InnateRepair

Revolutionizing Cancer Treatment:

Targeting the Hes3 Axis with siRNA technology in glioblastoma and other cancers

PITCH DECK

https://www.innaterepair.com/

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Problem Statement

Glioblastoma's aggressive nature, poor survival rates, and severe and rapid loss of life quality emphasize the urgent need for more effective and innovative therapeutic approaches

The Deadliest Brain Cancer

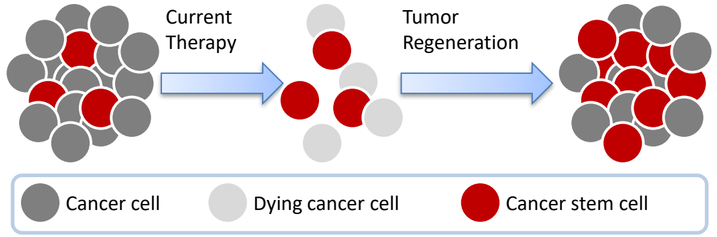
- Glioblastoma accounts for 45% of all primary malignant brain tumours with an annual incidence rate of approximately 3.21 per 100,000 people.
- Despite aggressive treatment, the median survival is around 12-15 months and tumor regrowth is inevitable.

Current & new therapeutic approaches are inadequate

- Standard care (surgery, radiation, and temozolomide chemotherapy) typically extends survival by only a few months. Costs range from $184K - $268K per patient.
- Recent therapies like Optune offer only marginal benefits while being cumbersome and expensive.
- New chemo (lomustine, carmustine wafers), immuno-oncology (checkpoint inhibitors, CAR-T, oncolytic viruses, cancer vaccines), targeted therapies (avastin, anti-EGFRIII, etc.), tumor treating fields etc., offer no solution.

The Underlying Problem

- The tumor contains **Cancer Stem Cells (CSCs)**.
- CSCs use an **alternative signaling pathway** to grow, which is not targeted by current therapeutics, so they evade therapy and regenerate the tumor.



Our Breakthrough

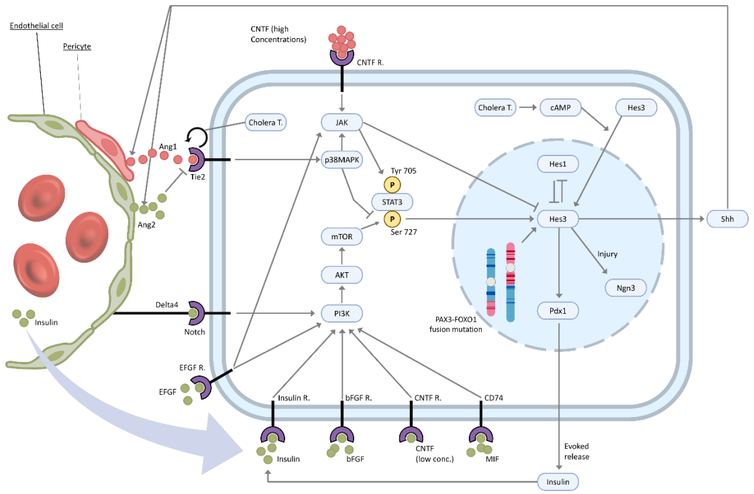
- Our R&D focuses on this novel signaling pathway, the **Hes3 Axis**, that controls Cancer Stem Cells.
- We elucidated the Hes3 Axis and identified targets and putative treatments.
- Earned our place in the 2024 “**Ones to watch**” list of the **Nature Awards Spinoff Prize**.

Our Solution

Identifying the Hes3 Axis

- Tissues contain **endogenous stem cells (eSCs)** which become **specifically activated** after injury and contribute to regeneration through a **specialized signaling pathway** instead of generic growth pathways that every cell uses.
- We identified the **Hes3 Axis**, and **pharmacologically activated it** to induce **disease modification** in rat models of **ischemic stroke** & **Parkinson's disease**.

  → The **first demonstration of disease modification** by targeting eSCs.



