TheraCryf

R&D Day Presentation

AIM: TCF.L
NOMAD: Cavendish
IR: Instinctif, CAG

13 June 2024

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TheraCryf

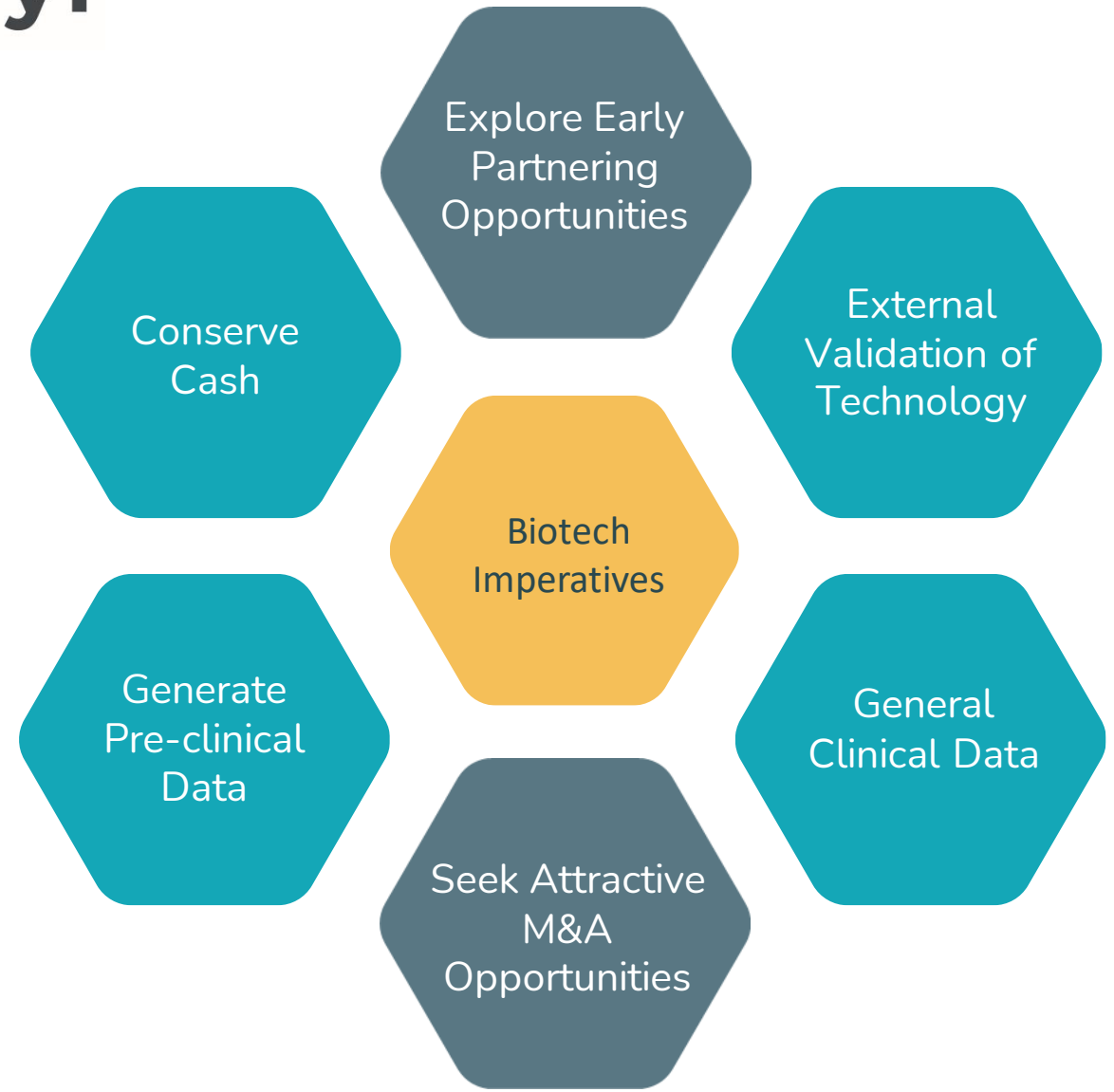
MISSION

To build a drug development powerhouse in profitable segments within oncology and behavioural brain disorders

AGENDA

Item	Presenters	Time
Introduction	Dr Huw Jones, CEO	09:30-09:35
Review of Chronos acquisition and FY Results	Dr Huw Jones/Toni Haenninen, CFO	09:35-09:45
Pipeline Review	Dr Glen Clack, CMO	09:45-10:00
Glioblastoma Programme	Dr Glen Clack, Dr Marjolein Geurts, Neuro-oncologist, Dr Wouter Vanbilloen, Erasmus MC, Rotterdam	10:00-10:30
Q/A	All	10:00-10:35
Break		10:35-10:50
Neuropsychiatry programmes, Ox-1 antagonist, DAT inhibitor	Dr Fraser Murray, Neuroscientist, consultant to TheraCryf	10:50-11:35
TheraCryf Market sizes and potential	Dr Helen Kuhlman, CBO	11:35-11:55
Outlook, Conclusion, Q/A	Dr Huw Jones	11:55-12:00

TheraCryf


Explore Early Partnering Opportunities
Conserve Cash
External Validation of Technology
Biotech Imperatives
Generate Pre-clinical Data
General Clinical Data
Seek Attractive M&A Opportunities

TheraCryf

EVGEN pharma

CHRONOS THERAPEUTICS

Clinical stage

- Developing a new class of pharmaceuticals - based on **highly biologically active "sulforaphane"** - applications in multiple therapeutic areas based on a network of targets
- Platform stabilisation technology, **extensive IP** for platform and lead asset SFX-01. **Orphan drug designation in USA**
- Internal programme – **glioblastoma (GBM)** the most fatal of the brain cancers. **Clinical POC is grant funded** by Dutch cancer society
- **Out-license deal with Stalicla SA** in neurodevelopmental disorders. $160.5m milestones, double digit royalty
- **Phase1b study on commercial grade tablet** complete with further *post hoc* genomic analysis in Q3 2024
- First clinical **read out in GBM 2026**

Late Pre-clinical stage

- Spin out of Oxford University, lifetime raise £15.4m
- 2016 acquisition of **3 NCE assets from Shire** with CNS, neurology/psychiatry focus
- 2 Assets developed to late pre-clinical by Chronos
- Main programmes
  - **Ox-1 antagonist** (anxiety and addictive disorders, BED) **class leading profile**
  - DAT inhibitor (fatigue, long COVID, MS fatigue, narcolepsy) **atypical, unique**
- **Patents granted** in major territories including USA, Ox-1 patent valid until 2038
- Entry to Phase 1 clinical studies as early as 2026, early clinical **POC 2026/7***

* Subject to separate funding

Rationale for Combination

- More than **triples the size of the TheraCryf portfolio**
- Capitalising on **renewed interest** and deal activity in Neuroscience
- Chronos neuropsychiatry assets are **complementary** to Evgen's neurodevelopmental disorders and brain cancer asset
- Evgen has the expertise to develop and commercialise the combined portfolio
- Multiple **potential inflection points**
- **High quality investor base in Chronos**

Highlights to 31 March 2024

- **Grant awarded** by the Netherlands government administered by Dutch Cancer Society
  - Pre-clinical work and a clinical trial in glioblastoma (GBM) led by Dr Marjolein Geurts, Erasmus MC, Rotterdam, €1.1m project
  - Activity of SFX-01 in GBM cells from Netherlands' patients corroborating previous data from academic partners in Italy and New Zealand
- **Full clinical study report** issued for the SFX-01 Phase 1b study confirming PK profile and absence of SAEs for commercial grade formulation
- **Evidence of activity of SFX-01** observed in models of colon cancer (University of Michigan, USA) and further SFX-01 activity seen *in vivo* in models of rare childhood cancer rhabdomyosarcoma (La Sapienza University, Rome)
- **Partners:** Constructive discussions continue with Stalicla SA on dispute resolution
- **Board changes**
  - Dr Susan Foden appointed Chair, succeeding Barry Clare following his retirement from board
  - CFO Toni Hänninen appointed as Executive Director, Dr Alan Barge appointed Senior Independent Non-executive Director; Susan Clement-Davies retired from board. Richard Moulson retired from board.

Financial Highlights

***Financial performance in-line with* expectations:**

	Year to 31 March 2024	Prior Year
Post tax loss	£3.1m	£4.0m
Cash outflow	£3.4m	£4.9m
Cash and short-term investments	£2.0m*	£5.0m

* Additional funds raised post period

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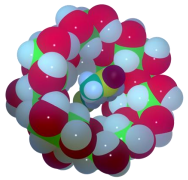
Group Pipeline

Discovery	Pre-clinical POC	Phase 1	Phase 2	Phase 3
SFX-01: Breast Cancer				
SFX-01: Neurodevelopmental Disorders				
SFX-01: Glioblastoma*				
SFX-01: Rhabdomyosarcoma				
NCE: Ox-1 in Addiction				
NCE: Ox-1 in Anxiety				
NCE: DAT in Fatigue / Narcolepsy*				

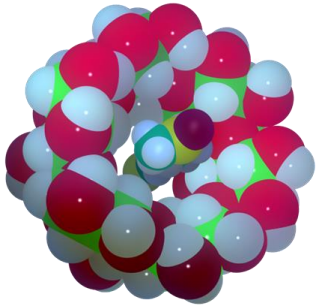


* Orphan Conditions

Glioblastoma (GBM)

- GBMs are a fast-growing type of brain tumour (glioma) that has a low survival rate.
- The most common type of cancerous (malignant) brain tumour in adults.
- Average length of survival for glioblastoma patients is 12-18 months.
  - Only 5-10% of patients survive more than five years.
- The survival time may vary depending on the patient's age, treatment type and their tumour genetics.
- The main treatments for GBMs are surgery, radiotherapy and chemotherapy.
  - New treatments are urgently needed.

SFX-01 and GBM



SFX-01 is a form of sulforaphane (SFN) that is stabilized by being complexed with α-cyclodextrin.

Effects on Cell Lines (*in vitro*):

- SFX-01 and reference SFN increased cell death of GBM cell lines and also inhibited the proliferation of GBM cell lines both in monolayers and in three-dimensional spheroids (models which mimic the in vivo state of GBMs).

Studies performed in mice (*in vivo*):

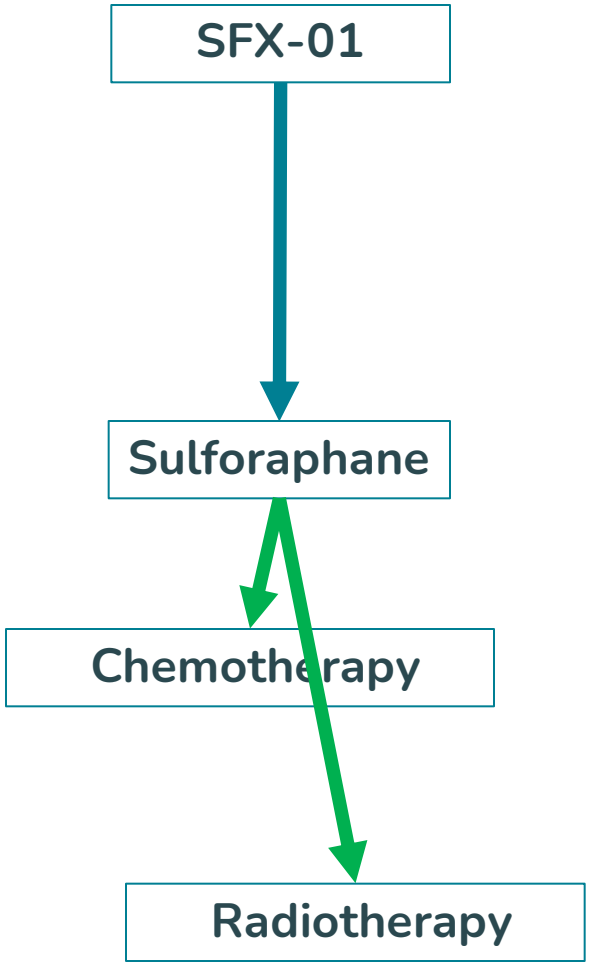
- SFX-01 reduced tumour growth and improved survival in subcutaneous and orthotopic xenograft models[+] of GBM.

Patient-derived glioma initiating cells [GICs]:

- SFX-01 increased cell death in patient-derived GICs with a stem cell* phenotype**

[+] This model involves the direct implantation of human GBM tumours into immunodeficient mice to create a primary human 'tumourgraft'
* Undifferentiated or partially differentiated cells that can change into various types of cells and proliferate indefinitely
** Observable characteristics or traits

How Might SFX-01 be working in GBM?



Himes et al. (2021) Immunosuppression in Glioblastoma: Current Understanding and Therapeutic Implications. Front. Oncol. 11:770561

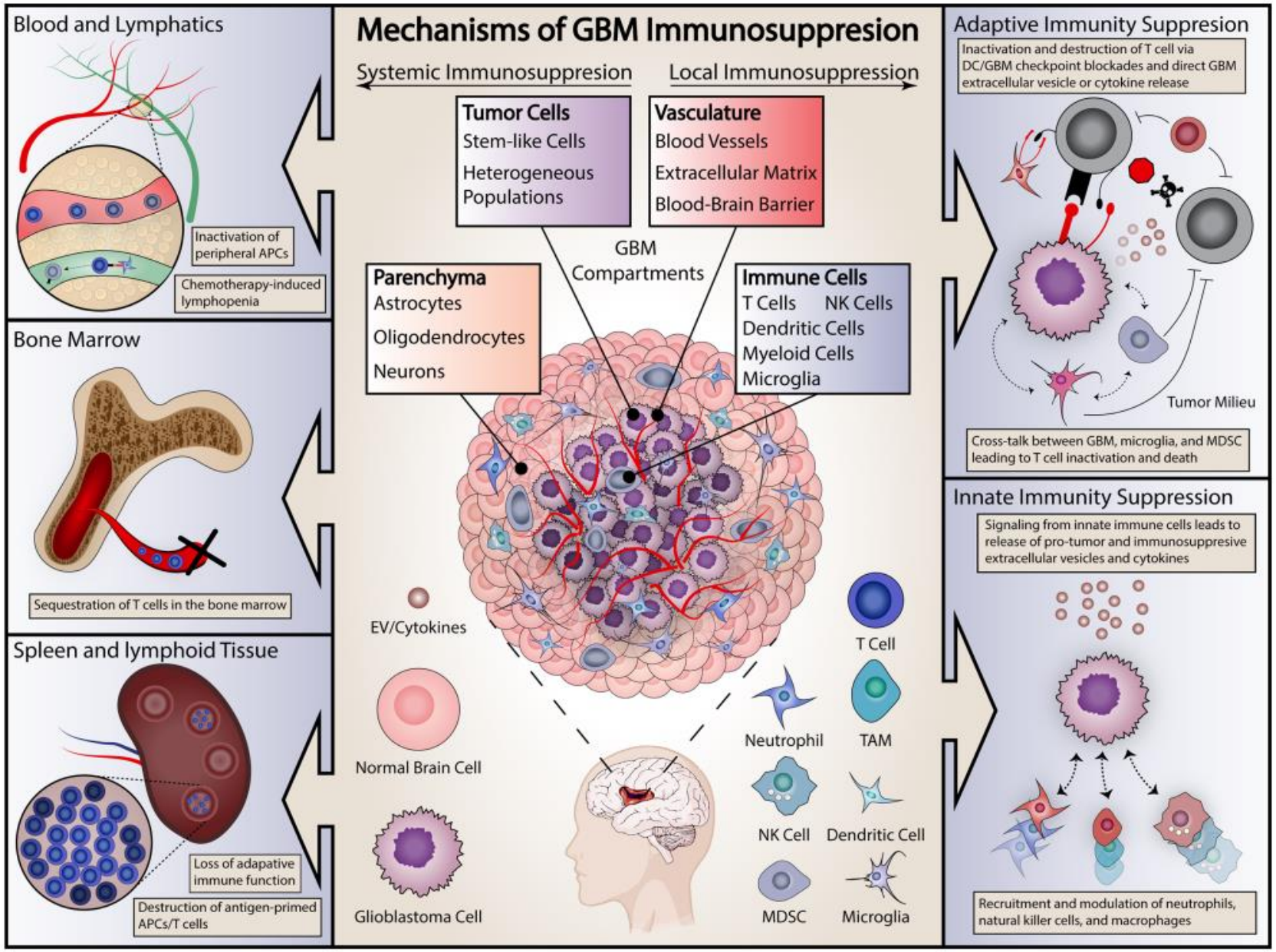
How Might SFX-01 be working in GBM?

SFX-01

Sulforaphane

Chemotherapy

Radiotherapy



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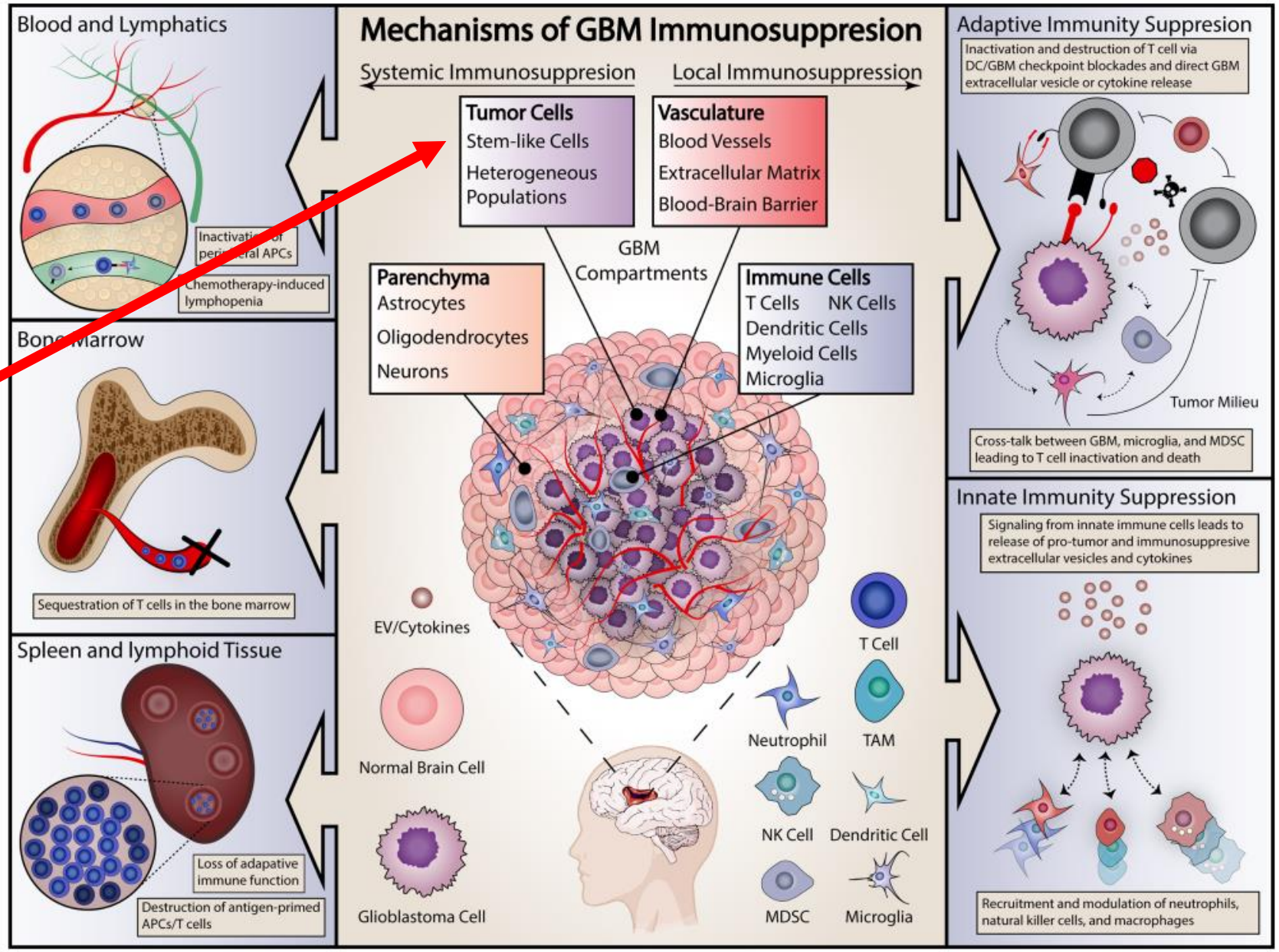
Radiotherapy



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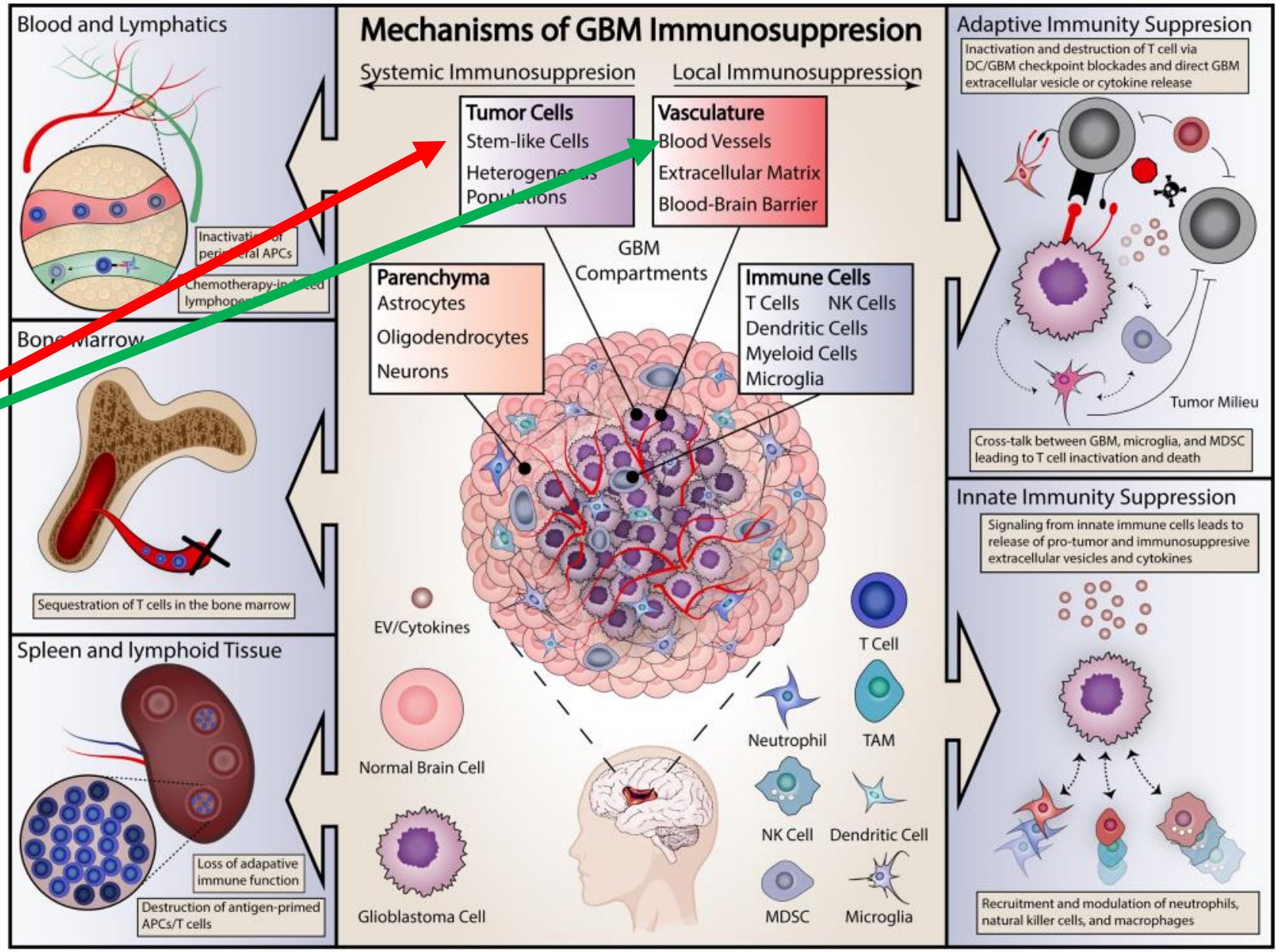

