

Pioneering Red Blood Cell Therapeutics

The future of medicine is in our blood

Scarlet's mission is to pioneer the use of **universal** red blood cells, unmodified or modified, for the benefit of human health



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Team Bios



Dr. Alistair Irvine (CEO)

Alistair has 30 years experience in biotech and medical device companies in senior R&D and corporate development roles. Prior to Scarlet he was Chief Business Officer of Kuros Biosciences AG which he took from 5 people to a commercial stage publicly quoted company (~\$1B Mkt Cap; Nov 2024).



Prof. Ash Toye (CSO)

Ash is a Professor of Cell Biology and Director of the NIHR Blood & Transplant Unit (BTRU) in red cell products at the University of Bristol. He is also a PI at NHS Blood & Transplant. Ash's research focusses on red blood cell development in health & disease, and synthetic biology approaches to engineer red blood cells for therapeutic applications.



Prof. Jan Frayne (CTO)

Jan is a Professor of Molecular Cell Biology at the University of Bristol. Her research is focussed on the development of in vitro systems to generate human erythroid cells from different stem cell sources, including adult, cord and iPSCs, and the molecular analysis of these cells.



Dr. Marjolein Meinders (Group Leader)

Marjolein ("MJ") has dedicated 15 years to study blood cell production, with the emphasis on red blood cells and megakaryocytes. Immediately prior to founding Scarlet she was a senior post-doctoral research in Prof Toye's lab. She also worked at Sanquin, the Dutch blood bank.



Why are red blood cells ideal therapeutic vehicles?

Safe

- **Mature red blood cells do not have a nucleus**
Very low tumorigenicity risk compared to nucleated cell therapies
- **Long history of safe red blood cell transfusion and well understood**
Excellent biocompatibility and predictable biodistribution

Enduring

- **Lasts 120 days in circulation**
Amenable to dosing every ~3 months

Smart

- **Payload is hidden from the immune system**
Allows broader range of payloads
- **Red blood cells can be engineered for a range of therapeutic applications**
Flexible platform that can generate a broad pipeline of therapeutic products

Pervasive

- **Red blood cells can travel anywhere in the body**
Potential to reach any tissue or organ



Revolutionizing the field

One platform, many applications

**Bioreactors for treatment of
metabolic disease** \$60B

Immunotherapy

(artificial antigen presenting cell, autoimmune disease treatment)

\$280B

Protein delivery vehicle

(enzyme replacement therapy)

\$10B

Specialist transfusion indications

(sickle cell, rare blood group recipients)

General transfusion indications

(avoiding the requirement for blood typing and donors)

\$7B

Key challenges for development of RBC therapies

All approaches to date have used cells from blood donations as the starting material for manufacturing



Scalable
manufacture

- Production from donated cells limits batch size
- **No scalability**



Reproducible
manufacture

- **Batch to batch variation** in final product
- Not all donors' cells act the same



Blood group
matching

- Product and patient **blood group matching required**
- O- blood group not good enough match



Sufficient loading of
red blood cells with
therapeutic proteins

- **Difficulty obtaining sufficiently loaded efficacious RBCs**

Scarlet's solutions

Production from cell lines

- Scarlet has **exclusive IP on the cell line generation** technology (only methodology known to date for RBC cell line production)
- Team has published paper on the world's best RBC producing cell line
- Manufacturing process more analogous to a biologic than a cell therapy



**Scalable
manufacture**



**Reproducible
manufacture**

Production of highly universal RBC

- Highly universal RBC appropriate for vast majority of the population
- **Off-the-shelf product** (one product for all patients)
- Not achievable when using donated blood as starting material – needs cell line technology



