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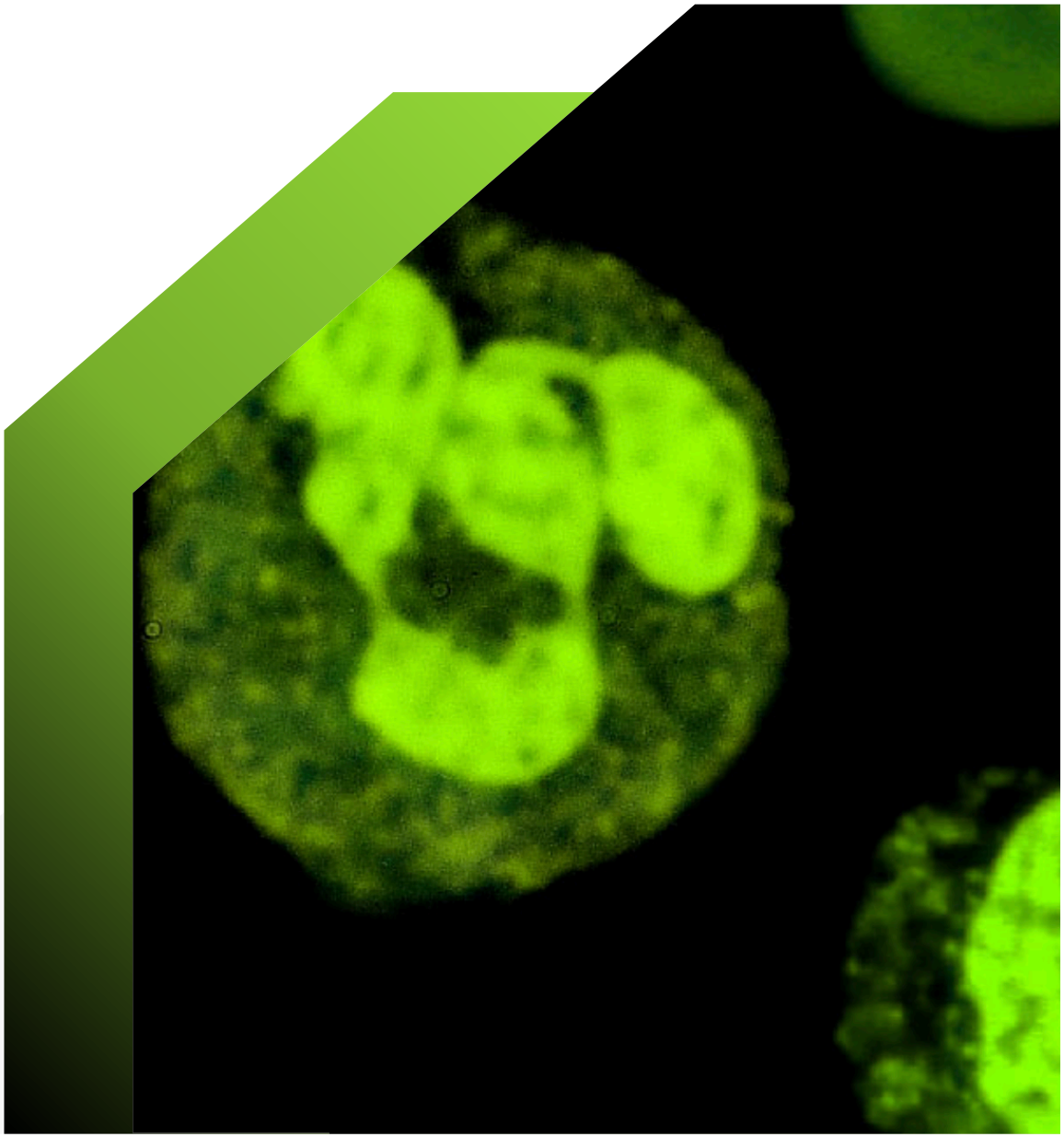
Off-the-shelf, universal, macrophage reprogramming cell therapies for life-threatening diseases



NASDAQ Ticker: ENLV

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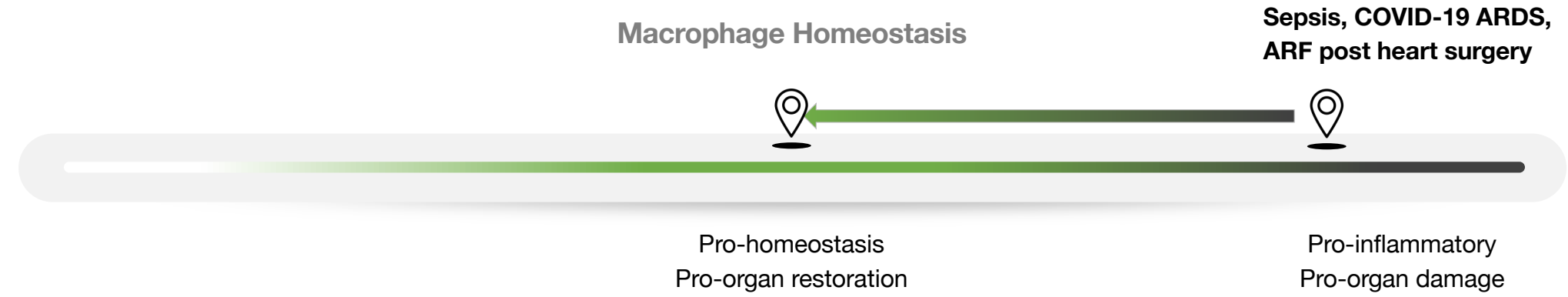
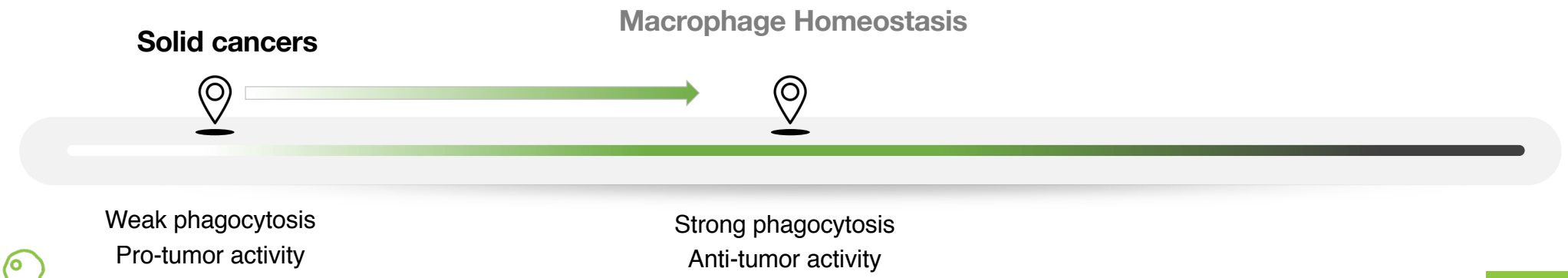
immune rebalancing

Macrophage homeostasis implies proper function for its specific tissue, environment and challenge

Reprogramming imbalanced macrophage populations can lead to disease resolution





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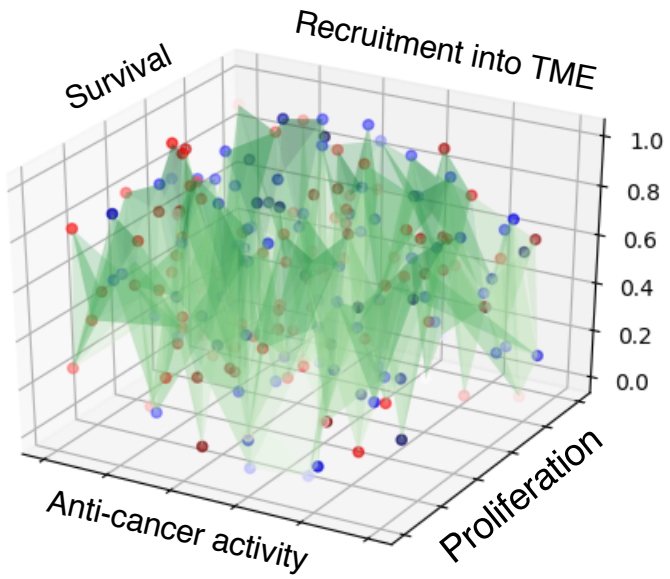
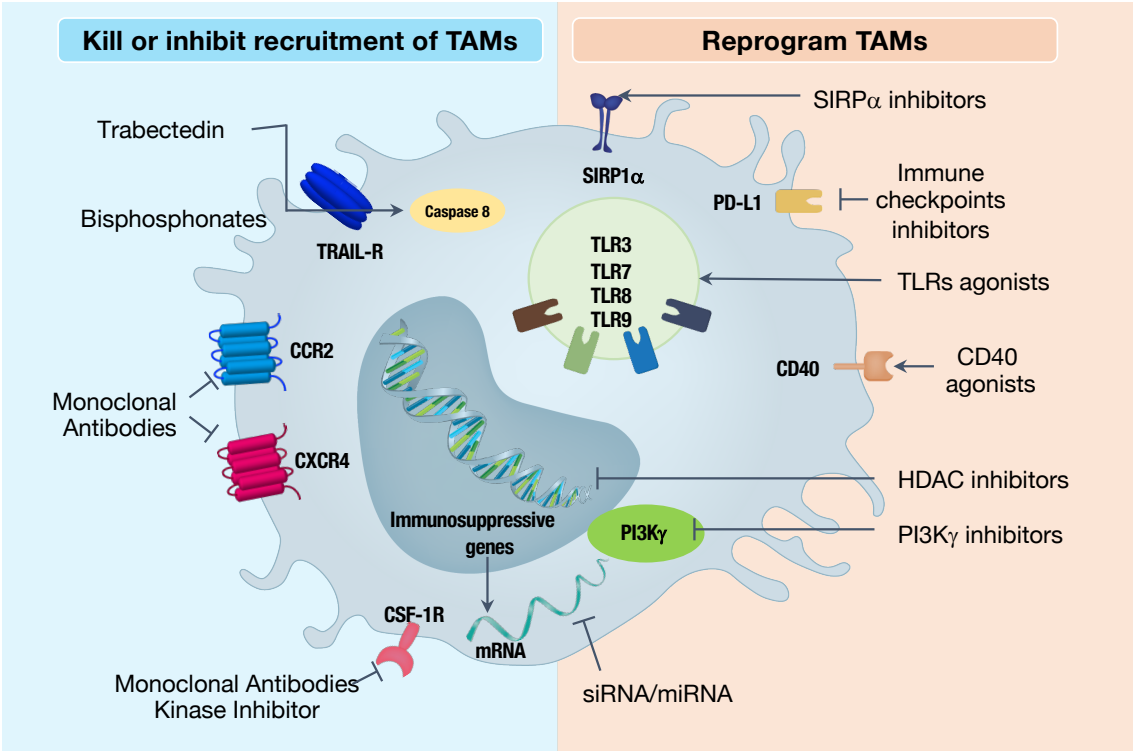
Solid cancer

