New Directions in Cancer Therapy

HELIXBIOPHARMA

Media Presentation

May 2023

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Executive Summary

- Helix BioPharma is developing a novel **first-in-class** anti-cancer therapy stemming from its proprietary technology platform
- Our lead Tumor Defence Breaker™ L-DOS47 is a unique **tumor microenvironment** modifying drug. It breaks the tumor defence against the innate (cellular) immune system by normalizing tumor acidification using a conjugate of a tumor specific antibody and urease - potentially allowing for better efficacy in **combination** with chemotherapy, checkpoint inhibitors and other mechanisms including CAR-T
- L-DOS47 has been used in **over 100 patients**, in mono-, and combo, treatments in NSCLC and PDAC demonstrating good tolerability and safety
- We have seen **promising data in a NSCLC trial** in combination with Pemetrexed/Carboplatin chemotherapy; a trial in pancreatic patients is underway
- Very recent promising preclinical data **combining L-DOS47 with PD1 inhibitor** (Checkpoint). Significantly **better tumor reduction** versus PD1 solo.
- The 2023 fund raising round of $10M will be used to finalise important preclinical experiments to secure the next significant value inflection point making the company attractive for partnering discussions

CORPORATE BRIEF

- Est. 1996, clinical-stage, biopharmaceutical company
- Listed/trades on the Toronto Stock Exchange (TSX): Helix BioPharma Corp. (“Helix”) / Ticker symbol – HBP
- Shares outstanding: around 200 M
- Share price: CAD 0.20 (05/04/2023)
- Market Capitalization: CAD 40 M
- Backed by high-net-worth investors
- Experienced Management team

MANAGEMENT TEAM

Jacek Antas, CEO
- Supervisory Board Chairman
- Over 25 years of experience in financial services/Board member for various companies

Gary Renshaw, MD, CMO
- Former CMO Zhejiang DTRM Biopharma
- Former oncology Director at Eisai

Hatem Kawar, CFO
- Experienced CFO with proven track record in managing financial business in a listed company

Advisors to the Board

Atul Deshpande, PhD MBA
- Experienced biotech entrepreneur, Commercial launch, fundraising and IPO experience for an IO company
- Former CEO, Immediate Therapeutics, Chief Strategist Harbour BioMed

Christof Boehler, PhD
- Biomedical scientist and experienced biotech entrepreneur
- Working with Big Pharma (Takeda) with a focus on drug delivery and oncology

BOARD OF DIRECTORS

Jacek Antas
CEO, Chair Board of Directors

Jerzy Leszczynski
Board Member

Christopher Maciejewski
Board Member

Malgorzata Laube
Board Member

ONCOLOGY REMAINS A SIGNIFICANT UNMET MEDICAL NEED

Lung Cancer in US

Estimated New Cases in 2022	236,740
% of All New Cancer Cases	12.3%
Estimated Deaths in 2022	130,180
% of All Cancer Deaths	21.4%

5-Year Relative Survival
22.9%
2012–2018

Colorectal Cancer in US

Estimated New Cases in 2022	151,030
% of All New Cancer Cases	7.9%
Estimated Deaths in 2022	52,580
% of All Cancer Deaths	8.6%

