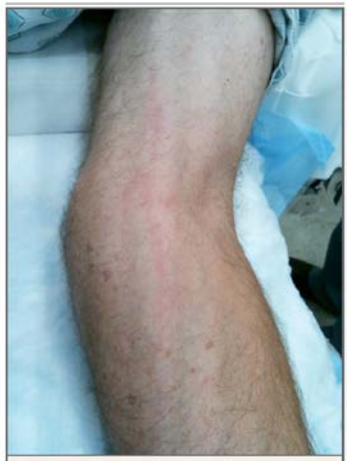


Figure 3. Erythema Tracking Up into the Proximal Upper Arm on Arrival in the Operating Room.

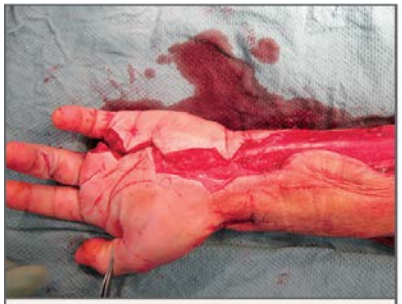


Figure 4. Intraoperative Image after Ray Resection of the Left Ring Finger, Débridement, and Radical Flexor Tenosynovectomy.

Scheduled irrigation and débridement the following morning revealed no signs of further necrosis in the hand or forearm. Later that day, spiking fevers recurred with rapidly worsening pain. Emergency exploration that evening revealed necrotic tissue and cloudy fluid along the flexor tendons extending proximally to the level of the distal forearm. After intraoperative consultation with another senior hand surgeon and the patient's wife, guillotine amputation at the midforearm was performed 5 cm proximal to all visibly infected tissue. The amputation stump was left open with povidone–iodine wound packing.

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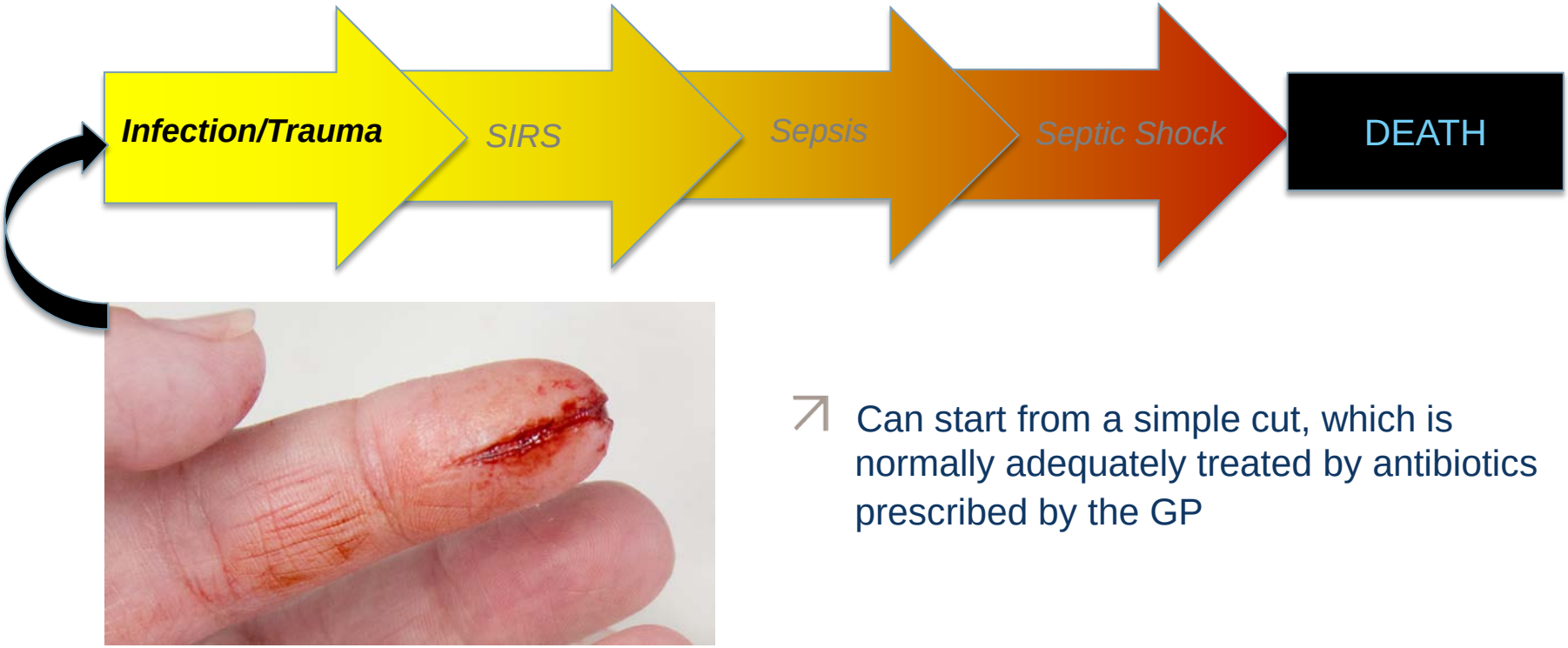
Sepsis - Medical perspectives (cont.)