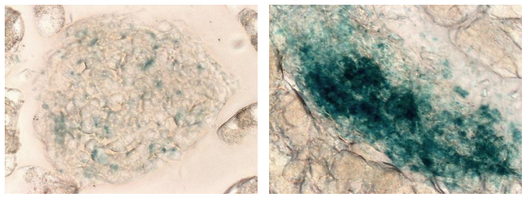
The Hes3 Axis, in its current form

Androutsellis-Theotokis et al, Nature, 2006
Androutsellis-Theotokis et al, Cold Spring Harb SQB, 2008
Androutsellis-Theotokis et al, PNAS, 2009

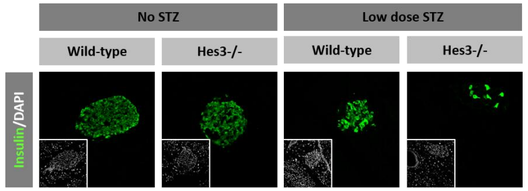
Validation Beyond the Brain

- We looked for the Hes3 Axis **beyond the brain**, in the **endocrine pancreas**, a highly plastic organ. We showed that:
  - **Hes3 is expressed** in the pancreatic islets.
  - **Damage** induces **massive Hes3 expression**
  - **Lack** of Hes3 **disrupts regeneration.**
- Therefore, the Hes3 Axis is **not confined to the brain**, it is **induced by damage**, and it is **necessary for efficient regeneration**.

No injury **Injury (10 days after)**



Damage to the pancreatic islets induces Hes3 expression



Hes3$^{-/-}$ mice fail to regenerate properly

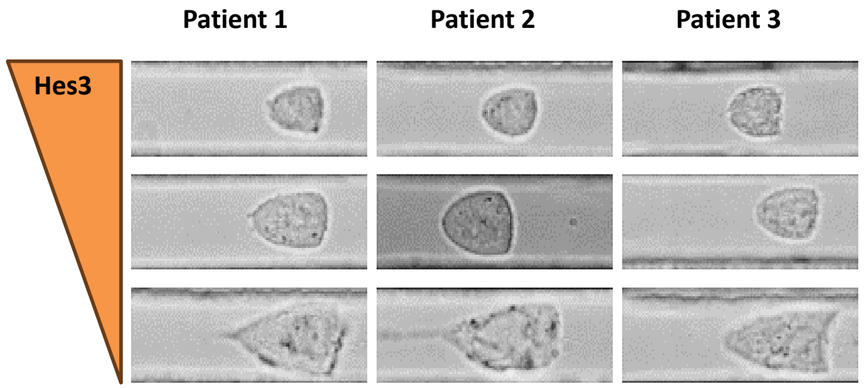
Masjkur et al, J Biol Chem, 2014
Masjkur et al, Diabetes, 2016
Nikolakopoulou et al, Sci Rep, 2018

Scientific Background: Our Preclinical in vitro Results

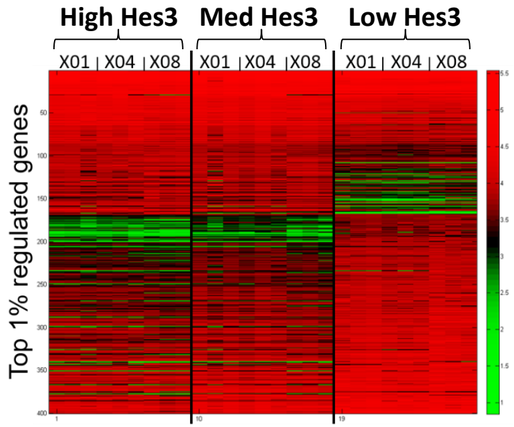
CSCs can have the Hes3 Axis ON or OFF

- Each of the two states is sensitive to very different treatments.
- Current treatments are designed to target **the Hes3 OFF state**,
- We are developing treatments against the **ON state**:
  - **Hes3 siRNA** was tested **in vitro** in multiple cell lines, including primary CSCs, and **found to kill Hes3+ CSCs**.
  - **Small molecule drugs** (also tested in multiple cell lines) were also **found to kill Hes3+ CSCs**.
- We have shown that depending on the **level of Hes3 Axis activation**, CSCs exhibit **different properties**.

