

Singapore Institute of Advanced Medicine Holdings



All AGM attendees & shareholders: 10% discount and free flu vaccination
- **please register after the AGM.**

*shareholder from 27 Dec 2024

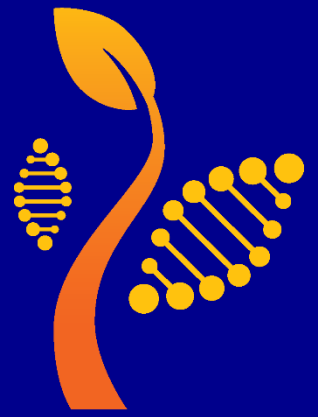
Singapore Institute of Advanced Medicine Holdings

We are making inroads and continue our best efforts for increasing our existing patient flows and our revenue streams.

While we build on our existing business, these are some our future developments:

- **Flash Proton Therapy**
- **Oncobeta**
- **EnGeneIC**
- **Radioisotope distribution**





SAM

Singapore Institute of Advanced Medicine Holdings

First-in-Class

Antibody-Nanocell-Drug Conjugate (ANDC)

meets Immunotherapy in one Therapeutic for multiple cancers

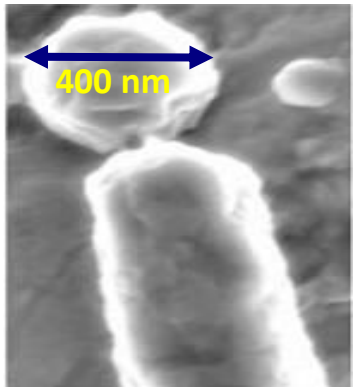
Fast Track to Market

December 2024

Technology Overview - EDV

1

Bacterially derived Nanocell



The Birth of an EDV™

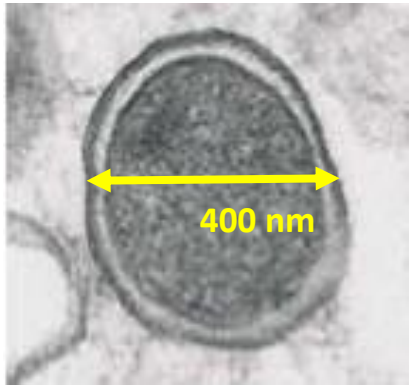
(**EnGeneIC Dream Vector**)

Non-living nanocells are generated by asymmetric cell division in genetically engineered safe strain (avirulent) of *Salmonella typhimurium* bacteria.

Cell division creates a uniform nanocell of 400 ± 20nm.

2

Transmission Electron Microscopy

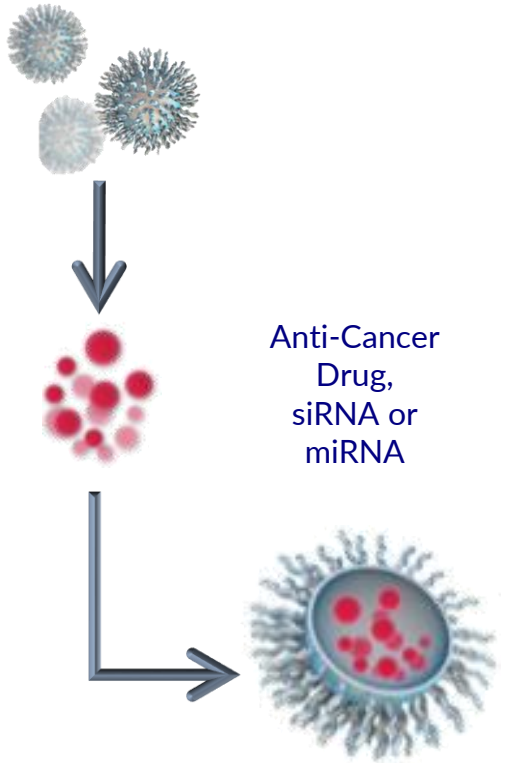


EDV is a non-living empty cytoplasmic sac with a robust double-walled membrane.

The EDV™ is sterile and non-toxic with no chromosome and no risk of replication or virulence.

3

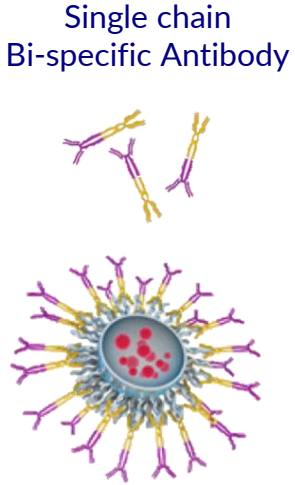
Unmatched Payload Capacity



EDVs™ can be readily packaged with diverse anti-cancer drugs or therapeutic nucleic acids or immune stimulating molecules: 0.5 - 1 million drug molecules or 10,000 siRNA copies per EDV.

4

Bi-Specific Antibody Targeting to cancer cell surface receptor – Precision tumor targeting



Multivalent, high affinity targeting single chain bispecific antibody binds nanocell O-polysaccharide at one end and tumor surface molecule of choice at the other.

