N4 PHARMA

Nanogenics Acquisition

September 2023

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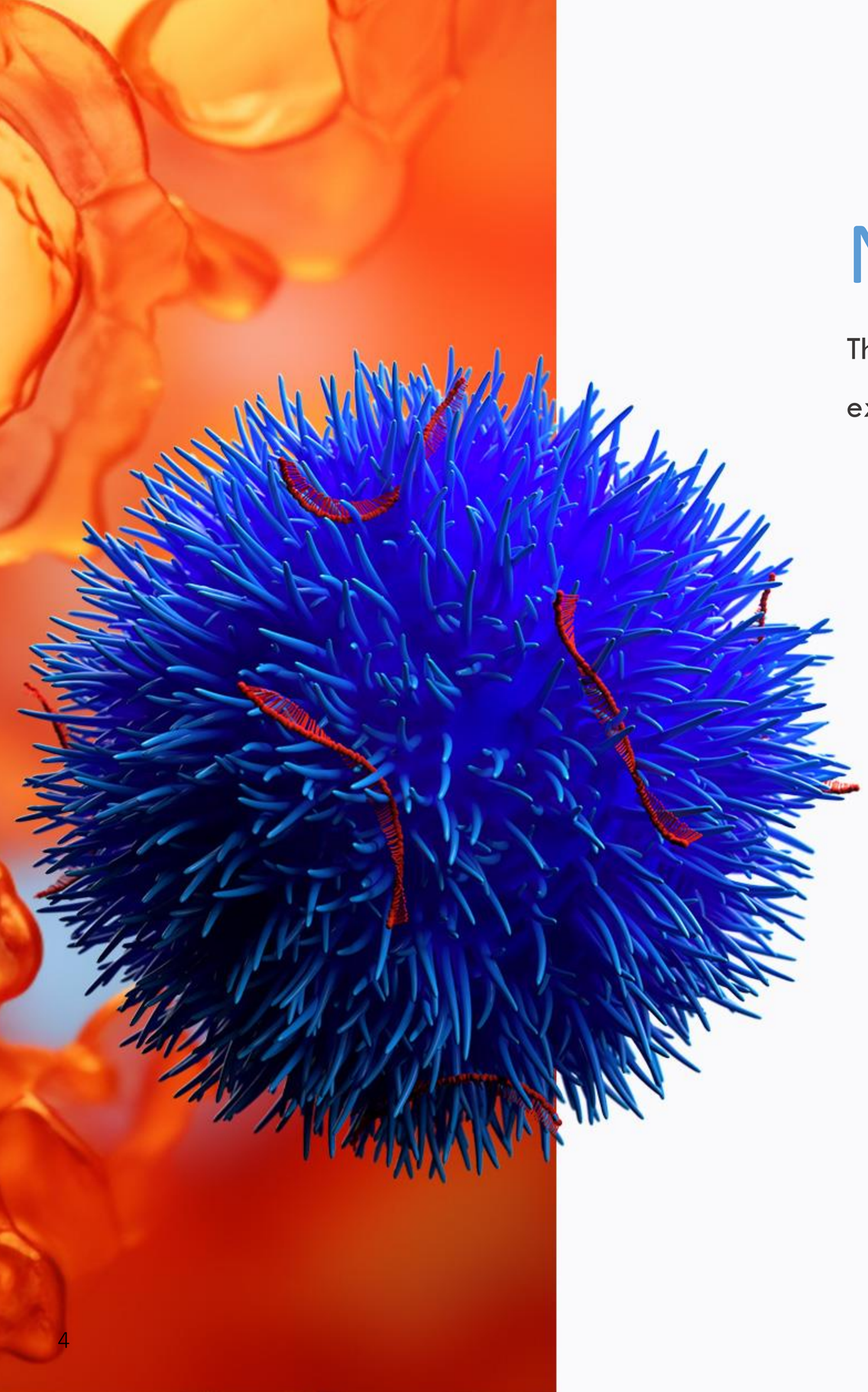
Introduction to N4 Pharma plc

- Pre-clinical stage specialist pharmaceutical company offering Nuvec®, a unique patented silica nanoparticle delivery system, for the reformulation and development of cancer treatments and vaccines using RNA

- Strong market and investor focus on the delivery of RNA therapy, following the success of the Covid vaccines

- Funded for proof of concept work investigating dual loaded siRNA nanoparticles to reduce cancer resistance

- Additional funding raised for acquisition opportunity to broaden participation in this exciting sector whilst maintaining cash resources for existing Nuvec® programme



Nuvec® System

The Nuvec® delivery system has unique characteristics compared to existing delivery systems:

- Unique spiky structure to allow binding of siRNA
- Simple process to load multiple siRNAs onto same nanoparticle
- Protects siRNA from enzymatic digestion and pH exposure
- Thermostability – Nuvec® can be dried, stored at room temperature, and reconstituted without degradation
    - No need for expensive cold chain storage
- Easy manufacture and chemical modification to allow cellular targeting

Nuvec mode of action

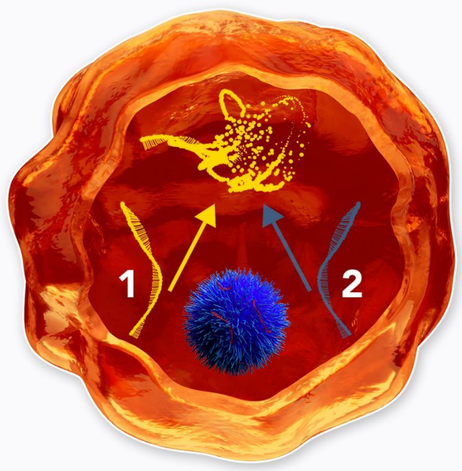
Click here to see a video of how Nuvec® works

Current Nuvec® R&D programme: Dual siRNA in cancer resistance

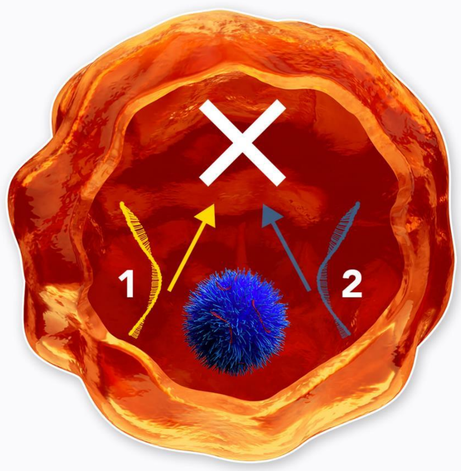
Nuvec® has ability to Deliver both siRNAs to same cell