Kill or reprogram non-homeostatic, pro-tumor macrophages (TAMs) in the tumor microenvironment (TME)

Multiple axes for homeostatic macrophage functionality within the tumor microenvironment (TME)



Multiple strategies to kill or reprogram non-homeostatic, pro-tumor macrophages (TAMs)*



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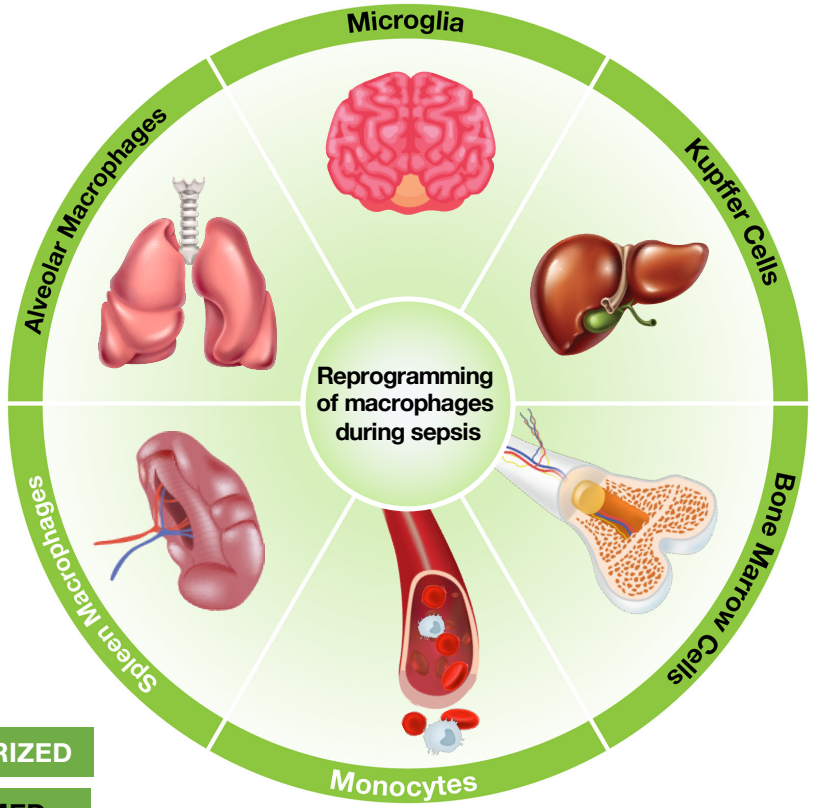
* Adapted from Current Strategies to Target Tumor-Associated-Macrophages to Improve Anti-Tumor Immune Responses, Anfray et al., Cells 2020, 9, 46

Sepsis: negative macrophage reprogramming, no homeostasis



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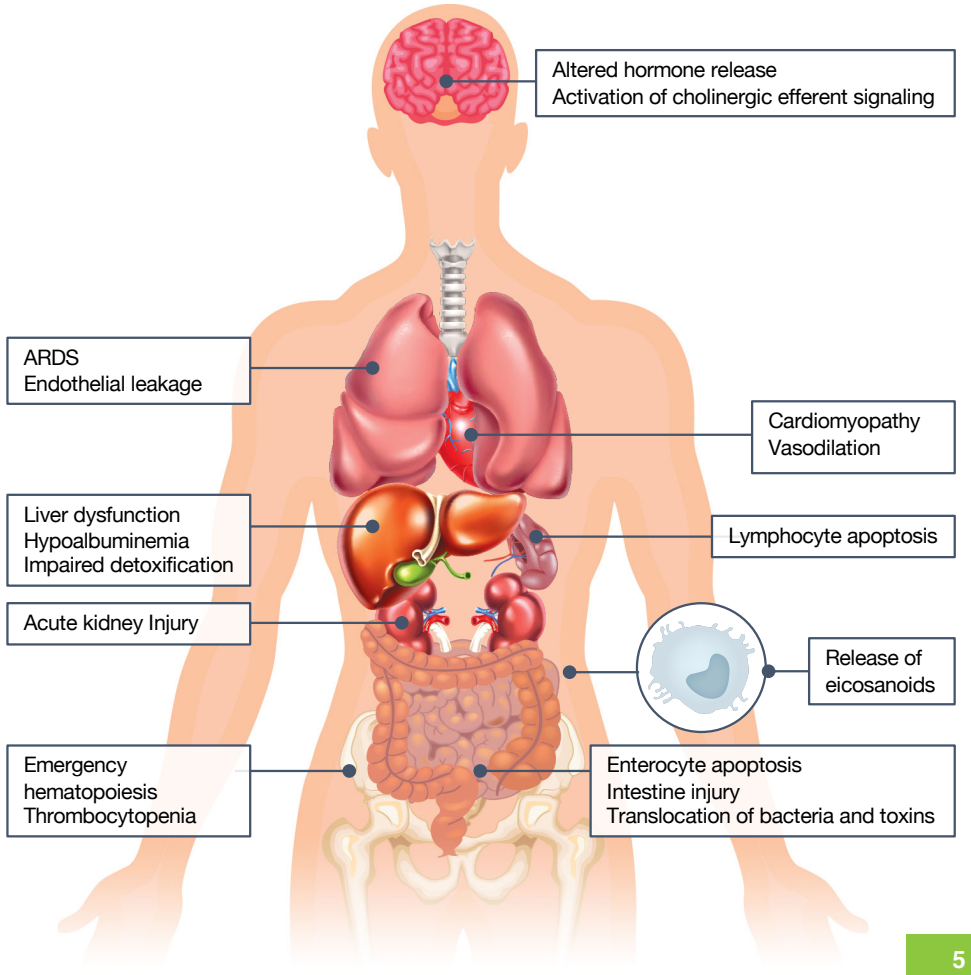

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Adapted from EMBO Molecular Medicine 12:e10128 | 2020

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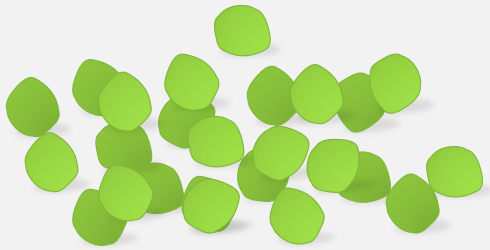
Allocetra™ Mechanism of Action

Restoring immune homeostasis through reprogramming of macrophages

Allocetra™ for macrophage reprogramming

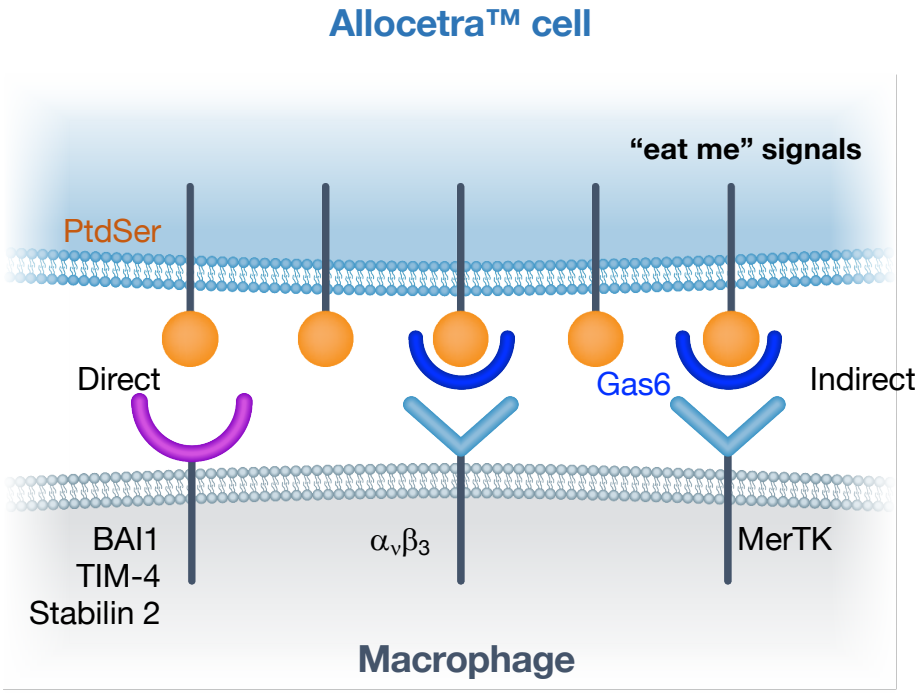
Proprietary, universal, off-the-shelf, macrophage-reprogramming cells