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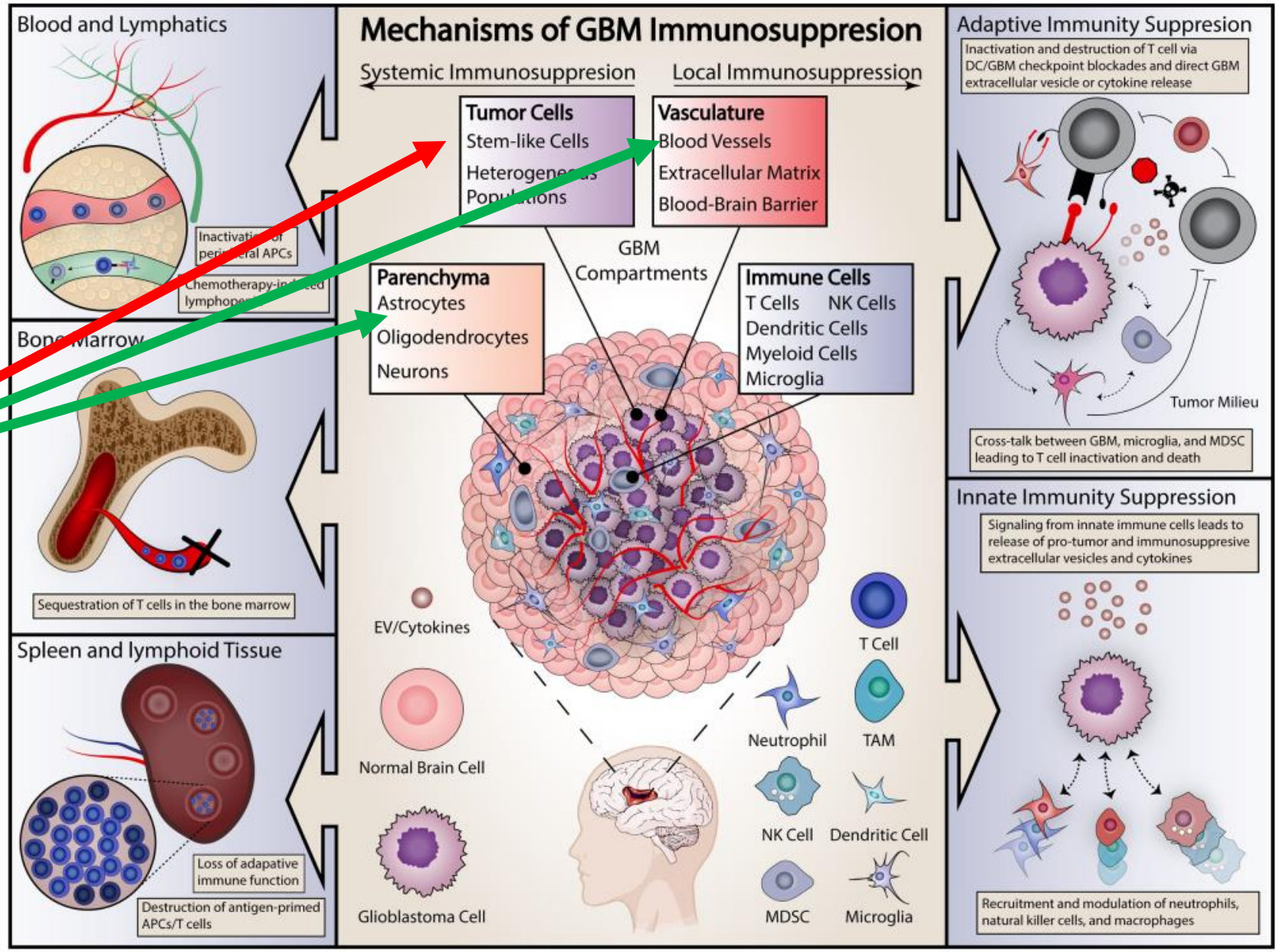


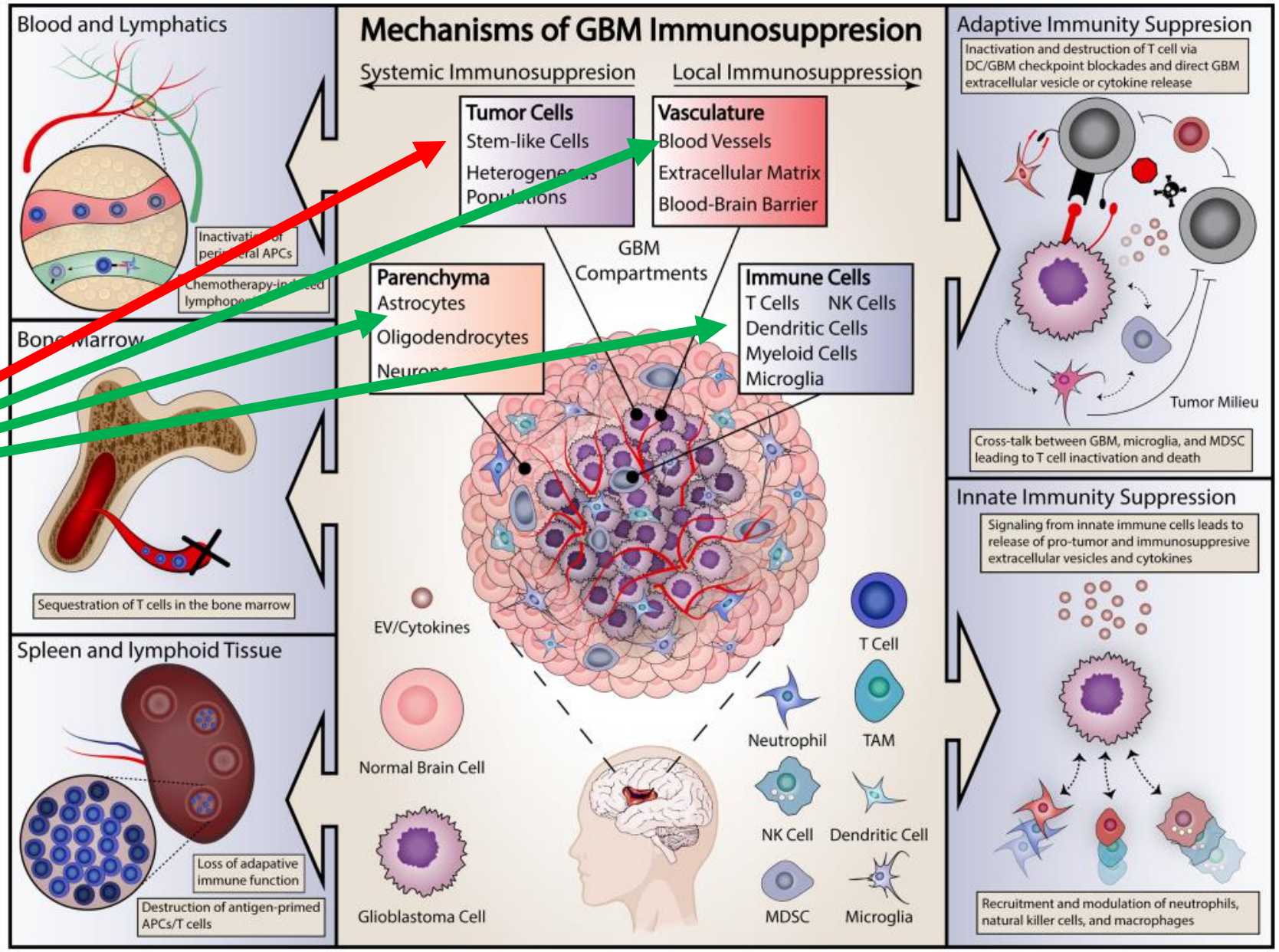
How Might SFX-01 be working in GBM?

SFX-01

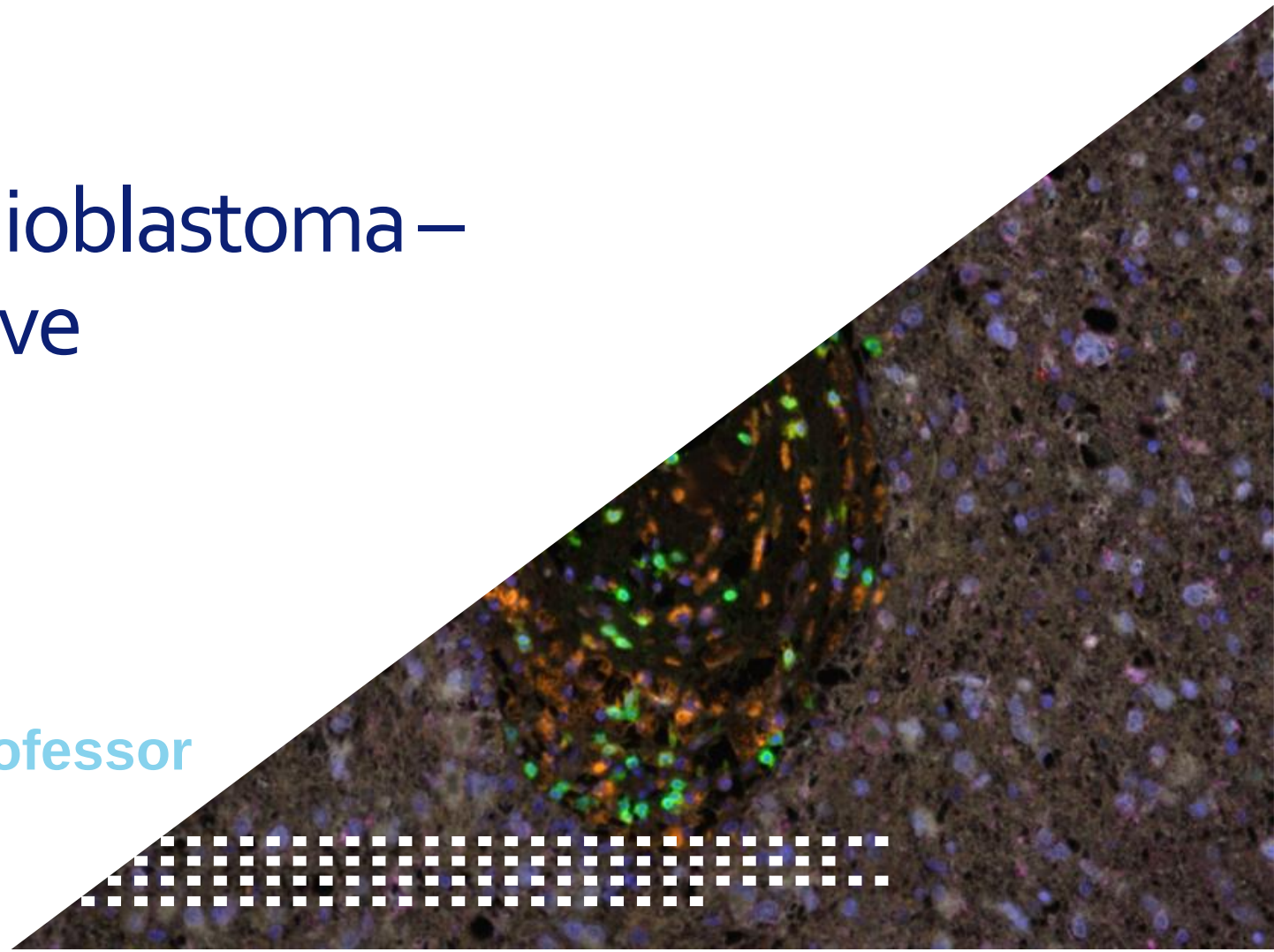
Sulforaphane

Chemotherapy

Radiotherapy



Drug Development in Glioblastoma – The Academic Perspective



Marjolein Geurts, MD PhD

Neuro-oncologist | Assistant professor

Erasmus MC

Neuro-oncology Erasmus MC

Primary brain tumours in adults

Martin J van den Bent, Marjolein Geurts, Pim J French, Marion Smits, David Capper, Jacoline E C Bromberg, Susan M Chang

Lancet 2023; 402: 1564-79
Published Online September 19, 2023 https://doi.org/10.1016/S0140-6736(23)01054-1

Department of Neurology, Brain Tumor Center, (Prof M J van den Bent MD, M Geurts MD, P J French PhD, J E C Bromberg MD), and Department of Radiology & Nuclear Medicine (Prof M Smits PhD), Erasmus MC Cancer Institute, University Medical Center Rotterdam, Netherlands; Medical Delta, Delft, Netherlands (Prof M Smits); Department of

The most frequent adult-type primary CNS tumours are diffuse gliomas, but a large variety of rarer CNS tumour types exists. The classification of these tumours is increasingly based on molecular diagnostics, which is reflected in the extensive molecular foundation of the recent WHO 2021 classification of CNS tumours. Resection as extensive as is safely possible is the cornerstone of treatment in most gliomas, and is now also recommended early in the treatment of patients with radiological evidence of histologically low-grade tumours. For the adult-type diffuse glioma, standard of care is a combination of radiotherapy and chemotherapy. Although treatment with curative intent is not available, combined modality treatment has resulted in long-term survival (>10–20 years) for some patients with isocitrate dehydrogenase (*IDH*) mutant tumours. Other rarer tumours require tailored approaches, best delivered in specialised centres. Targeted treatments based on molecular alterations still only play a minor role in the treatment landscape of adult-type diffuse glioma, and today are mainly limited to patients with tumours with $BRAF^{V600E}$ (ie, Val600Glu) mutations. Immunotherapy for CNS tumours is still in its infancy, and so far, trials with checkpoint inhibitors and vaccination studies have not shown improvement in patient outcomes in glioblastoma. Current research is focused on improving our understanding of the immunosuppressive tumour environment, the molecular heterogeneity of tumours, and the role of tumour microtube network connections between cells in the tumour microenvironment. These factors all appear to play a role in treatment resistance, and indicate that novel approaches are needed to further

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 17, 2023 VOL. 389 NO. 7

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

I.K. Mellinghoff, M.J. van den Bent, D.T. Blumenthal, M. Touat, K.B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W.P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A.F. Hottinger, Y. Arakawa, J.M. Sepulveda, W. Wick, R. Soffietti, I.R. Perry, P. Giglio, M. de la Fuente, E.A. Maher, S. Schoenfeld, D. Zhao, S.S

The NEW ENGLAND JOURNAL of MEDICINE

Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study

Martin J van den Bent, C Mircea S Tesileanu, Wolfgang Wick, Marc Sanson, Alba Ariela Brandes, Paul M Clement, Sarah Erridge, Michael A Vogelbaum, Anna K Nowak, Jean Français Baurain, Warren P Mason, Helen Wheeler, Olivier L Chinot, Sanjeev Gill, Matthew Griffin, Leland Rogers, Walter Taal, Roberta Rudà, Michael Weller, Catherine McBain, Jaap Reijneveld, Roelien H Enting, Francesca Caparrotti, Thierry Lesimple, Susan Clenton, Anja Gijtenbeek, Elizabeth Lim, Ulrich Herrlinger, Peter Hau, Frederic Dhermain, Iris de Heer, Kenneth Aldape, Robert B Jenkins, Hendrikus Jan Dubbink, Johan M Kros, Pieter Wesseling, Sarah Nuyens, Vassilis Golfinopoulos, Thierry Gorlia, Pim French, Brigitta G Baumert

ORIGINAL ARTICLE

Lomustine and Bevacizumab in Progressive Glioblastoma

Wolfgang Wick, M.D., Thierry Gorlia, Ph.D., Martin Bendszus, M.D., Martin Taphoorn, M.D., Felix Sahm, M.D., Inga Harting, M.D., Alba A. Brandes, M.D., Walter Taal, M.D., Julien Domont, M.D., Ahmed Idbaih, M.D., Mario Campone, M.D., Paul M. Clement, M.D., Roger Stupp, M.D., Michel Fabbro, M.D., Emilie Le Rhun, M.D., Francois Dubois, M.D., Michael Weller, M.D., Andreas von Deimling, M.D., Vassilis Golfinopoulos, M.D., Jacoline C. Bromberg, M.D., Michael Platten, M.D., Martin Klein, M.D., and Martin J. van den Bent, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

VOLUME 31 · NUMBER 3 · JANUARY 20 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

Martin J. van den Bent, Alba A. Brandes, Martin J.B. Taphoorn, Johan M. Kros, Mathilde C.M. Kouwenhoven, Jean-Yves Delattre, Hans J.J.A. Bernsen, Marc Frenay, Cees C. Tijssen, Wolfgang Grisold, László Sipos, Roelien H. Enting, Pim J. French, Winand N.M. Dinjens, Charles J. Vecht, Anouk Allgeier, Denis Lacombe, Thierry Gorlia, and Khê Hoang-Xuan

Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial

Walter Taal, Hendrika M Oosterkamp, Annemiek M E Walenkamp*, Hendrikus J Dubbink*, Laurens V Beerepoot, Monique C J Hanse, Jan Buter, Aafke H Honkoop, Dolf Boerman, Filip Y F de Vos, Winand N M Dinjens, Roelien H Enting, Martin J B Taphoorn, Franchette W P J van den Berkmortel, Rob L H Jansen, Dieta Brandsma, Jacoline E C Bromberg, Irene van Heuvel, René M Vernhout, Bronno van der Holt, Martin J van den Bent*

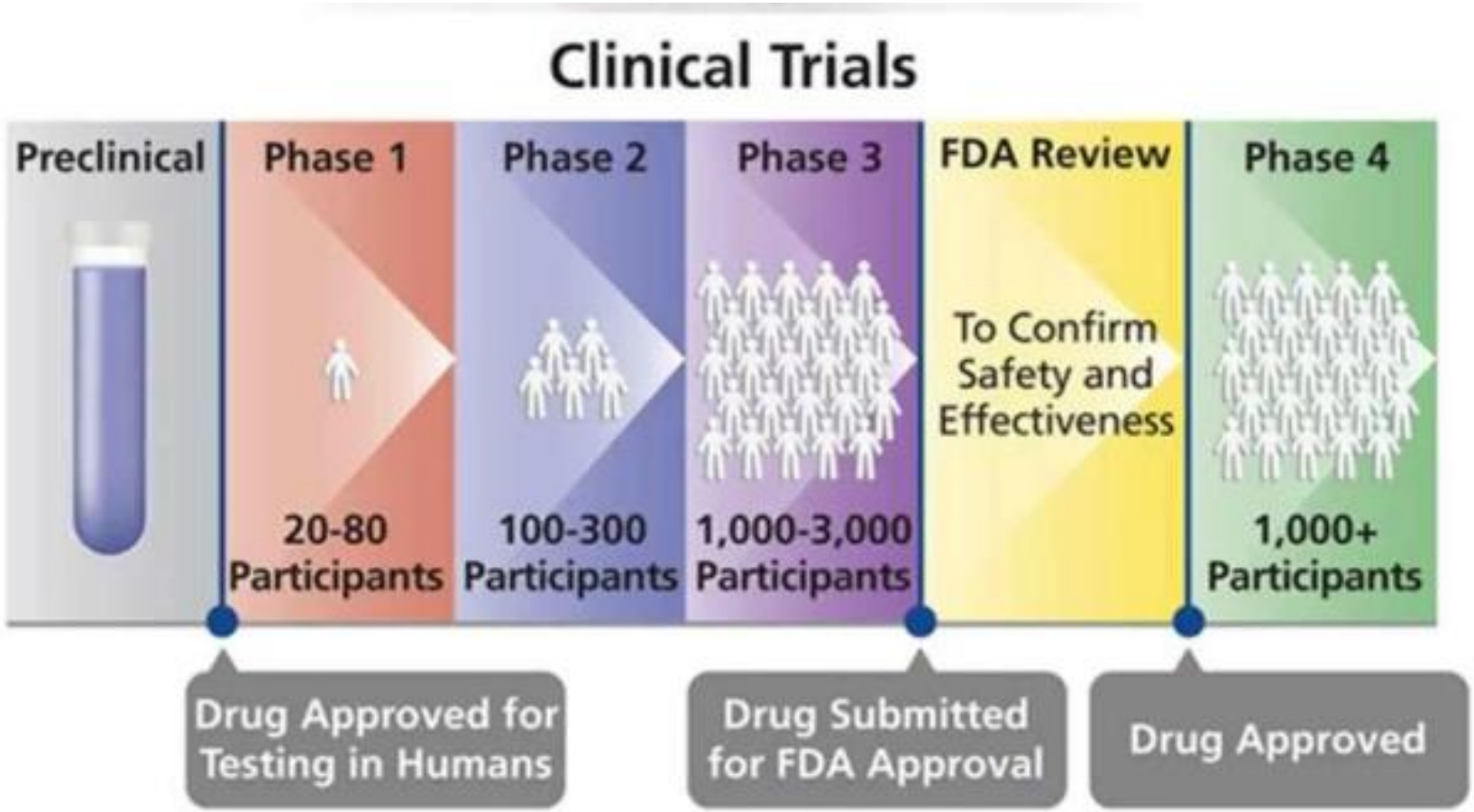
Summary

Background Treatment options for recurrent glioblastoma are scarce, with second-line chemotherapy showing only Lancet Oncol 2014; 15: 943-53

Phase 3 success?

Since 2005, more than 1,250 interventional glioblastoma trials have been registered on ClinicalTrials.gov. Of these, 1,100 are phase 1 or 2 trials, most of which are dose-escalation studies.

Singh et al Nat Comm 2023



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Comment

https://doi.org/10.1038/s41591-023-02464-8

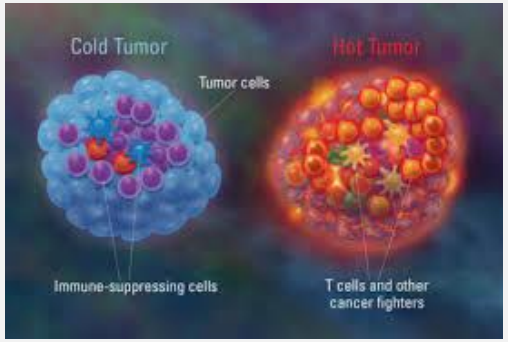
Correcting the drug development paradigm for glioblastoma requires serial tissue sampling

Kirit Singh, Kelly M. Hotchkiss, Ian F. Parney, John De Groot, Solmaz Sahebjam, Nader Sanai, Michael Platten, Evanthia Galanis, Michael Lim, Patrick Y. Wen, Giuseppe Minniti, Howard Colman, Timothy F. Cloughesy, Minesh P. Mehta, Marjolein Geurts, Isabel Arrillaga-Romany, Annick Desjardins, Kirk Tanner, Susan Short, David Arons, Elizabeth Duke, Wolfgang Wick, Stephen J. Bagley, David M. Ashley, Priya Kumthekar, Roel Verhaak, Anthony J. Chalmers, Anoop P. Patel, Colin Watts, Peter E. Fecci, Tracy T. Batchelor, Michael Weller, Michael A. Vogelbaum, Matthias Preusser, Mitchel S. Berger & Mustafa Khasraw

Singh et al Nat Comm 2023

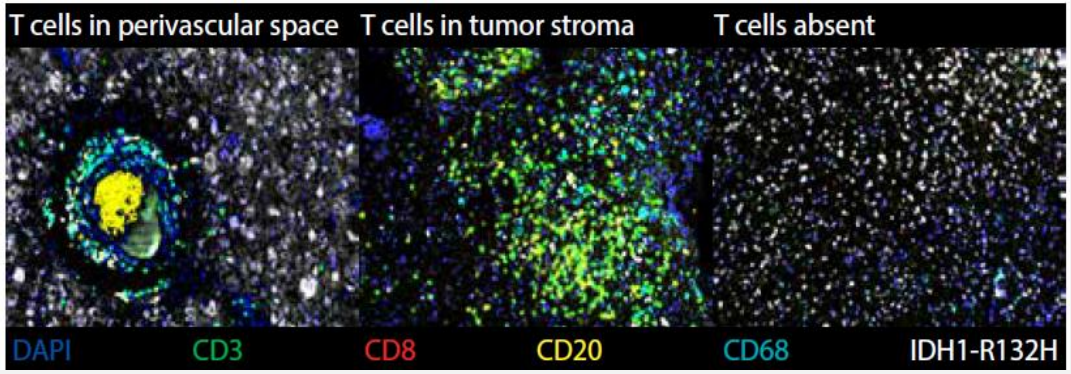
TRANSLATIONAL RESEARCH FOCUS: NEURO-ONCO-IMMUNOLOGY

Aim: Immunotherapy for glioma



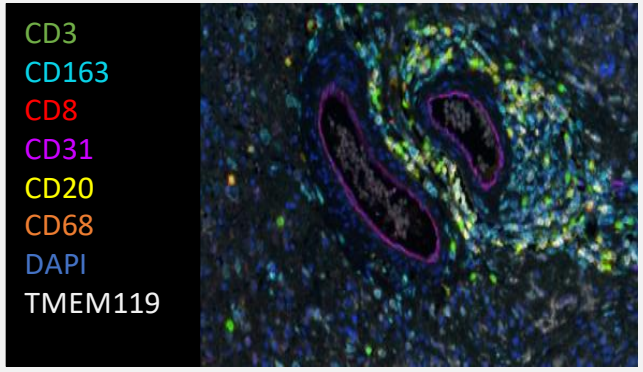
Step 1: Defining the immune cell landscape in glioma

Identification of three distinct patterns in the number and distribution of T cells in glioma

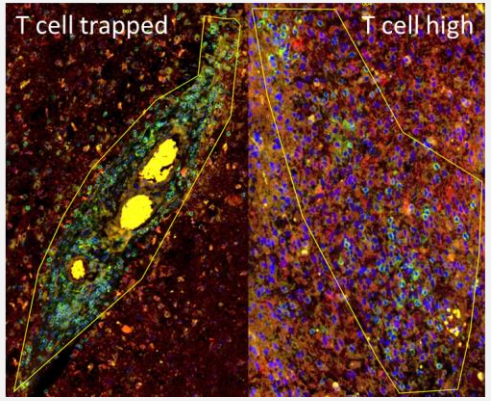


Multiplex immunohistochemistry
In collaboration with tumor immunology lab EMC (PI: Prof. Reno Debets)

Co-localization with macrophages

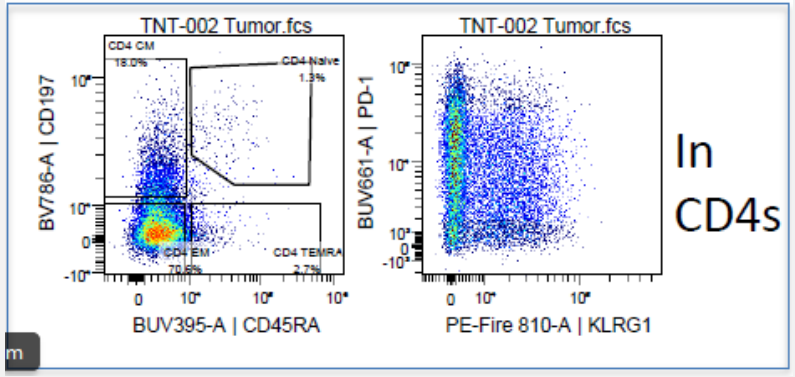


Step 2: Characterization of T cells



Spatial proteomics (Levi v Hijfte)

Characterization T cells in tumor vs peripheral blood



Spectral flow cytometry
Rosa Luning
Collab. with MS lab (Jasper Rip, Marvin v Luijn, Marie Jose Melief, Annet Wierenga)

SFX-01 IN GBM AT ERASMUS MC

Therapeutic failure in glioblastoma, A window of opportunity for SFX-01?