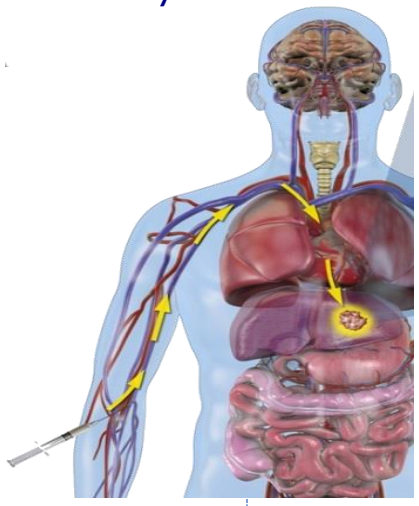
Delivering EDVs™: Passive Targeting = Safety – does not see normal tissues

Passive Accumulation in Tumor via Tumor-Associated Leaky Vasculature



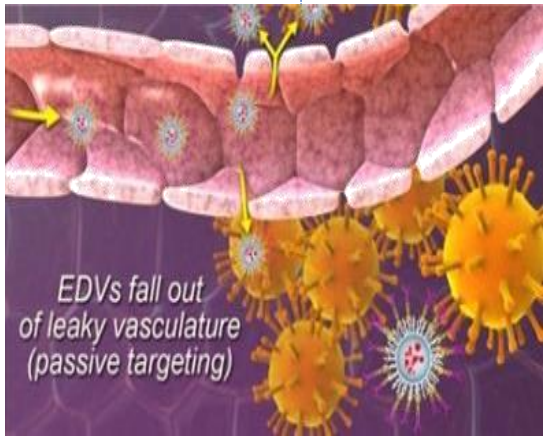
Leaky Vasculature

Antibody-targeted, drug-loaded EDVs™ accumulate passively in tumor tissue due to tumor-associated leaky vasculature



Simple Delivery

Transport of antibody-targeted, drug-packaged EDVs™ via bolus injection – 2ml

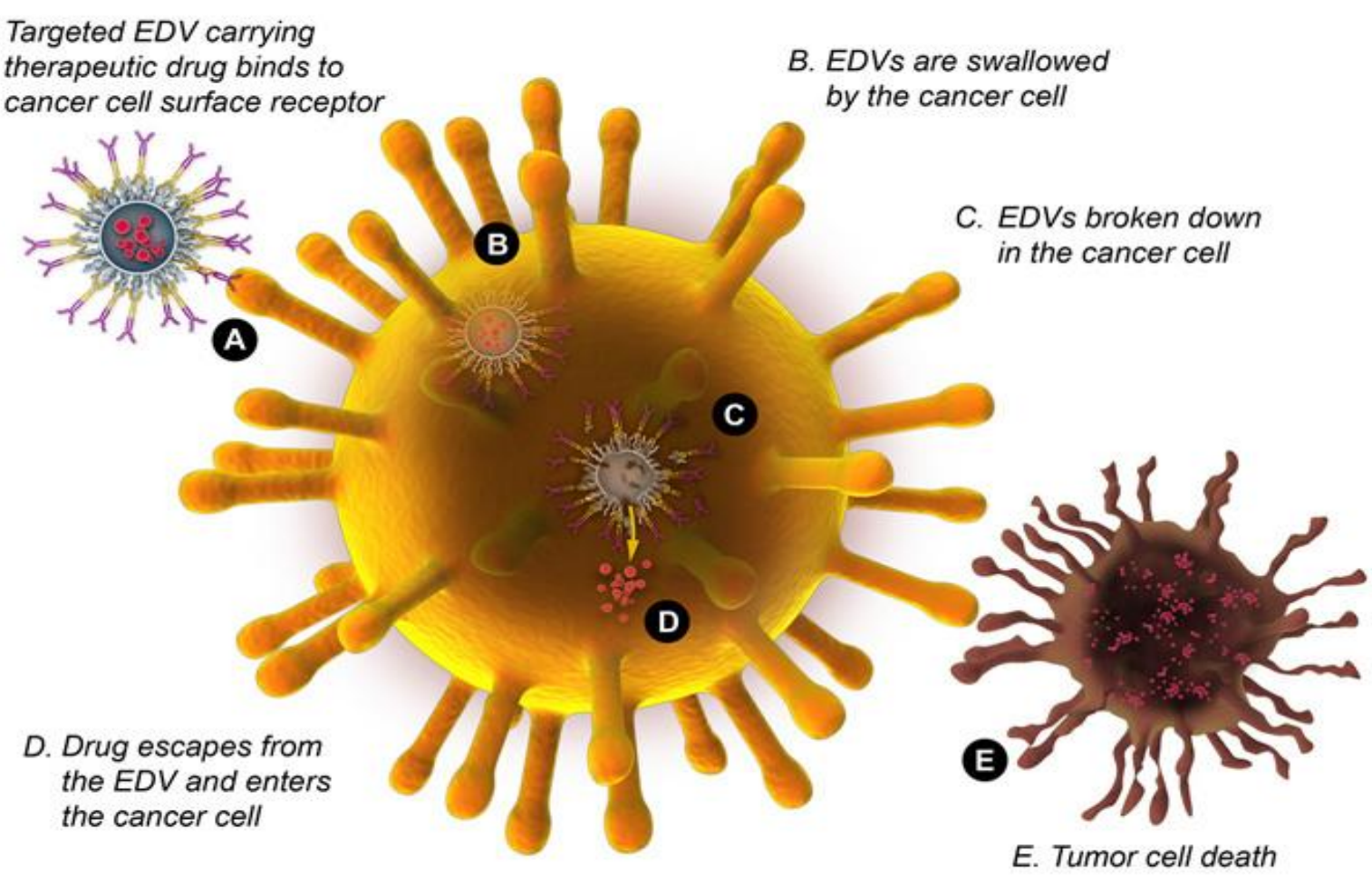


Passive Accumulation

EDVs extravasate and accumulate in the tumor microenvironment

Active Tumor Targeting = Direct killing of highly drug-resistant cancer cells

Once in the Tumor Environment, EDV™ Binds and Delivers Payload to Cancer Cell





Cancer Cell
Article

Bacterially Derived 400 nm Particles for Encapsulation and Cancer Cell Targeting of Chemotherapeutics