By dual or mulitple siRNA loading on one particle

Potentially leading to a reduction in relapse during cancer treatments

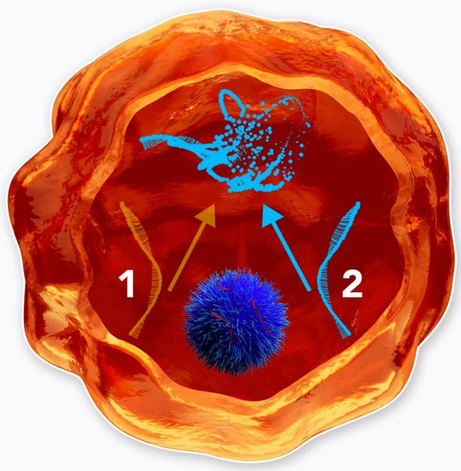


Cell Death by siRNA 1



Mutation causes resistance to siRNA => Cell growth

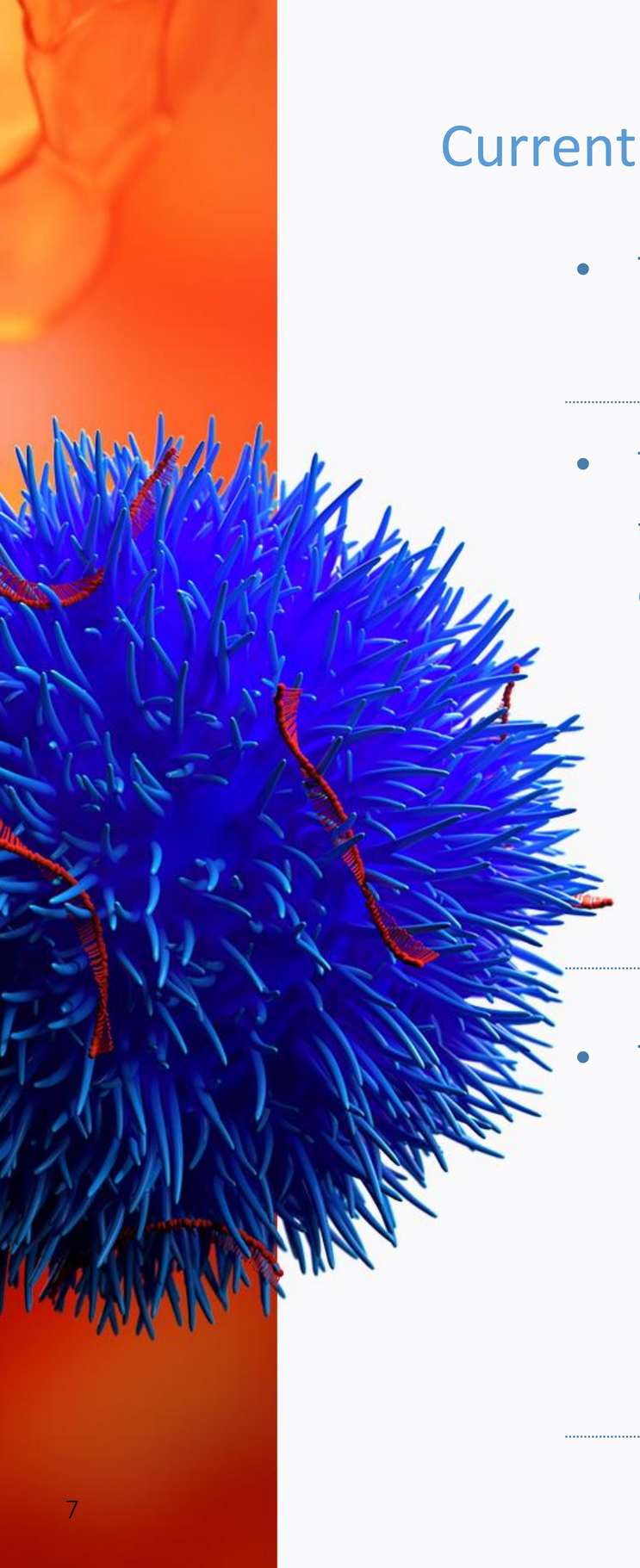
Mutated cell still dies if second siRNA in place
Single cell resistance can lead to tumour relapse



Chances of same cell becoming resistant to both siRNA is very slim, fewer or delayed relapses

- Combination therapy is the main means of preventing resistance (e.g. antibodies or small molecules)
- siRNAs could knock down two targets on one pathway, or two different pathways
- siRNA approach could be a safer and more efficacious alternative
- Potential to add targeting elements so Nuvec® can target specific cells

Current R&D: dual loading pre-clinical model



- Test dual loading of Nuvec®, with siRNA in a clinically relevant PC9 cancer cell model

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- Two siRNA compounds to be simultaneously loaded targeting both the epithelial growth factor receptor (EGF-R), to prevent cell growth and B-Cell Lymphoma 2 (BCL-2) to prevent cell mutation
  - Loading and characterisation of Nuvec with dual siRNA to determine maximum load
  - In vitro testing of gene silencing and biodistribution in PC9 cells
  - In vivo testing of preferred formulations using cancer model

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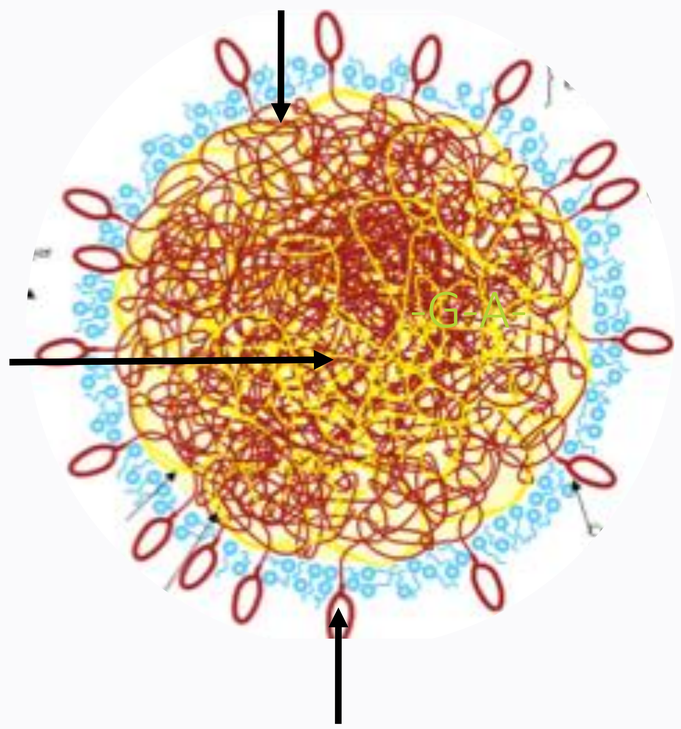
- To date have shown knockdown of EGF-R siRNA in vitro and cell apoptosis for BCL-2
  - Next steps complete response curve for BCL-2 knockdown (or other relevant target) and do in-vitro work on dual loading
  - In vivo testing of single and double siRNA doses

