NUCLEAR RNA NETWORKS

Blocking Therapy-Resistant KRAS-mutant Cancers by Blocking Gene-to-Gene Signaling

Nuclear RNA Networks, Inc.

Core Team

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CEO & Board Director
Experienced Biotech Executive & Entrepreneur
Chiron, Connecticut Innovations, iPierian, Renovis, UC Davis

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CFO & Board Director
Experienced Biotech CFO
Genenta Science, Biological Dynamics, OncoSec Medical, GenMark Dx, DigiRad Corp, C-N Biosciences, Vega Biotechnologies

Gail Brown, M.D.
Consulting CMO
Experienced Biotech CMO
Oncology drug research and development
Telik, Armo Biosciences, Tizona Therapeutics, Executive Director Abbie

Melanie Adams, M.D.
Founder, President, CSO & Board Director
Innovative physician/scientist with deep background in gene regulation and RNA viruses
UCSF Dept of Medicine, Blood Centers of the Pacific, UCSF Dept of Anatomic and Clinical Pathology

Leandro Castellano, Ph.D.
Scientific Advisor
Director of Sussex University RNA Center
Accomplished academic researcher with deep experience in RNA biology/biochemistry/genetics
Univ of Sussex, UK, Imperial College of Medicine

Dennis Fisher, M.D.
Founder & Board Director
Experienced Biopharmaceutical Consultant and Pharmacometrics Modeling Expert
P Less Than Co. (P<),
DURECT Corp. Pharsight Corp, UCSF

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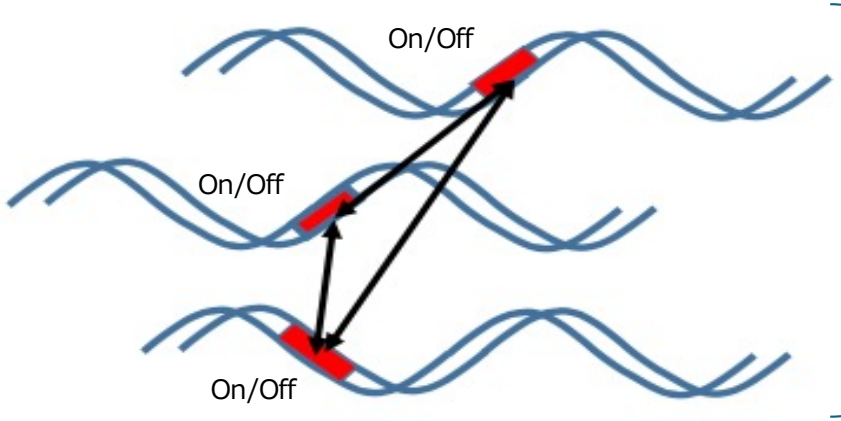
THE PROBLEM

- **How does one chose which individual gene and/or protein you are going to target to prevent and/or treat acquired resistance in KRAS-mut cancers?**
- **Block sequences shared between genes coordinating specific cellular pathways: block the pathway *itself***



Hub genes that coordinate a specific cellular pathway *e.g.* Metastasis

ONCO-TAG™

↓

Blocks multiple genes of the HIPPO/Yap1 Pathway

= required for acquired resistance in KRAS mutant cancers[1]

1. Mira A, Ambrogio C**. YAP and TAZ orchestrate adaptive resistance to KRAS inhibitors**. Nat Cancer. 2023 Jun;4(6):784-786. doi: 10.1038/s43018-023-00580-5

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OUR UNIQUE PLATFORM

- **SiRNA sequences are designed to block pathways instead of individual proteins or genes**

- **Our proprietary technology:**
  - Method by which targets are chosen

- **IP Protection:**
  - Morgan, Lewis & Bockius

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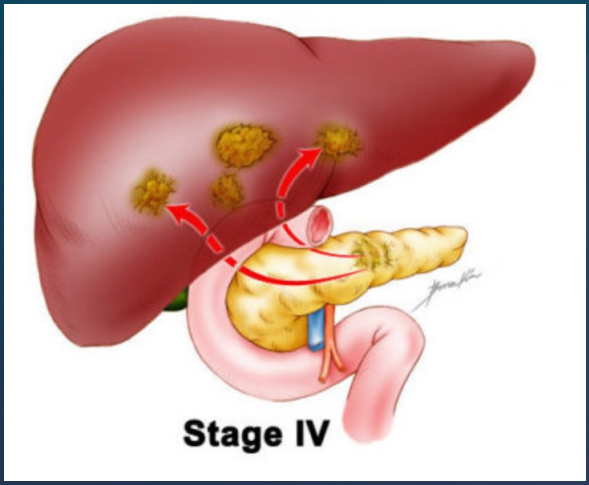
The Problem We Are Currently Addressing

Pancreatic Ductal Adenocarcinoma (PDAC)



PDAC: projected to be 2nd leading cause of cancer deaths in the US by 2030

Cancers with KRAS-mutations are highly refractory to conventional treatment

- **KRAS mutations ~ 25% of all human cancers**
- **To date: no FDA-approved therapies targeting the KRAS G12D mutation**

= 34% Pancreatic cancers, 13% Colorectal

Why?

