ROQUEFORT
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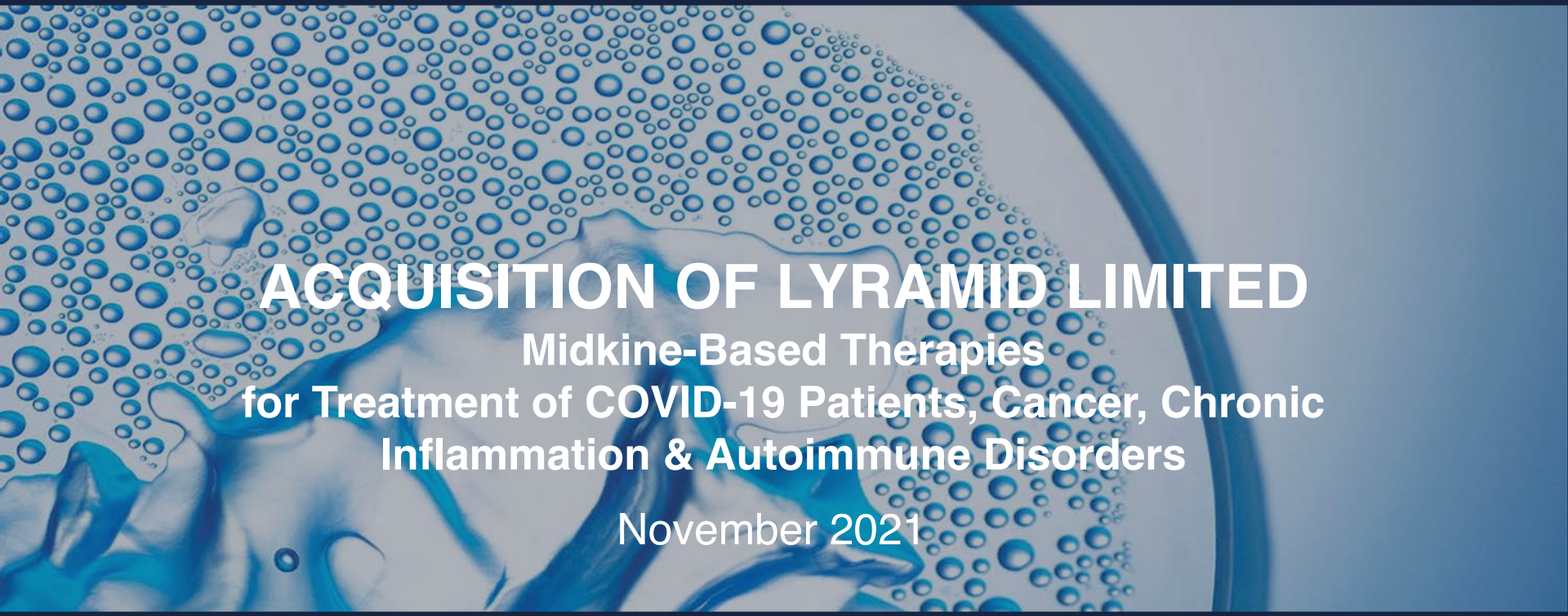

ACQUISITION OF LYRAMID LIMITED

Midkine-Based Therapies for Treatment of COVID-19 Patients, Cancer, Chronic Inflammation & Autoimmune Disorders

November 2021

Disclaimer

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Corporate Overview

Successful IPO in March 2021

- Roquefort Investments is listed on the LSE:ROQ
- Experienced Board with proven track record in bringing companies to market and completing value accretive transactions
- Raised £1 million in March 2021 IPO
- Established to acquire an early stage business in the medical biotechnology sector

Agreement Signed to Acquire Lyramid Limited

- LYRAMID is in the pre-clinical stages of developing *first-in-class* drugs for the treatment of COVID-19 patients, cancer, chronic inflammatory and autoimmune disorders
- Acquisition consideration is £1 million (50% in cash / 50% in ROQ shares)

LYRAMID

Proposing to raise up to £3 million to acquire Lyramid and fund pre-clinical drug development as a prelude to clinical trials

Board of Directors

Stephen West: Executive Chairman

- over 26 years' financial and corporate experience gained in public practice, oil and gas, mining and investment banking spanning Australia, UK, Europe, CIS and Africa
- Fellow Chartered Accountant (Australia) and Chartered Accountant (England & Wales), with Bachelor of Commerce (Accounting and Business Law)
- proven track record in working with growth companies, particularly in the resource sector, with extensive experience in IPOs, secondary listings, corporate finance, fundraisings, investor relations and financial and management reporting
- currently CFO/executive director at AIM listed Advance Energy plc and non-exec Chairman of Zeta Petroleum plc

Dr Mark Rollins: Non-Executive Director

- doctorate in Engineering Science from Oxford University and a Masters in Mathematics from Cambridge University
- has held senior positions at several large listed companies including Chairman and CEO of Ukrnafta in Ukraine with over 20,000 employees, and Senior VP at BG Group plc and Shell International
- Proven commercial track record with extensive experience in business development, government negotiation and private equity
- currently non-exec Chairman of Advance Energy plc

Dr Michael Stein: Non-Executive Director

- medical doctor (Honours) and biochemist (First Class Honours) from the University of Cape Town (1988) and from the University of Oxford (Rhodes Scholar) with a doctorate in Physiological Sciences (Immunology)
- a business leader and strategic adviser with C-suite experience in healthcare including being founding CEO of Valo Therapeutics and OxStem Ltd, a biotechnology spin-out from the University of Oxford
- founder and former CEO for Doctor Care Anywhere, acquired by Synergix in 2015. In 2001, he co-founded the Map of Medicine Ltd (the Map) with University College London. As founding CEO (and later CMO), the Map was nationally licensed across NHS England (2005-15) and acquired by Hearst Business Media (HBM) in 2008.