Allocetra™ characteristics



- Mononuclear cells collected from healthy donors
- Modified through a proprietary process to:
  - Express PtdSer (“eat me” signal) on their surface
    - Enabling engulfment into macrophages via binding to BAI, TIM4, and stabilin 2, annexin V
  - Yet maintain their membrane in-tact
- Universal, off-the-shelf

Allocetra™ delivery into macrophages via engulfment



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Allocetra™ for macrophage reprogramming

Pipeline of reprogrammable macrophage-modulated indications

Indication	Global Market Size	Pre-Clinical	Phase Ib	Phase IIb	EU Conditional Marketing Approval	Post EU Marketing US Phase 3
Organ failure associated with Sepsis	$33B		Completed	Phase IIb Initiatied Q1 2021	Completion of Phase IIb Q2 2022	
ARDS associated with severe/critical COVID-19 / Non-COVID-19 ARDS	$1B (COVID) $15B (ARDS)		Completed COVID-19	Phase II Completed COVID-19	Completion of Phase IIb or III Q2 2022[1]	
Solid tumors in combination with immune checkpoints	$4B		Phase Ib Q3 2021			

[1] Pending EMA regulatory feedback re type of study suitable to potentially obtain emergecny/conditional authorization

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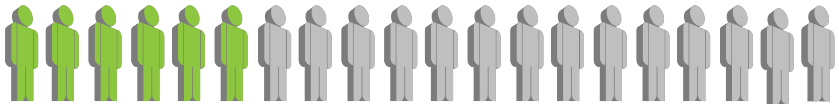
Reprogramming macrophages responsible for organ failure in sepsis and COVID-19

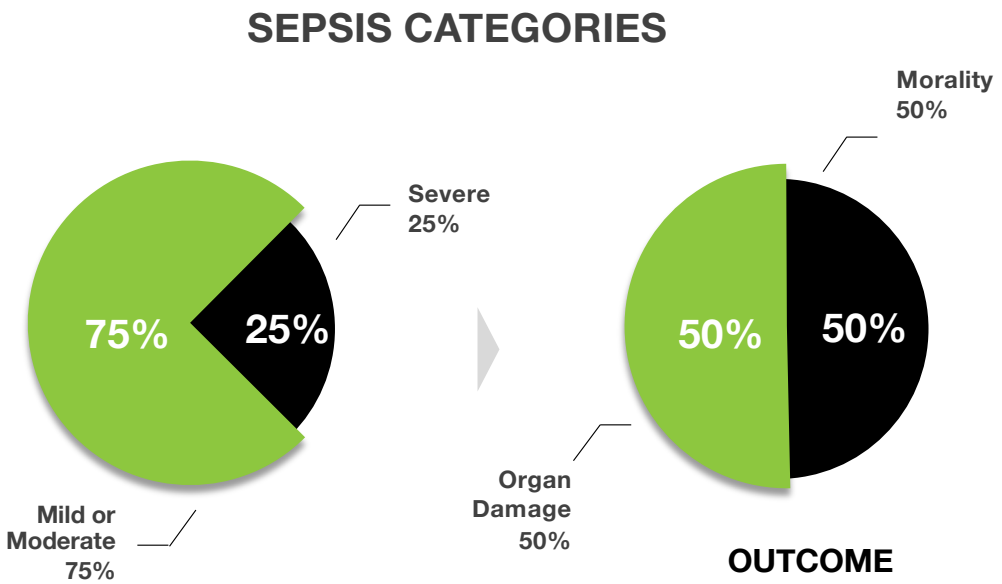
Sepsis is the 3rd leading cause of death in the U.S. – $33B target market*

There are currently no FDA approved drugs for the treatment of sepsis



Each year, at least **1.7 million** adults in America develop sepsis. Nearly **270,000** Americans die as a result of sepsis each year.

1 in 3 One in three patients who die in a hospital have sepsis.



$50,000 x 675,000 Patients PA (global) = $33B Total Addressable Market

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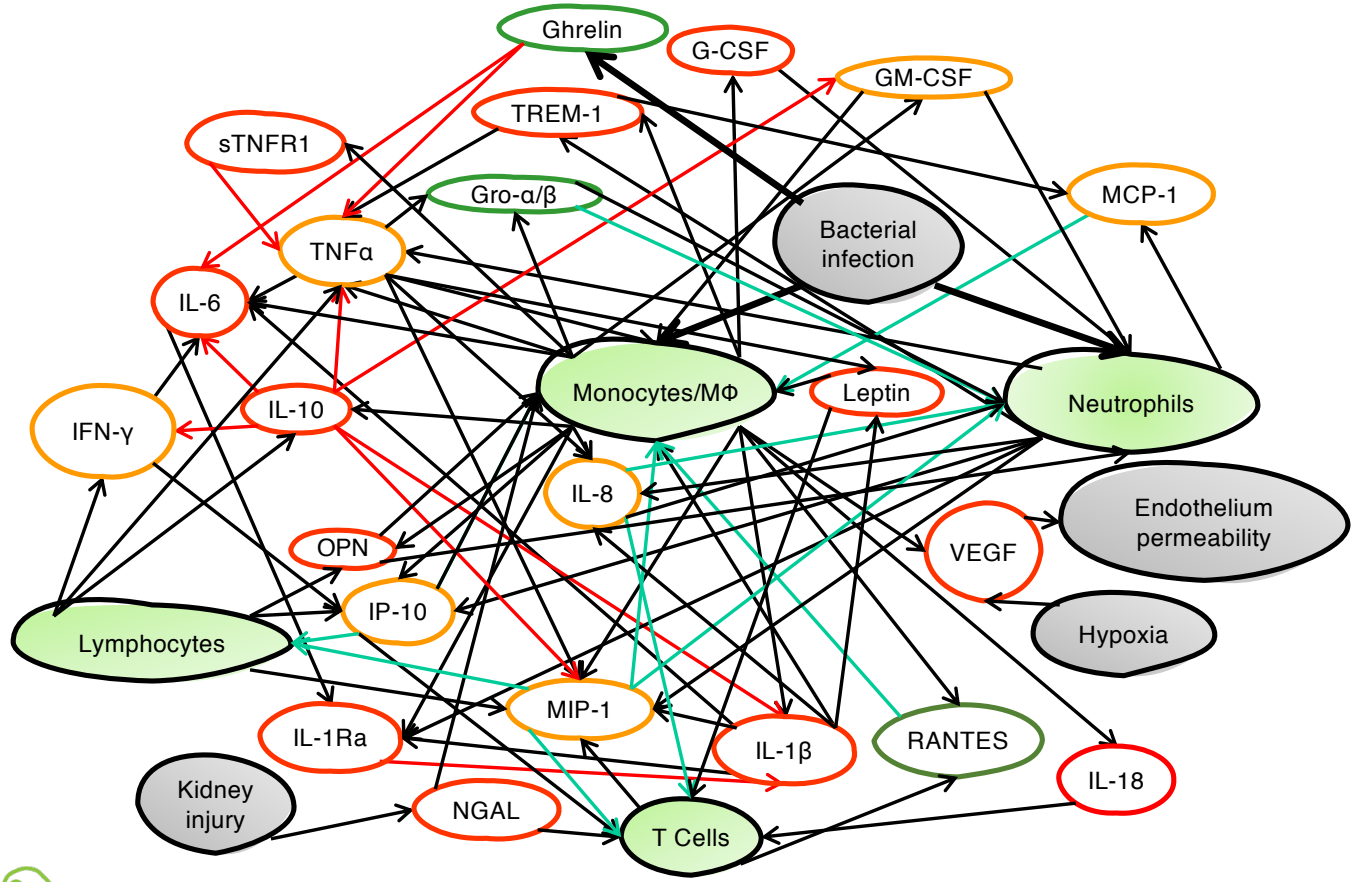
* U.S. & EU

Cytokine/Chemokine network in sepsis: the impossible task of resolving sepsis with inhibition of a certain cytokine or signaling pathway



MΦ: Macrophages

- Activation
- Inhibition
- Chemotaxis
- Downregulated in most of the patients
- Downregulated in 50% of the patients
- Upregulated in most patients

Macrophage reprogramming to "manufacturer settings" is required to obtain sepsis resolution