Acquired Resistance

Siegel RL, Miller KD, Fuchs HE, Jemal A. **Cancer statistics, 2022**. CA Cancer J Clin. 2022 Jan;72(1):7-33. doi: 10.3322/caac.21708. Epub 2022 Jan 12. PMID: 35020204.
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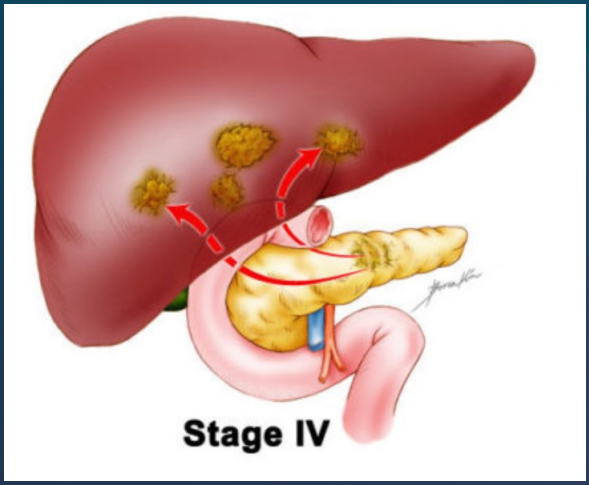
Our Molecule is Unique

Pancreatic Ductal Adenocarcinoma (PDAC)



PDAC: projected to be
2nd leading cause of cancer deaths in the US by 2030

- Targets many genes within the same pathway
- Targets the pathway on which KRAS-G12D cancers depend

Acquired resistance

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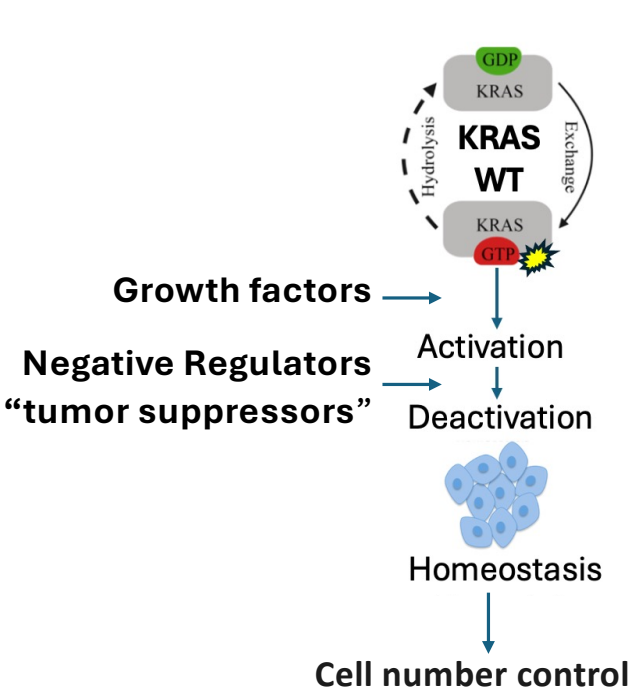
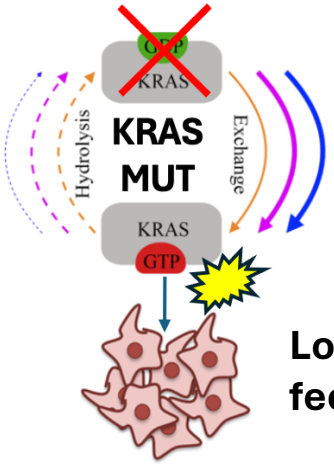
Why Are Treatment Options Limited?





KRAS-G12D lacks deep binding pockets for small molecule drugs

Loss of most negative feedback to proliferation

Treatment

"Survival of the Fittest" Depends on HIPPO/Yap1 Pathway

1. YAP/TAZ mediates resistance to KRAS inhibitors through inhibiting pro-apoptosis and activating the SLC7A5/mTOR axis. JCI Insight. 2024 Dec 20;9(24):e178535. doi: 10.1172/jci.insight.178535;
2. SRC Family Kinase Inhibition Targets YES1 and YAP1 as Primary Drivers of Lung Cancer and as Mediators of Acquired Resistance to ALK and Epidermal Growth Factor Receptor Inhibitors. JCO Precis Oncol. 2022 Aug;6:e2200088. doi: 10.1200/PO.22.00088.

