

# Phase 1 Dose Escalation of Rhenium ( $^{186}\text{Re}$ ) Obisbemedate (Reyobiq™) for the Treatment of Leptomeningeal Metastases (LM): Clinical Study Results for Safety and Efficacy

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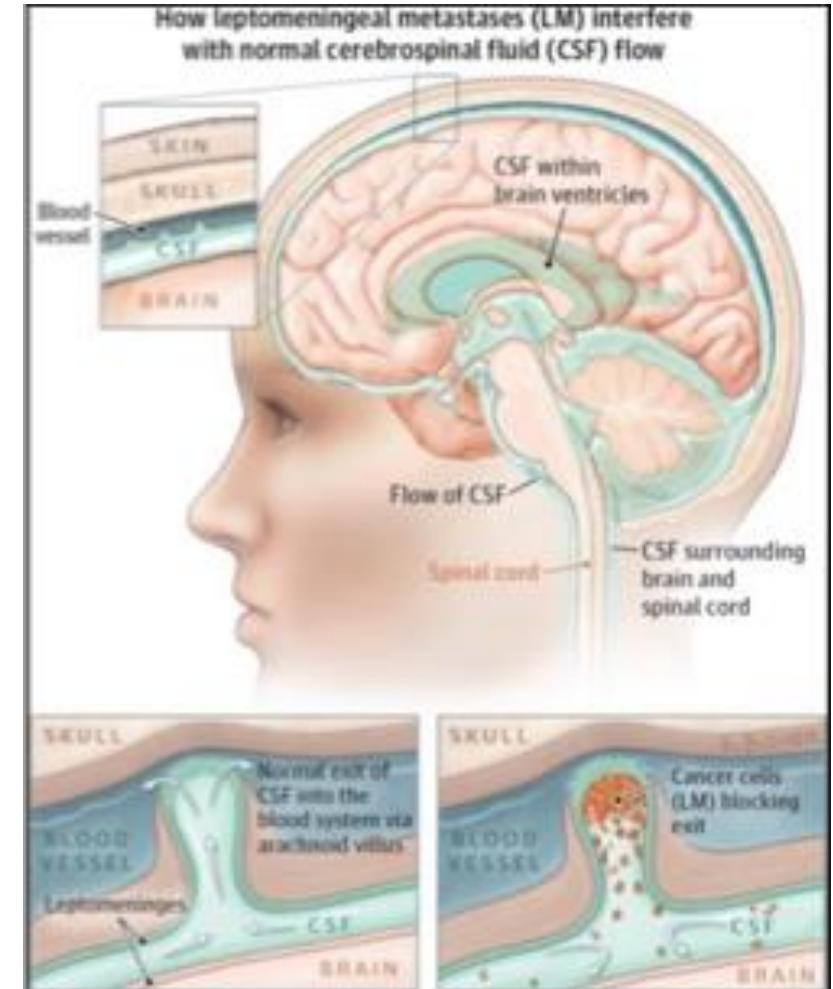




### LM is a Rare Disease With A High Unmet Medical Need

- + A typically fatal complication associated with advanced cancers that affect the fluid-lined structures of the central nervous system (CNS); prevalence of neurologic impairment is ~47%
- + Diagnosed in approximately 5% of cancer patients (20% at autopsy); U.S. annual incidence is ~110,000
- + Most common tumors giving rise to LM are breast cancer, lung cancer, melanoma, & gastrointestinal malignancies
- + No FDA-approved therapies; standard treatment includes radiation therapy (RT) to the affected sites followed by chemotherapy, given either orally, intravenously, or directly into the cerebrospinal fluid (CSF)
- + Median survival is 3 to 8.7 months (depending on primary tumor type) & 2-year survival is 3%

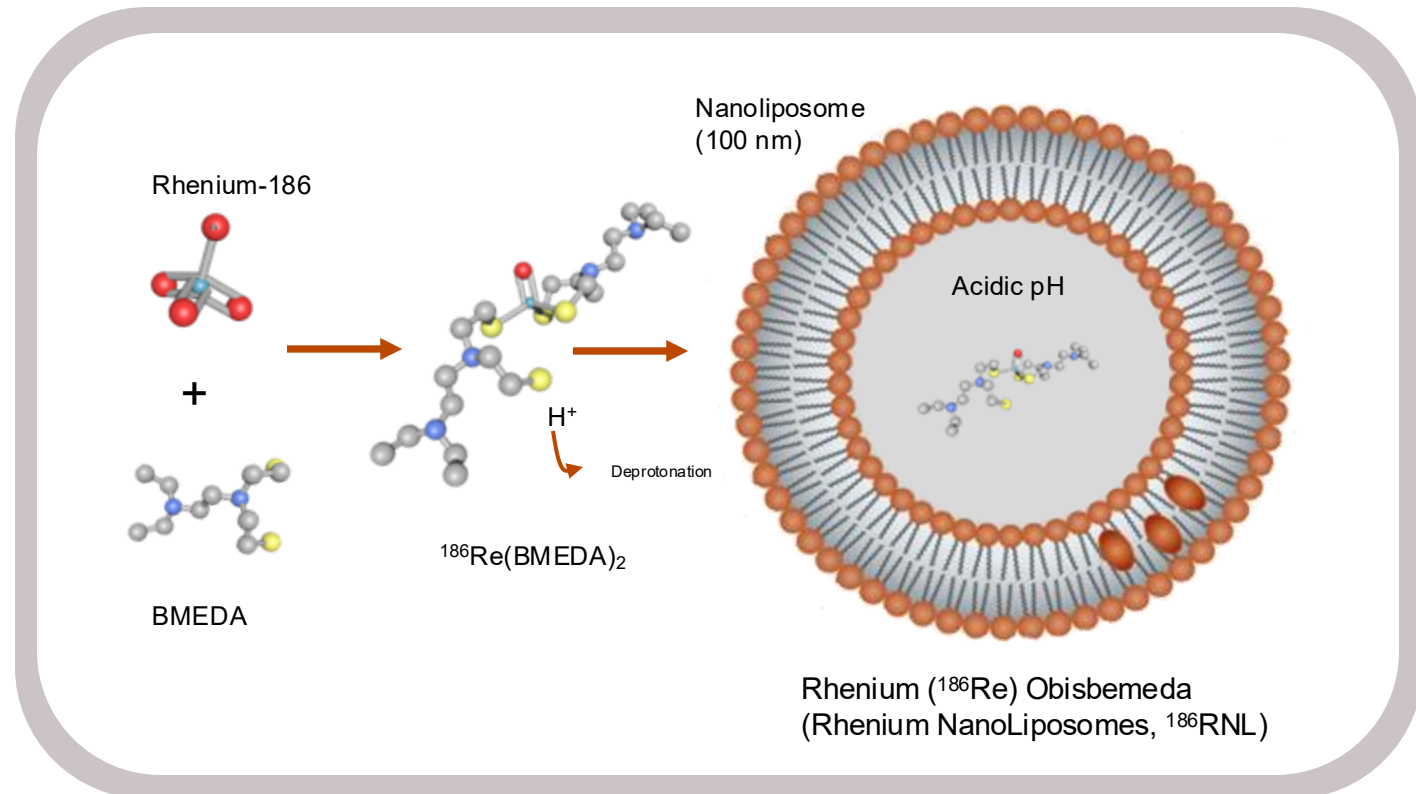
***Patients have limited treatment options & survival is measured in weeks (untreated) to months (treated)***





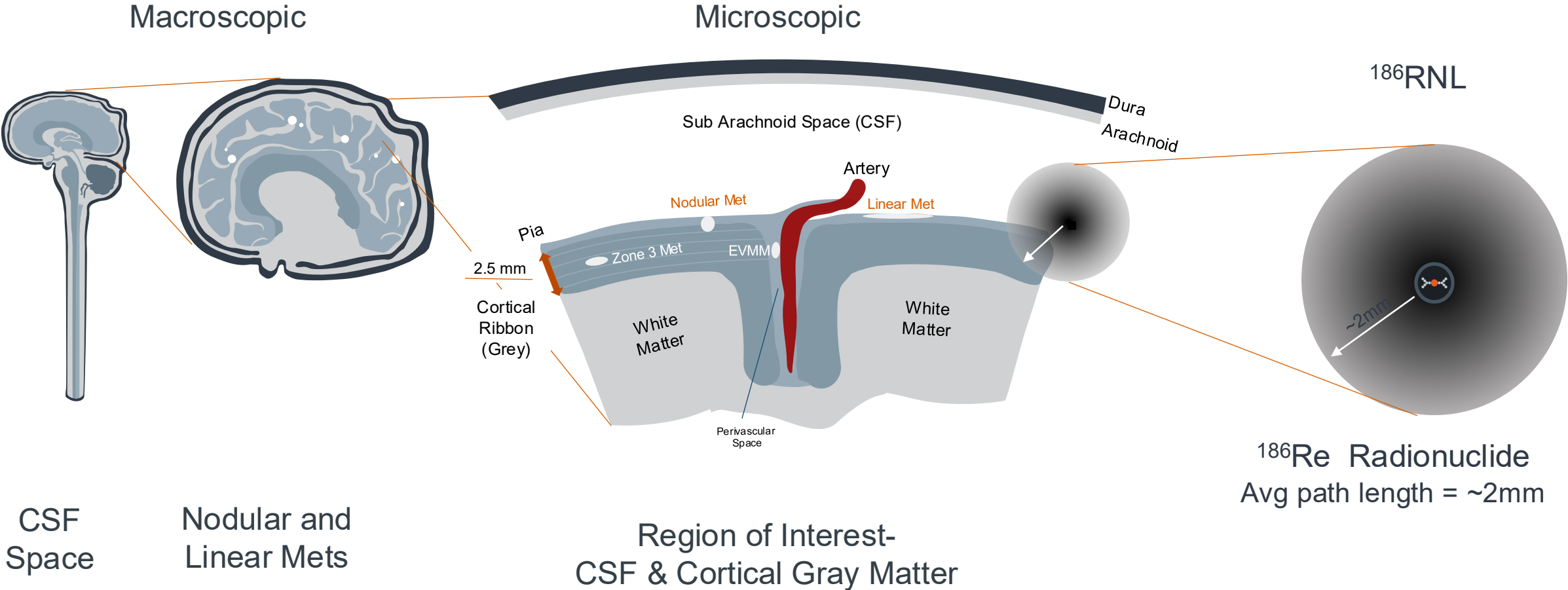
## $^{186}\text{Re}$ RNL- Rhenium Obisbameda – REYOBIQ™

- Investigational product is N,N-bis(2-mercaptoethyl)-N',N'-diethylethylenediamine (BMEDA)-chelated  $^{186}\text{Re}$  encapsulated within lipid vesicles (liposomes).
- BMEDA is an SNS pattern ligand with a tridentate structure that has one nitrogen and three sulfur atoms. These three atoms donate electrons to  $^{186}\text{Re}$ , resulting in a lipophilic complex in a neutral state.
- Nanoliposomes are composed of a within 80 – 130 nm diameter lipid bilayer of distearoylphosphatidylcholine (DSPC) and cholesterol, and confer drug delivery control on the chelated  $^{186}\text{Re}$ .