NANOGENICS opportunity

- Proprietary delivery technology
  - LipTide®: Patented peptide and lipid based delivery system for nucleic acids.
    - Peptide binds payload and targets specific cells
    - Lipid allows for efficient endosomal release into the cell
- siRNA Therapeutics
  - Proprietary siRNA sequence for reducing fibrosis
  - Delivery of siRNA using LipTide® for treatment after glaucoma surgery
  - Potential to create additional IP
- Directors believe this will lead to quick route to clinical trials and platform validation
- N4 taken 71.25% economic interest in Nanogenics for £250k investment
  (reducing to 63.75% on key milestones being hit)

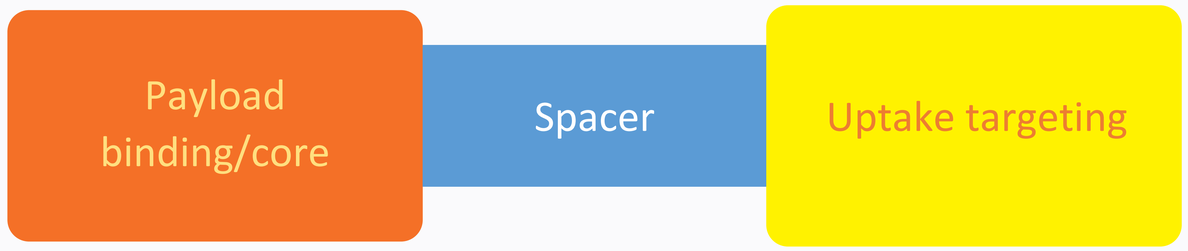
The LipTide® delivery platform is a peptide/lipid nanoparticle

Lipid
(10-20%)



Peptide core $[K]_{16}$
+ Payload
(80-90%)

Target cell
binding



The peptide mediates cell uptake as absence of targeting sequence dramatically reduces cell uptake

LipTide acts like an ‘artificial virus’

Glaucoma Commercial Opportunity[2]

- Total Glaucoma Treatment Market size exceeded USD 5.5 billion in 2021 and is expected to witness over 3.2% CAGR from 2022 to 2028

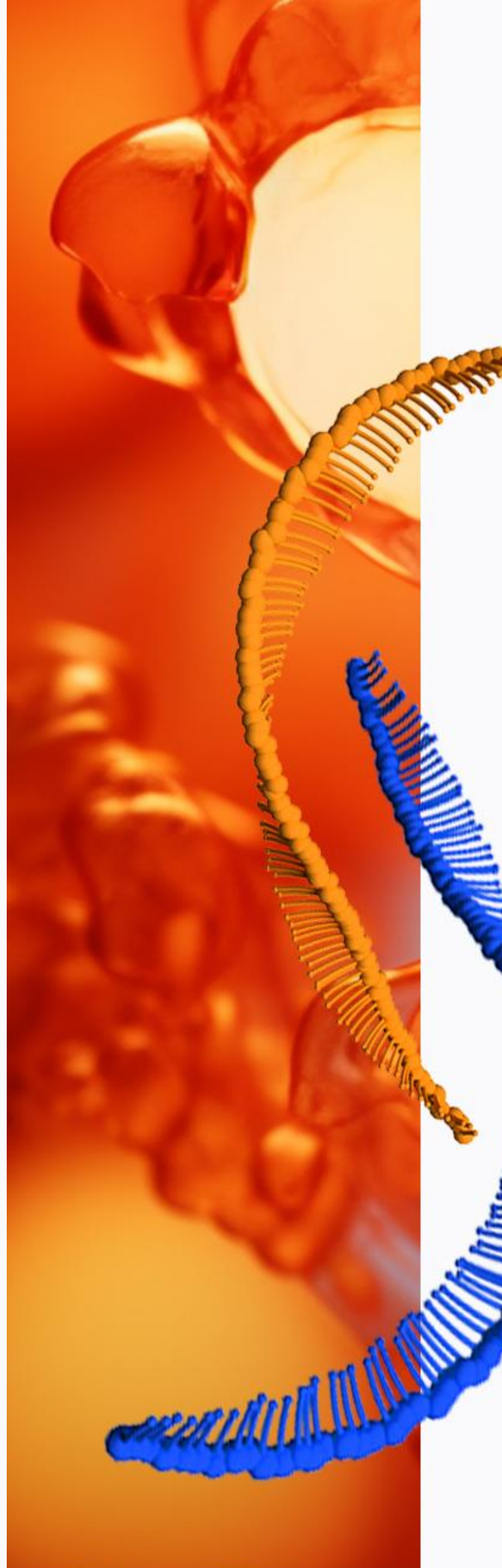
- In 2020, more than 75 million people worldwide were affected by glaucoma
    - Growing prevalence of glaucoma worldwide

