12 de noviembre de 2020

Gene editing therapy for human cancers driven by FUSION GENES (FUGE) and ONCOGENE AMPLIFICATIONS (AMP)

cnio stop cancer

Sandra Rodríguez-Perales, PhD

THE INSTITUTION

- CNIO is a flagship for cancer research in Spain
- Over 400 highly specialized professionals
- One of the best centres specializing in cancer research:

nature INDEX 5th place worldwide and 2nd in Europe

Our **identity signs**

RESEARCH

230
PUBLICATIONS IN 2019:
33 WITH IF>10, 24 WITH IF>15

136
ACTIVE PROJECTS IN 2019

€41.97M
CNIO BUDGET 2019

INNOVATION

34
ACTIVE PATENTS 2019

€24.5M
COLLABORATIONS WITH INDUSTRY (2012-2019)

231
TECH TRANSFER AGREEMENTS 2019

68%
INTERNATIONAL ACTIVITY 2019

5
DRUG DISCOVERY PRORAMMES IN PARTNERSHIP (2011-2019)

16
DRUG DISCOVERY PROGRAMMES UNDER DEVELOPMENT 2019

HEALTH

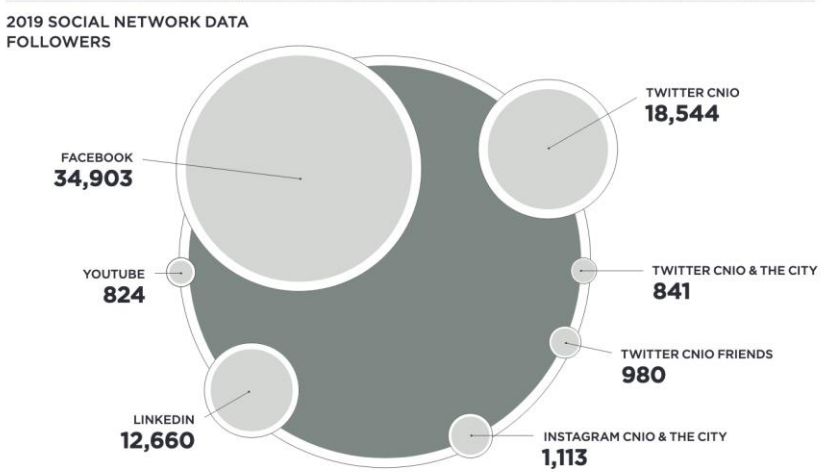
648
PATIENTS IN CLINICAL TRIALS COORDINATED BY THE CNIO IN 2019

570
FAMILIES ADMITTED TO THE CNIO FAMILIAL CANCER CONSULTANCY IN 2019

THE INSTITUTION

- CNIO is a flagship for cancer research in Spain
- Over 400 highly specialized professionals

Society **impact**



9 *La Sexta Noticias, La Sexta*, April 11, 2019
10 *El Mundo*, April 27, 2019
11 *Telediario, La 1*, May 31, 2019
12 *La Razón* (front page), July 9, 2019
13 *SINC*, August 22, 2019
14 *Gaceta Médica*, September 9, 2019
15 *El Correo Gallego*, September 14, 2019
16 *Diario Médico*, October 7, 2019
17 *Diario 24 Horas, Canal 24 Horas*, October 10, 2019

18 *ABC*, October 18, 2019
19 *El Mundo* (front page), October 30, 2019
20 *El País Semanal*, November 3, 2019
21 *Faro de Vigo*, November 5, 2019
22 *El Intermedio, La Sexta*, November 14, 2019
23 *Diario Médico* (front page), November 25, 2019
24 *El Mundo* (front page), November 26, 2019
25 *El País*, December 20, 2019

THE INSTITUTION

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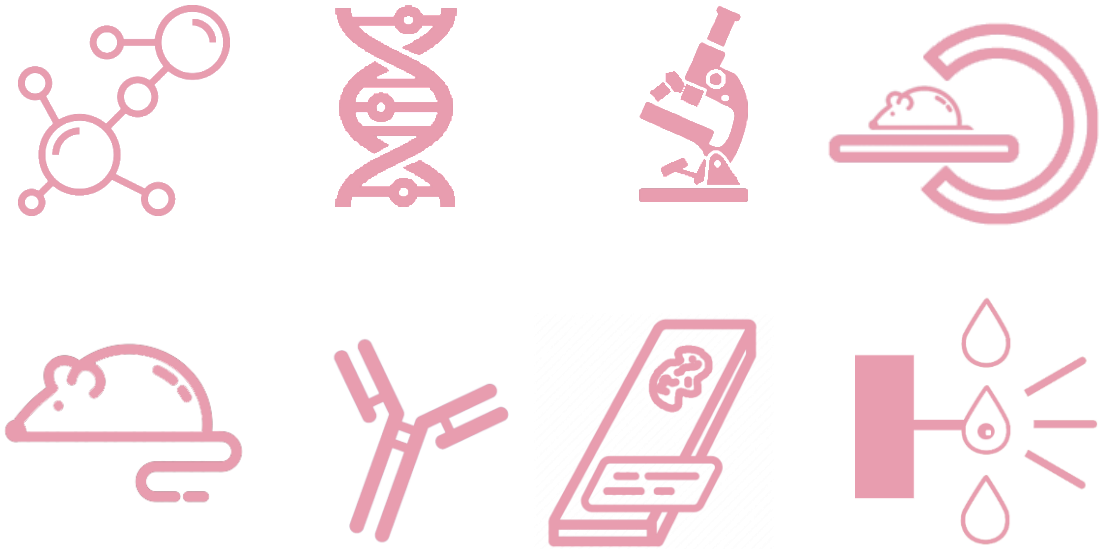
BASIC RESEARCH

INNOVATION

PATIENT-ORIENTED TRANSLATIONAL RESEARCH

Biotechnology Programme

- Proteomics Core Unit
- Genomics Core Unit
- Confocal Microscopy Core Unit
- Molecular Imaging Core Unit
- Mouse Genome Editing Core Unit
- Monoclonal Antibodies Core Unit
- Histopathology Core Unit
- Flow Cytometry Core Unit