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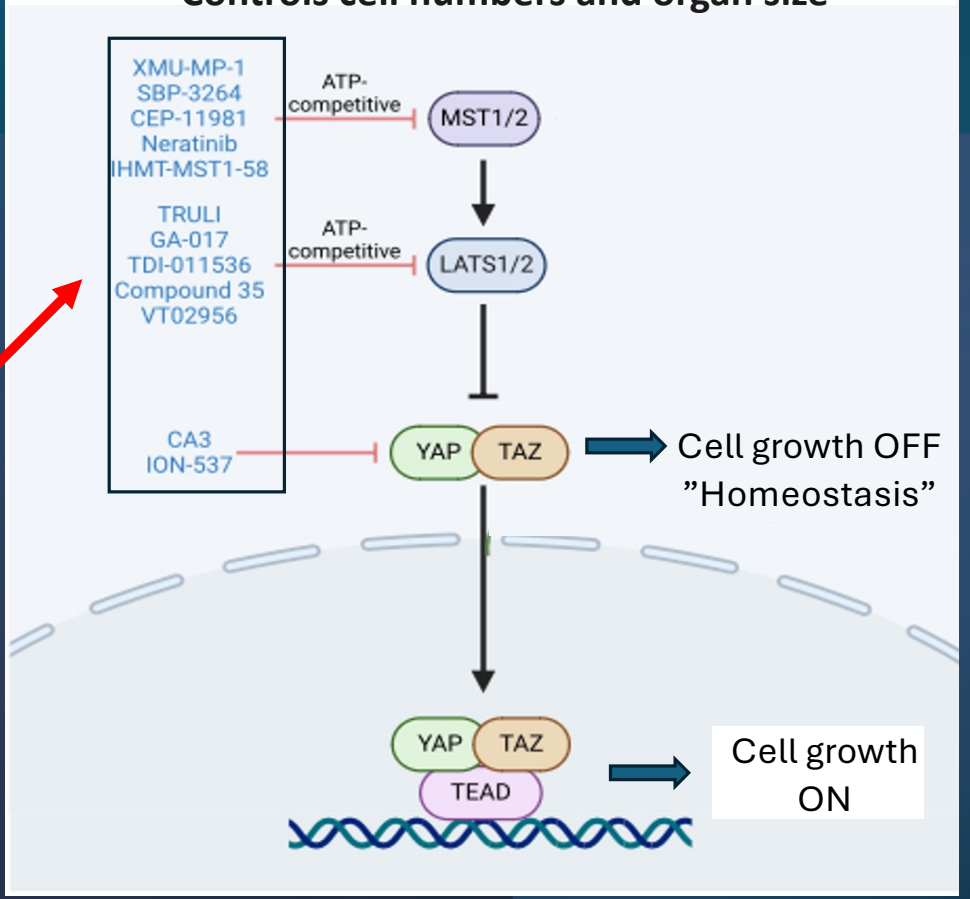
The Heart of the Acquired Resistance PROBLEM

Current cancer drugs target individual proteins

*Lao Z, Chen X, Pan B, Fang B, Yang W, Qian Y. Pharmacological regulators of Hippo pathway: Advances and challenges of drug development. FASEB J. 2025 Mar 31;39(6):e70438. doi: 10.1096/fj.202401895RR. PMID: 40100056.

HIPPO/Yap1 Pathway

Controls cell numbers and organ size



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THE HEART OF THE PROBLEM

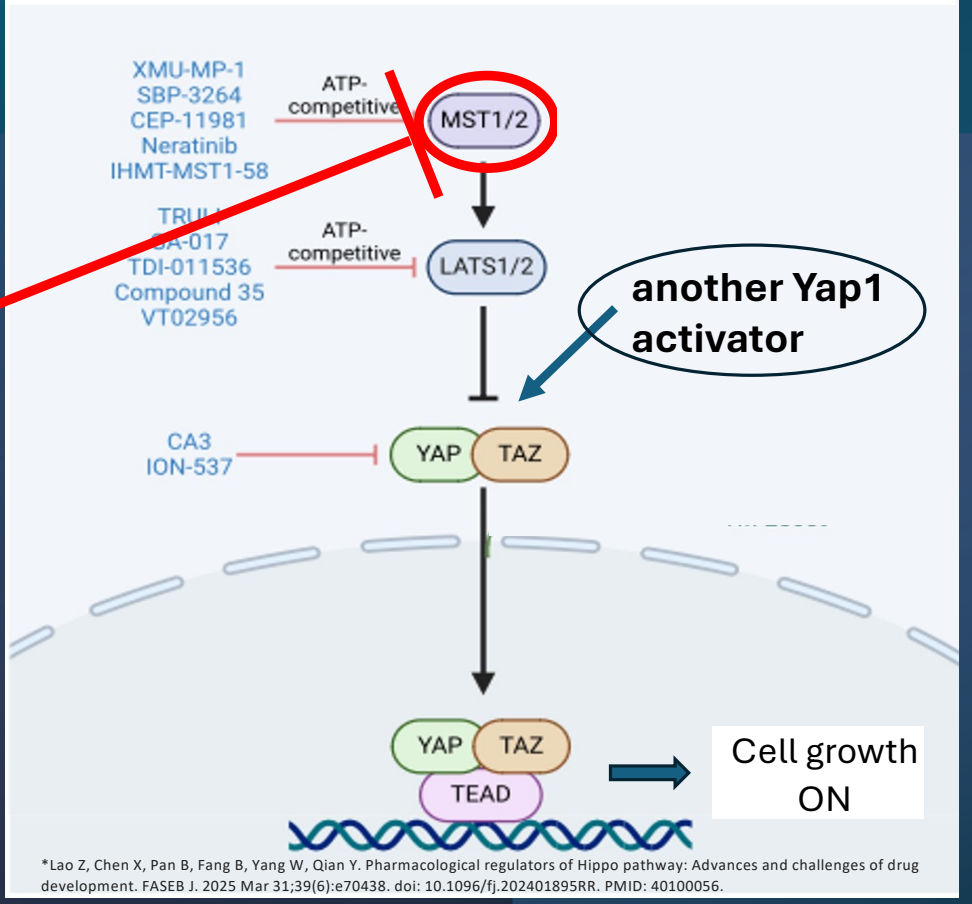
Current cancer drugs inhibit *ONLY* individual proteins