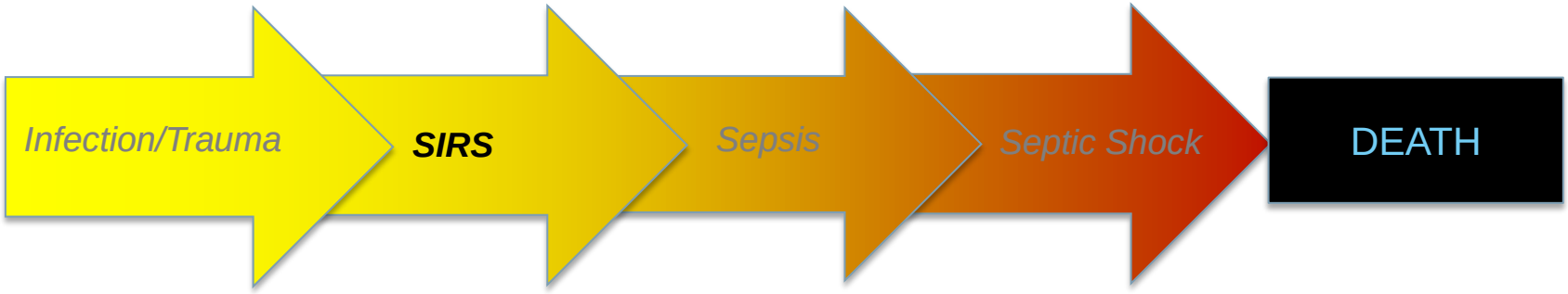
SEPSIS: A Disease Continuum



- Can start from a simple cut, which is normally adequately treated by antibiotics prescribed by the GP

Sepsis - Medical perspectives (cont.)

SEPSIS: A Disease Continuum



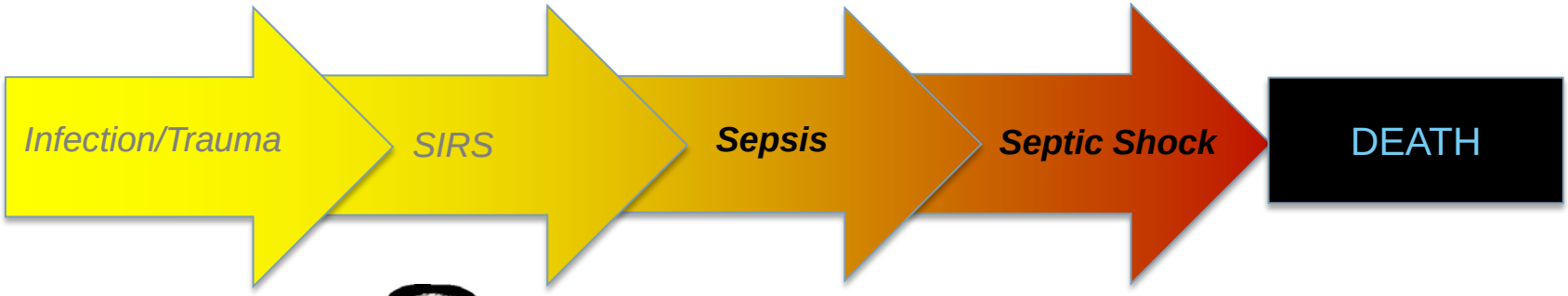
Systemic **I**nflammatory **R**esponse **S**yndrome **(SIRS)**

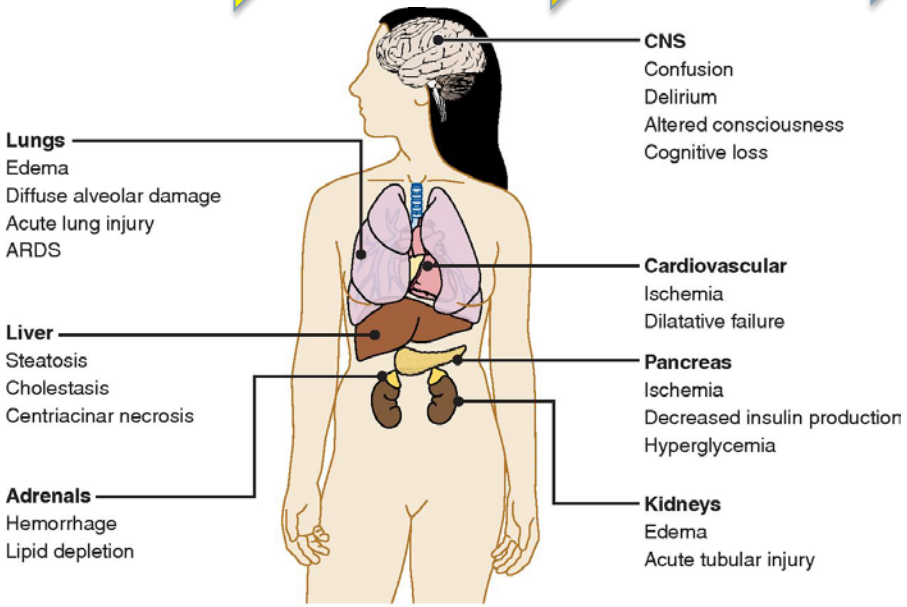
"Sepsis occurs when chemicals released into the bloodstream to fight the infection trigger inflammatory responses throughout the body. This inflammation can trigger a cascade of changes that can damage multiple organ systems, causing them to fail."