Jennifer A. MacDiarmid,[1] Nancy B. Mugridge,[1] Jocelyn C. Weiss,[1] Leo Phillips,[1] Adam L. Burn,[1] Richard P. Paulin,[1] Joel E. Haasdyk,[1] Kristie-Ann Dickson,[1] Vatsala N. Brahmbhatt,[1] Scott T. Pattison,[1] Alexander C. James,[1] Ghalib Al Bakri,[1] Rodney C. Straw,[2] Bruce Stillman,[3] Robert M. Graham,[4,5] and Himanshu Brahmbhatt[1,*]

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[2]Brisbane Veterinary Specialist Centre, Cnr. Old Northern Road and Keong Road, Albany Creek, Queensland 4035, Australia
[3]Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA
[4]Victor Chang Cardiac Research Institute, 384 Victoria Street, Darlinghurst, NSW 2010, Australia
[5]School of Biotechnology and Biomolecular Sciences, University of New South Wales, Kensington, NSW 2054, Australia
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DOI 10.1016/j.ccr.2007.03.012

SUMMARY

Systemic administration of chemotherapeutic agents results in indiscriminate drug distribution and severe toxicity. Here we report a technology potentially overcoming these shortcomings through encapsulation and cancer cell-specific targeting of chemotherapeutics in bacterially derived 400 nm minicells. We discovered that minicells can be packaged with therapeutically significant concentrations of chemotherapeutics of differing charge, hydrophobicity, and solubility. Targeting of minicells via bispecific antibodies to receptors on cancer cell membranes results in endocytosis, intracellular degradation, and drug release. This affects highly significant tumor growth inhibition and regression in mouse xenografts and case studies of lymphoma in dogs despite administration of minute amounts of drug and antibody; a factor critical for limiting systemic toxicity that should allow the use of complex regimens of combination chemotherapy.

INTRODUCTION

Severe toxicity remains a major factor limiting cancer chemotherapeutics. Lack of cancer cell specificity, indiscriminate drug distribution, and rapid clearance necessitate frequent administration of high doses of chemotherapeutics to elicit a satisfactory clinical response (Langer, 1998). Anticancer antibodies directed to overexpressed receptors on cancer cells, such as the epidermal growth factor receptor (EGFR; Nicholson et al., 2001) and HER2/*neu* (Rae and Lippman, 2004), are less toxic but do not possess the potency and wide spectrum antitumor activity of chemotherapeutic drugs. Efforts are being made to develop targeted drug delivery systems (DDSs), such as stealth liposomes (Medina et al., 2004), nanoparticles (Brannon-Peppas and Blanchette, 2004; Ferrari, 2005), and polymer therapeutics (Duncan, 2003), which encapsulate the cytotoxic drug in a vehicle and target it to cancer cells via tumor cell-surface receptors. However, these technologies are also hampered by shortcomings, such as drug leakage in vivo, lack of versatility in terms of packaging a diverse range of different drugs without significant derivatization, thereby reducing drug potency, and difficulties in production scale-up, particularly for nanoparticles.

Here we show that bacterial minicells which are anucleate nanoparticles produced as a result of inactivating

SIGNIFICANCE

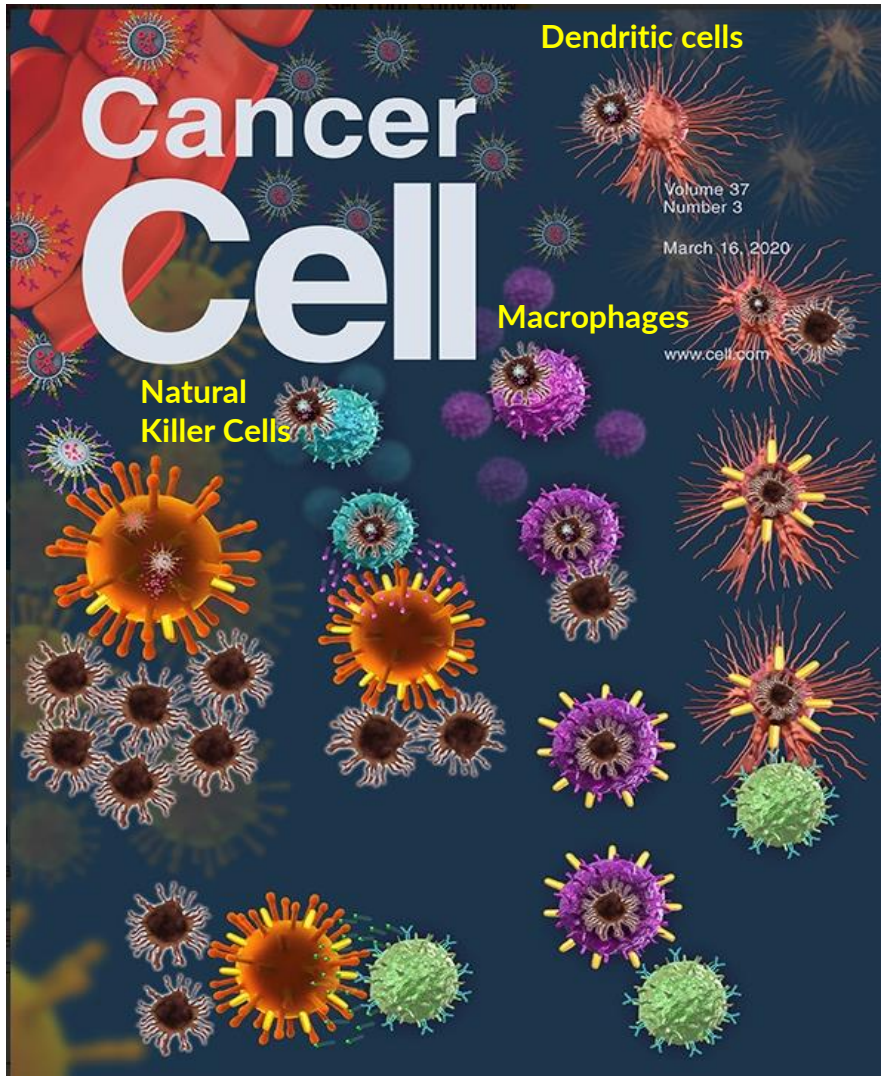
Nontargeted cancer chemotherapy is currently associated with severe toxicity. This report describes bacterially derived nano-sized particles (minicells) for encapsulation of a range of different chemotherapeutic drugs and specifically targeting the minicells to tumor cell-surface receptors via bispecific antibodies coating the minicells. Receptor engagement results in minicell endocytosis, intracellular degradation, and drug release. Consequently, highly significant tumor growth inhibition and regression is achieved despite administration of minute amounts of drug and antibody. The dramatic increase in therapeutic index may permit the use of multidrug combinations to achieve an improved outcome for cancer therapy.