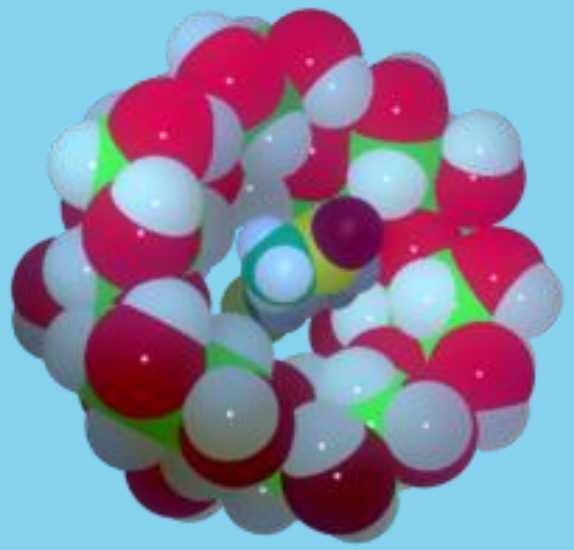
1 Experiments in test tubes 15-18 months

2 Experiments in mice 6-9 months

3 Early studies in patients

? Potential development of SFX-01 as treatment for glioblastoma

THERAPEUTIC FAILURE IN GLIOBLASTOMA – A WINDOW OF OPPORTUNITY FOR SFX-01?



Wouter Vanbilloen

PhD candidate, Neurology resident

Promotor Prof. Dr. P.J. French

Co-promotors Dr. Geurts and Dr. Lamfers

13-06-2024

SFX-01 IN GBM AT ERASMUS MC

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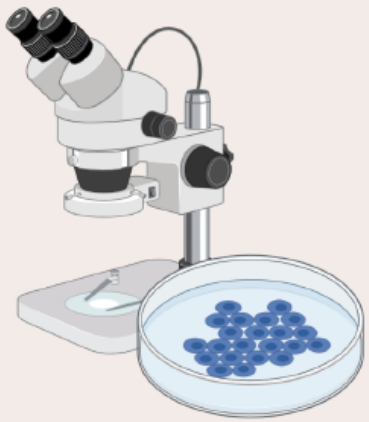

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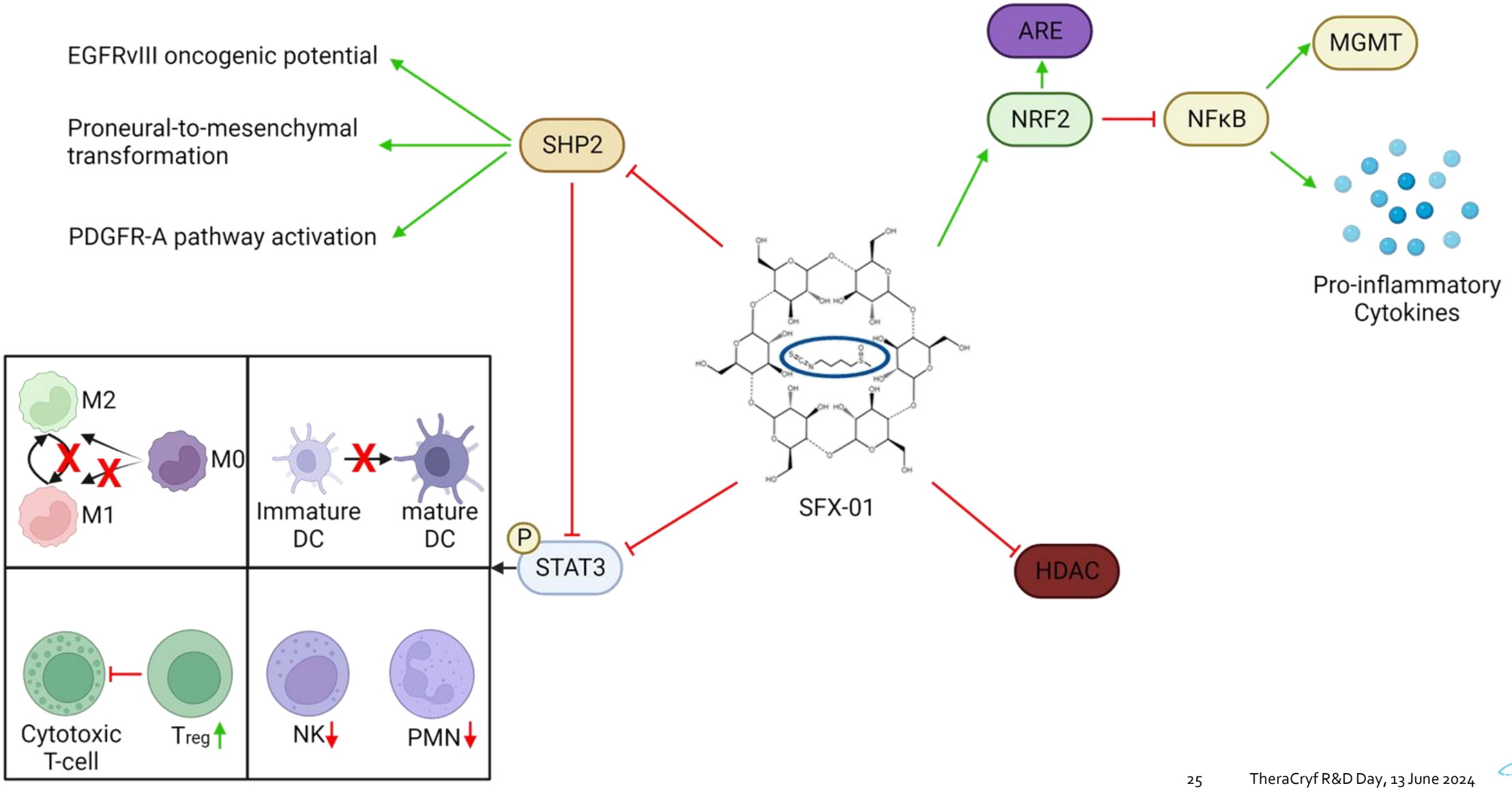
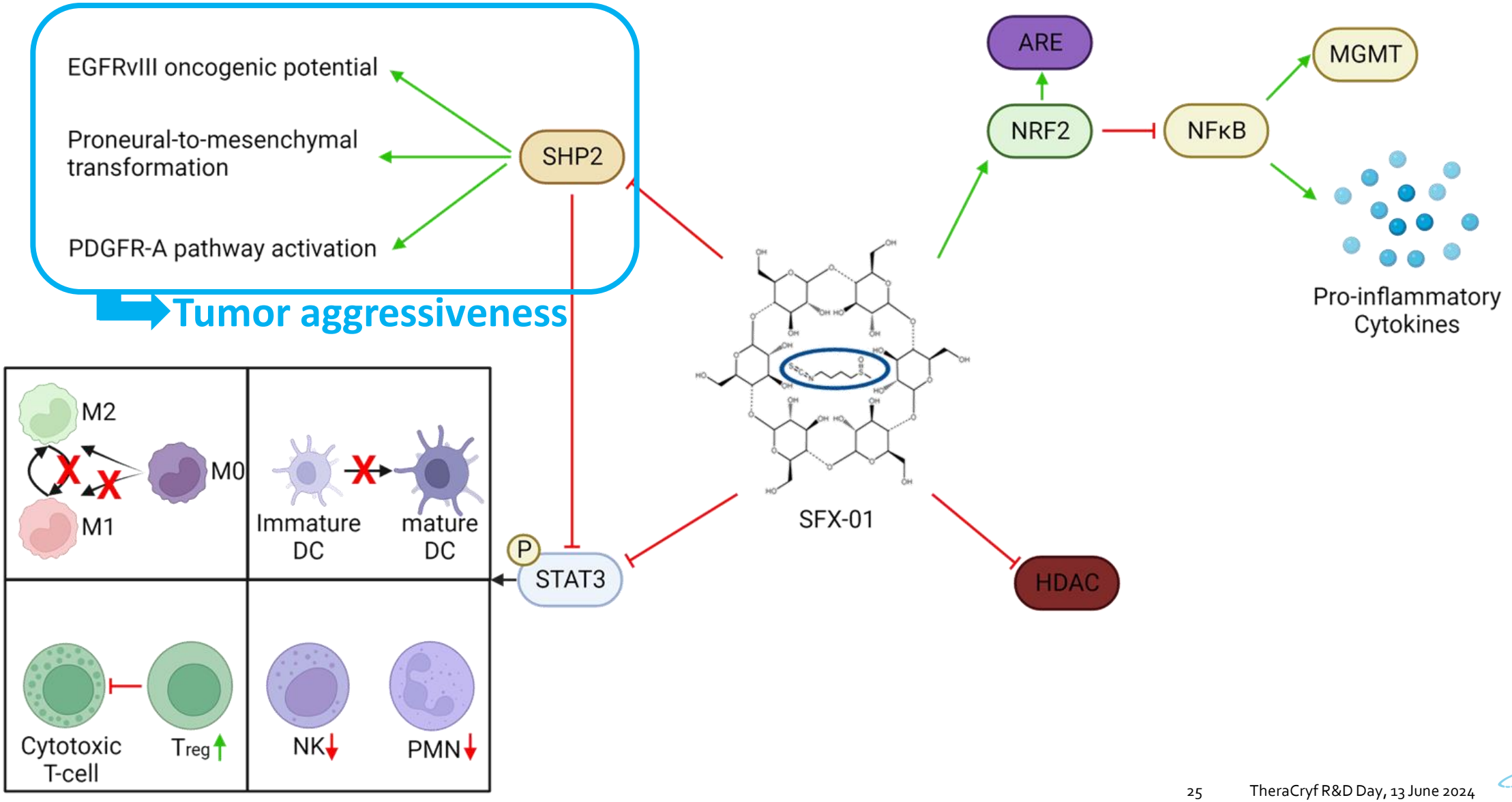
? Potential development of SFX-01 as treatment for glioblastoma