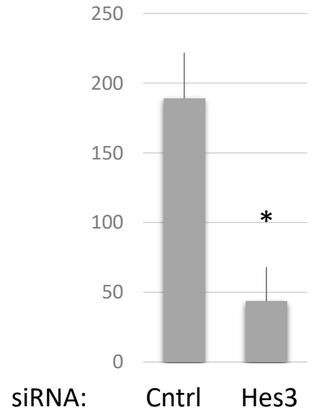
Park et al, Sci Rep, 2013
Poser et al., FASEB J, 2019



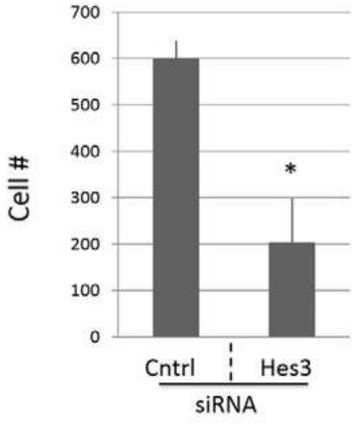
Primary human glioma CSCs exhibit **different mechanomic properties, depending on the level of Hes3 Axis activation**. High Hes3 expression correlates with a small and deformable morphology, as expected for SCs [Data from Real time deformability cytometry]



They also exhibit different gene expression profiles. Different primary human glioblastoma CSC cell lines (X01, X04, X08) **behave similarly to each other regardless of patient source**.



Hes3 siRNA kills Hes3+ CSCs and established brain cancer cell lines in culture [Example shown: U87 human brain cancer cell line].



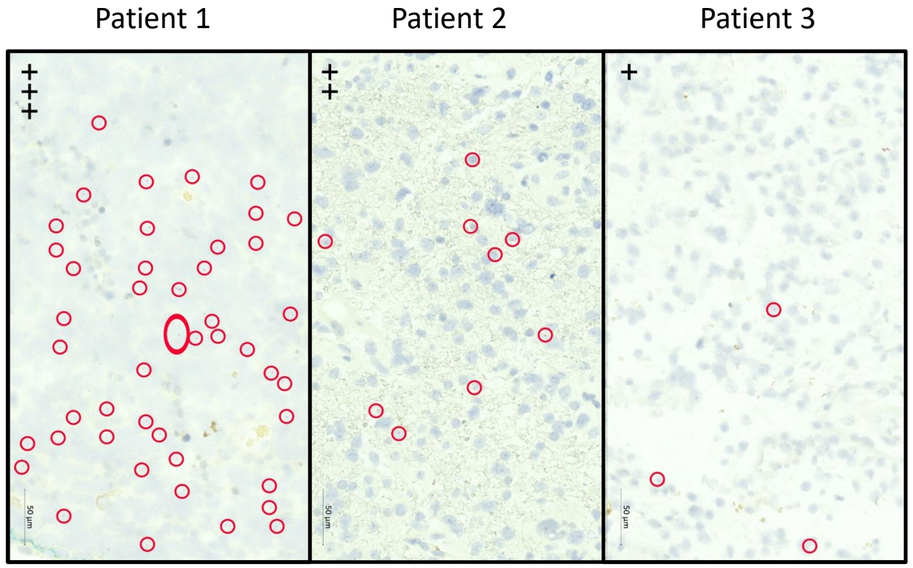
The anti-cancer effect is not confined to the brain. Hes3 siRNA also kills Hes3+ cancer cells from a mouse insulinoma cell line.

Scientific Background: Our Preclinical in vivo Results

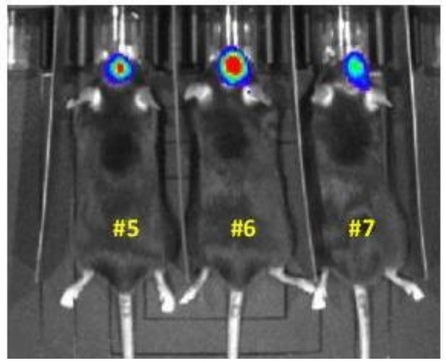
Two key prerequisites

Question:	**Are Hes3+ target cells present in patients?**
Answer:	**YES!** 8 out 11 patients have Hes3+ target cells in their biopsies.

Question:	**Do we have adequate animal models to use for demonstrating in vivo efficacy?**
Answer:	**YES!** Our orthotopic mouse models exhibit **40% (!)** incidence of Hes3+ target cells.

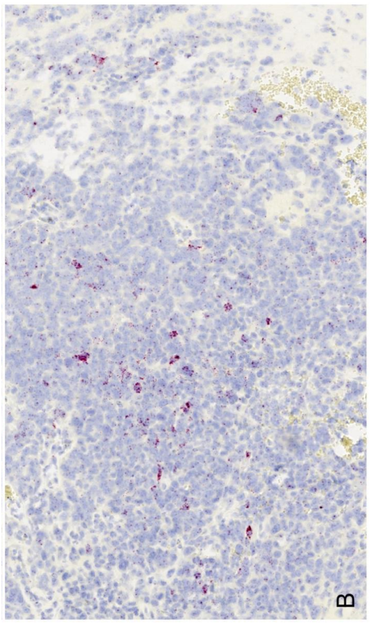


Examples of biopsies from three different glioblastoma patients, corresponding to high-, medium-, and low-expressing cases. Red circles mark Hes3+ cells (assayed by in situ hybridization).



