Four case studies on the use of exosomes derived from allogenic mesenchymal stem cells for canine renal diseases

A Case Series Highlighting Therapeutic Potential

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Background

- Canine renal failure is a complex condition, with conventional treatments often proving insufficient for effective management.

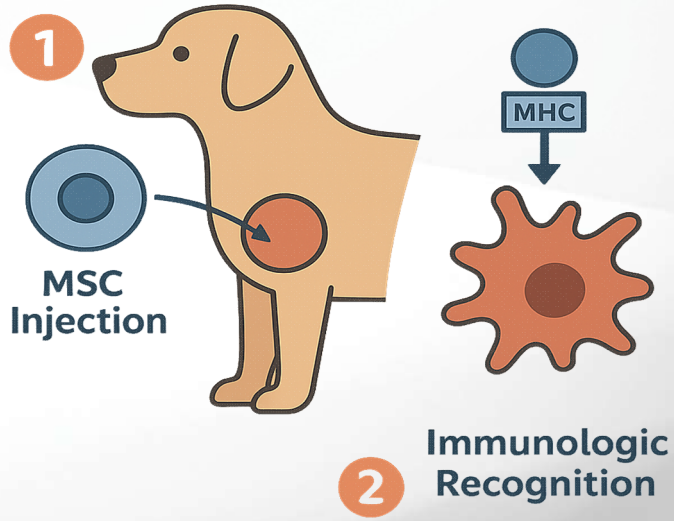
Objectives

1. Evaluate the therapeutic effects of exosomes derived from mesenchymal stem cells in dogs with renal failure.
2. Investigate the application of exosome therapy in cases involving complications like diabetes, pancreatitis, and heart disease.
3. Propose the potential of exosome therapy as an innovative approach to enhance the quality of life in canine patients with renal disease.

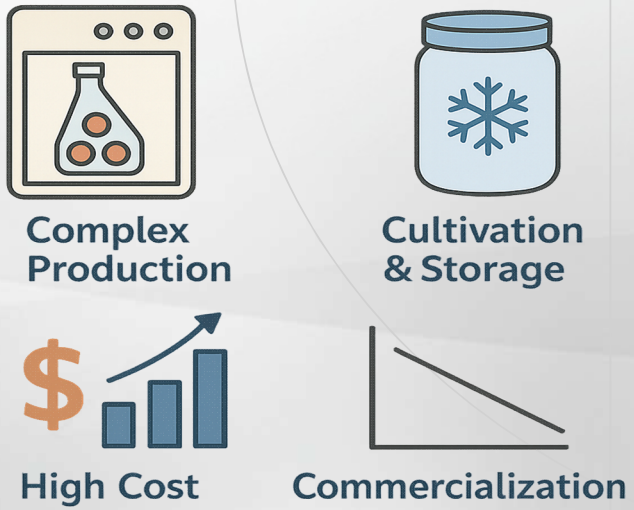
Mesenchymal Stem Cell Therapy

- MSC therapy is a well-established method for tissue regeneration and inflammation reduction
- Its efficacy and safety have been verified through numerous clinical studies, making it widely utilized.