- Rhenium-186: Emits tumor-destroying radiation over short distances while sparing healthy tissue
- BMEDA: Small molecule that chelates to rhenium and is loaded into the nanoliposome where it's irreversibly trapped
- Nanoliposome: Carries the trapped BMEDA-chelated  $^{186}\text{Re}$  to tumor

# Pathology of Leptomeningeal Disease Drives Therapeutic Approach



# ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

*Trial design: single administration delivery via standard Ommaya reservoir*

- + Dose escalation: 3+3 modified Fibonacci
- + Primary objective: Safety and tolerability
  - + Maximum Tolerated Dose (MTD) / Maximum Feasible Dose (MFD) via Ommaya reservoir
- + Secondary objectives: Efficacy
  - + Overall Response Rate (ORR)
  - + Duration of Response (DoR)
  - + Progression Free Survival (PFS)
  - + Overall survival (OS)
- + Other objectives: Analysis on CSF, pK
  - + CSF circulating tumor cells (CTCs)
  - + Pharmacodynamic (PD) markers & dosimetry
- + Funding: CPRIT

Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
1	5	6.6	1.32
2	5	13.2	2.64
3	5	26.4	5.28
4	5	44.10	8.82
5	5	66.14	13.23
6	5	75.0	15.00
7	5	TBD	TBD



CANCER PREVENTION & RESEARCH  
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# ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

*Study Completed- Final Data Monitoring and Study Report in Progress*

Mays Cancer Center



## Summary

- + Study completed
- + 29 patients dosed over 6 cohorts
- + Demonstrated feasibility, safety, and showed efficacy signal

## Safety

- + 1 DLT in cohort 5, 1 DLT in cohort 6
- + 1 death due to sepsis deemed unlikely related in cohort 6
- + No DLTs or SAEs in cohort 4
- + DSMB review of cohort 6 Feb 2025
- + RP2D (44.1 mCi) and MFD determined

## Results

- + Median OS of 9 months in cohorts 1-4 (RP2D) (2-6 months commonly reported in lit.)
- + CSF tumor cell enumeration decreased up to 100% following Reyobiq treatment
- + 5 of 7 patients with >80% reduction in CTC by CNSide survived at least 1 year

Single Administration Phase 1 Dose Escalation Plan

Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
1	5	6.6	1.32
2	5	13.2	2.64
3	5	26.4	5.28
4	5	44.10	8.82
5	5	66.14	13.23
6	5	75.00	15.00
7	5	109.96	21.99

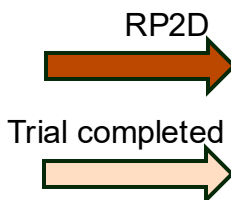
RP2D (44.10 mCi) is indicated for Cohort 4. Trial Stopped at Cohort 6.

# ReSPECT-LM Phase 1 Dosing, PK, and Absorbed Dose Data

*Excellent target/off-target absorbed dose ratio*

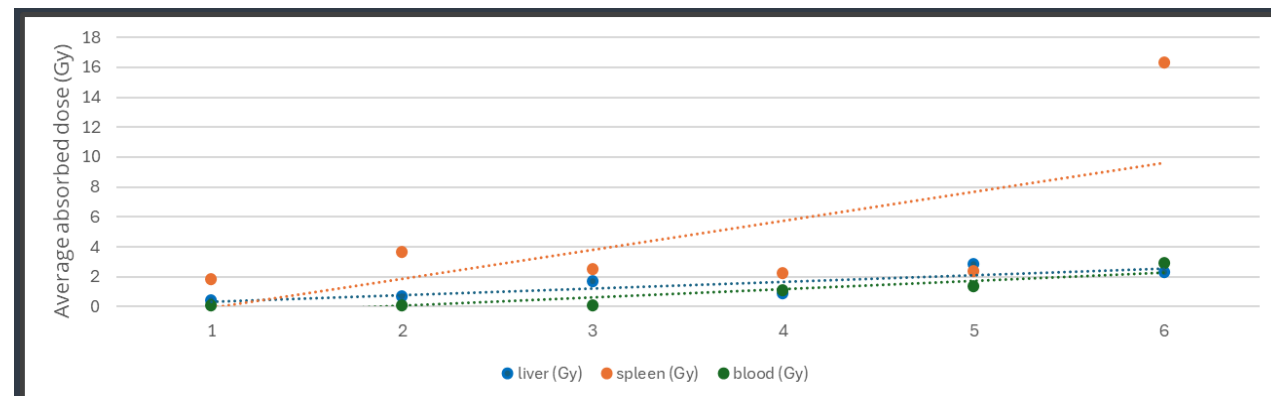
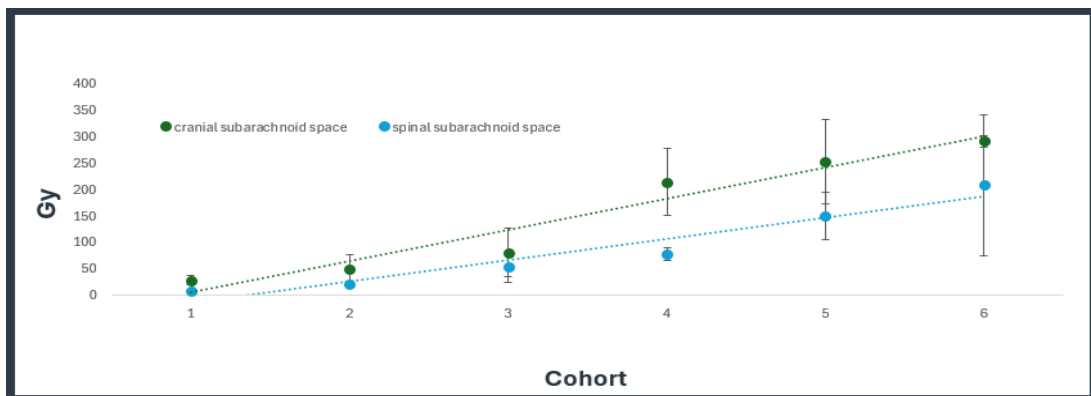


- + Target/off-target radiation absorbed dose ratio >100/1
- + Low radiation exposure to critical organs
- + Radiation measured in CSF space for 7 days
- + Complete CSF circulation of drug seen by 3.5-hour imaging timepoint



Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
1	5	6.6	1.32
2	5	13.2	2.64
3	5	26.4	5.28
4	5	44.10	8.82
5	5	66.14	13.23
6	5	75.0	15.00
7	5	TBD	TBD

## Average Absorbed Dose by Cohort



General toxicity limits: Liver: ~35-50 Gy; Spleen: ~40 Gy; Bone marrow: ~2-5 Gy

# ReSPECT-LM Phase 1 Safety Data

*Single dose Reyobiq for patients with LM was well tolerated up to 66.14 mCi/253Gy*