↓

Acquired resistance

Rewiring of Signaling Pathways

HIPPO/Yap1 Pathway



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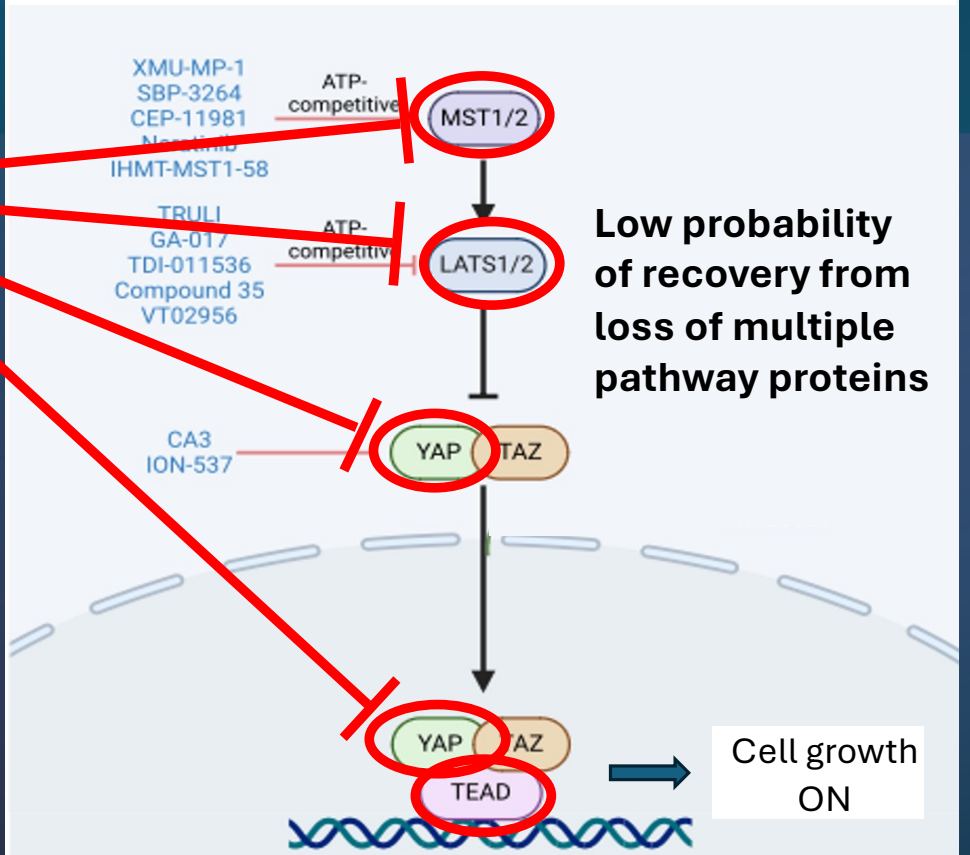
THE SOLUTION

"ONCO-TAG™"

Single proprietary siRNA sequence that targets multiple genes in the HIPPO/Yap1 pathway

HIPPO/Yap1 Pathway



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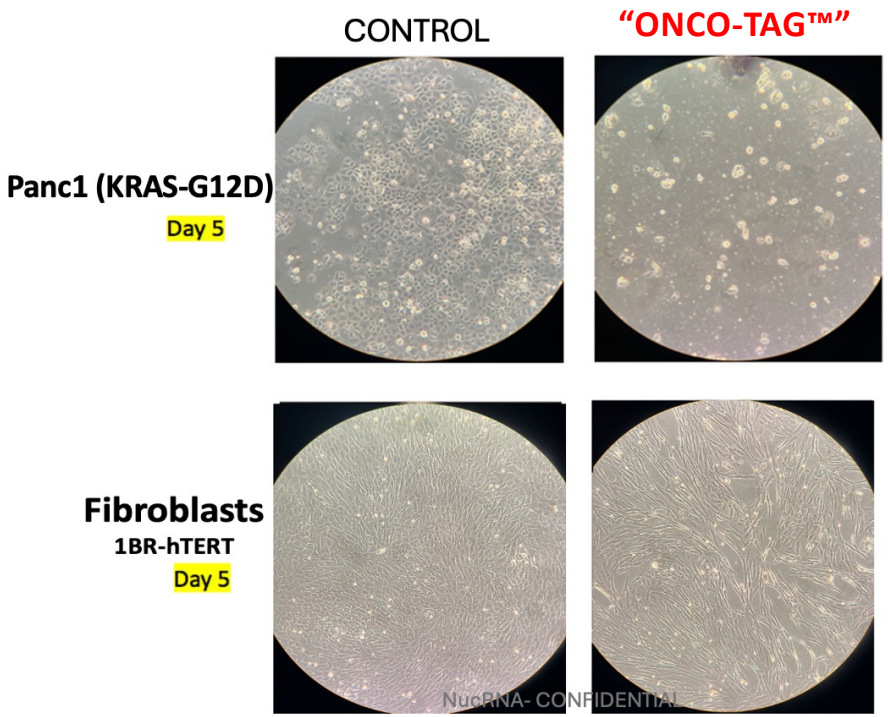
In Vitro Results