THE INSTITUTION

BASIC RESEARCH

INNOVATION

PATIENT-ORIENTED TRANSLATIONAL RESEARCH

Human Cancer Genetics Programme

Human Genetics Group

Genetic & Molecular Epidemiology Group

Hereditary Endocrine Cancer Group

Molecular Cytogenetics Unit

Familial Cancer Clinical Unit

Human Genotyping-CEGEN Unit

THE GROUP

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HOME | RESEARCH & INNOVATION | SCIENTIFIC PROGRAMMES | HUMAN CANCER GENETICS PROGRAMME | MOLECULAR CYTOGENETICS UNIT

Molecular Cytogenetics Unit

Sandra Rodríguez
Head of Unit
T +34 917328000 (Ext 3340)
srodriguezp@cnio.es

Staff Scientist
- Raul Torres, PhD

PhD Students
- Marta martinez-Lage
- Pilar Puig-Serra

Graduate Student
- M Cruz Casado

Technicians
- M Carmen Martín
- Francisco J Moya

Technology Transfer Office

Innovation Director, CNIO
- Carolina Pola, PhD

Tech Transfer Director, CNIO
- Irene Herrera, PhD

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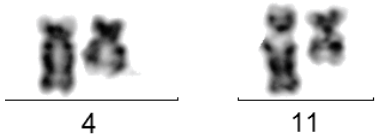
RESEARCH HIGHLIGHTS

- Understanding cancer-related chromosome aberrations



- Modelling cancer using CRISPR technology

- Cancer therapy by targeting chromosome reagangements

- Technological and translational activities

PUBLICATIONS

25

Publications in last 5 years:
14 in 1st Decil, 7 in 1st Quartile

FUNDING

Over 1mill€

Last 5 years:
Public calls & private funding

Need for novel treatments targeting FUSION GENES & AMPLIFICATIONS

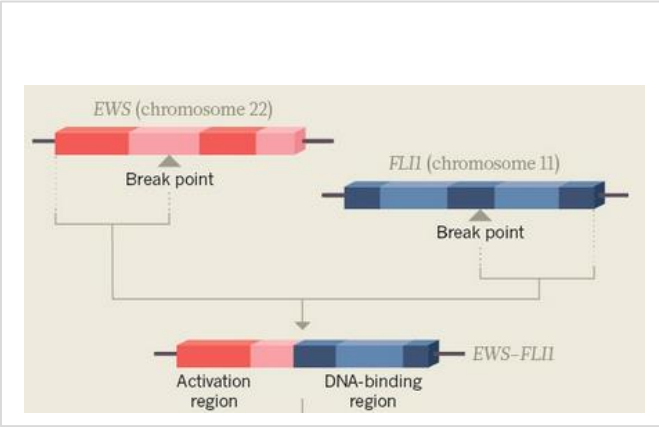
CANCER

- The second leading cause of death
- > 10 mill mortalities/year
- Cancer is a GENETIC disease

FUSION GENES (FUGE)

- Up to 20% of cancers

Hybrid genes form by two parts of different genes
Generated by chromosomal rearrangements

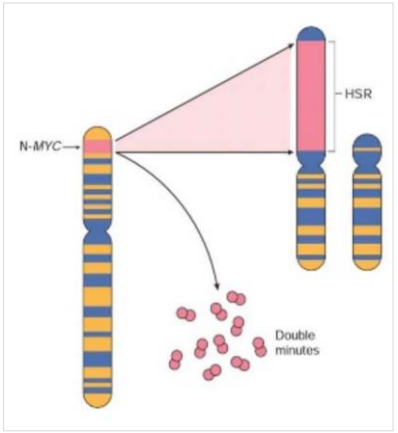


- Oncogenic properties
- Often act as driver mutations
- 390 recurrent fusion genes

ONCOGENE AMPLIFICATIONS (AMP)

- One of the most common molecular alterations in cancer

Overexpression of oncogenes
Generated by chromosomal rearrangements



- Often act as driver mutations
- 64 known driver oncogenes
- 587 tumours

➢ Excellent tumour-specific targets for therapy

Need for novel treatments targeting FuGe & AMP

TREATMENT TYPES

- Many FuGe or AMP-cancers are treated with standard approaches (Leukaemia, Sarcomas…)
- Many of others have limited or no treatment (Neuroblastoma, Glioblastoma, Prostate, Colon…)

TREATMENT LIMITATIONS

- Toxicity: severe side effects
- Efficacy: High level of mortality (40% colorectal cancer, 40% leukaemia, …)
  60-80% of death after recurrence/metastasis

GENE EDITING

- Clear medical need for novel treatments targeting FuGe and AMP with improved efficacy and safety
- Gene editing has the potential to address this need