**Blood group
matching**

Technology for ensuring maximal RBC activity

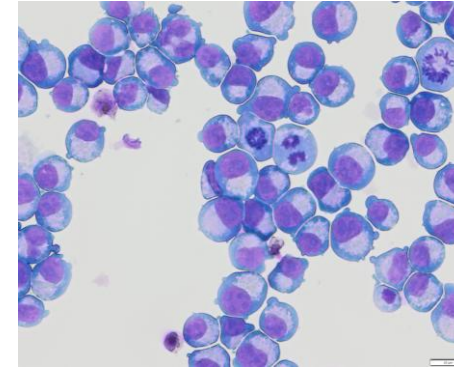
- **Exclusive IP to ensure high level therapeutic protein level in RBC**



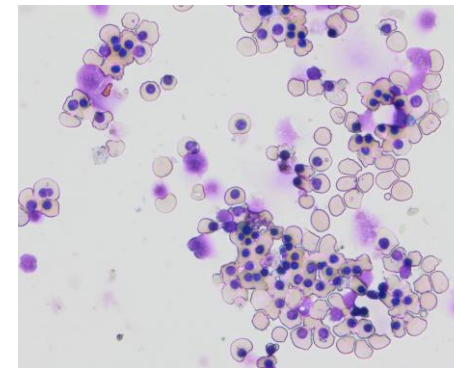
**Sufficient loading of
red blood cells with
therapeutic proteins**

Scarlet is world-leading in the development of universal RBC-producing cell lines

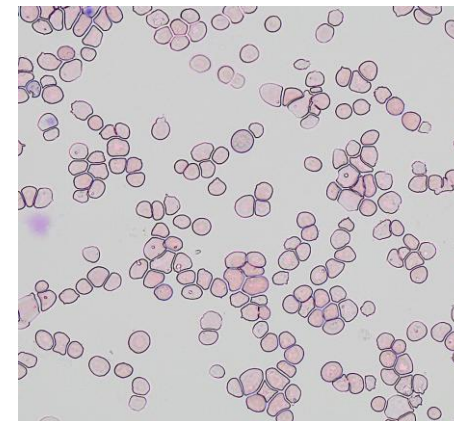
- Proprietary method for cell line creation
- Unique access to rare highly universal donors (to generate cell lines from)
- Cell line generation process is applicable to GMP
- >50 RBC producing cell lines generated to date



Expanding
cell line



Differentiating
cell line



Purified
immature
RBC

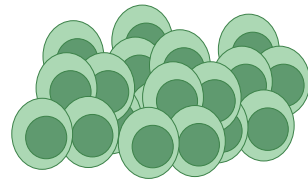
Our scalable manufacturing process for lab-grown RBCs



Thaw cell
bank



No blood donors required,
frozen universal RBC producing
cell bank is the starting material



Expand
cell line



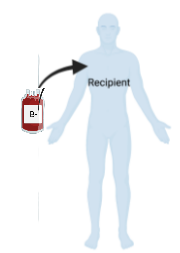
Each run from cell
bank so high degree
of reproducibility



Differentiate into
RBC and purify



Unlimited scale – cell
line can be expanded
indefinitely



Administer to
any patient



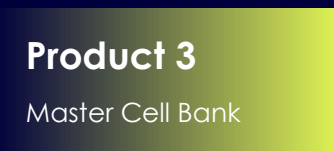
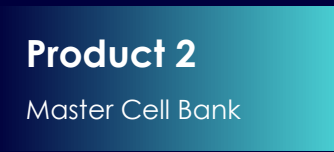
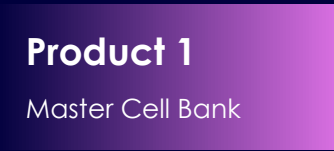
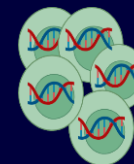
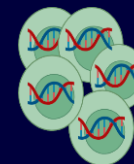
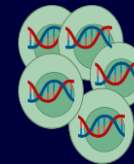
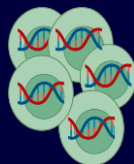
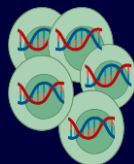
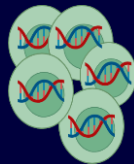
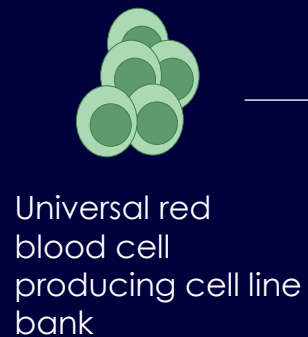
“One product for
all” product can
treat any patient