IMMUNE RESPONSE



ECONOMIC ISSUES



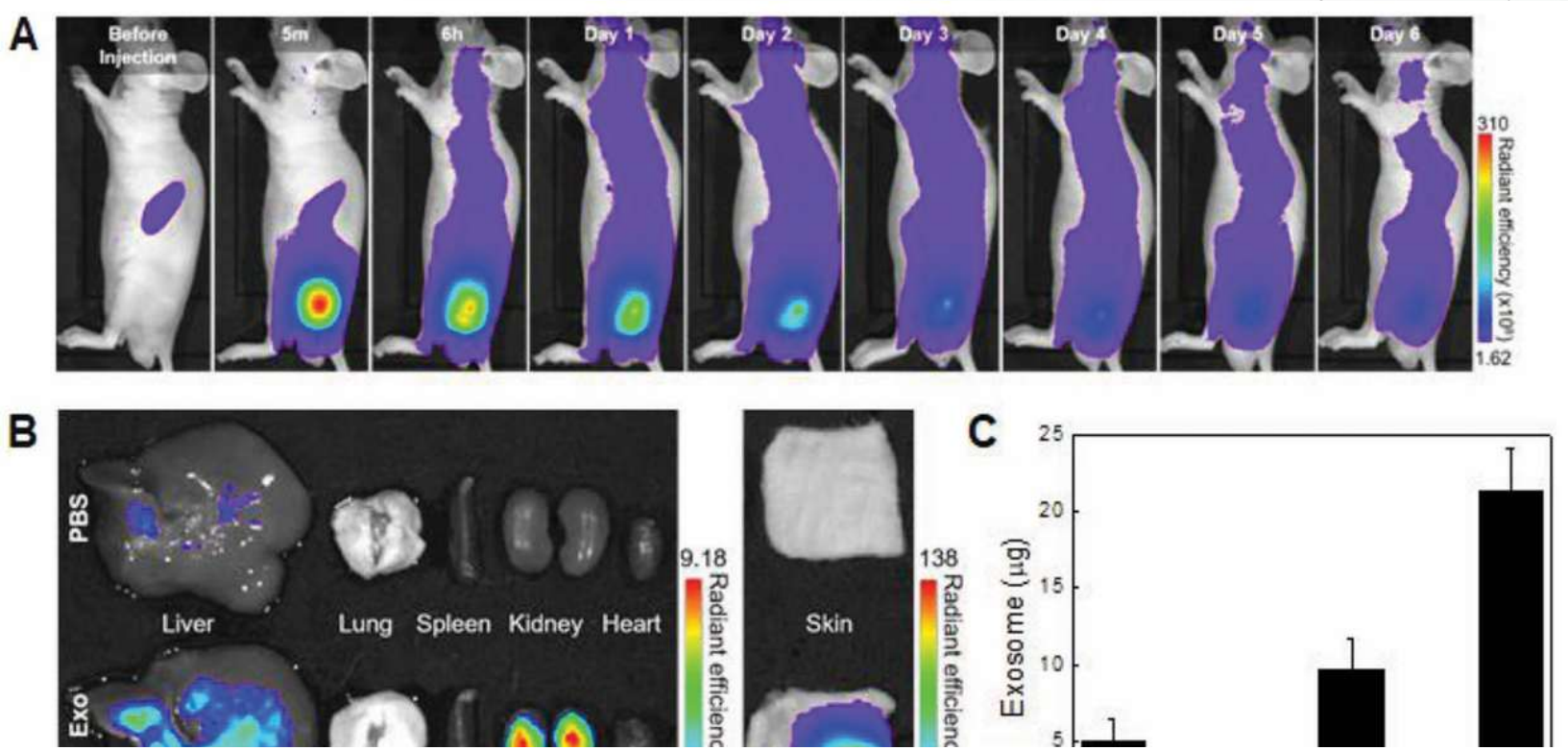
Exosome Therapy

- A New Frontier
  - Exosomes derived form MSCs offer similar therapeutic benefits to MSCs and are emerging as a novel approach to treatment.
  - Unlike stem cell cultivation, which requires complex growth conditions, exosome isolation and purification are more streamlined.
  - Exosome therapy is an innovative field under active research and development.

Advantages of Exosome Therapy

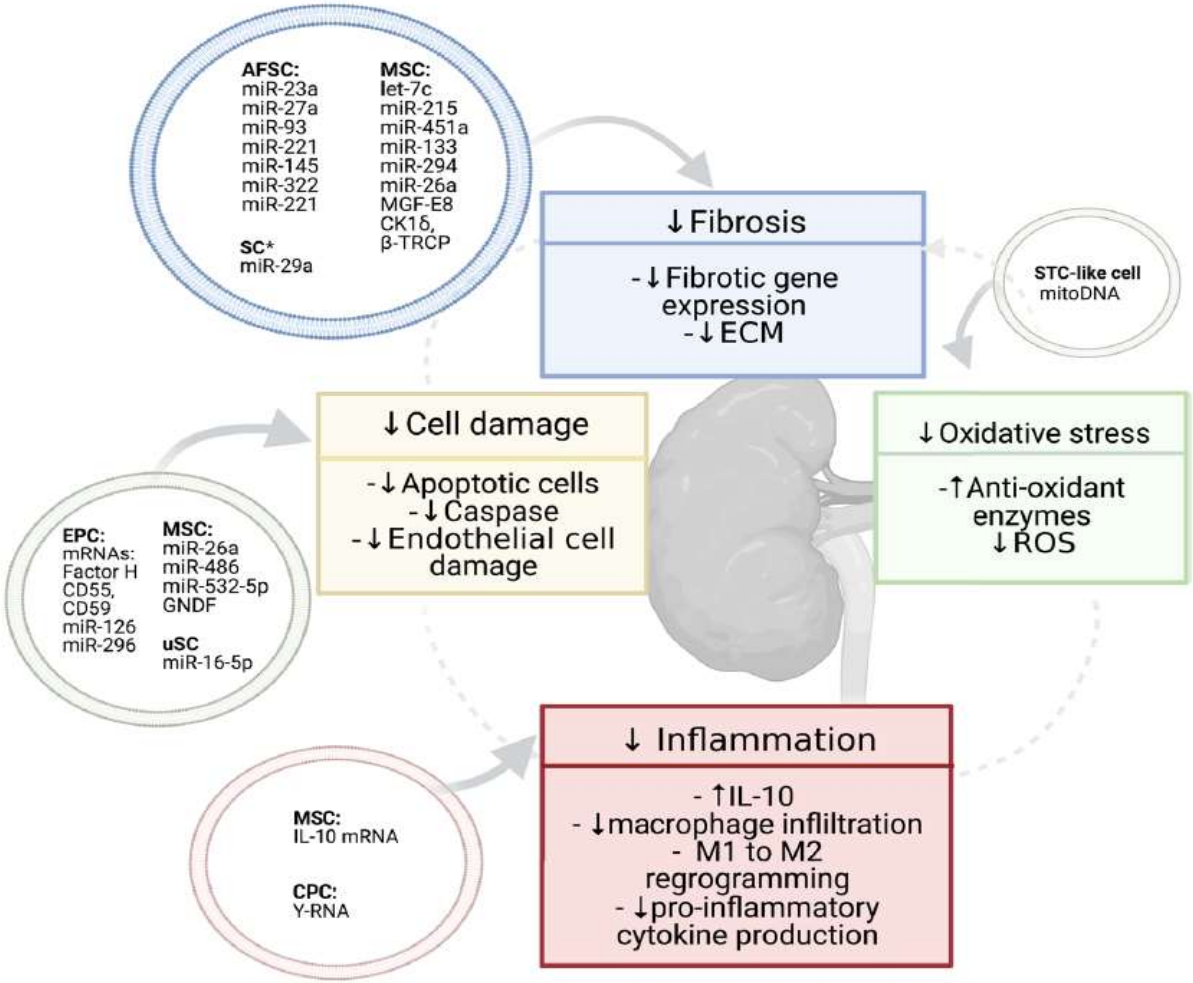
- Low Immunogenicity:
  - Reduced risk of immune rejection compared to stem cells.
- Effector Functions
  - Exosomes act as effectors, playing pivotal roles in tissue repair and metabolic regulation.
- Enhanced Delivery:
  - Their small size allows efficient transport within the body (Biocompatibility)
- Tissue Regeneration:
  - Promotes repair and reduces inflammation, vital for managing renal failure.
- Ready to Use:
  - Exosomes can be stored long-term and immediately administered
  - Ensuring quick availability in clinical settings.(point-of-care)
- Innovative approach for treating chronic diseases (especially renal failure).