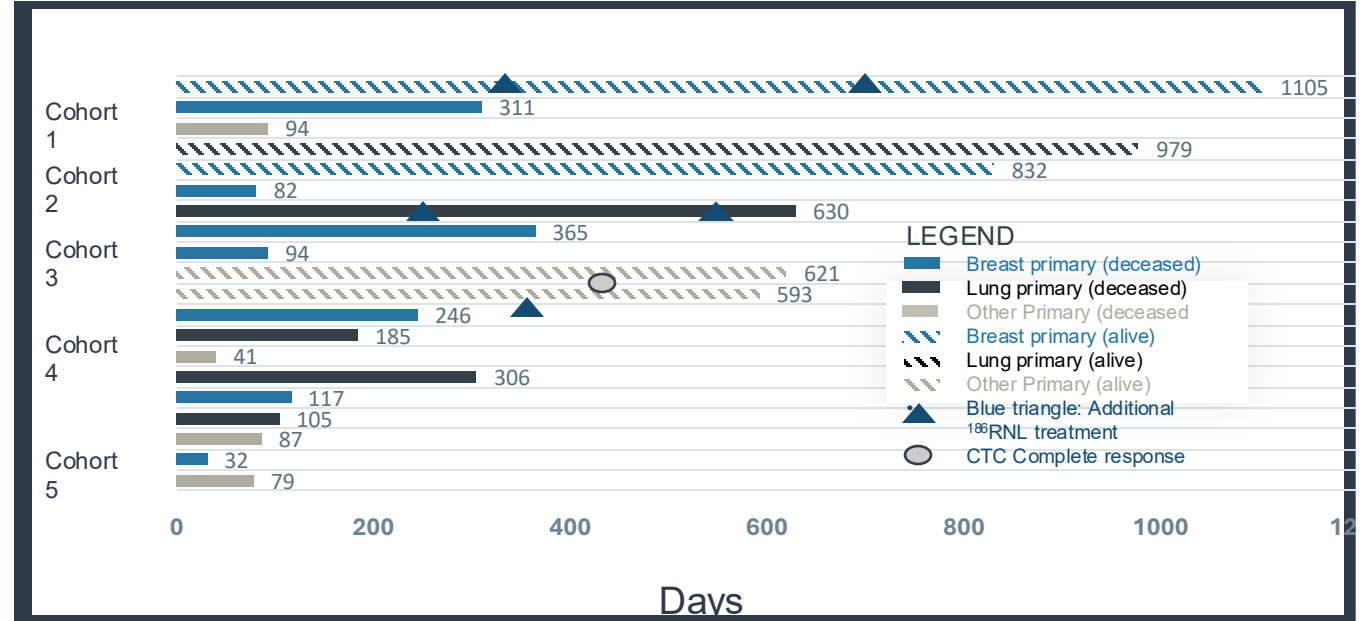
- + N = 37 enrolled, 8 screen failures, 29 intent to treat, 22 per treatment evaluable
- + A single DLT noted at 66.14 mCi administered dose (thrombocytopenia)
- + A single DLT noted at 75 mCi administered dose (thrombocytopenia and neutropenia)
- + DSMB: determined Recommended Phase 2 Dose of 44.10 mCi (cohort 4 dose) No DLTs or SAEs at this dose
- + Adverse Events
  - + Most AEs mild (grade 1, 55%) and moderate (grade 2, 25%)
  - + Most AEs unrelated (32%) or unlikely related (26%) to study drug
  - + Two AEs (headache) deemed definitely related to study drug (1 was grade 3 and resolved with treatment)
- + Serious Adverse Events
  - + 21 SAEs (9% of AEs)
  - + 5 SARs (SAEs with at least 'possible' attribution) – (1) encephalopathy (also attributed to steroid taper, resolved spontaneously), (2) headache (resolved with treatment), (3) thrombocytopenia (resolved with treatment) (4) WBC count decrease (resolved with treatment) and (5) lymphocytopenia (resolved spontaneously)

Treatment Related Adverse Events	Total N=21	
	Any Grade	Grade ≥ 3
Any TRAE	21 (100)	7 (33)
Headache	10 (48)	0
Lymphopenia	8 (38)	4 (19)
Vomiting	8 (38)	0
Thrombocytopenia	7 (33)	4 (19)
Nausea	6 (29)	0
Hypoalbuminaemia	5 (24)	0
Leukopenia	4 (19)	2 (10)
Alanine aminotransferase increased	2 (10)	0
Anaemia	2 (10)	0
Dizziness	2 (10)	0
Eye pain	2 (10)	0
Fatigue	2 (10)	0
Gait disturbance	2 (10)	0
Hyperglycemia	2 (10)	0
Muscle weakness	2 (10)	0

# ReSPECT-LM Phase 1 Response & Efficacy Data

*Positive efficacy signal in dose escalation phase*

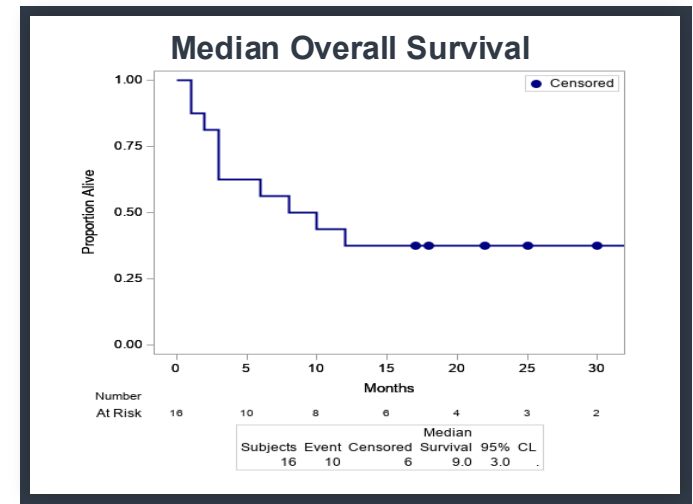
- + Overall survival
  - mOS of 9 months, compared to 4-6 months reported
  - n = 16 patients, Cohorts 1-4 (RP2D)
  - 5 patients remain alive (June 2025)
  
- + CSF tumor cell enumeration showed consistent decreases in the study population following treatment
  
- + Five of 7 patients with CTC response >80% survived at least 1 year (3 multiple treatment patients via compassionate use)



Single dose response assessed from pretreatment through 4 months (112 days) follow-up							
Response Measure <sup>1</sup>	Response	Stable Disease	Clinical Benefit Rate	Progression	Evaluable Patients	Data Not Available	Total Patients
CTC	13	1	14	1	15	5	20
Imaging	5	8	13	4	17	3	20
Clinical	2	11	13	2	15	5	20

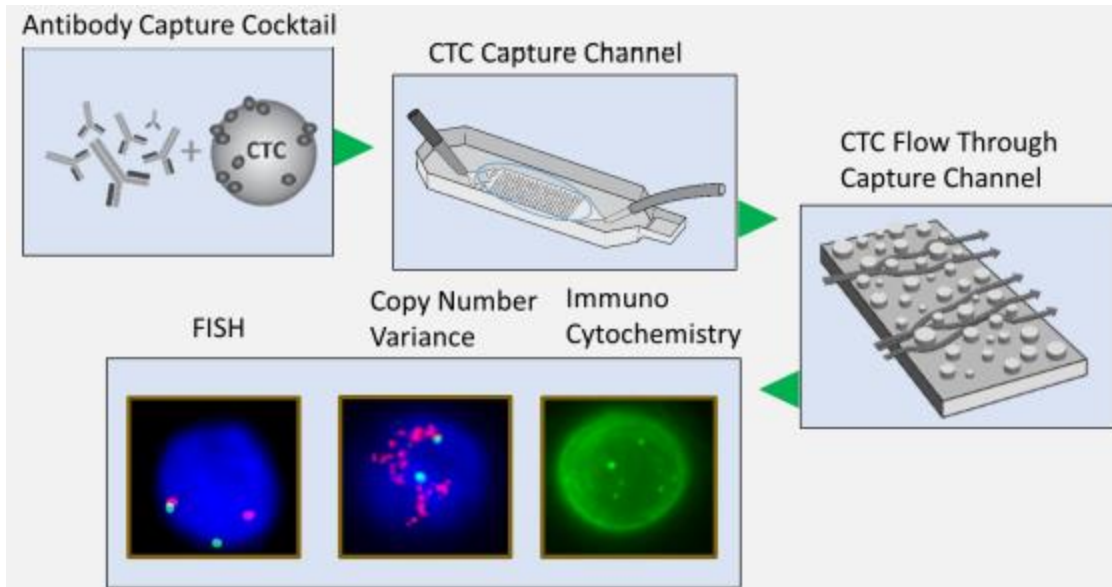
Clinical Benefit Rate (CR+PR+SD)

CTC response: 93% (14/15)  
 MRI Imaging response: 76% (13/17)  
 Clinical response: 87% (13/15)



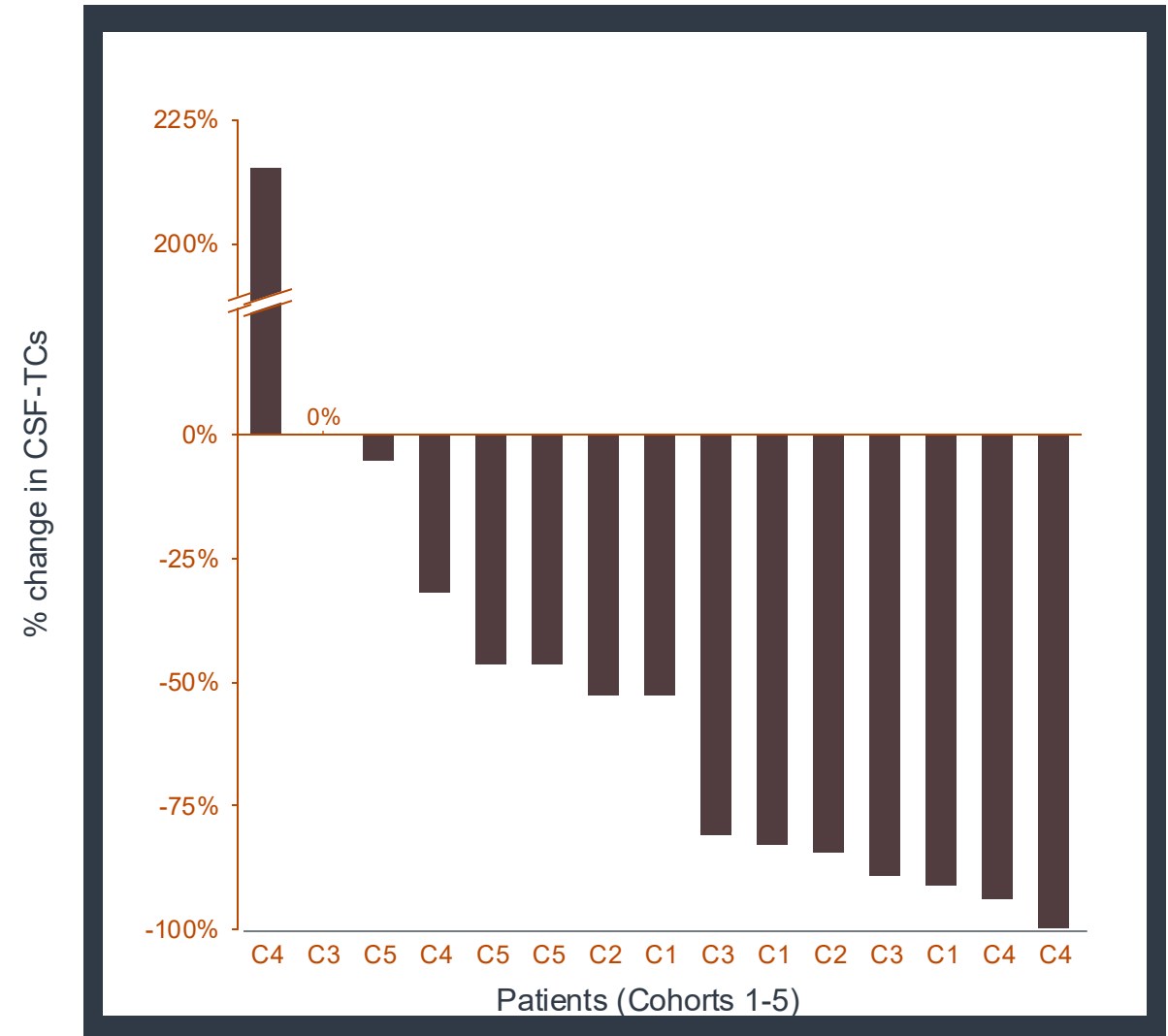
# ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