5-Year Relative Survival
65.1%
2012–2018

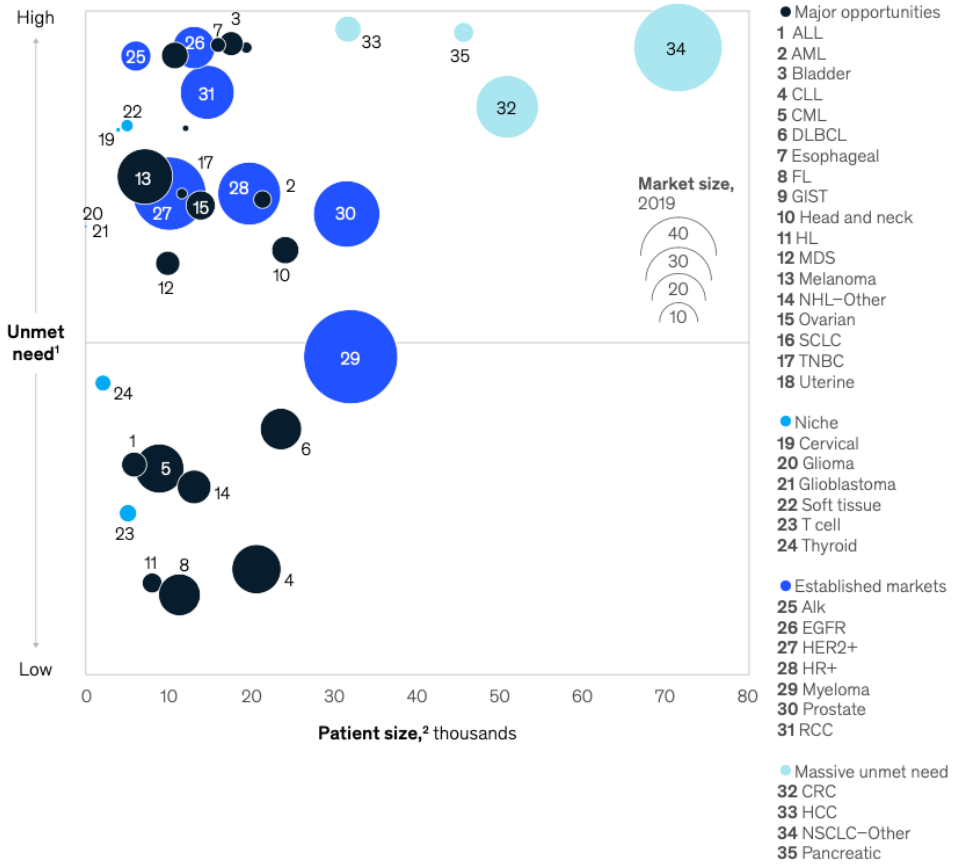
Head and Neck Cancer in US

Estimated New Cases in 2022	54,000
% of All New Cancer Cases	2.8%
Estimated Deaths in 2022	11,230
% of All Cancer Deaths	1.8%

5-Year Relative Survival
68.0%
2012–2018

From NCI SEER Program – Accessed 1/30/2023

Several tumor types impacting large populations have persistently high unmet need



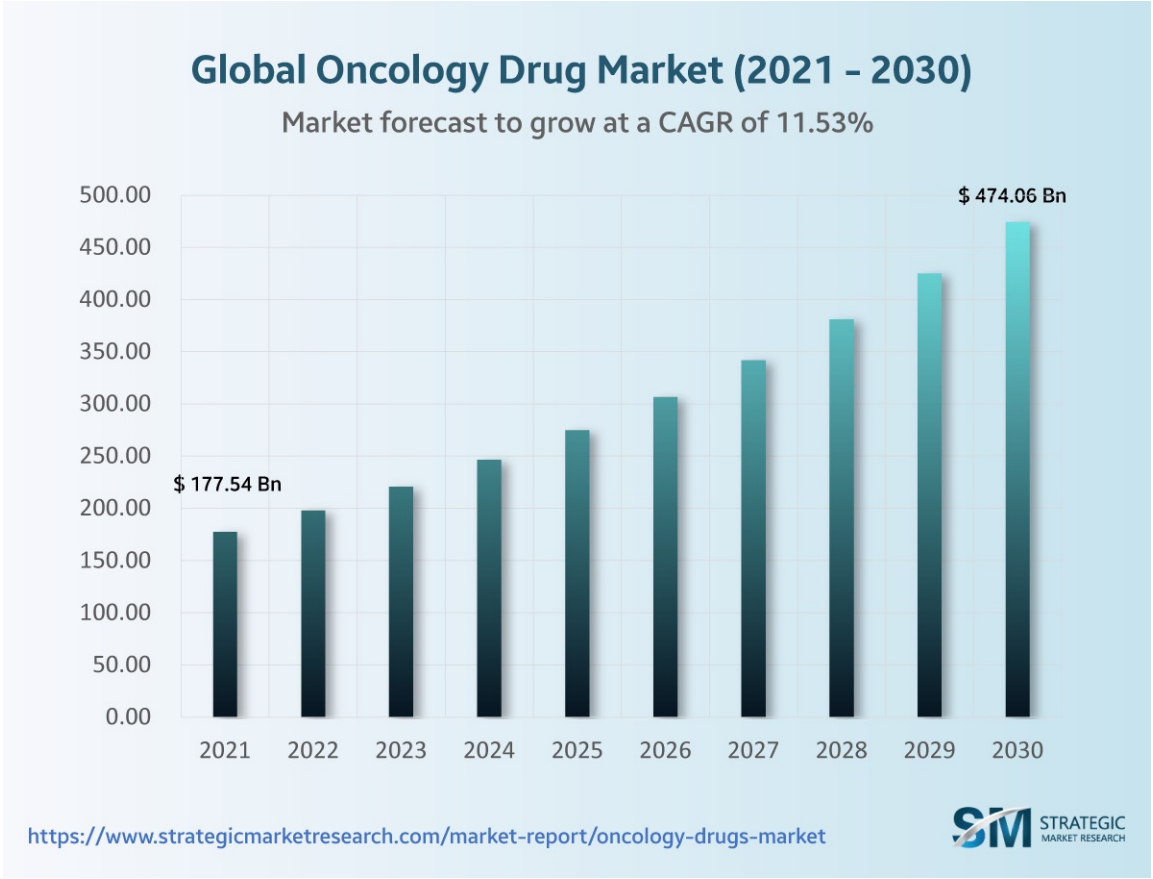
[1]Unmet need defined as one- minus five-year survival rate (overall for heme, metastatic for solid).
[2]Patient size calculated as annual incidence for heme, and larger of mortality and metastatic incidence for solid.