Advantages of Exosome Therapy



Kim, Hyosuk & Wang, Sun & Kwak, Gijung & Yang, Yoosoo & Kwon, Ick & Kim, Sun. (2019). Exosome-Guided Phenotypic Switch of M1 to M2 Macrophages for Cutaneous Wound Healing. Advanced Science. 6. 1900513. 10.1002/advs.201900513.

Advantages of Exosome Therapy



Nowak, N., Yamanouchi, M., & Satake, E. (2021). *The Nephroprotective Properties of Extracellular Vesicles in Experimental Models of Chronic Kidney Disease: a Systematic Review. Stem Cell Reviews and Reports.* doi:10.1007/s12015-021-10189-9

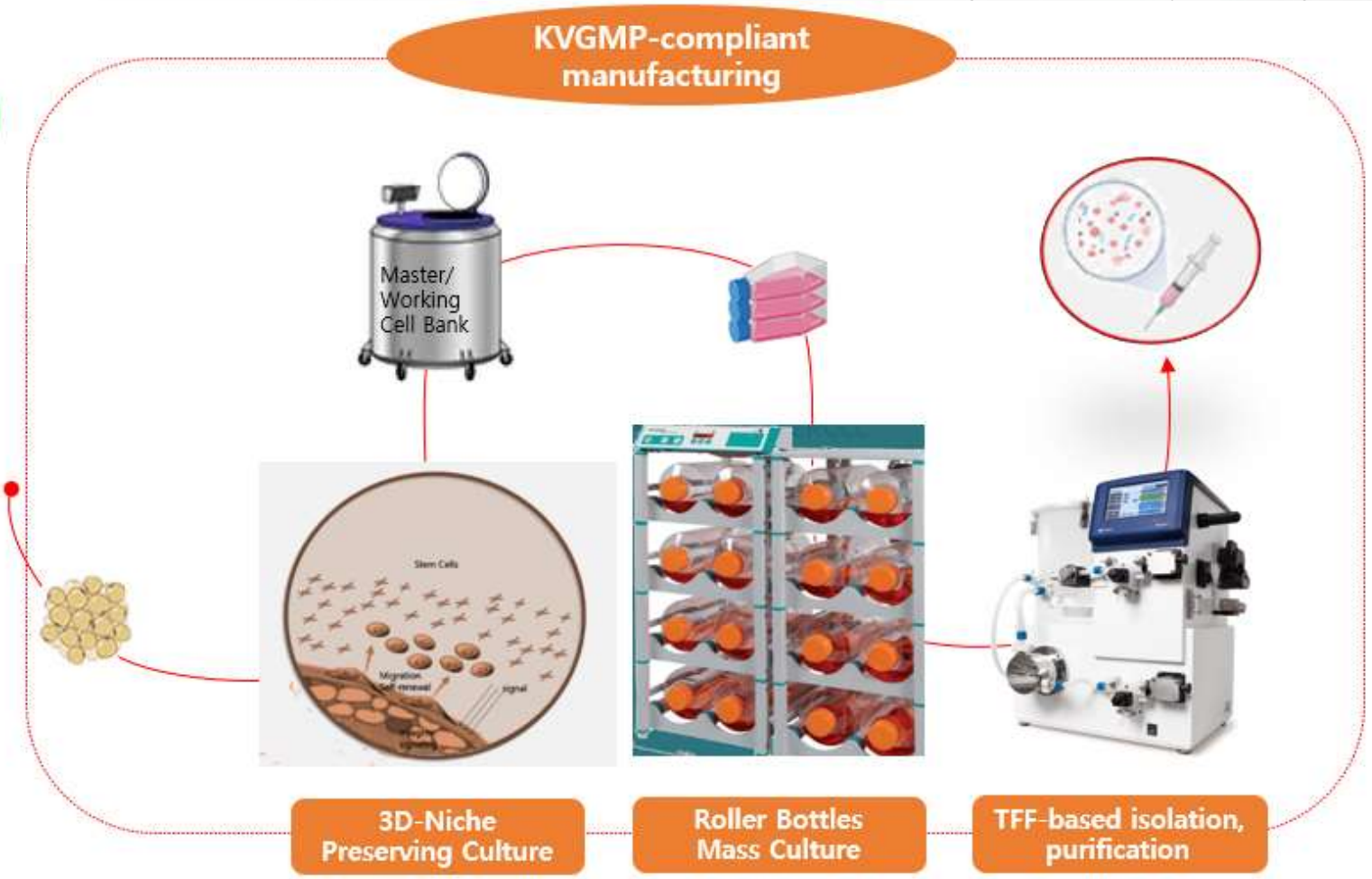
Exosome Production

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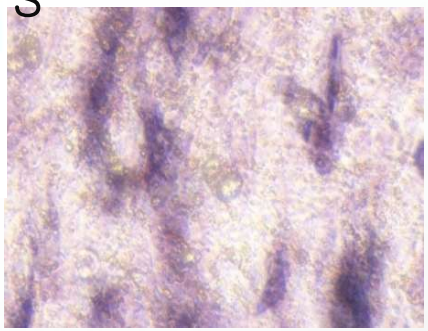
Identification of MSCs

