IMUGENE

Developing Cancer Immunotherapies

ASX: IMU

Developing Cancer Immunotherapies

November 2022

Release authorised by the Managing Director and Chief Executive Officer
Imugene Limited, Level 3, 62 Lygon Street, Carlton, VIC, 3053, Australia

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IMUGENE'S MANAGEMENT TEAM

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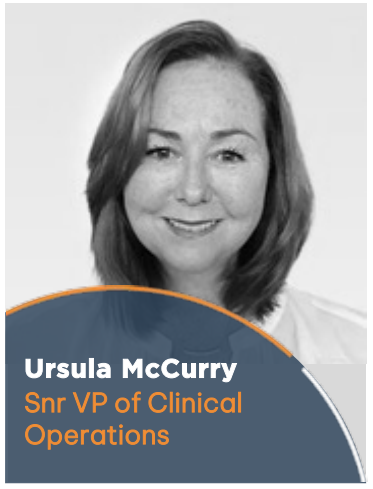
Experienced management team with significant clinical development expertise



INTRODUCTION TO IMUGENE

Imugene is a biotech company headquartered in Australia and publicly traded on the Australian Securities Exchange (ASX:IMU)

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2013
Paul Hopper builds Imugene around technology originating from the Medical University of Vienna

2015
Leslie Chong from Genentech joins Imugene

2017
HER-Vaxx enters the clinic

2018
Licensed extensive B cell portfolio and platform from OSU & Mayo Clinic invented by Prof Pravin Kaumaya

2019
Completed the acquisition of a prolific oncolytic virus from City of Hope invented by Dr Yuman Fong

2021
Licensed onCARlytics from City of Hope invented by Dr Y Fong, Dr S Priceman & Dr A Park

2021
Strategic Partnership with Celularity

2021
CHECKvacc enters the clinic

2021
Strategic Partnership with Eureka

2021
HER-Vaxx Clinical Trial Supply Partnership with Merck KGaA & Pfizer

2021
PD1-Vaxx Clinical Trial Supply Partnership with Roche

2021
Entered the S&P/ASX 200 Index

2022
VAXINIA enters the clinic

2022
HER-Vaxx Phase 2 Final OS

2022
Strategic Partnership with Arovella

THREE TECHNOLOGY PLATFORMS

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	IMUGENE Developing Cancer Immunotherapies			
PLATFORM	onCARlytics IMUGENE	CF33 Oncolytic Virus IMUGENE		B Cell Immunotherapy IMUGENE	
	CF33-CD19 CAR T Combination Therapy	CHECKvacc	VAXINIA	HER-Vaxx	PD1-Vaxx
IP	IP TO 2038	IP TO 2037	IP TO 2037	IP TO 2036	IP TO 2037
CLINICAL TRIALS	**TBC** Phase 1 Solid Tumours N = TBD USA & TBD celularity EUREKA	**COH TNBC IST** Phase 1 Tripe Negative Breast Cancer N = 33-78 USA (COH only) IND Enabled	**MAST** Phase 1 Metastatic Solid Tumours N = 52-100 USA & AUS IND Enabled	**HERIZON** Phase 1b/2 Gastric Cancer N = 36 Asia & Eastern Europe	**IMPRINTER** Phase 1 Non-Small Cell Lung Cancer N = 24-54 USA & AUS IND Enabled
		DOMINICA Phase 1 Solid Tumours N = TBD USA & TBD		**nextHERIZON** Phase 2 Metastatic Gastric Cancer N = 30 USA, AUS, Asia IND Enabled	
				neoHERIZON Phase 2 Neoadjuvant Gastric Cancer N = 22 Germany	
				TIGIT-Vaxx, PDL1-Vaxx, LAG3-Vaxx, TIM3-Vaxx, VEGF-Vaxx, CTLA4-Vaxx etc	

INVESTMENT HIGHLIGHTS

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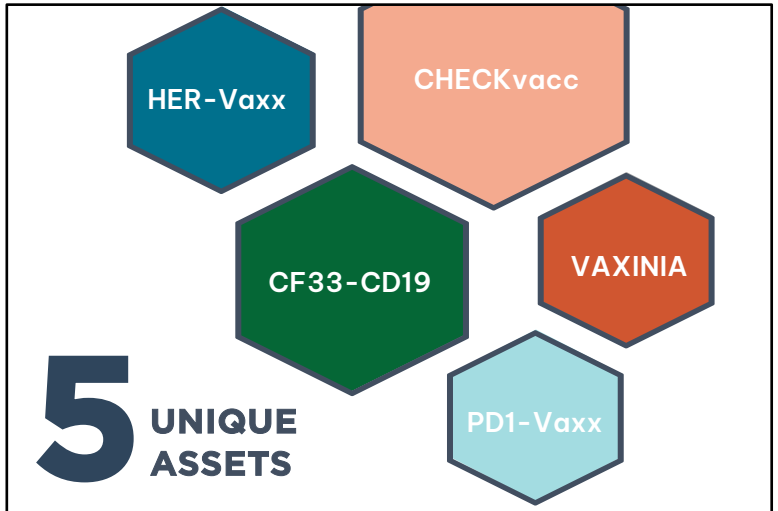
MARKET CAPITALISATION 11th Nov 2022 A$1.23B

CASH AS OF 30th Sep 2022 A$163.8M

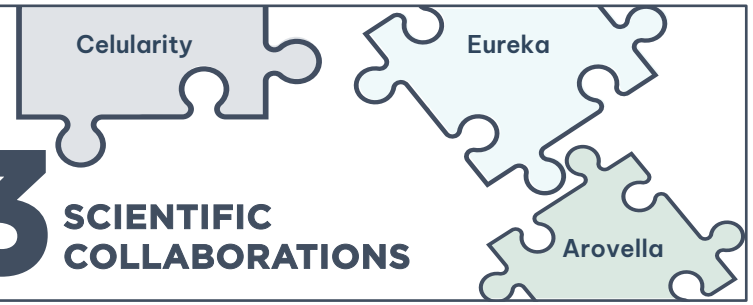


5 UNIQUE ASSETS

*Multiple potential platform targets | CF33-CD20 LAG3-Vaxx CTLA4-Vaxx TIGIT-Vaxx PDL1-Vaxx TIM3-Vaxx

CF33 Oncolytic Virus | onCARlytics | B-Cell Immunotherapies

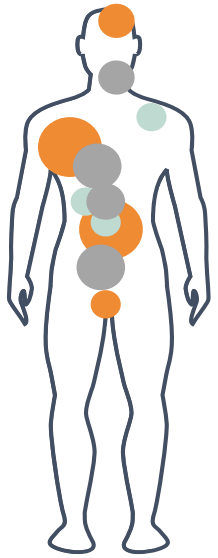
3 PLATFORM TECHNOLOGIES



3 SCIENTIFIC COLLABORATIONS

DISEASE AREAS

- Breast (TNBC)
- Lung (NSCLC)
- Gastric
- Gastroesophageal
- Colorectal (CRC)
- Melanoma
- Head and Neck
- Hepatocellular
- Pancreatic
- Glioblastoma (GBM)



10 CLINICAL STUDIES

HERIZON: Ph1b/2 First line Gastric Cancer
IMPRINTER: Ph1 NSCLC (FDA IND)
CHECKvacc COH IST: Ph1 TNBC (FDA IND)
neoHERIZON: Ph 2 Neoadjuvant Gastric Cancer
nextHERIZON: Ph2 Metastatic Gastric Cancer (FDA IND)
MAST: Ph1 Solid Tumours (FDA IND)
DOMINICA: Ph1 TNBC (FDA IND)
onCARlytics: Ph1 Solid Tumours (FDA IND)
neuHERIZON: Ph2 Biomarker Study
PD1-Vaxx IST: Ph1 CRC

2 SUPPLY AGREEMENTS

Merck KGaA/Pfizer | Roche

PROFESSOR YUMAN FONG

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The Sangiacomo Family Chair in Surgical Oncology and chair of The City of Hope Dept of Surgery is an internationally recognized expert in liver and pancreatic cancer. He has developed many new surgical techniques and instruments. He helped usher in robotic surgery for liver cancer. He has also led research efforts to use genetically modified viruses to destroy cancer cells.

Dr. Fong joined City of Hope in 2014 after more than three decades at Memorial Sloan-Kettering Cancer Center in New York City.

Dr. Fong has written and edited >1000 scholarly articles as well as 22 textbooks. He is the founding Editor-in-Chief of Molecular Therapy Oncolytics (Cell Press).

He is a fellow of the American Institute of Medical and Biologic Engineering, and the National Academy of Medicine.

Dr. Fong has had leadership roles in regulatory aspects of gene therapy, including serving as Chair or the Recombinant DNA Advisory Committee of the National Institutes of Health of the United States.

City of Hope, in Los Angeles, is a leading research and treatment center for cancer, diabetes and other life-threatening diseases. Founded in 1913, it is designated as a comprehensive cancer center, the highest recognition bestowed by the National Cancer Institute. City of Hope is also a founding member of the National Comprehensive Cancer Network, with research and treatment protocols that advance care throughout the US.
City of Hope has been ranked as one of the nation's "Best Hospitals" in cancer by U.S. News & World Report for over 10 years.
City of Hope has GMP facilities that produces clinical trials materials for many academic centers and is the alpha clinic trials site for CIRM

City of Hope

CF33 Oncolytic Virus
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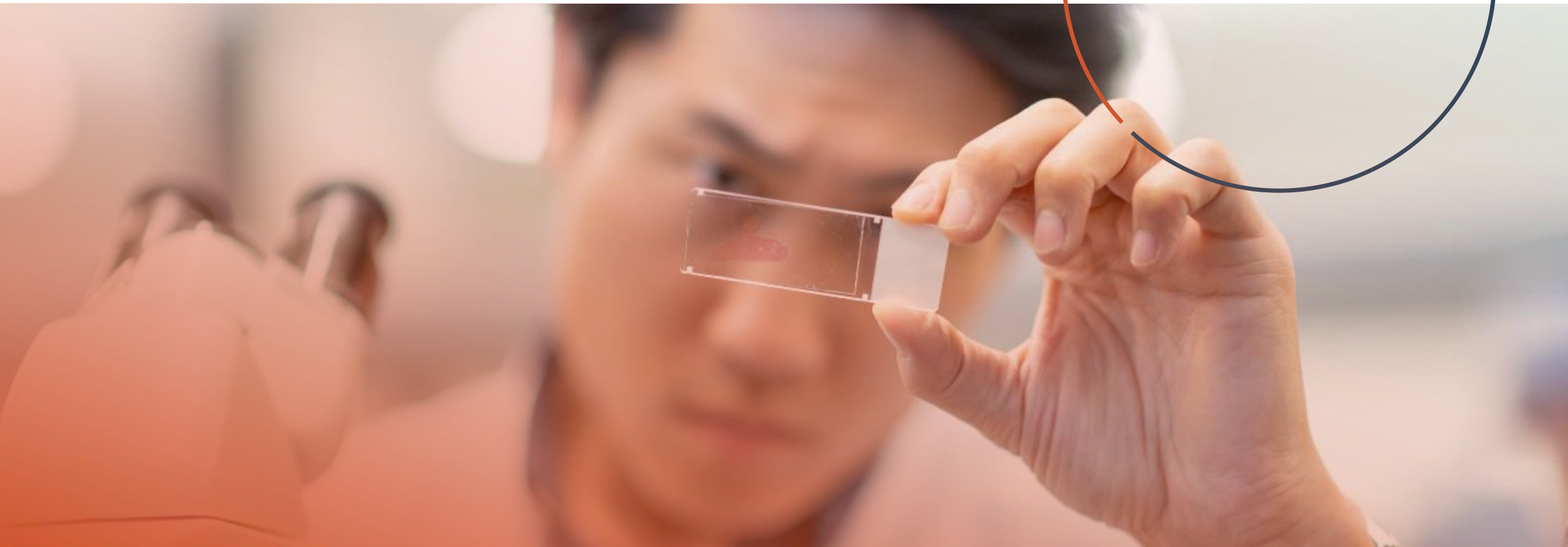
CF33 Oncolytic Virus