Our platform doesn't just simplify production, it unlocks the potential of engineered therapeutic RBCs

Genetic engineering of cell population. Multiple modification steps are possible to create complex products.

Selection of clone with optimal RBC yield and activity.

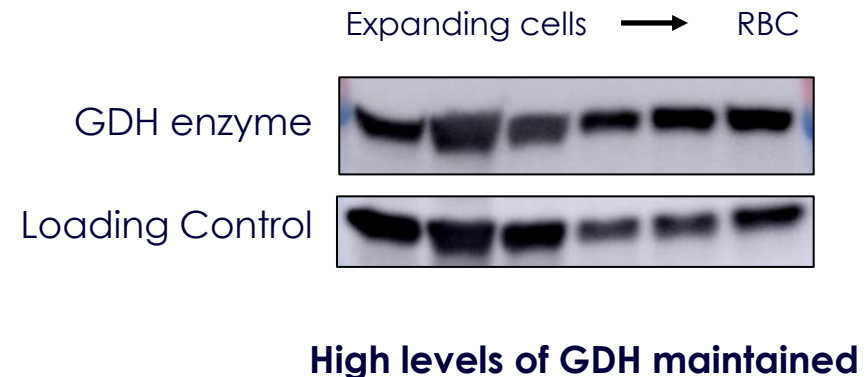
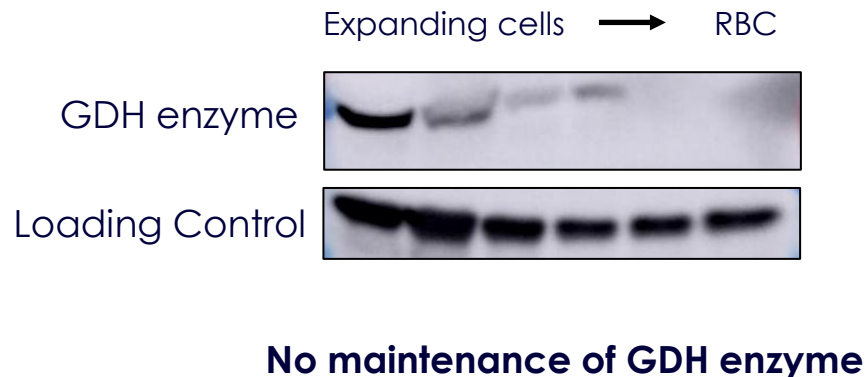
Generation of product producing Master Cell Banks.