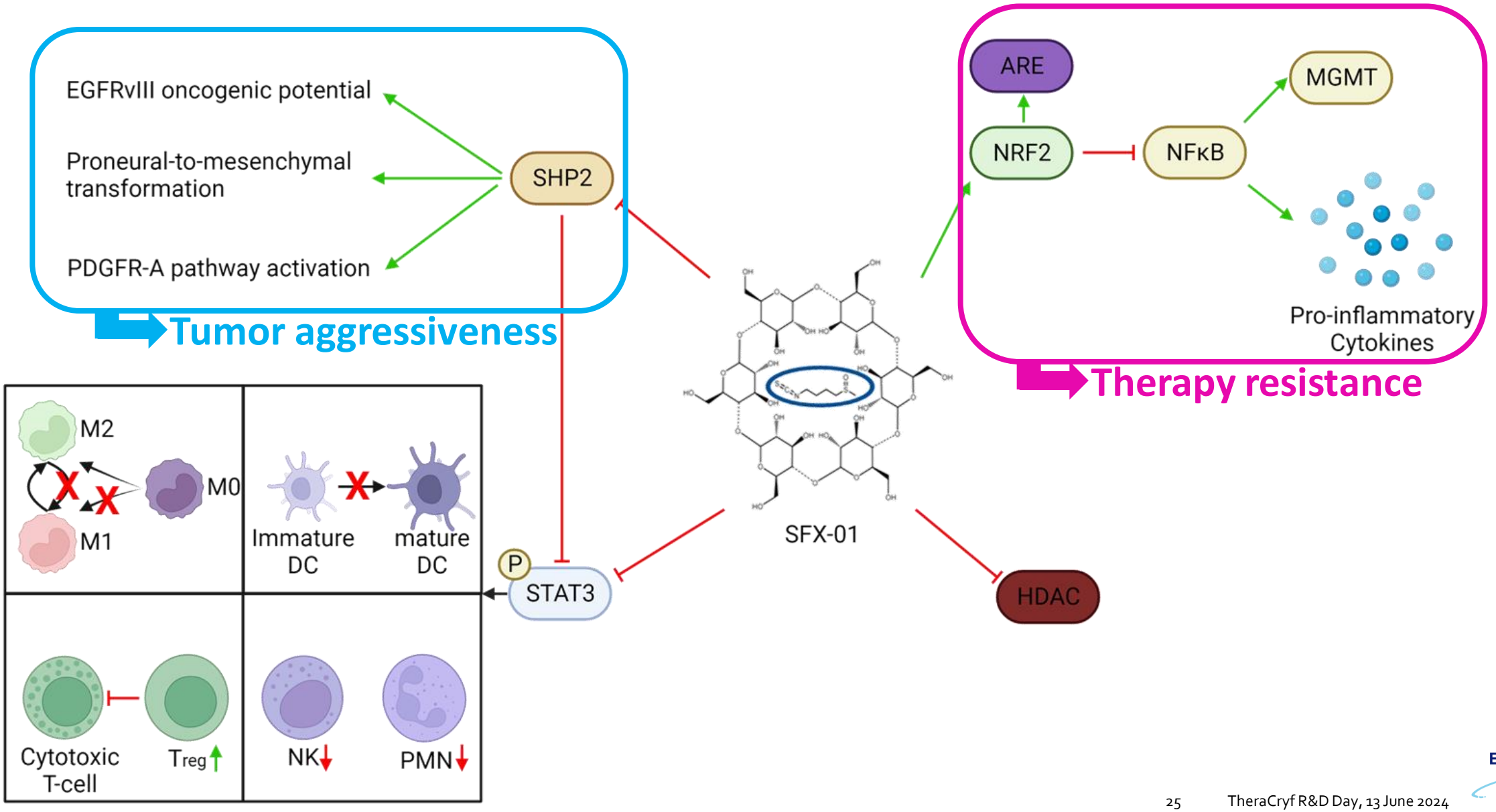
SFX-01 IN GBM AT ERASMUS MC



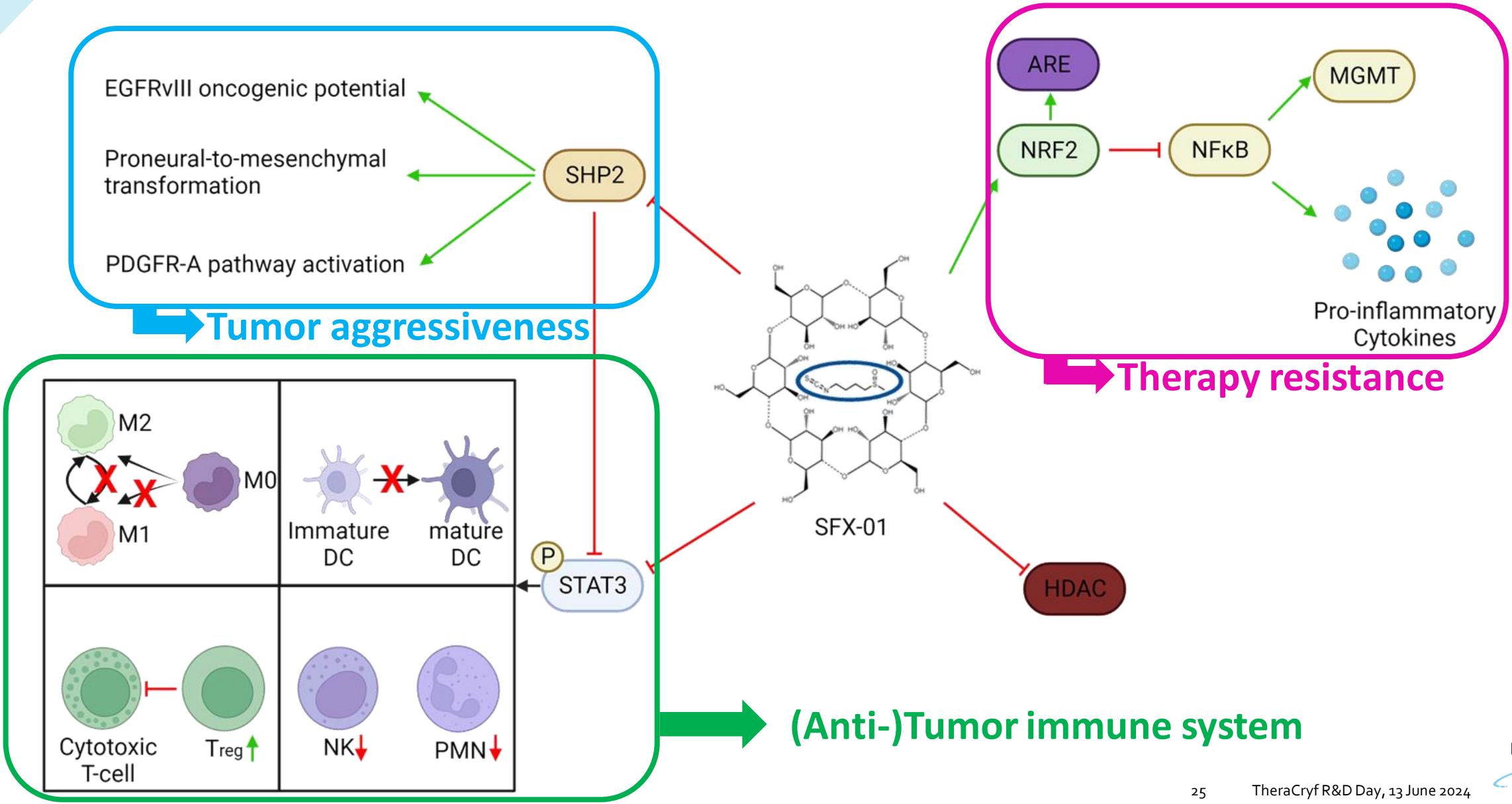
SFX-01 IN GBM AT ERASMUS MC



SFX-01 IN GBM AT ERASMUS MC

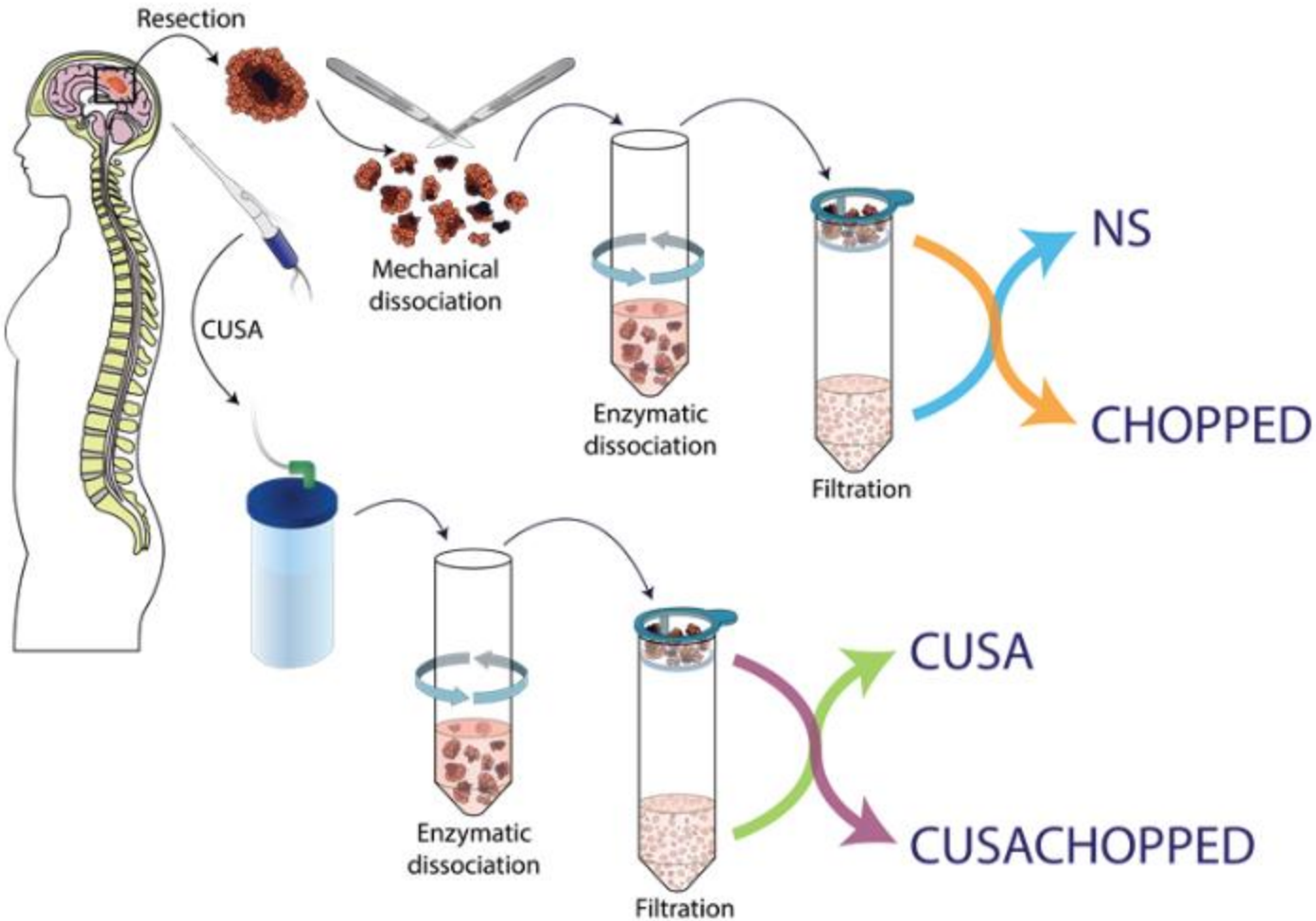


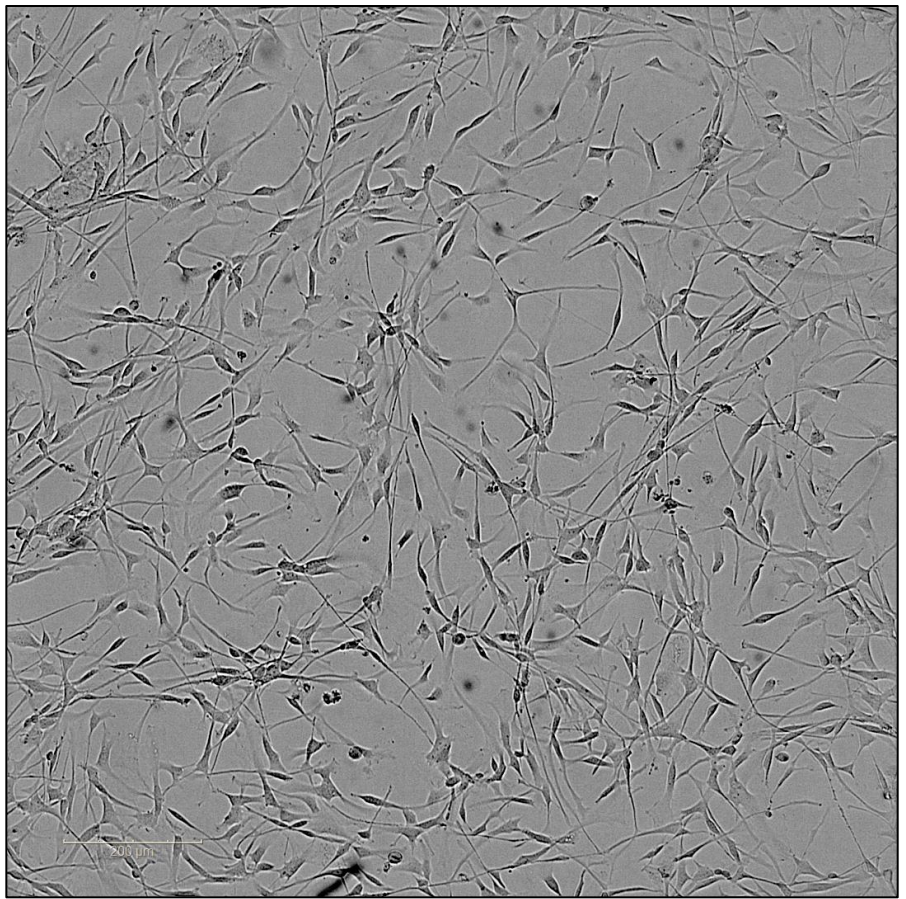
SFX-01 IN GBM AT ERASMUS MC



PATIENT-DERIVED TUMOR CELLS

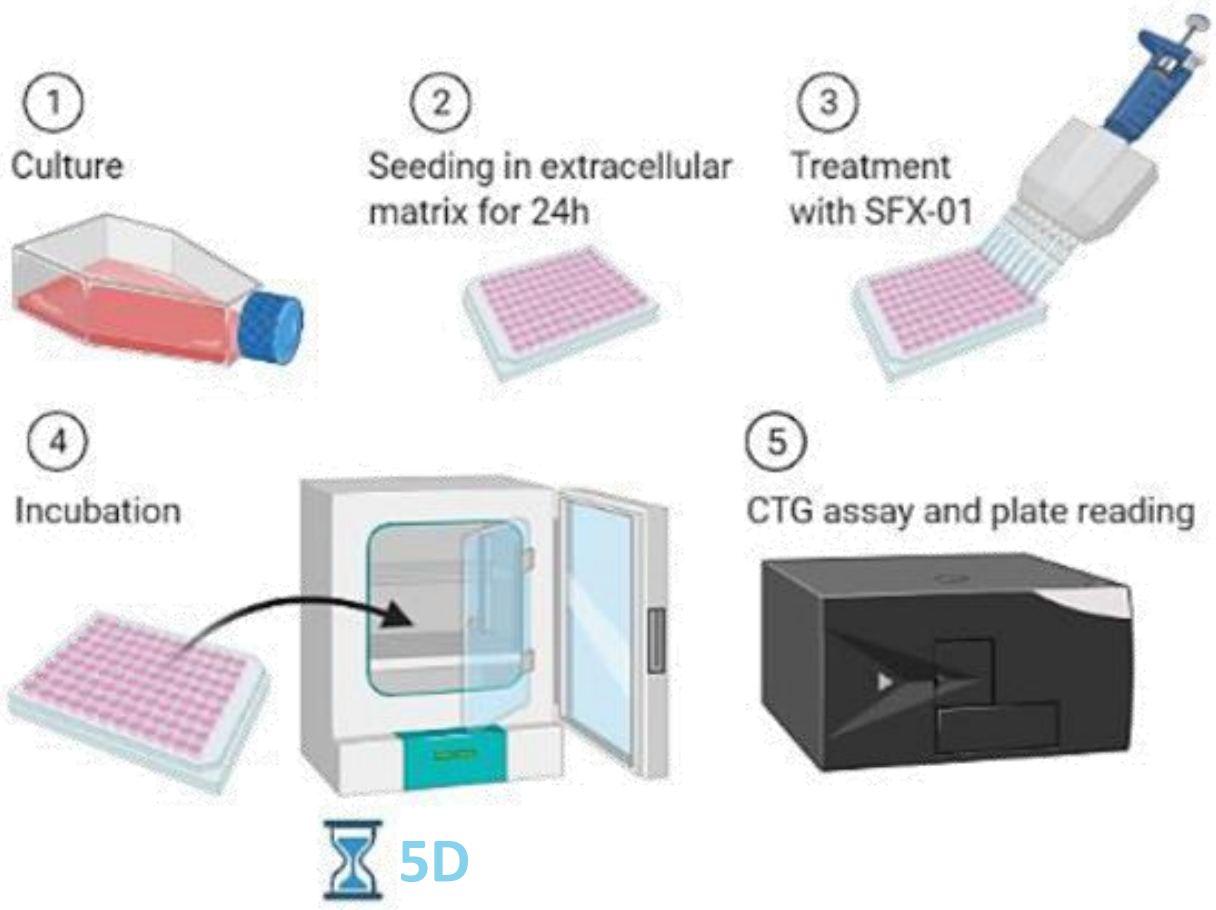
Dr. M.L.M. Lamfers



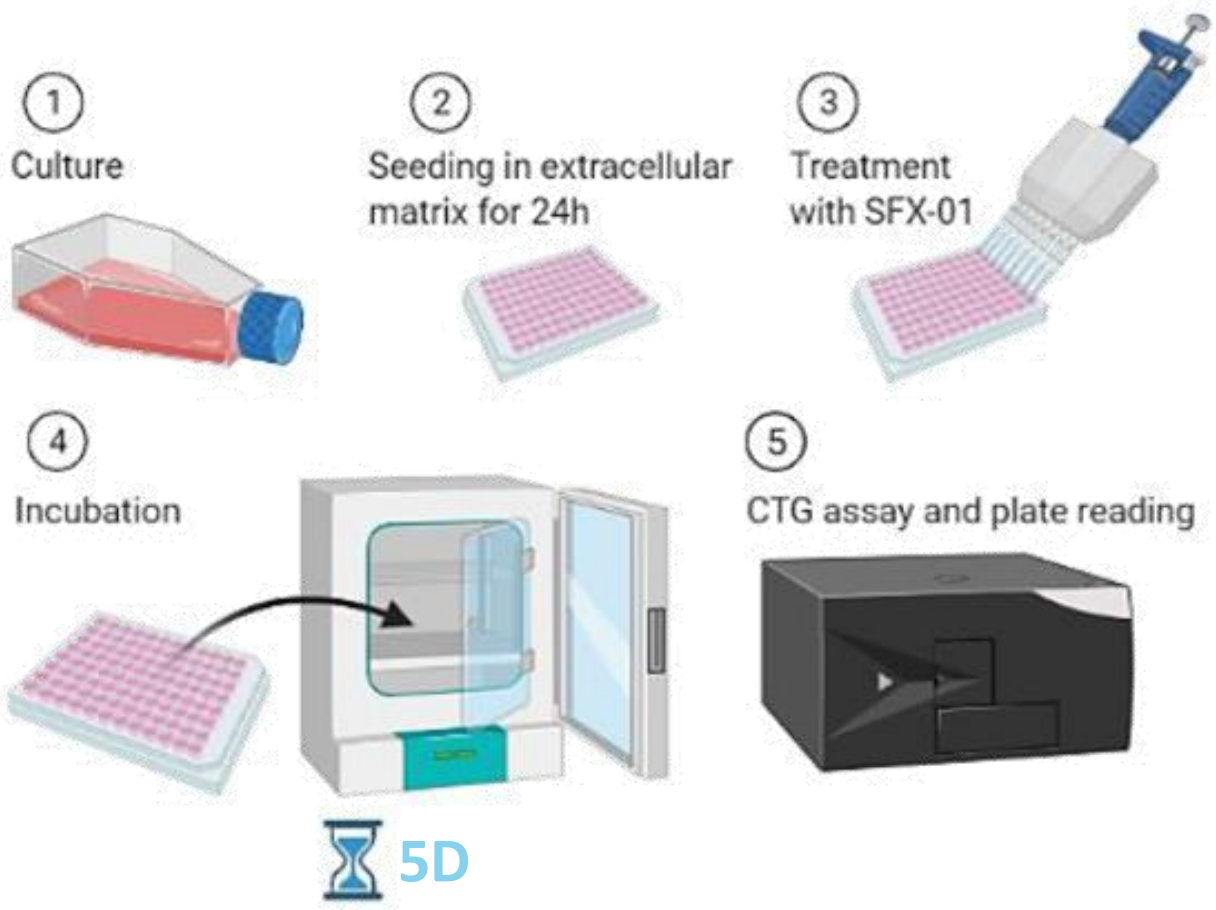


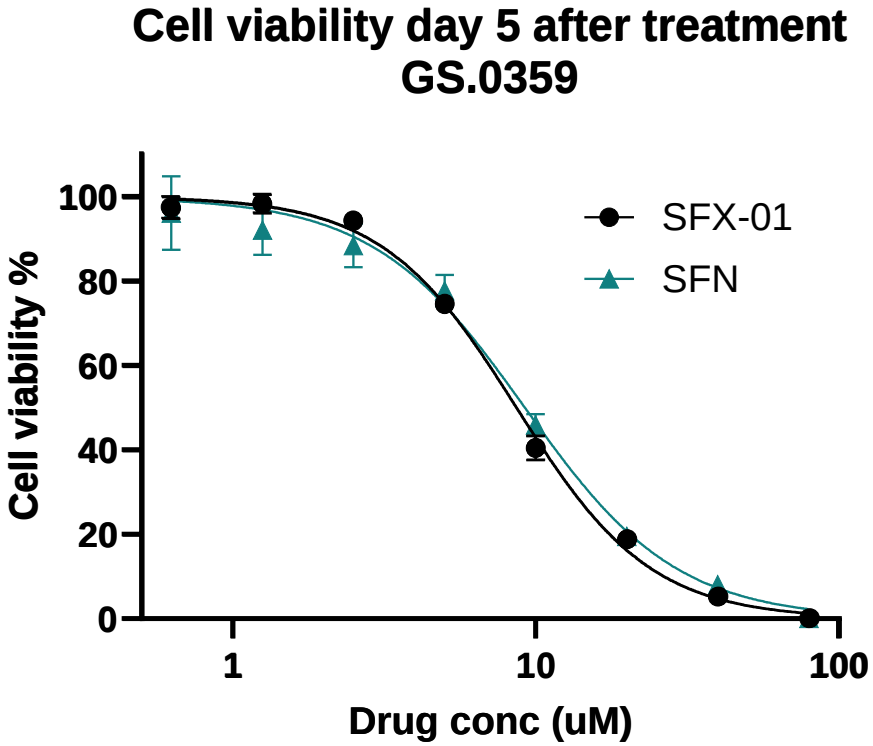
Ntafoulis et al, 2023, British Journal of Cancer