ONCOLYTIC VIRUSES

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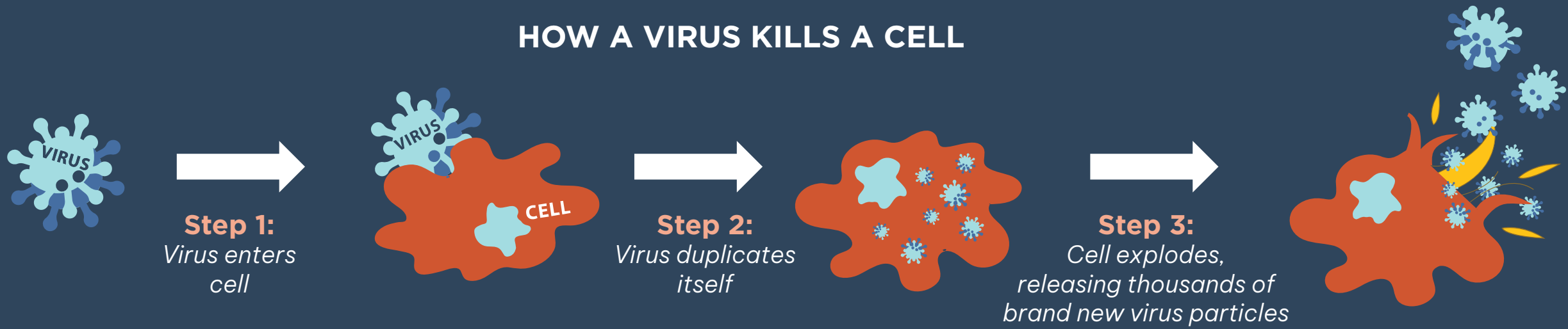
HOW A VIRUS KILLS A CELL



Step 1: *Virus enters cell*

Step 2: *Virus duplicates itself*

Step 3: *Cell explodes, releasing thousands of brand new virus particles*

Goal is to engineer viruses that;

- Infect and kill only cancer
- Carry additional payloads to kill cancer (Check point inhibitors, Cytokines, Anti-angiogenics)

Methods of cancer cell killing

- Direct Lysis
- Immuno-activation

- Tvec approved 2015 for melanoma
- Oncolytic viruses can prime tumor microenvironment to enhance response to checkpoint inhibitors

Ribas et al., Cell 170:1109, 2017

LAST GENERATION ONCOLYTIC VIRUSES

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PRODUCT	TARGET/VIRUS	COMPANY	DEVELOPMENT PHASE & KEY RESULTS
	Squamous cell carcinoma of the head and	Sunway	Approved in China
			A
Pe	nia		
	d and		
		Viralytics	Phase II
ColoAd1	Solid tumors/Ad	PsiOxus	Phase I/II
SEPREHVIR	Malignant Pleural Mesothelioma/HSV	VIRTTU	Phase I/IIa
GL-ONC1	Ovarian cancer/vaccinia	Genelux	Phase I

Too worried about toxicity

- Made viruses too attenuated
- Trial path too slow
  - Single dose, multiple dose, combination Rx

- Running out of IP
- Too expensive to deliver
- Poor efficacy

WHY A VACCINIA VIRUS?

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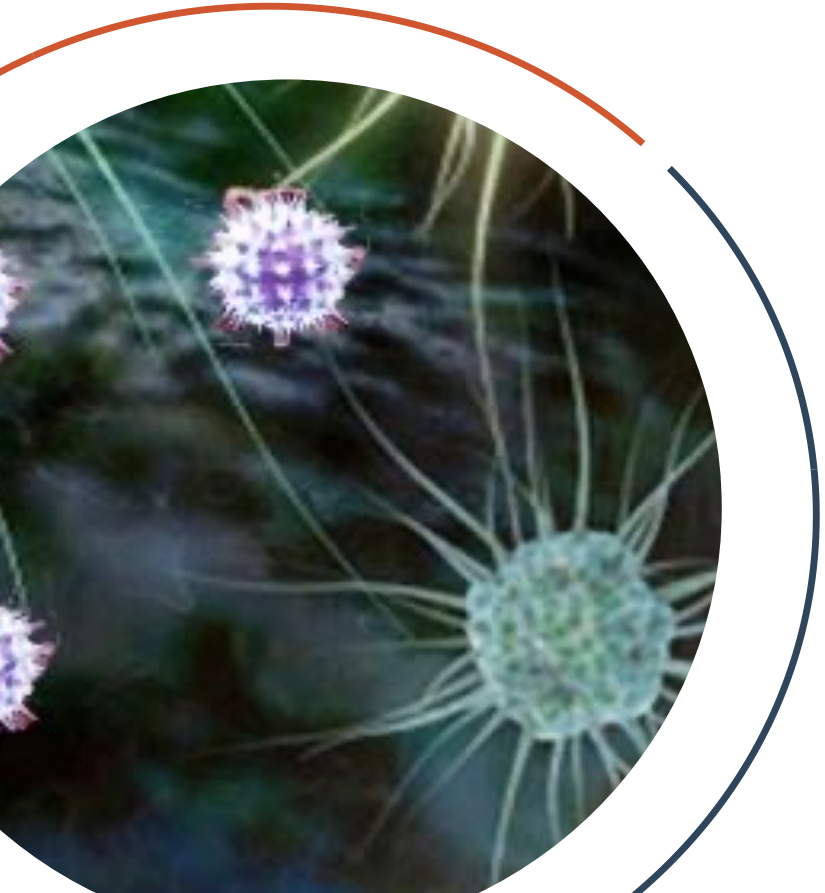
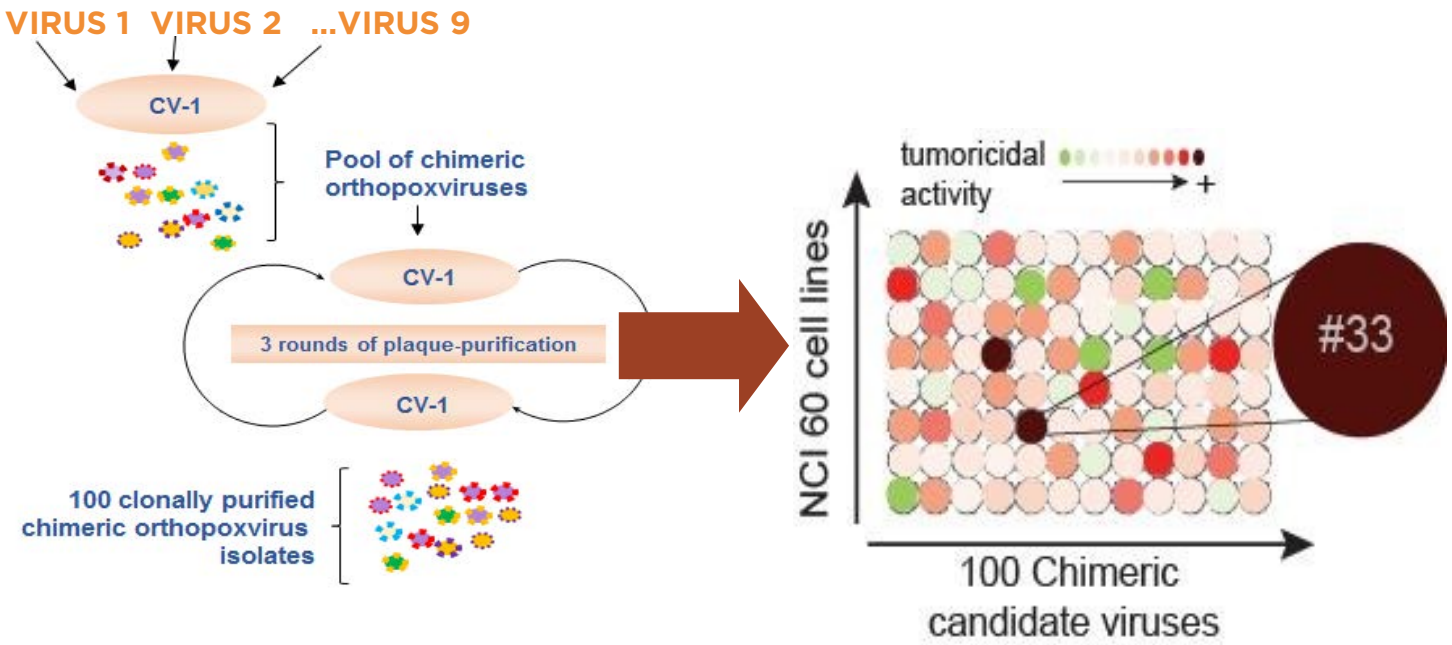


- Large DNA virus that is genetically very stable
- Most effective biologic therapy in history of man:

  vaccine that eradicated smallpox
- Highly cytolytic for a broad range of tumor cell types
- Amenable to large scale production
- Does not integrate into the host genome
- May be administered via intratumoral (IT) and intravenous (IV) routes
- Can carry large transgenes and large numbers of transgenes

GENERATION & EVALUATION OF NOVEL CHIMERIC POXVIRUSES



- 200 new backbones (new species)
- High through-put screening for cancer killing in the NCI-60 cell lines
- Arming with transgenes

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STRATEGY

Engineer Novel Chimeric Viruses

High Through-put Screening for Efficacy Against NCI60

Safe in Animals

Arming with Additional Payloads

Hope Oncolytic Viruses (HOV)

COMPELLING KILLING OF MANY TUMOUR TYPES AT LOW DOSES

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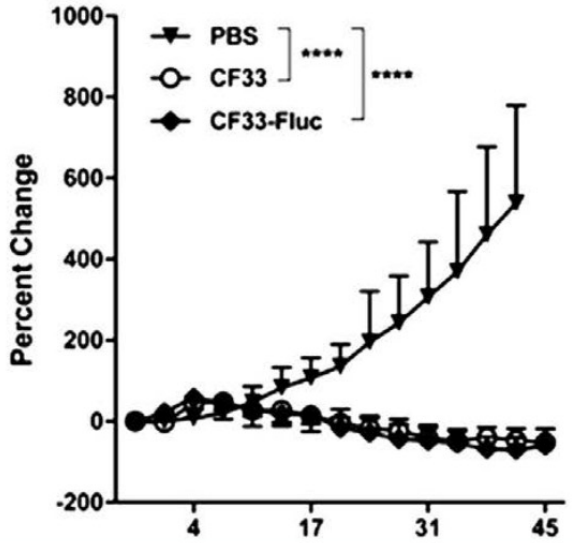
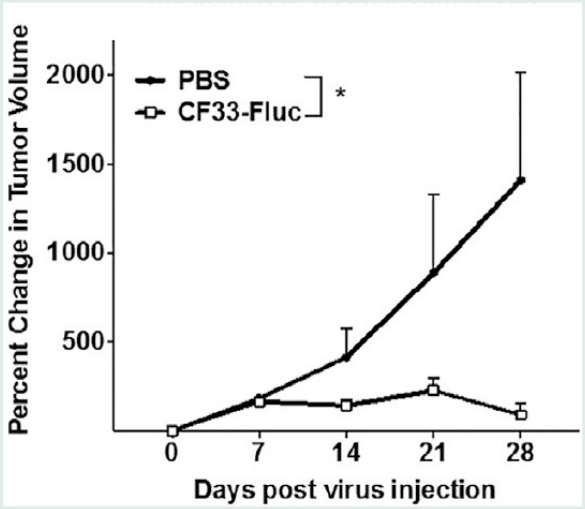
PANCREATIC