SIRTeX

Sepsis - Medical perspectives (cont.)

SEPSIS: A Disease Continuum



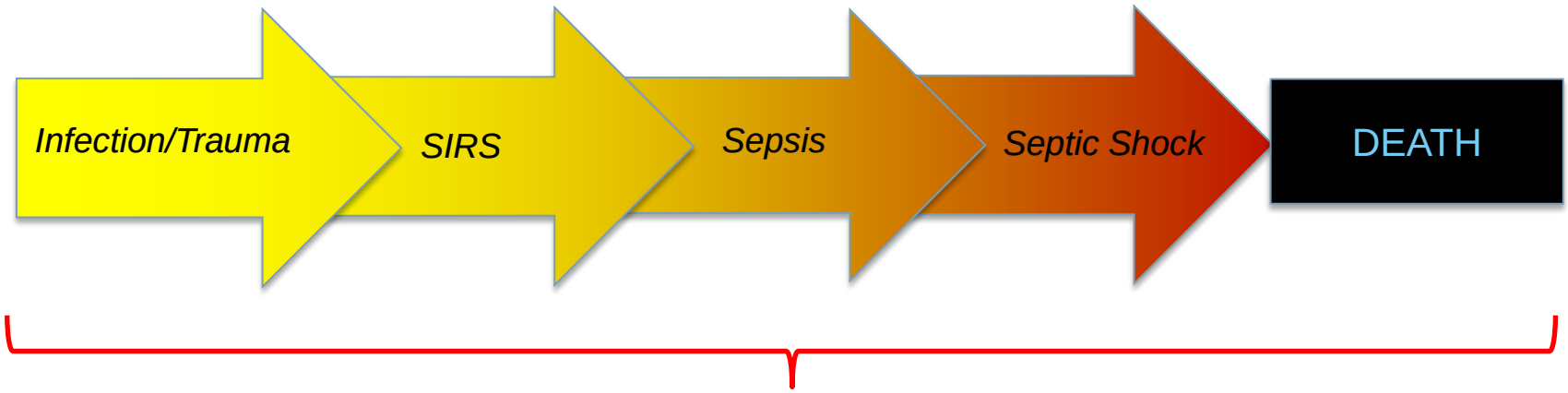


End Organ Damage in Sepsis

- Multiple Organ Dysfunction Syndrome (MODS)
- Treatment in ICU to support:
  - Cardiovascular system
  - Lungs
  - Kidney
  - Liver
  - Hypotension

Sepsis - Medical perspectives (cont.)