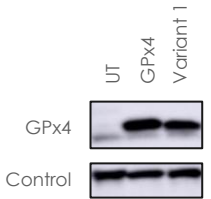
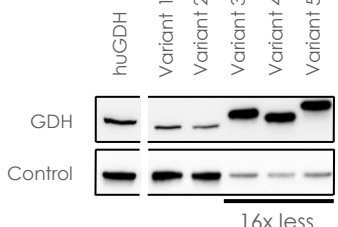
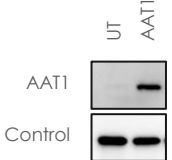
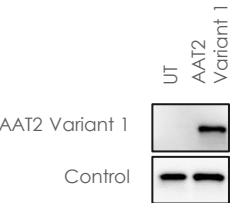
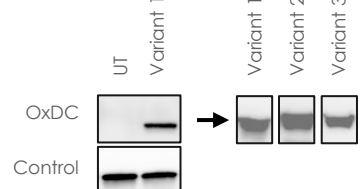
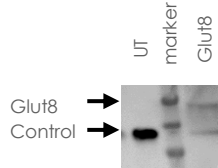
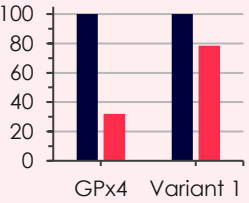
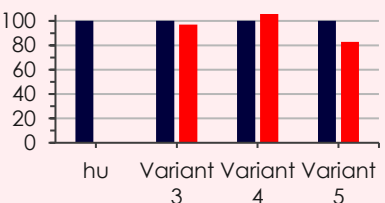
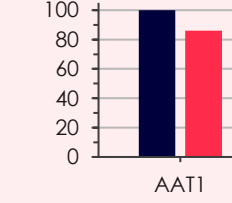
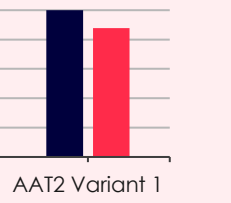
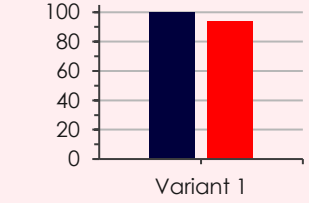
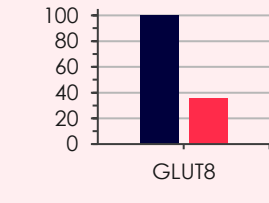
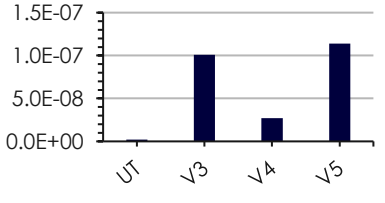
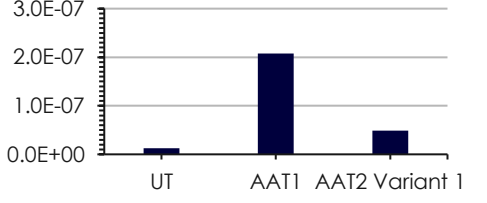
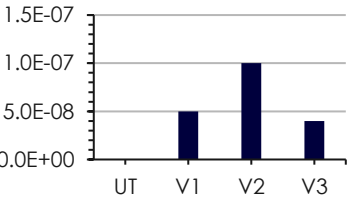
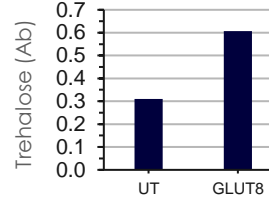
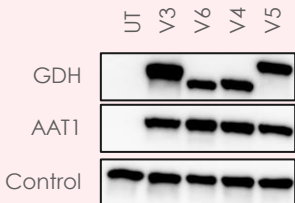
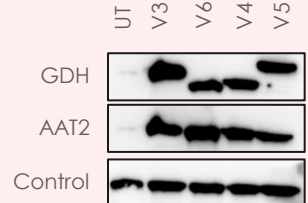
Our proprietary technology overcomes barriers to the creation of high activity therapeutic RBCs

Many proteins are normally lost during the cell differentiation process into RBCs, and mature RBCs cannot make new proteins...

...however, Scarlet has proprietary technologies to maintain specific proteins during differentiation, unlocking new therapeutic opportunities.