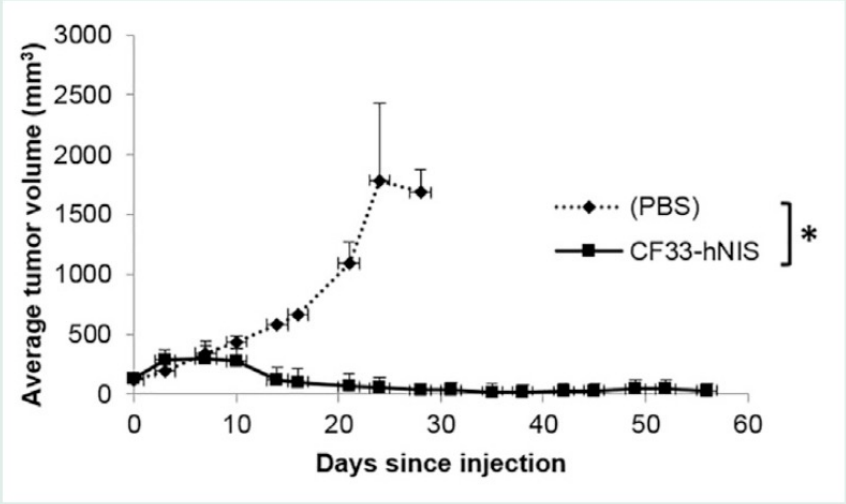
J Transl Med. 2018, 16, 110

COLORECTAL



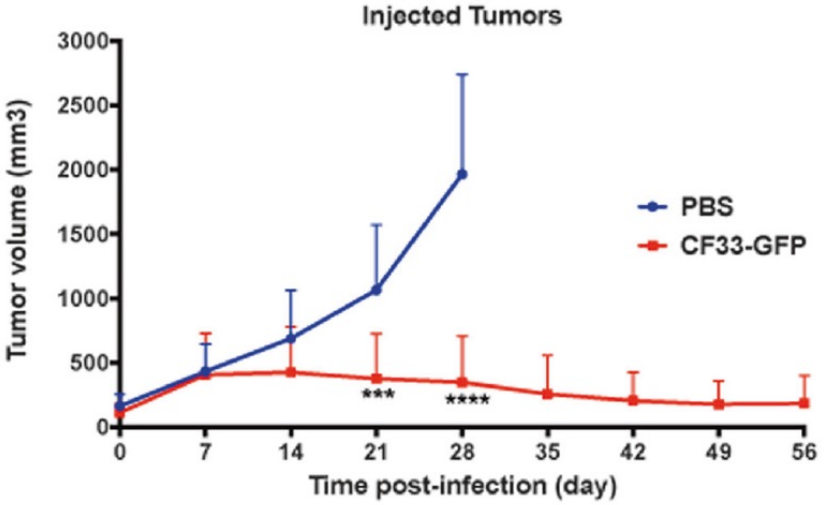
Mol Ther Oncolytics. 2018, 9, 13

COLON



Mol Ther Oncolytics. 2019, 13, 82

LUNG



Cancer Gene Ther. 2019

VAXINIA: CF33-hNIS “Parental Virus”

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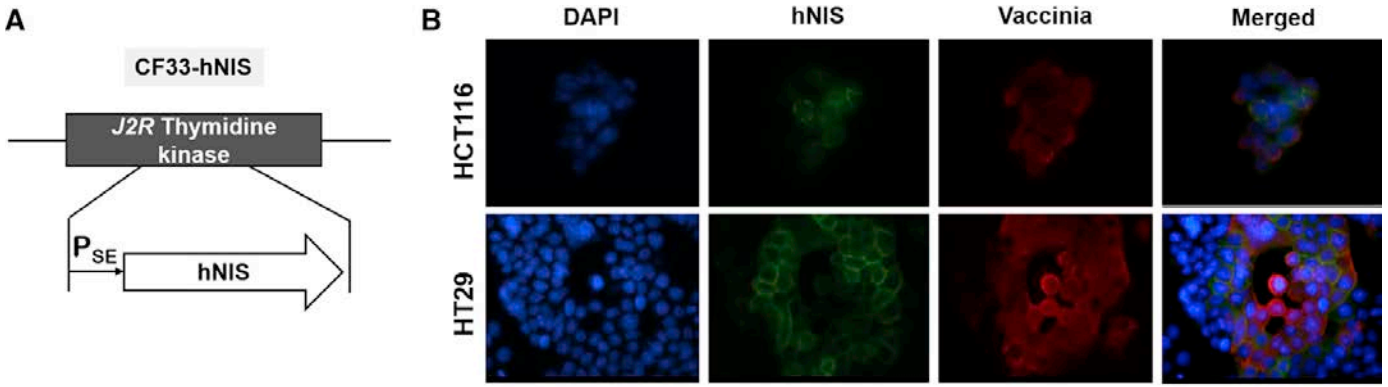
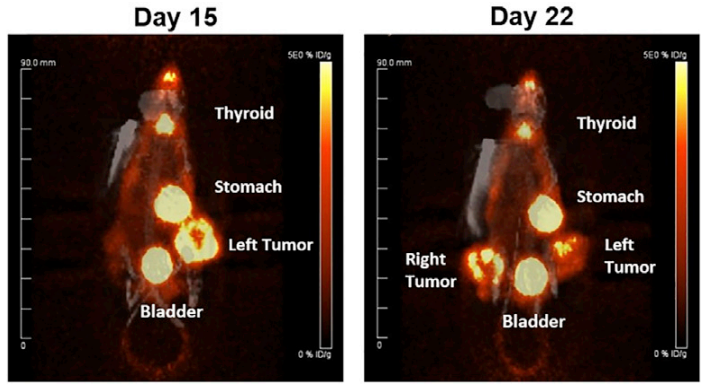
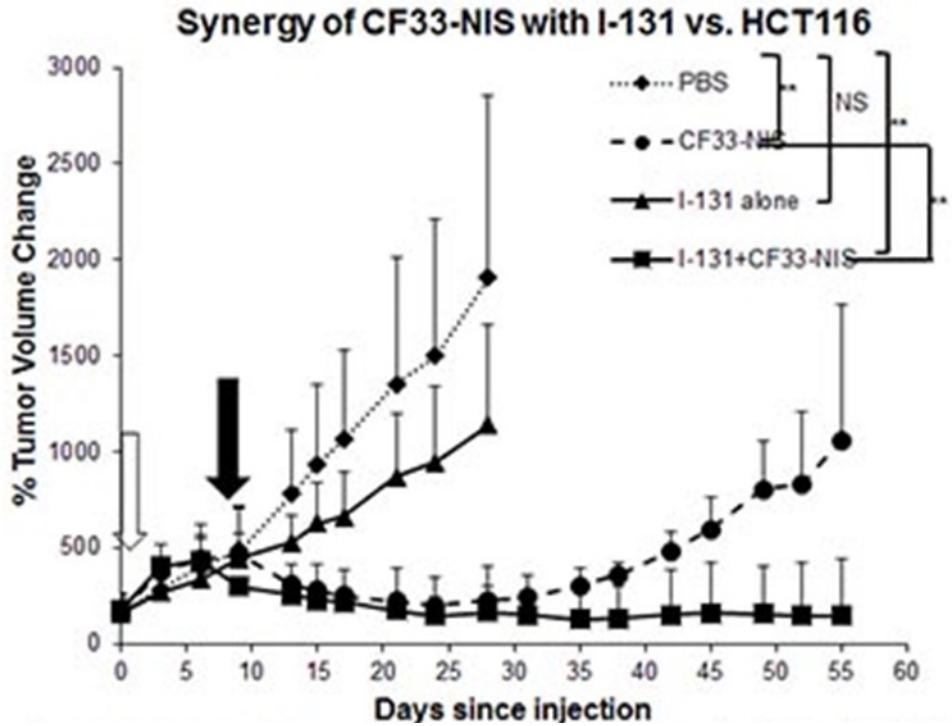


PET/CT I-124 imaging of CF33-hNIS



- hNIS transgene inserted within J2R locus (Tk) to transport radioactive iodine for imaging or therapy
- hNIS protein expressed on tumour cell surface (green)
- PET imaging shows virus in injected tumour at day 15 and virus infecting non-injected tumour by day 22
- CF33-hNIS infection is synergistic with I-131 radioisotope and induces sustained tumour growth abrogation in HCT116 colorectal cancer xenografts

Ref: Mol Ther Oncolytics, 2019, 13, 82



SAFELY DELIVERED IT, IP, IV WITH LARGE THERAPEUTIC INDEX

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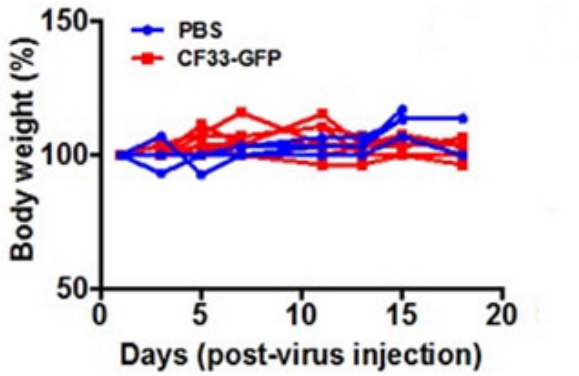

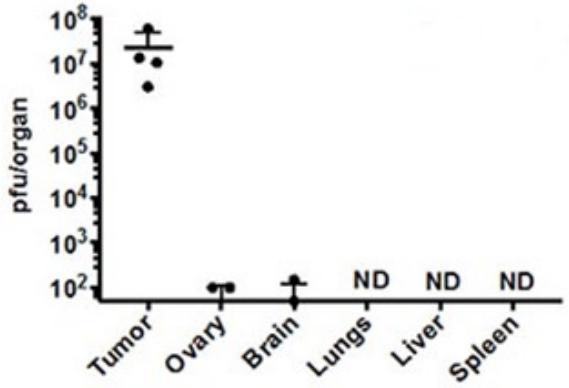

- In many tumor models, animals cured with a single injection of 1000 pfu
- NO TOXICITY UNTIL OVER 10^9
- Virus restricted to tumor

VIRUS	MOUSE	# OF MICE	DOSE	DELIVERY	TOXICITY
CF33-NIS	Nude	73	1e3-1e5	IT	No findings
CF33-miR	Nude	41	1e3-1e5	IT	No findings
CF33-Luc	Nude NSG	48 8	1e3-2e5 1e6	IT, IV & IP IT	No findings
CF33-GFP	Nude NSG	18 8	1e3-2e7 1e6	IT IT	No findings
CF33-hNIS-αPDL1	Nude Black/6 BALB/c	52 67 31	1e4 1e5-1e8 1e7	IT IT & IV (1e6) IT & IV	No findings
CF33-hNIS-Δ14.5	Nude Black/6 BALB/c	36 16 16	1e4 1e6 – 1e8 1e7-3e7	IT IT IT & IV (2e7)	No findings
CF33-CD19	NSG	288	1e6-1e8	IT	No findings

MAJOR ADVANTAGES OF CF33

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- Preclinical data has demonstrated that CF33 is more efficacious than all parental viruses and most viruses in clinical trials
- Can shrink multiple types of cancer at an extremely low dose (1000 pfu).

- Tumor type-agnostic: 'universal' approach to targeting solid tumors
- Turns immunologically 'cold' tumors to immunologically responsive 'warm' tumors
- CF33 shrinks not only injected tumors, but also non-injected distant tumors, indicating tumor tropism and abscopal effect

- Novel combination use of FDA-approved cellular immunotherapy (CD19-CAR T cells) along with OV that presents CAR target, CD19, on solid tumors
- CAR T cell-mediated cancer killing helps OV spread in tumors

KEY DIFFERENTIATION

1. CF33 OV Platform:
   - high potency in cancer killing
   - range of cancer cell types infectible
   - Big therapeutic window
2. CF33 can be made in high titres
3. Great stability profile
   - Genetic stability
   - Storage stability
   - Clinic stability after mixing
4. CF33 can be used in multiple doses without complete neutralization by host immune system

CHECKvacc PHASE 1 TNBC STUDY

CF33+hNIS+aPD-L1 ("Armed" Virus)

SAN ANTONIO BREAST CANCER SYMPOSIUM

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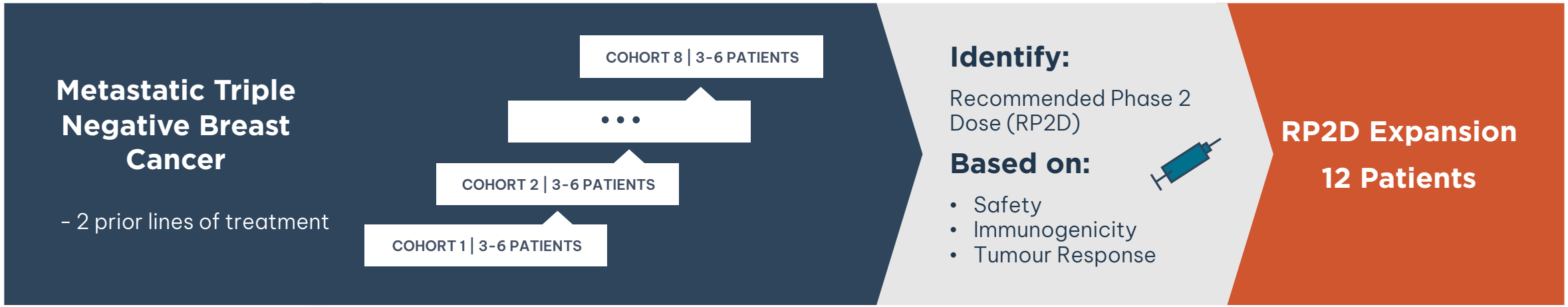
ACCEPTED TO SABC 2022