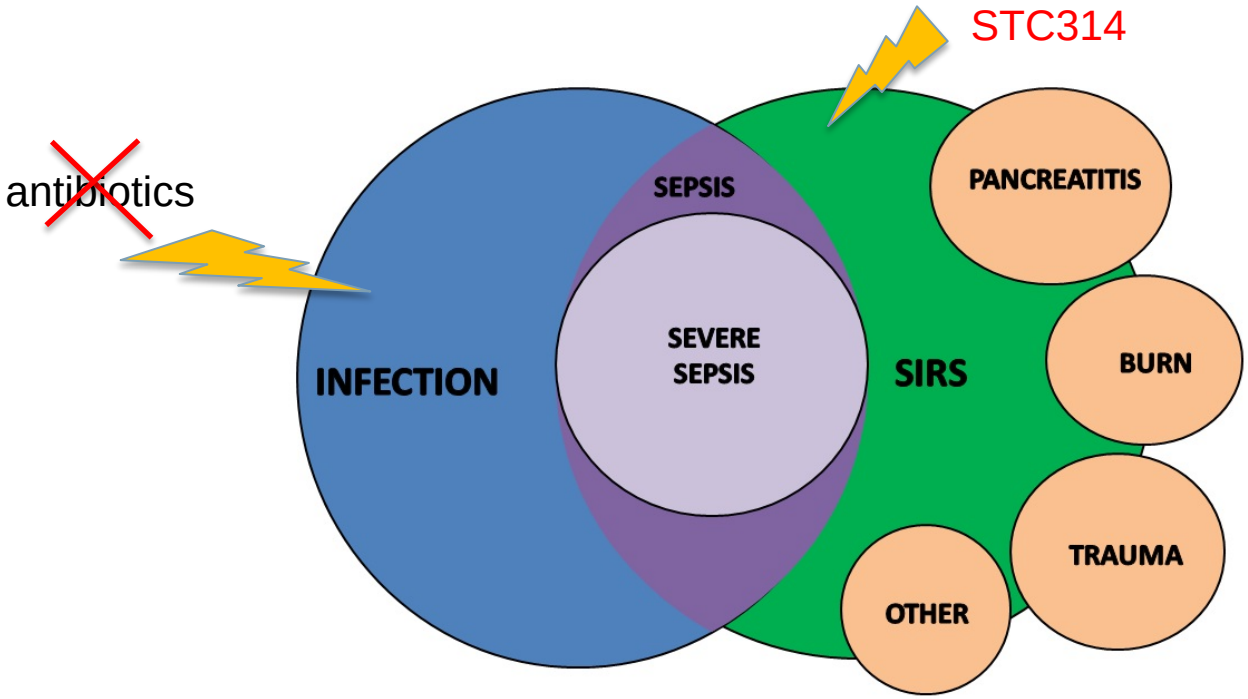
SEPSIS: A Disease Continuum



Time from infection until death could be as short as a few days or even hours

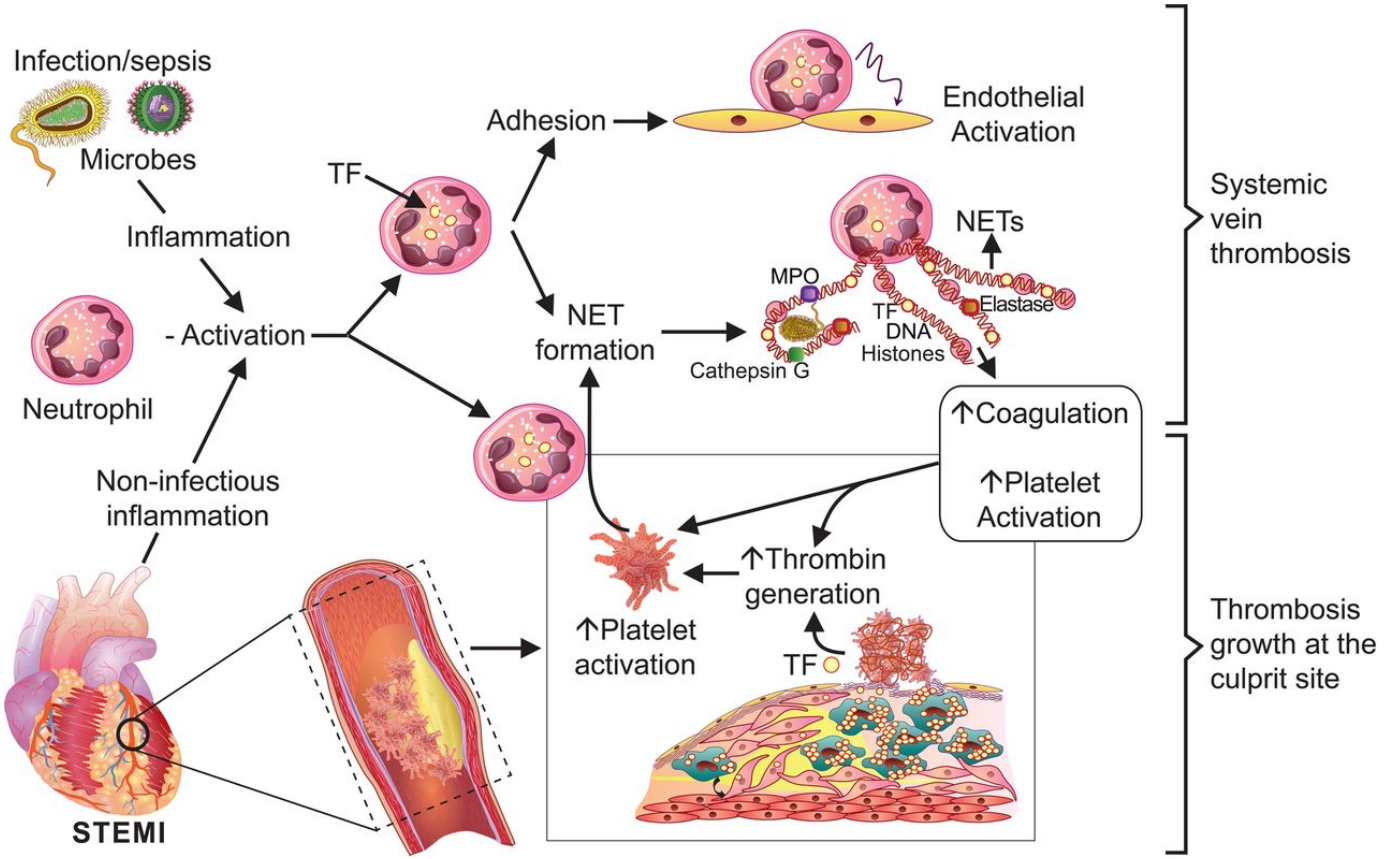
Sepsis - Medical perspectives (cont.)