95% tumor growth inhibition in pancreatic KRAS-G2D cell lines



PANCREATIC CANCER CELLS
95% dead

NORMAL, activated

LESS TOXIC?

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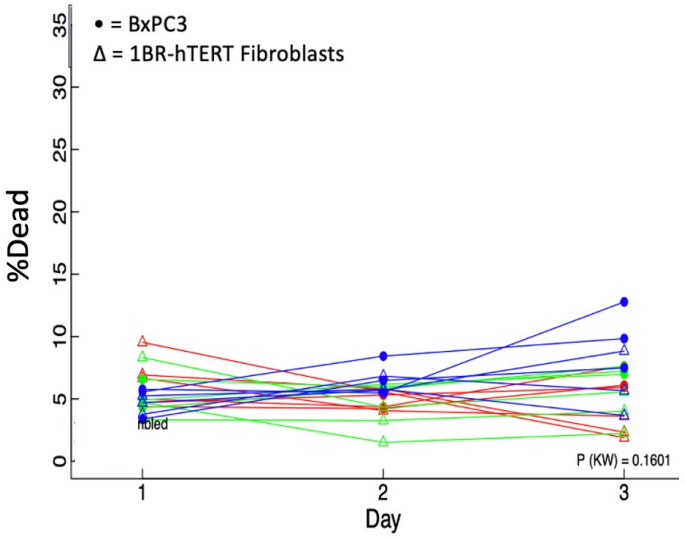
In Vitro Results

KRAS-Mutant PDAC are more sensitive to ONCO-TAGs than are KRAS-WT

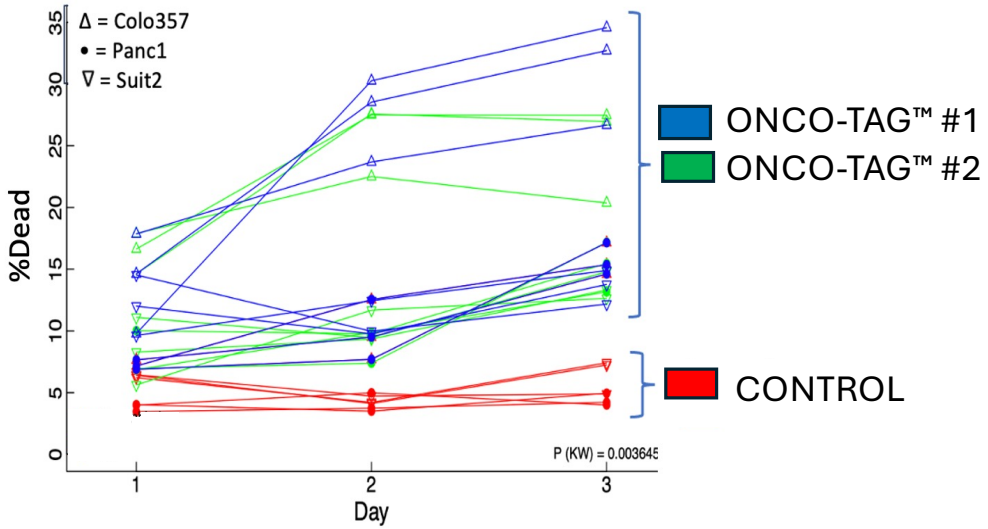
KRAS-WT



P <0.2
Control vs C1, C2; Day 3

Day 3 %Dead nsd

KRAS-G12D



P <0.004
Control vs C1, C2; Day 3

Day 3: Significant %Dead

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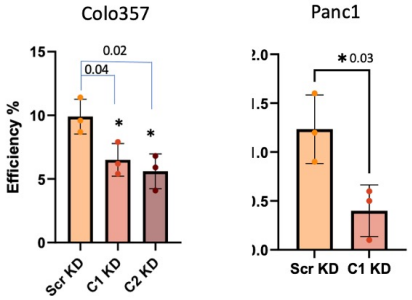
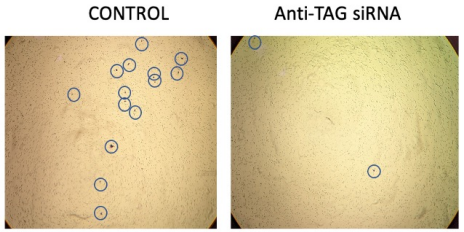
Functional Studies

ONCO-TAGs™ decreased stem cell growth and infiltration in pancreatic cell lines and decreased adhesion in both pancreatic and breast cancer cell lines