Mark Freeman: Non-Executive Director

- 25 years' experience in corporate finance and the public markets, including strategic planning, business development, acquisitions and mergers, project commercialisation and project development
- Chartered Accountant with a Bachelor of Commerce of the University of Western Australia
- currently a director of Lyramid Limited, Pursuit Minerals Ltd, Calima Energy Ltd and Grand Gulf Energy Ltd

Overview of LYRAMID Limited

Licence holder of the largest global IP portfolio on Midkine

- Patent portfolio covering composition of matter and method of use of Midkine inhibitors

Novel disease target

- Potential to exploit the broad therapeutic potential of Midkine for a number of clinical indications of unmet needs

Developing first in class oligonucleotide drugs

- IP provides a platform to develop *first-in-class* drugs for the treatment of COVID-19 patients, cancer, autoimmune disorders and chronic kidney disease

Extensive validation by LYRAMID

- Therapeutic potential of Midkine blocking drugs validated during more than 10 years of research including collaborations with leading academic centres and clinicians resulting in over 1,000 scientific publications

Headquartered in Australia

- Collaborations with leading Medical Research Institutes
- 42.5% R&D cash rebate for Australian and overseas activities

World-wide collaborations

- Supports IP portfolio research with reduced cost to Lyramid
- Adds diversity of people and research into different disease targets

LYRAMID Management Team

Graham Robertson: CSO

- Associate Professor who gained his PhD in molecular virology before undertaking post-doctoral training at Oxford
- As group leader at the ANZAC and Garvan Institutes in Sydney (2004-2014), explored the impact of tumour-associated inflammation on multi-organ syndromes in cancer patients via systems biology and clinical studies
- Extensive experience in drug metabolism, inflammatory/fibrotic diseases, cancer
- Expert in Midkine biology and role in disease
- Published 70+ papers with ~4,000 citations

Maria Halasz: Strategic Advisor

- Over 28 years of experience in commercialising and funding medical research
- Named as an Inventor on several Midkine patents licenced to Lyramid
- Former CEO of Lyramid Limited, and the current CEO of Cellmid Limited (ASX:CDY) and Chairman of the Midkine Research Institute

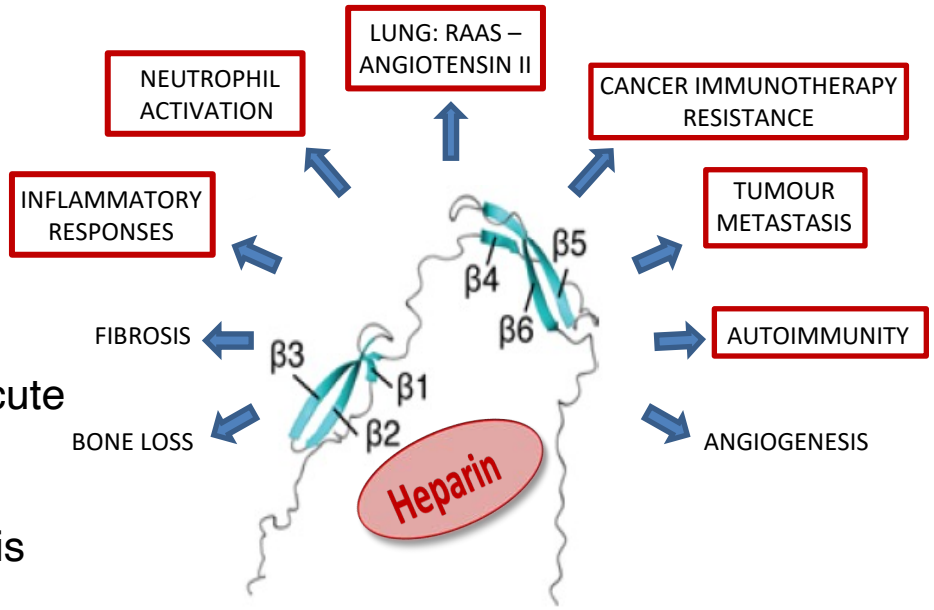
Scientific Advisers

- International pioneer in 'concept to patient' development of oligonucleotide-based drugs
  Designed one of the first oligonucleotide drugs to enter the clinic
- Cardiologist/scientist based in Germany
  Discoveries on Midkine in inflammatory processes and autoimmune disease
- US based cancer researcher
  Specialises in tumour immunology and testing reagents targeting Midkine
- ICU and renal disease specialist based in Australia
  Clinical studies on Midkine in chronic kidney disease

LYRAMID Midkine Research

Midkine: Novel Disease Target

- Midkine is a heparin binding growth factor involved in many diseases - chronic inflammation, autoimmunity and cancer
- Prominent in embryogenesis, barely detectable in healthy adults
- Midkine contributes to lung pathology in Acute Respiratory Disease Syndrome (ARDS), ventilation induced lung injury, sepsis, pulmonary arterial hypertension and fibrosis
- Midkine levels are elevated in hospitalized COVID-19 patients



Midkine: Highly basic protein that binds anionic heparin

A key factor of cancer treatment is overcoming resistance to immunotherapy

Midkine causes resistance to immune checkpoint inhibitors in cancer patients. Blocking Midkine may restore efficacy of immunotherapy drugs.