- Sepsis-like inflammation can also arise from non-infective causes, e.g. trauma, pancreatitis, burns, as well as from an infection
- STC314 will target the inflammatory response of the innate immune system, i.e. Systemic Inflammatory Response Syndrome (SIRS)
- Sirtex is NOT developing a new antibiotic



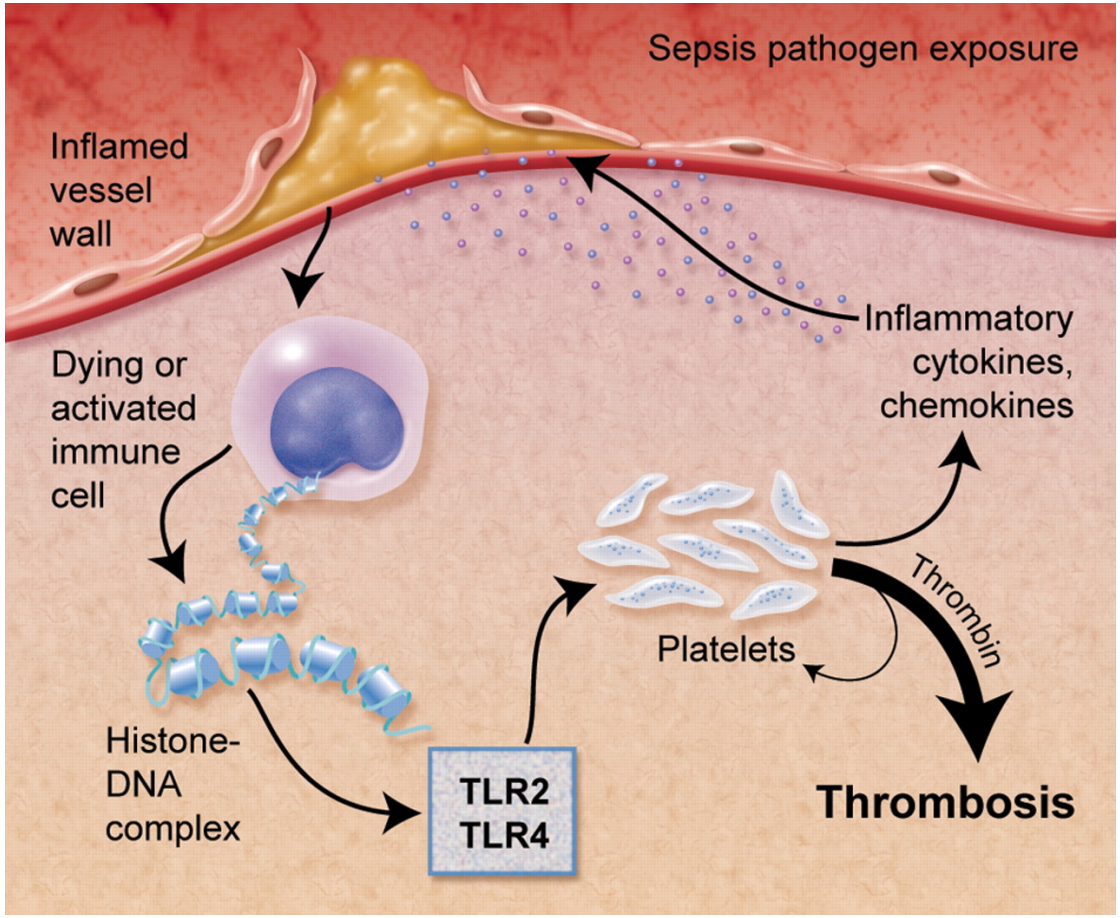
Sepsis - Medical perspectives (cont.)