Published:

- MacDiarmid, J.A., *et al*. Bacterially-derived 400nm particles for encapsulation and cancer cell targeting of chemotherapeutics. ***Cancer Cell* 11:** 431-445 (2007).
- MacDiarmid, J.A., *et al*. Sequential treatment of drug-resistant tumors with targeted minicells containing siRNA or a cytotoxic drug. ***Nature Biotechnology* 27:** 643-651 (2009).

Promotes INNATE and ADAPTIVE anti-Tumor immune response

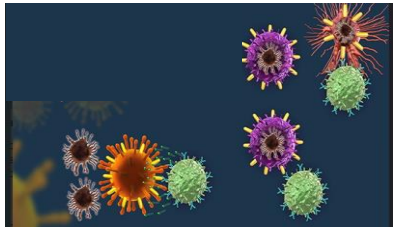


EDV (bacterial origin) activates main cells of the immune system

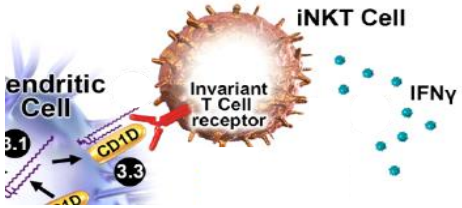
- **Dendritic cells**
- **Macrophages**
- **Natural Killer cells**

These cells swallow dying tumor cells and display tumor antigens on their surface

Tumor-specific CD8+ T cells



Tumor-specific iNKT cells



Only technology in the world that activates both major types of T cells to mount major killing of cancer cells

Published:
Sagnella, SM, Yang L, Stubbs GE, Boslem E, Echarri EM, Smolarczyk K, Vanegas N, Pattison SL, Clair ES, Clarke S, Boockvar J, MacDiarmid JA, Brahmbhatt H. Cyto-Immuno-Therapy for cancer: A novel pathway elicited by tumor-targeted, cytotoxic drug-packaged bacterially derived nanocells. ***Cancer Cell*, 37:** 354-370 (2020). Includes cover-art for the journal designed by Brahmbhatt and MacDiarmid.

Globally Protected Patent Portfolio

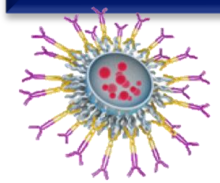
17	200	34	2040+	Overlapping scope of protection makes design around extremely difficult
PATENT FAMILIES	GRANTED PATENTS	GRANTED US PATENTS	PATENT LIFE CURRETLY	

EnGeneIC = sole owner of entire patent portfolio

Foley & Lardner LLC (Washington DC) have handled all IP since inception

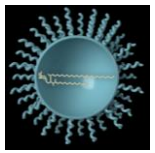
Highly significant anti-tumor efficacy in end-stage PDAC patient - minimal to no toxicity & dramatic increase in overall survival

2ND generation EDV-based ANDC for Low Survival cancers



Antibody-targeted EDV carrying a super-cytotoxic drug to overcome drug resistance

+



α-galactosyl ceramide (glycolipid) to attract iNKT cells

End-stage pancreatic cancer patient





8 doses over 8 weeks of $^{EGFR}EDVs_{PNU-159682}$ + $EDV_{\alpha GC}$

Single Patient IND (SPIND), Los Angeles

- Metastatic PDAC in pancreas, liver and lungs.
- Eligible for "Right to try" (SPIND) since she had exhausted all treatment options.
- Since start of EDV treatment – alive and well after 24 months.
- Excellent quality of life with two treatment breaks for holidays
- Scans from July 2023 to now show no measurable tumours =

COMPLETE RESPONSE





Oct 2024 publication



US FDA has given “FAST-TRACK” designation for EDV therapeutics in pancreatic ductal adenocarcinoma (PDAC)

Phase II trials planned to start in Q1/Q2 Calender 2025 in the US

- Statistical Package being finalized by a top biostatistician at the Mayo Clinic (USA)
- Prof. Gulam Manji MD (Co-Director of Pancreas Center, Columbia University Herbert Irving Cancer Center (New York)





Source: EnGeneIC

October 01, 2024 08:00 ET

Distinguished Oncologist, Professor Daniel Von Hoff joins the Scientific/Clinical Advisory Board of EnGeneIC Cancer Therapeutics

SYDNEY and NEW YORK, Oct. 01, 2024 (GLOBE NEWSWIRE) -- EnGeneIC, a clinical-stage biopharmaceutical company pioneering the development of a First-in-Class targeted nanocell for cancer therapy has today announced the appointment of Dr. Daniel Von Hoff to its Scientific/Clinical Advisory Board to advise EnGeneIC's on its upcoming trial in metastatic pancreatic cancer.