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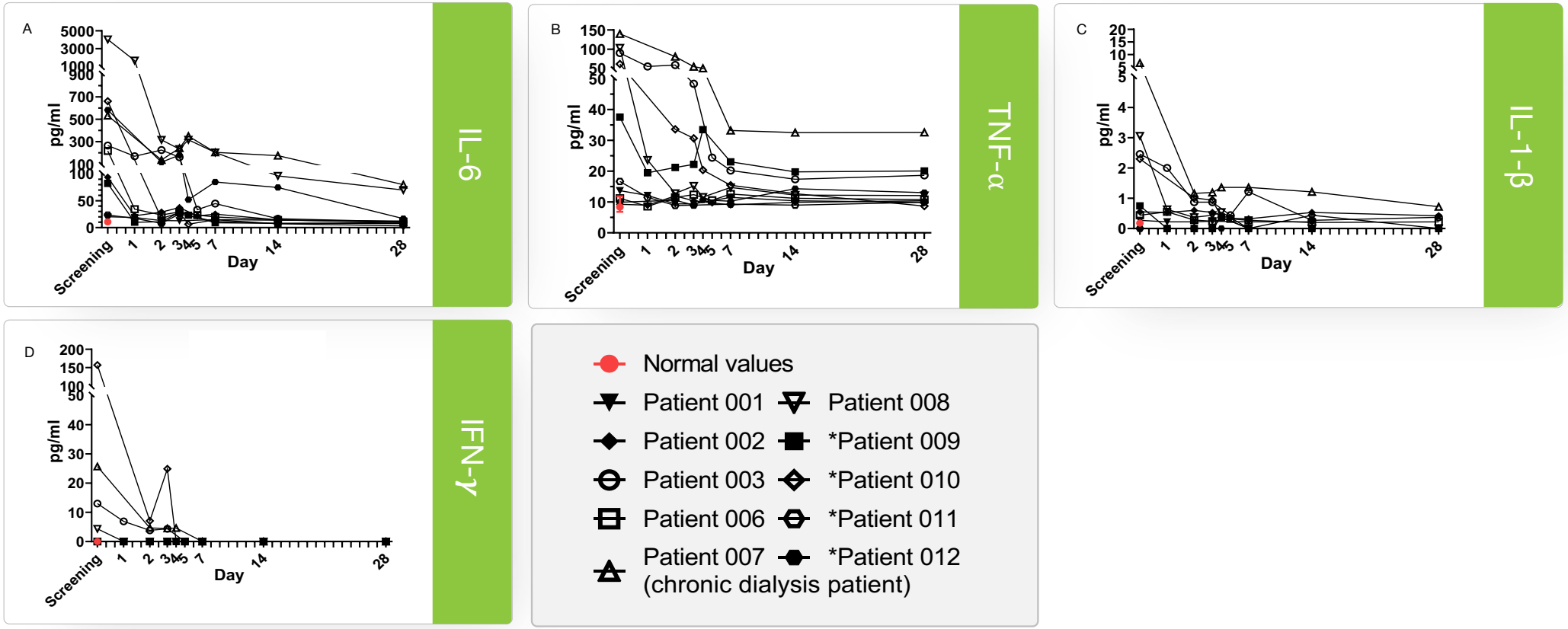
Phase Ib clinical trial of macrophage reprogramming in sepsis patients

Reprogrammed macrophages in sepsis patients return to homeostatic state (1)

Phase Ib clinical trial data, change from screening, pro-inflammatory cytokines



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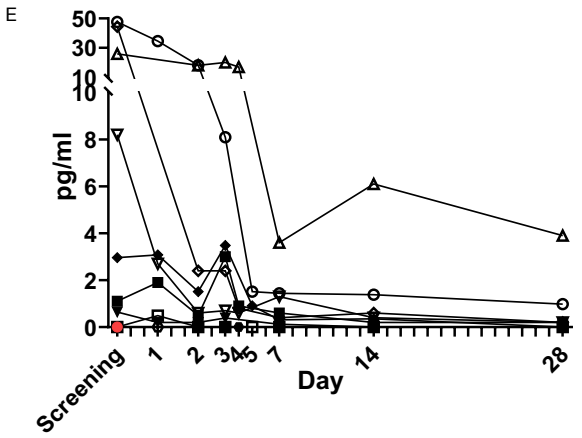
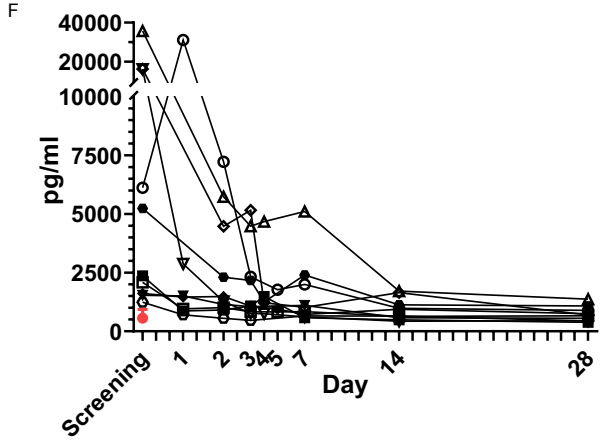
Reprogrammed macrophages in sepsis patients return to homeostatic state (2)

Phase Ib clinical trial data, change from screening, anti-inflammatory cytokines

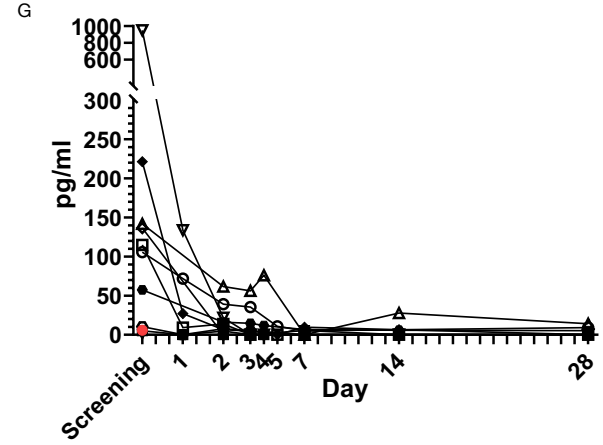
IL-10

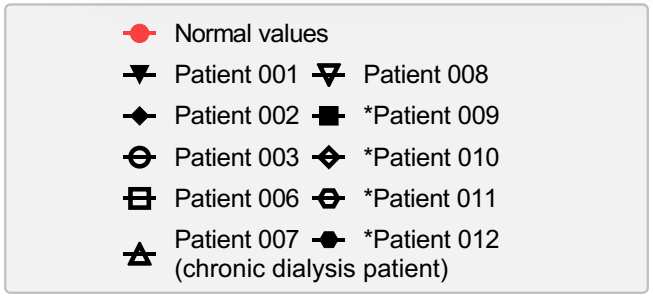


IL-1Rα



G-CSF





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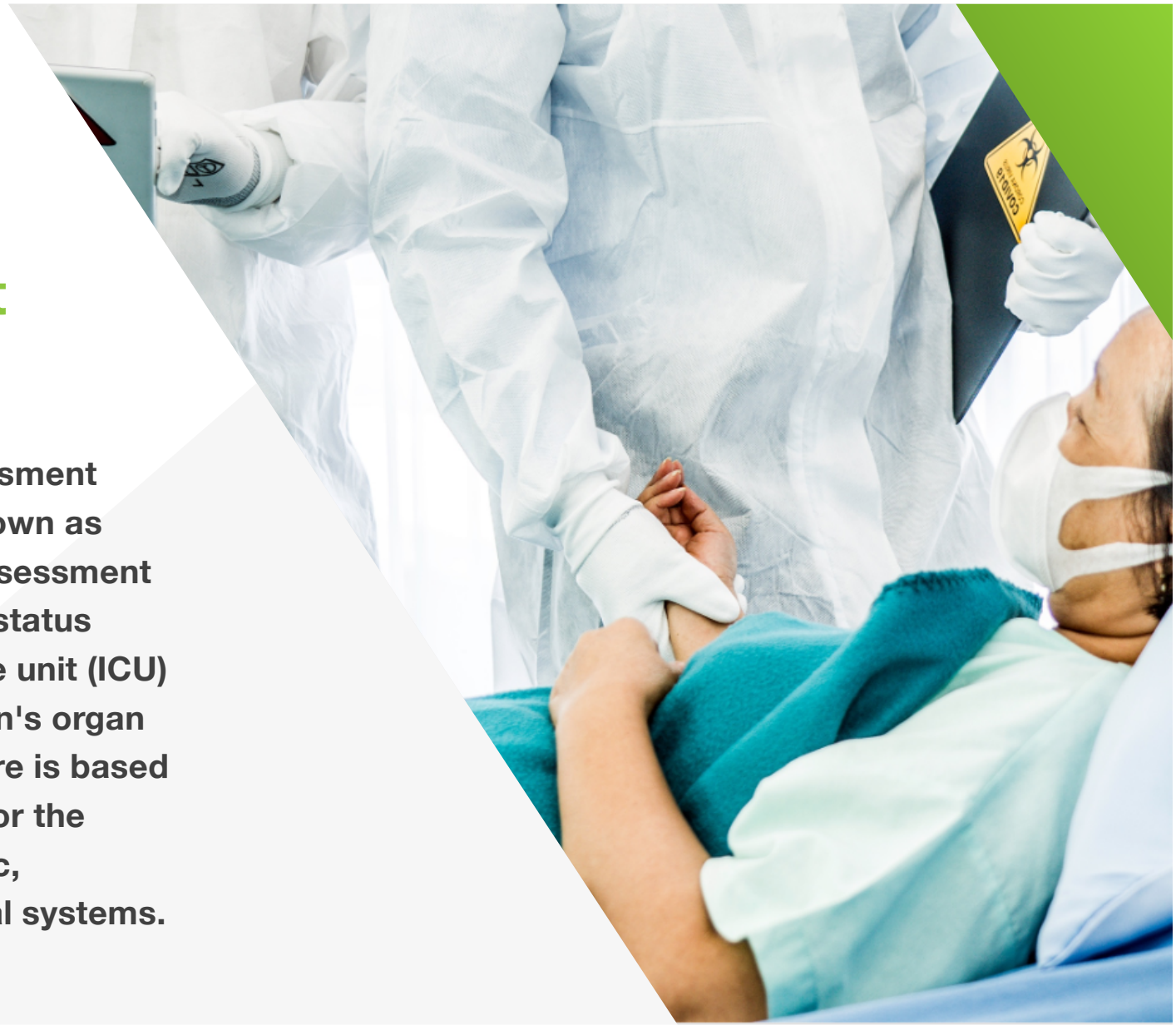
Sequential Organ Failure Assessment (SOFA) Score