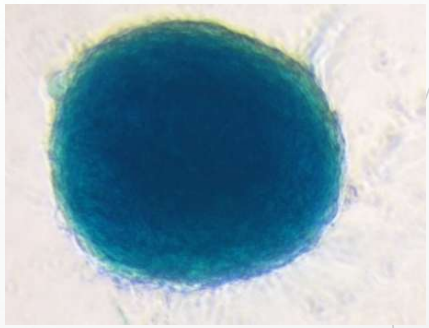
GNG CELL

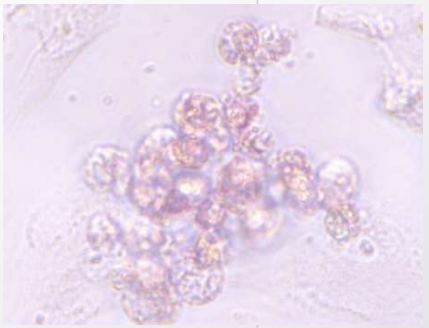
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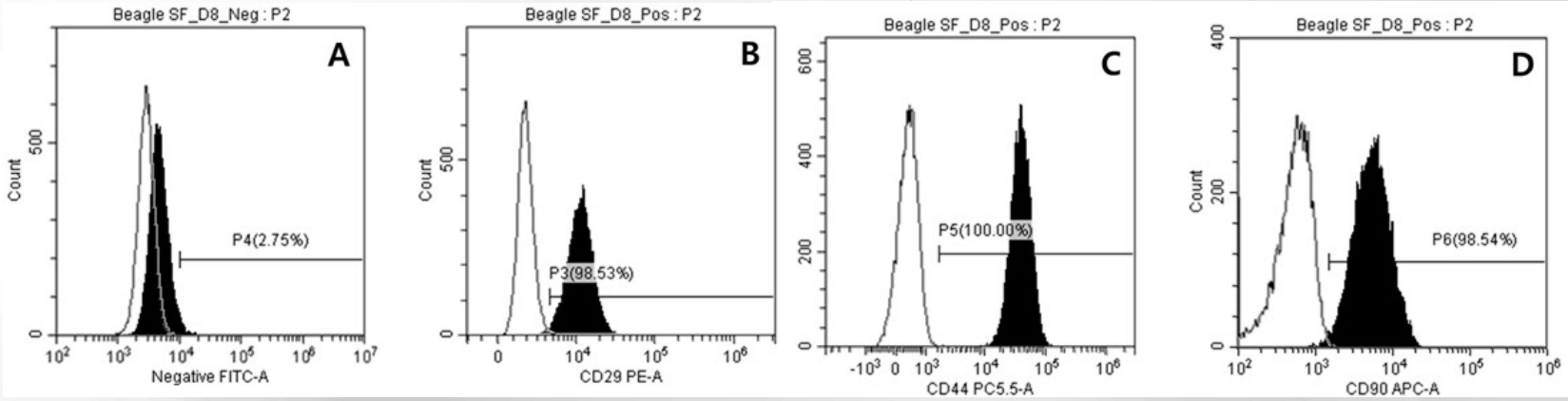
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- Markers



EXOSOMES – MARKERS

- Positive for CD9, CD81 (exosome markers), and CD49e (cell origin marker).



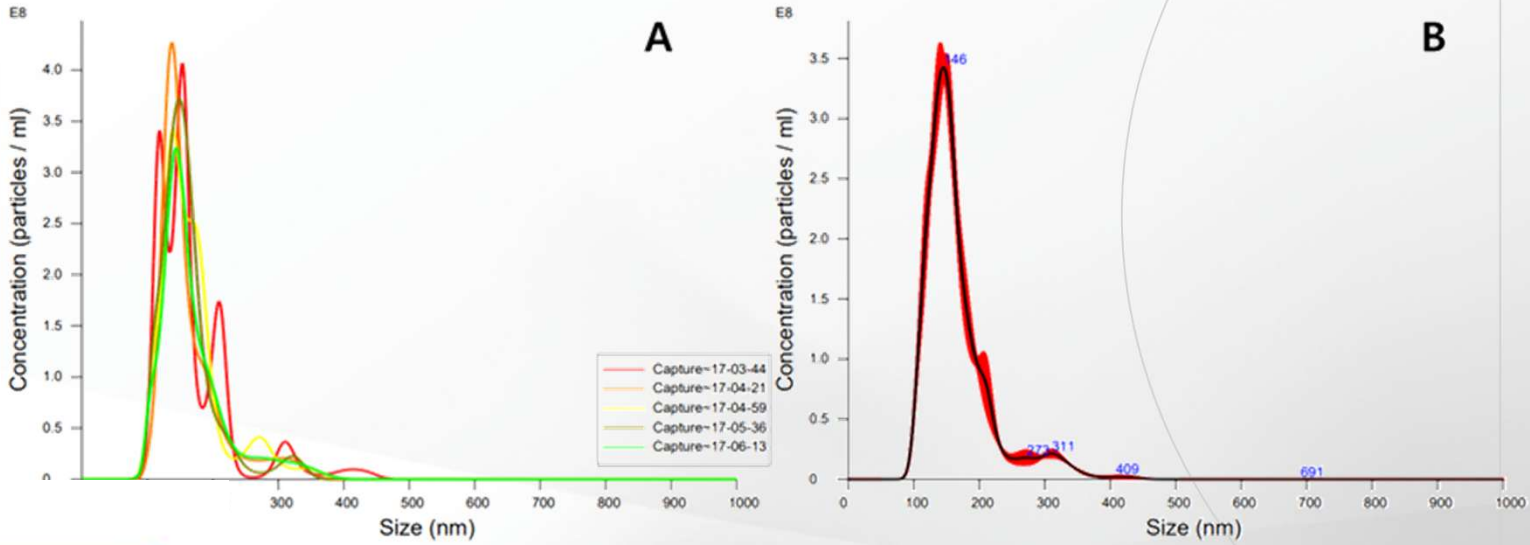
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Exosomes – Size

- Mode size of 146 nm, confirmed by nanoparticle tracking analysis (NTA)



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Overview of Case Studies

- Objective: To evaluate the therapeutic potential of exosome therapy derived from mesenchymal stem cells in canine renal failure.
- Patient Demographics:
  - **Total of 4 cases involving dogs diagnosed with renal failure.**
  - **Included complications such as diabetes, pancreatitis, and heart disease.**
- Enrollment Criteria
  - **Dogs with renal disease were selected based on persistent elevation in BUN and creatinine levels despite fluid therapy for 2 days to 2 weeks**
  - **Owners participated in the study after observing insufficient improvement with standard treatments.**