The cancer cells are luciferase-labelled, allowing the non-invasive visualization of the tumor progression.

Post-mortem, biopsies show the high (40%) expression of Hes3 in these models



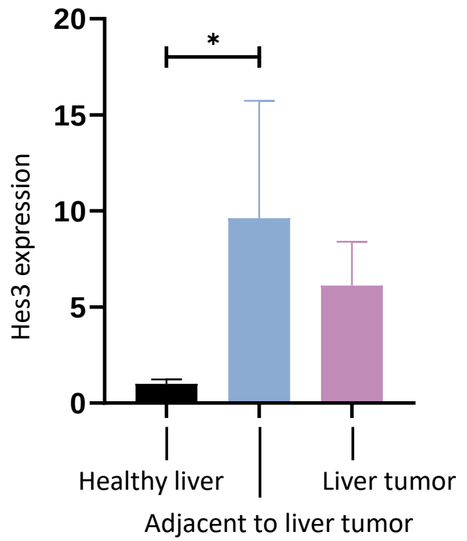
Collaboration with the [Medicines Discovery Catapult]

Scientific Background: Expanding beyond brain cancer

Current list of cancers that involve the Hes3 Axis

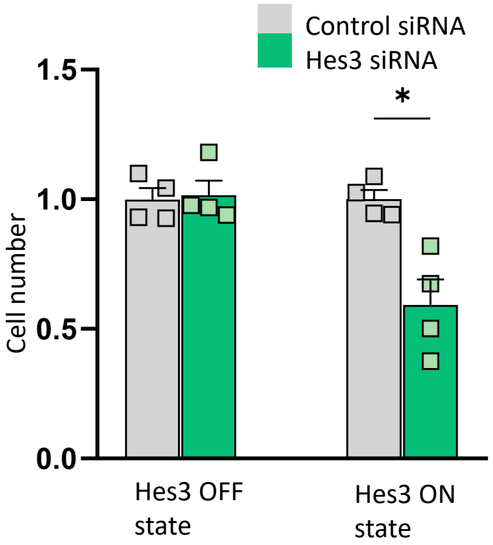
- Liver / Hepatocellular carcinoma (HCC) [unpublished data]
  - Transition from NAFLD → NASH → HCC
- Glioma
  - Hes3 predicts anti-cancer response to a γ-secretase inhibitor
- Ependymoma
  - Patient biopsies and xenograft models show increased Hes3
- Prostate
  - STAT3-Ser mediates carcinogenesis in vivo (mice)
- Breast
  - Hes3 expression in vivo predicts anti-cancer response to a γ-secretase inhibitor; Hes3 promotes carcinogenicity in TNBC
- Lung
  - Hes3 promotes proliferation in vitro, predicts short patient survival
- Alveolar Rhabdomyosarcoma
  - Hes3 mediates PAX3-FOXO1 rhabdomyosarcoma in vivo (fish); predicts short patient survival
- Colon
  - Hes3 expressed in colon cancer spheroids

Mouse liver, in vivo



In HCC models, **tumors and adjacent tissue exhibit increased Hes3 expression.**
→ Preliminary patient biopsy data **corroborate this finding**.

Human HCC, in vitro



Hes3 siRNA kills human HCC cells in the Hes3 ON, **but not the OFF state**.
→ Hes3 siRNA is **not an indiscriminate killer**.

Strong independent corroboration in oncology: The papers above fully confirm our thesis and extend it to multiple types of cancer representing all developmental lineages.

Strong independent corroboration in regeneration: Other papers fully confirm our findings that Hes3 Axis activation promotes cell number in vitro and in vivo and implicate it in neural stem cell reprogramming.