Professor Daniel Von Hoff, M.D. F.A.C.P. FASCO, FAACR is an internationally recognized physician and scientist. He is currently Distinguished Professor at the Translational Genomics Research

- Prof Dan Von Hoff joined the EnGeneIC Scientific board in October 2025
- He is very experienced in bringing new cancer drugs to commercialization

7 Compassionate case studies – pancreatic ductal adenocarcinoma (PDAC) – Singapore with 3 oncology groups

1 Compassionate case study – Hong Kong - Osteosarcoma

3 Compassionate case studies – Melbourne - Glioblastoma

EDV doses associated with little to no toxic side effects ✓

November 2024: EnGeneIC received approval to start trials for many other cancers including: Lung, Breast, Bladder, Kidney cancer

Multiple other uses for EDV

- Boron-Proton & Neutron Capture Therapy
- Diagnostic Imaging Agent
- Theranostics
- Vaccines

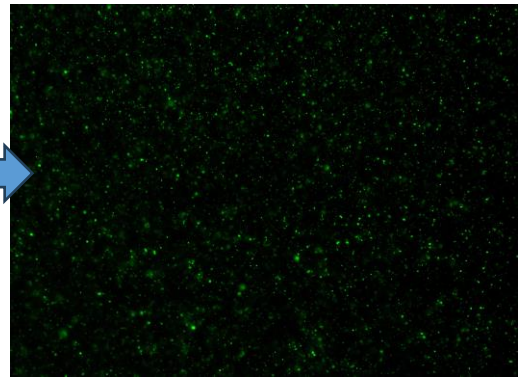
Boron successfully packaged in EDVs & Cancer Spheroids

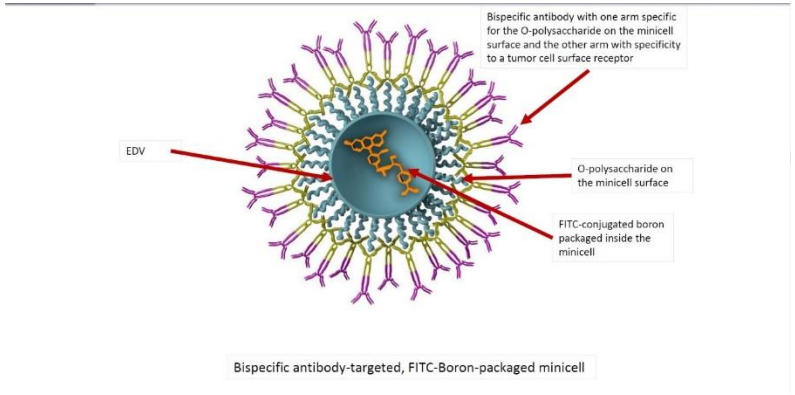
World's first: Boron has been successfully packaged in EDVs & Cancer Spheroids