ESTIMATED IO MARKET BY 2030

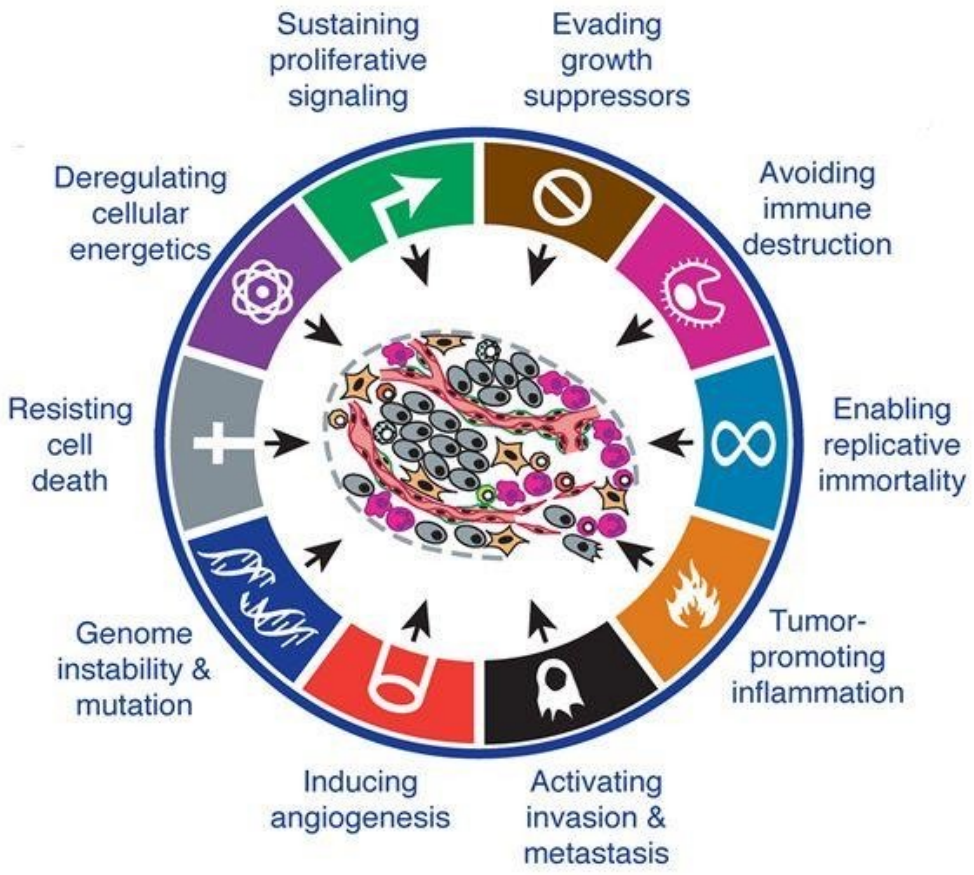
Growing aging populations, increasing obesity and changes in lifestyle including smoking and drinking has led to a significant increase in patients suffering from various kinds of cancers.

Increasing clinical and economic burden is putting a significant stress on our healthcare systems across the world.

Newer and more expensive therapies add to the toolkit to fight cancers thereby leading to a significant increase in market size over the next several years.