The sequential organ failure assessment score (SOFA score), previously known as the sepsis-related organ failure assessment score, is used to track a person's status during the stay in an intensive care unit (ICU) to determine the extent of a person's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems.



High degree of matching: treated vs controls

	Treated (n=10)	Matched Controls (n=37)
Average age	71.5 (51-83)	71.25 (50-83)
Male/female	80/20	80/20
Average diagnosis SOFA	3.4 (2-6)	3.47 (2-7)
Average diagnosis Apache II score	12.3 (8-21)	14.25 (5-24)

Sepsis source		
Pneumonia	50%	53%
Biliary infections	30%	25%
Endovascular	10%	8.3%
UTI	10%	14%

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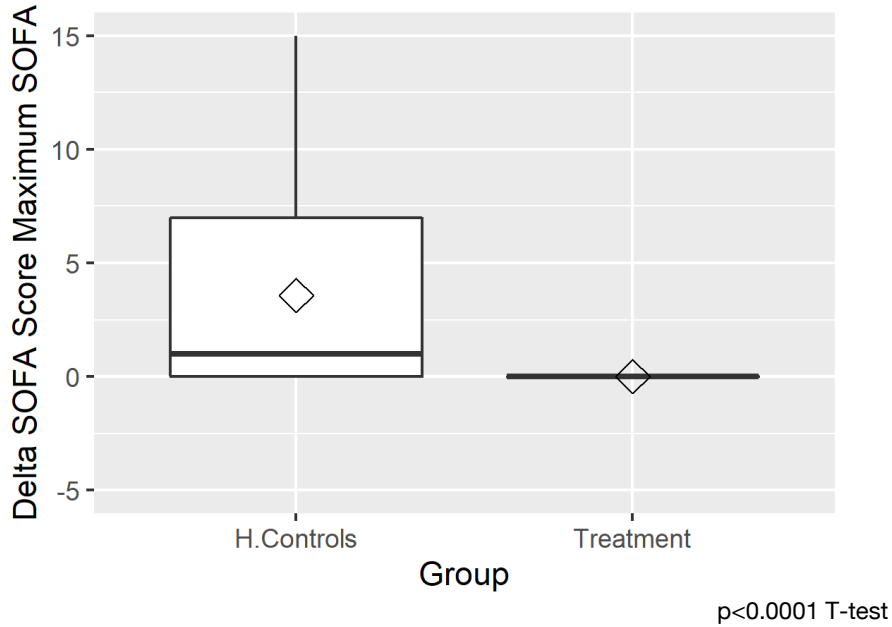
Allocetra™ macrophage reprogramming leads to improved outcomes for sepsis patients

Alive and organs recovered on day 28: 100% vs 41%

Maximal change in SOFA score, diagnosis to day 28



		#		
Total Patients	Controls	37		
	Treated	10		
Day 28		#	%	
Died	Controls	10	27%	–
	Treated	0	0	–
Alive				
Recovery Prospects	Day 28 of SOFA delta vs pre-sepsis baseline	Day 28 alive by category		Avg. SOFA delta
		#	%	
Good	0-1	15	41%	0.6
		10	100%	0.1
Fair	2	4	11%	2
		0	0%	–
Poor	≥3	8	22%	5
		0	0%	–

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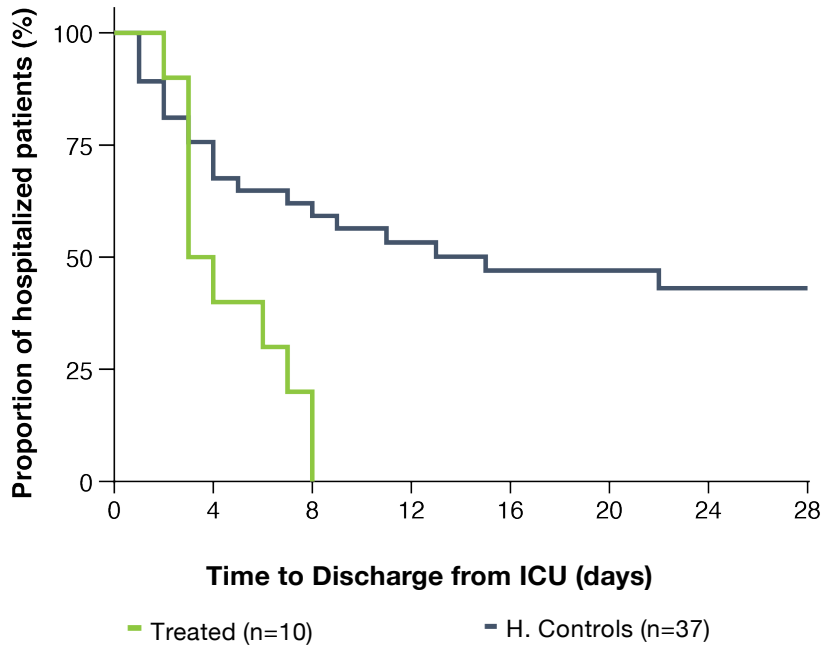
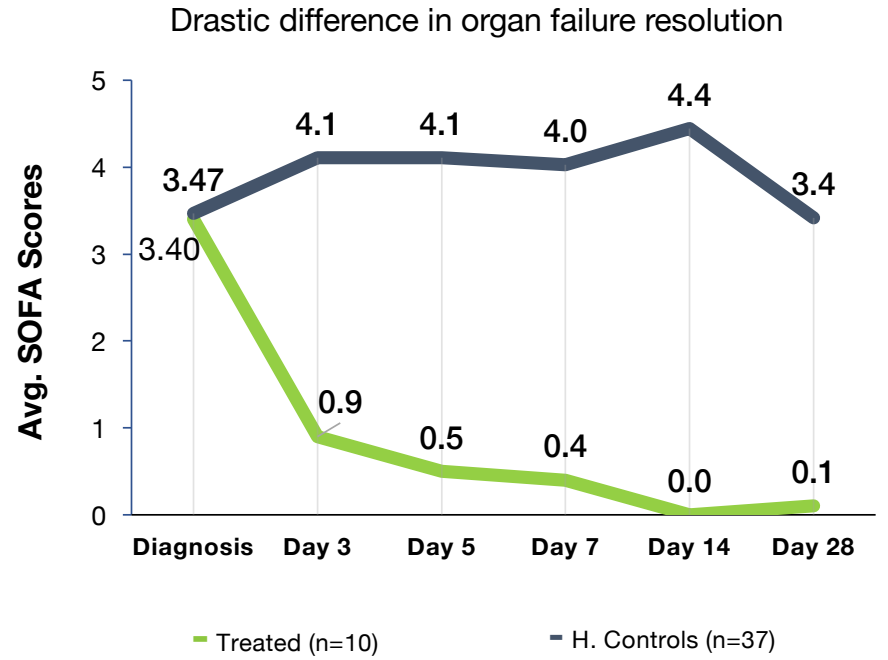
Allocetra™ macrophage reprogramming leads to improved outcomes for sepsis patients

Statistically significant improvement in hospitalization and SOFA vs. matched controls

Time to ICU discharge



Average SOFA score during 28 days



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Clinical summary of macrophage reprogramming in sepsis Phase Ib: complete recovery from any organ failure for all 10 patients and 100% 28-day survival

Sepsis clinical characteristics and organ recovery

Organ Dysfunction	Each patient had at least 2 organ dysfunctions, maximum of 5
Kidney	3/9 patients (33%) had new-onset acute kidney injury, all have completely recovered to baseline kidney function
Lungs	5/10 (50%) of patients had lung involvement, no patient required mechanical ventilation, all patients recovered to normal saturation and no oxygen supplement upon discharge
Cardiovascular	3/10 (30%) of patients had mean arterial pressure <70 but none needed vasopressors
Hematological	8/10 patients (80%) had significant thrombocytopenia, with complete recovery in all.
Liver	4/10 patients (40%, of which 3 had biliary tract infection) had hyperbilirubinemia, with complete recovery in all. 5/10 patients had elevated liver enzymes (AST ALT) >3 above normal range, with complete recovery in all.