- Growth driven by:
    - Advancements in therapeutic interventions
    - Rising patient pool of geriatric population
    - Increased clinical trials
    - Increased awareness of eye care / earlier diagnosis

Beyond Glaucoma, Commercial Opportunity

- The therapeutic target (MRTF) is linked to additional fibrotic indications including lung and liver[3]
- Unmet need for non-viral delivery vehicles for ophthalmology and beyond for both RNA and DNA payloads[4]. NanoGenics ECP105 delivery platform, Directors consider LipTide® may be one such platform and that:

- ECP105 delivers potentially both commercial product and LipTide® platform validation



[2] https://www.gminsights.com/industry-analysis/glaucoma-treatment-market

[3] Hetzler PT 3rd, Dash BC, Guo S, Hsia HC. Targeting Fibrotic Signaling: A Review of Current Literature and Identification of Future Therapeutic Targets to Improve Wound Healing. Ann Plast Surg. 2019 Dec;83(6):e92-e95. doi: 10.1097/SAP.0000000000001955. PMID: 31246672; PMCID: PMC6851445.

[4] Nucleic acid delivery: Are you developing what Big Pharma seeks? By Dr. Daniel Sieiro & Richard A. Brown September 2021

Glaucoma Problem

- Surgery (trabeculectomy) is widely used to lower intraocular pressure when pharmaceutical management is unsuccessful. This creates a channel into a reservoir (bleb) underneath the surface of the eye

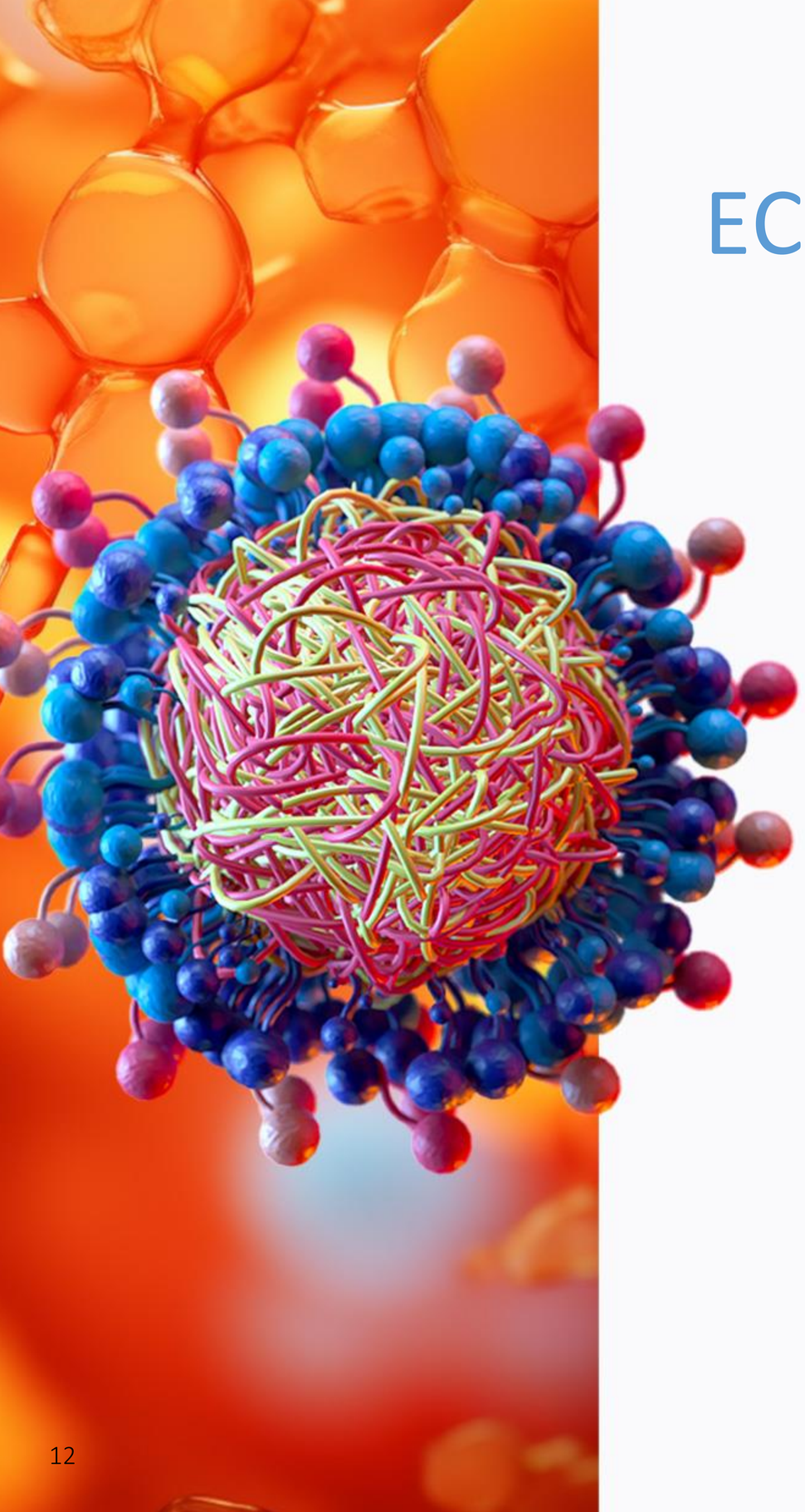
- The natural response of the body is to 'heal' this newly made drain. This fibrosis often leads to failure of the surgery and even with adjunctive anti-fibrotic therapy five year failure rates can be as high as 50%