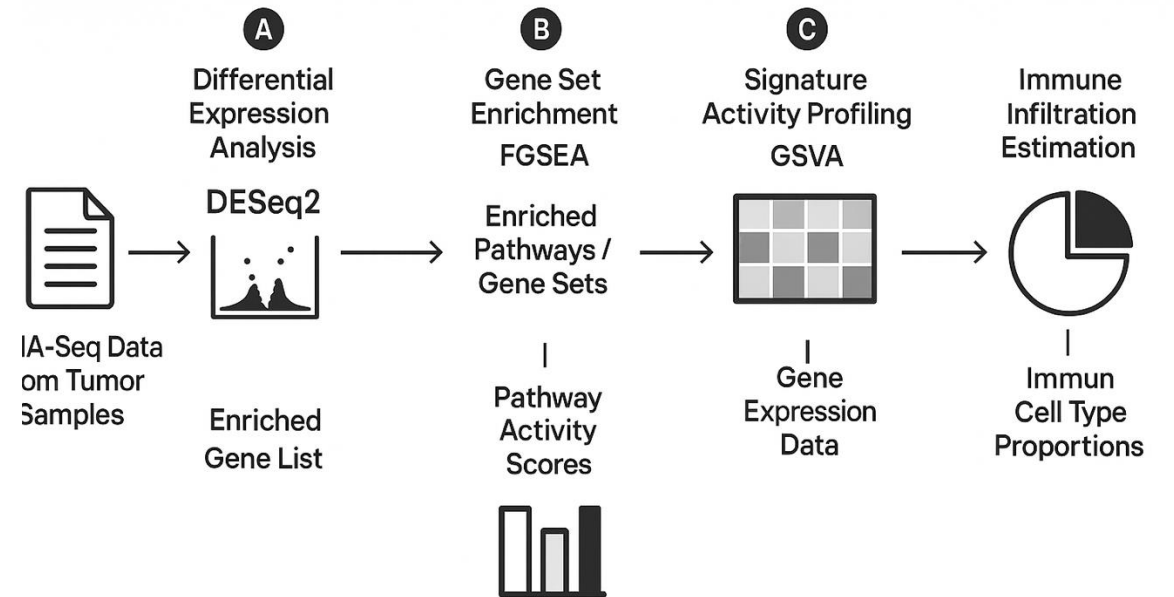
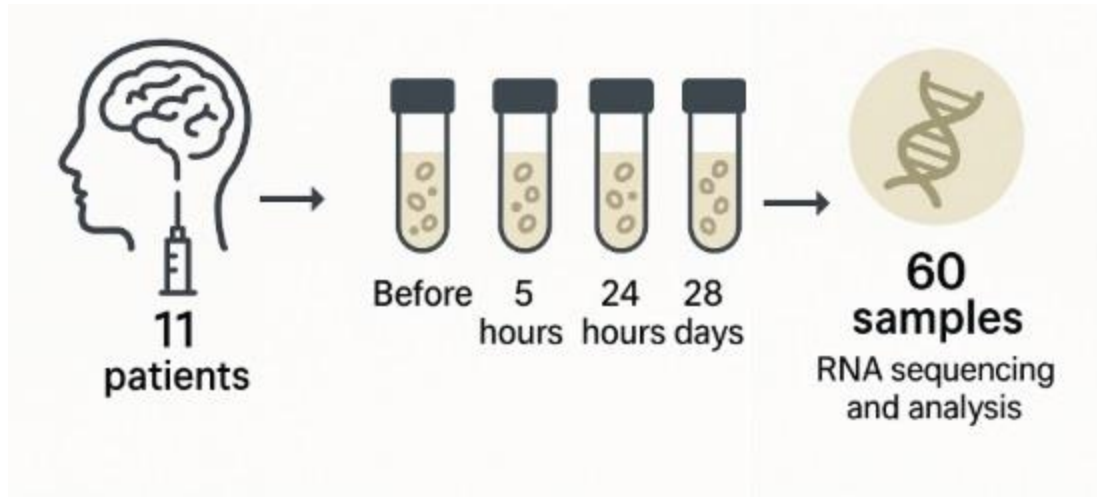
*Best response in tumor cells (CTCs) vs. baseline*



- + 13/16 showed reduction in CSF-TCs following  $^{186}\text{RnL}$  treatment
- + 5/7 showing >80% response survived 1 yr or more

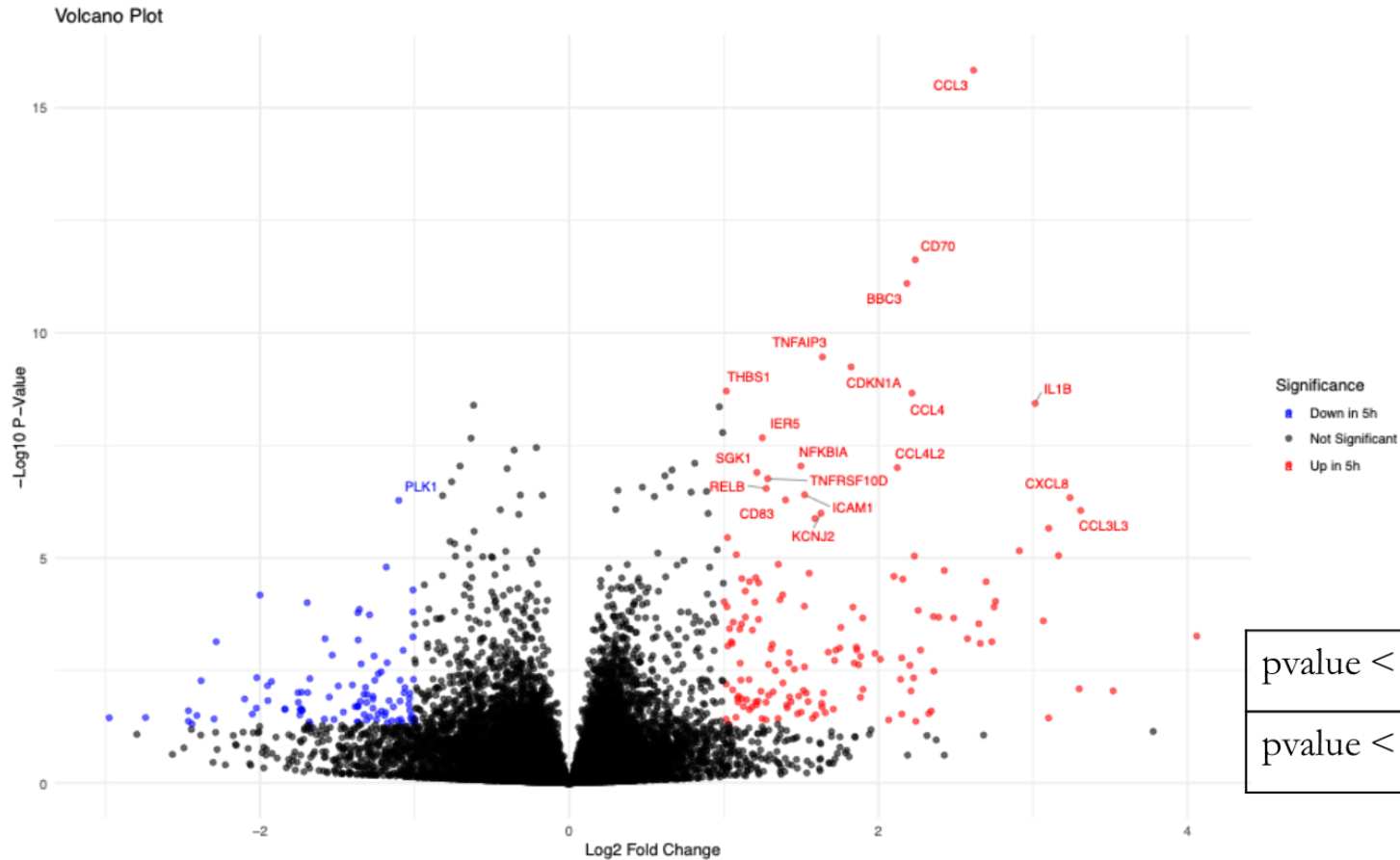
## Best Response Following $^{186}\text{RnL}$ Single Administration