Overview of Case Studies

- Study Design
  - **Exosome therapy (5 billion exosome particles) was administered subcutaneously as a supplementary treatment.**
  - **Renal function and clinical signs, such as appetite, were monitored over 1–2 weeks.**
  - **Evaluation methods included blood tests (BUN, creatinine) and a 4-point appetite scale to measure recovery progress.**
    - **4/4: Normal intake level before illness**
    - **3/4: More than 50% of normal intake**
    - **2/4: Less than 50% of normal intake**
    - **1/4: Minimal intake**
    - **0/4: No intake**

CASE 1: SAEBOM

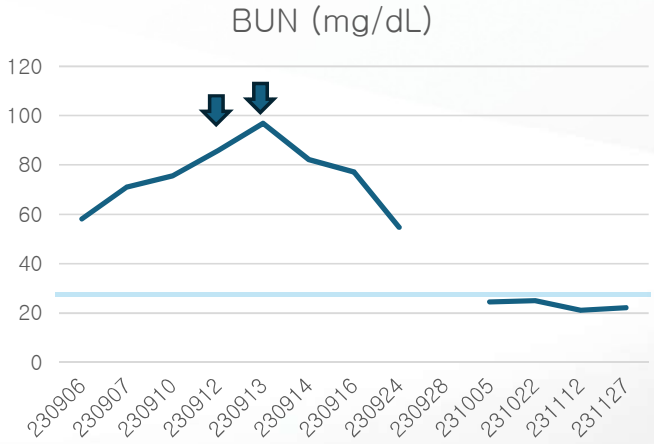
- Signalment:
  - **5-year-6-month-old spayed female Border Collie, weighing**
- Chief Complaint:
  - **Lethargy and anorexia.**
- Diagnosis:
  - **Diabetes, diabetic pancreatitis,**
  - **Progression of renal failure during hospitalization.**
    - **like Acute renal failure**
- Treatment:
  - **Insulin**
  - **Pancreatitis: antibiotics, analgesics, antiemetics**
  - **Renal failure: following Iris guideline conventional treatments (fluid, AST 120(kremezin)…)**
  - **Administered exosome injections two times**

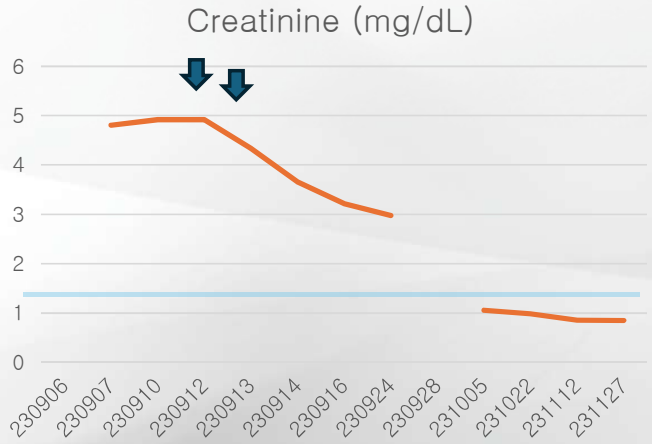


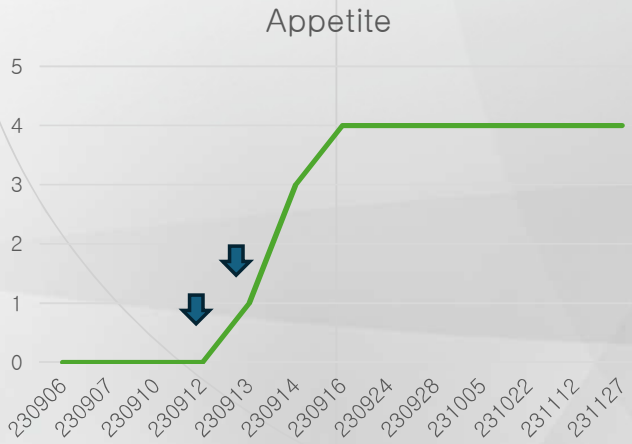
CASE 1: SAEBOM (CONTINUED)

	230829	230906	230907	230910	230912	230913	230914	230916	230924	230928	231005	231022	231112	231127
BUN (mg/dL)	24.6	58.1	71.1	75.6	85.9	96.9	82.3	77.2	54.8		24.5	25	21.1	22.2
Creatinine (mg/dL)	1.21		4.81	4.92	4.92	4.34	3.66	3.22	2.98		1.06	0.99	0.86	0.85
CPL (ug/L)	>2000		1763.3					989		499.1				
AST (U/L)	306	273			211			153	72	66	31			
Appetite (0~4/4)	0	0	0	0	0	1	3	4	4	4	4	4	4	4
Exosome Injection					V	V								

Hospitalization





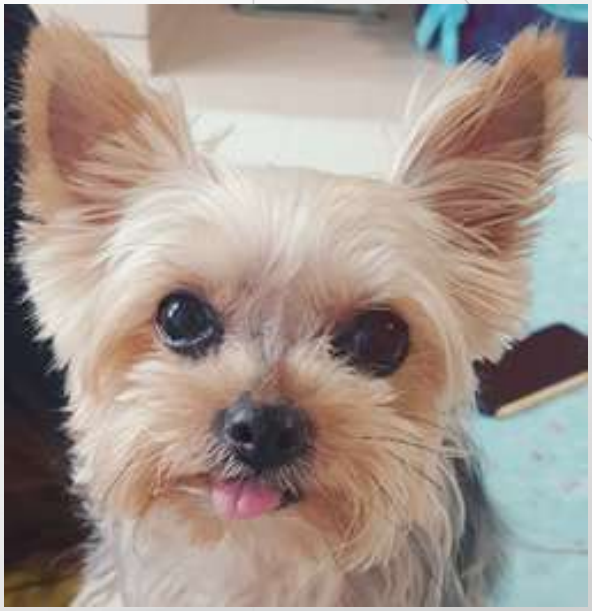


CASE 1: SAEBOM (CONTINUED)

- Clinical Implications
  - Overall clinical recovery enhancement: Exosome therapy not only improves renal function but also promotes overall health recovery.
  - Appetite improvement: The therapy enhances appetite, contributing to better nutritional intake and overall well-being
  - Rapid response and sustained effects: Unlike traditional treatments with limited efficacy, Exosome therapy facilitates quick recovery and continues to show improvement even after discharge.
  - Safety: No adverse effects were observed, including in the liver and pancreas.