SFX-01 IN GBM CELLS

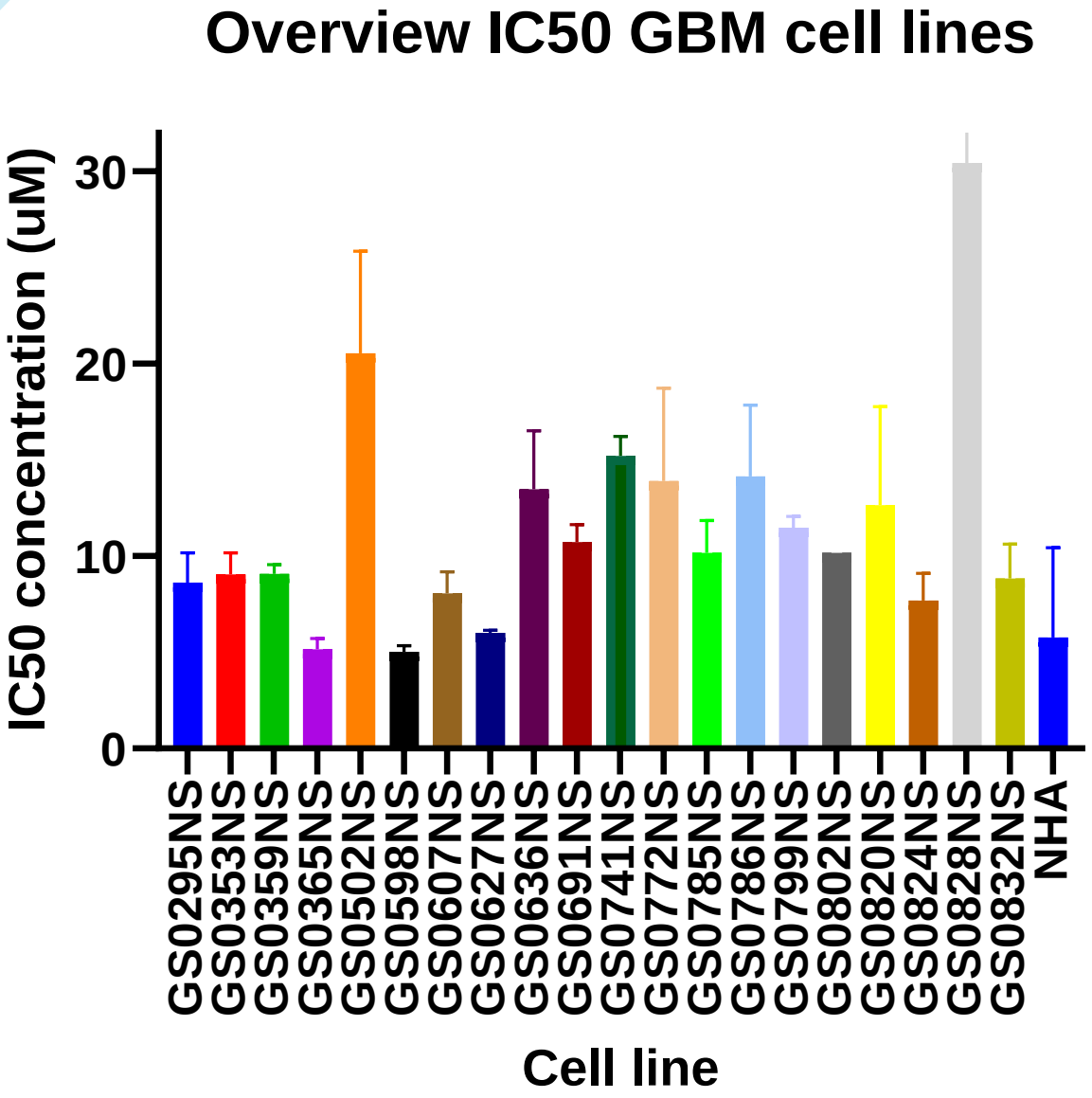


SFX-01 IN GBM CELLS



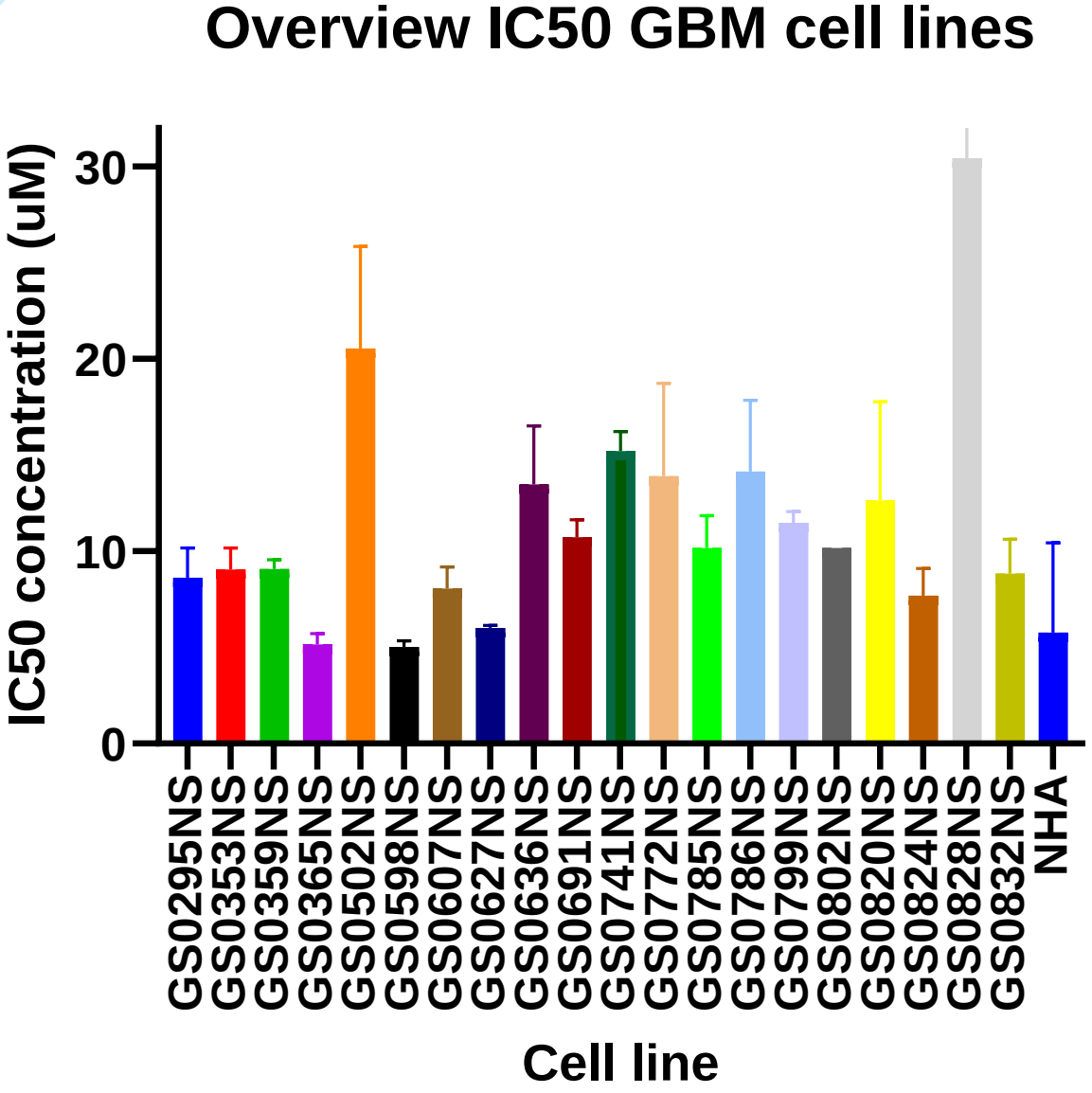


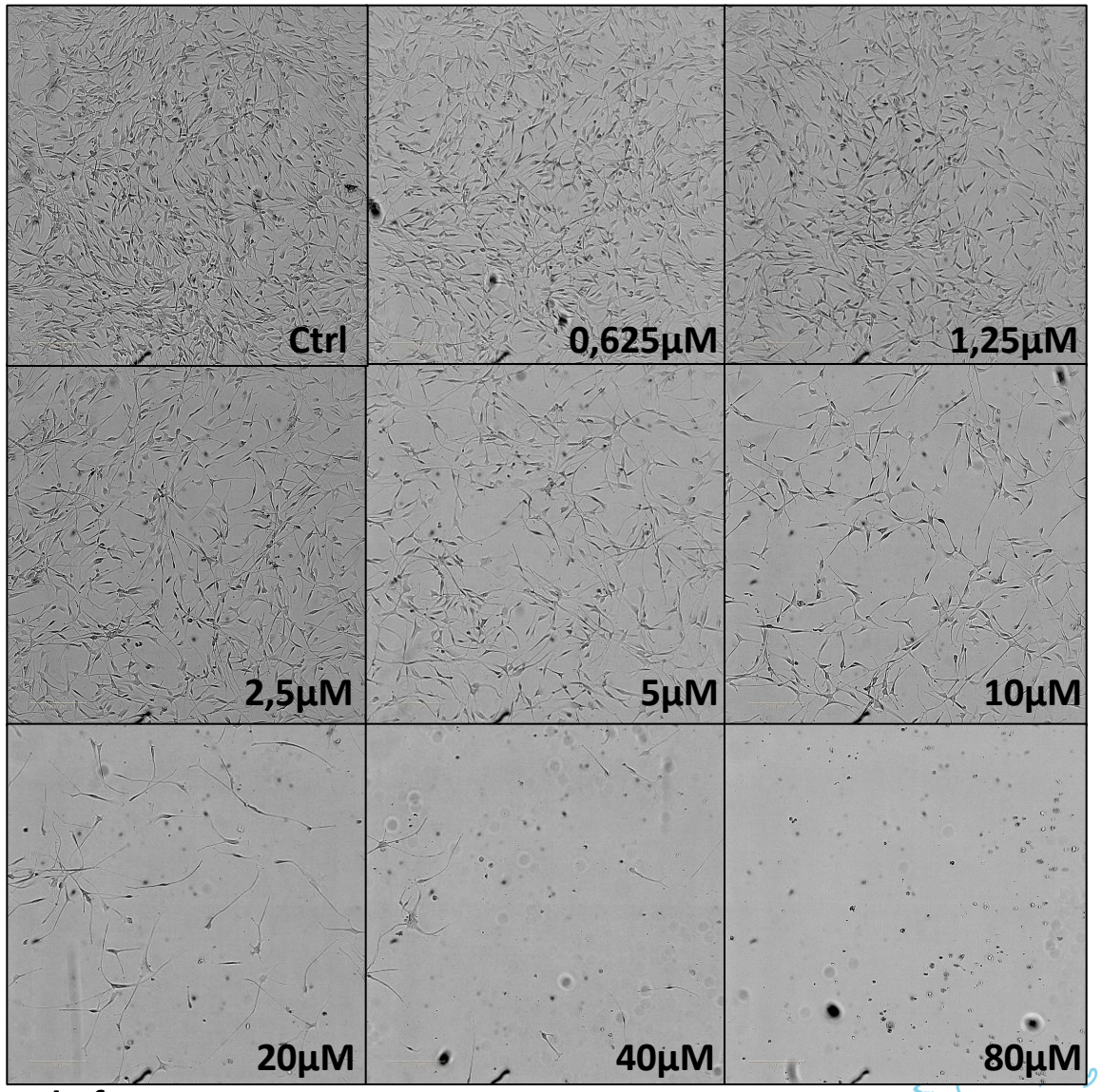
SFX-01 IN GBM CELLS



Erasmus MC

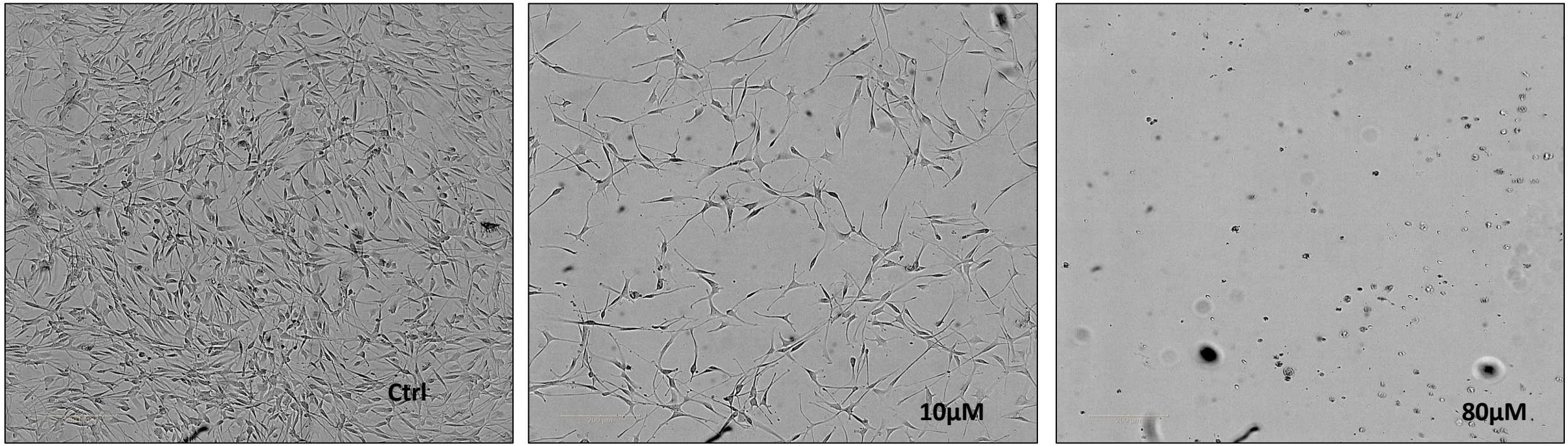
SFX-01 IN GBM CELLS





7d after treatment

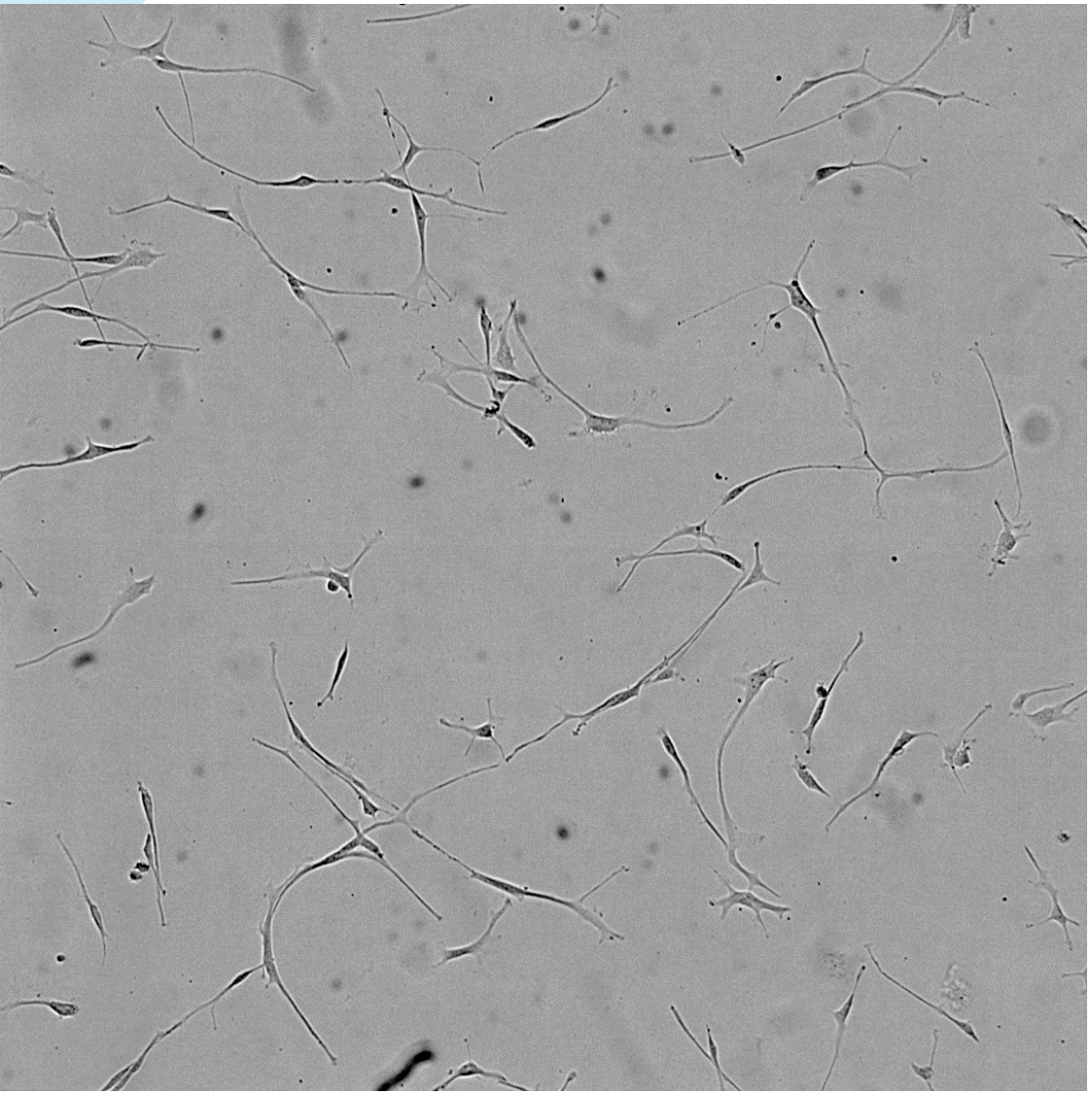
SFX-01 IN GBM CELLS



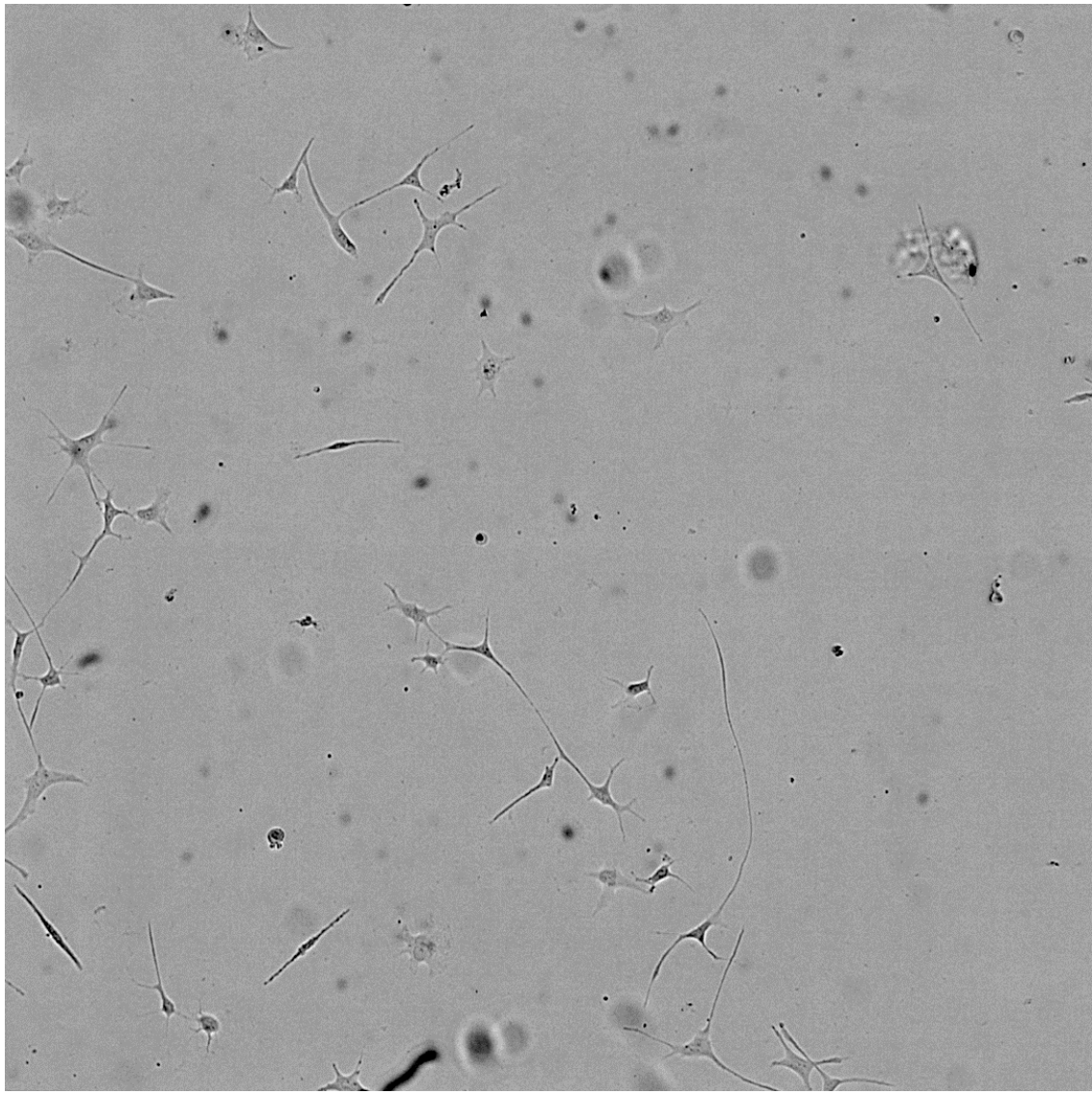
7d after treatment

Erasmus MC

SFX-01 IN GBM CELLS



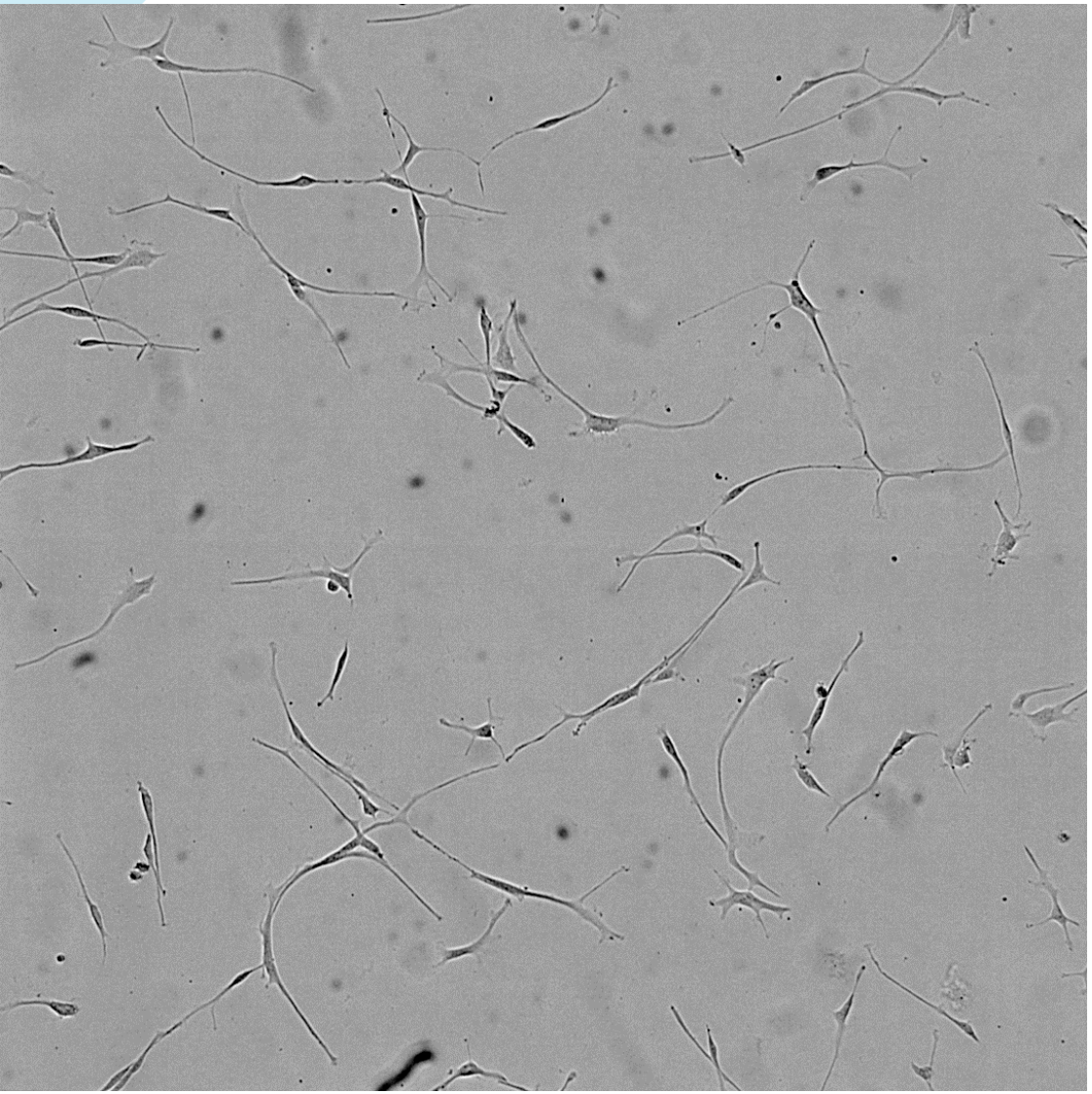
Control

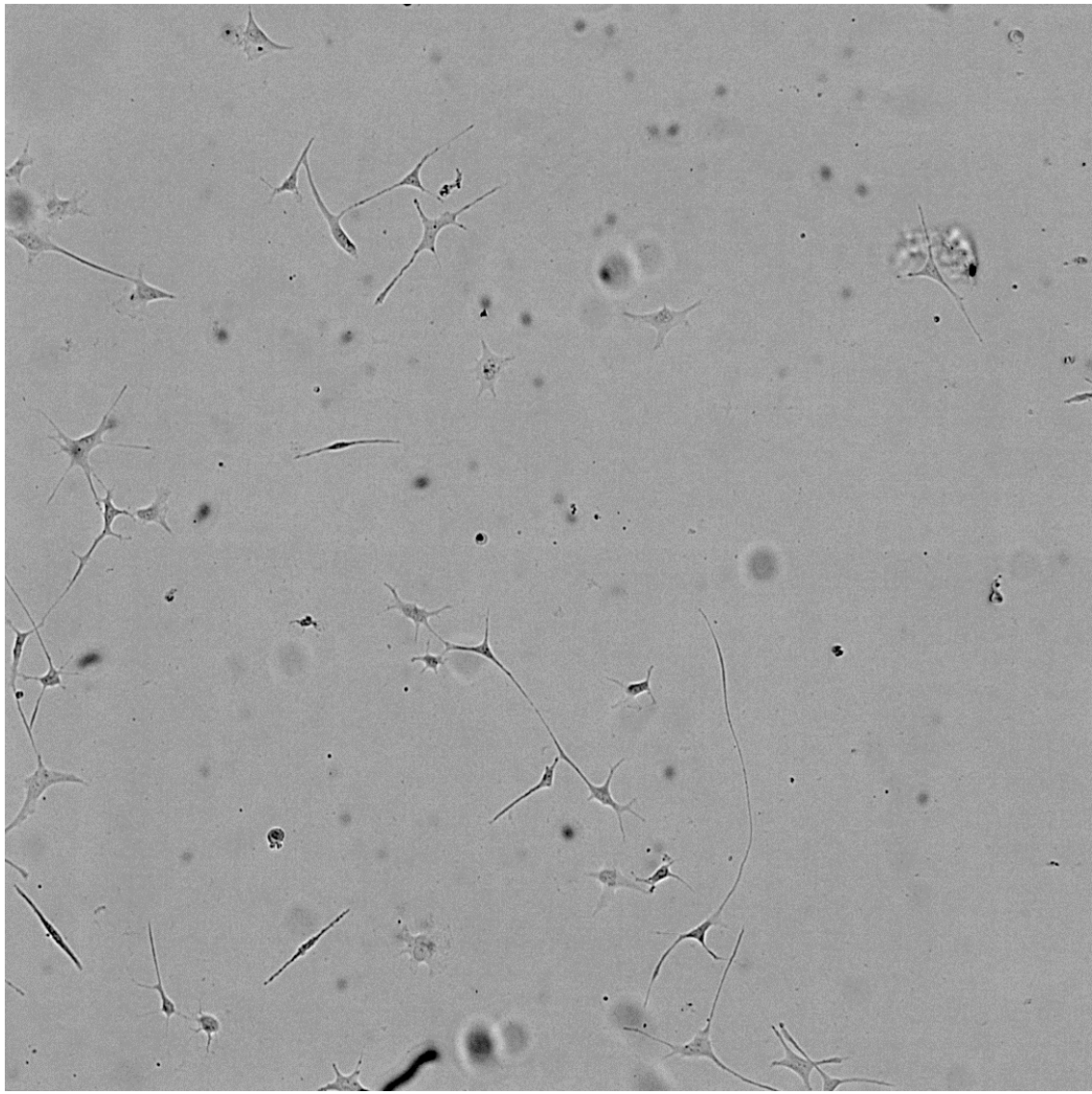


20µM

Erasmus MC

SFX-01 IN GBM CELLS





Control **20µM**

→ SFX-01 kills and slows growth rate of patient-derived glioblastoma cells in flasks

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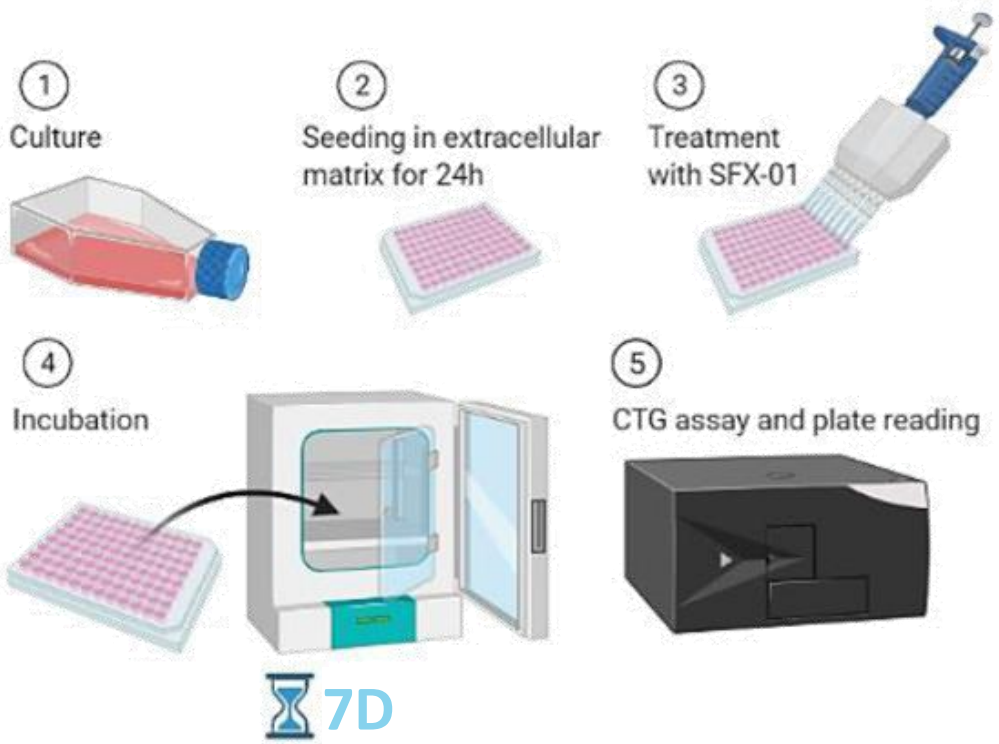
COMBINATION THERAPY SFX-01 - RADIOTHERAPY



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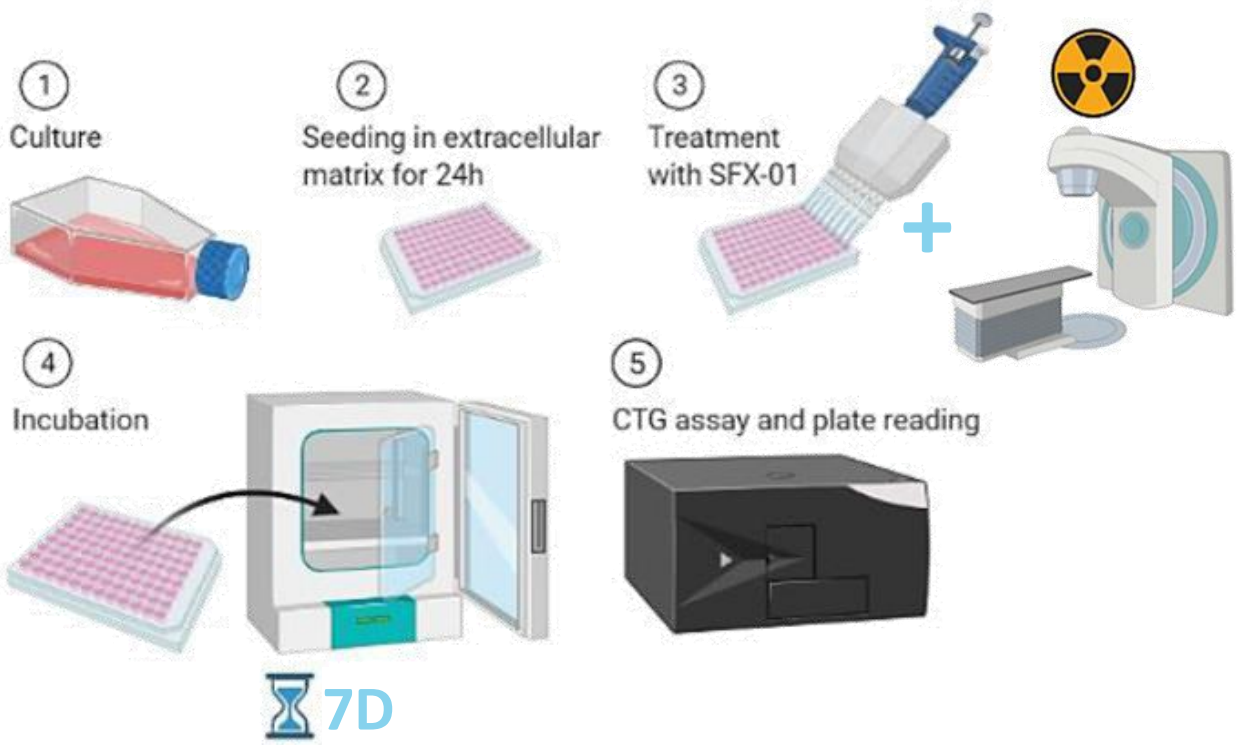
COMBINATION THERAPY SFX-01 - RADIOTHERAPY



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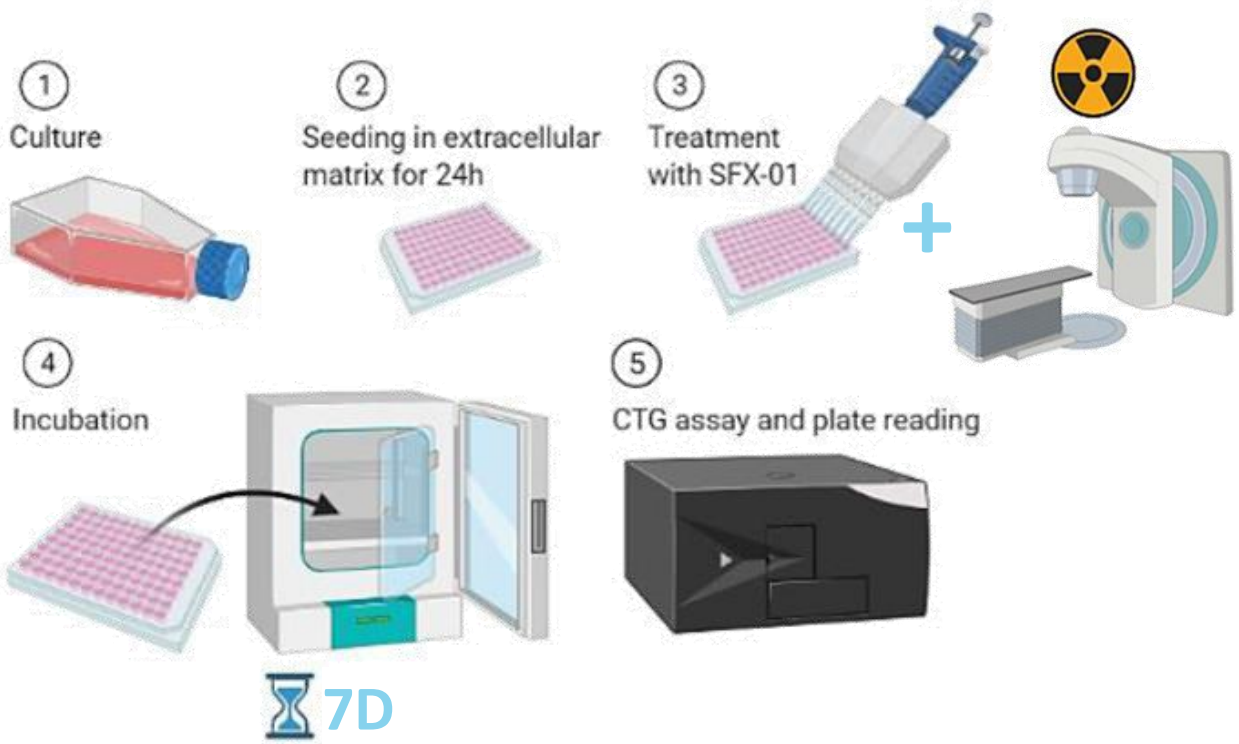
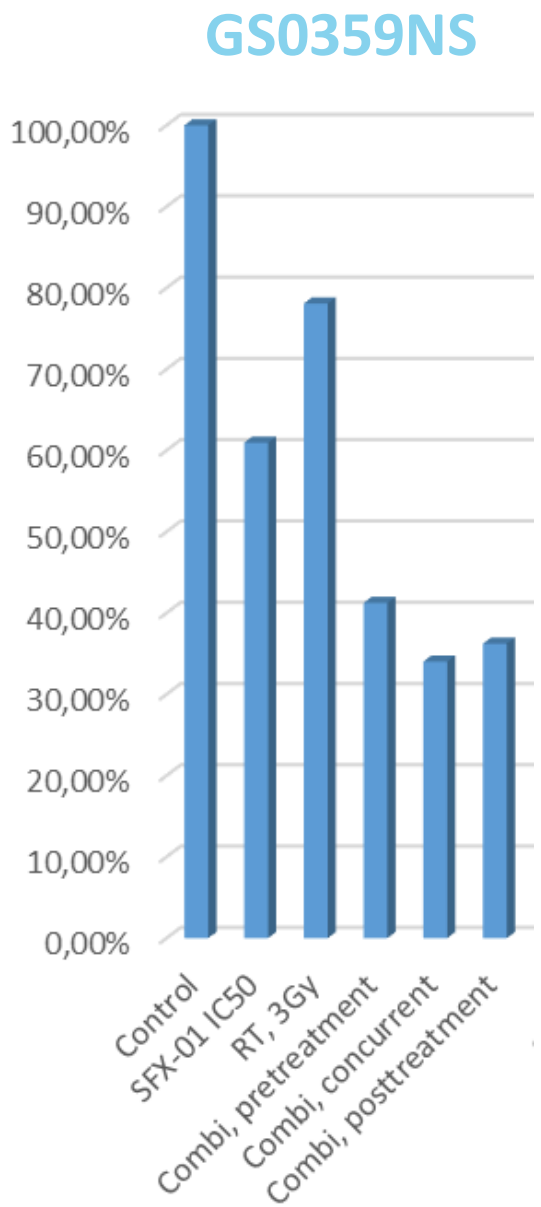
COMBINATION THERAPY SFX-01 - RADIOTHERAPY





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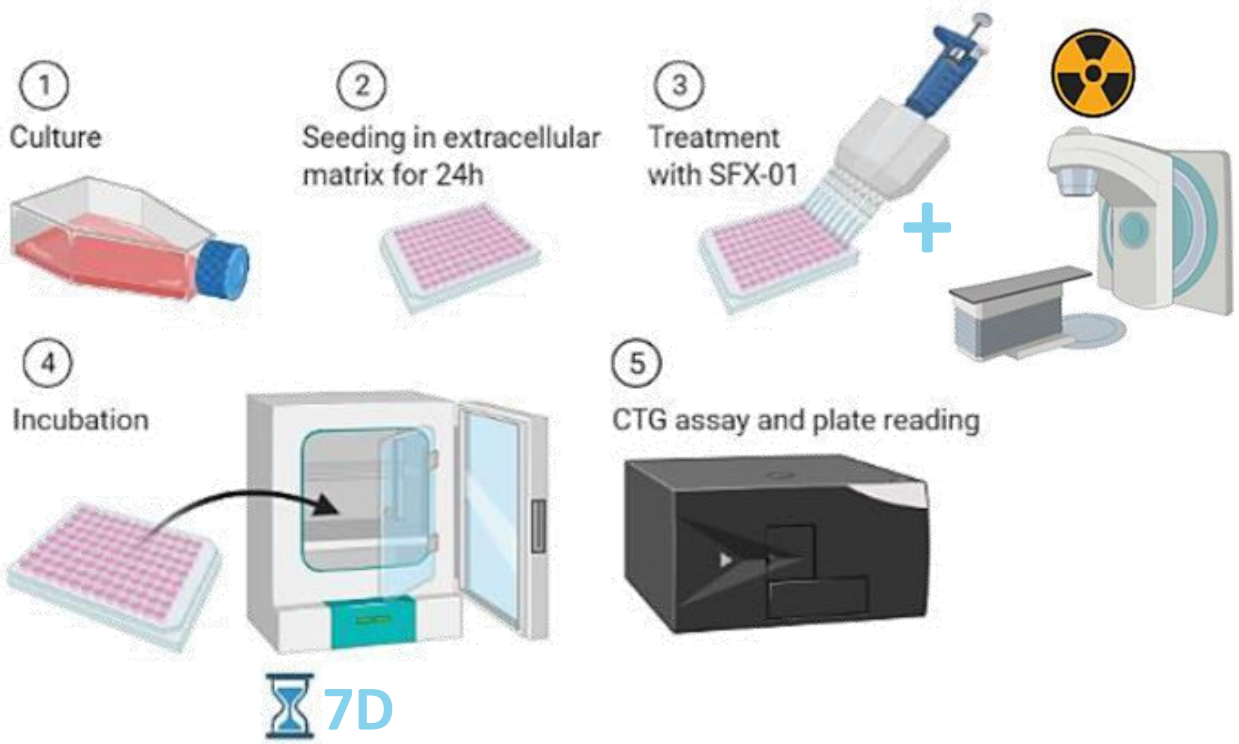