Midkine based drugs may block SARS-CoV-2 infection and reduce symptoms of COVID-19

Targeting Midkine may alleviate severe lung disease, multi-organ failure and mortality from both acute and long COVID-19

LYRAMID Midkine-Based Therapeutics

- Over A$40 million invested in licenced Midkine intellectual property portfolio

- LYRAMID is now in the pre-clinical stages of developing *first-in-class* drugs targeting Midkine for treatment of many diseases with a focus on:
  - COVID-19 Patients
  - Cancer
  - Chronic inflammation
  - Autoimmune Disorders

LYRAMID Business Model

RESEARCH

- Extensive research (10 years) identifies Midkine as being involved in many diseases
- Focused on inflammatory diseases, autoimmune disorders and cancer
- Blocking Midkine reduces severity of diverse diseases
- Midkine gene silencing prevents resistance to immuno-oncology drugs

COMPLETED

PRE-CLINICAL

- Design & testing of oligonucleotide drugs to block Midkine
- Initial focus on COVID-19 and cancer
- Intend to then focus on chronic inflammatory and autoimmune diseases
- Optimise for clinical deployment
- Intend to scale production, safety testing, pharmacokinetic & biodistribution studies
- Recent progress in mRNA therapeutics has led to a reduction in drug development timelines & costs

UNDERWAY

PHASE I/II

- Proposed rapid entry of Midkine oligonucleotide drugs into the clinic
- Proposed Phase 1b clinical trials in cancer patients to assess safety and initial efficacy
- Proposed accelerated clinical trials for COVID-19 eg FDA and EMA CTAP/EUA programs

PARTNER WITH OR TRADE SALE TO BIG PHARMA

Midkine Program: Proposed Milestones

MIDKINE OLIGONUCLEOTIDE (MK-ON) DRUG DEVELOPMENT

2021	2022				2023	
Q4	Q1	Q2	Q3	Q4	Q1	Q2
Collaboration for MK-oligonucleotide design and testing	Phosphoro-diamidate Morpholin-Oligonucleotide (PMO) drug production	Oligonucleotide delivery vehicle design	In vivo test inflammatory disease	In vivo test autoimmune disease	Scalable Good Manufacturing Practice (GMP) production	Investigational New Drug (IND) Application
In vitro optimisation and screening	Cancer in vivo efficacy testing	COVID testing			Pharmacokinetic /Toxicity/ Biodistribution studies	Clinical trial preparation
Composition of Matter Provisional Patent 1	Composition of Matter Provisional Patent 2	Methods Patent 1	Methods Patent 2	Methods Patent 3		Patent Cooperation Treaty (PCT) International Filing

LYRAMID Market Potential

PROPOSED FOCUS OF MIDKINE BLOCKING DRUG DEVELOPMENT

COVID-19	Cancer	Anti-Inflammatory	Autoimmune
US$25.6 Billion	US$75 Billion	US$98 Billion	US$110 Billion
COVID-19 therapeutics market expected to reach US$25.6 Billion in 2030	Cancer immunotherapy market (2019) - 50% of all oncology drugs	Global anti-inflammatory therapeutics market (2020) - 70% biologic drugs	Autoimmune disease therapeutics market (2017)
https://ipsnews.net/business/2021/08/30/the-covid-19-therapeutics-market-to-reach-us-25-6-billion-by-2030/ (Aug 2021)	researchandmarkets.com/reports/5185341/global-cancer-immunotherapy-market-analysis-and (Dec 2019)	alliedmarketresearch.com/anti-inflammatory-therapeutics-market (Jun 2021)	researchandmarkets.com/reports/4828880/autoimmune-disease-therapeutics-market-by-drug (Feb 2019)

LYRAMID Exit Potential

2019 – 2020 Pharma Deals

Acquiror/Partner	Deal ($B)	Upfront ($M)	M&A licence	Drug	Target	Disease (s)	Stage
J&J/Momenta	6.5	-	M&A	Nipocalimab	Fc receptor	Autoimmune	Ph 2
Gilead/Forty Seven	4.9	-	M&A	Magrolimab	CD47	Cancer	Ph 1b
Merck/VelosBio	2.75	-	M&A	VLS-101, conjugated mAb +chemo drug	ROR1-receptor	Cancer	Ph 2
Amgen/Five Prime	1.9		M&A	Bamrituzumab	FGFR2b	Cancer	Ph 2
Boehringer Ingelheim/ NBE	1.4	-	M&A	NBE-002, conjugated mAb chemo drug	ROR1 receptor	Cancer	Ph 1
NJCCTQ/Abpro	4.0	60	licence	Bispecific mAb platform	Immune	Cancer immuno-oncology	Discovery
Gilead/Nurix	2.35	45	licence	Protein degradation platform	Ubiquitin+ E3 ligase	Cancer & immune	Preclinical
Novo-Nordisk/ Corvidia	2.1	725	licence	Ziltivekimab	IL-6	CKD Cardio-renal, Chronic inflammation	Ph 2b
Mallinckrodt/Silence	2.1	25	licence	RNAi platform	Various	Diversified	Preclinical + Ph1
Genetech/Skyhawk	2.0	undisclosed	licence	Oligonucleotide splice modifiers	Various, platform	Cancer, autoimmune neurodegenerative	Discovery, Preclinical
Alexion/Zealand	2.0	40	licence	Peptides platform	Complement	Diversified	Discovery

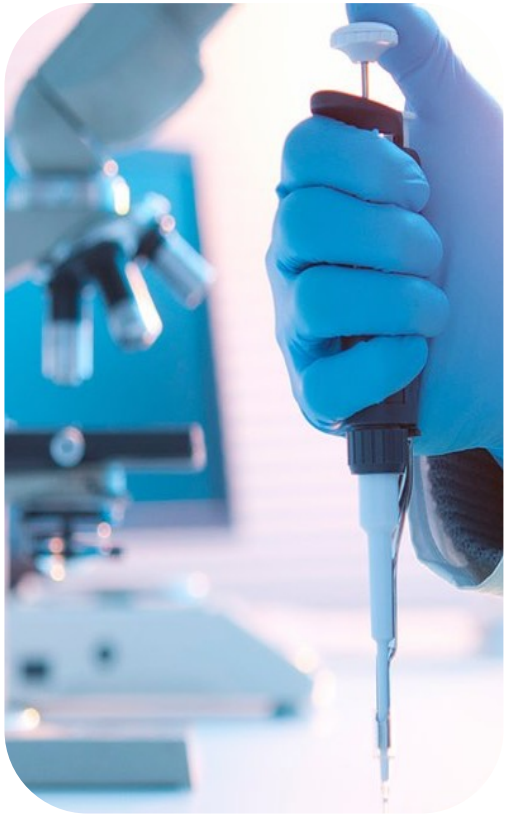
Comparable early stage oligonucleotide/mRNA based drug programs