- Hes3 Axis activation increases SC # in the brain
- Hes3 Axis activation increases neural SC yield
- Hes3 role in direct reprogramming to neural SCs
- Hes3 Axis mediates MIF's pro-neural SC actions

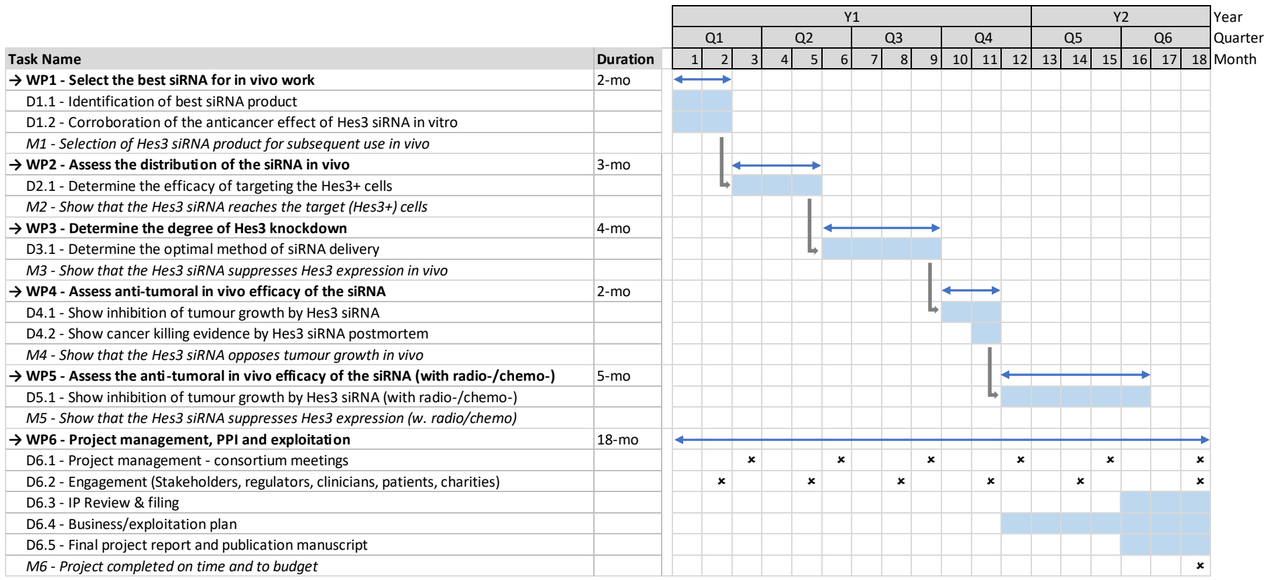
Planned experiment to be carried out with funds raised

In vivo efficacy validation

Using commercially available **anti-Hes3 siRNA products by Thermofisher** we will test the anti-cancer efficacy of the treatment as a **monotherapy**, and in **combination with chemo- & radio-therapy**.

Readouts will include:

- Tumor growth progression by non-invasive imaging
- Tumor size post-mortem
- Cell death in the tumor
- Cancer and CSC biomarker expression
- Hes3 expression



Task Name	Duration
→ **WP1 - Select the best siRNA for in vivo work**	2-mo
D1.1 - Identification of best siRNA product	
D1.2 - Corroboration of the anticancer effect of Hes3 siRNA in vitro	
M1 - Selection of Hes3 siRNA product for subsequent use in vivo	
→ **WP2 - Assess the distribution of the siRNA in vivo**	3-mo
D2.1 - Determine the efficacy of targeting the Hes3+ cells	
M2 - Show that the Hes3 siRNA reaches the target (Hes3+) cells	
→ **WP3 - Determine the degree of Hes3 knockdown**	4-mo
D3.1 - Determine the optimal method of siRNA delivery	
M3 - Show that the Hes3 siRNA suppresses Hes3 expression in vivo	
→ **WP4 - Assess anti-tumoral in vivo efficacy of the siRNA**	2-mo
D4.1 - Show inhibition of tumour growth by Hes3 siRNA	
D4.2 - Show cancer killing evidence by Hes3 siRNA postmortem	
M4 - Show that the Hes3 siRNA opposes tumour growth in vivo	
→ **WP5 - Assess the anti-tumoral in vivo efficacy of the siRNA (with radio-/chemo-)**	5-mo
D5.1 - Show inhibition of tumour growth by Hes3 siRNA (with radio-/chemo-)	
M5 - Show that the Hes3 siRNA suppresses Hes3 expression (w. radio/chemo)	
→ **WP6 - Project management, PPI and exploitation**	18-mo
D6.1 - Project management - consortium meetings	
D6.2 - Engagement (Stakeholders, regulators, clinicians, patients, charities)	
D6.3 - IP Review & filing	
D6.4 - Business/exploitation plan	
D6.5 - Final project report and publication manuscript	
M6 - Project completed on time and to budget	

WP1 – Select the best siRNA for in vivo work, by testing efficacy in vitro [£10K - 2 months].