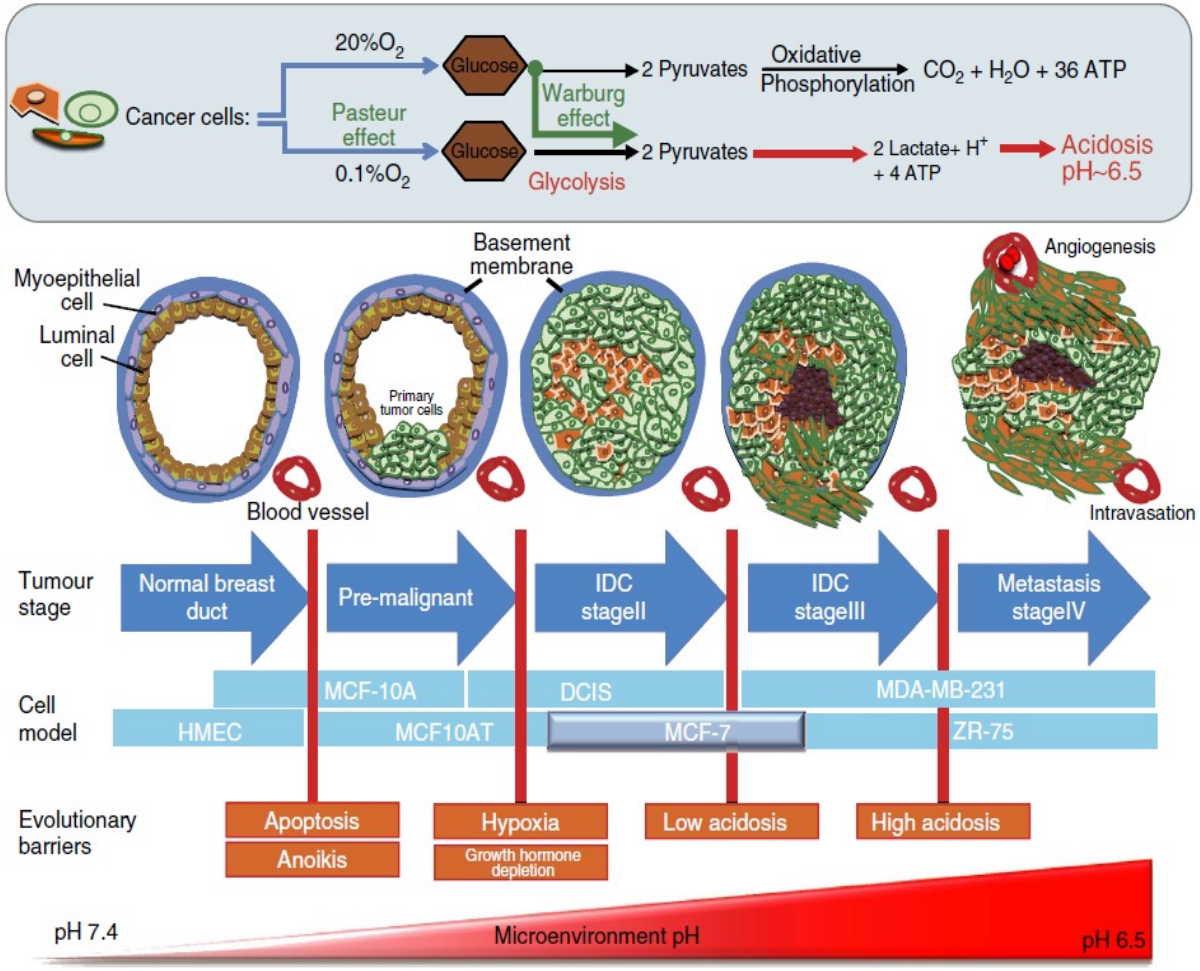
THE HALLMARKS OF CANCER



- The characteristics of cancer can be organized into multiple hallmarks or traits
- These hallmarks provide a framework to study cancer and to develop drugs
- **Targeted drugs** are developed against specific traits, but cancers often acquire resistance and escape
- Missing are therapeutics against an emerging cancer hallmark focused on **tumor acidity,** which serves a general **defense** for the tumor