Funding

Equity Raise

Proposed raising £3 million at a price of 10p per share

Intended Use of Proceeds	£'000
Acquisition consideration	500
Acquisition working capital adjustment	160
Midkine-blocking drug development	1,000
Contingency: other development work	500
Costs of RTO & fundraise	440
Working capital (>2 years)	1,300
Sub-Total	**3,900**
Less: cash at bank	(900)
TOTAL FUNDRAISE	**3,000**



Capital Structure

	Cash £'m	Number	%
SHARES			
Current Shares on Issue	0.90	36,900,000	51%
LYRAMID Consideration	(0.50)	5,000,000	7%
£3 million Placing @ 10p[+]	3.00	30,000,000	42%
Costs[+]	(0.44)	-	-
TOTAL	**2.96**	**71,900,000**	**100%**
WARRANTS			
Warrants on issue pre-RTO (10p)		23,980,000	
Deal origination warrants (10p)		3,000,000	
Broker & Advisor Placing Warrants (10p)[++]		1,975,000	
Director Warrants (50% 5p /50% 10p)		1,500,000	
Director Warrants (15p)		4,500,000	
TOTAL		**34,955,000**	

[+]assuming full £3 million is raised and total costs to date of IPO of £440k (including 6% broker commission)
++ broker placing warrants equal to 6% of total shares placed by the broker (assumed to be 30 million shares) & 175,000 advisor warrants

APPENDIX

LYRAMID

- MIDKINE RESEARCH -

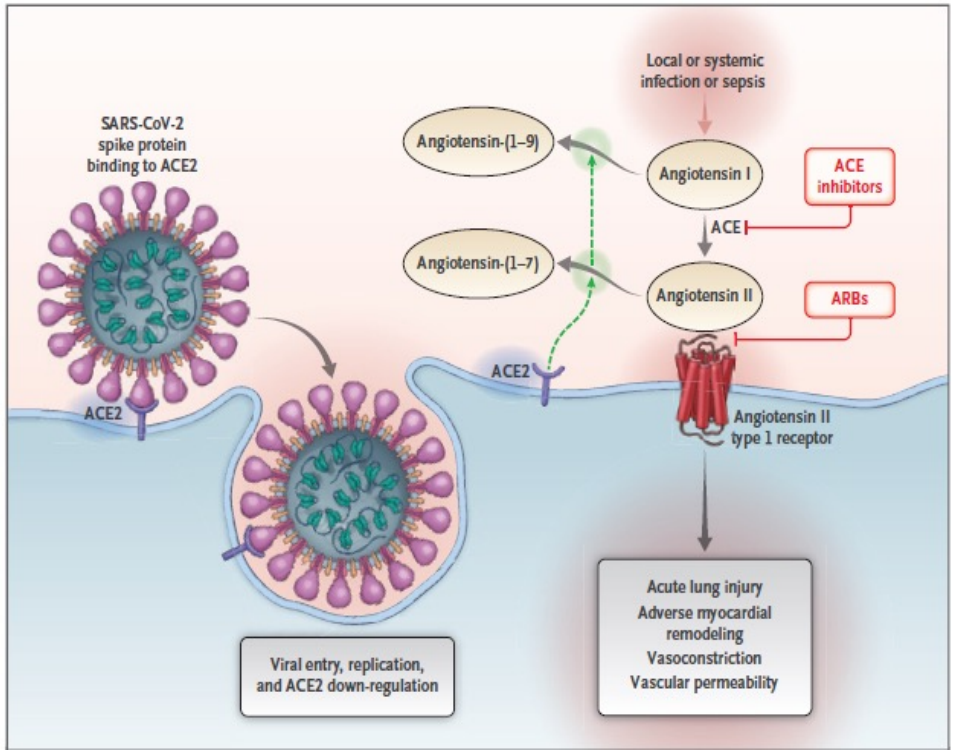
COVID-19 PATIENTS

COVID-19: Midkine Drug Development

- Midkine levels are elevated in hospitalized COVID-19 patients (*Unpublished data*) providing support for the concept that Midkine impacts on progression of COVID-19 and associated multi-organ failure by:
  - Exacerbating the imbalanced RAAS that causes significant pathology in lungs and other organs
  - Promoting excessive blood clots in the lungs and other organs due to excessive recruitment of neutrophils and NET formation in blood vessels
  - Driving aberrant angiogenesis that causes further lung damage
  - As a potent pro-inflammatory mediator, contributing to the cytokine storm associated with COVID-19
- LYRAMID intends to develop novel Midkine-based drugs for COVID-19 and other indications using oligonucleotide drug technologies
- In collaboration with a world leader in the design and testing of antisense oligonucleotide drugs, LYRAMID has devised a potential strategy to block Midkine. We can draw on the expertise of a pioneer in the field who developed one of the first oligonucleotide drugs from concept to life-saving patient treatment.

COVID-19 and Midkine:
SARS-CoV-2 Viral Entry & Lung Injury

- Initial entry of SARS-CoV-2 into lungs is mediated by binding of the spike protein to Angiotensin Converting Enzyme 2 (ACE2) located on lung respiratory cells
- Viral particle internalization depletes ACE2 alongside further reduction of ACE2 production
- Lack of ACE2 results in imbalanced RAAS with enhanced Angiotensin II action causing acute lung injury, widespread vascular complications and multi-organ defects including heart failure