CASE 2: IBBUNI

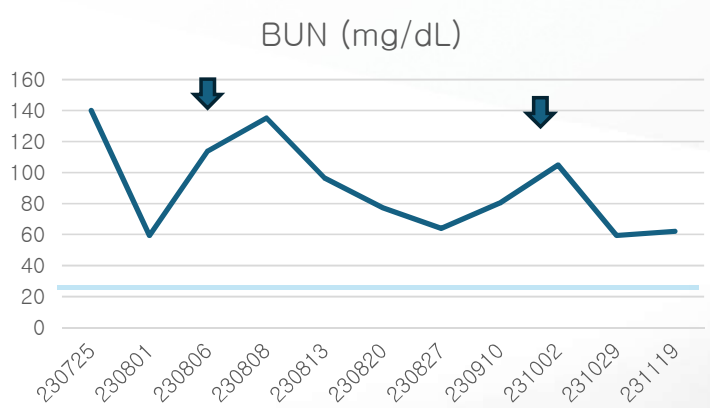
- Signalment:
  - 11-year-old spayed female Yorkshire Terrier, weighing 3.5 kg.
- Chief Complaint:
  - Anorexia.
- Diagnosis:
  - Under treatment chronic pancreatitis
  - Chronic renal failure
- Treatment:
  - Pancreatitis: antibiotics, antiemetics…
  - Renal failure: following Iris guideline conventional treatments (fluid, AST 120(kremezin)…)
  - Administered exosome injections on different days two times

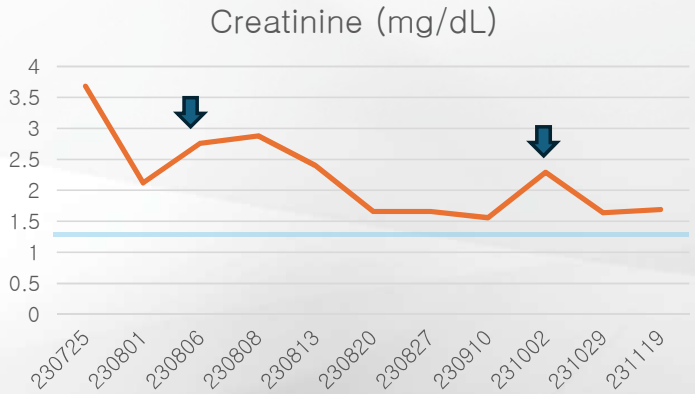


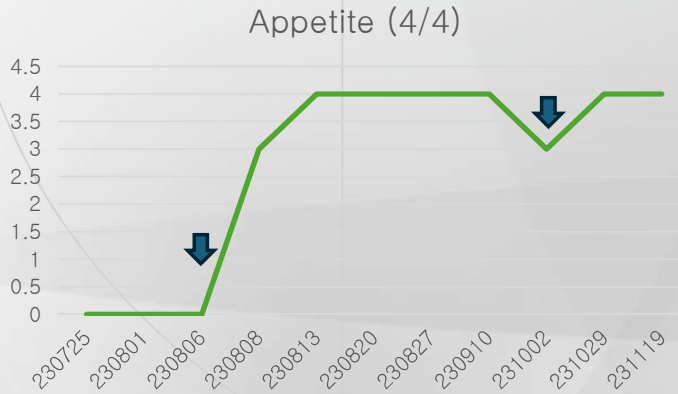
CASE 2: IBBUNI (CONTINUED)

	230725	230801	230806	230808	230813	230820	230827	230910	231002	231029	231119
BUN (mg/dL)	>140	59.4	114	135.3	96.4	77.2	64.1	80.3	105	59.4	62.2
Creatinine (mg/dL)	3.68	2.12	2.76	2.88	2.4	1.66	1.66	1.56	2.29	1.64	1.69
Phosphorus (mg/dL)	>15	9.1	12.8	>15	12.4	8.5	6.7	8	11.3		6.5
CPL (ug/L)	1394.8	1667.8	2000	1380.3	923.9	1274.8	1382.9				
Appetite (4/4)	0	0	0	3	4	4	4	4	3	4	4
Exosome Injection			v						v		

Hospitalization







CASE 2: IBBUNI (CONTINUED)

- Clinical Implications
  - Renal function support: Exosome therapy contributes to gradual improvements in renal markers, suggesting potential benefits for chronic kidney disease management.
  - Appetite restoration: Observed enhancement in appetite indicates possible metabolic benefits beyond renal function, supporting overall well-being.
  - Sustained stability: Patients maintained stable conditions for months post-treatment, highlighting the therapy's long-term potential.
  - Repetitive therapeutic effects: Exosome reapplication upon symptom recurrence led to further clinical improvements, reinforcing its suitability for chronic conditions.