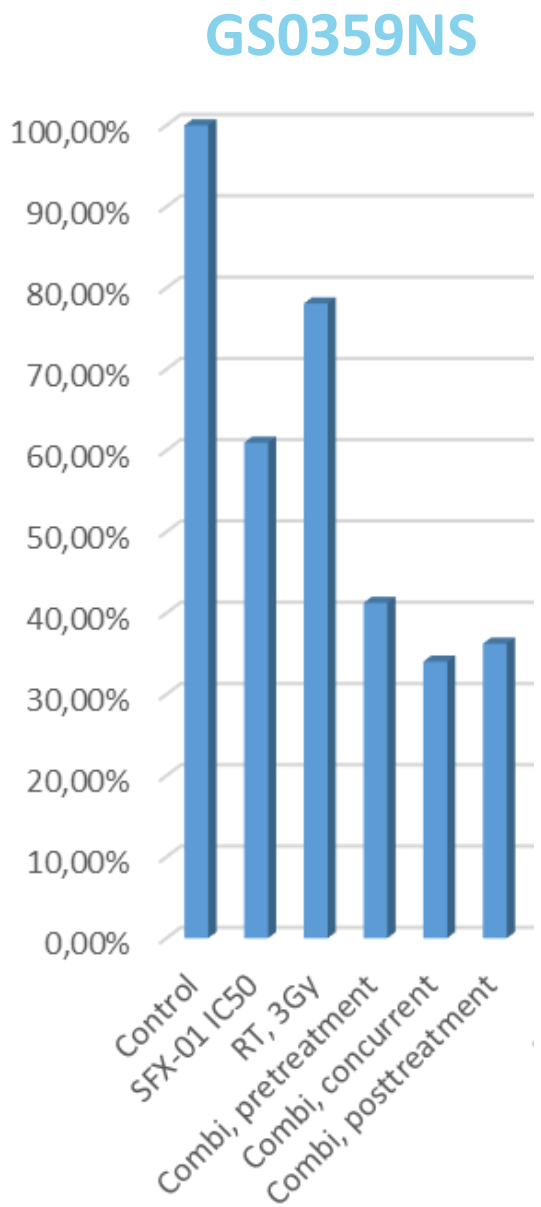

→ SFX-01 could add to radiotherapy effect in some patient-derived glioblastoma cells

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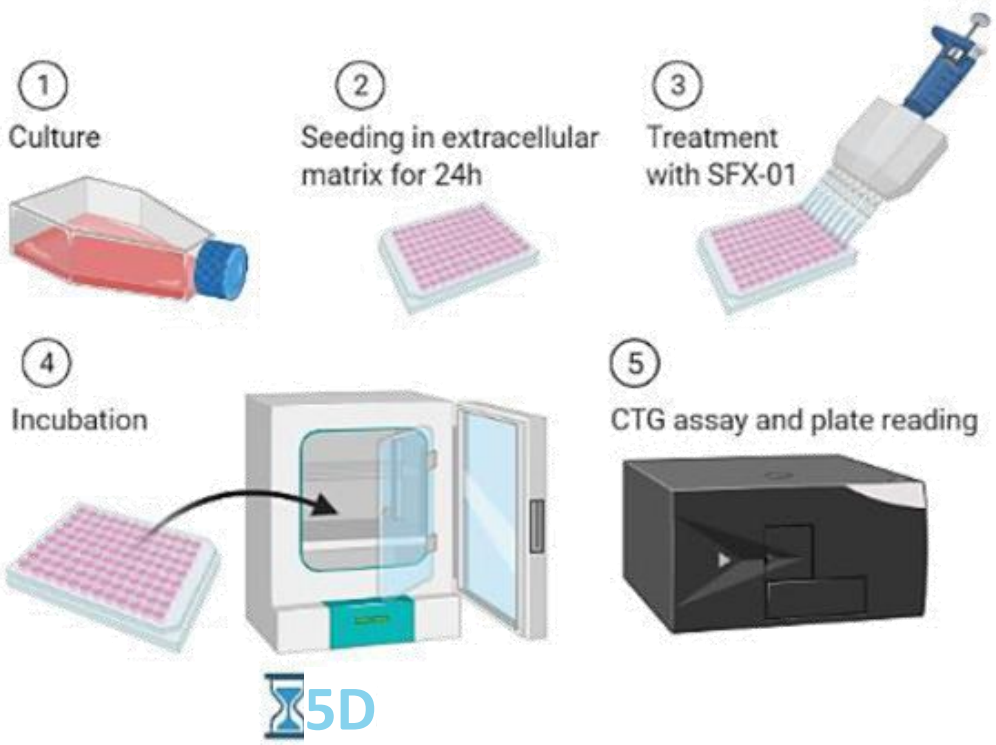
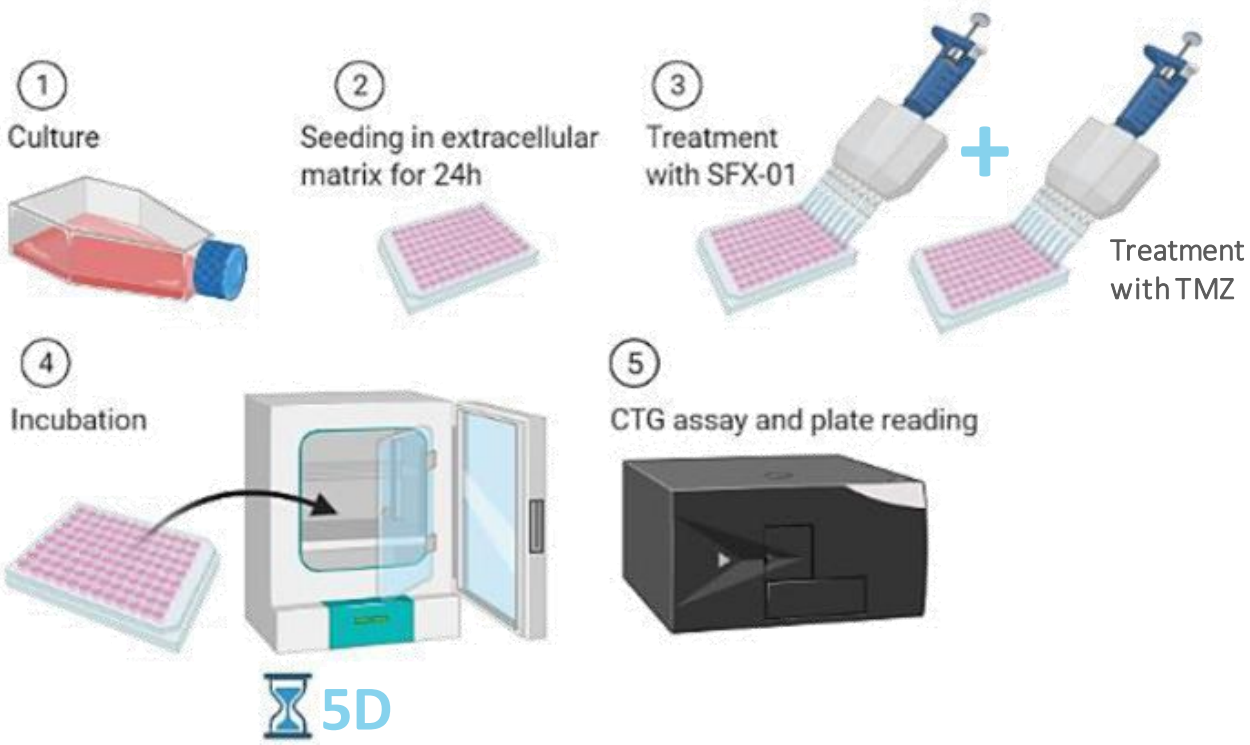
COMBINATION THERAPY SFX-01 - TEMOZOLOMIDE

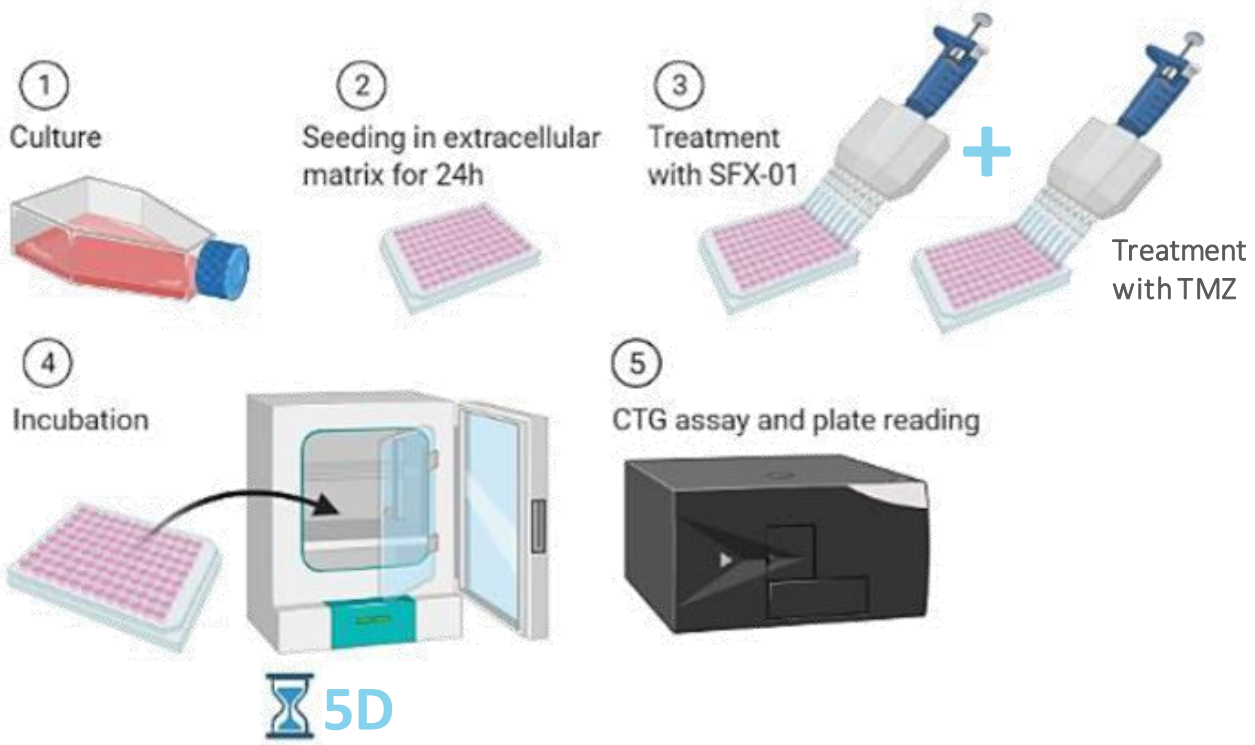


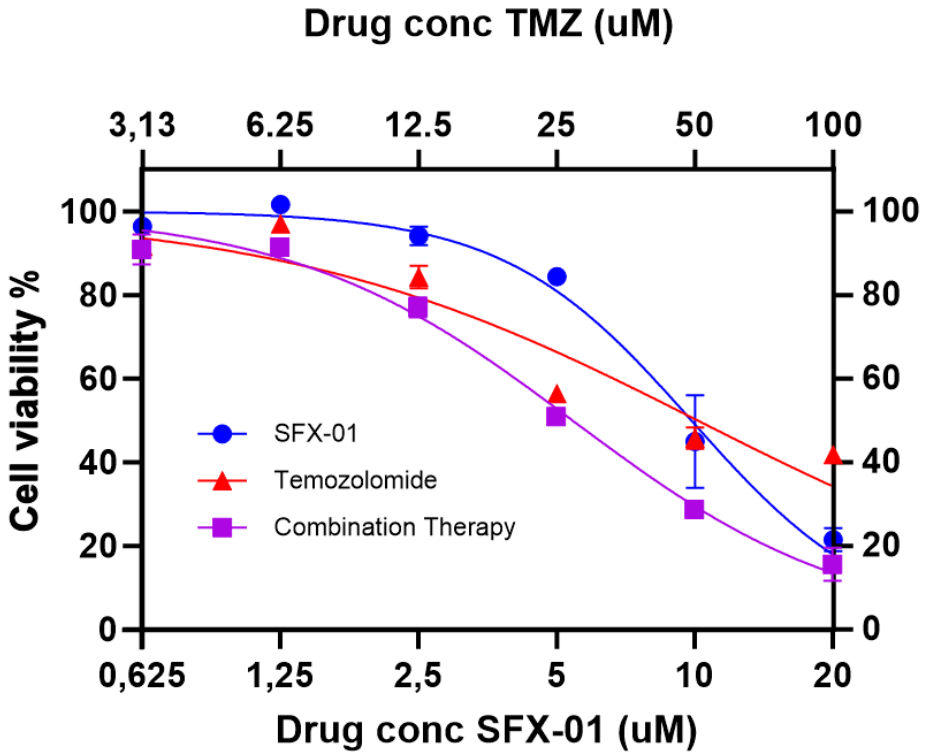
COMBINATION THERAPY SFX-01 - TEMOZOLOMIDE



COMBINATION THERAPY SFX-01 - TEMOZOLOMIDE

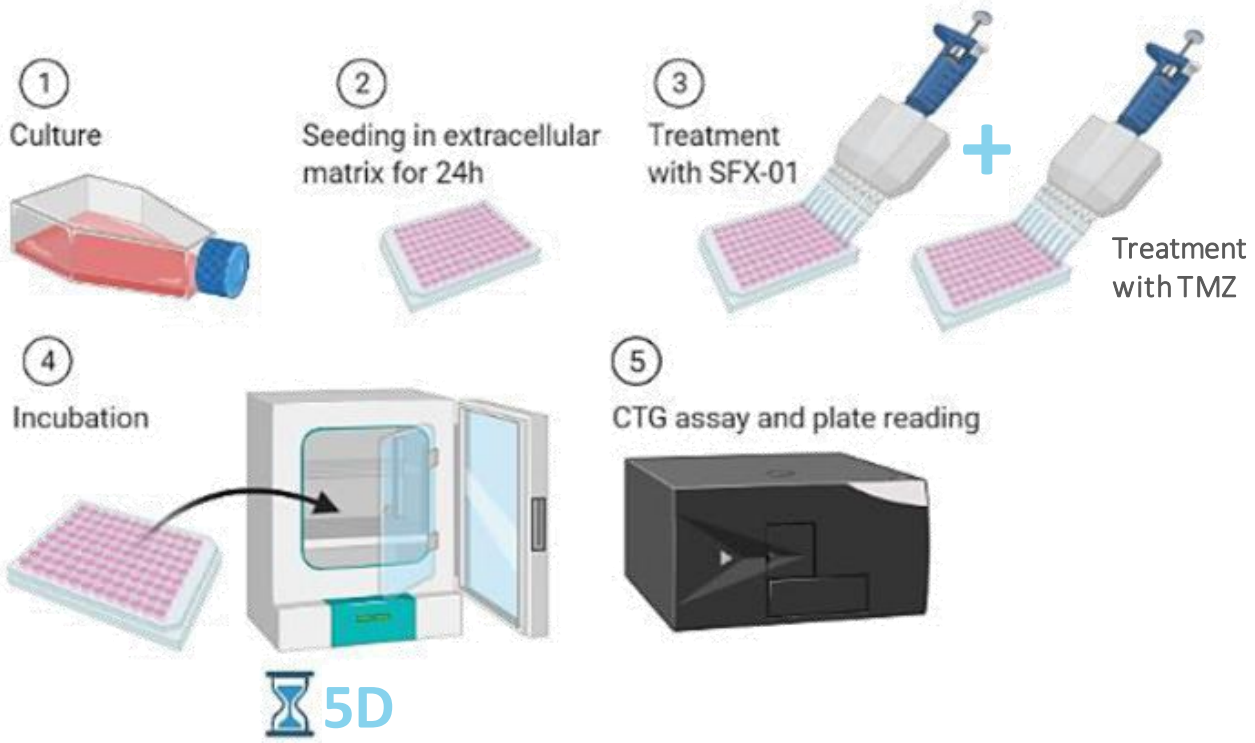
GS0359NS

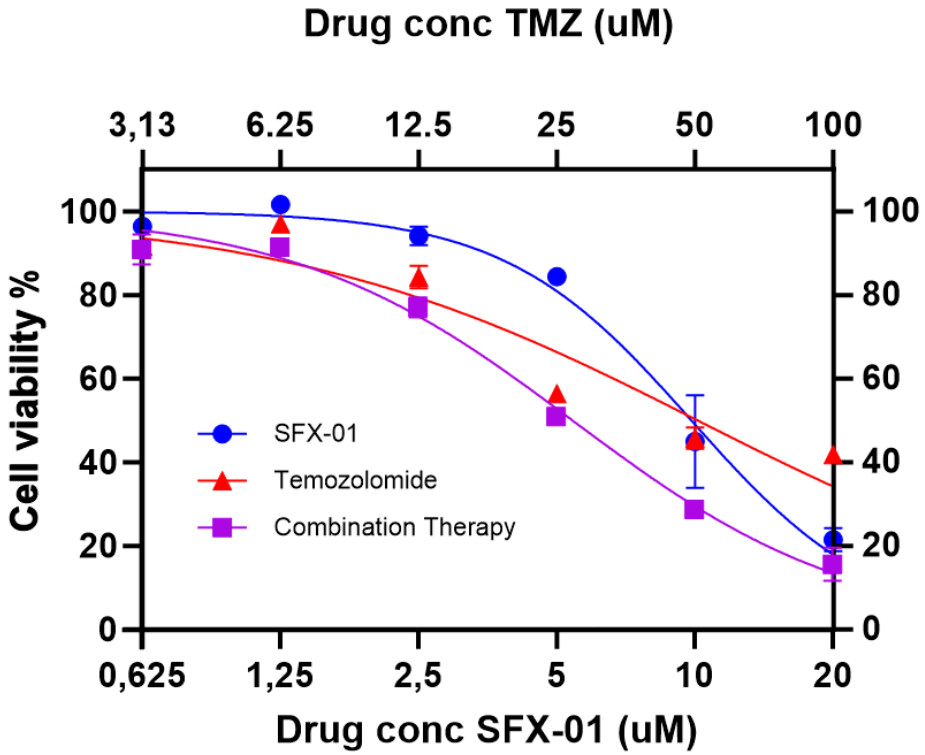




COMBINATION THERAPY SFX-01 - TEMOZOLOMIDE

GS0359NS



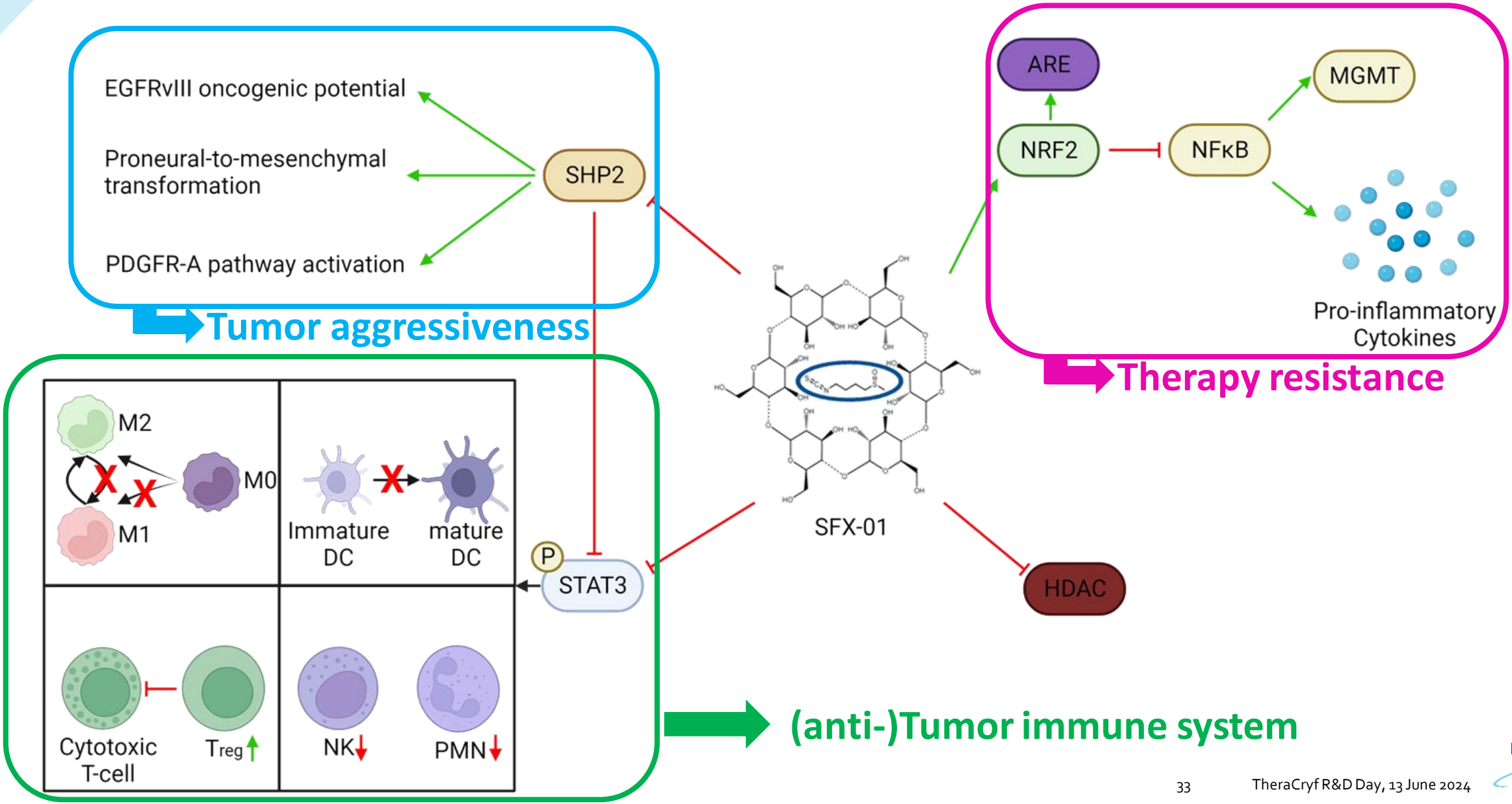


→ SFX-01 could add to temozolomide effect in specific patient-derived glioblastoma cells

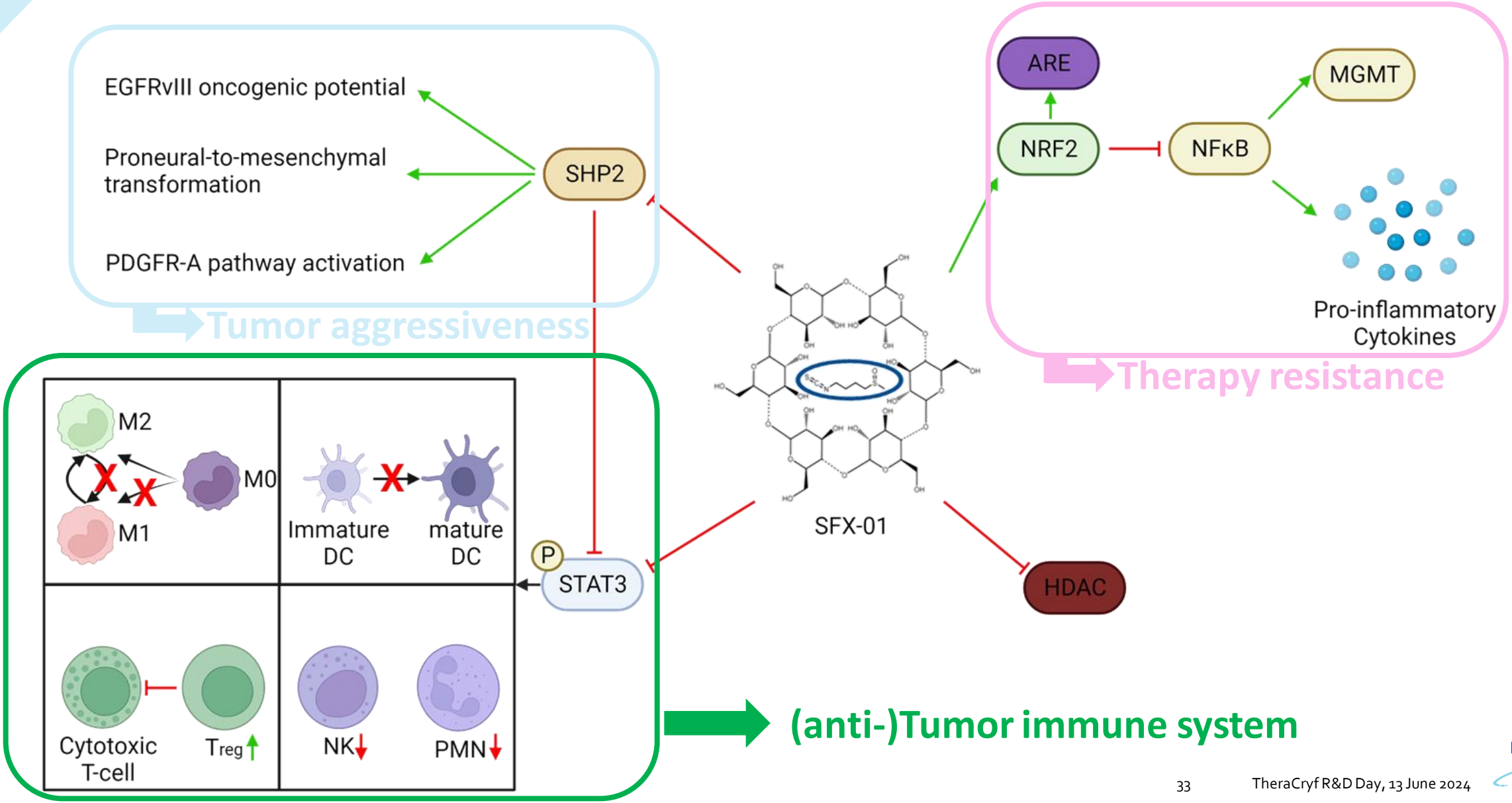
PRELIMINARY CONCLUSIONS

- SFX-01 kills patient-derived glioblastoma cells and slows tumor growth in flasks
- SFX-01 could add to radiotherapy effect in specific patient-derived glioblastoma cells
- SFX-01 could add to temozolomide chemotherapy in specific patient-derived glioblastoma cells