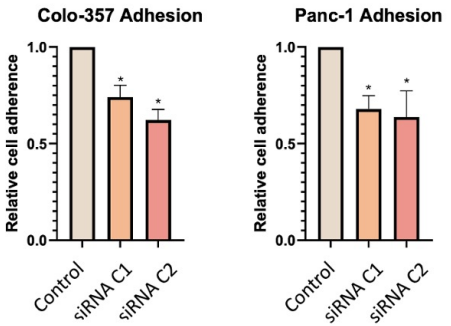
Sphere Formation Efficiency



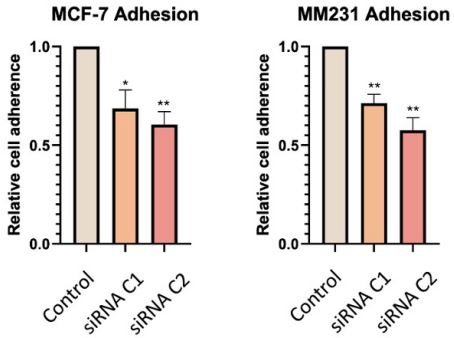
Infiltration Assay –Colo357(Panc1 pending)



Pancreatic Cancer Cell Lines



Breast Cancer Cell Lines



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Transcriptomics Studies

Significant decrease in multiple genes required for HIPPO/Yap1 signaling

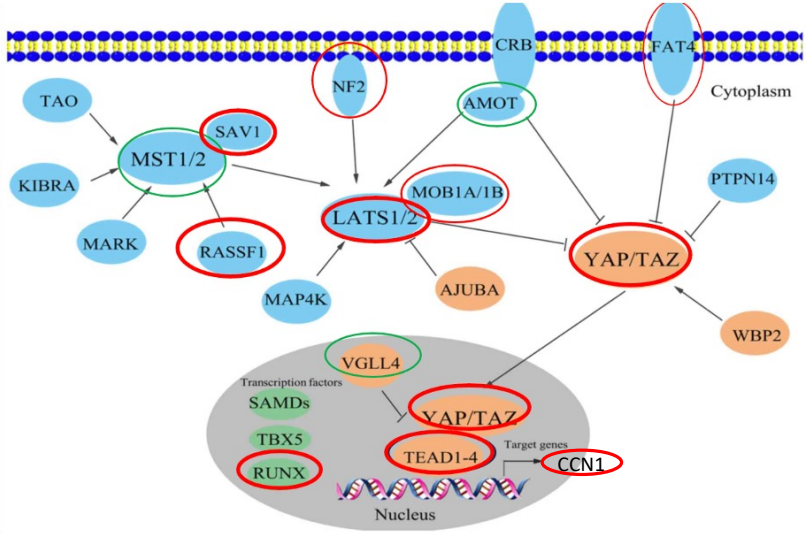
Elsevier Pathway Collection

- Hippo/YAP1 Signaling Deregulation in Cance
- Proteins with Altered Expression in Cancer-A
- Hedgehog Signaling in Mantle Cell Lymphon
- Integrins in Cancer Cell Motility, Invasion an

KEGG 2021 Human

- Hippo signaling pathway
- Hedgehog signaling pathway
- Acute myeloid leukemia
- Pathways in cancer

HIPPO/Yap1 Pathway



= genes with decreased expression

*Enrichr gene set enrichment analysis tool; Ma'ayan Lab https://maayanlab.cloud/Enrichr

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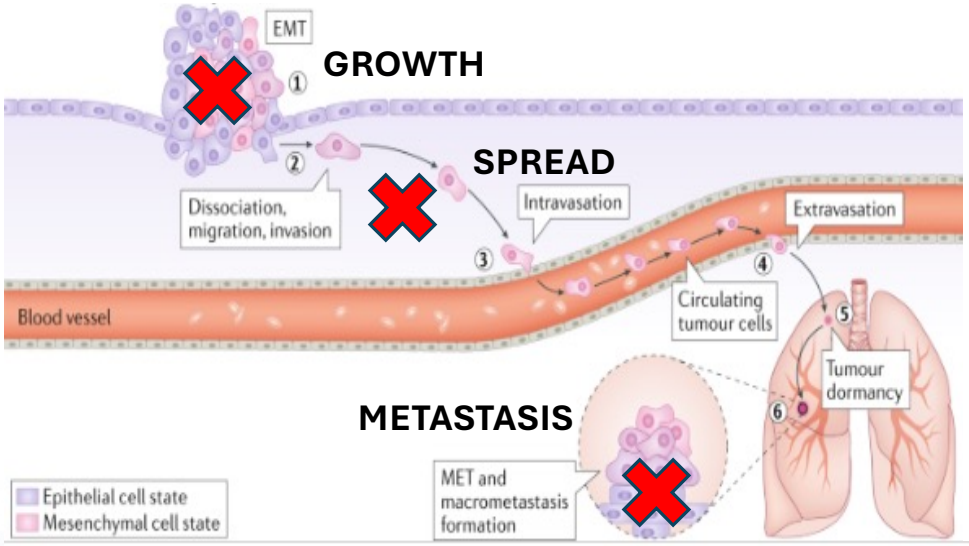
ONCO-TAGs™ affect multiple ways in which cancers spread and metastasize