**0h vs 5h**  
10 samples      10 samples

→ Filtered count matrix



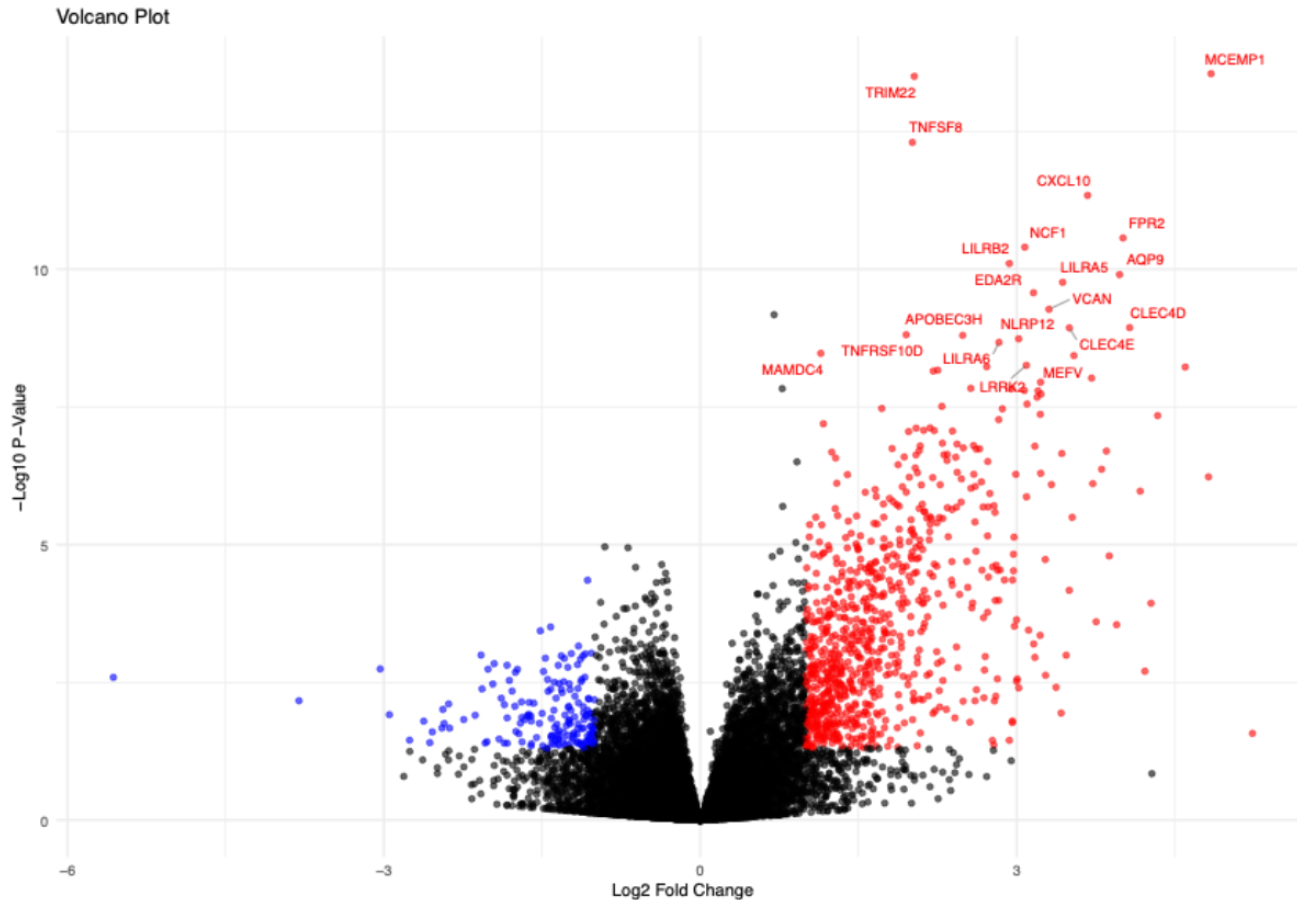
← L  
DEGSeq2

$pvalue < 0.05 \ \& \ log2FoldChange > 1$	148 genes
$pvalue < 0.05 \ \& \ log2FoldChange < -1$	99 genes

**0h vs 24h**  
12 samples      12 samples

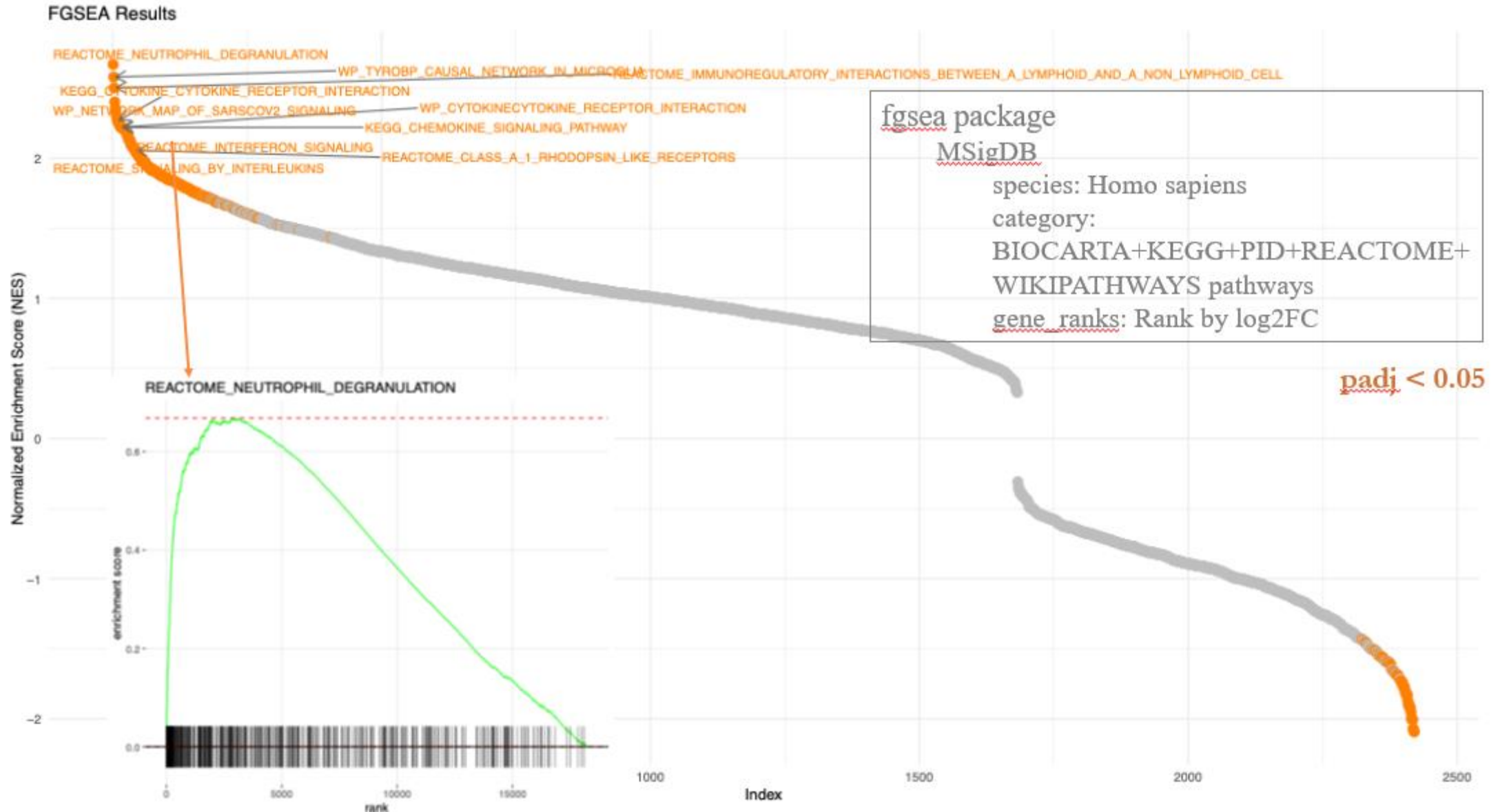
→ Filtered count matrix

1. Remove all rows containing only zeros.
2. Retain genes that are expressed in at least two samples per group (18,235 genes).



← DESeq2

$pvalue < 0.05 \ \& \ log_2FoldChange > 1$	810 genes
$pvalue < 0.05 \ \& \ log_2FoldChange < -1$	174 genes