First Patient Enrolled October 2021

Disease of need

- 8-13 month survival for metastatic disease with few treatments

Potential target for immunotherapy

- Expresses PD1, PD-L1

Treatment responses to Atezolizumab (JAMA Oncology, 5:74, 2019)

- 1st line: 24%; 2nd line: 6%
- Approved by FDA 8 March 2019

Potential for registration in well-designed, randomised P2 study

Indication	TNBC
FDA IND	CHECKvacc: CF33-hNIS-aPDL1
N	33-78
Location	Single Center: COH
Admin Route	Intratumoral (IT)

VAXINIA Phase 1 MAST Study
(Metastatic Advanced Solid Tumours)

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First Patient Enrolled May 2022, IT Cohort 1 Cleared Sept 2022

Dose Administration (Parallel Groups)

n=52-100

IT

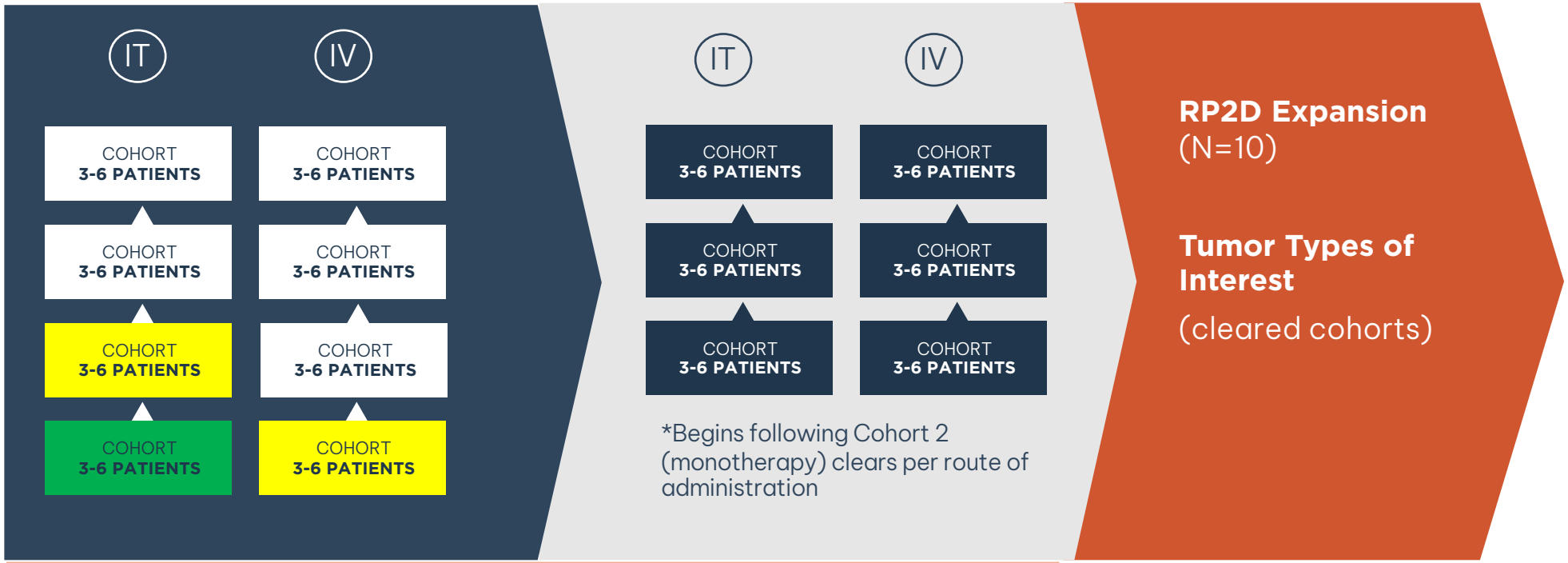
IT Administration
Metastatic and Advanced Solid Tumours

IV

IV Administration
Metastatic and Advanced Solid Tumors

Site Location: USA, AUS

VAXINIA Monotherapy Dose Escalation



VAXINIA + Pembrolizumab Combination Dose Escalation*

Cohort Expansion

Identify: Recommended Phase 2 Dose (RP2D) – Monotherapy and Combination
Based on: Safety, Immunogenicity, Tumour Response

DR SAUL PRICEMAN

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Saul Priceman, Ph.D., is an assistant professor and associate director of Translational Sciences & Technologies in the T Cell Therapeutics Research Laboratories at City of Hope, as well as a trained tumor immunologist with expertise in T cell biology and cancer immunotherapy. He is developing chimeric antigen receptor (CAR)-based T cell immunotherapy primarily for solid cancers, with a strong focus on metastatic disease in breast, prostate and pancreatic cancer.

Dr. Priceman received his B.S. in microbiology at University of California Santa Barbara, and his Ph.D. in molecular and medical pharmacology at University of California Los Angeles.

Dr. Priceman is a principal investigator on a Prostate Cancer Foundation Young Investigator award, a co-principal investigator on a Prostate Cancer Foundation Challenge Award and a principal investigator on a National Comprehensive Cancer Network Young Investigator award, leading the development of HER2-specific CAR T therapy for metastatic breast cancers and working with his team optimizing new CAR T cell therapies for various other solid cancers.

Dr. Priceman is deeply committed to rapidly advancing potentially paradigm-shifting immunotherapy on behalf of patients with cancer, in part because of personal experiences with family and friends who have struggled with the disease. His overarching goal is to develop a range of effective immunotherapies for solid cancers, based on the powerful CAR T cell platform, with the knowledge that any single therapy will not likely provide durable responses in advanced disease.

City of Hope, in Los Angeles, is a leading research and treatment center for cancer, diabetes and other life-threatening diseases. Founded in 1913, it is designated as a comprehensive cancer center, the highest recognition bestowed by the National Cancer Institute. City of Hope is also a founding member of the National Comprehensive Cancer Network, with research and treatment protocols that advance care throughout the US.
City of Hope has been ranked as one of the nation's "Best Hospitals" in cancer by U.S. News & World Report for over 10 years.
City of Hope has GMP facilities that produces clinical trials materials for many academic centers and is the alpha clinic trials site for CIRM

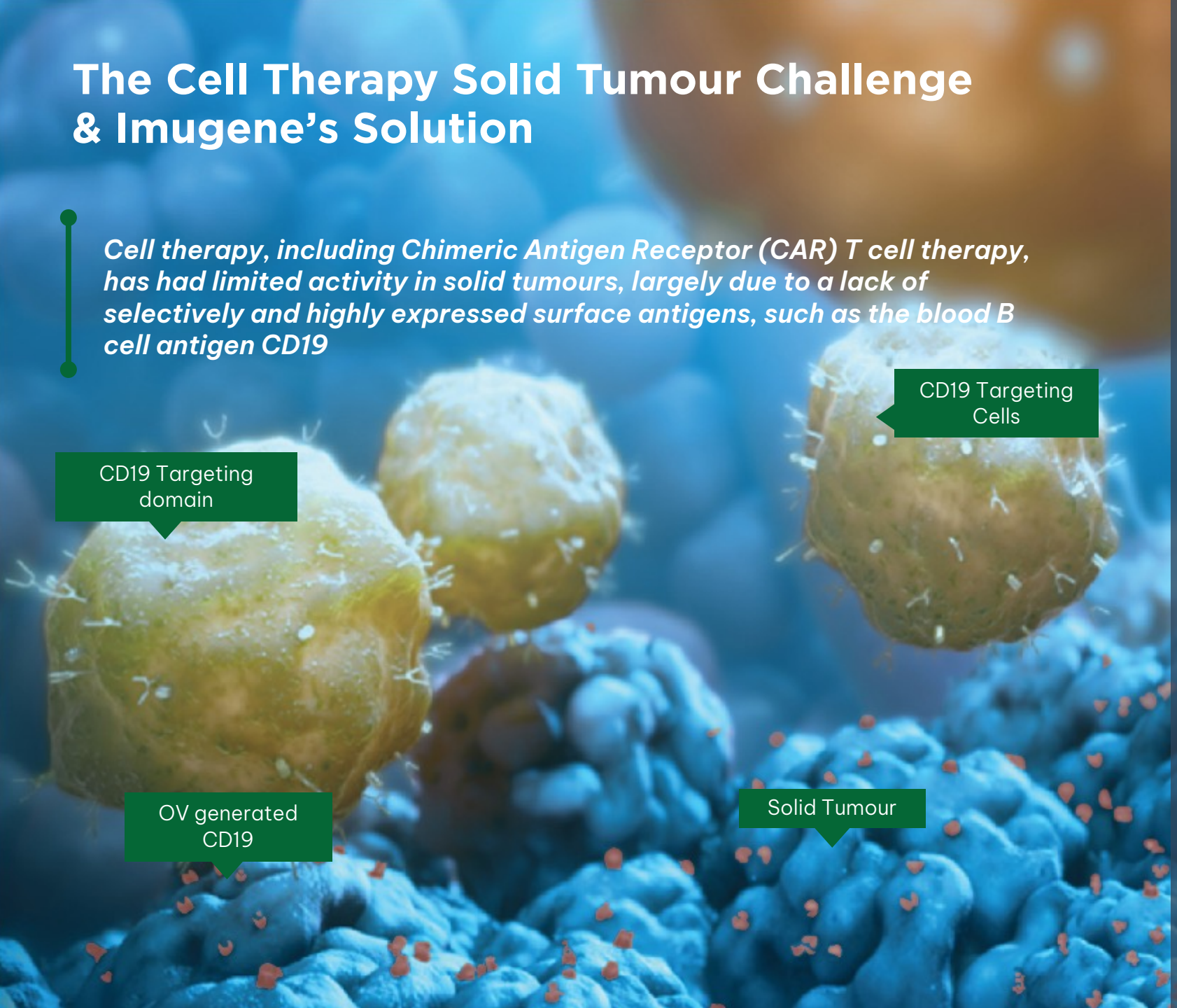
City of Hope

onCARlytics
IMUGENE

CF33-CD19

The Cell Therapy Solid Tumour Challenge & Imugene's Solution

Cell therapy, including Chimeric Antigen Receptor (CAR) T cell therapy, has had limited activity in solid tumours, largely due to a lack of selectively and highly expressed surface antigens, such as the blood B cell antigen CD19