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

COVID-19: Infection & Pathology

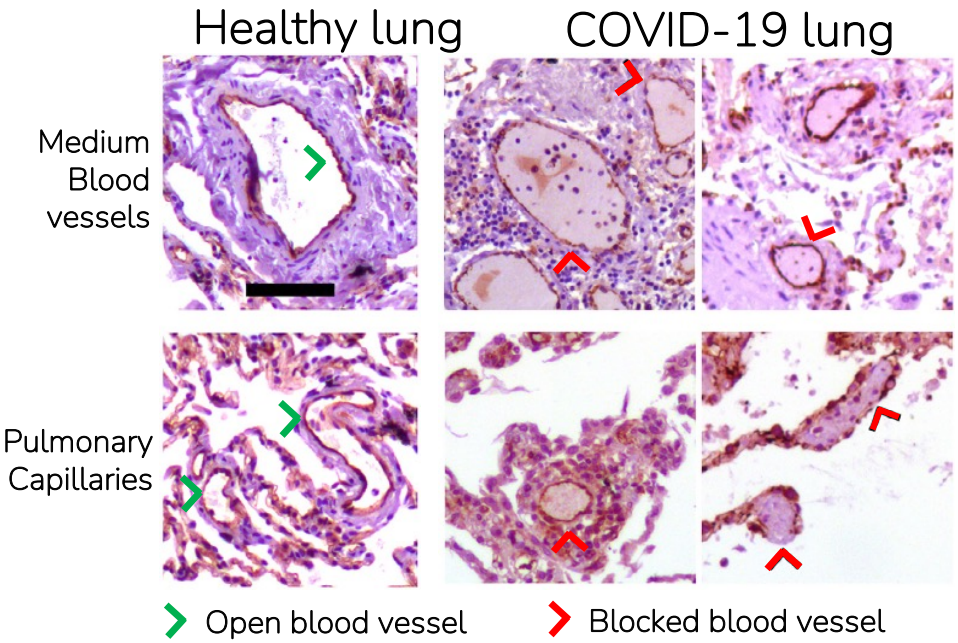
- SARS-CoV-2 viruses first enter respiratory cells by attachment of viral spike protein to ACE2.
- Imbalanced Renin-Angiotensin-Aldosterone-System (RAAS) due to reduced ACE2 and unfettered Angiotensin II action causes further collateral damage to lungs and other organs
- Injury to pulmonary blood vessels enables subsequent viral infection of vascular cells in the lung
- Leukocytes such as neutrophils invade the lung vasculature where they form NETs that provoke blockage of micro- and macro-blood vessels in the lung
- COVID-19 represents a hypercoagulable state that contributes to increased mortality
- In addition to vascular blockage, excessive inflammation promotes aberrant angiogenesis causing further lung damage and ultimately respiratory failure
- Combined with a cytokine storm these processes also operate in kidney, liver, brain and heart leading to multi-organ failure and death for COVID-19 patients with many survivors experiencing chronic symptoms i.e. LONG-COVID complications

Midkine-based drugs may block:

i) excessive Angiotensin II action;
ii) NET formation associated with blood clots; and
iii) aberrant pulmonary blood vessel formation

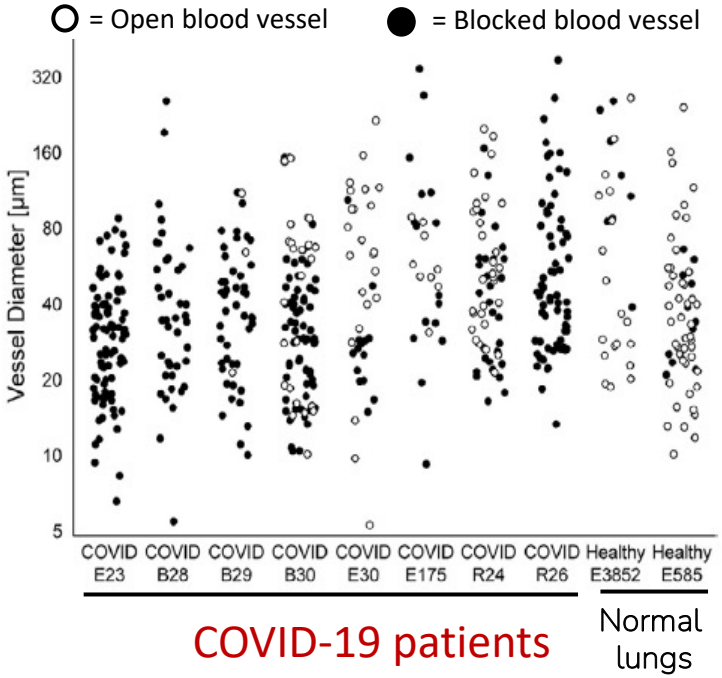
All of which can contribute to the Multi-organ dysfunction and mortality of severe COVID-19

COVID-19: Vascular Thrombosis



Neutrophils and aggregated Neutrophil Extracellular Traps (NETs) are abundant in blocked blood vessels in lungs, kidneys and liver of COVID-19 patients

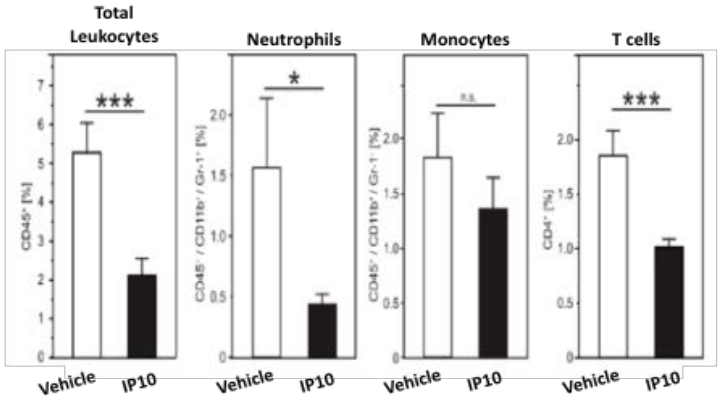
In lungs of COVID-19 patient, 80% of blood vessels are blocked compared to 22% in healthy lungs