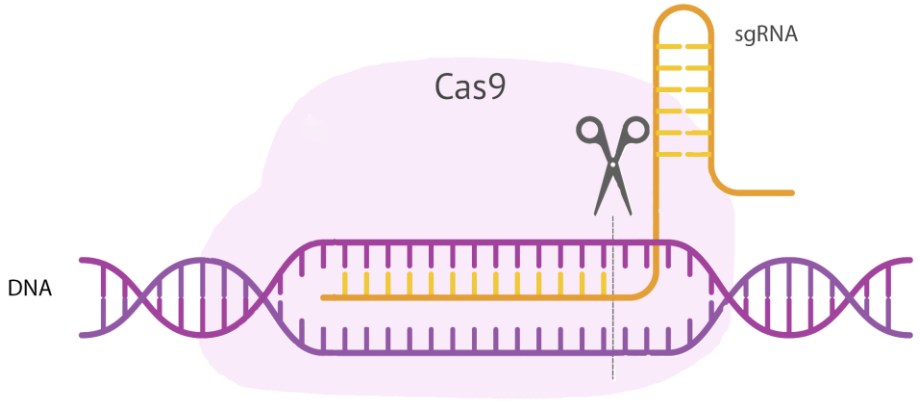
GENE EDITING

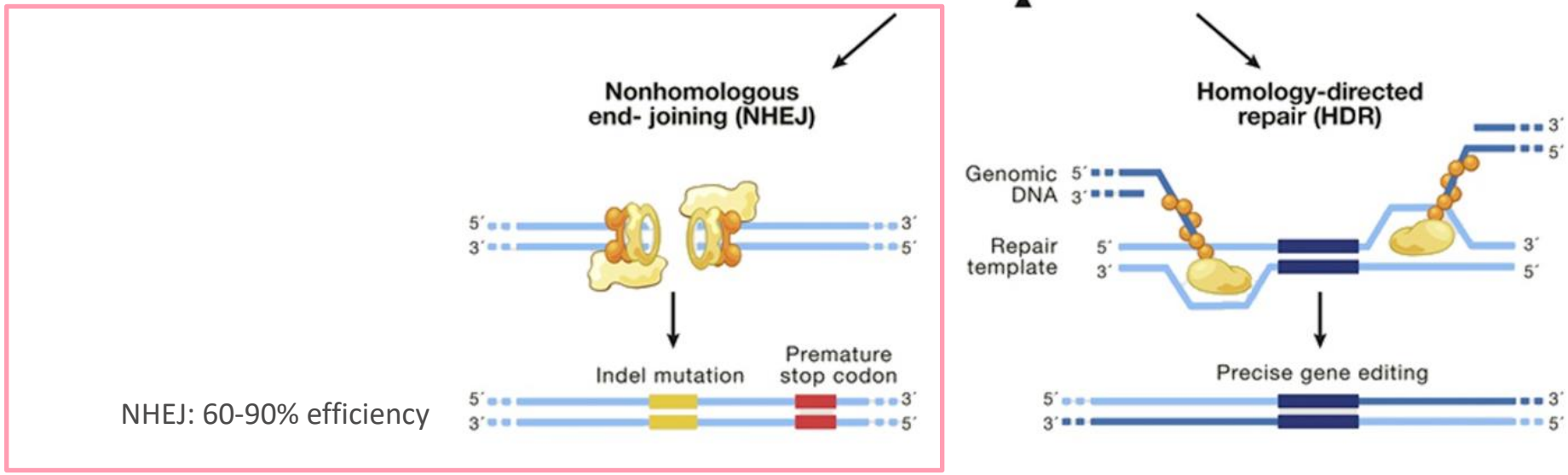
- Alter the genome to attack cancer cells based on their specific DNA defects

- We will focus our efforts on cancer types driven by FuGe or AMP oncogenes

GENE EDITING

CRISPR-Cas9 system





NHEJ: 60-90% efficiency

HDR: 0,01-20% efficiency

THE ASSET: CRISPR-BASED GF & Am TARGETING THERAPY

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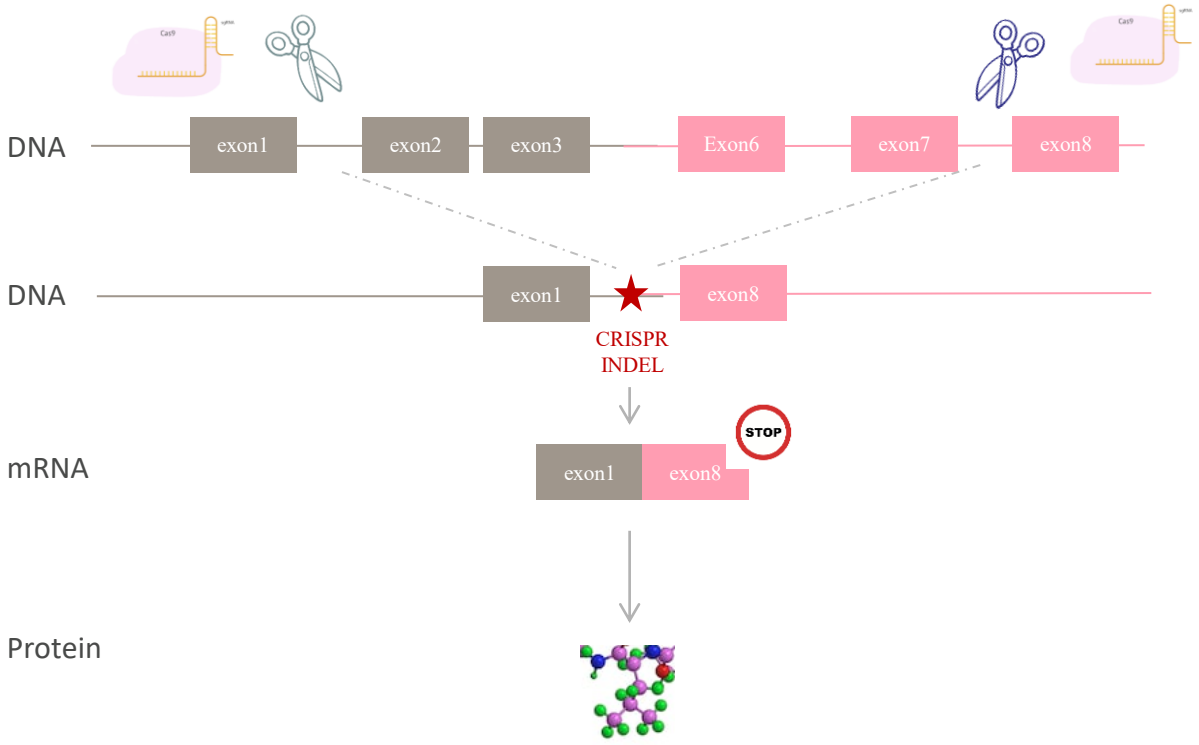
THE APPROACH

Development of an innovative therapy for the treatment of cancers addicted to the expression of FuGes and AMPs through a selective eliminating of them in cancer cells