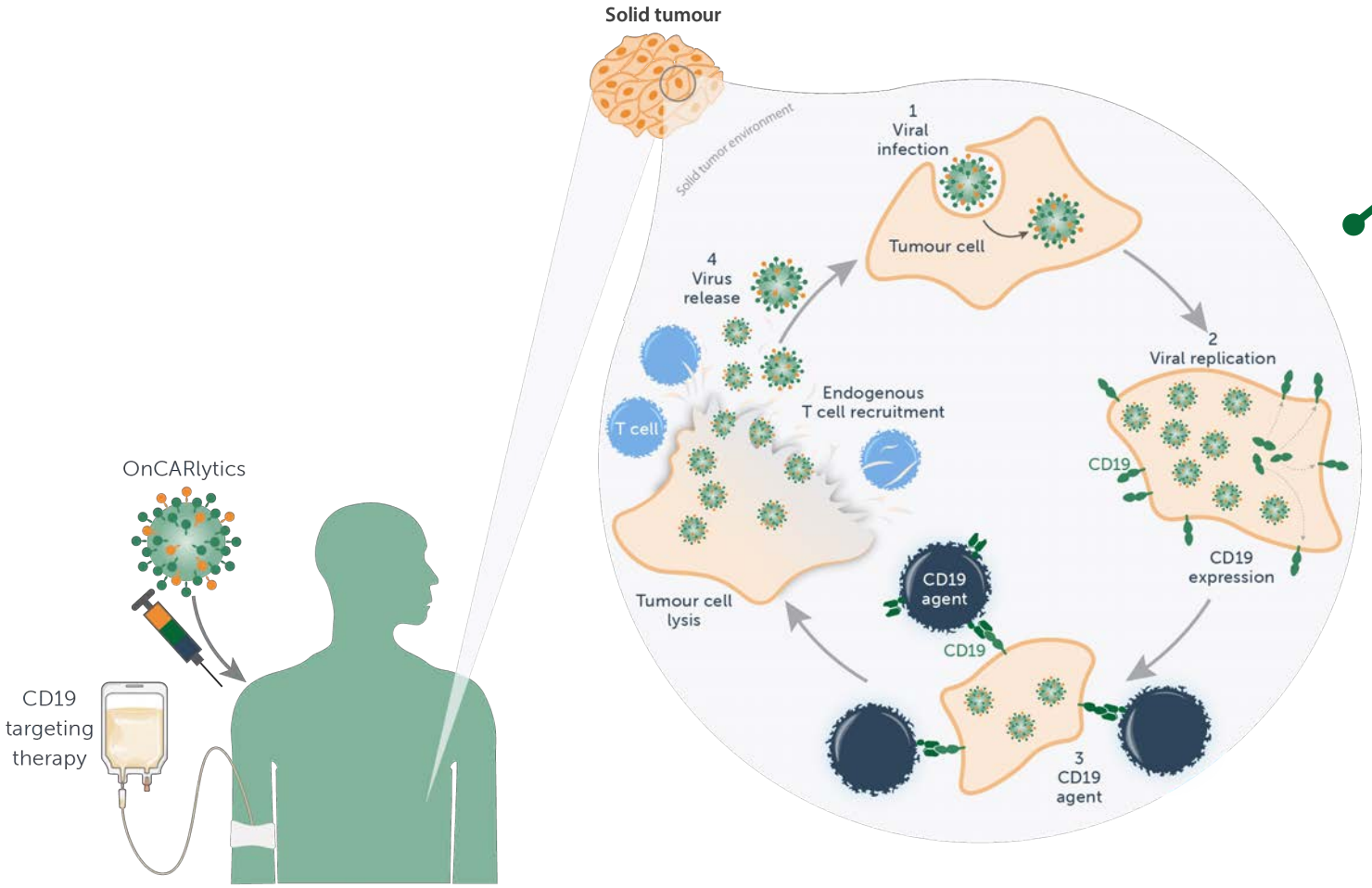
NEW CONCEPT

Utilise OV's as a delivery vector to deliver CD19 antigen to solid tumour cells

Engineer Imugene's CF33 to infect solid tumour cells and insert CD19 transgene to enable presentation of CD19 over the tumour cells during tumour cell infection, onCARlytics (CF33-CD19)

Combination use of CD19 targeting therapies, including autologous or allogeneic CD19 CAR Ts and bispecifics, with onCARlytics (CF33-CD19) presented CD19 targets on solid tumours

MECHANISM OF ACTION:
How does it work?



onCARIytics makes solid tumours "seen" by CD19 targeting therapies

1. OnCARIytics infects tumour cells
2. Virus replication and production of CF33-CD19 on the cell surface enabling CD19 cell targeting
3. Tumour cell lysis leads to viral particle release and the combination promotes endogenous immune cell recruitment to tumours
4. Released viral particles re-initiate virus infection of surrounding tumour cells.

onCARLYTICS DELIVERS CAR TARGETS TO "TARGETLESS" SOLID TUMOURS

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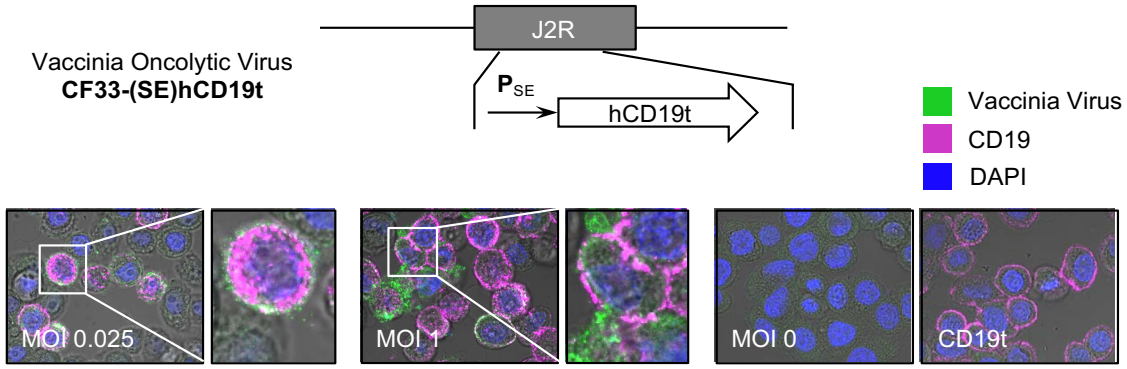
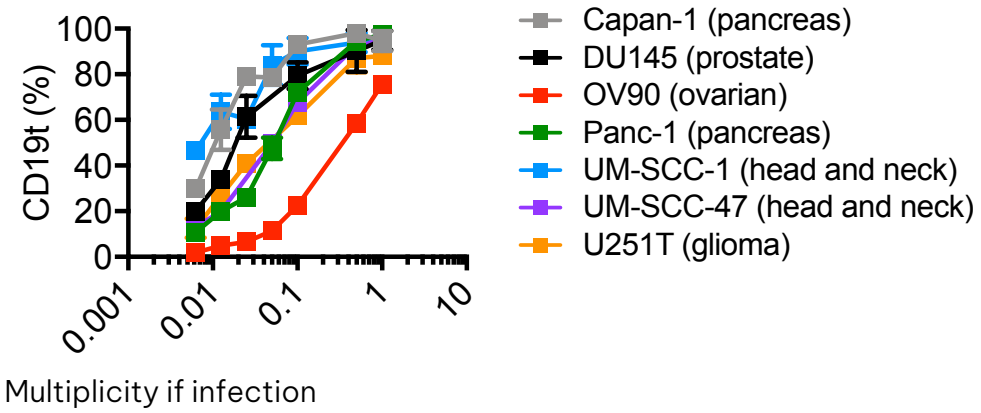
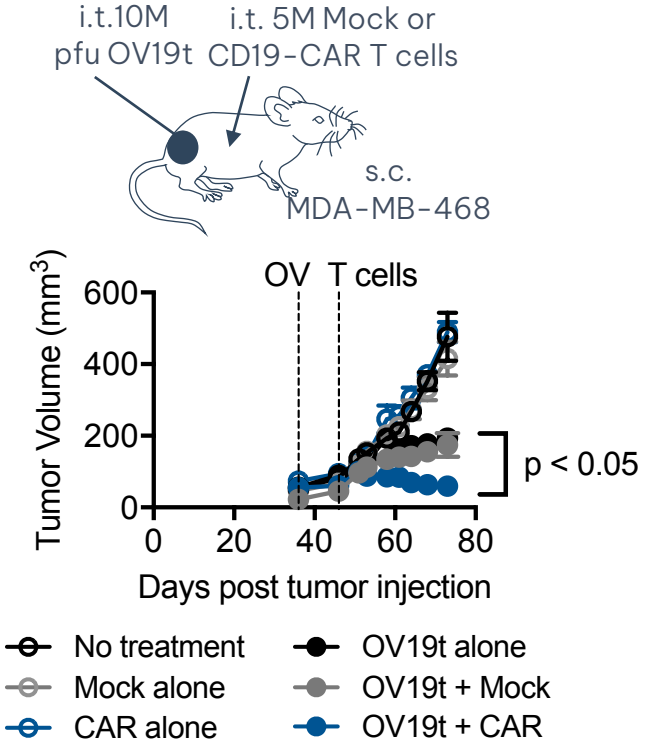


onCARlytics (CF33-CD19) infects a wide array of solid tumour cell lines, with dose-dependent CD19 cell surface expression



Combination of onCARlytics (CF33-CD19) and CD19-CAR T cells promotes tumour regression in xenograft model of TNBC



Park et al. *Science Translational Medicine* 2020

onCARLYTICS COMBINATION WITH CD19 TARGETING THERAPIES

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CF33-CD19T ONCOLYTIC VIRUS (onCARlytics) IN COMBINATION WITH OFF-THE-SHELF ALLOGENEIC CYCART-19 T-CELLS TARGETING DE NOVO CD19T EXPRESSING TUMORS

Anthony K. Park[1], Isabel Monroy[1], Colin Cook[2], Shuyang He[3], Kathy Karasiewicz[3], Monil Shah[4], Leslie M.O. Chong[4], Nimali P. Withana[4], Robert Hariri[3], Yuman Fong[2], and Saul J. Priceman[1]

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Introduction

Autologous chimeric antigen receptor (CAR) T Cell therapy has shown impressive clinical responses against CD19+ B-Cell hematological malignancies and is being actively explored in the treatment of solid tumors. However, several barriers have precluded therapeutic responses in solid tumors, including limited tumor-restricted CAR targets and the immunosuppressive tumor microenvironment. We have recently reported the successful combination immunotherapy using a novel chimeric vaccinia-based oncolytic virus (OV), called onCARlytics (Imugene Limited), that is engineered to express a non-signaling, truncated CD19 (CD19t) antigen for tumor-selective delivery, enabling de novo targeting of tumor cells by autologous CD19-CAR T Cell. One of the field's unanswered questions is whether treatment-naïve allogeneic CAR T Cell are superior to cancer patient-derived T-Cells for product manufacturing to improve overall responses against solid tumors.

Here, we evaluated this combination strategy using two allogeneic CAR T Cell products generated from peripheral blood mononuclear cells (PBMC) and placental T-Cells, respectively. PBMC-derived CAR T Cell were manufactured from normal, healthy donors. CYCART-19 (Celularity®, Inc.) Cells were derived from postpartum human placental T-Cells that are genetically modified to express the CD19-CAR followed by CRISPR-Cas9- mediated knockout of the endogenous TCR and expanded to produce multiple doses of allogeneic "off the shelf" treatment.

CYCART-19 T-Cells induced potent cytolytic activity against solid tumor cells infected with onCARlytics. Interestingly, while we observed comparable anti-tumor activity between PBMC-derived CD19-CAR T Cells and CYCART-19, significant differences in cytokine secretion were detected. This warrants the possibility that the placental-derived CAR T product may elicit reduced CRS potential in patients with maintained or improved efficacy. This combination approach demonstrated impressive in vivo anti-tumor response in human tumor xenograft models. In summary, our results have demonstrated that further development of this combination immunotherapy for the potential treatment of a wide array of solid tumors is warranted.

Figure 1

Delivering truncated CD19t (CD19t) to tumor cells using oncolytic virus (OV) as a target for CD19-CAR T Cell.

onCARlytics selectively infect solid tumor cells and deliver truncated CD19 (CD19t) as a target for CD19-CAR T Cell.

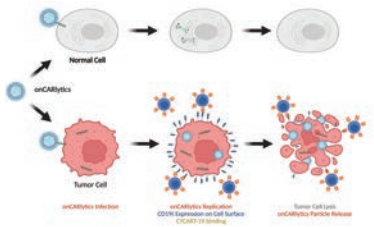


Figure 2

Postpartum human placental derived allogeneic T-Cells expressing CAR-CYCART-19

Celularity® has developed an allogeneic placental T-Cell with knockout of endogenous T-Cell receptors, derived from postpartum human placenta expressing CD19-CAR called CYCART-19. Placental-derived T-Cells are mostly naïve (CD45RA+ CCR7+), expand readily ex vivo, express markers of stem cell memory, and have lower expression of effector or exhaustion markers, which has been associated with greater stemness, enhanced proliferative capacity, and increased persistence in vivo.

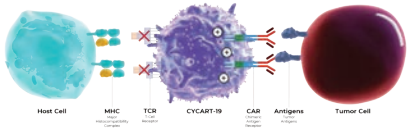


Figure 3

Specific CYCART-19 tumor cell killing following onCARlytics infection

A Bright-field microscopy (10X magnification) of MDA-MB-468 tumor cells at 24h following onCARlytics infection or MDA-MB-468-CD19t (positive control lentivirally transduced to stably express CD19t) in the presence of untransduced (NT) or CYCART-19 T-Cells. B In vitro killing assay at 24h and C 48h of MDA-MB-468 tumor cells infected with onCARlytics and treated with untransduced autologous T-Cells, autologous CD19-CAR T Cell, NT (1 donor), or CYCART-19 (3 donors) T-Cells. Graph on the left represents tumor killing, and in the middle represents CD19t expression on tumor cells. Graph on the right represents tumor count against MDA-MB-468-CD19t treated with untransduced autologous T-Cells, autologous CD19-CAR T Cell, NT (1 donor), or CYCART-19 (3 donors) T-Cells.