Sepsis

Allocetra™ macrophage reprogramming Phase IIb clinical plan

	Sepsis Phase IIb
Addressable global market	$33 Billion market (severe Sepsis only)
Type	Controlled, randomized, multi-center (10 centers)
Patients	120-160, SOFA < 10, Pneumonia-sourced
Duration	28 days / patient
Recruitment	12 Months
End-points	Safety, Change in SOFA score
Secondary	Mortality
First patient dosed	Q2/2021

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Allocetra™

Phase Ib & II Clinical Trials in COVID-19 Patients in Severe or Critical Condition

COVID-19 as a business segment

- We believe COVID-19 will transfer from a pandemic state to an endemic state, and will remain a problem, although for a smaller population
- The primary reasons:
  - Vaccine effectiveness less than 100%
  - 10-15% of vaccinated population do not show sufficient levels of SARS-2 antibodies
    - Cancer patients, immuno-compromised patients, etc.
  - 10-15% of population refuses to get vaccinated for variety of reasons
  - All resulting in an environment for the virus to continue to constantly mutate
- Allocetra™ is positioned as “last line” therapy for severe/critical patients, post other treatments that did not help (e.g., steroids, Remdesivir, Actemra and others)

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Patient classification as defined by the NIH classification guide

Allocetra™: Positive Phase Ib and top line Phase II results in COVID-19

Clinical Trial	# Patients enrolled	Disease Severity	Clinical Outcome		Hospitalization Post Administration of Allocetra™	
			Recovered Day 28	Mortality Day 28	Discharged Day 28	Duration (days, avg.)
Phase Ib	5	2 Severe, 3 Critical	5/5 (100%)	0/5 (0%)	5/5 (100%)	6.6
Phase II	16	9 Severe, 7 Critical	14/16 (87.5%)	0/16 (0%)	14/16 (87.5%)	5.3
Total	21	11 Severe, 10 Critical	19/21 (90.5%)	0/21 (0%)	19/21 (90.5%)	5.6

- 0/21 (0%) mortality on day-28
- 19/21 (90.5%) patients recovered and were discharged from the hospital by day-28
- Average duration of hospitalization post administration of Allocetra™ for discharged patients was 5.6 days
- 2/21 (9.5%) patients, both of whom had critical illness at the time of Allocetra™ treatment, were hospitalized in the ICU on a respirator on day-28

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Patient classification as defined by the NIH classification guide

Allocetra™: COVID-19 regulatory pathway

- Objective: obtain emergency/conditional approval for Allocetra™ in Europe, indicated for severe/critical patients
- Expected study requirements, pending EMA scientific advice meeting
  - Phase IIb could potentially be sufficient for obtaining emergency/conditional approval , or
  - Phase III may be required
- Phase IIb typically recruits fewer patients, completes faster, and so if the Phase IIb pathway is available, it would most likely be the choice for moving forward
- In the case Allocetra™ obtains emergency/conditional approval in Europe, we expect that regulatory approvals in other territories, such as India, Brazil, would be obtainable.
- Clinical trial execution focus has shifted away from Israeli medical centers to European centers, due to the expected decline of number of patients in Israel. We expect that recruitment will initiate in Israeli medical centers first in Q2/Q3, followed by European centers.

Patient classification as defined by the NIH classification guide

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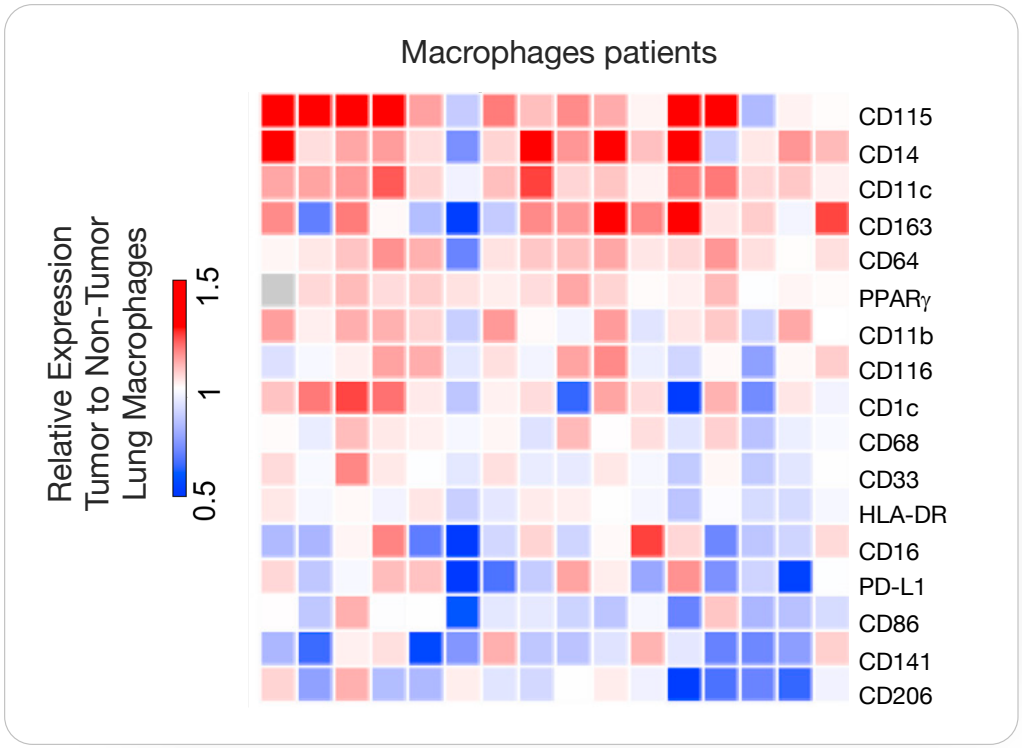
Macrophage reprogramming in solid tumor microenvironment

Unique & differentiated value proposition

The TME is loaded with pro-tumor macrophages (TAMs), which are macrophages reprogrammed by the tumor and have a drastically different gene expression

Gene expression varies drastically in TAMs vs anti-cancer macrophages*



TAMs are macrophages that were reprogrammed by the cancer cells out of their homeostatic state and into a pro-tumor state

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*Innate Immune Landscape in Early Lung Adenocarcinoma by Paired Single-Cell Analyses . Lavin et al., 2017, Cell 169, 750–765

Allocetra™: novel reprogramming of pro-tumor macrophages

Key company universe Macrophage properties	Novartis, BMS, Amgen, Syndax	47, Trillium, ALX, Celgene, Surface	Infinity, Arcus, MedImmune, Corvus, Pfizer	Celgene, Nektar, GSK	Celldex, AbbVie, MedImmune	Enlivex
Programming method	Inhibit or trigger surface target	Inhibit or trigger surface target	Inhibit or trigger surface target	Inhibit or trigger surface target	Inhibit or trigger surface target	Reprogramming to homeostatic state
Desired functionality change						
Recruitment ↑	CSF1-CSF1R	✗	✗	✗	✗	✓
Proliferation ↑	✗	✗	✗	TLRs	CD40	✓
Survival ↑	CSF1R	✗	✗	✗	✗	✓
Anti-tumor activity ↑	CSF1-CSF1R	CD47-SIRPα	PI3Kγ, A2AR, CD73, GM-CSF, M-CSF	TLRs	CD40	✓
Safety & tolerability profile (potential negative effect on non-TAM macrophages)	Effect on non-cancer macrophages?	Effect on red blood cells, non-cancer macrophages?	Effect on non-cancer macrophages?	Effect on non-cancer macrophages?	Effect on non-cancer macrophages?	No negative effect on non-cancer macrophages

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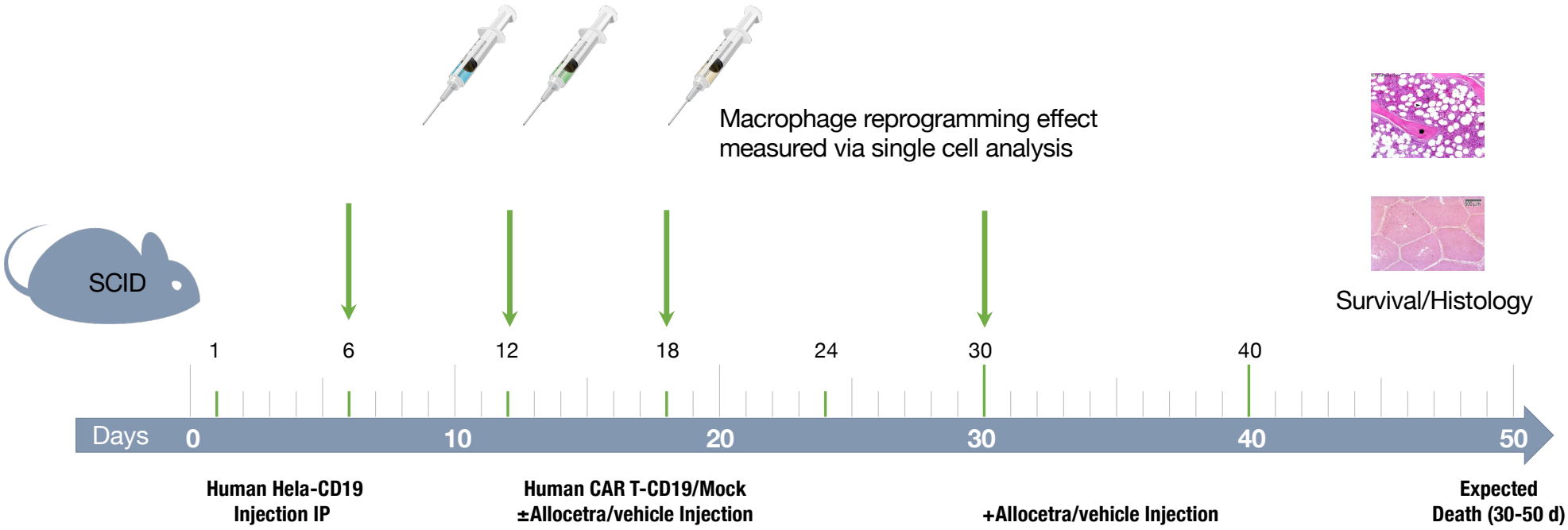
Allocetra™