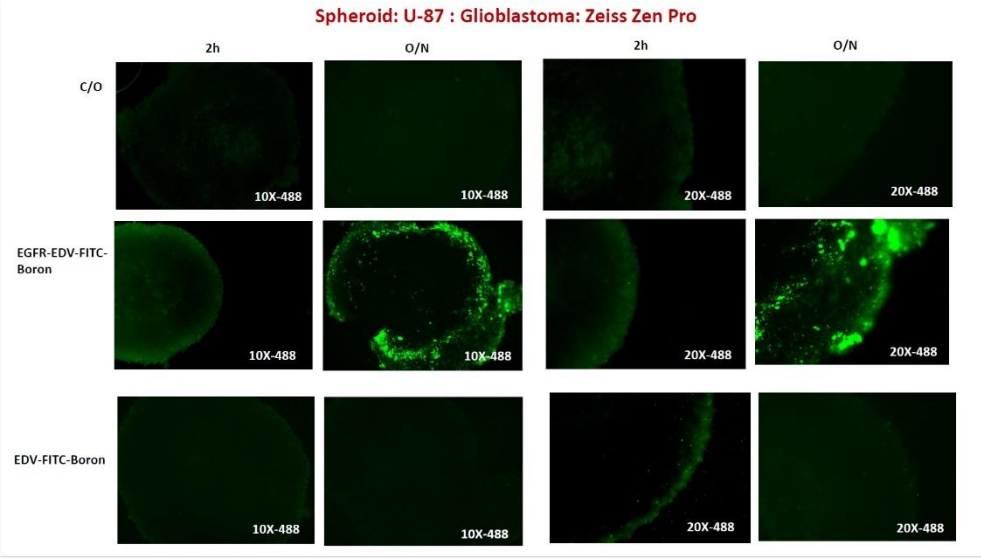
Empty EDVs

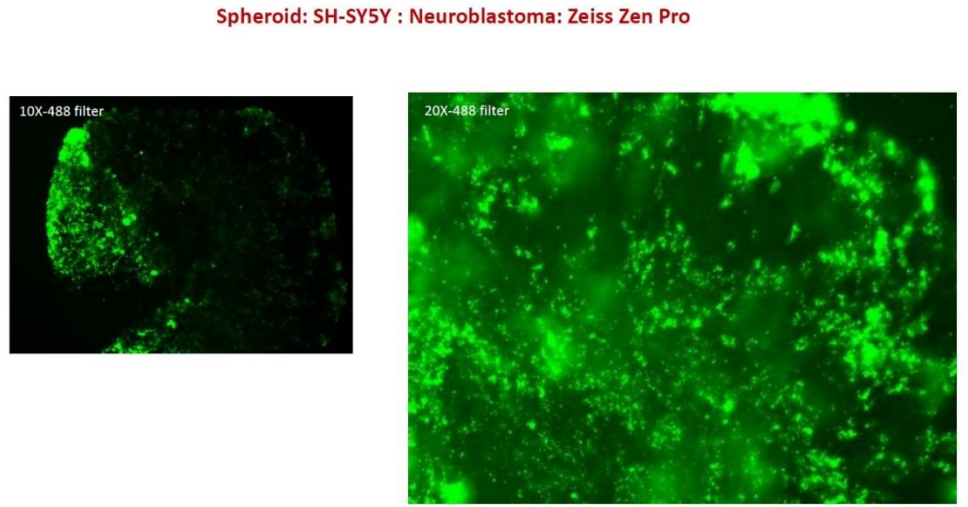


EDVs with Boron









Singapore Institute of Advanced Medicine Holdings

profit sharing and exclusive distribution rights to 17 countries including China and India.



Singapore Institute of Advanced Medicine Holdings Ltd.
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Singapore 138622

For Immediate Release

Singapore Institute of Advanced Medicine Holdings enters into a strategic partnership with Australia-based biopharmaceutical company, EnGeneIC to revolutionize cancer treatment in Asia

- Dual-pronged expansion of revenue streams through profit-sharing agreement
  - SAM Holdings will have exclusive distribution rights for sales of EDV therapeutics in 17 countries within Asia.
  - Both parties will also collaborate on the development of EDV-based Theranostics to improve cancer outcomes and SAM Holdings will be granted exclusive distribution rights worldwide.
- Investing into next generation technology to achieve our core vision
  - First-in-class antibody nanocell drug conjugate platform for delivering a range of therapeutic payloads via antibody-targeting a cancer cell's surface, with minimal toxicity.
  - EDV-based theranostics can provide precise, personalized care, enabling early detection and targeted therapy, which aligns with the Group's vision.
- The partnership will bring the latest cancer treatment innovation to Singapore and increase Singapore's attractiveness as the medical tourism hub of Asia.

Singapore, 10 June 2024 – Singapore Institute of Advanced Medicine Holdings Ltd. ("**SAM Holdings**" or the "**Company**", and together with its subsidiaries, the "**Group**"), has entered into a strategic partnership with EnGeneIC Pty Limited ("**EnGeneIC**"), an Australia-based clinical-stage biopharmaceutical company pioneering the development of a First-in-Class targeted nanocell for cancer therapy. The partnership aims to revolutionize the cancer treatment landscape in Asia and provide better outcomes of life for our patients.

Under the partnership, the Group will collaborate with EnGeneIC on a profit-sharing basis for:
- Manufacturing and distribution of anti-cancer products based on EnGeneIC's proprietary technology platform, EnGeneIC Dream Vector ("**EDV-based Products**"); and
- Development of EnGeneIC Dream Vector-based theranostics for use in the imaging and treatment of various cancers ("**EDV-based Theranostics**").

EDV-based Products

The Group will help EnGeneIC secure funding and regulatory authorizations for building a manufacturing plant in Singapore for the manufacture of EDV-based Products, conduct clinical

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trials in Singapore, and obtain regulatory authorization to market and sell the EDV-based Products. In turn, SAM Holdings will be granted exclusive distribution and marketing rights of these products in 17 countries within Asia.

EDV-based Theranostics

Leveraging on the Group's experience in theranostics, it will collaborate with EnGeneIC for pre-clinical testing of EDV-based Theranostics and obtain regulatory approval for commercialization and sale of EDV-based Theranostics. Subsequently, the Group will be granted exclusive distribution rights worldwide for EDV-based Theranostics.

Commenting on the partnership, Dr Djeng Shih Kien, Executive Director and CEO, and founder, of SAM Holdings, said, "We have always been committed to providing our patients with easier access to the latest cancer treatment technologies and our partnership with EnGeneIC is another step forward in that direction. We are excited at the prospect of bringing cutting edge EDV-based therapeutics to Singapore and Asia and collaborating on the development of EDV-based Theranostics. Our experience in cancer treatment coupled with EnGeneIC's advanced medical innovations will propel us forward in our journey to provide early diagnosis and better outcomes for our patients throughout the region."

- - End - -

*Singapore Institute of Advanced Medicine Holdings Ltd. (the "**Company**") was listed on Catalist of the Singapore Exchange Securities Trading Limited ("**SGX-ST**") on 16 February 2024. The initial public offering of the Company was sponsored by PrimePartners Corporate Finance Pte. Ltd. (the "**Sponsor**").*

This press release has not been examined or approved by the SGX-ST. The SGX-ST assumes no responsibility for the contents of this document, including the correctness of any of the statements or opinions made or reports contained in this press release.

The contact person for the Sponsor is Ms. Ng Shi Qing, 16 Collyer Quay, #10-00 Income at Raffles, Singapore 049318, sponsorship@ppcf.com.sg.

ONCOBETA®
epidermal radioisotope therapy

Rhenium-SCT®

SAM
Singapore Institute of Advanced Medicine Holdings

Rhenium-SCT



What is Rhenium-SCT®?