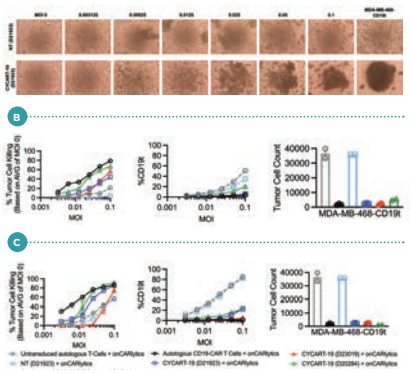


Figure 4

Activation of CYCART-19 by targeting of tumor cells expressing CD19t following onCARlytics infection

A Expression of activation marker (CD137) on untransduced autologous T-Cells, autologous CD19-CAR T Cell, untransduced [NT] (1 donor), or CYCART-19 (3 donors) T-Cells following 24h (left) and 48h (right) in vitro co-culture with MDA-MB-468 tumor cells infected with onCARlytics. B IFNγ and C IL-2 production following in vitro infection of MDA-MB-468 tumor cells with onCARlytics in the presence of autologous untransduced, autologous CD19-CAR, NT, or CYCART-19 T-Cell measured at 24h (left) and 48h (right) by ELISA. D IFNγ and E IL-2 production following in vitro co-culture of MDA-MB-468-CD19t with autologous untransduced, autologous CD19-CAR, NT (1 donor), or CYCART-19 (1 donors) T-Cells measured at 24h (left) and 48h (right) by ELISA.

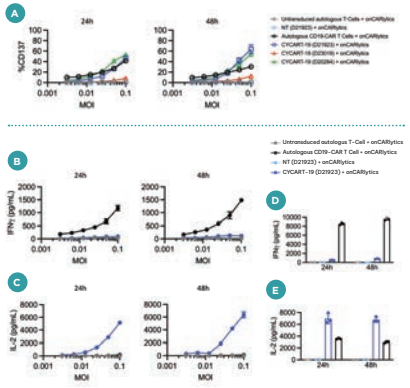


Figure 5

CD19t expression in tumor cells following onCARlytics infection in vivo

Subcutaneously engrafted MDA-MB-468 tumors were collected 3, 7, or 10 days from NSG mice following onCARlytics infection at three indicated virus pfu per mouse and analyzed via flow cytometry for the expression of CD19t. MDA-MB-468 lentivirally transduced to stably express CD19t were used as a positive control (+ctrl).

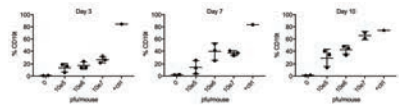


Figure 6

Schema of in vivo studies testing onCARlytics in combination with CYCART-19

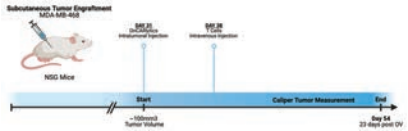


Figure 7

Comparing anti-tumor activity of CYCART-19 against autologous CD19-CAR T Cell in MDA-MB-468-CD19t bearing NSG mice

Mice were engrafted with subcutaneous MDA-MB-468-CD19t ($5x10^6$ cells) and were intravenously treated with untransduced autologous, autologous CD19-CAR, NT, CYCART-19 (2 donors) T-Cells ($5x10^6$ cells). Tumors were measured to determine T-Cell efficacy against a positive control tumor cell line in vivo.

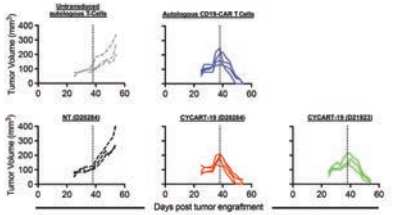
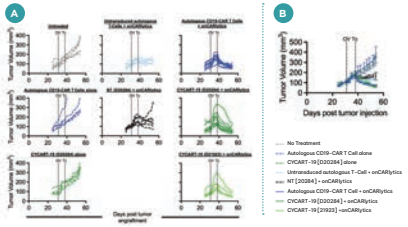


Figure 8

Anti-tumor activity of CYCART-19 in combination with onCARlytics in human xenograft triple negative breast cancer tumor model

Mice were engrafted with subcutaneous MDA-MB-468 ($5x10^6$ cells) and were intratumorally treated with 0 or 10^6 pfu of onCARlytics per mouse. Mice were intravenously treated with untransduced autologous, autologous CD19-CAR, NT, CYCART-19 (2 donors) T-Cells ($5x10^6$ cells). A Lines represent tumor volumes of individual mice per group (n=5-10) and B average of each group.



Summary

- onCARlytics can target triple negative breast cancer cell line MDA-MB-468 to express CD19t as a CAR T Cell target in an MOI-dependent manner.
- CYCART-19 demonstrated efficacy against MDA-MB-468 expressing CD19t following onCARlytics infection.
- There is an increasing trend in CYCART-19 activation and IL-2 production in an MOI-dependent manner.
- Allogeneic CYCART-19 T-Cell produced significantly less IFNγ compared to autologous CD19-CAR T Cell after CD19t expressing tumor killing.
- CD19t expression was detected in tumors following onCARlytics infection in vivo.
- CYCART-19 treatment 7 days post onCARlytics infection shows significant tumor regression compared to onCARlytics or T-Cells alone in a xenograft model of triple negative breast cancer.

References

1. Park AK, et al. Effective combination immunotherapy using oncolytic viruses to deliver CAR targets to solid tumors. Sci Transl Med. 2020. **2.** McCart JA, Ward JM, Lee J, Hu Y, Alexander HR, Libutti SK, Moss B, Bartlett DL. Systemic cancer therapy with a tumor-selective vaccinia virus mutant lacking thymidine kinase and vaccinia growth factor genes. Cancer Res. 2001. **3.** Chaurasiya S, et al. A chimeric poxvirus with J2R (thymidine kinase) deletion shows safety and anti-tumor activity in lung cancer models. Cancer Gene Ther. 2020. **4.** Gattinoni L, et al. Paths to stemness: building the ultimate antitumour T-Cell. Nature Reviews Cancer. 2012. **5.** Busch D, et al. Role of memory T-Cell subsets for adoptive immunotherapy. Seminars in Immunology. 2016. **6.** Sadeline M, et al. Therapeutic T-Cell engineering. Nature. 2017. **7.** Rafiq S, et al. Engineering strategies to overcome the current roadblocks in CAR T Cell therapy. Nature 2020.

CF33-CD19T ONCOLYTIC VIRUS (onCARlytics) TARGETS HEPATOCELLULAR CARCINOMA (HCC) AND IN COMBINATION WITH CD19 ARTEMIS® T-CELLS RESULTS IN SIGNIFICANT TUMOR KILLING

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths in the world with a 5-year survival rate at less than 12%. Currently, curative treatments include ablation, surgical resection, and liver transplantation. For majority of patients with advanced-stage disease, treatment with agents such as sorafenib, lenvatinib, and atezolizumab/bevacizumab and other investigational agents yield modest success rates and justify the need for further development of new therapies. T-Cell therapy against HCC targeting antigens such as alpha-fetoprotein (AFP) and glypican-3 (GPC-3) have shown some efficacy in clinical trials with conventional challenges against solid tumors including antigen heterogeneity, the immunosuppressive tumor microenvironment, and off-tumor on-target activity. Therefore, novel therapies are desperately needed to improve clinical outcomes for patients with HCC.

We have developed a novel chimeric vaccinia-based oncolytic virus, called onCARlytics (CF33-CD19t, Imugene Limited in collaboration with City of Hope®), that delivers a non-signaling, truncated CD19t (CD19t) antigen to tumors that allows for targeting of solid tumors by CD19 T-Cells. Once the CD19t is expressed on solid tumor cells, to enable cell killing, we have combined onCARlytics with CD19 ARTEMIS® T-Cell, a CD19-targeting adoptive engineered T-Cell powered by the ARTEMIS® antibody-T-Cell receptor (AbTCR) platform (Eureka Therapeutics®, Inc). ARTEMIS® AbTCR is distinct from CAR by recruiting the endogenous CD3 complex and utilizing the same activation and regulatory signaling pathways employed by natural TCRs, which enables both potent killing activity against CD19+ tumor cells and a superior safety profile. When administrated after onCARlytics, CD19 ARTEMIS® T-Cells were able to induce potent cytolytic activity against triple negative breast cancer and HCC tumor cells. OnCARlytics demonstrated expression of CD19t and robust in vivo anti-tumor efficacy against human HCC tumor xenografts. In summary, CD19 ARTEMIS® T-Cells combined with onCARlytics is a potentially effective immunotherapy strategy for the treatment of patients with HCC and can be applied to other solid tumors.

Figure 1

Delivering truncated CD19t (CD19t) to tumor cells using oncolytic virus (OV) as a target for CD19 ARTEMIS® T-Cells.

onCARlytics selectively infect solid tumor cells and deliver truncated CD19 (CD19t) as a target for CD19 ARTEMIS® T-Cells.

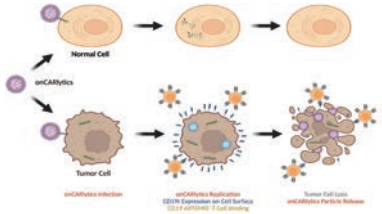


Figure 2

CD19 ARTEMIS® T-Cells (Eureka Therapeutics®, Inc)

Schematic of A ARTEMIS® platform compared to B TCR and C second-generation CAR platform.

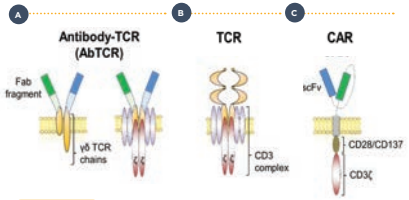


Figure 3

CD19 ARTEMIS® T-Cells effectively targets triple negative breast cancer cell line MDA-MB-468 following onCARlytics infection

A Bright-field microscopy (10X magnification) of MDA-MB-468 tumor cells at 24h following onCARlytics infection or MDA-MB-468-CD19t (positive control lentivirally transduced to stably express CD19t) in the presence of Mock (untransduced), CD19 ARTEMIS®, or City of Hope® (COH) CD19-CAR T Cells using donor D45757. B In vitro killing assay at 24h and C 48h of MDA-MB-468 or MDA-MB-468-CD19t tumor cells infected with onCARlytics and treated with Mock (D45757), CD19 ARTEMIS® (D45757), or COH CD19-CAR (D45757) T-Cells. Graphs on the left represents tumor killing, and in the middle represents CD19t expression on tumor cells. Graphs on the right represents tumor count against MDA-MB-468-CD19t treated with Mock (D45757), CD19 ARTEMIS® (D45757), or COH CD19-CAR (D45757) T-Cells.

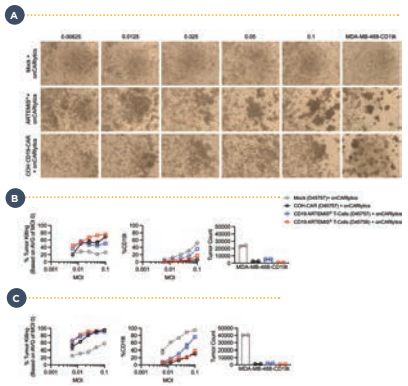


Figure 4

Activation of CD19 ARTEMIS® T-Cells by targeting of triple negative breast cancer cell line MDA-MB-468 expressing CD19t following onCARlytics infection

A Expression of activation marker (CD137) on Mock (D45757), CD19 ARTEMIS® (D45757), CD19 ARTEMIS® (D45758), or COH CD19-CAR (D45757) T-Cells following 24h (left) and 48h (right) in vitro co-culture with MDA-MB-468 tumor cells infected with onCARlytics. B IFNγ and C IL-2 production following in vitro infection of MDA-MB-468 tumor cells with onCARlytics in the presence of Mock (D45757), CD19 ARTEMIS® (D45757), CD19 ARTEMIS® (D45758), or COH CD19-CAR (D45757) T-Cells measured at 24h (left) and 48h (right) by ELISA. D IFNγ and E IL-2 production following in vitro co-culture of MDA-MB-468-CD19t with Mock (D45757), CD19 ARTEMIS® (D45757), CD19 ARTEMIS® (D45758), or COH CD19-CAR (D45757) T-Cells measured at 24h (left) and 48h (right) by ELISA.