Source: Cell 2011 144, 646-674

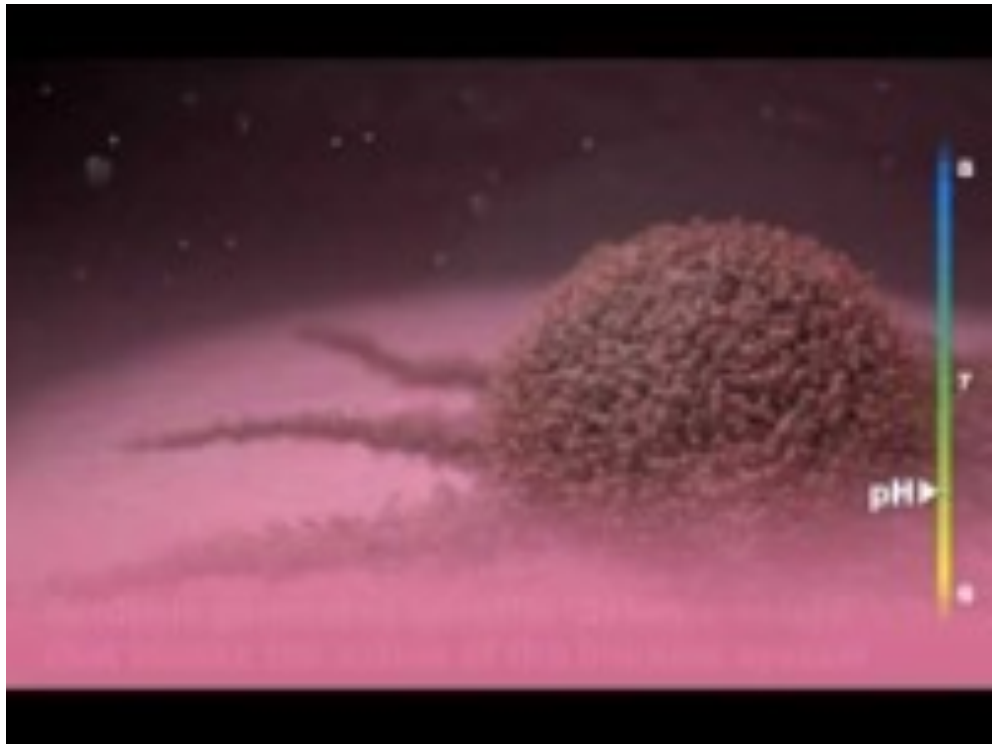
EFFECT OF ACIDOSIS ON TUMOR PROGRESSION



- Hypoxia, poor vasculature and increased flux of carbons through fermentative glycolysis leads to extracellular acidosis in solid tumors (Pasteur effect).
- Cancer cells can maintain the glycolytic phenotype even in the presence of oxygen (Warburg effect) causing further and constant acidification of the tumor microenvironment.
- Adaptation and development of resistance to acidosis is one of the key issues in cancer development and evolution that leads to a more aggressive phenotype.

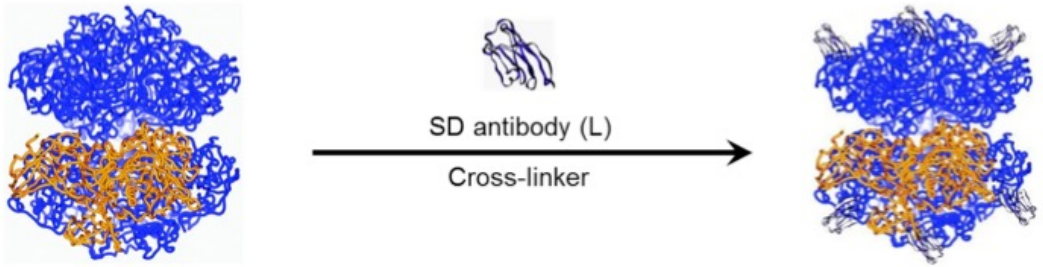
Source: Damaghi, M. et al. (2015). Nature Communications | 6:8752 | DOI: 10.1038/ncomms9752 |www.nature.com/naturecommunications

L-DOS47: A PLATFORM TECHNOLOGY TARGETING TUMOR MICROENVIRONMENT



1. Tumor acidity is an escape mechanism that cancer cells utilize to evade the anti-tumor immune response.
2. Tumor acidity has been shown to correlate with resistance to anti-cancer treatment and poor prognosis for cancer patients.
3. L-DOS47 is designed to reduce tumor acidity with a novel mechanism of action that is synergistic with other therapies
   i. It is an immune bioconjugate that binds to CEACAM6-expressing cancer cells
   ii. It converts urea into ammonia and raises pH: Acidity reversal may augment and repair immune function
   iii. L-DOS47 may improve uptake of weak-base chemotherapeutics
   iv. Preliminary data suggest that L-DOS47 can enhance efficacy of Anti-PD1 therapy
4. Favorable drug safety profile