Histones are fundamental to the inflammatory response generated by neutrophils



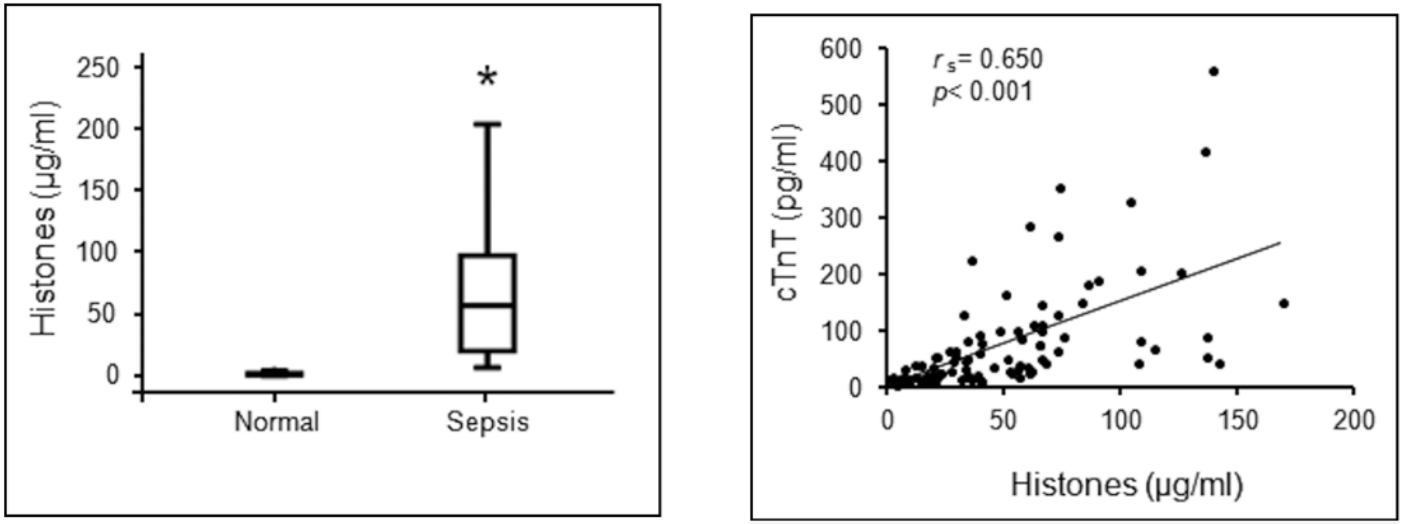
Sepsis - Medical perspectives (cont.)

Histone-mediated inflammation begets inflammation and thrombosis



Sepsis - Medical perspectives (cont.)

- Circulating extracellular histones are now scientifically validated as important mediators of a range of pathologies, including sepsis
- Supported by a wealth of scientific literature. e.g. this data for septic cardiomyopathy



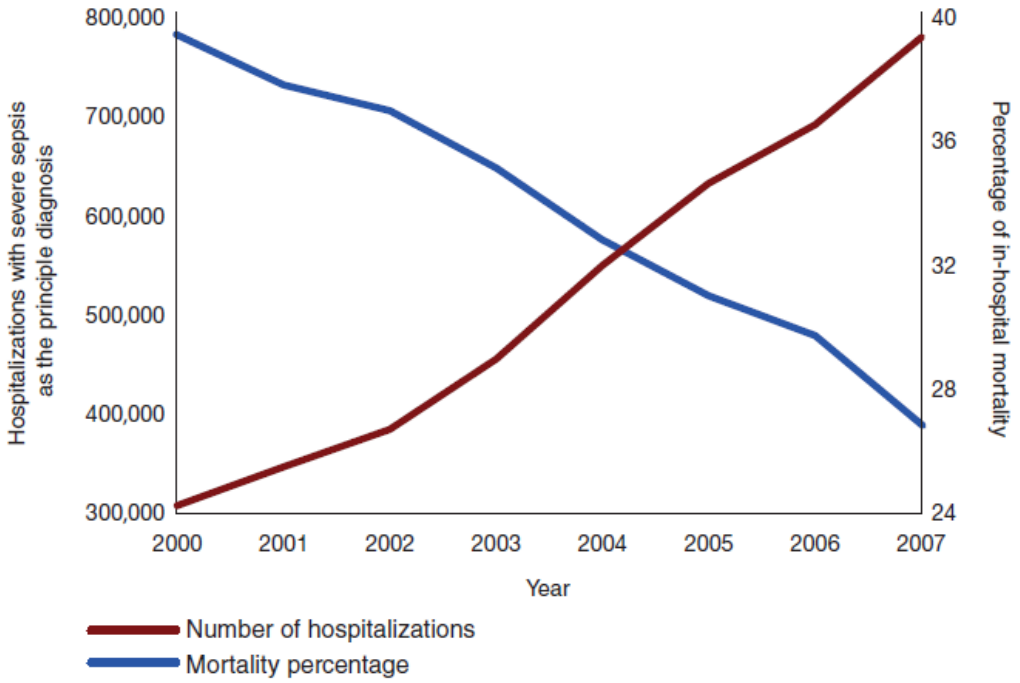
Elevated circulating histones in patients with sepsis correlate with circulating cardiac troponin T

- **Conclusion:** Circulating histones are novel and important mediators of septic cardiomyopathy, which can potentially be utilized for prognostic and therapeutic purposes

Source: Alhamdi et al., Crit Care Med 2015;43:2094–2103

Sepsis - Medical perspectives (cont.)

- Mortality rates from sepsis are decreasing[1] due to improvements in hospital care and heightened awareness
- However, the incidence of severe sepsis is increasing rapidly



[1] *Source: Chest **140** (2011)*

Sepsis - Medical perspectives (cont.)