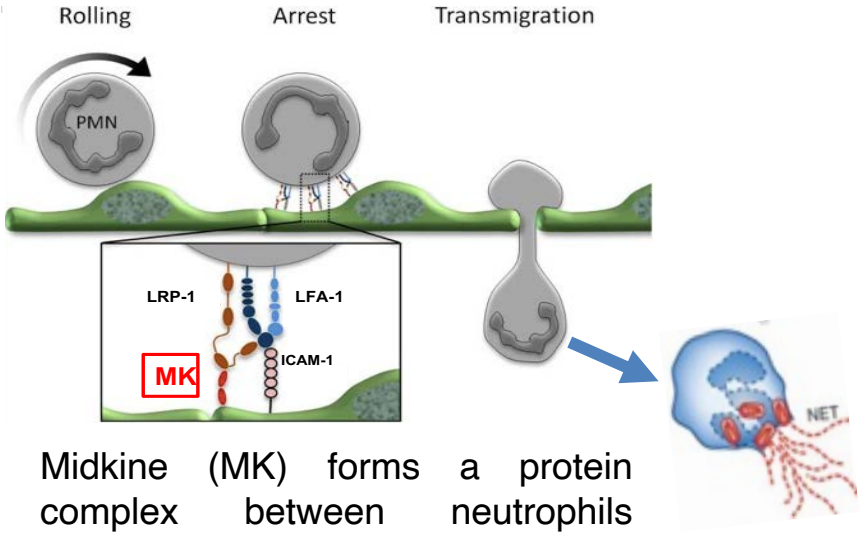
(Leppkes M *et al* 2020, *eBioMed*)

COVID-19: Midkine, inflammation & neutrophils

- Midkine promotes recruitment of inflammatory cells such as neutrophils from the circulation into sites of tissue injury such as lungs
- In autoimmune myocarditis Midkine antibody IP10 reduced infiltration into heart muscle of:
  - Neutrophils
  - Macrophages
  - T cells



Ludwig Weckbach (2019) *J Exp Med*



Midkine (MK) forms a protein complex between neutrophils (PMN) and blood vessels to initiate inflammation

In autoimmune myocarditis blocking Midkine reduced:

Neutrophil infiltration **by 75%**

NETosis of neutrophils **by 80%**

CANCER

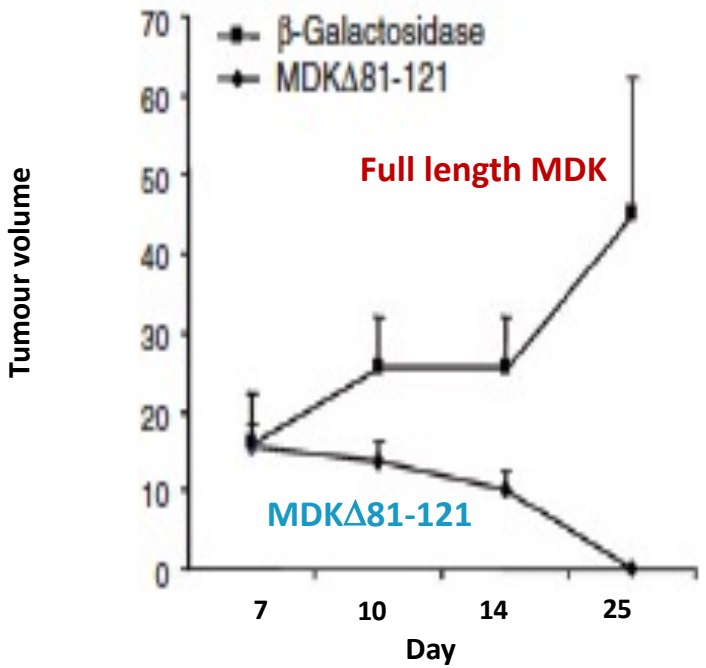
Cancer: Midkine-Based Drugs

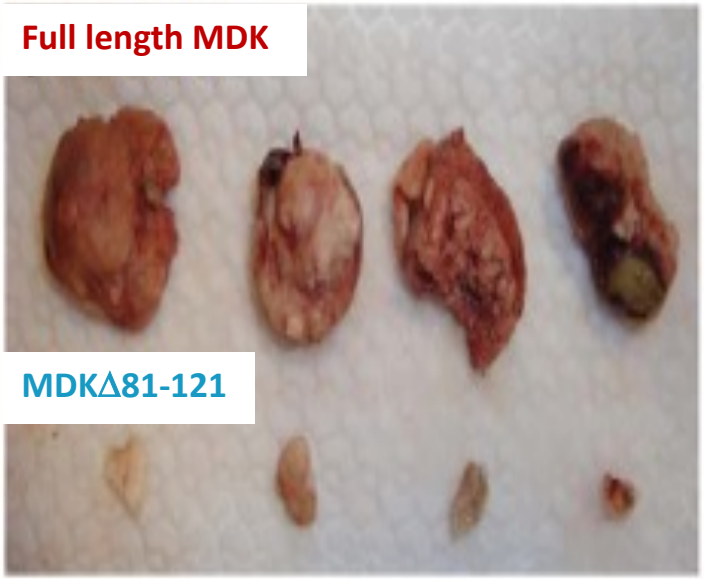
- Midkine is a growth factor/cytokine that is involved in most cancer types
- Midkine contributes to critical tumour processes:
  - Rewiring the tumour immune microenvironment
  - Promoting immunotherapy resistance to Yervoy, Keytruda and Opdivo
  - Metastasis and lymphangiogenesis
  - Promoting tumour cell survival/Inhibiting apoptosis
  - Tumour cell growth and invasion
  - Angiogenesis that establishes blood supply to tumours
- Midkine inhibition by gene silencing, small molecules, deletion proteins or antibodies prevents tumour growth and metastasis while restoring response to cancer immunotherapy
- Targeted delivery of Midkine oligonucleotide drugs to tumours represents a novel anti-cancer treatment strategy

Cancer: Example of Targeting Midkine on Tumour Growth

- Shortened form of Midkine protein (MDKΔ81-121) inhibits tumour cell proliferation while promoting apoptosis resulting in dramatic reduction in tumour growth