L-DOS47: ANTI-CEACAM6 -UREASE BIOCONJUGATE



CEACAM6

- Glycosylated 90 kDa (286 aa) GPI-linked membrane protein
- Intercellular adhesion molecule forming homotypic and heterotypic bonds with CEACAM-1, -5 and -8
- Tumor antigen highly expressed on lung, colon, pancreatic and other cancer cells

Anti-CEACAM6 antibody: AFAIKL2

- Proprietary camelid single chain antibody
- As urease is a large protein, the small size of the camelid antibody (15 kDa) is beneficial – multiple antibodies conjugated to urease do not considerably increase total protein size

Conjugation of urease to a tumor-specific antibody allows targeted urease delivery by iv injection

Clinical Studies

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TUMOR DEFENCE BREAKER TECHNOLOGY PLATFORM

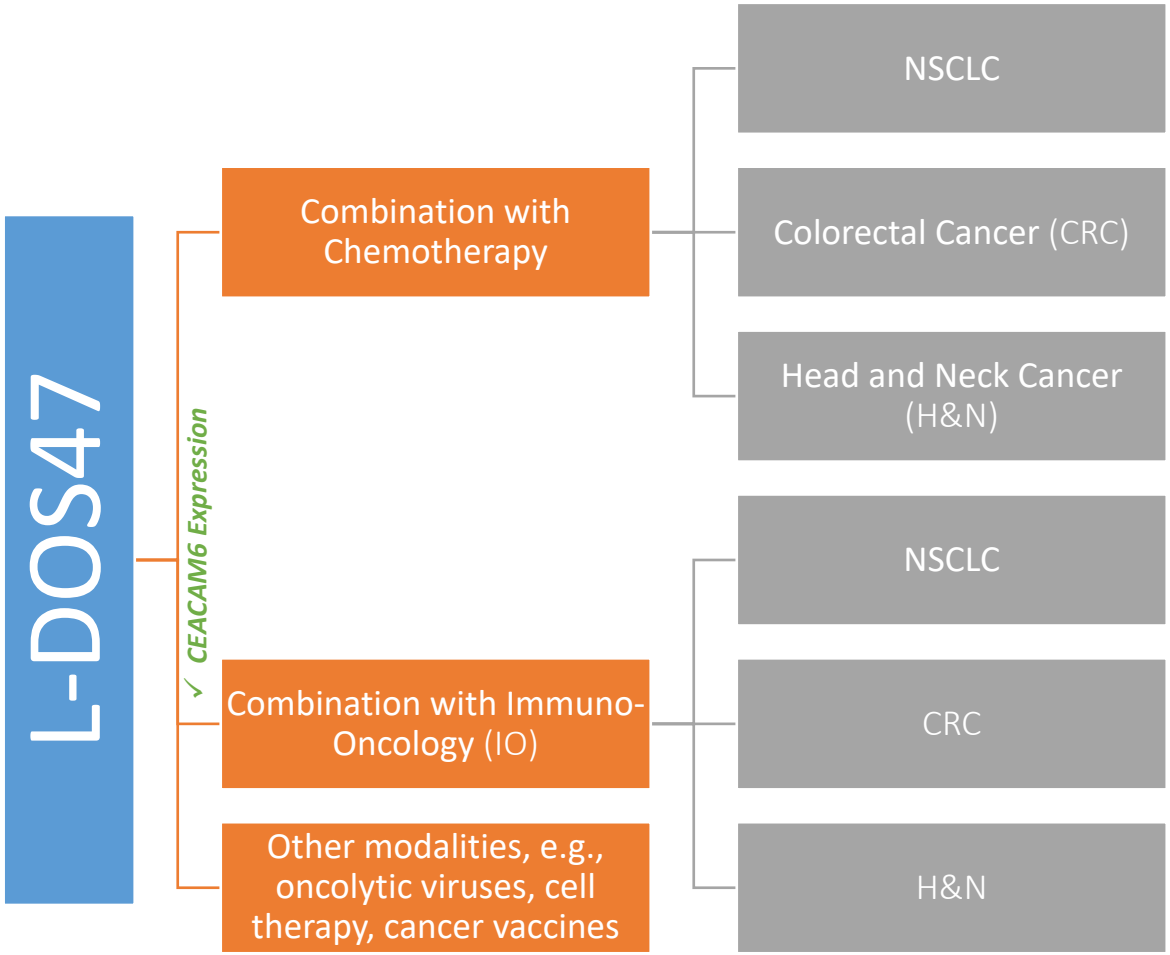
CLINICAL TRIALS		
L-DOS47 monotherapy NSCLC (clinical trial # NCT02340208)		
PRECLINICAL	PHASE 1	PHASE 2
L-DOS47 combo PEM/CARBO NSCLC (clinical trial # NCT02309892)		
PRECLINICAL	PHASE 1	PHASE 2
L-DOS47 combo DOXO Pancreas (clinical trial # NCT04203641)		
PRECLINICAL	PHASE 1	PHASE 2