- **Rhenium-SCT®** or Rhenium-Skin Cancer Therapy (SCT) is a medical device* for the treatment of non-melanoma skin cancer (NMSC), including basal and squamous cell carcinoma (BCC / SCC).

- Rhenium-SCT® utilises the Beta-emitting radioisotope, rhenium-188, to deliver a painless, non-surgical, single-session treatment that preserves functionality and cosmesis.

- Rhenium-SCT is administered as a paste allowing conformal application to complex surfaces.

* Rhenium-SCT® is registered with ARTG, MedSafe (NZ), CE (Europe) and SAPHRA (South Africa).

NMSC: Can have a dramatic impact on quality of life[1]



NMSC can be difficult to treat due to:

- Lesion size and location (face, lips, ears, genitals, etc.)

Treatment **can be unsatisfactory** due to:

- Disfigurement
- Loss of function
- Need for reconstruction
- Recurrence
- Pain
- Complications
- Waiting lists and/or recovery time

An effective, non-invasive, single-session treatment is a valuable option.

Reference: Philipp-Dormston et al. Patient-reported health outcomes in patients with non-melanoma skin cancer and actinic keratosis: results from a large-scale observational study analysing effects of diagnoses and disease progression. J Eur Acad Dermatol Venereol. 2018;32(7):1138-1146. doi: 10.1111/jdv.14703.

Images courtesy of Cipriani, C. - S. Eugenio Hospital, Rome, IT; Sedda, A. - S. Eugenio Hospital, Rome, IT; Castellucci, P - IRCCS Azienda Ospedaliero-Universitaria, Bologna, IT.





What is Rhenium-SCT?

- The Rhenium-SCT® is a resin/paste utilising the beta emitter radioisotope Rhenium-188 for the treatment of Non-Melanoma Skin Cancer.

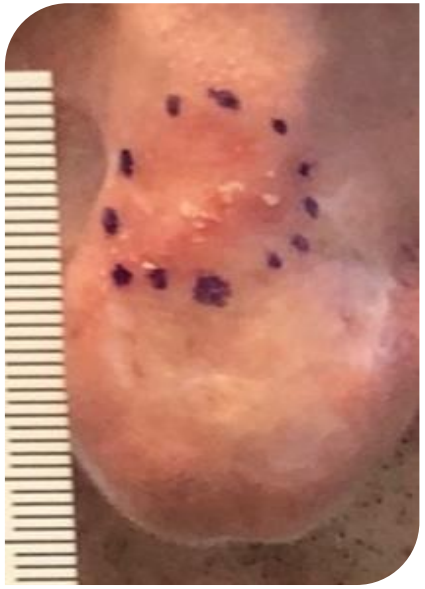
- Mechanism of action is same as other radiation therapy modalities.

References: 1. Sedda AF, et al. Dermatological high-dose-rate brachytherapy for the treatment of basal and squamous cell carcinoma. Clin Exp Dermatol. 2008;33(6):745-749. doi: 10.1111/j.1365-2230.2008.02852.x 2. Cipriani C, et al. Personalized irradiation therapy for NMSC by rhenium-188 skin cancer therapy: a long-term retrospective study. J Dermatolog Treat. 2020:1-7. doi: 10.1080/09546634.2020.1793890. 3. Castellucci P, et al. High dose brachytherapy with non sealed 188Re (rhenium) resin in patients with non-melanoma skin cancers (NMSCs): single center preliminary results. Eur J Nucl Med Mol Imaging. 2021;48(5):1511-1521. doi: 10.1007/s00259-020-05088-z. 4. Cipriani C, et al. Personalized high-dose-rate brachytherapy with non-sealed rhenium-188 in non-melanoma skin cancer. Int J Nucl Med. 2017;114–112.

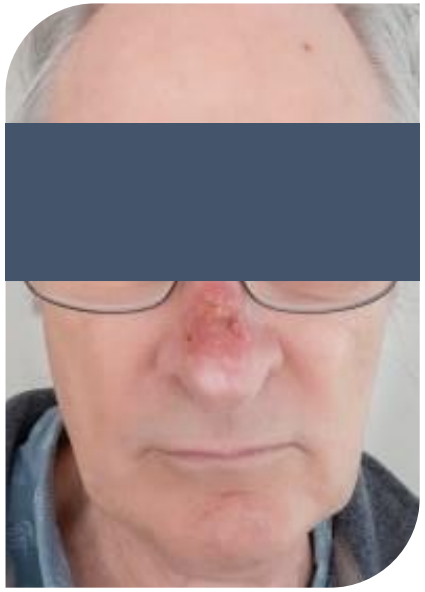
Rhenium-SCT®

Rhenium-SCT: Skin reactions / cosmesis

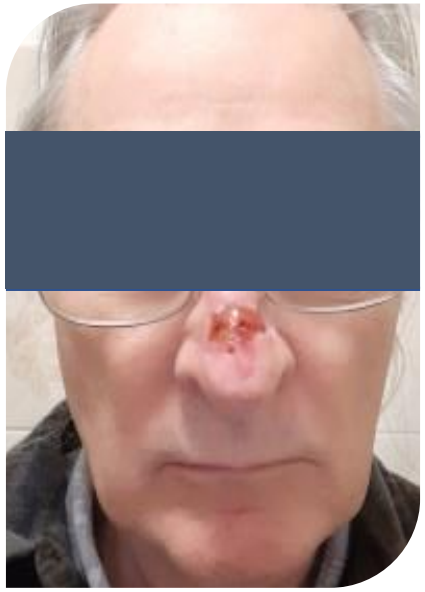
Results in areas with cosmetic considerations: BCC