GL261 cells will be cultured under defined conditions that lock the cells in the Hes3+ state. Three Hes3 siRNA products from Thermofisher will be used to test Hes3 knockdown and cytotoxic efficacy, for the purpose of selecting the most efficacious product for subsequent use in vivo (WP2-5).

Deliverable D1.1	Identification of best siRNA product (MDC)
Deliverable D1.2	Corroboration of the anticancer effect of Hes3 siRNA in vitro (MDC)
Milestone M1	**Selection of Hes3 siRNA product for subsequent use in vivo**

WP2 - Assess the distribution of the siRNA in vivo, following direct intratumoural delivery [£30K - 3 months].

Mouse orthotopic models of brain cancer using the GL261 cell line, lentivirally transduced with mCherry-Fluc to allow tumour cells identification by non-invasive imaging, will be treated with GFP-tagged Hes3 siRNA (Thermofisher), mixed with LNPs (Pfizer). We will assess, post-mortem, the distribution of the siRNA, including its relative affinity for Hes3+ target cells, compared to other cell types within the tumor such as infiltrating macrophages, resident microglia, and endothelial cells.

Deliverable D2.1	Determine the efficacy of targeting the Hes3+ cells (MDC)
Milestone M2:	**Show that the Hes3 siRNA reaches the target (Hes3+) cells**

WP3 – Determine the degree of Hes3 knockdown in vivo, following intratumoural delivery of the siRNA [£30K - 4 months].

One week after GL261 cell implantation, 1-2 separate bolus intratumoural injections of siRNA/LNP (according to Thermofisher recommendations) will be given at an interval of 5-days. Hes3 expression will be measured by in situ hybridization for the generation of data on a spatial scale, and by qPCR of whole tumors for a more quantitative measurement (techniques already established at the MDC).

Deliverable D3.1	Determine the optimal method of siRNA delivery (MDC)
Milestone M3:	**Show that the Hes3 siRNA suppresses Hes3 expression in vivo**

WP4 - Assess in vivo anti-tumoral efficacy of the siRNA as monotherapy [£20K - 2 months].

Using the delivery method determined in WP3, we will obtain evidence of tumour growth inhibition mediated by Hes3 knockdown using siRNA/LNPs. This will be assessed by luciferase-based radiance measurements and by post-mortem analyses of the tumor tissue.

Deliverable D4.1	Show inhibition of tumour growth by Hes3 siRNA (MDC)
Deliverable D4.2	Show cancer killing evidence by Hes3 siRNA postmortem (MDC)
Milestone M4:	**Show that the Hes3 siRNA opposes tumour growth in vivo**

WP5 – Assess the anti-tumoral in vivo efficacy of the siRNA in combo with radiation (X-ray) and chemotherapy (TMZ) strategies [£40K - 4 months].

This is an alternative therapeutic approach based on our past observations that tissue damage paradigms and anti-cancer treatments (total body radiation) greatly increase Hes3 expression. Such treatments might sensitize the cancer tissue to Hes3 siRNA. siRNA treatment from WP4 will be combined with radiation and chemotherapy. We will assess the effect of the Hes3 siRNA on cancer progression.

Deliverable D5.1	Show inhibition of tumour growth by Hes3 siRNA in combination with radiation and chemotherapy. (MDC)
Milestone M5:	**Show that the Hes3 siRNA opposes tumour growth in vivo when combined with radiation and chemotherapy**

Company

- iR was founded in 2019 in the UK, as a spin-off of the Technische Universitaet Dresden (TUD).
- Its leadership team brings together **decades of experience** in cutting-edge cancer research, strategic business development, and successful partnerships, ensuring a robust foundation for transformative innovation.
- iR's IP is patent protected (Relevant patent family: WO2014096399A1)
- Patent family belongs to TUDAG; iR has exclusive use & purchasing rights at a pre-arranged price.
- Current shareholders include the founders, TUDAG, and two other angel investors.

Dr Andreas Androutsellis-Theotokis
Cofounder & CEO

Andreas **discovered the Hes3 Signalling Axis**, holds a BSc and a **PhD from Imperial College London in Biochemistry**, and held former roles at Yale, NIH, University of Dresden, and University of Nottingham.