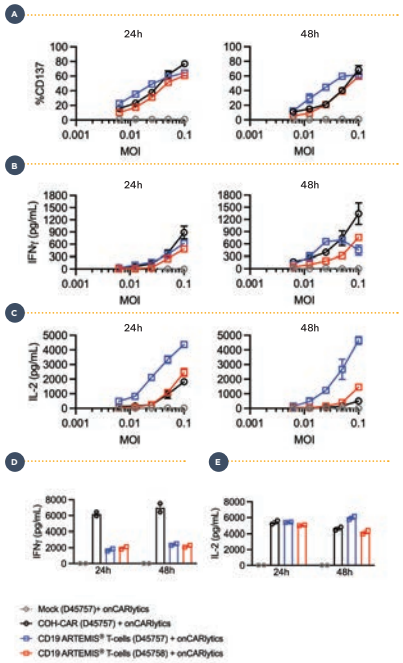


Figure 5

CD19 ARTEMIS® T-Cells effectively targets hepatocellular carcinoma tumor cell lines HepG2 and HEP3B following onCARlytics infection

In vitro killing assay combining onCARlytics and CD19 ARTEMIS® T-Cells at 24h and 48h against A HepG2 and B Hep3B. CD19t expression on C HepG2 and D Hep3B tumor cells following onCARlytics infection at varying MOIs (0.003125, 0.00625, 0.0125, 0.025, 0.05, and 0.1) co-cultured with untransduced (mock) T-Cells, CD19 ARTEMIS®, or COH CD19-CAR T Cells. Activation marker CD137 E and CD69 G expression on T-Cells following co-culture with HepG2 tumor cells infected with onCARlytics. F H Co-culture against Hep3B tumor cells.

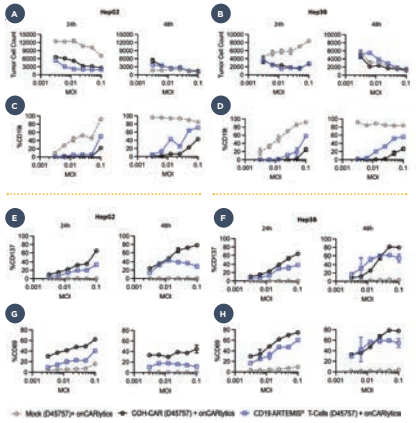
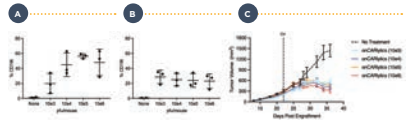


Figure 6

In vivo efficacy and CD19t expression of HepG2 tumor cells following onCARlytics infection

NSG mice were subcutaneously engrafted with HepG2 tumors. Tumors were treated with 10^3, 10^4, 10^5, and 10^6 plaque-forming units (pfu) per mouse of onCARlytics intratumorally when tumor volumes reached approximately 250 mm³. Tumors were harvested A 3 or B 7 days following onCARlytics treatment to determine CD19t expression via flow cytometry. C Tumor volumes were measured to determine in vivo efficacy of onCARlytics against subcutaneous HepG2 tumors.



Summary

- onCARlytics can target triple negative breast cancer cell line MDA-MB-468 to express CD19t as a target for engineered T-Cells in an MOI-dependent manner.
- onCARlytics can target hepatocellular carcinoma cell lines HepG2 and Hep3B to express CD19t as a target for engineered T-Cells in an MOI-dependent manner.
- Eureka's CD19 ARTEMIS® T-Cells in combination with onCARlytics demonstrated greater in vitro efficacy against MDA-MB-468, HepG2, and Hep3B tumor cell lines compared to onCARlytics alone.
- There is an increasing trend in CD19 ARTEMIS® T-Cell activation in an onCARlytics MOI-dependent manner.
- CD19 ARTEMIS® T-Cells demonstrated higher trend of IL-2 production and lower IFNγ production compared to COH CD19-CAR T Cells when co-cultured with onCARlytics.
- CD19t expression was detected in tumors following onCARlytics infection in vivo.
- CD19 ARTEMIS® T-Cells and onCARlytics combination therapy efficacy will be tested in multiple in vivo models.

References

1. Park AK, et al. Effective combination immunotherapy using oncolytic viruses to deliver CAR targets to solid tumors. Sci Transl Med. 2020. 2. McCart JA, Ward JM, Lee J, Hu Y, Alexander HR, Libutti SK, Moss B, Bartlett DL. Systemic cancer therapy with a tumor-selective vaccinia virus mutant lacking thymidine kinase and vaccinia growth factor genes. Cancer Res. 2001. 3. Chaurasiya S, et al. A chimeric poxvirus with J2R (thymidine kinase) deletion shows safety and anti-tumor activity in lung cancer models. Cancer Gene Ther. 2020. 4. O'Leary MP, Warner SG, Kim SI, Chaurasiya S, Lu J, Choi AH, Park AK, Woo Y, Fong Y, Chen NG. A Novel Oncolytic Chimeric Orthopoxvirus Encoding Luciferase Enables Real-Time View of Colorectal Cancer Cell Infection. Mol Ther Oncolytics. 2018. 5. Yiyang Xu, et al. A novel antibody-TCR (AbTCR) platform combines Fab-based antigen recognition with gamma/delta-TCR signaling to facilitate T-Cell cytotoxicity with low cytokine release. Cell Discovery. 2018.

COMBINATION IMMUNOTHERAPY USING A NOVEL CHIMERIC ONCOLYTIC VIRUS (ONCARLYTICS) TO REDIRECT CD19 BISPECIFIC T-CELL ENGAGERS TO TARGET SOLID TUMORS

Anthony K. Park[1], Isabel Monroy[1], Colin Cook[2], Monil Shah[3], Leslie M.O. Chong[3], Nimali P. Withana[3], Stephen J. Forman[1], Yuman Fong[2], and Saul J. Priceman[1]

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[3] Imugene Limited, Sydney Australia

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Introduction

Bispecific T-Cell engager (BiTE) monoclonal antibodies have emerged as a promising immunotherapy strategy for the treatment of hematological malignancies. Blinatumomab, an FDA approved BiTE carrying CD19 and CD3 scFv's has shown durable clinical responses for the treatment of B-Cell acute lymphoblastic leukemia (B-ALL) and non-Hodgkins lymphomas. Despite a wide array of research in hematological malignancies, BiTE therapies for the treatment of solid tumors have remained a significant challenge in demonstrating comparable efficacy. Solid tumors often lack amenable and targetable tumor antigens, and in many tumor types the tumor microenvironment (TME) is largely known to be immunologically "cold" and a barrier to immunotherapy responses.

Oncolytic viruses have recently gained traction in the field for the treatment of solid tumors because of their ability to target tumor-intrinsic properties and reshape the immunosuppressive TME. We have previously described the use of a chimeric oncolytic vaccinia virus (OV), CF33, for the treatment of a variety of tumor cell types, including triple-negative breast cancer, lung cancer, and liver cancer. Building on this, we generated an OV that expresses a non-signaling, truncated CD19 (CD19t) antigen called onCARlytics (CF33-CD19t), onto the surface of infected tumor cells prior to virus mediated tumor lysis, which redirected CD19-targeting chimeric antigen receptor (CAR) T Cell activity against solid tumors (Park et al. STM 2020). Using this OV, we have created a universal system that is agnostic to solid tumor type and can be provided with a targetable and well-characterized antigen. We now demonstrate that onCARlytics can redirect cytolytic functions of blinatumomab. We have demonstrated that tumors infected with onCARlytics in combination with blinatumomab show improved tumor cell killing, comparable to CD19-CAR T Cell. Using this approach, we show that a clinically-approved CD19-directed BiTE can be combined with onCARlytics to activate endogenous immune responses against solid tumors.

Figure 1

Delivering truncated CD19t (CD19t) to tumor cells using oncolytic virus (OV) as a target for bispecific T-Cell engagers (BiTEs)

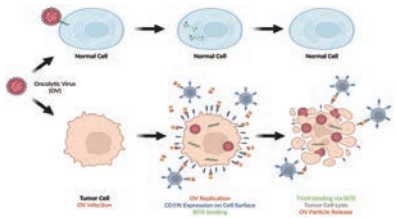


Figure 2

CD19t expression following onCARlytics infection leads to naïve T-Cell activation in combination with blinatumomab

A Quantification of T-Cells activation following in vitro co-culture (48h) of infected MDA-MB-468 triple negative breast cancer cells at varying MOIs of CF33-CD19t in the presence or absence of blinatumomab in combination with untransduced T-Cells. B C IFNγ and IL-2 production following in vitro infection of MDA-MB-468 tumor cells with CF33-CD19t in the presence or absence of blinatumomab in combination with untransduced T-Cells, measured at indicated time points by ELISA.

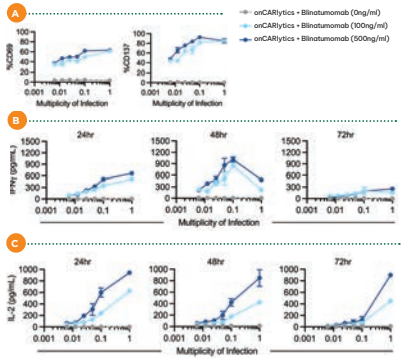


Figure 3

Blinatumomab-mediated T-Cell killing of triple negative breast cancer cell line following onCARlytics infection

Bright-field microscopy (10x magnification) of MDA-MB-468 tumor cells at 48h following CF33-CD19t infection (MOI 0, 0.0125, 0.5, and 1) or MDA-MB-468-CD19t (positive control lentivirally transduced to stably express CD19t) in the presence or absence of blinatumomab in combination with untransduced T-Cells or CD19-CAR T Cell.

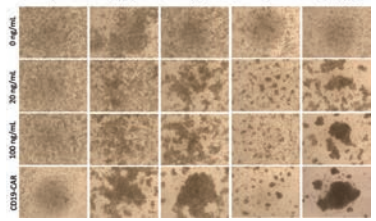


Figure 4

T-Cells specifically target and kill CD19t expressing tumor cells following onCARlytics infection in combination with blinatumomab

Killing assay combining varying MOIs of CF33-CD19t in the presence or absence of blinatumomab with naïve T-Cells against MDA-MB-468 tumor cells. A Tumor killing percentage relative to uninfected tumor cell count and B CD19t expression post CF33-CD19t infection.

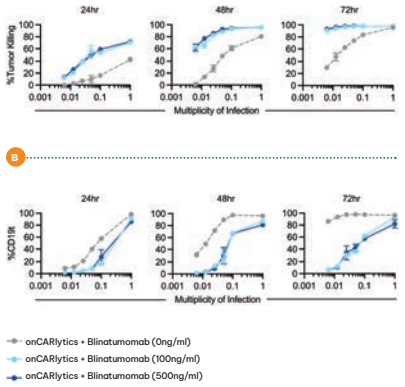


Figure 5

In vivo studies testing onCARlytics and blinatumomab combination therapies

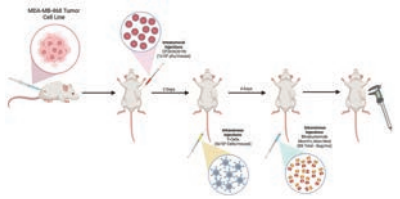


Figure 6

Anti-tumor activity of onCARlytics in combination with blinatumomab and PBMCs in human xenograft TNBC tumor model

Mice were engrafted with subcutaneous MDA-MB-468 ($5x10^6$ cells) and were intratumorally treated with 0 or 10^6 pfu of CF33-CD19t per mouse. Mice were intravenously treated with PBMCs ($5x10^6$ cells) followed by blinatumomab (8 ug/mouse) treatment. A Lines represent tumor volumes of individual mice per group (n=5-11) and B average of each group.

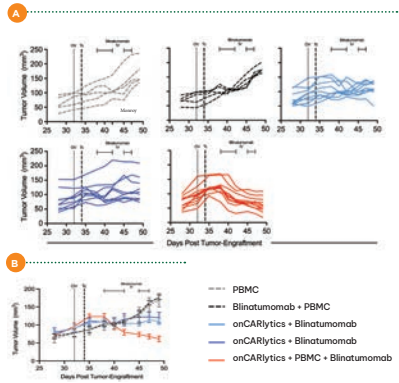
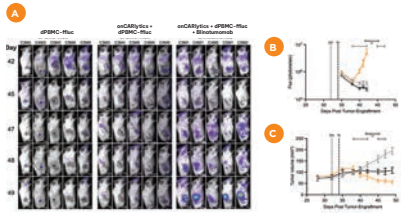


Figure 7

Blinatumomab dependent T-Cell infiltration following onCARlytics infection

Mice were engrafted with subcutaneous MDA-MB-468 ($5x10^6$ cells) on day 0 and were intratumorally treated with 0 or 10^6 pfu of CF33-CD19t per mouse on day 39. Mice were intravenously treated with depleted PBMCs (dPBMC) expressing firefly luciferase (ffluc) ($5x10^6$ cells) on day 41 followed by blinatumomab (8 ug/mouse) treatment from day 45. A Flux imaging tracking T-Cells after treatment with dPBMC-ffluc alone, dPBMC-ffluc with CF33-CD19t, and dPBMC with CF33-CD19t and blinatumomab. B Quantification of T-Cell flux from the regions of interest shown in A. C Average tumor volumes.