- Repeat surgery to re-introduce the bleb is a common solution

- The current preventive measure against the fibrosis is to use, untargeted, cytotoxic anti-fibrotic drugs (Mitomycin C [a chemotherapy drug]) which have a poor safety profile and are used off-label in the US market

The Solution

- Directors consider the development of a breakthrough anti-fibrotic siRNA therapy to improve surgical outcomes and reduce re-admission rates for patients with severe glaucoma; ECP105 = MRTF-B siRNA delivered by the novel peptide delivery platform LipTide® could provide this solution



ECP105

- ECP105 is designed to enhance glaucoma outcomes post-surgery without toxic side effects

- In vitro proof of concept demonstrated siRNA inhibition of proteins related to fibrosis and ophthalmic indications

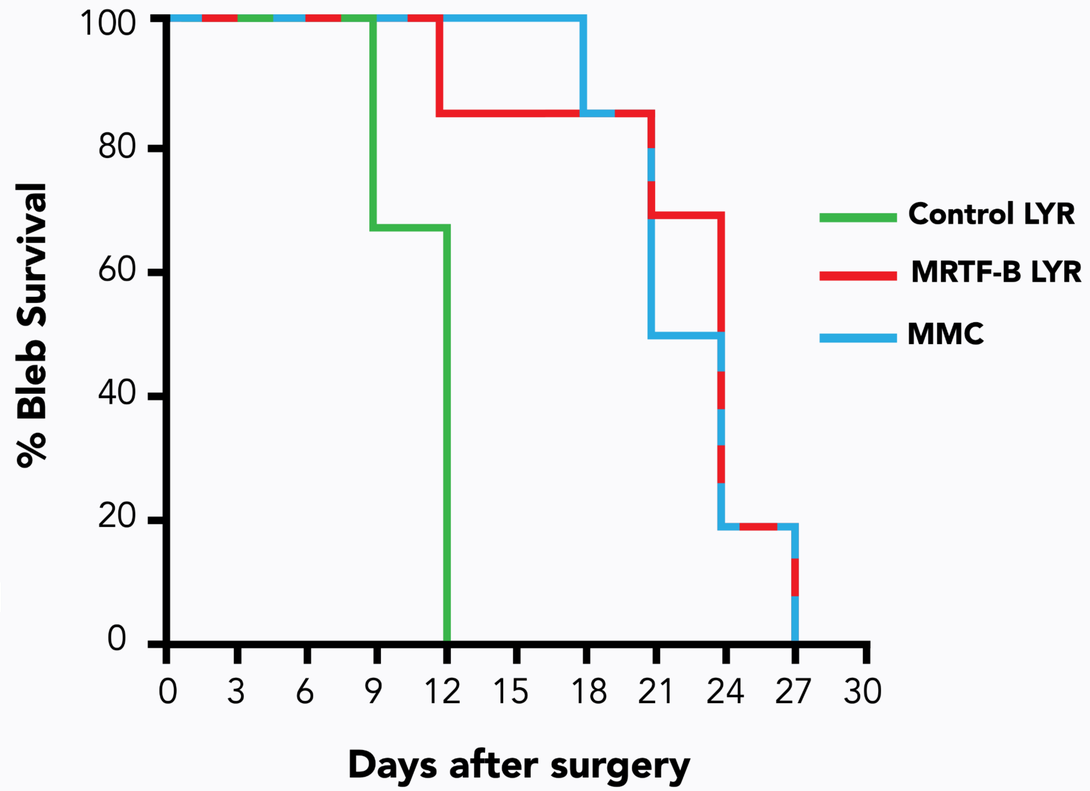
- Positive preliminary data for delivery (siRNA) and efficacy in vivo for prevention of glaucoma surgery failure