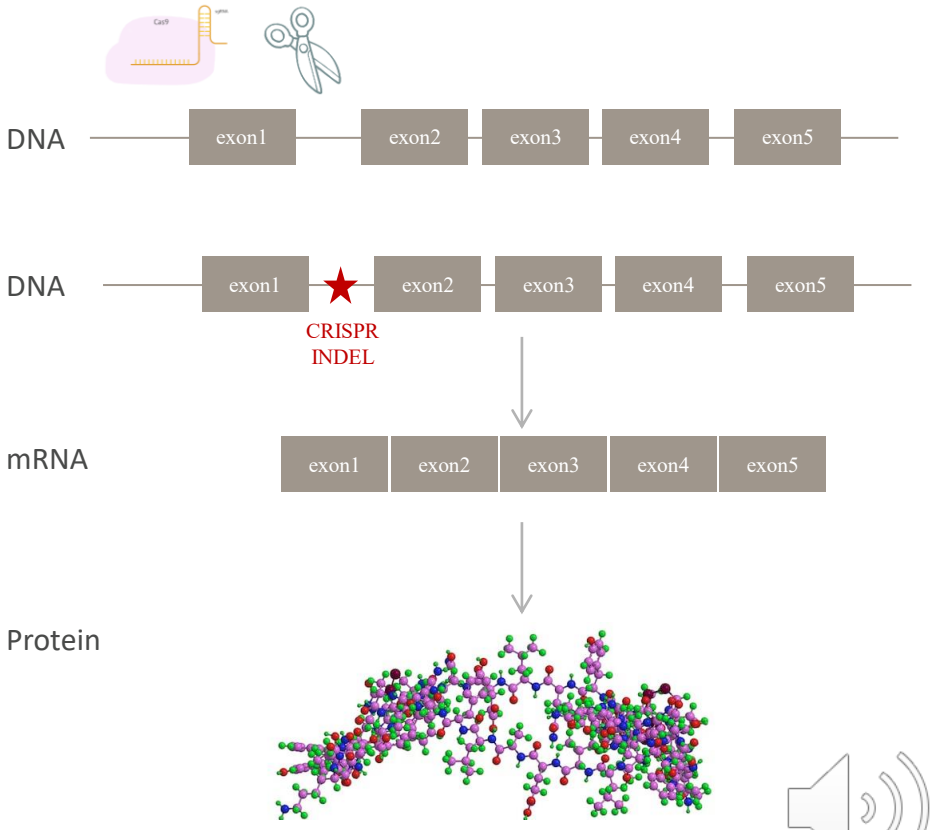
GENE FUSIONS (FuGe)



Non-functional truncated protein

ONCOGENE AMPLIFICATIONS (AMP)

Wild-type ALLELEs

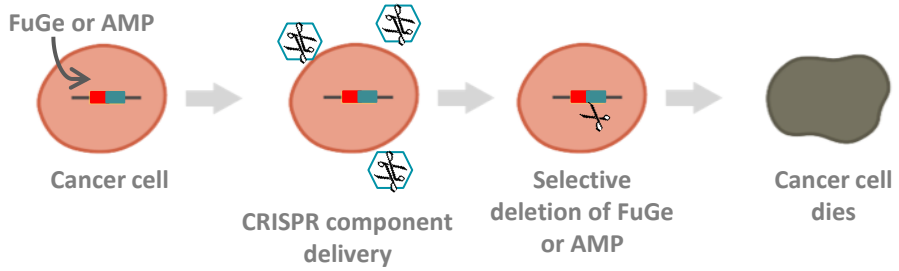


Functional complete protein

THE ASSET: CRISPR-BASED GF & Am TARGETING THERAPY

THE APPROACH

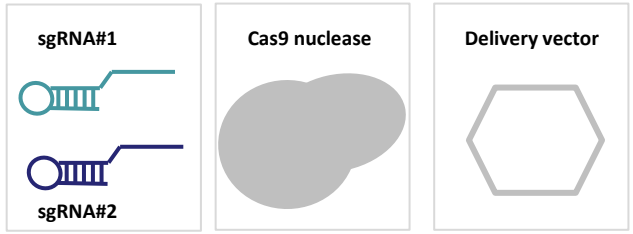
Development of an innovative therapy PLATFORM against FuGe or AMP essential for tumour viability



GENE EDITING THERAPY COMPONENTS

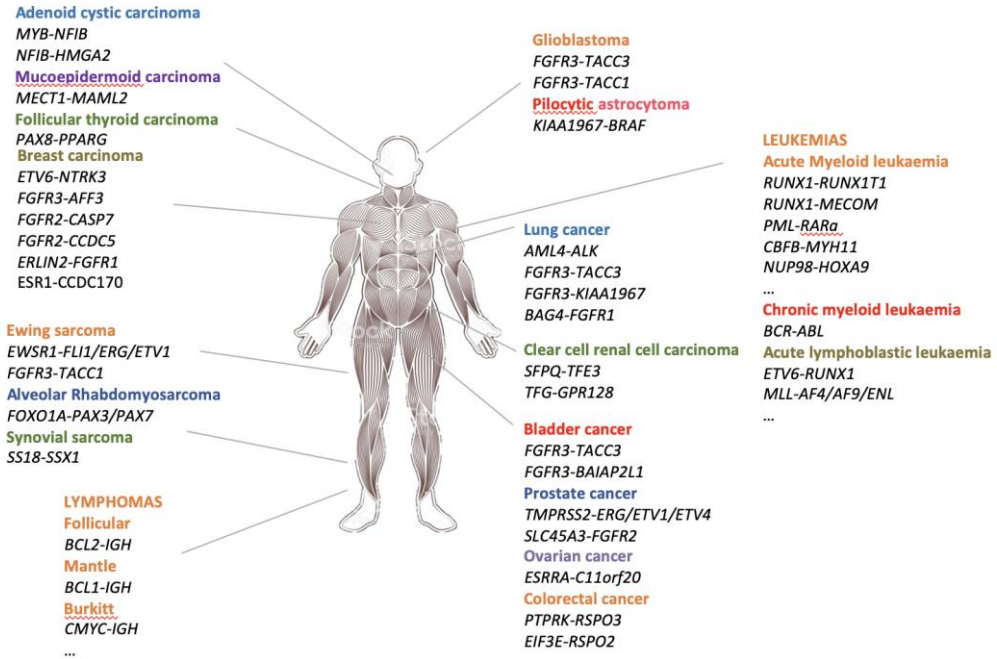
Our asset is a product for in vivo therapy ready to selectively attack cancer cells