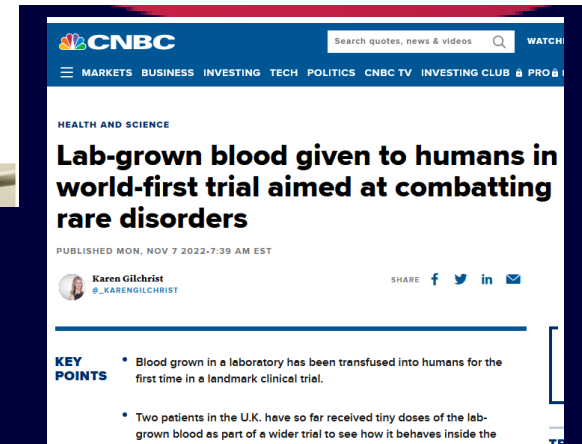
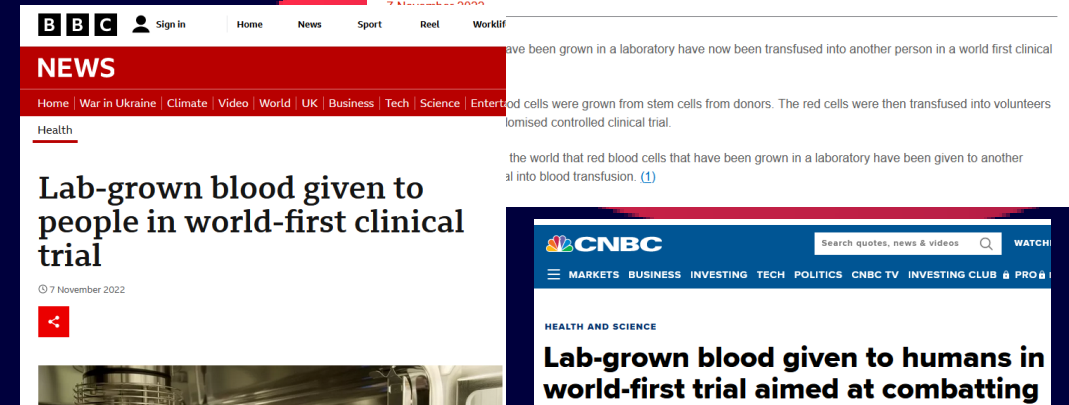
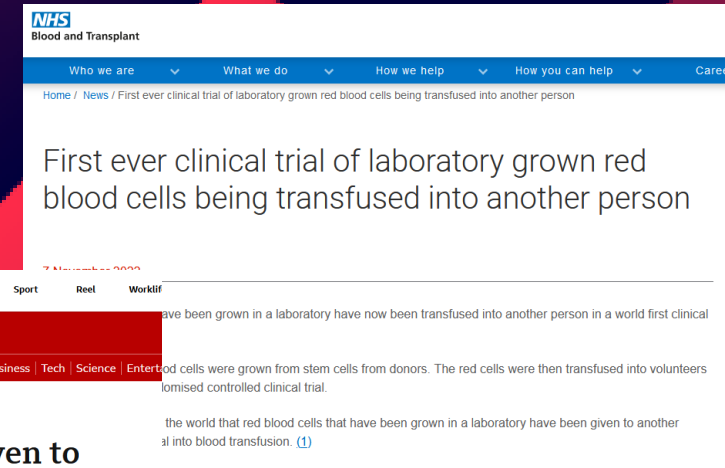
We have demonstrated retention and activity for a wide range of protein types

Type of Protein	Cytoplasmic	Mitochondrial	Cytoplasmic	Mitochondrial	Bacterial	Membrane
	GPx4 - antioxidant	Glutamate Dehydrogenase (GDH)	Alanine Aminotransferase 1 (AAT1)	Alanine Aminotransferase 2 (AAT2)	Oxalate Decarboxylase (OxDC)	GLUT8 – Trehalose transporter
Expression						
Retention (red bars – percentage retention upon differentiation compared to progenitor level)						
Activity (enzyme activity per cell)						
Co-expression of multiple proteins (Variants are GDH variants)						

We have experience in clinical grade lab-grown RBC production

The RESTORE clinical study

- Prof Ash Toye, Scarlet's CSO, is a PI
- Compares lab-grown RBC survival with donated red blood cells in human volunteers
- Experience of production of clinical grade lab-grown RBCs
- Protocol stated the study may be stopped for safety concerns or if the half-life is significantly worse for the manufactured cells
- **Conclusion:** At the interim analysis there are no safety concerns and the half-life of the lab-grown cells is promising