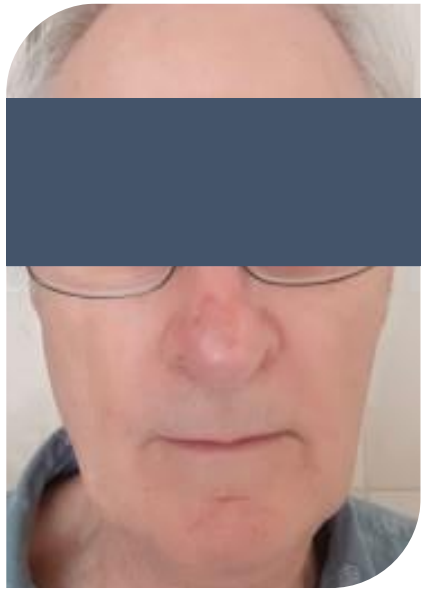
Before
Rhenium-SCT



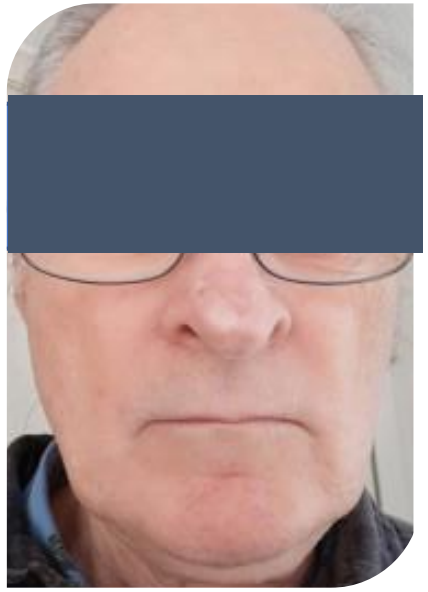
2 weeks



4 weeks



6 weeks



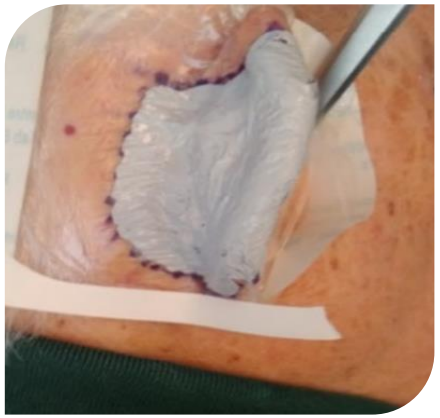
12 weeks

Rhenium-SCT: Lesions in areas with cosmetic considerations

Results in areas that have cosmetic considerations: SCC



Pre-treatment



Pre-treatment



Day 14



Day 30



Day 30



Day 48



Day 90



1 year

Male, 93 years-old

- SCC
- 2mm thickness
- No prior treatment

Rhenium-SCT: Lesions in areas with cosmetic considerations

Results in areas that have cosmetic considerations: BCC

Female, 92 years-old

- BCC
- 0.4mm thickness
- 3.3cm^2
- Prior Mohs therapy



Pre-treatment



Day 14



Day 28



Day 180

Rhenium-SCT: Lesions in areas with cosmetic considerations

Results in areas that have functional considerations: BCC

Male, 84 years-old

- SCC
- 0.6mm thickness
- 2.5cm^2 treatment area
- Prior CO_2 laser, cryotherapy



Pre-treatment



Day 14



Day 28



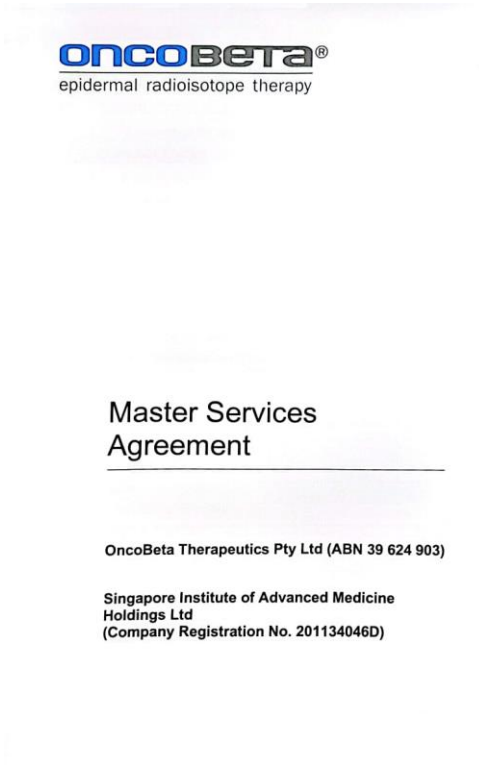
Day 60



Day 90

Singapore Institute of Advanced Medicine Holdings

finalizing a Master Services Agreement with Oncobeta for supply and sales, training and research for 18 countries including China and India, with exclusivity for 16 countries


ONCOBETA®
epidermal radioisotope therapy

Master Services Agreement

OncoBeta Therapeutics Pty Ltd (ABN 39 624 903)

Singapore Institute of Advanced Medicine Holdings Ltd
(Company Registration No. 201134046D)



Singapore Institute of Advanced Medicine Holdings Ltd. (the "Company") was listed on Catalist of the Singapore Exchange Securities Trading Limited ("SGX-ST") on 16 February 2024. The initial public offering of the Company was sponsored by PrimePartners Corporate Finance Pte. Ltd. (the "Sponsor").

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