ASSET COMPONENTS

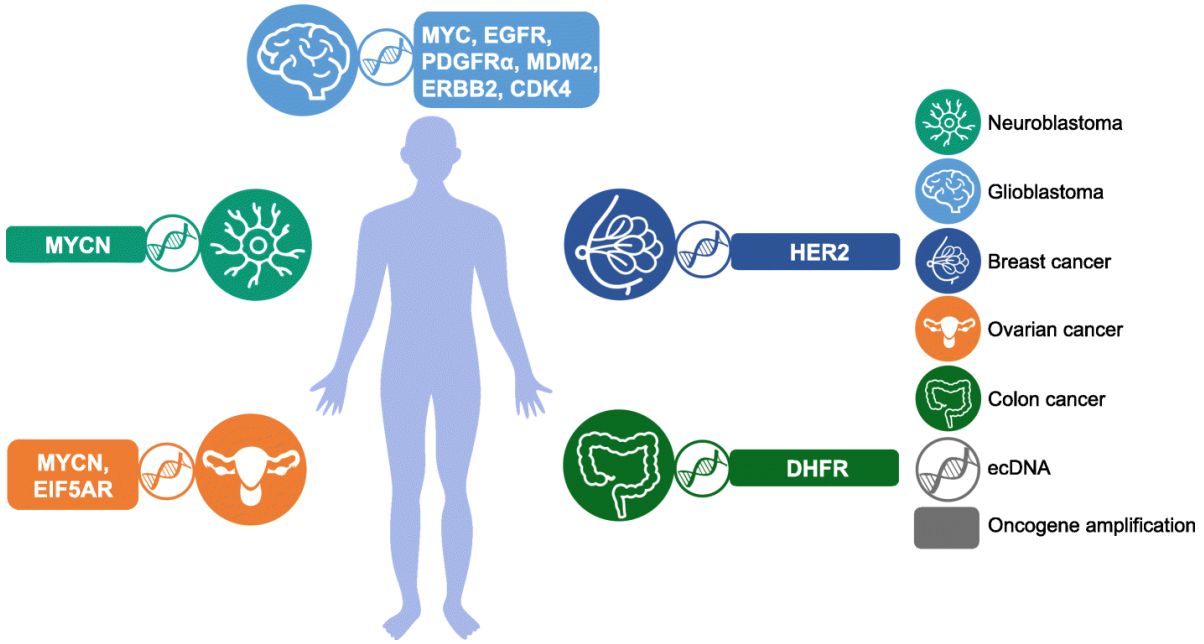


TARGET INDICATION

GENE FUSIONS (FuGe)



ONCOGENE AMPLIFICATIONS (AMP)



TARGET INDICATION

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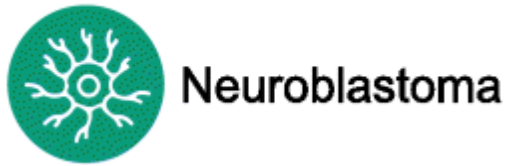
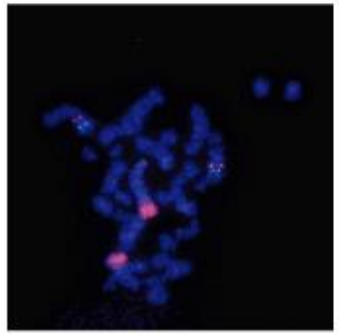
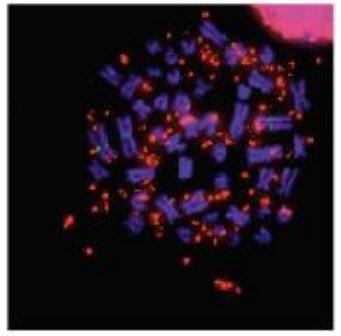
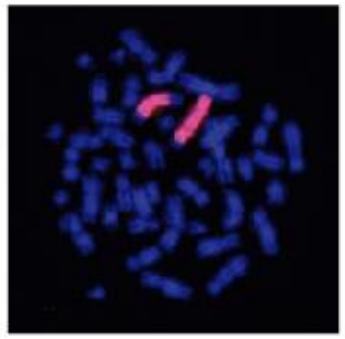
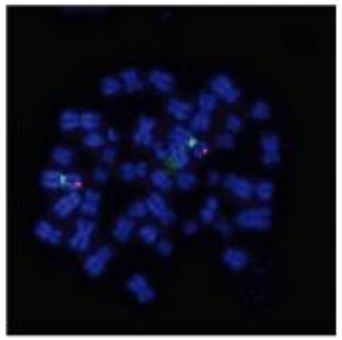
ONCOGENE AMPLIFICATIONS (AMP)



- Neuroblastoma (NB) is a heterogenic childhood tumour of the sympathetic nervous system
- Accounts for about 8–10% of all cases of childhood cancer and is the cause of 12–15% of cancer-related childhood mortality
- Clinical behaviour ranging from spontaneous regression to poorly differentiated tumours and metastasis.
- Risk in NB is classified as low, intermediate, or high.
  - Low- and intermediate-risk patients: favourable outcome (~90% event-free survival rate)
  - High-risk patients have <50% event-free survival rate
  - Ultra-high risk patients who do not respond to therapy
- Established characteristics for high-risk NB patients include: age, unfavorable histopathology, and **amplification of *MYCN***.