- **Cannot crawl and spread** (decreased integrins, focal adhesion and actin gene expression)
- **Cannot re-form nests in new tissues** (decreased tight junction, adherens junction genes)
- **Death** (decreased key cell cycling genes)



- IV administration
- Liposome formulation planned
- Adjunct to small molecule inhibitors, antibodies, and immunotherapy

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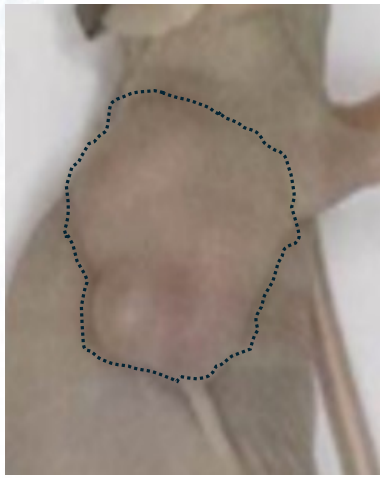
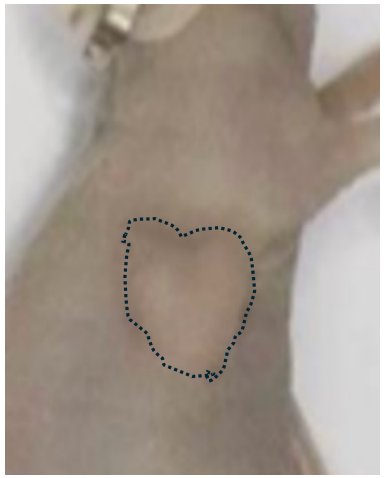
Preliminary Animal Results

Strong tumor growth inhibition using **"ONCO-TAG™"**



Control



ONCO-TAG™

- Inhibition in mouse model equals commercial mix of siRNA cancer inhibitors*
- No systemic toxicity observed with intra-tumoral injection
- *In vitro* evidence of less toxicity in normal cells

* Qiagen AllStars Death Control

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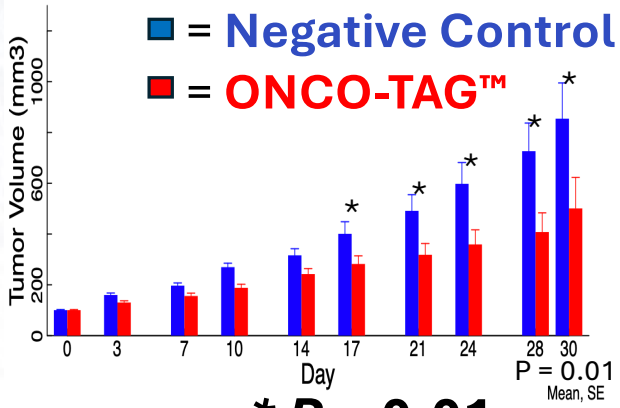
Significant difference in *in vivo* tumor growth
ONCO-TAG™ *vs.* Control group

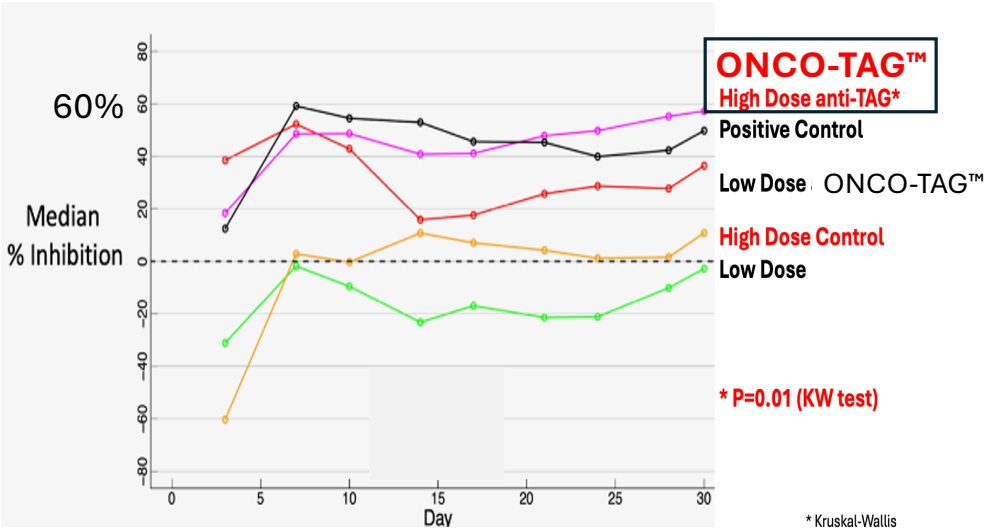
Tumor Volume Compared to Vehicle



*** *P* = 0.01**

By Day 17

Median % Inhibition Compared to Vehicle



60% inhibition of tumor growth (D30)

Competitive Landscape (KRAS-G12D Pancreatic Cancer)