Macrophage reprogramming in solid tumor microenvironment

Preclinical data

Allocetra™: reprogramming of peritoneal pro-tumor macrophages

Preclinical study model: solid tumor engineered to express CD19, making it potentially responsive to CD19 CAR-T



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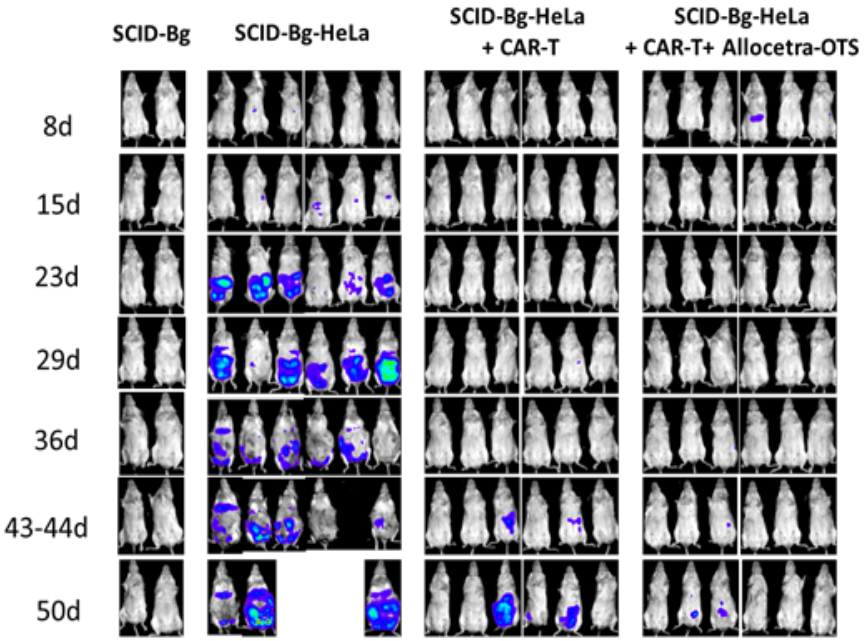
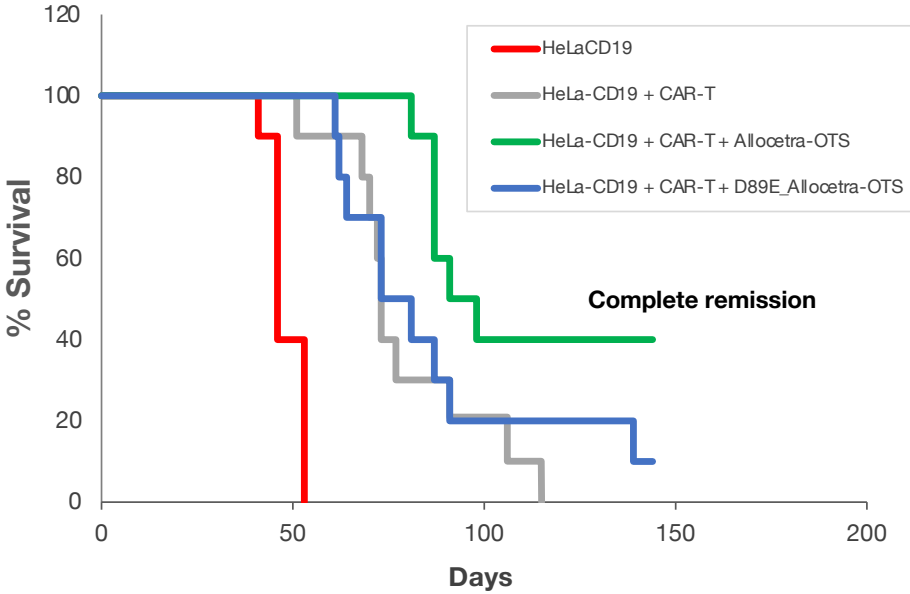
Allocetra™ macrophage reprogramming synergistic with CD19 CAR-T

D89* Allocetra (opsonized, not engulfed by macrophages) has no programming nor clinical effect





Avg. survival, days		
No therapy	CAR-T	CAR-T + Allocetra™
30±5	55±11 (p<0.001)	74±10 (p<0.01)

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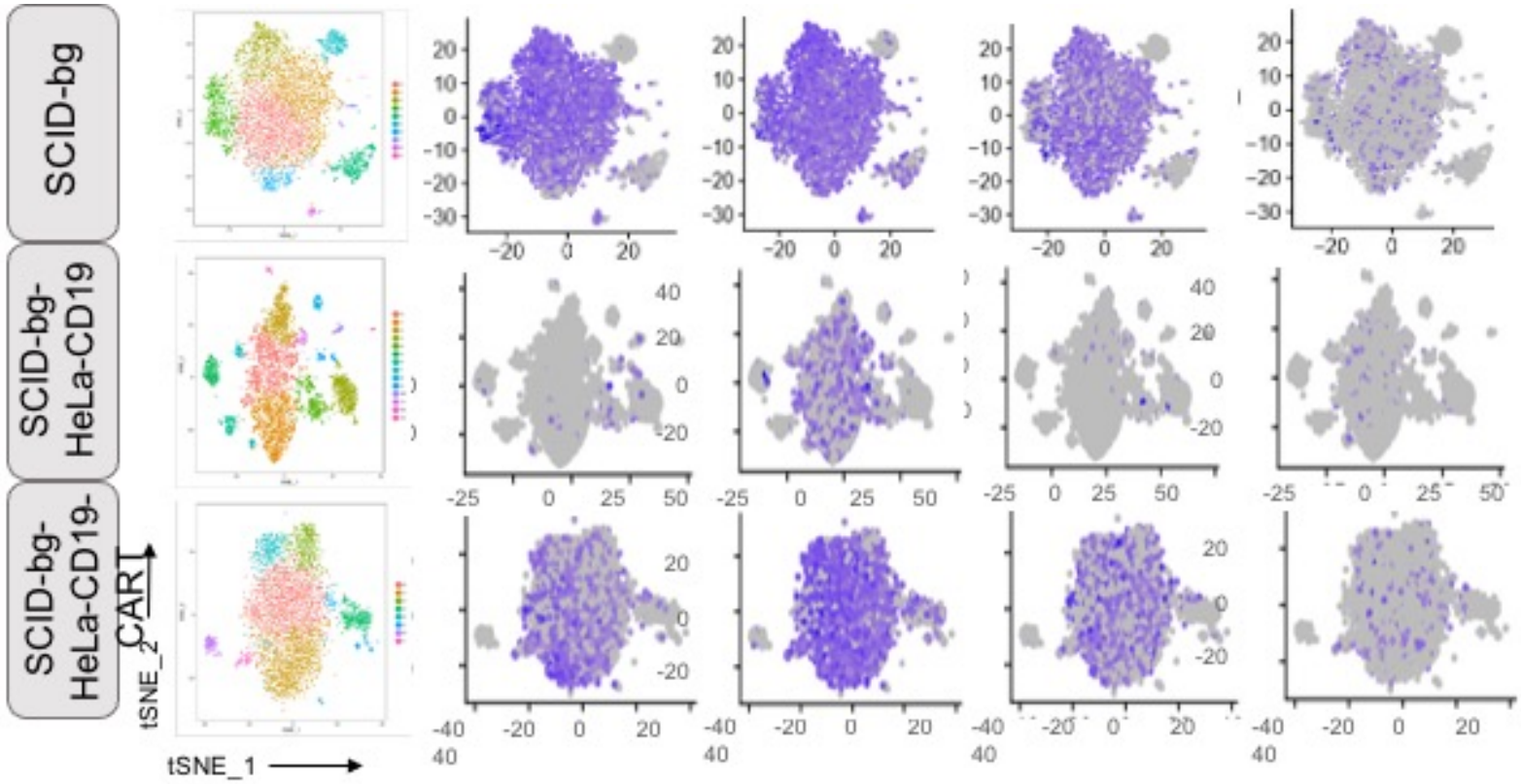
* D89E mutant plasmid was received from N. Nagata, transfected using Lenti X HEK293T cells (Clontech-Takara), and the protein was generated and added to apoptotic cells before intra-peritoneal injection

Single cell analysis: negative reprogramming of peritoneal macrophages to become pro-tumor; and reversal trend to anti-tumor upon effective anti-cancer therapy

Healthy mice

Disese only

Disease + effective anti-cancer therapy



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Allocetra macrophage reprogramming research collaborations