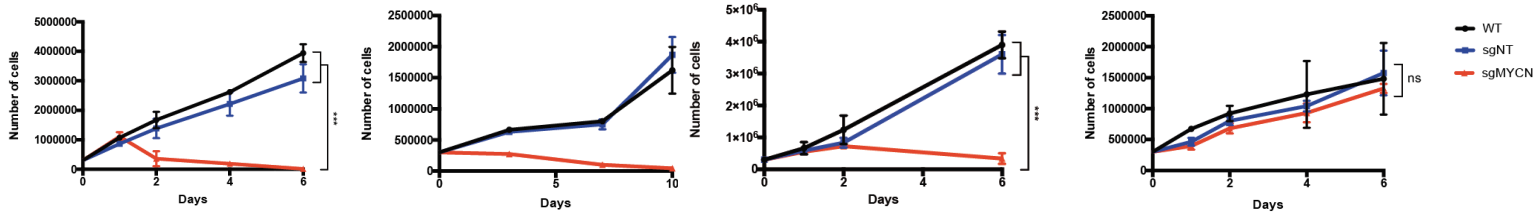
CURRENT STATUS OF DEVELOPMENT

In vitro VALIDATION (Lentivirus delivery)

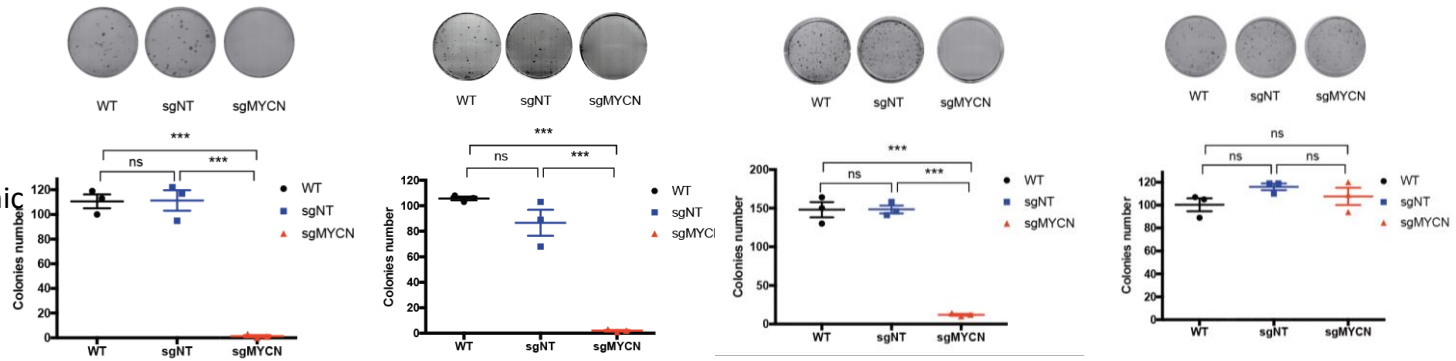
IMR32	LAN5	KELLY	SKNAS
			
MYCN AMP+	*MYCN* AMP+	*MYCN* AMP+	CONTROL *MYCN* wt

Targeting of *MYCN* inhibits tumor cell growth in vitro

Decreased cell growth

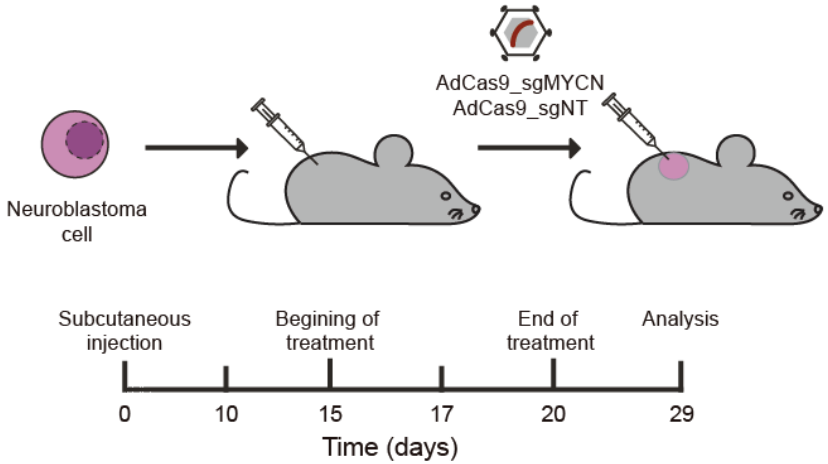


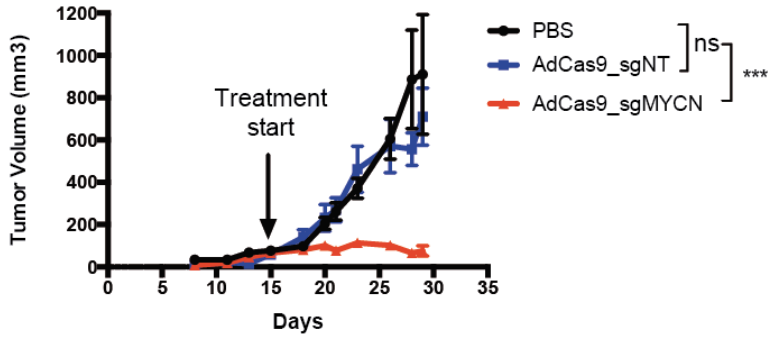
Decreased clonogenic growth



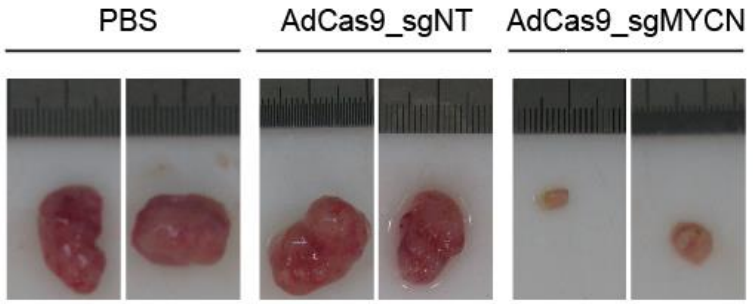
CURRENT STATUS OF DEVELOPMENT

In vivo VALIDATION (Adenovirus delivery)