- Current treatment options are based on antibiotics, fluid resuscitation and organ specific support
- However, there are currently no drug therapies specifically for the treatment of sepsis
- There is a desperate unmet need for new safe and efficacious products

Thank you

Commercial Opportunities

Dr Fintan Walton
CEO & Founder
Pharma Ventures

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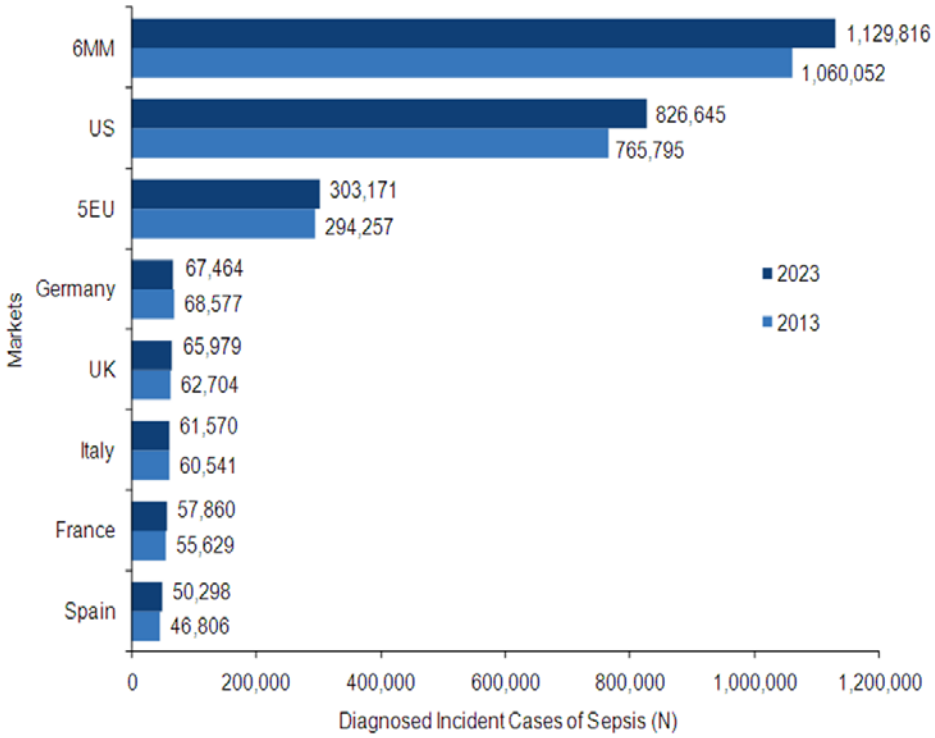
Histone Inhibition Program – Sepsis

- Sepsis is a clinical syndrome characterized by an uncontrolled systemic host response to infection, resulting in organ dysfunction
- Leading cause of death in intensive care units and in the top 10 causes of mortality worldwide
- Very high incidence of sepsis, including septic shock, means the potential market for an effective treatment is sizeable, measured in the billions
- Huge pharmacoeconomic burden of >US$20 billion in annual hospital costs in the US, making sepsis the most expensive condition treated in hospitals[1]
- Histone inhibition shows promise as a therapeutic target for clinical development

[1] Sepsisalliance.org; Torio, CM and Andrews, RM. "National Inpatient Hospital Costs: The Most Expensive Conditions" (2013). Healthcare Cost and Utilization Project (HCUP) and Agency for Healthcare Research and Quality.

Histone Inhibition Program – Sepsis (cont.)

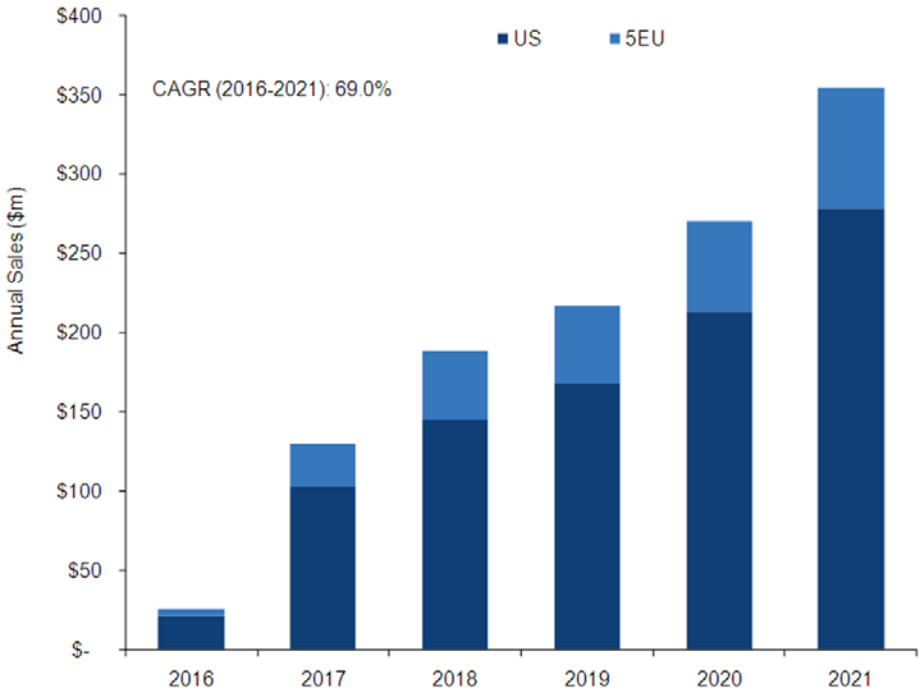
- Very large unmet market need, with high incidence and no approved drugs
- Xigris® withdrawn in 2011, pre-launch forecast sales of >US$2 billion
- Potential for fast-track, orphan drug (in defined subpopulations) and breakthrough therapy designation by the FDA



Source: Global Data

Histone Inhibition Program – Sepsis (cont.)