Scarlet's IP position

Exclusive License:

Scarlet has an exclusive license to the patent application and the know-how covering the method of retaining therapeutic proteins expressed in RBCs

Exclusive Access:

Scarlet has an exclusive research license to other BEL lines (BEL-P & BEL-C)

Exclusive License:

Scarlet has an exclusive license covering the cell line generation technology

Unrivalled know-how:

Scarlet has an exclusive commercial license to BEL-A cells and the know-how related to generating them

Exciting future:

Scarlet will file IP related to specific constructs, product candidates, cell lines and production methodologies

All competitors rely on donor-derived red blood cells.

These are difficult to manufacture reproducibly and at scale. They also require blood group matching, which requires personalised tailoring of product with patient.

Encapsulation



- **Ataxia Telangiectasia** candidate therapy in phase 3
- Preclinical stage **enzyme replacement therapy** programs

Genetic engineering



- Flagship Ventures company
- Raised \$241m in IPO in 2018 (Mkt Cap - **\$1.7B 2018, \$2.4B 2021**)
- Various candidate therapies **for relapsed/refractory or locally advanced solid tumors** progressed into clinical studies
- After poor clinical results company has now **ceased activities**

First indications focusing on high unmet clinical need

Hyperammonemia

Causes:

- Urea cycle disorders (1:35,000⁽⁴⁾)
- Cirrhosis (1:400)

High Unmet Need (Urea Cycle Disorders):

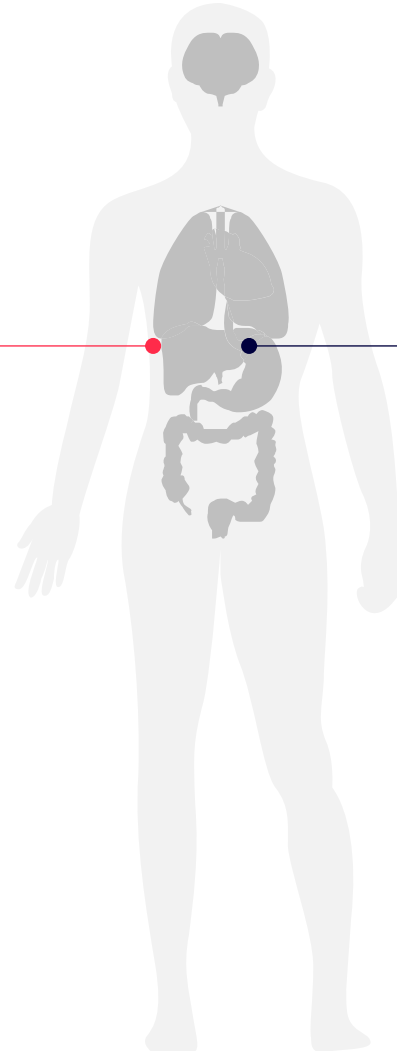
- Neonatal onset mortality 24%⁽³⁾
- Late onset mortality 11%⁽³⁾

Market Leading Treatment: Ravicti®

- Cost per annual treatment course ~\$700'000⁽¹⁾
- Sales in US in 2022 : \$326M⁽²⁾, CAGR 12.5%

Potential Market for Urea Cycle Disorders only:

- US patient population estimated at ~5'000
- At annual treatment cost of \$500'000 the **potential US market would be \$2.5B**



Hyperoxaluria (oxalosis)

- **Primary Hyperoxaluria:** Three types, each caused by genetic defects in different genes
- **Secondary Hyperoxaluria:** caused by excess consumption of oxalate or precursor molecules, gut microflora imbalances, and bowel disease

High Unmet Need:

- Surgical removal of kidney stones
- Liver, kidney or dual liver/kidney transplantation

Current treatments:

- Focused on Primary Hyperoxaluria 1 – Oxlumo™, Pyridoxine

Potential Primary Hyperoxaluria Market:

- It has been estimated that there are 5'000 individuals in the US⁽⁵⁾, although estimates vary
- 5'000 individuals with an annual treatment cost of \$400'000 would give a **potential US market of \$2B.**

(1) [FiercePharma, Pharmaceutical Technology.com, STATnews](#)

(2) [Horizon Annual Report](#)

(3) [Batshaw et al.](#)

(4) [Summar et al.](#)

(1) [MedlinePlus](#)

(2) [FiercePharma](#)

(3) [Canadian Journal of Health Technologies](#)

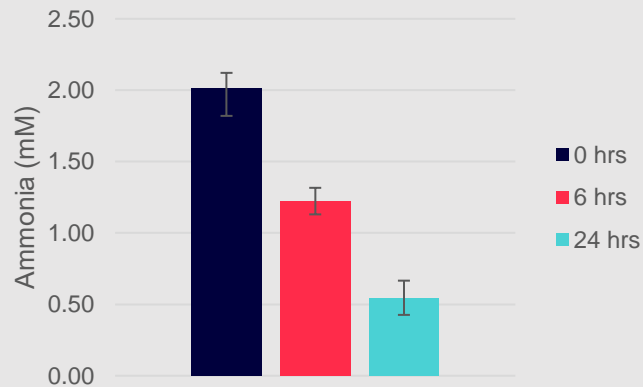
(4) [Alynam Annual Report](#)

(5) [Cleveland Clinic](#)

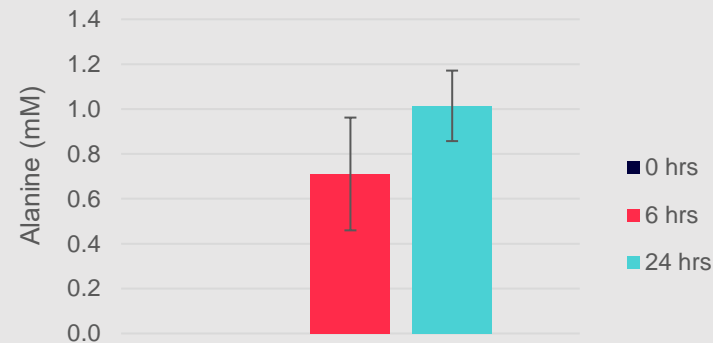
Proof of Concept for Hyperammonemia

- Reticulocytes that converts ammonia to an amino acid

Ammonia reduction by reticulocytes



Amino acid production by reticulocytes



Cellular activity

nmol/min/cell	2.73E-07
nmol/day/cell	3.93E-04

- Normal systemic ammonia concentration $<50\mu\text{M}$, severe hyperammonemia $\sim 200\mu\text{M}$
- To reduce systemic ammonia by $160\mu\text{M}$ in 24hrs would require $\sim 2 \times 10^9$ reticulocytes

Roadmap to significant value generation:

1

Clinical proof of concept for the platform in high unmet need metabolic disease indications

2

Expand platform into other high value therapeutic indications via internal programs and/or through partnerships

3

Further expand platform into transfusion indications through internal programs and/or partnerships

Potential exits and valuation comparators:

1

Acquisition by
therapeutics company
(Biotech/Pharma) prior to
clinical data

e.g. \$1.5B – Poseida
Therapeutics
acquisition by Sanofi

2

Acquisition by
therapeutics company
(Biotech/Pharma) at
the clinical stage

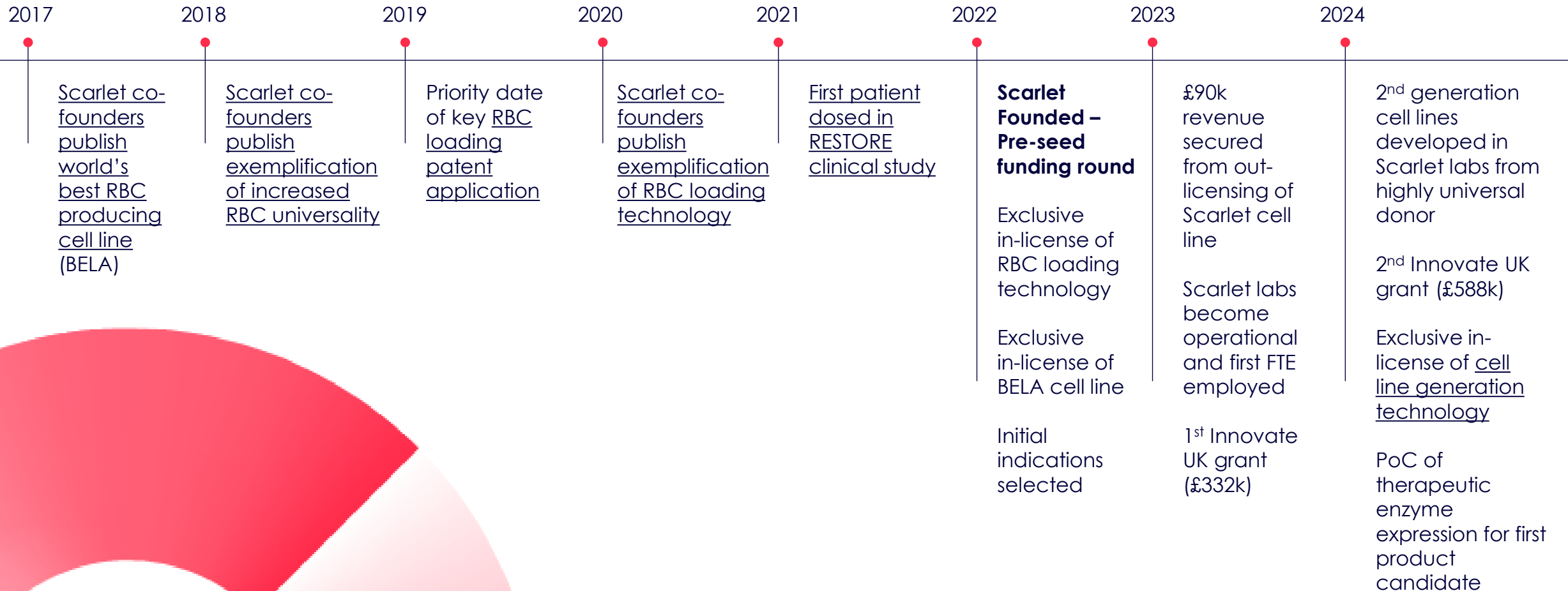
e.g. \$1B – Gracell acquisition
by AstraZeneca

3

Initial Public Offering
(IPO)

e.g. ~\$2B – Rubius Therapeutics
(no clinical data)

We have been pioneering RBC technologies for over a decade



Financing requirements and milestones

£5M

in equity financing

Funding will last **24 months** and achieve the following milestones:

- In vivo exemplification data for, first product candidate
- Generation and selection of parental manufacturing cell line for universal RBC
- Generation of manufacturing cell line for first product candidate
- Determination of regulatory package for first clinical study
- Expansion of IP portfolio

Summary

Pioneering a new therapeutic modality of **universal red blood cells for therapy and transfusion**

Game-changing cell line platform **enabling scalable and reproducible universal red blood cell production**, revolutionising manufacturing and greatly expanding platform applicability

Exclusive IP position on red blood cell producing cell line technology and technology for retention of therapeutic proteins to **ensure maximal therapeutic effect and “one product for all” product**

In vitro proof of concept for two metabolic disease indications

Experience with GMP production of lab grown red blood cells and red blood cell-based clinical studies; NHSBT/NIHR funded RESTORE clinical trial is ongoing

Broad applicability to **multi-billion dollar markets**

Thank you

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Scarlet
Therapeutics