CASE 3: AZI



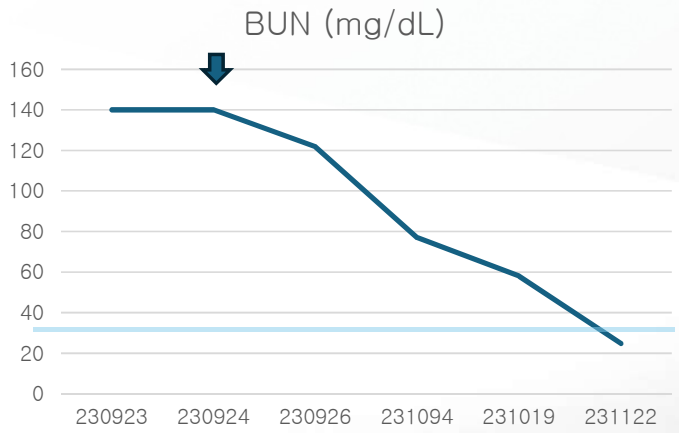


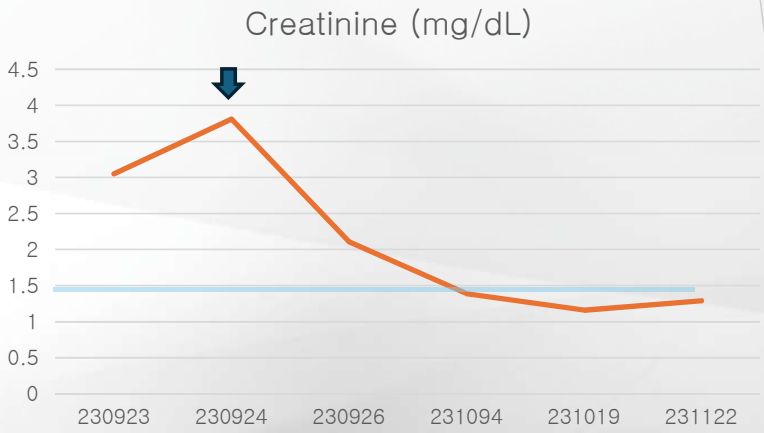
- Signalment:
  - 12-year-old spayed female Maltese, weighing 2.55 kg.
- Chief Complaint: Anorexia.
- Diagnosis: Cardiorenal syndrome (CRS) due to MMVD (Myxomatous Mitral Valve Disease) stage C
  - After increasing the diuretic dose (Due to cardiogenic pulmonary edema)
- Treatment
  - Minimal fluid therapy, AST-120(kremezin), probiotics
  - Continued use of diuretics to manage heart disease. (Following ACVIM guideline)
  - Exosome Therapy: Administered exosome injection once

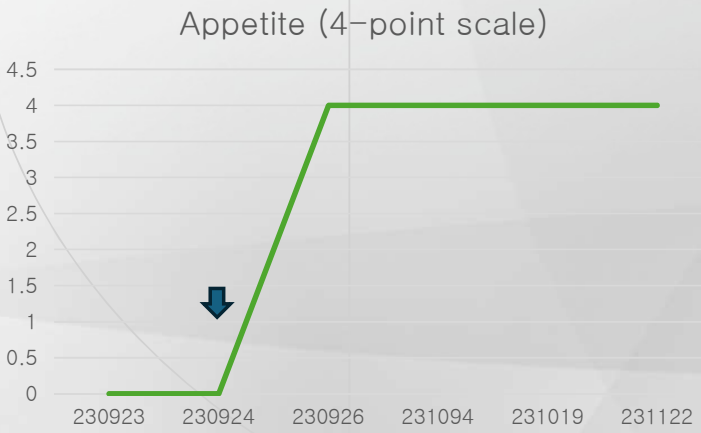
CASE 3: AZI (CONTINUED)

	230923	230924	230926	231094	231019	231122
BUN (mg/dL)	>140	>140	121.8	77	58.1	24.8
Creatinine (mg/dL)	3.05	3.81	2.11	1.39	1.16	1.29
Phosphorus (mg/dL)	5.1	8.7	5.6	3.5		2.9
Appetite (4-point scale)	0	0	4	4	4	4
Exosome Injection		v				

Hospitalization







CASE 3: AZI (CONTINUED)

- Clinical Implications
  - Rapid appetite recovery: Exosome therapy promotes appetite restoration, improving nutritional status and overall well-being.
  - Early intervention in cardiorenal syndrome (CRS): Exosome therapy helps manage renal dysfunction caused by heart disease, enhancing stabilization and recovery.
  - Potential for CRS management: Exosome therapy serves as a promising supportive treatment for renal failure in heart disease patients, ensuring kidney function stability even in CRS cases.