Dr Nikos Kassapakis
Cofounder & Chief of Corporate & Legal Strategy

Nikos holds a BSc and a **PhD in Physics from Imperial College London**, he is **Managing Director at a global investment bank**, and an expert in company creation and investments.

Prof. Stefan Bornstein
Cofounder & Medical Advisor

Stefan is a **clinical director**, **vice dean**, supervisory board member (TU Dresden Hospital), and **Chair** (King's College London). He is a member of the **German Academy of Sciences** and received the **order of merit** from the President of Germany.

Collaborators

Our collaborations are pivotal, supporting in vivo efficacy studies, regulatory preparation, clinical-grade product development, and business development, ensuring our path to clinical trials

- The UK Government's premier RTO, part of the highly selective Catapult Network with a track record of success
- Nine work packages since 2019
- 3x-3.5x cheaper than private CROs
- Top Government scientists validate our R&D

- Strong ties as a spinoff
- Multiple collaborative grants
- Co-founder Prof. Stefan Bornstein's pivotal role

- RNA delivery collaboration with Prof. George Malliaras, Prince Philip Professor of Technology and Director of the Bioelectronics Laboratory
- Research on Metal-Organic Frameworks with Prof. David Fairen-Jimenez

- Liver disease and cancer research with Prof. Antonios Chatzigheorghiou
- Supported by Greek Government grant

External Advisors

- Clinical and regulatory guidance from Dr. Deric Minwoo Park, Pitkin Foundation Endowed Professor and Prof. Ronen Leker, Director, Comprehensive Stroke Center and the Peritz and Chantal Sheinberg Cerebrovascular Laboratory

Traction

Showcasing significant industry interest, scientific recognition, and key publications that highlight our novel approach and strong market potential

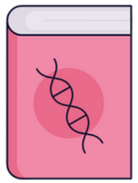
nature awards
the spinoff prize

Nature Journal's "Ones to Watch"

Recently (Jul 24) recognised by Nature Journal—one of the world's most prestigious scientific publications—for pioneering a novel therapeutic strategy targeting an untapped molecular mechanism, offering treatments that enhance existing cancer therapies

Big Pharma Interest

Big Pharma executives and scouts have shown significant interest in our innovative technology at key industry conferences, contingent on in vivo efficacy data—conversations set to advance upon milestone achievement