TO DO: ANTI-TUMOR IMMUNE SYSTEM



TO DO: ANTI-TUMOR IMMUNE SYSTEM



(anti-)Tumor immune system

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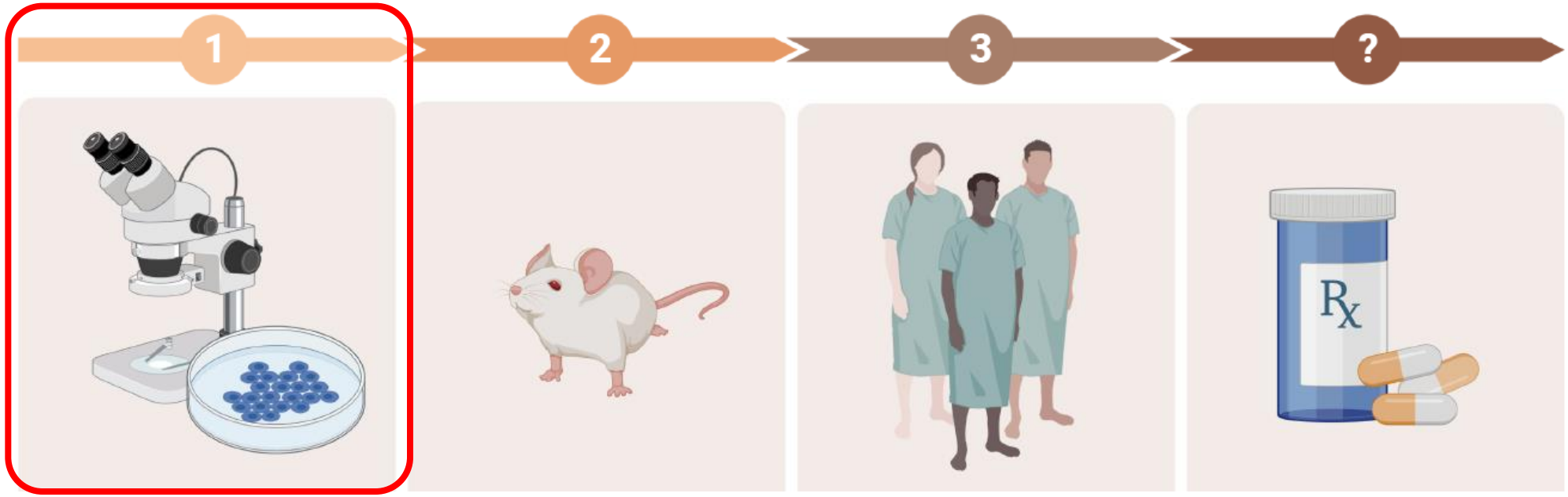
NEXT STEPS



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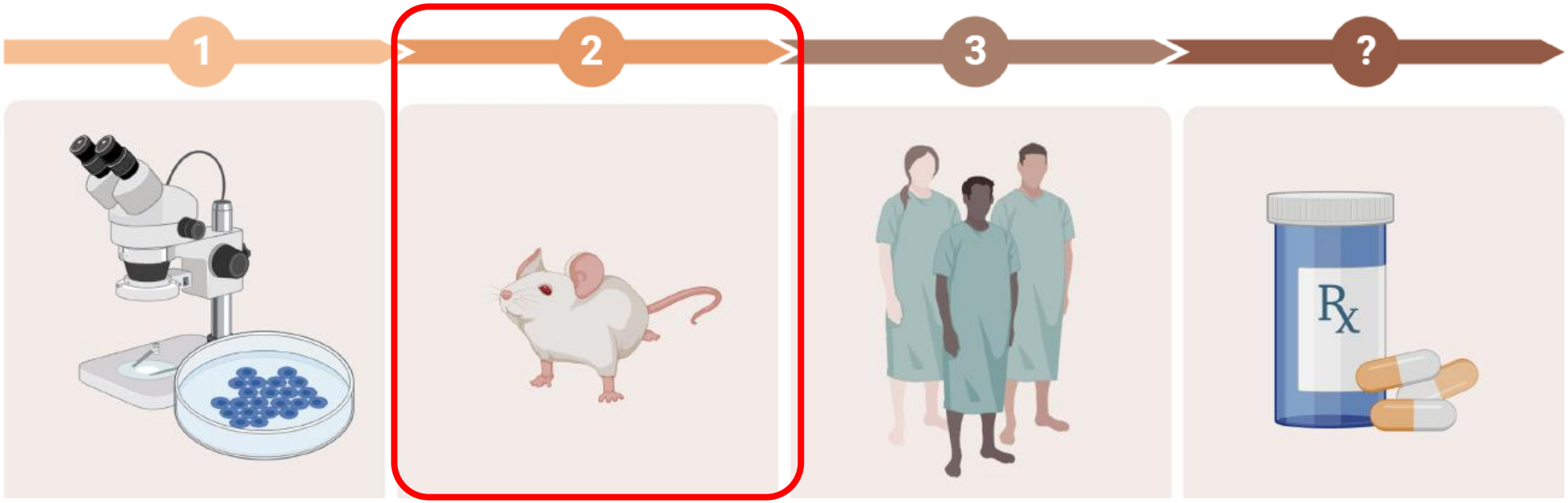
NEXT STEPS



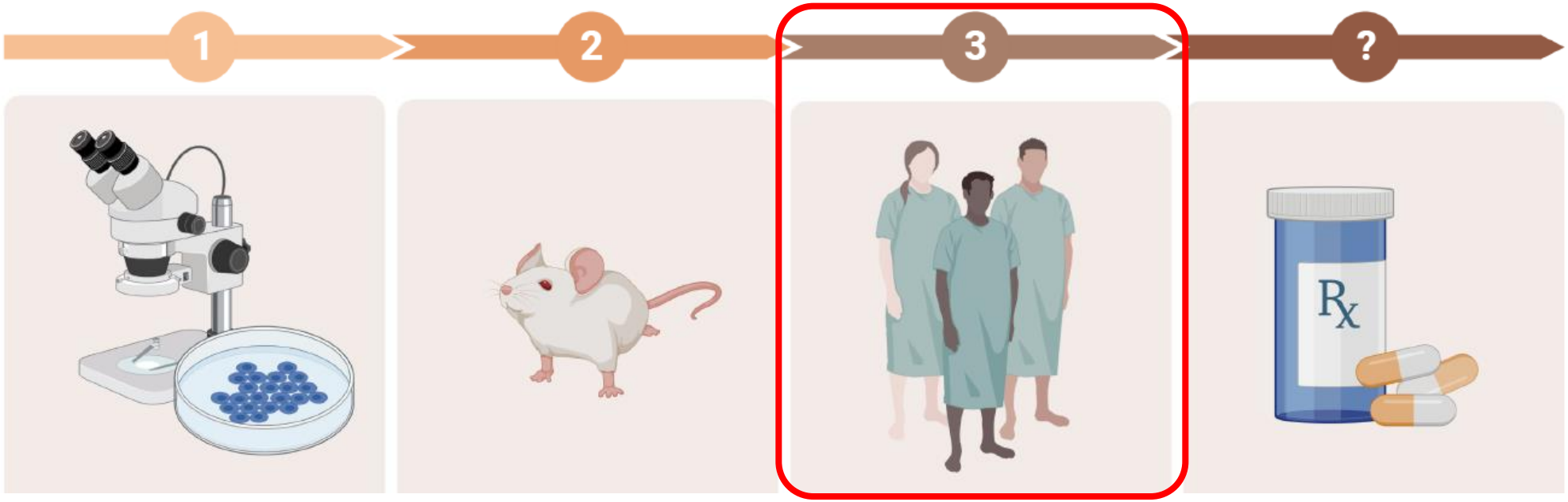
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

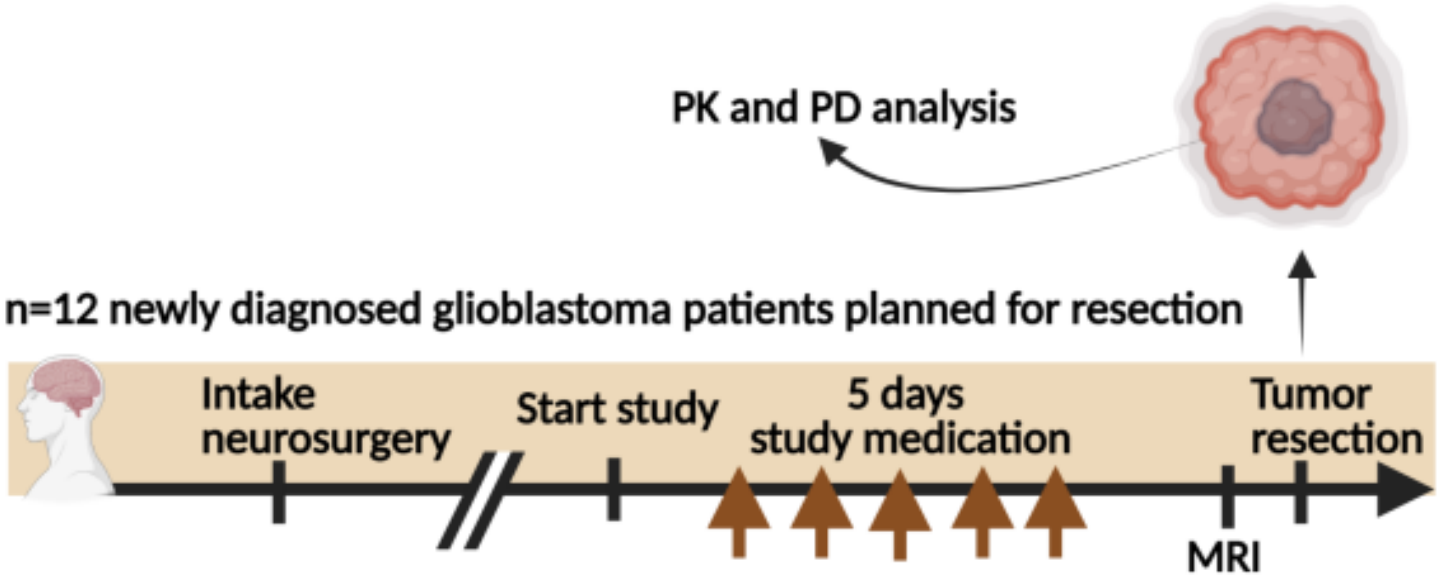
Dr. Akkari

Dr. van Tellingen

Erasmus MC

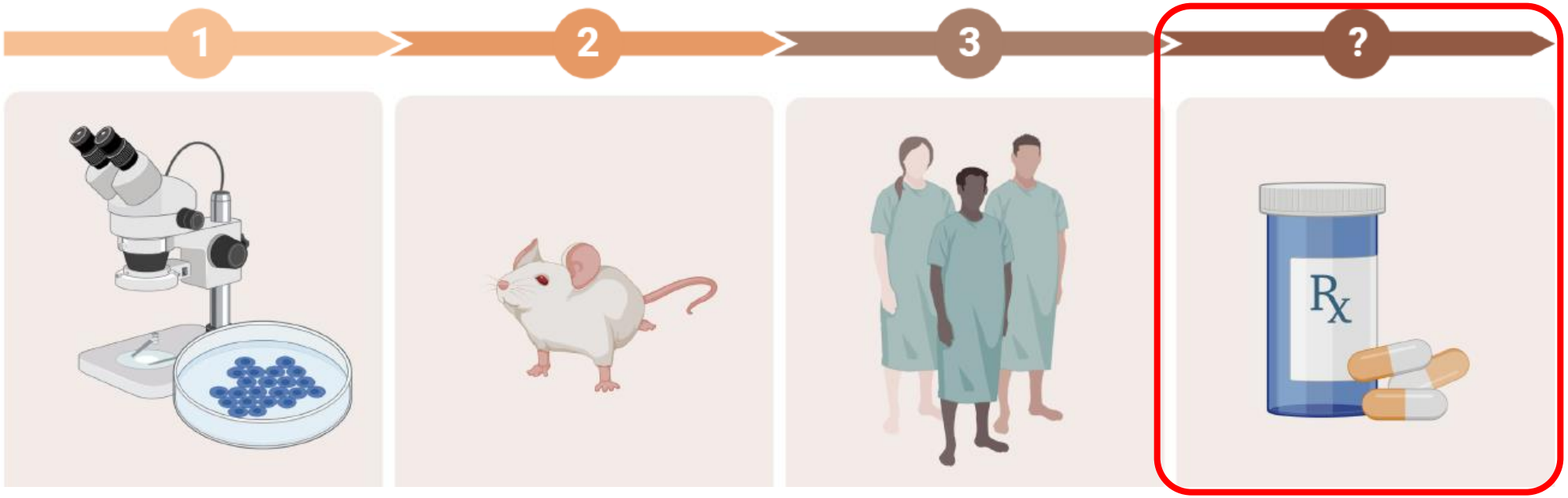
NEXT STEPS





Erasmus MC
Universitair Medisch Centrum Rotterdam

NEXT STEPS



Ultimate aim: to build a rational to proceed with the development of SFX-01 to treat glioblastoma patients that are most likely to benefit

Erasmus MC

TheraCryf

THANK YOU!

Erasmus MC

AGENDA

Item	Presenters	Time
Introduction	Dr Huw Jones, CEO	09:30-09:35
Review of Chronos acquisition and FY Results	Dr Huw Jones/Toni Haenninen, CFO	09:35-09:45
Pipeline Review	Dr Glen Clack, CMO	09:45-10:00
Glioblastoma Programme	Dr Glen Clack, Dr Marjolein Geurts, Neuro-oncologist, Dr Wouter Vanbilloen, Erasmus MC, Rotterdam	10:00-10:30
Q/A	All	10:00-10:35
Break		10:35-10:50
Neuropsychiatry programmes, Ox-1 antagonist, DAT inhibitor	Dr Fraser Murray, Neuroscientist, consultant to TheraCryf	10:50-11:35
TheraCryf Market sizes and potential	Dr Helen Kuhlman, CBO	11:35-11:55
Outlook, Conclusion, Q/A	Dr Huw Jones	11:55-12:00

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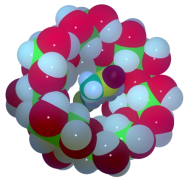
Outlook, Conclusion, Q/A	Dr Huw Jones	11:55-12:00

Group Pipeline

Discovery	Pre-clinical POC	Phase 1	Phase 2	Phase 3
SFX-01: Breast Cancer				
SFX-01: Neurodevelopmental Disorders				
SFX-01: Glioblastoma*				
SFX-01: Rhabdomyosarcoma				
NCE: Ox-1 in Addiction				
NCE: Ox-1 in Anxiety				
NCE: DAT in Fatigue / Narcolepsy*				

* Orphan Conditions



Ox-1 Antagonist for Anxiety, Addiction, Impulse disorders

Rationale for potential effectiveness - Anxiety

Orexin 1 receptor antagonists

- Early clinical efficacy shown in anxiety by J&J tool molecule, 2020
  - Experimental medicine, carbon dioxide inhalation Ph1b study
- Idorsia and AZ - addiction
- Indivior - cocaine addiction
- Cerevance – schizophrenia, others

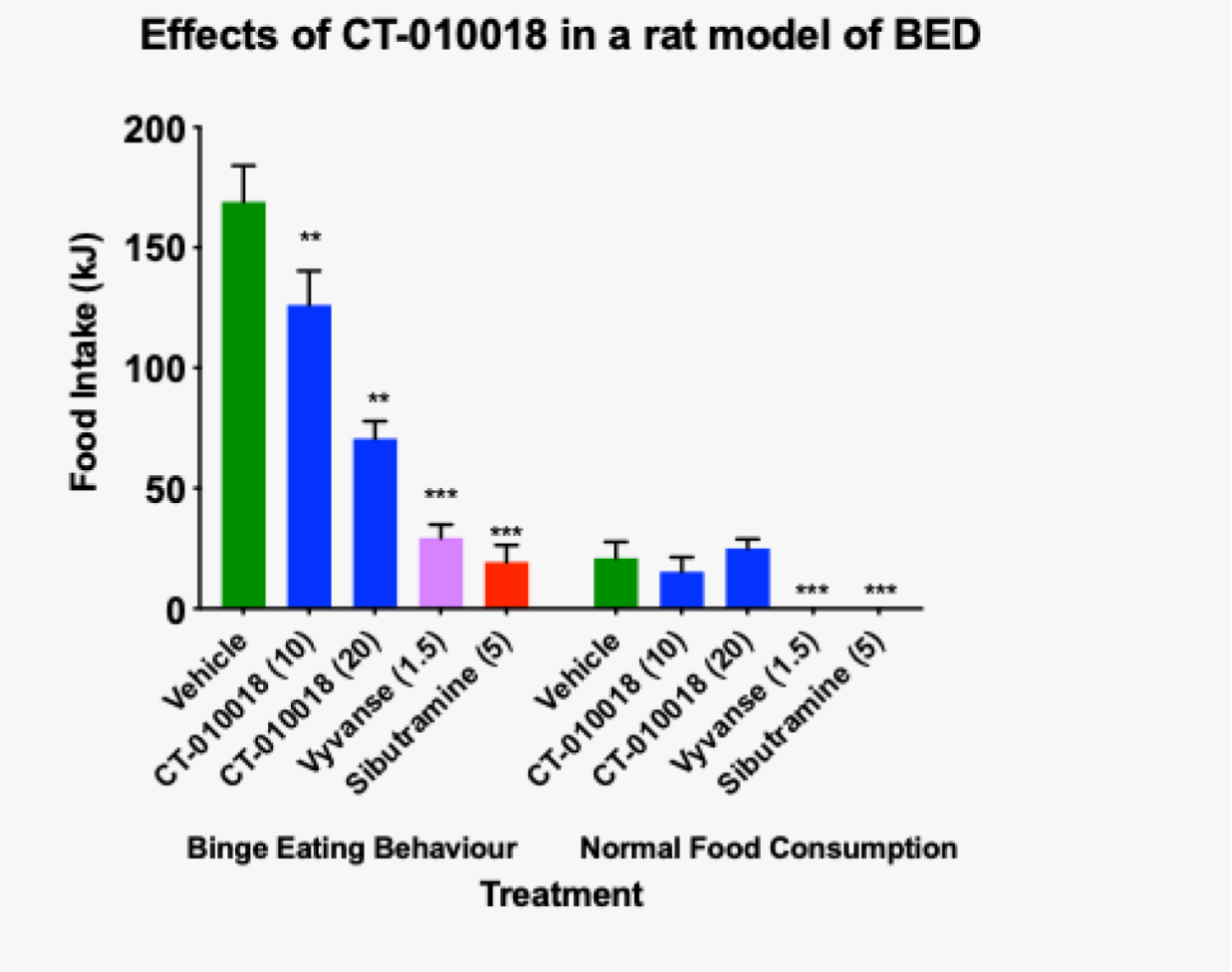
TheraCryf molecule - the most selective Ox-1 antagonist thus far discovered

- Strong proof of concept in animal models for addiction, early toxicology work complete
- Composition of matter patent granted, including in the USA
- Clinical stage in 18 months subject to additional funding

Binge Eating Disorder (BED)

- BED is a psychiatric condition, validated by American Psychiatric Association handbook DSM 5
- More common than anorexia and bulimia combined
- BED is not simply being overweight
- BED is not treatable with anti-obesity drugs
- ~25% have a history of substance abuse: 20% of women and 40% of men
- Vyvanse, a class II scheduled drug, is the only approved BED medication
- Orexin 1 antagonism is viewed as one of the most attractive targets in BED, with no abuse liability and no anhedonia. Orexin 1 antagonism will target both aberrant reward and anxiety driven aspects of the disease

in vivo Pharmacology Binge Eating Disorder (BED) Comparison of TheraCryf molecule with Vyvanse



TheraCryf OX-1 Antagonist Summary

- Structurally distinct from competitor molecules
- Improved properties vs first generation Ox-1 antagonists and differentiation from competitor molecules
- Excellent pharmacological selectivity, good brain penetration and physicochemical properties as well as good metabolic stability
- Target engagement in vivo and positive POC in a preclinical Binge Eating Disorder model
- Utility in other addictive disorders, impulse control disorders, panic disorder
- Initial scale up and formulation complete
- Clean in 7 day non GLP toxicology
- Composition of Matter patent granted (UK, USA, Other territories)

DAT Inhibitor for Fatigue

Fatigue Associated with Multiple Sclerosis Clear Opportunity

- Up to 80% of MS patients suffer from moderate to severe fatigue depending on type of disease.
- ~50% of these patients require drug treatment

- Currently NO approved fatigue drug treatments with a label in MS

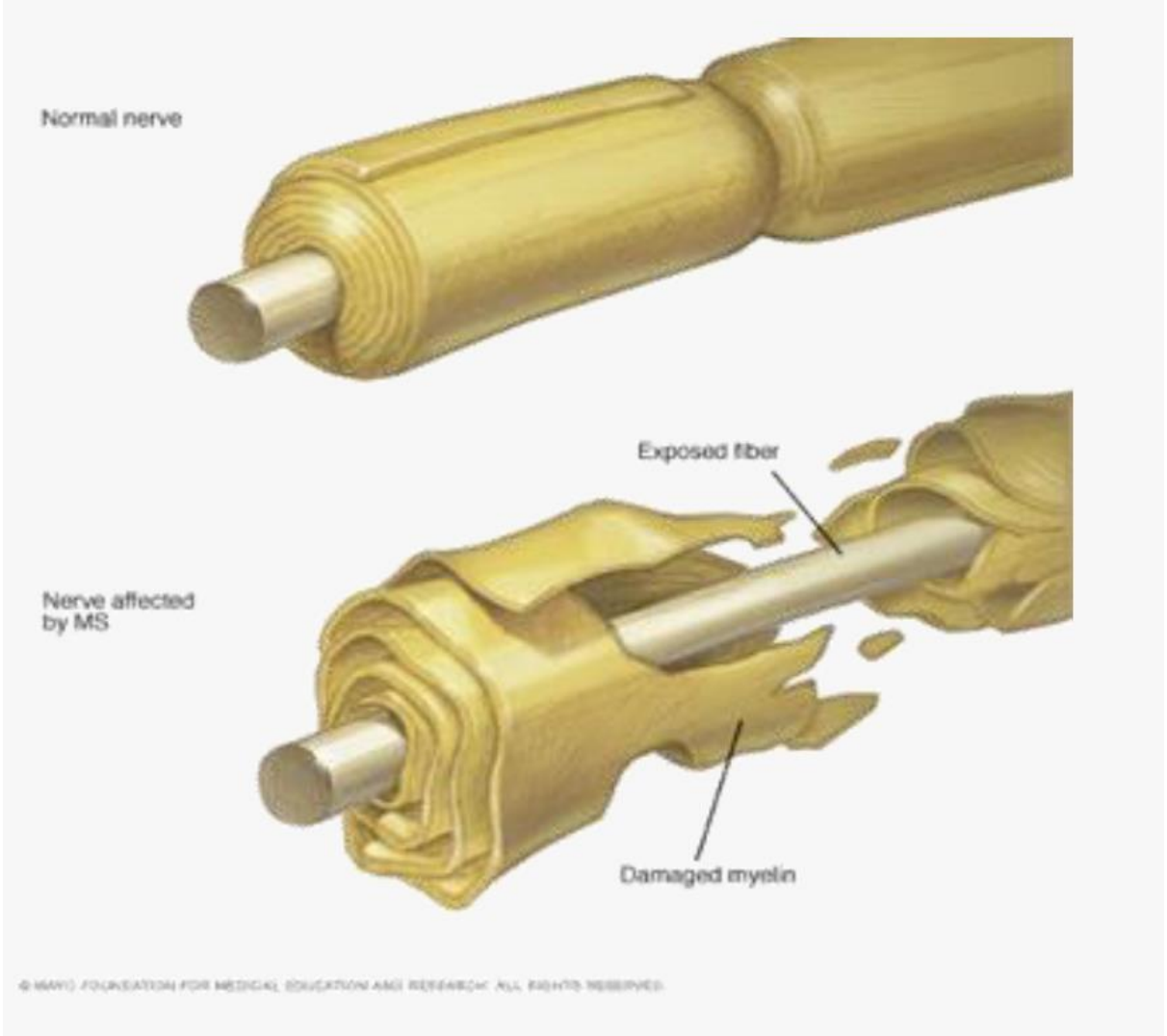
- Cause of central fatigue is conserved across multiple diseases

USA KOL Market Research for Chronos

1st to be labeled in MS fatigue, preferential re-imbursement vs off label drugs (modafinil, amantadine)

"none of them [MS treatments] are perfect drugs, and how much of this fatigue is drug and how much of this fatigue is disease is not something we can separate out. So I would not hesitate to use it [Product X]" KOL US 05

APEX HEALTHCARE CONSULTING



Rationale for potential effectiveness - Fatigue

- No competitors in the Long COVID Fatigue field as yet, none approved in MS fatigue, old drugs used off label
- Therapeutics for treatment are expected to reduce incidence of long COVID
- Fatigue is reported in half to two thirds of post COVID patients
- Fatigue is reported by up to 80% of MS patients
- IL 1beta is known to be one of the cytokines associated with post COVID fatigue

TheraCryf's DAT inhibitor:

- Strong proof of concept in animal models for fatigue including fatigue induced by IL 1 (relevant in post COVID and MS), early toxicology work complete, synthetic route optimized
- Composition of matter patent granted
- **Clinical stage in 18 months subject to additional funding**

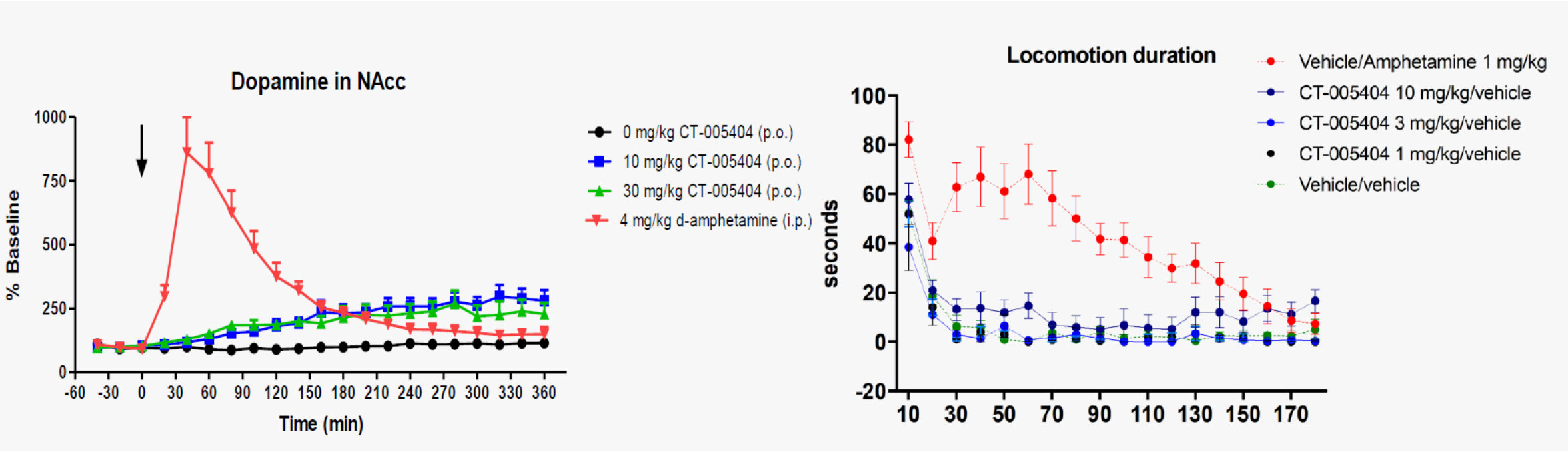
Why have others failed/stopped?