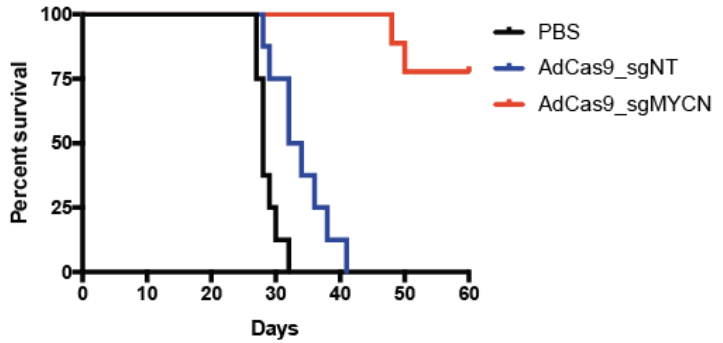




Decreased tumor size



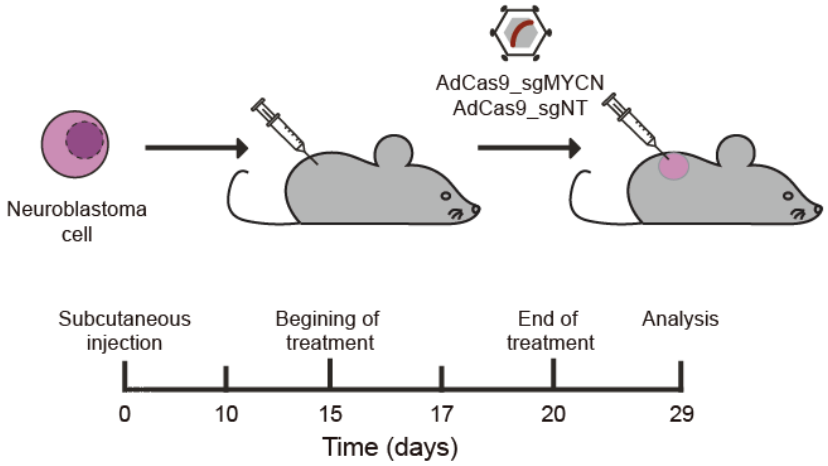
MYCN targeting controls tumor growth in a xenograft model

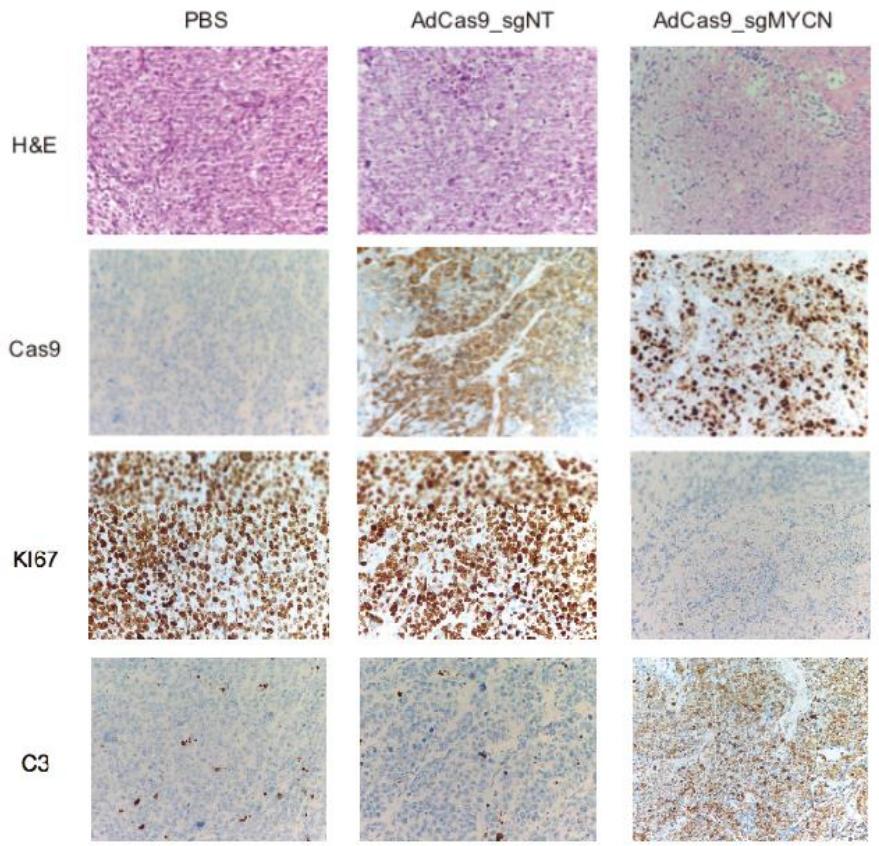


Increased survival

CURRENT STATUS OF DEVELOPMENT

In vivo VALIDATION (Adenovirus delivery)



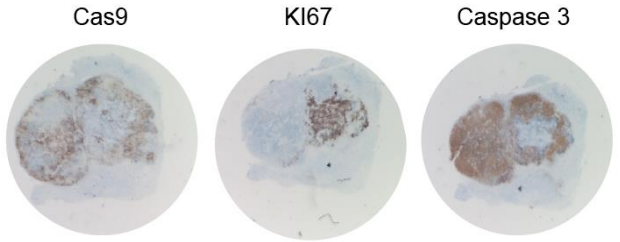


More extensive necrotic regions

Confirmed AdV delivery

Lower number of proliferative cells

Lower number of viable cells

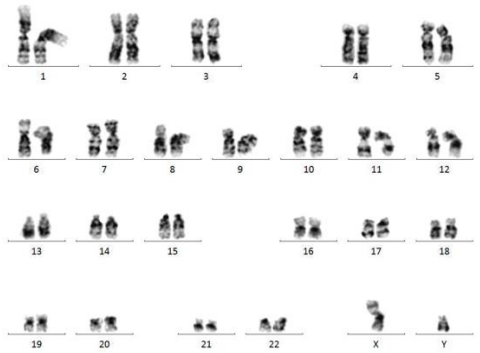


Colocalization of AdV expression (Cas9) with hiah and low expression of Ki67 and Caspase3