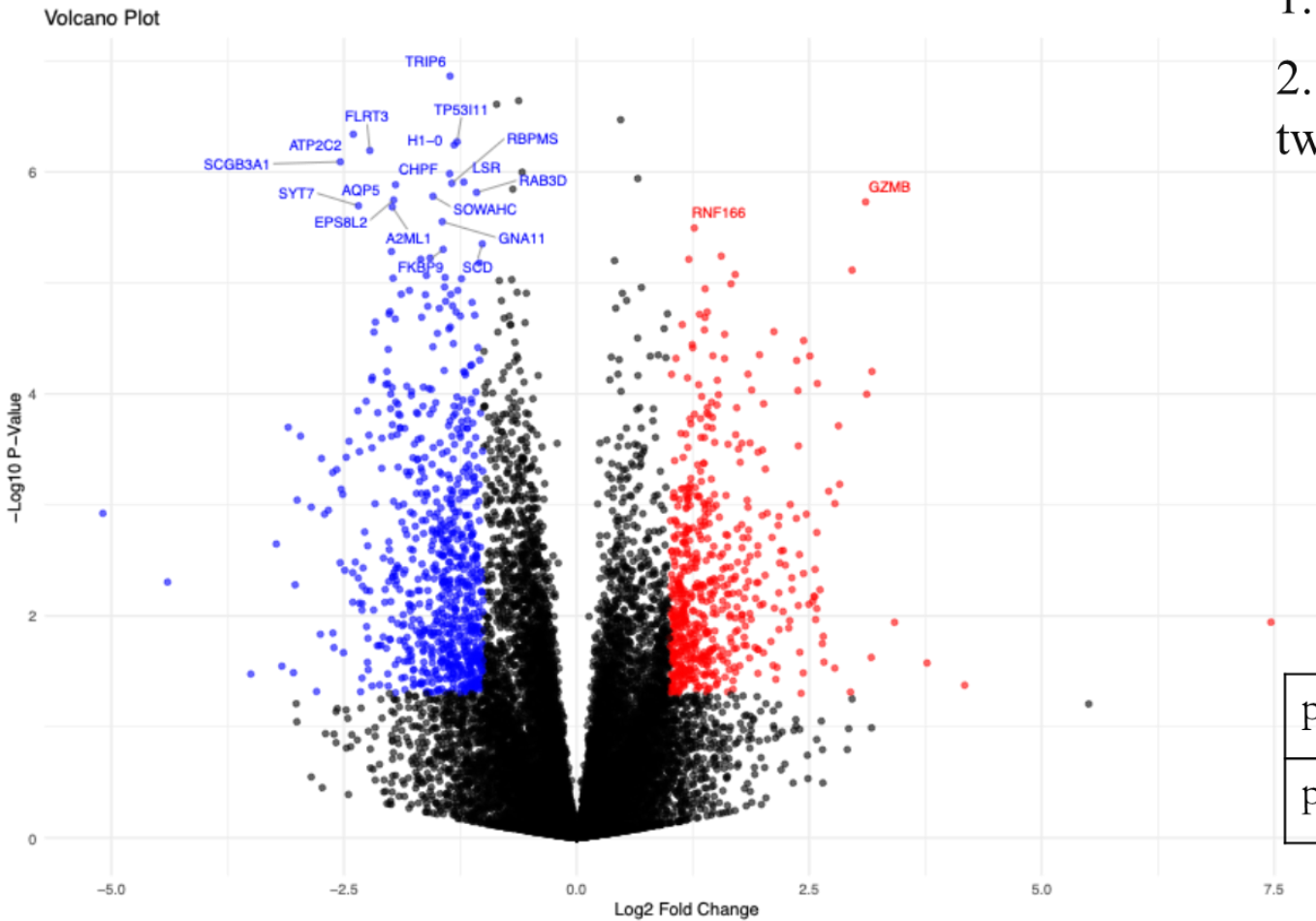


**0h vs 28D**  
 11 samples      11 samples



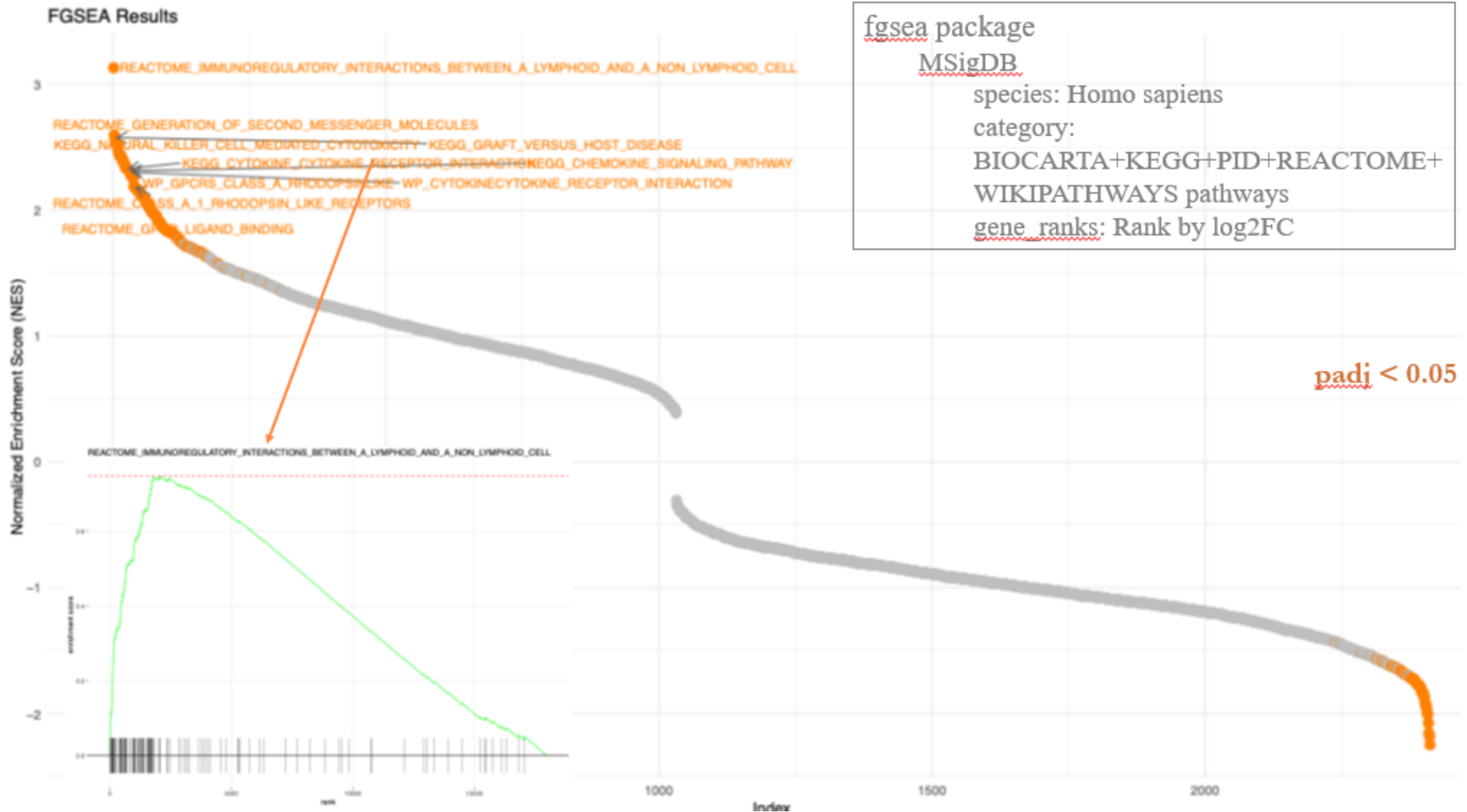
Filtered count matrix

1. Remove all rows containing only zeros.
2. Retain genes that are expressed in at least two samples per group (17,976 genes).



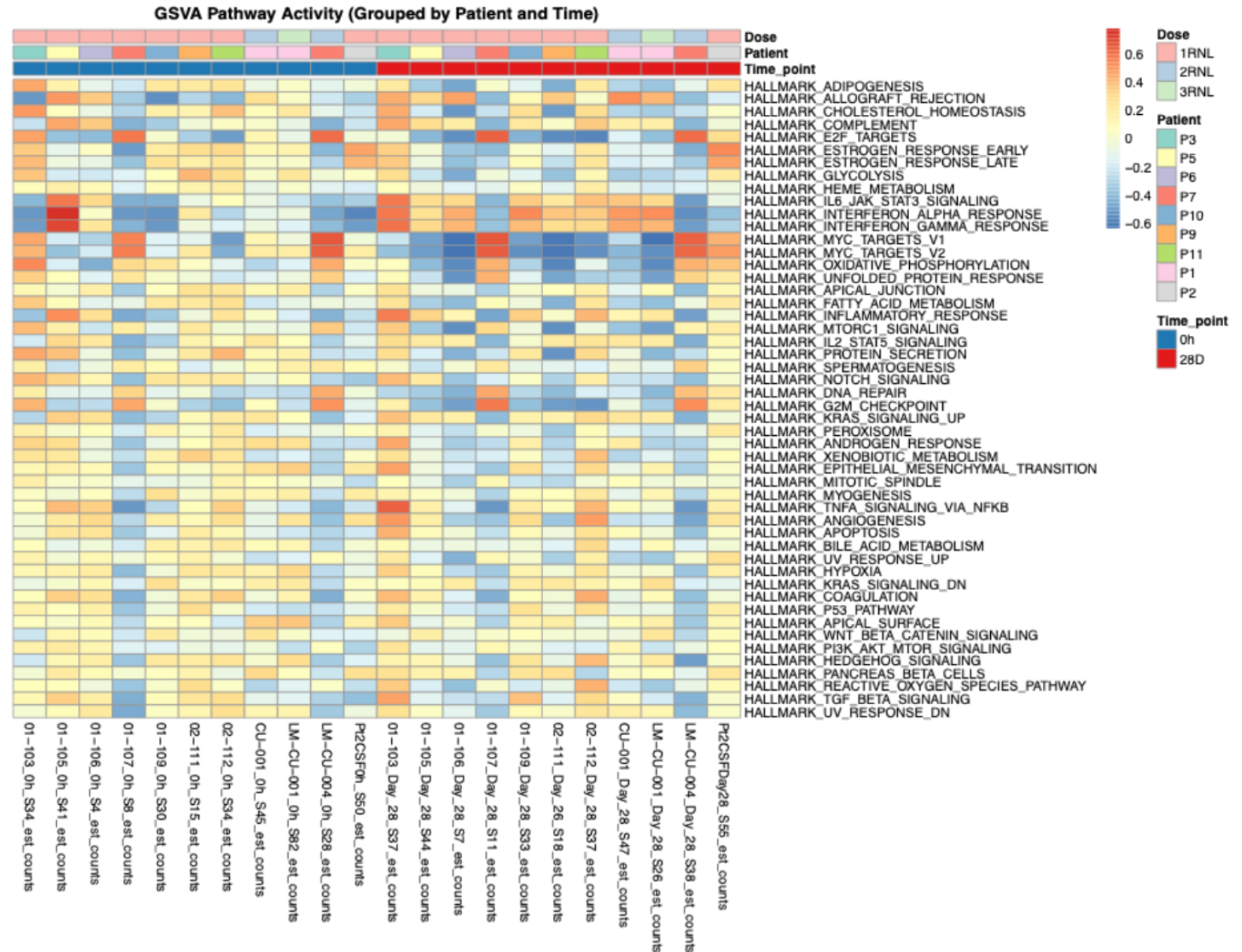
DEGSeq2

$pvalue < 0.05 \ \& \ log_2FoldChange > 1$	598 genes
$pvalue < 0.05 \ \& \ log_2FoldChange < -1$	768 genes