Neuroblastoma xenograft model



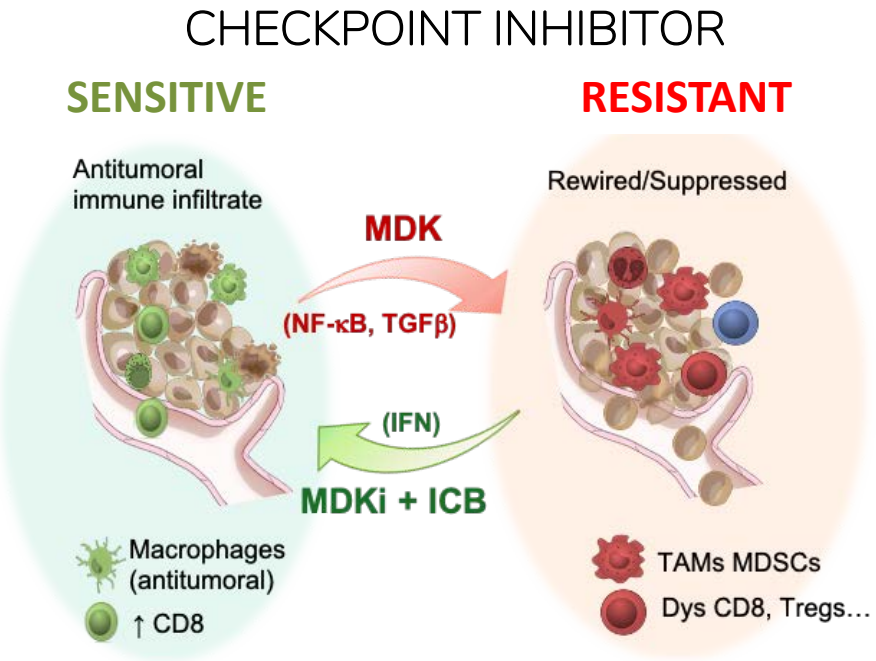


Cancer: Midkine Causes Resistance to Immunotherapy Drugs

LYRAMID

- **Midkine's immunomodulatory actions:**
  - disrupt macrophage and T cell functions, thereby promoting immune evasion in melanoma
  - drive resistance to immune checkpoint inhibitors Keytruda and Opdivo
  - only 50% of melanoma, 25% of kidney, bladder, lung and 10% of other types of cancer patients benefit from immunotherapy
- **Findings not restricted to melanoma:** Immunomodulatory actions of MDK operate in lung cancer, glioma, and renal carcinoma

Therefore Midkine inhibitors may improve the efficacy of immunotherapy for many cancer patients



MDK = midkine

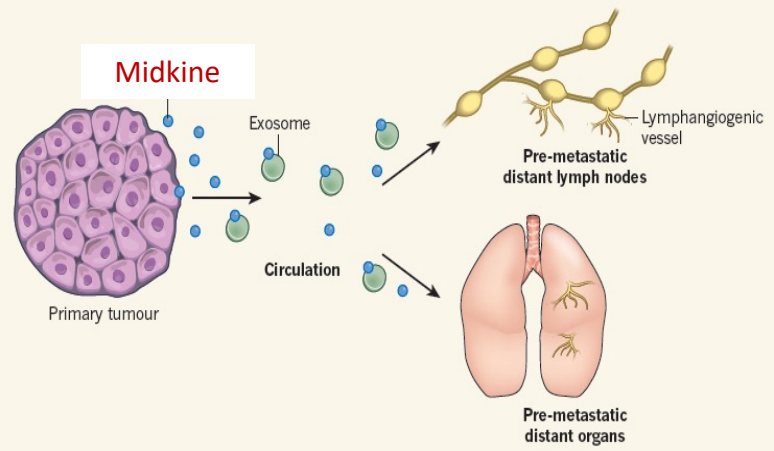
Midkine rewires the melanoma microenvironment toward a tolerogenic and immune-resistant state

Cerezo-Wallis *D et al* 2020, *Nature Medicine*

Cancer: Midkine & Melanoma Metastasis

RESEARCH NEWS & VIEWS

29 JUNE 2017 | VOL 546 | NATURE | 609

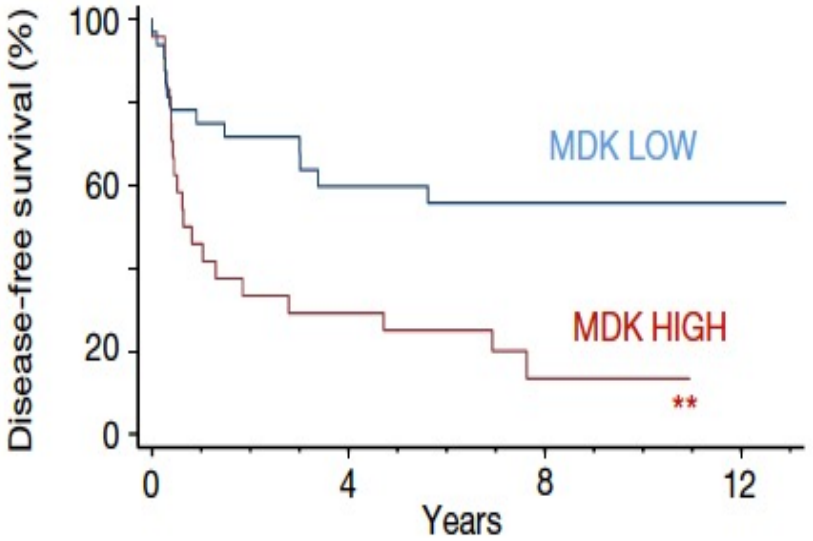


Tumour-derived Midkine (MDK) promotes lymphangiogenesis and metastasis in distal sites such as the lung independent of localized lymph vessels adjacent to the primary melanoma.