CURRENT STATUS OF DEVELOPMENT

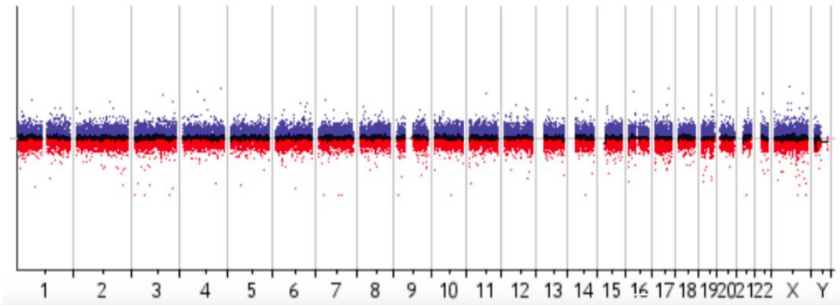
GENOMIC SAFETY VALIDATION (hMSCs)

Karyotype



No numerical or structural abnormalities

High-resolution array CGH



No large copy number gains or deletions

NGS off-target analysis

Genomic safety validation

Targeted NGS ruled out mutations in *MYCN*-targeted hMSCs

CRISPR MYCN targeting does not impair genomic stability

CURRENT STATUS OF DEVELOPMENT

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ONGOING TASKS

1.- Evaluate clinically relevant CRISPR delivery systems: pseudotyped adeno-associated viral vectors (therapeutic efficacy and toxicity).

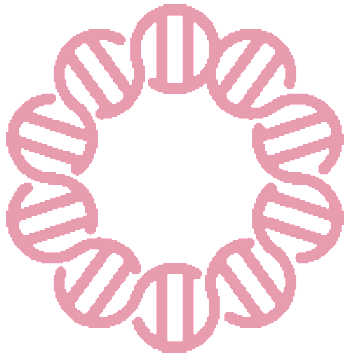
2.- Deepen the safety analysis of the CRISPR-mediated *MYCN* targeting strategy at genomic and mRNA expression level in in vitro and in vivo human PDX NB murine models (therapeutic safety).

3.- Development of an NB cell specific targeting expression system for Cas9 nuclease.

PITFALLS & RISKS TO BE CONSIDERED

- In the case of low efficient tumour distribution alternative delivery systems will be tested.

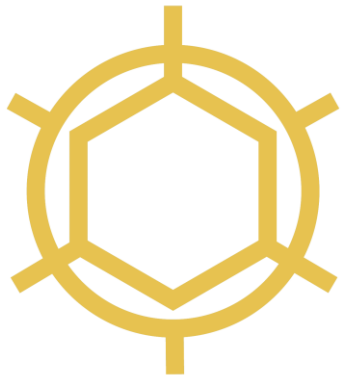
Non-Viral



Lipid Nanoparticles

- Increased potency
- Improved tolerability

Viral

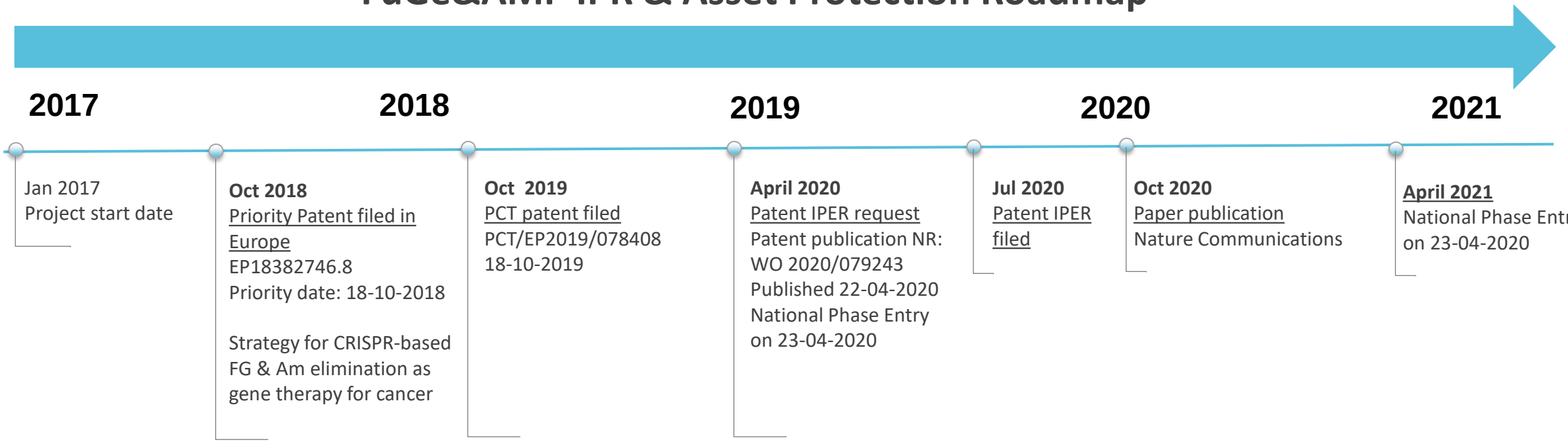


Pseudotyped Virus-like particles

- Improved tissue specificity
- Non-integrative
- Non-viral genome

IPR AND PUBLICATION STATUS

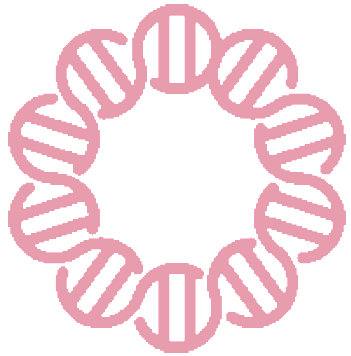
FuGe&AMP IPR & Asset Protection Roadmap

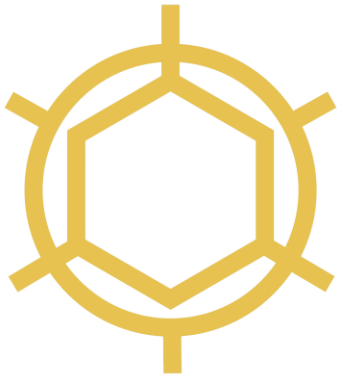


PARTNERING OPPORTUNITIES

Biopharma companies

Delivery technologies companies





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