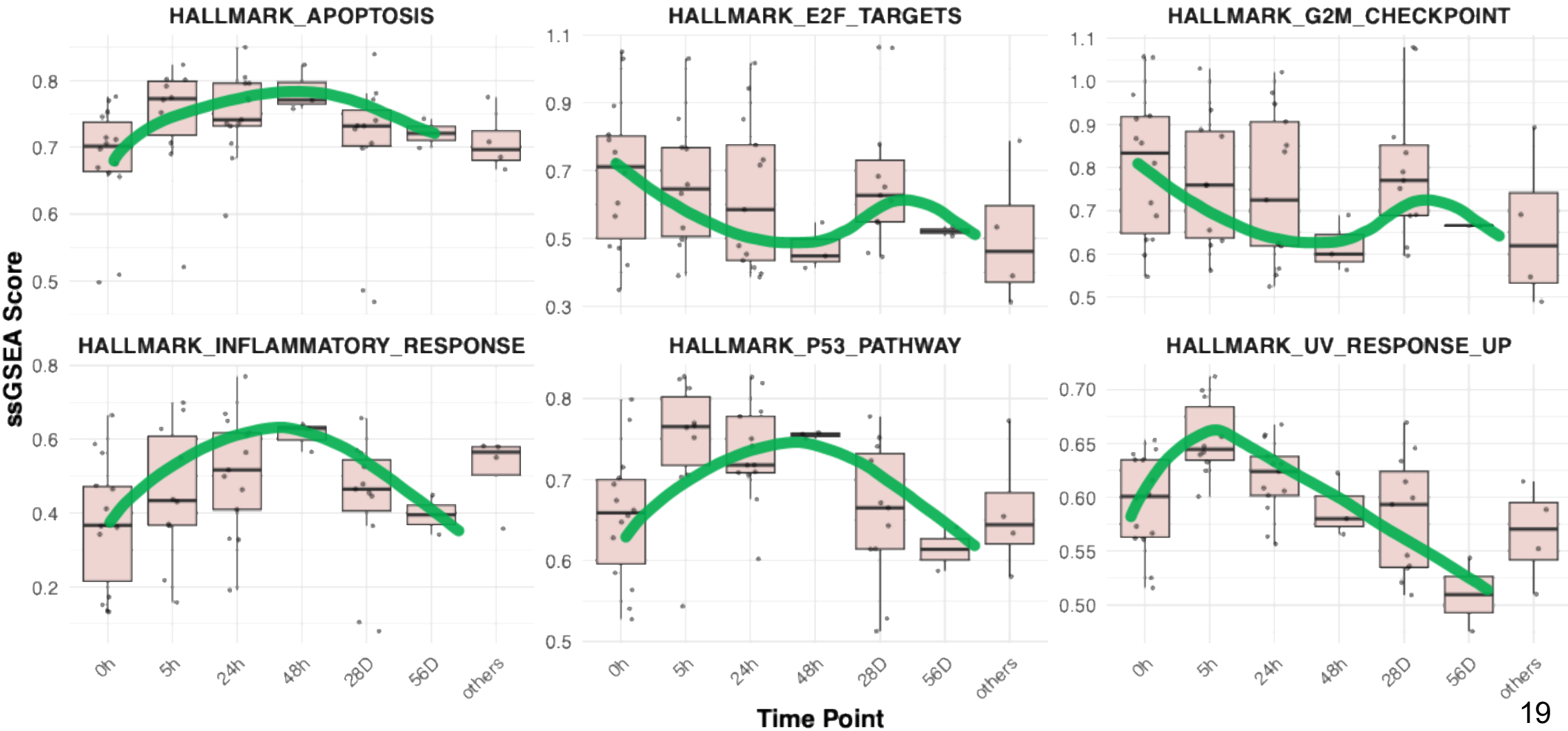
```
gsva(expr_matrix,
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      kcdf = "Gaussian")
```

Hallmark pathway  
t.test adjust pvalue  
increasing order



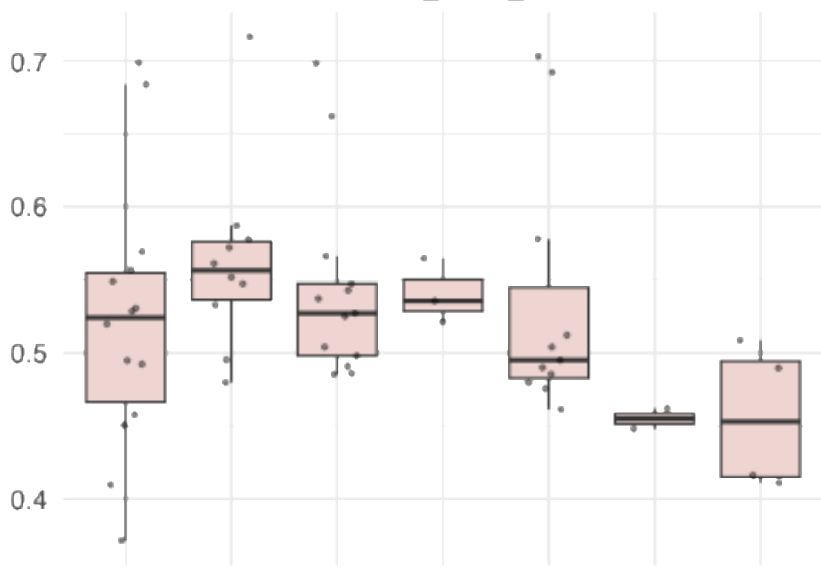
Time point	0h	5h	24h	48h	96h	8D	28D	42D	56D	112D
Sample size	14	10	13	3	1	1	11	1	2	1