Whole-body imaging of lymphovascular niches identifies pre-metastatic roles of midkine

David Olmeda[1], Daniela Cerezo-Wallis[1], Erica Riveiro-Falkenbach[2], Paula C. Pennacchi[1], Marta Contreras-Alcalde[1], Nuria Ibarz[3],

676 | NATURE | VOL 546 | 29 JUNE 2017



Kaplan-Meier survival analysis shows melanoma patients with high levels of midkine (MK) in sentinel lymph nodes have worse outcome. Disease Free Survival = Time to first metastasis since diagnosis.

Cancer: Midkine Signalling Promotes Glioma

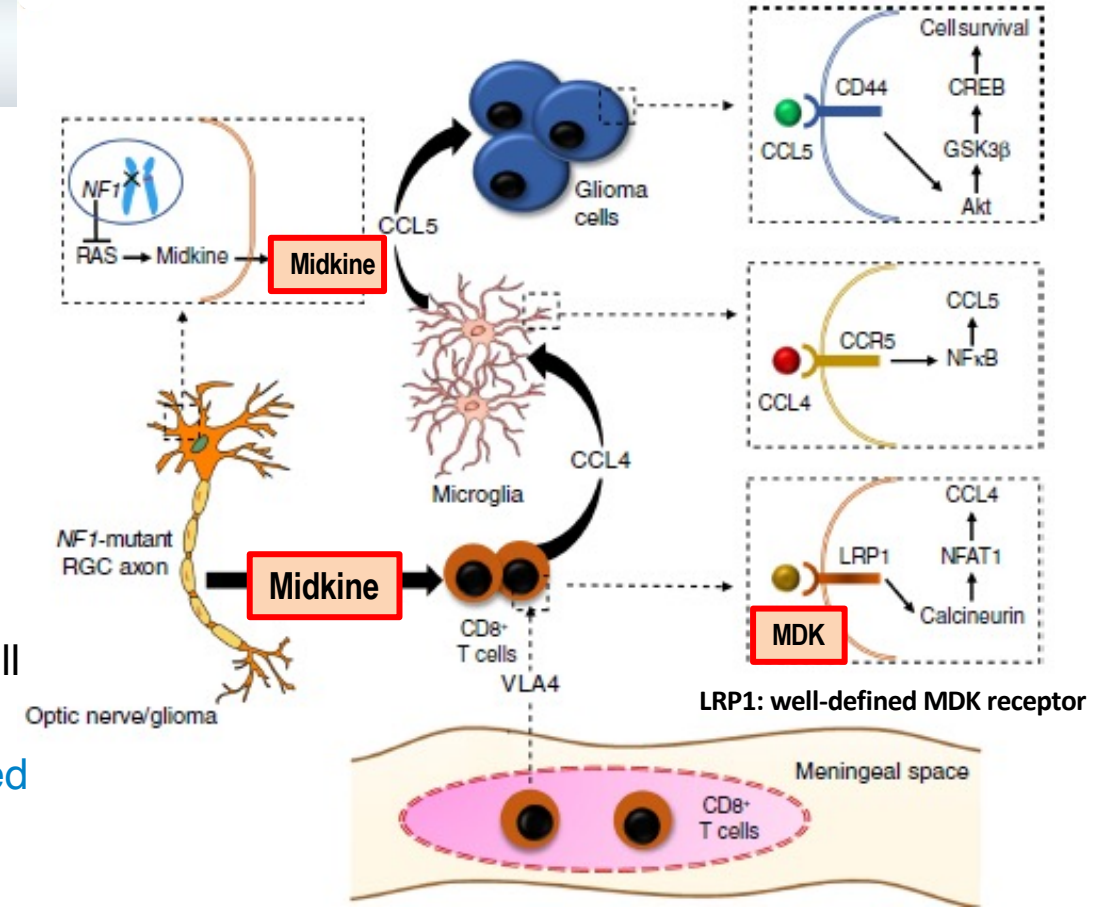
nature COMMUNICATIONS

Midkine activation of CD8+ T cells establishes a neuron–immune–cancer axis responsible for low-grade glioma growth

Guo X *et al* 2020, *Nature Communications* **11**:2177

- RAS promotes production of Midkine (MDK) in NF1 mutant neurons
- Neuron-derived midkine drives chemokine CCL4 release from CD8+ T cells
- CCL4 elicits CCL5 signalling by microglia to suppress glioma stem cell apoptosis

The neuron-immune-cancer axis initiated by Midkine culminates in enhanced glioma tumour growth



LRP1: well-defined MDK receptor

CHRONIC INFLAMMATION & AUTOIMMUNE DISORDERS

Chronic inflammation and Autoimmune Disorders: Midkine-Based Drugs

Blocking Midkine activity via MK gene silencing, therapeutic antibodies or with MK gene knockouts improves disease and preserves organ function via multiple important mechanisms:

- Reduced leukocyte recruitment to the sites of inflammation
- Reduced autoimmunity by expansion of regulatory T cells and suppression of autoreactive T helper cells
- Inhibiting neutrophil accumulation and activation (NETosis)
- Reduced inflammatory cytokines and chemokines
- Minimized development of fibrosis
- Reduced tissue remodeling

Chronic inflammation and Autoimmune Disorders: Midkine-Based Drugs

The therapeutic efficacy of blocking Midkine has been demonstrated in multiple in vivo models of:

- Renal Diseases
- Autoimmune disorders
- Chronic inflammatory heart failure
- Neurodegenerative disease
- Lung disease/ARDS
- Fibrosis

Inflammatory Disease. Lyramid proposes an initial clinical focus on treating Chronic Kidney Disease (CKD) . From a clinical perspective, blocking Midkine has significant advantages as a disease modifier over CKD drugs in late-stage development. The clinical and experimental evidence for Midkine in different forms of CKD is very strong.

Autoimmune disorders. Lyramid intends to evaluate rheumatoid arthritis, multiple sclerosis, SLE and Crohn's as potential autoimmune disorders for clinical deployment of its novel Midkine-based drugs.

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