Mount Sinai

Yale University School of Medicine

Collaborations aim to evaluate the potential of Allocetra™ in combination with immune-checkpoint inhibitors in solid cancer patients that do not respond to stand-alone checkpoint inhibitor therapies

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Planned/executed milestones

Q1 2021

Top-line data from macrophage reprogramming COVID-19 Phase II

Q1 2021

Mount Sinai research collaboration: macrophage reprogramming PD-1 combination

Q2/Q3 2021

Phase II-III initiation; Designed to obtain Emergency-use designation for COVID-19 Severe/critical patients

Q3 2021

Initiation of macrophage reprogramming PD-1 combination (undisclosed indication) Phase Ib

Q4 2021 or Q1 2022

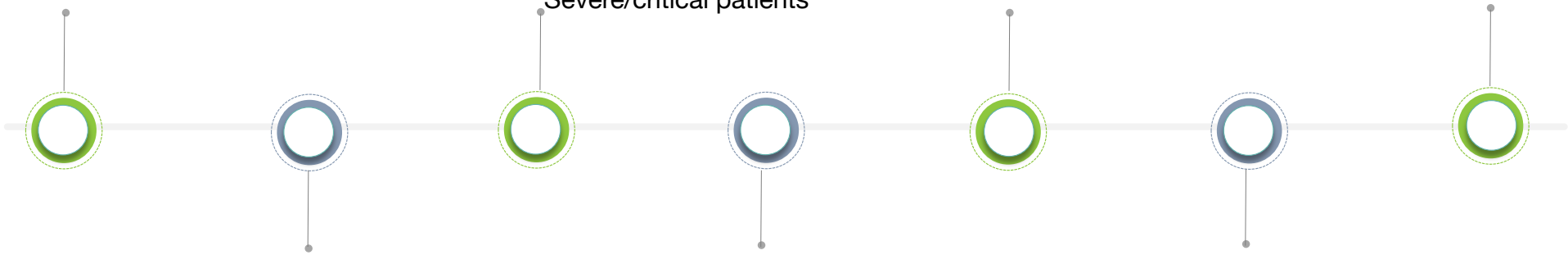
Interim data macrophage reprogramming sepsis Phase IIb

Q1 2022

Initiation of macrophage reprogramming PD-1 combination (undisclosed indication) Phase Ib

Q2 2022

Top line data macrophage reprogramming sepsis Phase IIb & Phase II-III COVID-19



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Financial Summary

NASDAQ GS	**ENLV**
Cash	**$96MM (Dec 31, 2020[1])**
Debt	**None**
Shares Outstanding	**18.2 MM**
Funded Through	**Q1-2024**

[1] Cash balance as reported for Dec 31 2020 plus recent financings

Management

Shai Novik Executive Chairman	Founder and President of PROLOR Biotech, Sold in 2013 ($560mm transaction). Lead product partnered to Pfizer, $295 million down payment, $275 upon FDA & other regulatory approvals. BLA filed by Pfizer late 2020.	
Oren Hershkovitz CEO	Former Director of CMC, VP R&D and General Manager of OPKO Biologics (PROLOR Biotech). Led multiple clinical programs in Phase I, II and III. Ph.D. in Immunology.	
Dror Mevorach Chief Scientific Officer	Director, Rheumatology Research Centre and Molecular Immunology; and Director, Centre for Rare diseases, Hadassah Medical Center, Jerusalem.	
Odelia Ben-Shitrit Head of Clinical Operations	Over 20 years of experience in clinical trials and operational management in various therapeutic areas. Former Teva and PAREXEL clinical leader.	
Dan Fishelovitch Head Of CMC	Former CMC Director, NeuroDerm Ltd, and Formulation Scientist at Teva Pharmaceutical Industries Ltd. Ph.D. from the faculty of Medicine, Tel-Aviv University in structural Bioinformatics.	
Shachar Shlosberger CFO	~Former PROLOR Biotech Ltd Finance Director where she was responsible for the overall financial operations in Israel and US. A C.P.A., and holds a M.B.A. in Accounting and Business Administration.	

Board Of Directors

Shai Novik Executive Chairman	Founder and President of PROLOR Biotech, Sold in 2013 ($560mm transaction). Lead product partnered to Pfizer, $295 million down payment, $275 upon FDA & other regulatory approvals. BLA filed by Pfizer late 2020.
Sangwoo Lee Director	Executive Director of the Investment Department & Head of U.S. Branch at Korea Investment Partners Co. Ltd
Bernhard Kirschbaum, PhD Director	Former Executive Vice President & Member of the Board at Merck Serono, and Head of Global Research & Early Development
Gili Hart, Ph.D Director	Formerly with PROLOR Biotech, led the pre-clinical, clinical and pharmacological activities. CEO of Mitoconix Bio, a biopharmaceutical company developing disease modifying therapies addressing unmet medical needs
Brian Schwartz, M.D. Director	Former CMO of Arqule through its $2.7 billion acquisition by Merck in 2020. Previously, responsible for the global clinical development of sorafenib (Nexavar®) at Bayer Healthcare.
Abraham Havron, Ph.D. Director	Former CEO of PROLOR Biotech. Founding team and Director of R&D of Interpharm (Merck Serono) ,VP CMC of BioTechnology General Ltd., and VP of Clal Biotechnology Industries Ltd.
Baruch Halpert Director	Over 20 years of experience in VC and Private Equity as an entrepreneur, corporate finance advisor, senior executive and an investor
Michel Habib Director	Managing partner of ALIVE, a medical device VC fund; Former CEO of HBL, former Managing Partner of Agate-MaC Fund, a healthcare VC

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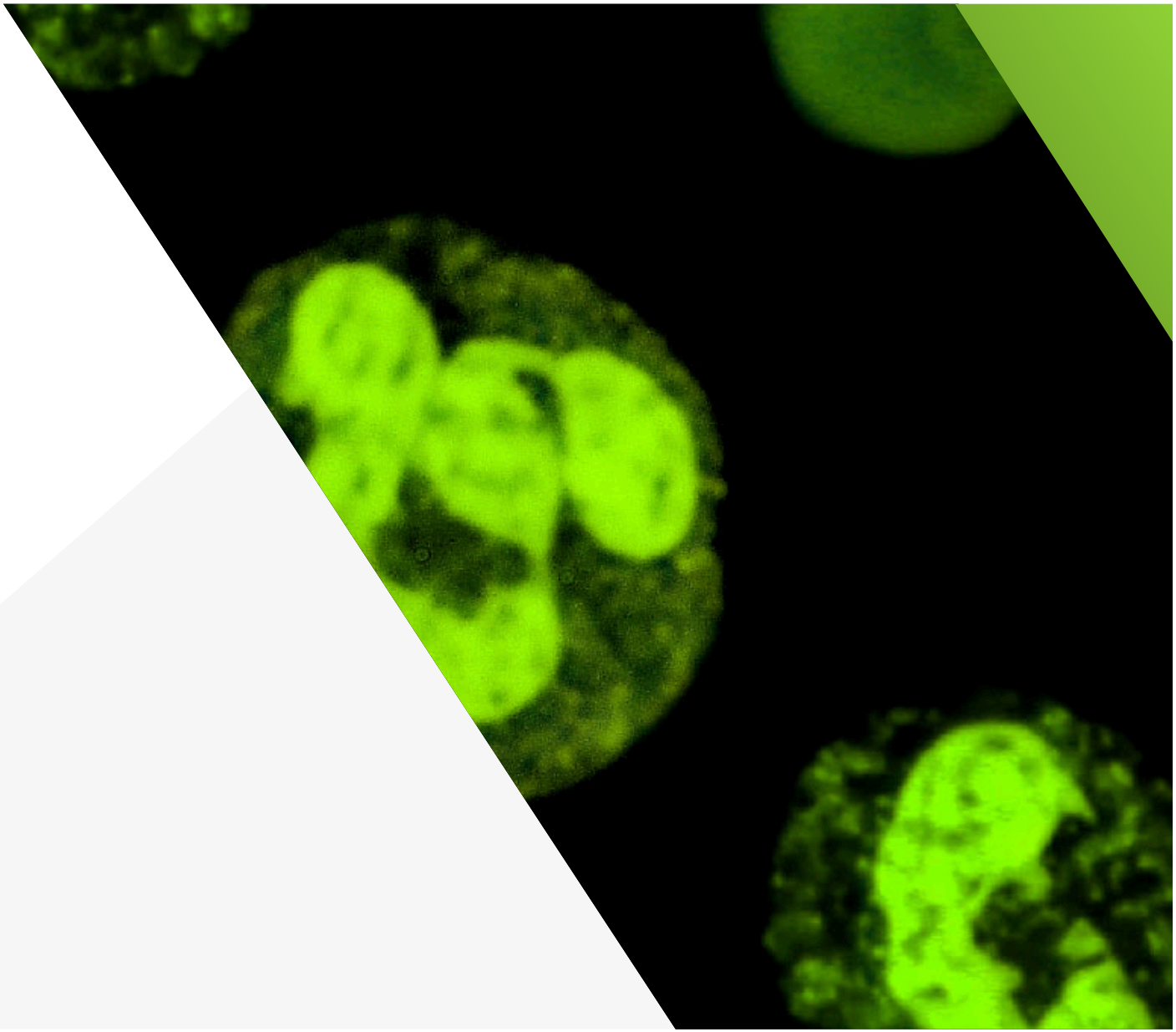
Thank You