Based on publicly-available data

- **No FDA-approved KRAS-G12D-selective inhibitors exist**

Suyal C, *et al*. Structure–activity relationships of KRAS-G12D inhibitors for pancreatic cancer. Drug Discovery Today 30 Number 7, July 2025

- **11 Clinical trials targeting single KRAS G12D protein or mRNA**

clinicaltrials.gov/search?cond=metastatic%20pancreatic%20ductal%20adenocarcinoma%20&term=KRAS%20G12D

Examples:

- siRNA directed at KRAS-mutant mRNA:

"iExosomes in Treating Participants With Metastatic Pancreas Cancer With KrasG12D Mutation"
MD Anderson, Texas (intravenous, mesenchymal stromal cells-derived exosomes); clinicaltrials.gov #NCT03608631

- Small molecule inhibitors:

- **RMC-7977** (Revolution Medicines); **Fast-track designation**
  small molecule RAS inhibitor attached to cyclophilin carrier
- **VS-7375** Verastem Oncology; Fast-track designation;
  oral KRAS G12D (on/off) inhibitor; clinicaltrials.gov #NCT07020221
- **MRTX1133** Mirati Therapeutics (acquired by **Bristol Myers Squibb** for $4.8 billion)
  Clinical trial terminated 4/6/2025 (Formulation challenges); clinicaltrials.gov #NCT05737706

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The Market for Treatment of Pancreatic Cancer

Global

- Market size:
  2023: $2.86 billion
  2024: $3.30 billion
  2032: $10.69 billion (projected)
- Compound annual growth rate (through 2032): 15.8%

United States

- Market size projected to grow significantly
- Estimated value by 2032: $5.25 billion

Source: www.fortunebusinessinsights.com/pancreatic-cancer-treatment-market-101989

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Our Platform is Unique

- SiRNA sequences are designed to block pathways instead of individual proteins or genes

Our Molecule is Unique

- ONCO-TAG™ targets many genes within the HIPPO/Yap1 pathway
- KRAS-G12D cancers depend on HIPPO/Yap1 for therapy breakthrough

Results summary

- KRAS-G12D pancreatic tumor inhibition:
  - *In vitro:* 95%
  - *In vivo:* 60%
- Inhibition of breast cancer cell lines

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Needs: $300K for 1st year

Milestones:

1. **ONCO-TAG™ preclinical studies of PDX from patients who relapsed or experienced resistance to the current lines of treatments**

→ **Crown Bioscience CRO** (CrownBio.com) specializing in oncology and immuno-oncology drug discovery and development.

2. **Formulation studies focused on LNP encapsulation for systemic administration.**

→*e.g.*, **Lonza** (www.lonza.com/knowledge-center/biologics/es/mrn-nucleic-acid-based-therapeutics-encapsulation)

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Our Patent

COMPOSITIONS AND METHODS FOR MODULATING GENE TRANSCRIPTION NETWORKS

US Patent Application No. US-20240360442-A1

Morgan, Lewis & Bockius LLP

1111 Pennsylvania Avenue, NW | Washington, DC 20004-2541

Event	Date	Comment
Application Filed	April 25, 2023	
Petition to make special granted	July 17, 2023	Application fast-tracked under PPH
Restriction Requirement received	November 16, 2023	
Response filed with amendments	January 17, 2024	
First non-final Office Action received	February 1, 2024	
Examiner Interview	March 15, 2024	
Response to NFOA filed	June 6, 2024	Claims amended in view of the discussion with the Examiner
Final Office Action received	July 17, 2024	
Response to FOA filed	September 5, 2024	With AFCP
Advisory Action received	September 16, 2024	
RCE filed	October 2, 2024	A supplemental response also filed with the RCE
Second non-final Office Action received	November 22, 2024	
Response to NFOA2 filed	February 12, 2025	Claims further amended
Final Office Action received	March 24, 2025	
Response to FOA2 filed	June 24, 2025	
Advisory Action received	July 2, 2025	
Second RCE filed	July 23, 2025	No further amendments or supplemental response filed with RCE
Third non-final Office Action received	August 11, 2025	No prior art rejections; only rejections under 112 and 101 remaining
Examiner interview	September 17, 2025	

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References

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Yang W, Zhang M, Zhang TX, Liu JH, Hao MW, Yan X, Gao H, Lei QY, Cui J, Zhou X. **YAP/TAZ mediates resistance to KRAS inhibitors through inhibiting proapoptosis and activating the SLC7A5/mTOR axis**. JCI Insight. 2024 Dec 20;9(24):e178535. doi: 10.1172/jci.insight.178535.

Sato H, Kubota D, Qiao H, Jungbluth A, Rekhtman N, Schoenfeld AJ, Yu HA, Riely GJ, Toyooka S, Lovly CM, Paik P, Ladanyi M, Fan PD. **SRC Family Kinase Inhibition Targets YES1 and YAP1 as Primary Drivers of Lung Cancer and as Mediators of Acquired Resistance to ALK and Epidermal Growth Factor Receptor Inhibitors.** JCO Precis Oncol. 2022 Aug;6:e2200088. doi: 10.1200/PO.22.00088.

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Pancreas
with KRAS G12D mutant
cancer