RESEARCH		
L-DOS47 combo Immune Checkpoints		
PRECLINICAL	PHASE 1	PHASE 2

A ROBUST CLINICAL STRATEGY TO ESTABLISH SAFETY AND EFFICACY OF L-DOS47 IN CANCER PATIENTS

Objective	Studies	Status	Outcomes
Safety and tolerability as a monotherapy	**LDOS002** Phase I/II Monotherapy in advanced non-small cell lung cancer (NSCLC)	Phase I and stage 1 of phase II complete	***L-DOS47 is safe and tolerated at all doses studied*** ***Limited efficacy observed – moved to combination studies***
Combo therapy with chemotherapy	**LDOS001** Phase I Combination with Pem/Carbo Phase I in advanced NSCLC	Published in J Thoracic Oncology - Clinical Research Reports (Piha-Paul, *et al*; Sept. 2022)	***L-DOS47 in combination with pemetrexed/carboplatin is well tolerated with promising anti-tumor activity***
Broaden utility and indications	**LDOS006** Phase Ib/II Combination with Doxorubicin in advanced pancreatic cancer	3 cohorts – 3, 6, 9 µg/Kg 20 patients dosed; 9 enrolled Amendment filed for higher dose at 13.55 µg/kg	***Dose escalation ongoing*** ***No L-DOS47-related DLTs seen to date***
Combining L-DOS47 with immunotherapy	Preclinical - Combination with immunotherapy in lung cancer or other indications	Planning	

L-DOS47 PLATFORM: PORTFOLIO-IN-A-PRODUCT STRATEGY



L-DOS47 Platform

Combination with Chemotherapy

- ✓NSCLC – proof of concept with clinical data
- ➢ *CRC*
- ➢ *H&N*

Combination with IO Therapies

- ➢ *NSCLC*
- ➢ *CRC*
- ➢ *H&N*

Ongoing preclinical testing

Example companies

Lilly · Bristol Myers Squibb · Roche · Novartis · GSK · Pfizer · sanofi · Merck · Amgen · Johnson & Johnson

Intellectual Property

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STRONG BARRIER TO ENTRY WITH IP

RESTORING FUNCTION TUMOR ACIDIFIED T CELLS	METHOD AND COMPOSITION FOR INHIBITING CANCER CELL GROWTH USING UREASE AND WEAKLY BASIC ANTI-CANCER COMPOUNDS	ANTIBODY-UREASE CONJUGATES FOR THERAPEUTIC PURPOSES		USE OF ANTIBODY-UREASE CONJUGATES FOR DIAGNOSTIC AND THERAPEUTIC PURPOSES	USE OF UREASE FOR INHIBITING CANCER CELL GROWTH (foundation technology)	
pH/urease direct effects on T cell function (Con't: Method to decrease expression of PD-L1 on cancer cell using urease) PCT/CA2017/051116	Use of composition to reduce amount of weakly basic anti-cancer compound to reduce tumor growth, unit dose of 10-50 units/mL urease & an anti-tumor antigen antibody to enhance the delivery of the urease to tumor. unit dose reduces the amount of said weakly basic anti-cancer compound 2-5-fold lower than without urease.	sdAb:AFAIKL2 urease conjugate (CEACAM6) optimized with novel conjugation ratios (3-12) PCT/IB2016/050342		2.5 120kDa Abs conjugated to urease enzyme, multiple points of conjugation on the antibody PCT/CA2014/050334	Pharmaceutical composition for inhibiting growth of cancer cells, comprising urease enzyme, and chemical entity effective to enhance the delivery of the enzyme to cancer cells. PCT/CA2003/001061	
U.S. 10,640,806 *U.S. 16/847,490 *CA 3,045,327 *EP 3515473 *CN 110011891	CA 2,493,282	U.S. 15/545,549 CA 2,973,538 AU 2016210551 EP 3261678 (validated in CH, DE, FR, GB, IT, NL, SE, and ES)	IN 367556 IL 253549 JP 6876618 SK 10-2318994 PL 238187	U.S. 10,316,311 AU 2014252666 CA 2,908,475 *EP 2984170	U.S. 7,211,250 U.S. 7,264,800 CA 2,492,472 EP 1530482+ (validated 30 countries) EP 2324846 (DE, FR,UK)	IN 245306 & 293956 JP 5850561 SK 10-1352826 NZ 538284 PL 217626 IL 166249 NO 336811
** Patent term expires Sept 22, 2037 (if all required annuities paid)	** Patent term expires Jan 31, 2025 (if all required annuities paid)	** Patent term expires January 22, 2036 (if all required annuities paid)		** Patent term expires April 3, 2034 (if all required annuities paid)	** Patent term expires July 16, 2023 (if all required annuities paid)	