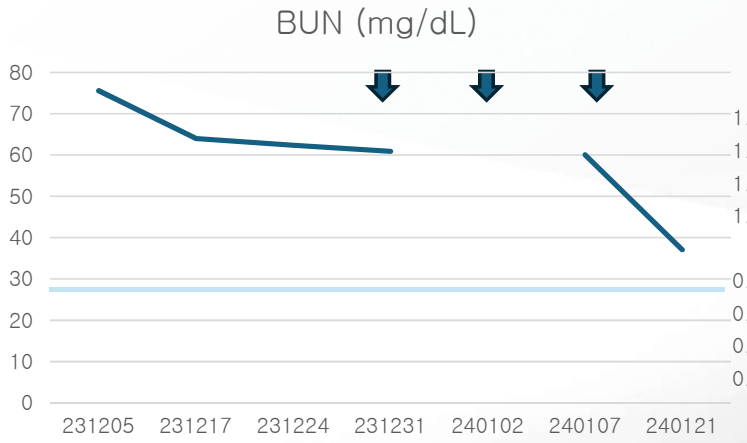
CASE 4: YEBBI

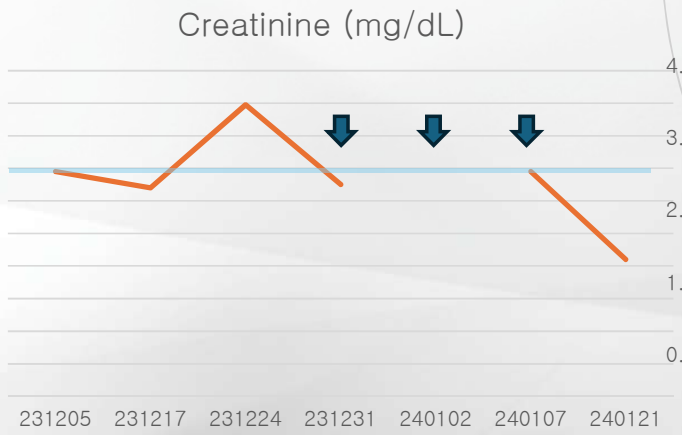


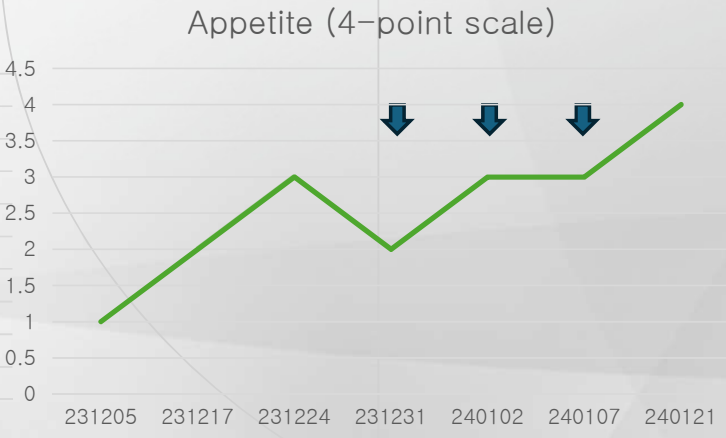
- Signalment:
  - 15-year-old spayed female Maltese, weighing 3.4 kg.
- Chief Complaint: Poor oral intake.
- Diagnosis:
  - Under treatment Cardiorenal syndrome, MMVD stage C
  - exacerbated by increased diuretic dosage.
- Treatment
  - AST-120(kremezin), probiotics
  - Continued use of diuretics to manage heart disease. (Following ACVIM guideline)
  - Exosome Therapy: Administered exosome injections three times for a week

CASE 4: YEBBI (CONTINUED)

	231205	231217	231224	231231	240102	240107	240121
BUN (mg/dL)	75.6	64	62.4	60.9		60.1	37.1
Creatinine (mg/dL)	1.38	1.28	1.79	1.3		1.38	0.84
SDMA (μg/dL)	20						14
Appetite (4-point scale)	1	2	3	2	3	3	4
Exosome Injection				v	v	v	







CASE 4: YEBBI (CONTINUED)

- Clinical Implications
  - Appetite improvement: Over two weeks, exosome therapy demonstrated clear benefits in improving nutritional intake.
  - Tolerance of repeated applications: Multiple exosome therapy applications were well tolerated, with no adverse reactions reported.
  - Potential for advanced cardiorenal syndrome management: The therapy may help stabilize and relieve symptoms even in patients with advanced renal failure or chronic cardiorenal syndrome.

Discussion

- Acute Kidney Injury (AKI) Response:
  - Case 1 (SAEBOM)
- Chronic Kidney Disease (CKD) Management:
  - Case 2 (IPPUNI)
- Cardiorenal Syndrome Applications:
  - Acute: Case 3 (AZI)
  - Chronic: Case 4 (YEBBI)

Discussion

- Therapeutic Potential of Exosomes in Renal Diseases
  - Point of care: Exosome therapy can be administered promptly after clinical decision-making, offering a fast-acting and readily available treatment option. Early and repeated administration has shown to improve treatment outcomes.
  - Consistent Appetite Recovery: Across multiple cases, exosome therapy effectively restored appetite
    - It was the aspect with the highest level of owner's satisfaction
  - Improvement in Renal Function: Treatment was associated with measurable decreases in BUN and creatinine, indicating stabilized or improved kidney function.

Discussion

- Therapeutic Potential of Exosomes in Renal Diseases (continued)
  - Safe and Well-Tolerated: Even in patients with complex comorbidities (e.g., pancreatitis, diabetes, heart disease), exosome therapy was well tolerated without adverse effects. Treated animals maintained stable health throughout.
  - Compatibility with Standard Therapies: Exosome treatment may serve as a complementary modality alongside fluid therapy and conventional medications for managing renal disease, without interfering with standard care protocols.

LIMITATIONS

- Treatment diversity based on patient condition
  - Treatment methods and hospitalization vary depending on the patient's condition.
  - Patients often have comorbid conditions, not just kidney failure, which further complicates treatment.
- Limitations due to owner's circumstances
  - Evaluations and treatments are often restricted by the owner's situation.
  - Financial burdens significantly influence treatment choices.
- Lack of awareness about exosome therapy
  - Owners show low awareness of exosome therapy.
  - Insufficient information about new treatments reduces accessibility.

Limitations → Next steps

- Lack of Standardized Protocols
  - inject 10 billion exosome particles once a week for four weeks and once a month thereafter.
- Incomplete Understanding of Mechanisms
  - MSC-derived exosomes reduce inflammation, which is a major contributor to kidney damage (Janockova et al., 2021).
  - They enhance the regeneration of damaged kidney tissues by delivering bioactive molecules (Liao et al., 2021).
  - Exosomes help reduce aging-related cellular dysfunction in renal epithelial cells (Liao et al., 2021).
  - Exosomes promote the formation of new blood vessels, improving oxygen and nutrient delivery to the kidney (Toghiani et al., 2024).
  - Inhibition of fibrosis (Janockova et al., 2021).
- Cost?
  - The production costs of exosomes have significantly decreased

Conclusion

- Exosome Therapy as an Innovative Treatment for Renal Diseases
  - Exosomes derived from mesenchymal stem cells represent a promising therapeutic approach, with significant potential to improve renal function and clinical symptoms in dogs suffering from renal disease.

Acknowledgment

- Thank you to GNG CELL Co., Ltd. for providing the mesenchymal stem cell-derived exosomes that made this study possible.


JUST
THANK
YOU!