- The science plan will focus on generating new IP relating to;
  - Novel bi-species (rabbit/human) siRNA sequences
  - Formulation methodology/final product formulation/intended use of ECP105

ECP105 Preliminary data[5-7]

Following a single subconjunctival administration of LipTide® containing a MRTF-B siRNA (ECP105 prototype, MRTF-B LYR);

- MRTF mRNA expression reduced by 30%
- Immunohistochemistry revealed less scarring versus untreated
- Bleb survival increased from 11 days to 22 days
- A single dose of LipTide with 25ug MRTF siRNA had the same effect in this in vivo model of glaucoma fibrosis as the current standard treatment mitomycin C (MMC)



- Initial *in vivo* data highly promising,
- Need to optimise LipTide particle and siRNA sequence to ensure optimal formulation
- Progress to subsequent pre-clinical *in vivo* regulatory safety studies

[5] Fernando O, Tagalakis AD, Awwad S, Brocchini S, Khaw PT, Hart SL, Yu-Wai-Man C. Development of targeted siRNA nanocomplexes to prevent fibrosis in experimental glaucoma filtration surgery. *Mol Ther*. 2018;26(12):2812-22.

[6] Sanghani, Amisha et al. "Novel PEGylated Lipid Nanoparticles Have a High Encapsulation Efficiency and Effectively Deliver MRTF-B siRNA in Conjunctival Fibroblasts." *Pharmaceutics* vol. 13,3 382. 13 Mar. 2021, doi:10.3390/pharmaceutics13030382

[7] Grover, Davinder S et al. "Historical Considerations and Innovations in the Perioperative Use of Mitomycin C for Glaucoma Filtration Surgery and Bleb Revisions." *Journal of glaucoma* vol. 29,3 (2020): 226-235. doi:10.1097/IJG.0000000000001438

Nanogenics Scientific Team

- Professor Alex Mullen at the University of Strathclyde [UoS] (Formulation PI)
  - 30 years+ of academic experience in parenteral and colloidal drug delivery system development
  - Pharma consultant with extensive experience of being an expert court witness in patent litigation
  - Founder of two pharma start-ups, performing CSO roles and overseeing phase II clinical product development

- Dr Cynthia Yu-Wai-Man at King's College London [KCL] (In vivo PI)
  - Group Leader and Assistant Professor at King's College London
  - Developed ECP105 concept
  - Consultant Ophthalmic Surgeon and glaucoma specialist
  - Experience across in vitro/ in vivo models and clinical trials in glaucoma

- Dr Simon Newman (Project oversight and strategy)
  - Seasoned CSO with over 20-years in drug development
  - Experience across all modalities working with both academia and industry
  - 55 peer-reviewed publications and over 2900 citations

- Postdoctoral researchers will be used at UoS to undertake the formulation and in vitro testing and KCL to assist with the key in vivo studies.

Use of placing funds

£300k
for initial investment into Nanogenics
(£250k investment £50k loan*)

£50k
deal costs

Results of successfully completed pre-clinical project (12-15 months) expected to deliver the following:

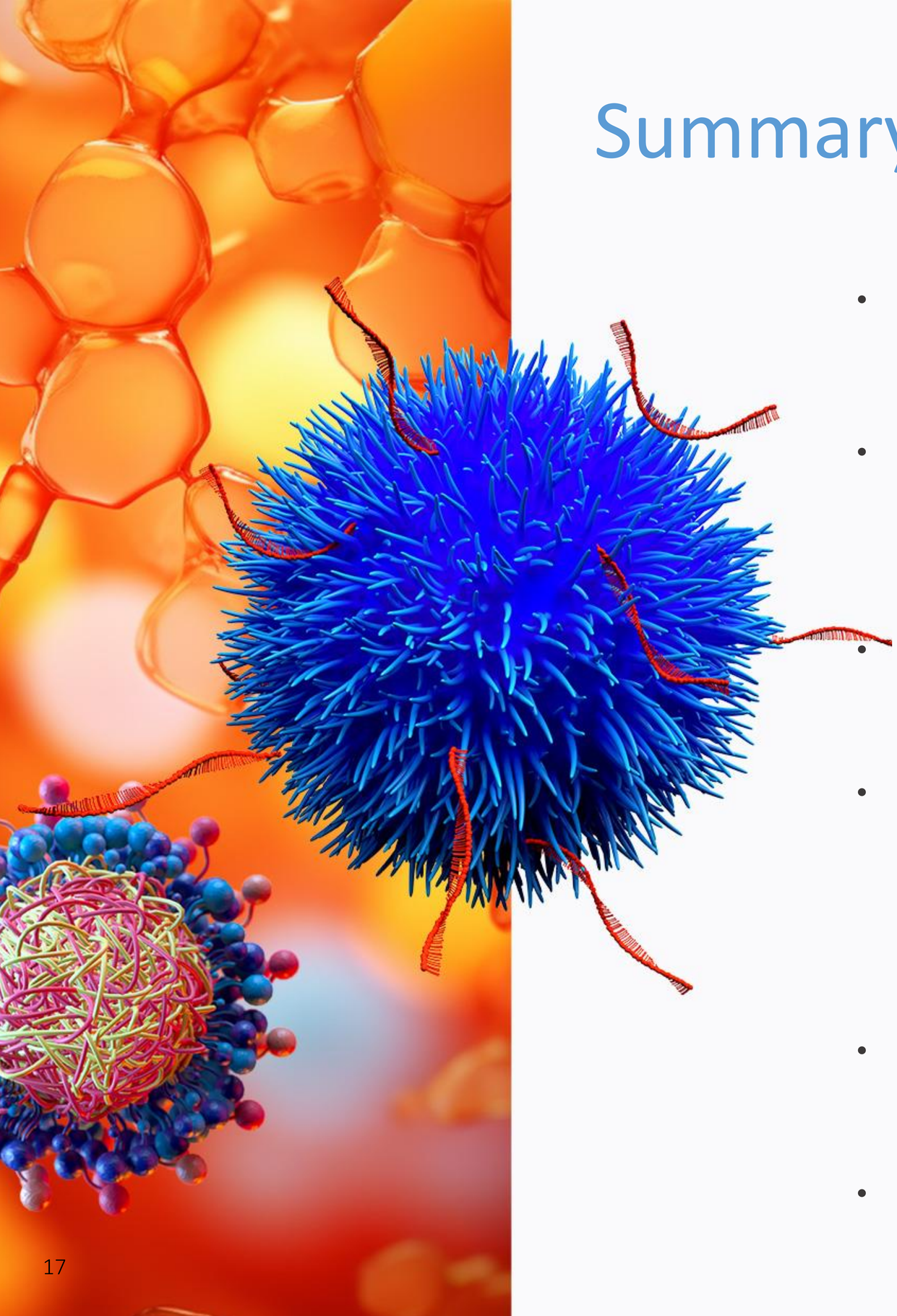
- Identified optimal lead formulation / siRNA sequence
- Demonstrated in vivo efficacy
- Transferred manufacture from manual lab process to GMP-compatible microfluidics platform
- Generated additional / new IP
- FDA pre IND and EMA/MHRA guidance discussions
- Be ready for rapid progress into GLP pre-clinical regulatory safety studies (outsourced CRO)

* 2 year discretionary loan at base rate repayable prior to any dividends

ECP 105 Next Steps

- Move ECP105 into First-in-Human studies
  - In vivo GLP-toxicity regulatory study
  - Preparatory work can start on this during our initial 12-months funding
    - Gathering quotes from leading CROs (CRL/Charles river)
    - Developing a SoW
    - Sourcing components and manufacturing pathway for ECP105 (GMP-compliant, doesn't have to be GMP)
    - Seeking EMA/FDA advice on pre-clin study and our proposed trial designs
  - First-in-Human studies
    - Transfer manufacture and source components to GMP
    - Prepare IB/IMPD
    - MHRA/EMA/FDA meetings/advice
    - Submit CTA
    - Start trial, 6-month dosing with up to a year follow up

- On strength of in vivo PoC data and new IP from the first 12-months work, look for partnering/licencing opportunities for LipTide®, ophthalmology first.
- Consider additional well-designed, low cost, in vivo PoCs to demonstrate LipTide® capabilities looking beyond fibrosis (nucleic acid vaccines / CAR-T / airway delivery)



Summary

- Strong market and investor focus on the delivery of RNA therapy, following the success of Covid vaccines
- Invest at early stage/ attractive valuation, in an siRNA product which meets an unmet clinical need in the growing market of ophthalmology
- Opportunity to target other anti-fibrotic markets which are far bigger (liver and lung)
- Complementary non-viral delivery technology, LipTide®
    - Non-viral delivery technologies are high in demand in the gene therapy space
- Technical synergies from developing programmes using both delivery platforms
- Preclinical and clinical validation will open up third party licencing opportunities for both Nuvec® and LipTide®

Thank you

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