Business Development

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EXAMPLE OF TARGETS COMPANIES THAT COULD HAVE INTEREST IN L-DOS47

- Ongoing outreach to these and several other companies
- Interest to use LDOS47 in combination with their assets
- Could be of interest beyond current IO therapies to their growing portfolio
- In combination with newer modalities like mRNA, oncolytic vaccines among others

EXAMPLE COMPS FOR HELIX BIOPHARMA

Licensor and licensee	Total deal value ($ million), date	Description
Cullinan Oncology and Harbour BioMed	$588 ($25M upfront; $148M development milestones, $415 sales based tiered royalties) 14 Feb 2022	**Cullinan Oncology Licenses U.S. Rights to the First Clinical-Stage B7H4 x 4-1BB Bispecific Immune Activator from Harbour BioMed** Under the agreement, Cullinan Oncology will pay Harbour BioMed an upfront license fee of $25 million at closing for the exclusive right to develop and commercialize CLN-418/HBM7008 in the U.S. Harbour BioMed will be eligible to receive up to $148M in development and regulatory milestones plus up to an additional $415M in sales-based milestones as well as tiered royalties up to high teens on potential U.S. commercial sales.
Astrazeneca and Harbour BioMed	$350 ($25M upfront; $325M development milestones, sales based tiered royalties) 7 April 2022	**Harbour BioMed Announces Global Out-License Agreement with AstraZeneca for CLDN18.2xCD3 Bispecific Antibody HBM7022** Pursuant to the license agreement and subject to the terms and conditions thereof, HBM shall receive an upfront payment of US$25 million with the potential for additional payments up to US$325 million pending achievement of certain development, regulatory and commercial milestones. HBM is also eligible to receive tiered royalties on net sales.
Astrazeneca and Neogene Therapeutics	$320 ($200 upfront; $120 milestone based please royalties)	**AstraZeneca to acquire Neogene Therapeutics, accelerating ambition in Oncology cell therapy** AstraZeneca will acquire all outstanding equity of Neogene for a total consideration of up to $320m, on a cash and debt free basis. This will include an initial payment of $200m on deal closing, and a further up to $120m in both contingent milestones-based and non-contingent consideration.
Merck and Imago Biosciences	$1,350 (Terms not disclosed) November 21, 2022	**Merck to Acquire Imago BioSciences, Inc.** Merck, through a subsidiary, will acquire Imago for $36.00 per share in cash for an approximate total equity value of $1.35 billion. *Multiple assets in pipeline.*

SUMMARY

1. **Current standards of care,** including checkpoint inhibitors, are **limited** by the efficacy in addressing cancers
2. Helix is developing novel anti-cancer therapies stemming from its proprietary technology platforms that could help address these efficacy challenges turning it into a significant **multi-pronged business opportunity** to potentially partner with different pharma companies
3. **L-DOS47**
   a) Unique tumor microenvironment immuno-conjugate drug
   b) proven safe and tolerable in a monotherapy lung cancer study
   c) gained additional clinical data when combined with chemo in lung cancer
   d) in clinical development for both lung and pancreatic cancer
4. Additional **clinical and pre-clinical milestones are expected in 2023** that will augment partnership discussions with pharma partners

Contact PR / IR:

Torsten Biallas
b-communication GmbH
Tengstrasse 27, D - 80798 München

Mobile +49 172 4229605
Mobile +41 79 4753386
t.biallas@b-communication.de