- Inability to achieve pharmacological selectivity
  - TheraCryf molecule has a greater selectivity for DAT vs SERT and NET than any competitor molecule

- Stimulant like profile
  - CT 005404 does not have an amphetamine like neurochemical profile
  - CT 005404 does not cause dopamine release from striatal synaptosomes
  - CT 005404 does not induce increased locomotor activity in rodents

- Lack of therapeutic index vs hERG channel
  - CT 005404 is >3,500x selective vs hERG (compared to less than 100x for historic DAT inhibitors)

in vivo Pharmacology – <u>not</u> amphetamine-like



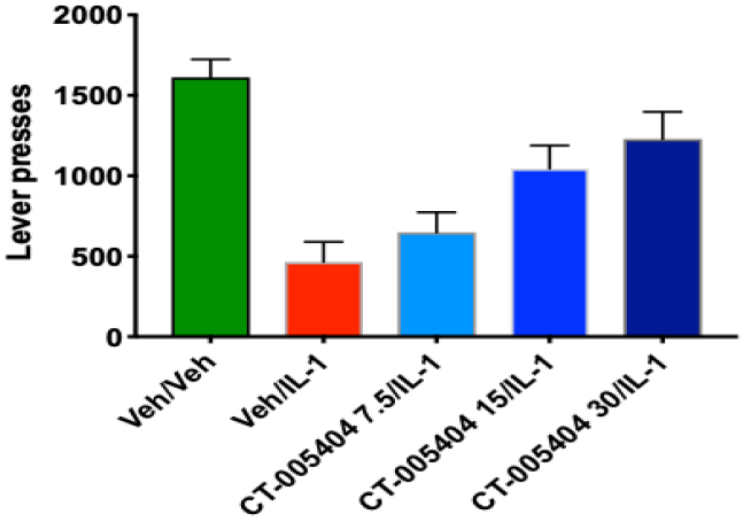
- Exciting neurochemical profile for CT-005404 - brain dopamine changes mirror
- locomotor activity

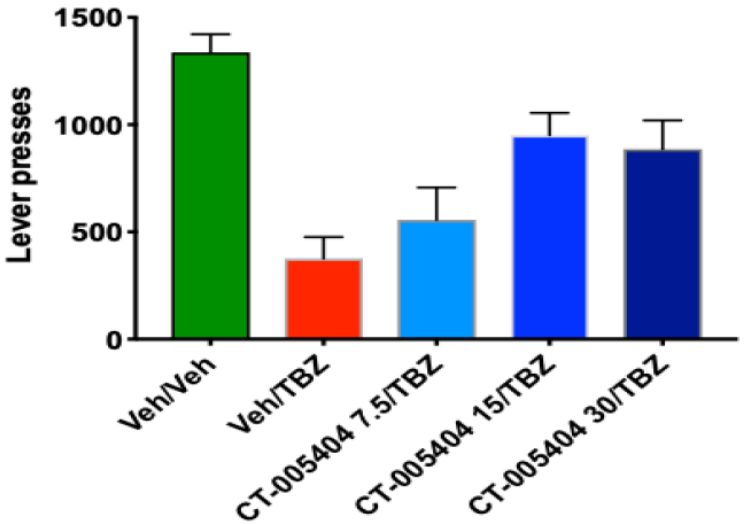
- Consistent with a selective DAT inhibitor profile

- CT-005404-induced a gradual release of dopamine in freely moving rats
  - CT-005404 induces a slow building long-lived ~3x increase in brain dopamine

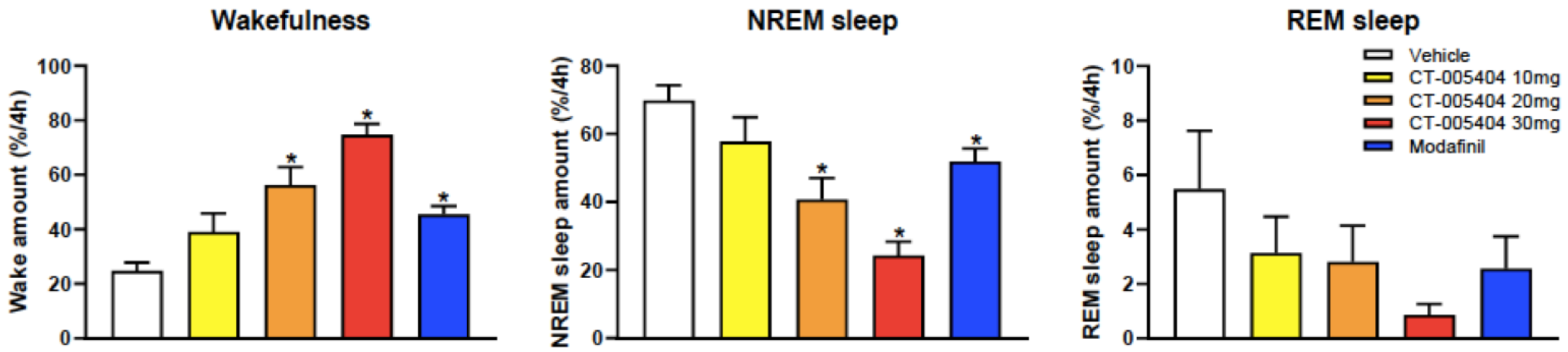
in vivo Pharmacology Proof of Concept

- Well established and validated model of CNS fatigue
- Work carried out by world leaders in the behavioural model
  - Salamone Lab, University of Connecticut
- Rats trained to lever press for a food reward
- CNS fatigue induced by chemical insult
  - tetrabenazine, fluoxetine, cytokine IL 1
- Fatigue results in reduced effort related choice (analogous to human condition)
- CT 005404 reverses CNS Fatigue
  - Final data (n=12)
  - Oral dosing with 4h pre treatment





CT005404 has potential in Narcolepsy



Rat Wakefulness study: CT-005404 (10, 20 and 30 mg/kg, p.o.) increased the amount of wakefulness at the expense of NREM sleep in a dose-dependent manner.

DAT Summary

- Potent and selective DAT inhibitor with a non stimulant profile
- Highly differentiated from previous DAT inhibitors
- The compound is clean in 7 day early toxicology studies
- Potential to be the first approved drug with a label for MS Fatigue
- Due to the conserved underlying mechanisms of CNS fatigue, this would allow expansion into other diseases characterised by CNS fatigue, such as depression, ALS, HIV and cancer chemotherapy
- Composition of Matter patent filed, granted (US & EU)

AGENDA

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Introduction	Dr Huw Jones, CEO	09:30-09:35
Review of Chronos acquisition and FY Results	Dr Huw Jones/Toni Haenninen, CFO	09:35-09:45
Pipeline Review	Dr Glen Clack, CMO	09:45-10:00
Glioblastoma Programme	Dr Glen Clack, Dr Marjolein Geurts, Neuro-oncologist, Dr Wouter Vanbilloen, Erasmus MC, Rotterdam	10:00-10:30
Q/A	All	10:00-10:35
Break		10:35-10:50
Neuropsychiatry programmes, Ox-1 antagonist, DAT inhibitor	Dr Fraser Murray, Neuroscientist, consultant to TheraCryf	10:50-11:35
TheraCryf Market sizes and potential	Dr Helen Kuhlman, CBO	11:35-11:55
Outlook, Conclusion, Q/A	Dr Huw Jones	11:55-12:00

SFX-01: GBM

Glioblastoma

Therapeutic Market forecasts
USD 549.1 million 2020 – 868.5 million 2030 (CAGR 4.7%), Global Data

>45 programmes in clinical development
Branded standard of care treatment, Temodar approx. $29k per patient per annum

Characteristics
Total 5-year prevalent population: 243,850
Total treated newly diagnosed (in 2020): 33,985
Total treated recurrent diagnosed (in 2020): 13,914

The major drivers of growth:

- An increasing number of incident cases of GBM, particularly in the US (due to underlying population growth) and China (due to urbanization)

- A high level of unmet need in GBM that warrants faster uptake of the pipeline agents expected to launch as patients have few other treatment options

KAZIA THERAPEUTICS

SYDNEY, March 29, 2021 /PRNewswire/ -- Kazia Therapeutics Limited (ASX: KZA; NASDAQ: **KZIA**), an oncology-focused drug development company, is pleased to announce that it has entered into a licensing agreement with Simcere Pharmaceutical Group Ltd (Simcere) (HKSE: 2096) to develop and commercialise Kazia's investigational new drug, paxalisib, in Greater China.

MIMIVAX

BUFFALO, N.Y. and SHANGHAI, Nov. 18, 2019 /PRNewswire/ -- MimiVax LLC and Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd. (Fosun Pharma Industrial) today announced the companies have entered into a China-exclusive licensing agreement for SurVaxM, a novel anti-cancer immunotherapy in the treatment of glioblastoma brain cancers.

SFX-01: ASD

STALICLA

Autism Spectrum Disorder

Therapeutic Market forecasts
USD 3.78 billion 2021 – 5.15 billion 2028 (CAGR 4.5%), Fortune Business Insights (2021)

11 programmes currently in clinical development
Treatment estimate $15-30k per patient per annum

Characteristics
Prevalence rate 1:100 children worldwide (WHO, 2022), 1:44 (US, CDC, 2018)
Increasing rates of diagnosis (CDC)

The major drivers of growth:

- Increasing incidence worldwide
- Diagnosis and prescribing increases enabled by growing acceptance of telehealth during pandemic, and recognition of novel diagnostic tools
- Supportive regulatory environment to fast-track therapeutic development

Ox-1: Addiction

- Addiction: the most severe form of substance use disorder (SUD).
- Involves continued substance use despite negative consequences. Addiction to substances happens when the reward system in the brain “takes over” and amplifies compulsive substance-seeking.
- Affects people of all ages, races, genders and socioeconomic levels.
- Highest frequency among males and in people aged 18 to 25.
- Therapies currently available include:
  - Opioids: Methadone, buprenorphine and naltrexone are FDA-approved for the treatment of opioid use disorder.
  - Alcohol: Three FDA-approved drugs include naltrexone, acamprosate and disulfiram.
  - Tobacco: nicotine replacement (patch, spray, gum or lozenge), bupropion or varenicline.

The global substance abuse treatment market size reached $11.6 billion in 2022 and is projected to surpass around $31.06 billion by 2032, registering a CAGR of 10.4% during 2023 to 2032.*

* Precedence Research Market Report Nov 2023

Ox-1: Anxiety

- Anxiety disorders are the most common psychiatric disorders.
- Generalized anxiety disorder (GAD) is the most prevalent anxiety disorder in primary care settings, often accompanied by a significant burden of comorbidity, impairment, and disability.
- Estimated to occur in 7 to 8% of patients.
- Is most common in people aged between 35 and 55 and more common in women than in men.
- According to DelveInsight's estimates, the total 12-month diagnosed prevalent cases of GAD in the 7MM were 16 million in 2022. Among these cases (52% in US).
- Approved therapies include; selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors however around 50% of patients do not respond to first-line treatment.
- While benzodiazepines have shown benefit in the short-term use of TR-GAD, long-term use is not recommended secondary to the potential for dependence, misuse, and correlation to cognitive decline.

The generalized anxiety disorder market size in the US was found to be $1 billion in 2022 and is expected to grow positively at a significant CAGR during 2019–2032.*

* DelveInsight GAD Market Report Oct 2023

DAT: Fatigue

“One in four consultations in primary care involve fatigue — it’s the most common reason why people go to see their GP” UK, KOL

- Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME): complex disorder characterized by extreme fatigue that cannot be explained by any underlying medical condition and does not improve with rest.
- At least 250,000 people in the UK live with ME/CFS
- 50% of people with chronic conditions — such as rheumatoid arthritis, cancer, Parkinson’s disease, or multiple sclerosis experience fatigue.
- There are currently no approved therapies for chronic fatigue, across any of the conditions it is present in.

The global chronic fatigue syndrome treatment market size was valued at $47.2 million in 2022 and is projected to grow at a CAGR of 4.2% during 2023-2031 to reach a value of $68.2 million by 2031*

*Research and Markets report, May 2023

DAT: Narcolepsy

- Narcolepsy: a rare, disabling chronic neurological disorder, characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, and sleep paralysis.
- Estimated to affect 20 to 50 people per 100,000 worldwide, with incidences tending to increase with age.
- Currently no disease-modifying drugs available.
- Symptomatic treatments include: methylphenidate and amphetamines for narcolepsy in general, modafinil, armodafinil and solriamfetol for EDS only, and sodium oxybate, pitolisant (Wakix), and lower-sodium oxybate for both EDS and cataplexy.

The global narcolepsy therapeutics market size accounted for $3.3 billion in 2022 and is expected to reach around $6.90 billion by 2032, registering a CAGR of 7.7% during the period 2023 to 2032*

*Precedence Research report, Nov 2023

Ox-1 & DAT: Competitive Environment

Company	Stage	Status	Indication
Idorsia (Actelion)	Ph2	2022 missed Ph2a endpoint in BED (query receptor occupancy), shelved	BED, anxiety
Cerevance (Takeda)	Ph2	Completed Ph1, planned initiation of Ph2 during 2023	Schizophrenia
Indivior (C4X)	End Ph1	Phase 1 study MAD, LSLV Q3 2023, end of Ph 1 meeting with FDA Q4 2023	Opioid use disorder
AZ (Eolas)	Ph1	Completed Ph1 dosing in healthy recreational opioid users H2 2023 (results not available at this time)	Smoking cessation, opioid use disorder
JnJ	Ph1/2	Unknown, not currently reported in pipeline	Panic/anxiety, depression
GSK	Preclinical	Unknown	

Company	Stage	Status	Indication
Axsome (Reboxetine)	Ph3	Completing Ph3 end 2023 awaiting readout	Narcolepsy
Takeda (TAK-994)	Ph2	Completed Ph2, development halted in narcolepsy due to hepatotox findings	Narcolepsy
Merck (MK-6552)	Ph1	To begin recruitment early 2024	Narcolepsy
Suven LS (Samelisant)	Ph2	Ph2 complete readout/status unknown	Narcolepsy
Axcella Therapeutics (AXA1125)	Ph2	Ph2a positive readout Apr 2023. Business announced liquidation Dec 2023	Long Covid Fatigue
AIM Immunotech (ampligen/rintatolimod)	Ph2	Topline data expected QTR12024	Long Covid Fatigue

Ox-1 & DAT: Opportunity

- Current standards of care; limited effectiveness and burdened by side-effects
- Future therapeutic options must be:
  - ✓ Effective
  - ✓ Durable
  - ✓ Non-abusable (non-scheduled)
  - ✓ Limit side effects

- Resurgence of interest in CNS indications by Pharma
- Opens up partnering opportunities at early clinical stages for differentiated assets

PR Newswire® for Journalists

Indivior Enters Into an Exclusive Global License Agreement for C4X Discovery's Orexin-1 (Ox-1) Antagonist Program for $294m

FIERCE Biotech

AbbVie pads neuroscience portfolio with $8.7B deal to acquire Cerevel
Annalee Armstrong

FIERCE Biotech

As J&J outlines bullish pipeline goals, neuroscience pipeline takes a starring role
By Max Bayer

PharmaTimes online

AZ buys into Eolas' anti-addiction programme in $145m deal

CNBC

HEALTH AND SCIENCE

Karuna Therapeutics surges 47% after Bristol Myers Squibb announces $14 billion deal
Published Dec 22, 2023
Ashley Capoot

BioSpace®

Axsome Therapeutics Enters into License Agreement with Pharmanovia to Expand Commercialization and Further Develop Sunosi® (solriamfetol) in Europe
Published: Feb 22, 2023

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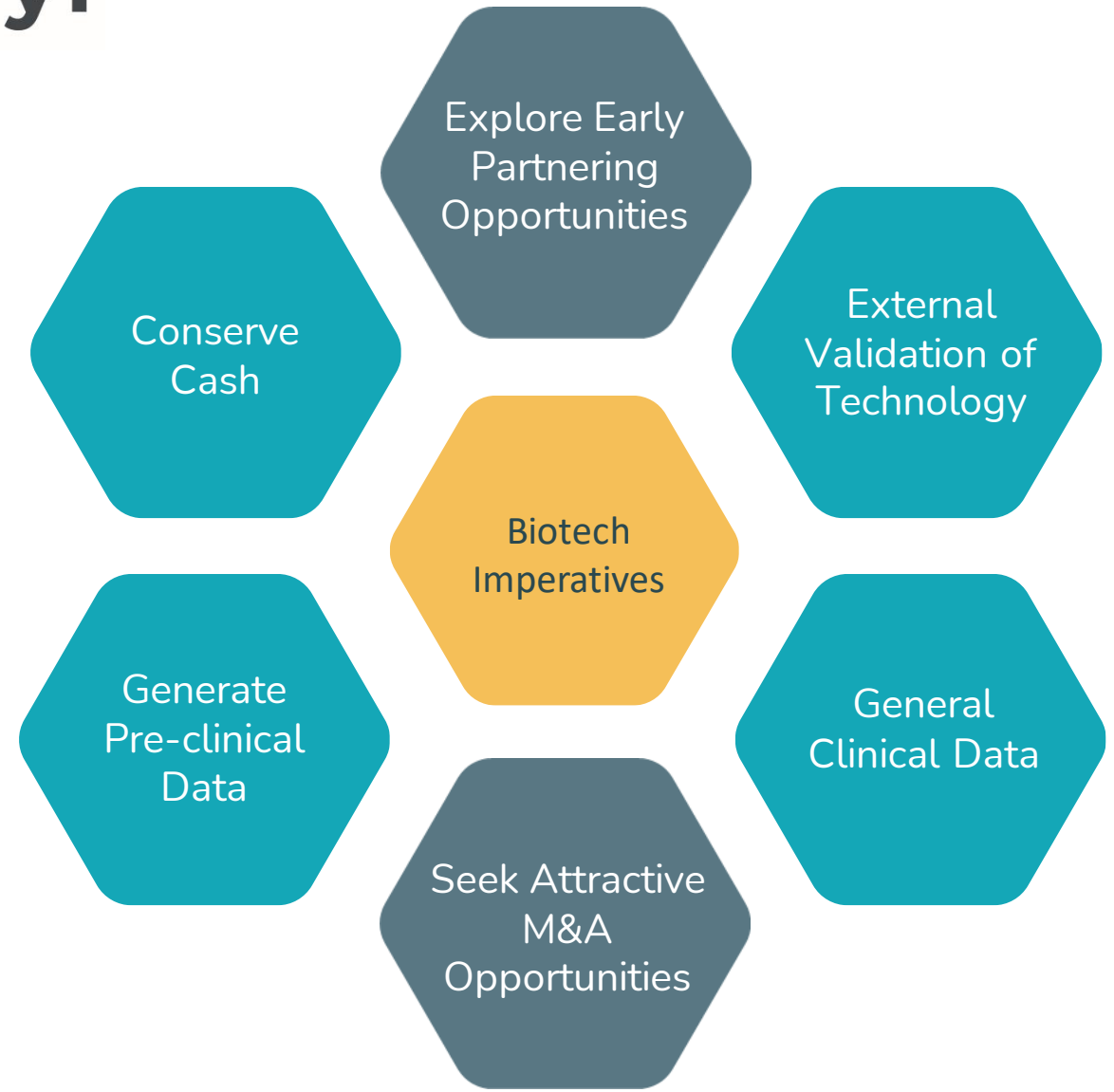
TheraCryf


Explore Early Partnering Opportunities
Conserve Cash
External Validation of Technology
Biotech Imperatives
Generate Pre-clinical Data
General Clinical Data
Seek Attractive M&A Opportunities

Outlook

Item	Outlook
GBM	Regulatory work and approvals in support of GBM clinical trial via the grant to Erasmus MC
Acquisition	Completion of integration of Chronos Therapeutics Ltd
Funding	Non-dilutive Grants sought for acquired Ox-1 and DAT programmes
Patents	Grant of further patents for our new programmes
Publications	Publication of clinical paper on SFX-01 Phase 1b pharmacokinetic study
SFX-01 Data	Further PD data from SFX-01 Phase 1b study

TheraCryf

Thank You

13 June 2024

AIM: TCF.L
NOMAD: Cavendish
IR: Instinctif, CAG

TheraCryf

Appendix

Post Period

Post period Highlights

- **Acquisition** of Chronos Therapeutics Ltd adding substantial pre-clinical neuropsychiatry portfolio effective 5 April 2024; integration progressing well
  - Adds addiction/anxiety/fatigue programmes in resurgent areas for pharma

- **Company name change** to TheraCryf plc and ticker symbol change to TCF effective 26 April 2024

- **£0.9m raised** in a placing and retail offer; management and board invested c.10% of the raise

Transaction Details

Low upfront, de-risked and back-weighted

- **Acquisition of entire issued share capital of Chronos Therapeutics**
  - Single share class, no warrants, no debt, on a cash and debt free basis
- **£1m in Evgen shares upfront to Chronos shareholders***
  - Includes Vulpes, Odey, Oxford University, WA Capital, Takeda, HNWs
  - Chronos shareholders locked in for 18 months
- **£1m in shares or loan at Evgen's discretion on start of first Phase 1 clinical trial**
- **£1.5m in shares or loan at Evgen's discretion on end of first successful Phase 1 clinical trial**
- **10% of first three milestones of any out-licensing transaction involving of a former Chronos asset, capped**
  - Payment in shares or loan notes at Evgen's discretion

*Approx 10% of upfront consideration in cash

TheraCryf Management and Board

Dr Huw Jones
CEO

Over 30 years' experience of leadership in public and private R&D-based companies within the biotechnology and pharmaceutical sector. Huw is also a non-executive director of biotech industry body OBN. Ashbourne, CVT, Elan, SB (GSK)

Toni Haenninen
CFO

Over 20 years' experience of financial leadership in public and private companies in the US, APAC and Europe: Danaher Group, Faron Pharmaceuticals

Dr Sue Foden
Chair

Executive Chair of QBiotics Group Ltd and an NED on the board of Laverock Therapeutics Ltd. She is a member of the Investment Committee of CD3, the joint drug discovery initiative between the University of Leuven & the European Investment Fund (EIF), and a Trustee of the Roslin Foundation.

Dr Alan Barge
NED

Former CMO of ASLAN Pharmaceuticals and former VP and Head of Oncology and infection at AZ.

Chronos Nominee
NED

Under the agreement Chronos has the right to nominate one NED subject to TheraCryf Board approval.

Dr Nicholas Mallard
VP - Project Management

Over 30 years' experience in research and early/late phase development spanning large pharma (Takeda, AZ, Scherer DDS), biotech (Oxford Glycosciences, Amarin Neuroscience, Shield Therapeutics) and several CROs.

Dr Helen Kuhlman
CBO

Over 20 years' experience in government funding and equity investment together with scientific and business roles in public and private R&D-based biotechnology companies

Dr Glen Clack
CMO

Over 25 years' experience in oncology drug development with a specialism in translational medicine. AZ, multiple small Biotech Co's

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