### ssGSEA Scores of Selected Hallmark Pathways

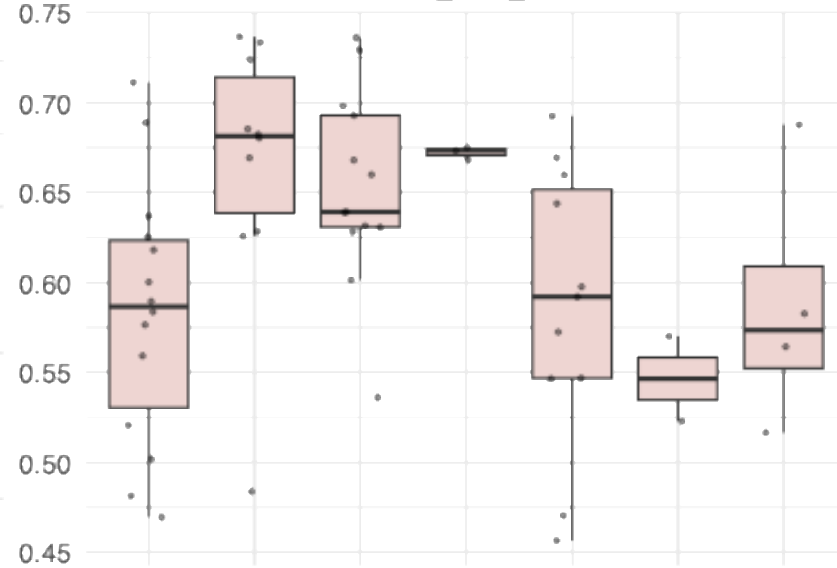


# ssGSEA Scores of DNA repair Pathways

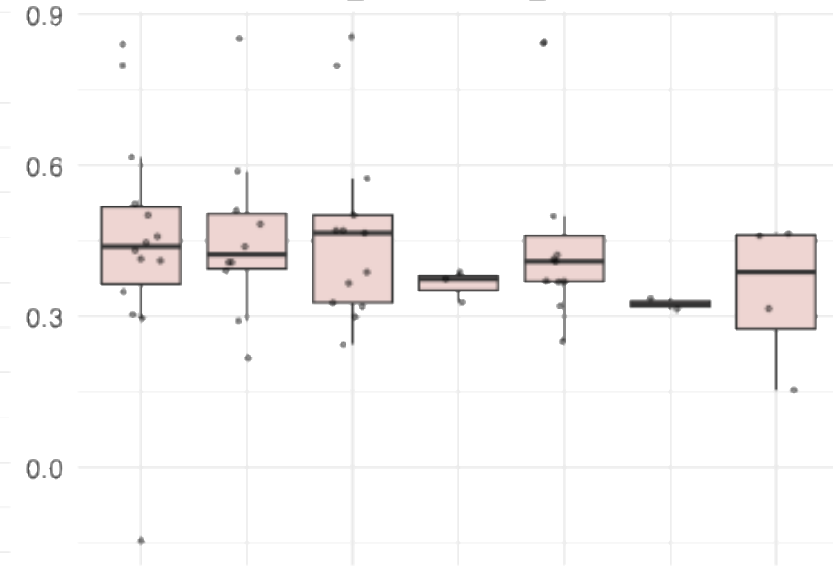
## HALLMARK\_DNA\_REPAIR



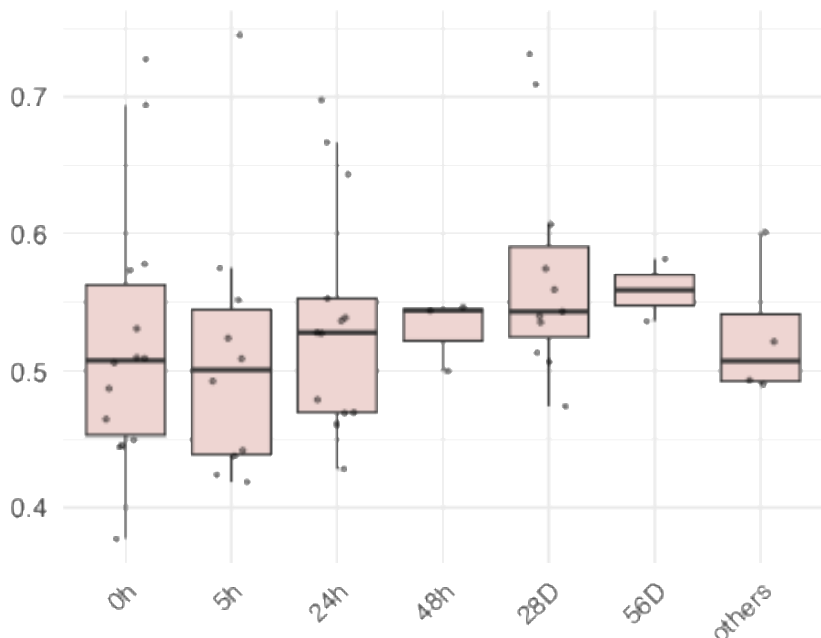
## HALLMARK\_P53\_PATHWAY



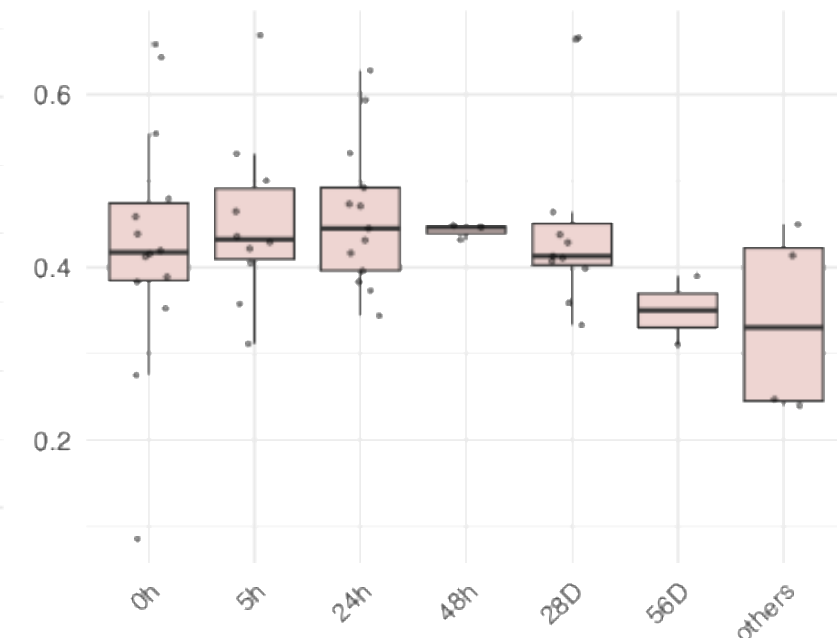
## KEGG\_MISMATCH\_REPAIR



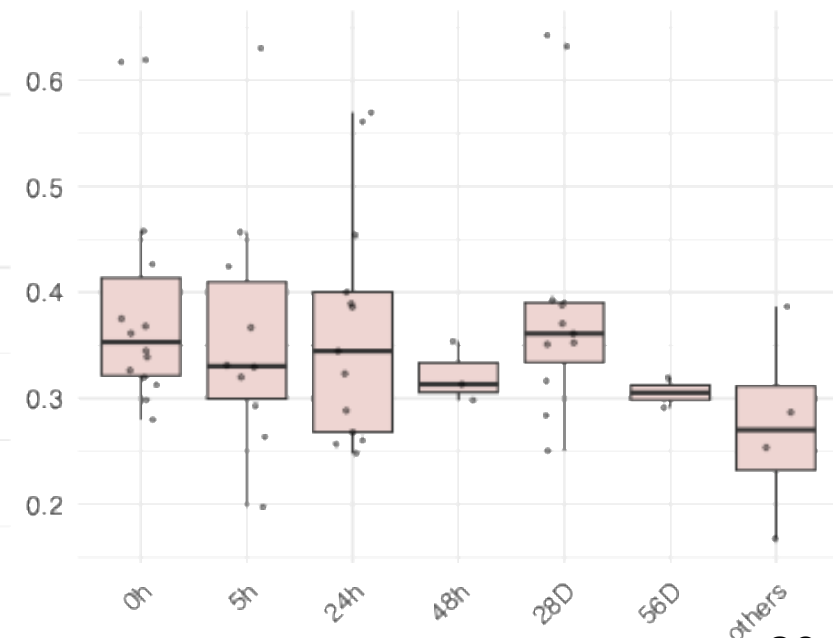
## KEGG\_NON\_HOMOLOGOUS\_END\_JOINING



## KEGG\_NUCLEOTIDE\_EXCISION\_REPAIR



## REACTOME\_FANCONI\_ANEMIA\_PATHWAY



Time Point

## Key elements

A Multicenter Phase 1 Study to Determine the Safety and Efficacy of Multiple Doses at Defined Intervals of Rhenium ( $^{186}\text{Re}$ ) Obisbameda (Rhenium-186 NanoLiposome,  $^{186}\text{RNL}$ ) Administered via Intraventricular Catheter for Any Primary Solid Tumor Cancer with Leptomeningeal Metastases

**Primary Objectives:** To characterize the safety and tolerability of multiple doses at defined intervals of  $^{186}\text{RNL}$  administered via intraventricular catheter (i.e., Ommaya reservoir) for patients of any primary solid tumor cancer with leptomeningeal metastases and identify an MTD/MFD for a given dose, interval duration, and number of doses

Study now enrolling at UTHSCSA

Phase/Part	Cohort	Dose (mCi)	% Total Activity Increase	Dosing Interval	Doses/Patient	~Total Time of Dosing (months)	Total Administered Dose (mCi)
Phase 1/Part A	1	13.2	NA	56 days	3	4	39.6
	2	13.2	NA	28 days	3	3	39.6
	3a	13.2	NA	14 days	3	1.5	39.6
	3b	13.2	NA	14 days	6	3 months	79.2

- **Phase 1 ReSPECT-LM single dose escalation study completed**
  - Reyobiq is feasible, safe at recommended Phase 2 dose (RP2D), with signs of efficacy in LM- study also supports the value of circulating tumor cell (CTC) counts
- **LM Multiple Dose/Dose Optimization- now opened at UTHSCSA**
  - Goals of study are dose level and interval optimization- safety and efficacy
  - Treating patients at defined intervals (56, 28, and 14 D with 3 doses)
  - Aligns with FDA's initiative Project Optimus
- **Bulk RNA sequencing from 14 patients at multiple timepoints has been conducted, including at progression and retreatment- continuing analysis**
- **Further exploring TME modulation, including immune cell infiltrations following Reyobiq**
- **Developing Phase 2/path to pivotal strategy in LM with advisory board/neuro-oncology steering committee**
  - Planning for definitive study for LM with FDA Type B meeting to follow

## Collaborators

Priya Kumthekar, M.D.  
Michael Schulder, M.D.  
Ande Bao, Ph.D.  
Barbara Blouw, Ph.D.  
Melissa Moore, Ph.D.  
Michael Rosol, Ph.D.  
Joel Michalek, Ph.D.  
William Phillips, M.D.  
John Floyd, M.D.  
Marc Hedrick, M..D., M.B.A.  
Michael Youssef, M.D.

## Brenner Lab

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## Mays RNL Team

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**Beth Goins Ph.D.**  
William Phillips M.D.  
Ofelia Romero R.N.  
Mays IDD Team

## Funding





Andrew Brenner, Priya Kumthekar, Michael Schulder, Ande Bao, Barbara Blouw, Melissa Moore, Michael Rosol, Joel Michalek, William Phillips, John Floyd, Marc Hedrick, Michael Youssef

Leptomeningeal disease (LMD) is a devastating cancer complication with poor survival. Rhenium obisbemedate (Reyobiq) is a liposomal encapsulated radiopharmaceutical evaluated in a phase 1 dose escalation study (ReSPECT-LM) for patients with LMD from any cancer. Patients received a single dose of Reyobiq via intraventricular route (Ommaya reservoir) to determine the maximum tolerated/feasible dose, safety, and tolerability using a 3+3 design. A total of 29 subjects received 6.6, 13.2, 26.4, 44.10, 66.14, or 75 mCi of Reyobiq (cohorts 1-6, respectively). No dose limiting toxicity (DLT) was observed in cohorts 1-4, with 1 DLT in each of cohorts 5 and 6 of grade 4 cytopenia. After safety review, dose escalation and enrollment was concluded with cohort 6 and the recommended phase 2 single dose was 44 mCi. The majority of adverse events across the trial were Grade 1 and 2. There were no serious adverse events reported in cohort 4 (n=6). A dose dependent increase was observed in the absorbed dose to the cranial and spinal subarachnoid space reaching a mean of 272 Gy in cohort 6.

Radiographic response data available for 17 patients showed 5 partial responses and 8 stable disease through day 112 (76% benefit rate). Additionally, a clinical response with decrease in disease symptoms was noted in 2/15 evaluable patients (13%), and 11 showing stable symptoms through day 112 (clinical benefit rate of 87%). CSF tumor cell enumeration (TCE) assays (CNSide test) were performed with a maximum reduction over baseline of 100% seen at Day 28. Five of the 7 patients with a TCE response >80% survived at least 1 year. Across cohorts 1-4 (20 patients) median overall survival was 9 months, comparing favorably with literature reports of ~4 months. Reyobiq shows excellent safety and promising activity for LM. Both single-dose expansion and multidose studies are planned.