Summary

- T-Cell activation markers along with IFNγ and IL-2 secretion increase in response to blinatumomab in a onCARlytics dose-dependent manner in co-culture.
- Blinatumomab initiates T-Cell- mediated tumor killing in onCARlytics infected tumor cells.
- Blinatumomab treatment following onCARlytics infection and T-Cell treatment shows a significantly higher tumor regression compared to onCARlytics, blinatumomab, or T-Cells alone in xenograft models of TNBC.
- This combination immunotherapy approach shows that blinatumomab treatment leads to significantly higher T-Cell infiltration following OV-mediated delivery of CD19t antigen with onCARlytics when compared to OV alone.

References

1. Park AK, Fong Y, Kim SI, Yang J, Murad JP, Lu J, Jeang B, Chang WC, Chen NG, Thomas SH, Forman SJ, Priceman SJ. Effective combination immunotherapy using oncolytic viruses to deliver CAR targets to solid tumors. Sci Transl Med. 2020. **2.** McCart JA, Ward JM, Lee J, Hu Y, Alexander HR, Libutti SK, Moss B, Bartlett DL. Systemic cancer therapy with a tumor-selective vaccinia virus mutant lacking thymidine kinase and vaccinia growth factor genes. Cancer Res. 2001. **3.** O'Leary MP, Warner SG, Kim SI, Chaurasiya S, Lu J, Choi AH, Park AK, Woo Y, Fong Y, Chen NG. A Novel Oncolytic Chimeric Orthopoxvirus Encoding Luciferase Enables Real-Time View of Colorectal Cancer Cell Infection. Mol Ther Oncolytics. 2018. **4.** Chaurasiya S, Chen NG, Lu J, Martin N, Shen Y, Kim SI, Warner SG, Woo Y, Fong Y. A chimeric poxvirus with J2R (thymidine kinase) deletion shows safety and anti-tumor activity in lung cancer models. Cancer Gene Ther. 2020. **5.** Dreier T, Baeuerle PA, Fichtner I, Grün M, Schlereth B, Lorenczewski G, Kufer P, Lutterbüse R, Riethmüller G, Gjorstrup P, Bargou RC. T-Cell costimulus-independent and very efficacious inhibition of tumor growth in mice bearing subcutaneous or leukemic human B-Cell lymphoma xenografts by a CD19-/CD3-bispecific single-chain antibody construct. J Immunol. 2003. **6.** Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, Horst HA, Raff T, Viardot A, Schmid M, Stelljes M, Schaich M, Degenhard E, Köhne-Volland R, Brüggemann M, Ottmann O, Pfeifer H, Burmeister T, Nagorsen D, Schmidt M, Lutterbuese R, Reinhardt C, Baeuerle PA, Kneba M, Einsele H, Riethmüller G, Hoelzer D, Zugmaier G, Bargou RC. Targeted therapy with the T-Cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011.

MILESTONES

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✓	TECHNOLOGY	MILESTONE
	onCARlytics	Phase 1 – 1st Patient Dosed
	HER-Vaxx	nextHERIZON Arm 2 Cleared
	CHECKvacc	Sponsored Study FDA IND
	VAXINIA	Combination – 1st Patient Dosed
	onCARlytics	FDA IND
	PD1-Vaxx	Combination – 1st Patient Dosed
	CHECKvacc	Cohort 3 Cleared
	VAXINIA	IV Cohort 1 Cleared & IT Cohort 2 Cleared
	CHECKvacc	Publication and Presentation (SABC)
	HER-Vaxx	Publication and Presentation (ESMO Asia & ASCO GI)
✓	onCARlytics	Publication and Presentation (SITC)
✓	onCARlytics	Strategic Partnership with Arovella on CAR19-iNKT
✓	VAXINIA	IV Arm – 1st Patient Dosed
✓	HER-Vaxx	nextHERIZON Phase 2 – 1st Patient Dosed
✓	HER-Vaxx	Phase 2 Final OS
✓	VAXINIA	IT Cohort 1 Cleared
✓	VAXINIA	IT Arm – 1st Patient Dosed
✓	CHECKvacc	Cohort 1 and 2 Cleared

FINANCIAL SUMMARY

IMUGENE
Developing Cancer Immunotherapies

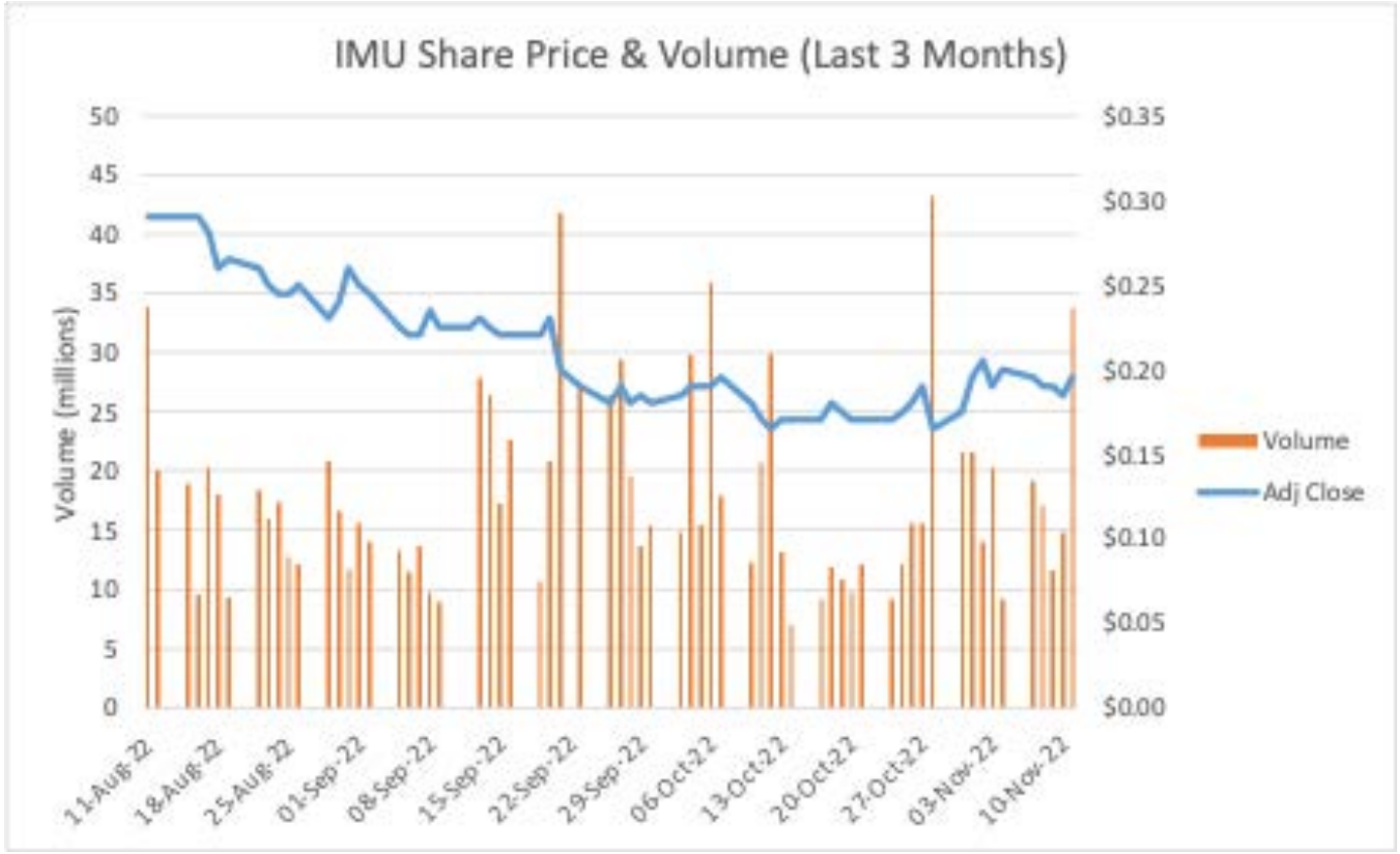
PUBLIC MARKET OVERVIEW (11 Nov 22)

Share Price	A$0.195
52 week range	$0.13 - $0.625
Market Capitalisation[1]	A$1.23B
Cash equivalents (30 Sep 22)	A$163.8M
Enterprise Value	A$1.07B

TOP 5 SHAREHOLDERS (AS AT 11 NOVEMBER 2022)

JP Morgan Nominees Australia Pty Limited	7.10%
HSBC Custody Nominees (Australia) Limited	6.00%
Paul Hopper	5.04%
Citicorp Nominees Pty Limited	4.76%
Mann Family	4.61%

SHARE PRICE PERFORMANCE



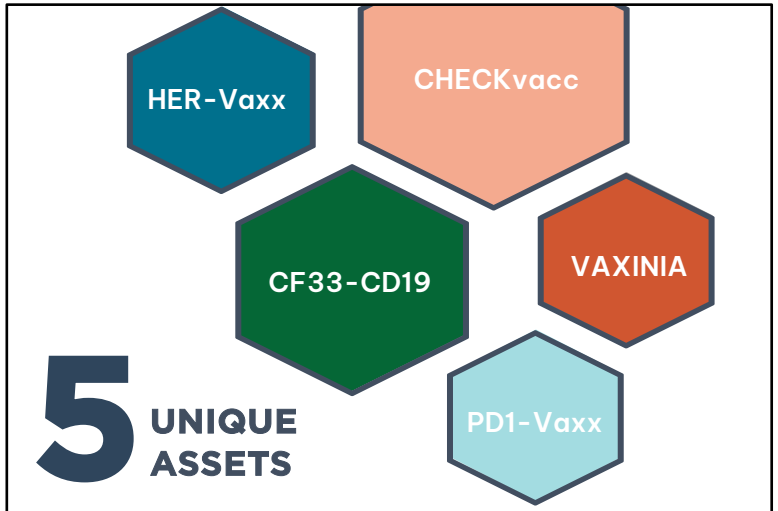
Note:
1. Market capitalisation calculations based on ordinary shares (6.294 bn) only and excludes the dilutive impact of options outstanding (0.543 bn)

INVESTMENT HIGHLIGHTS

IMUGENE
Developing Cancer Immunotherapies

MARKET CAPITALISATION 11th Nov 2022 A$1.23B

CASH AS OF 30th Sep 2022 A$163.8M



5 UNIQUE ASSETS

*Multiple potential platform targets | CF33-CD20 LAG3-Vaxx CTLA4-Vaxx TIGIT-Vaxx PDL1-Vaxx TIM3-Vaxx

CF33 Oncolytic Virus | onCARlytics | B-Cell Immunotherapies

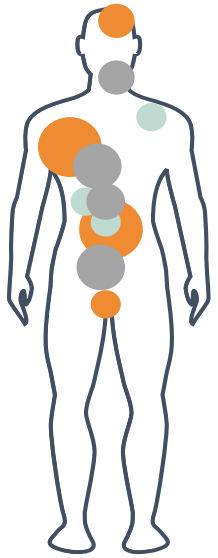
3 PLATFORM TECHNOLOGIES

Celularity | Eureka | Arovella

3 SCIENTIFIC COLLABORATIONS

DISEASE AREAS

- Breast (TNBC)
- Lung (NSCLC)
- Gastric
- Gastroesophageal
- Colorectal (CRC)
- Melanoma
- Head and Neck
- Hepatocellular
- Pancreatic
- Glioblastoma (GBM)



10 CLINICAL STUDIES

HERIZON: Ph1b/2 First line Gastric Cancer
IMPRINTER: Ph1 NSCLC (FDA IND)
CHECKvacc COH IST: Ph1 TNBC (FDA IND)
neoHERIZON: Ph 2 Neoadjuvant Gastric Cancer
nextHERIZON: Ph2 Metastatic Gastric Cancer (FDA IND)
MAST: Ph1 Solid Tumours (FDA IND)
DOMINICA: Ph1 TNBC (FDA IND)
onCARlytics: Ph1 Solid Tumours (FDA IND)
neuHERIZON: Ph2 Biomarker Study
PD1-Vaxx IST: Ph1 CRC

2 SUPPLY AGREEMENTS

Merck KGaA/Pfizer | Roche

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