- Competition in clinical development remains modest
- Two Phase 3 candidates in development (not antibiotics)
  - Toraymyxin® (Spectral Medical)*
  - Selepressin (Ferring Pharmaceuticals)
- Toraymyxin® anticipated to show peak sales of US$800 million[1]
- Strong CAGR growth in sepsis sales from 2016-2021 of 69%, predicated on clinical success



Source: Global Data

[1] *Source: PharmaVentures, Sirtex Medical*

[*] *Oct 2016: Announced that Phase III failed to show benefit, further trials required*

Histone Inhibition Program – Beyond sepsis

- Role of histones as mediators of inflammation and toxicity is well established in the scientific literature
- A search of the scientific database (PubMed) highlights ~3,500 published articles on ‘histones and disease’
- Potential for HIP indications to be expanded beyond sepsis

Journal of Molecular Medicine
May 2014, Volume 92, Issue 5, pp 465–472

Extracellular histones in tissue injury and inflammation

Authors | Authors and affiliations

Ramanjaneyulu Allam, Santhosh V. R. Kumar, Murthy N. Darisipudi, Hans-Joachim Anders

Review
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OPEN

Citation: Cell Death and Disease (2014) 5, e1370; doi:10.1038/cddis.2014.337
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www.nature.com/cddis

Review

Release and activity of histone in diseases

R Chen[1,2], R Kang[2], X-G Fan*[,1] and D Tang*[,2]

Histones and their post-translational modifications have key roles in chromatin remodeling and gene transcription. Besides intranuclear functions, histones act as damage-associated molecular pattern molecules when they are released into the extracellular space. Administration of exogenous histones to animals leads to systemic inflammatory and toxic responses through activating Toll-like receptors and inflammasome pathways. Anti-histone treatment (e.g., neutralizing antibodies, activated protein C, recombinant thrombomodulin, and heparin) protect mice against lethal endotoxemia, sepsis, ischemia/reperfusion injury, trauma, pancreatitis, peritonitis, stroke, coagulation, and thrombosis. In addition, elevated serum histone and nucleosome levels have been implicated in multiple pathophysiological processes and progression of diseases including autoimmune diseases, inflammatory diseases, and cancer. Therefore, extracellular histones could serve as biomarkers and novel therapeutic targets in human diseases.

Cell Death and Disease (2014) 5, e1370; doi:10.1038/cddis.2014.337; published online 14 August 2014

Thank you

Histone Inhibition Program – Strategy

Gilman Wong
CEO

Histone Inhibition Program – Strategy

- The Histone Inhibition Program leverages Sirtex's R&D, clinical and regulatory infrastructure to enable diversification
- The science has been extensively and independently vetted and deemed to offer significant risk/reward benefits for Sirtex through execution of a clinical development pathway
- Complete pre-clinical development of lead compound STC314
- Commence a Phase 1 human clinical study in 1H CY17
- Upon confirmation of safety and toxicity, then move into a Phase 2 efficacy study in sepsis during CY18
- Evidence of clinical benefit provides excellent optionality on the most appropriate commercial pathway moving forward

Q&A

Questions

Summary & Review

Gilman Wong
CEO

Summary & Review

- Sirtex is committed to a long term investment into R&D
- R&D as a percentage of revenues of 5.9% averaged over past five years remains modest in global healthcare terms: Europe (~14%), North America (~9%)[1]
- Collaborative approach with academic centres of excellence provides access to cutting edge research and access to innovative new technologies
- Cost-effective and de-risked R&D model compared with internalising R&D infrastructure and expertise

[1] *Source: http://www.strategyand.pwc.com/global/home/what-we-think/innovation1000/rd-intensity-vs-spend-2014*

Summary & Review (cont.)

Radioprotector, Carbon-Cage Nanoparticles and Polymer Coated Nanoparticles

- There are a number of pathways for Sirtex to potentially realise value
- Out-licensing model the preferred option, prior to major clinical studies
- A number of important milestones for each program expected in the next 12-18 months, with important go/no-go decision points for continued investment

Summary & Review (cont.)

Histone Inhibition Program

- Addresses a very large, unmet market need in sepsis with potential for fast-track, orphan drug and breakthrough therapy designation by the FDA
- Phase 1 clinical study to commence in 1H of CY17
- Potential to expand across other indications where role of histones in disease pathogenesis is scientifically validated, offering multi-billion dollar contestable market opportunities

SIRTeX

Thank you