Key Published Papers

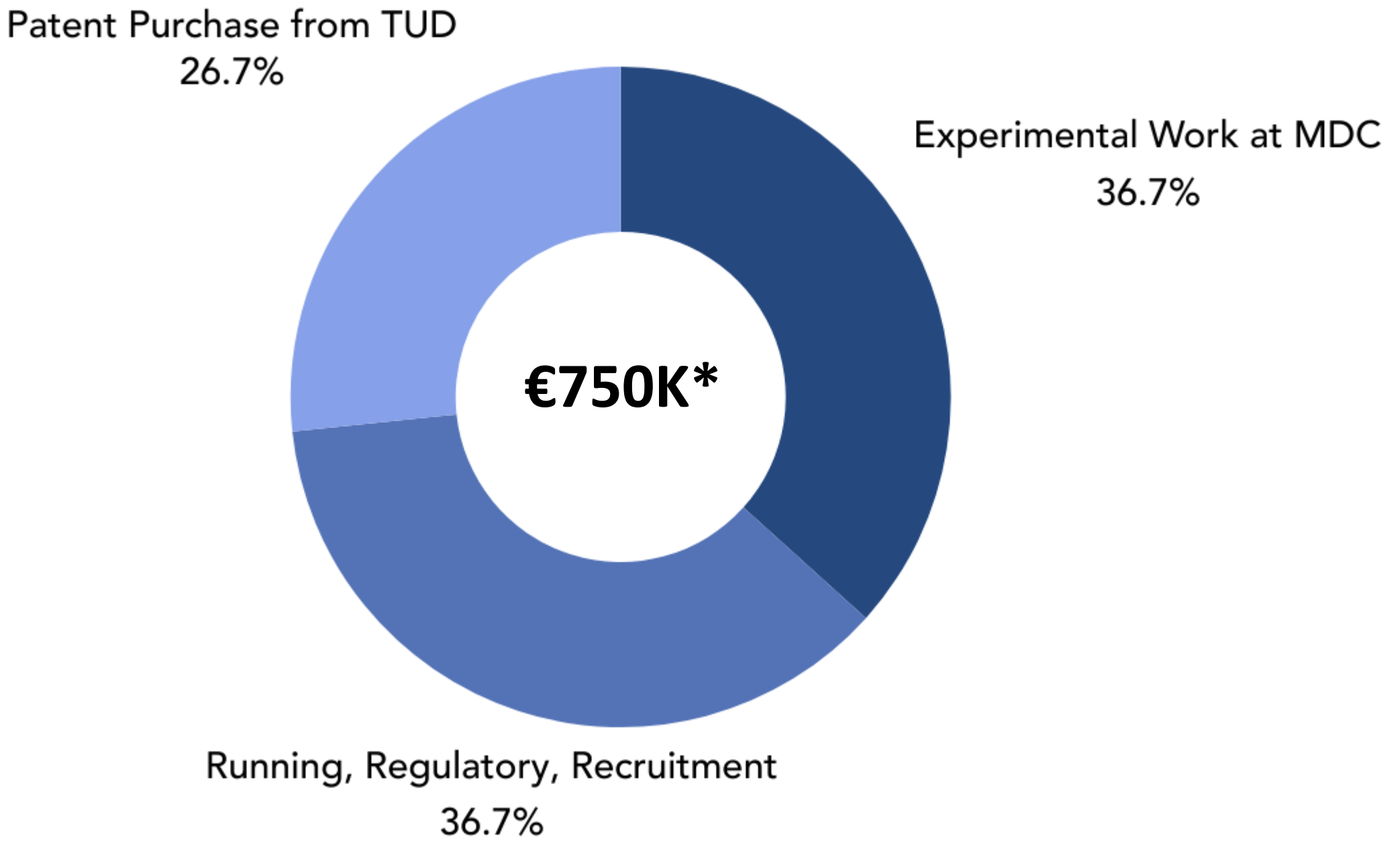
- Notch Signalling Boosts Stem Cell Survival, *Nature,* 2006
- Hes3: A Key Player in Brain Cancer, *Scientific Reports,* 2013
- Innovative Approach to Cancer Drug Development, *FASEB J*, 2019

Prominent Media Features

- The FASEB Journal: Alternative molecular mechanisms observed in cancer cells, *EurekAlert!*
- Killing the unkillable cancer cells, *EurekAlert!*
- Brain can be made to self-repair, *Nature*

Use of Funds

Funds dedicated to experimental work, regulatory processes, and intellectual property acquisition



*€300K immediately + €450K after successful completion of the In Vivo Efficacy Studies

Experimental Work at MDC

€275,000

- **In Vivo Efficacy Studies**: Demonstrate the anti-cancer effect in mouse models
- **Data Collection**: Crucial data for pharma engagement and regulatory submission
- **Adaptive Experimentation:** Allows for repeated experiment runs

Running, Regulatory, Recruitment

€275,000

- **Regulatory Work:** Orphan drug designation and initial regulatory approvals
- **Operational Costs:** IP, legal, and accounting expenses
- **Team Expansion:** Hire key staff to ensure clinical success

Patent Purchase from TUD

€200,000

- **Secure Exclusive Rights:** Full control over oligonucleotide patent family
- **Intellectual Property:** Strengthen IP portfolio for strategic partnerships

High Acquisition Appeal

Potential **exit in under 2 years**, given that in vivo efficacy data within 12-18 months could attract significant Big Pharma attention, accelerated by orphan disease status and faster regulatory approvals

High Unmet Medical Need

- **High Prevalence and Aggressiveness:** Most common and aggressive glioma, limited effective treatments
- **High Mortality Rate:** Often referred to as “1-year death sentences”

Booming RNA Market

- **Interest from Big Pharma:** Regeneron, Novartis, Roche, and Sanofi actively pursuing RNA therapeutics
- **Growing Market:** RNA therapeutics target a broad range of genes, valuable for untreatable conditions

Credibility with MDC Collaboration

- **High Standards and Ethical Conduct:** MDC performs experiments at the highest standards
- **Previous Successful Collaborations:** MDC has completed nine work packages for Innate Repair

Comparable Transactions

- **Pierre Fabre**: $553M for **preclinical** lung cancer assets (Apr 23)
- **Boehringer Ingelheim**: $530M for T3 Pharmaceuticals at **Phase I** (Nov 22)