EFFICACY OF INTRARTICULAR EXOSOMES INJECTION FOR SEVERE KNEE OSTEOARTHRITIS:

AN INITIAL EXPERIENCE IN 45 PATIENTS

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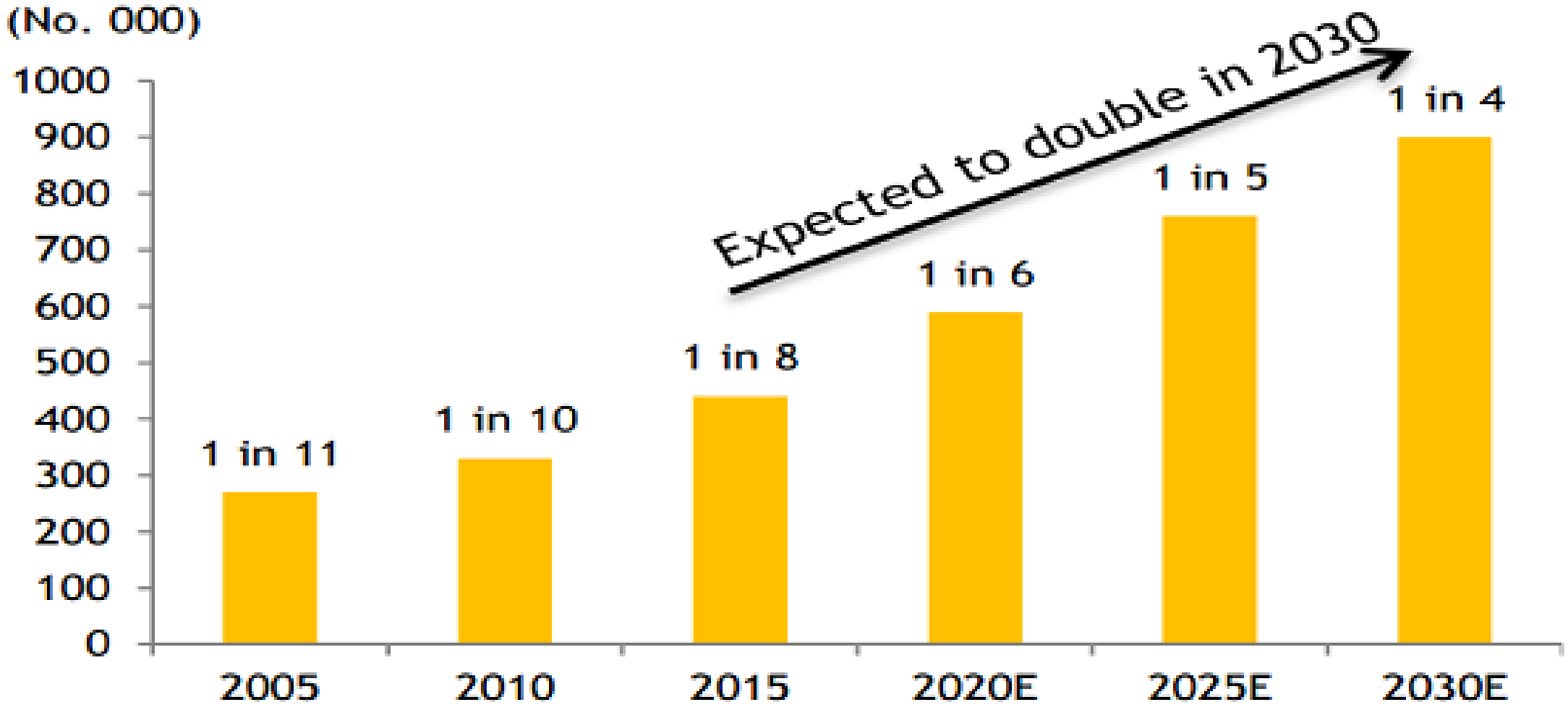
DBS
ATM
Deposit
Withdrawal
Balance Enquiry
Funds Transfers
Passbook Update
Top Up Services
Card Services
Investment Services
Bill Payments
ATM
Deposit
Withdrawal
Balance Enquiry
Funds Transfers
Passbook Update
Top Up Services
Card Services
Investment Services
Bill Payments

Ageing population

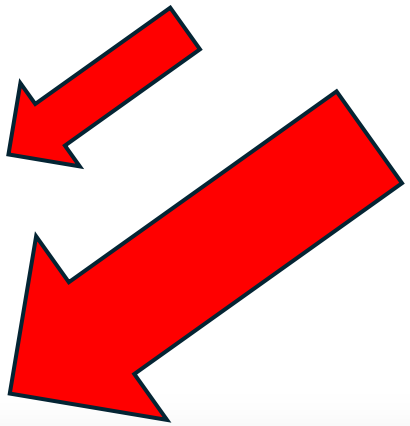
Fig 3: No. of Singapore citizens aged 65 and above



Source: Population.sg

Table 4 Prevalence of symptomatic knee osteoarthritis in NHSS follow-up study, Singapore (n = 3364)

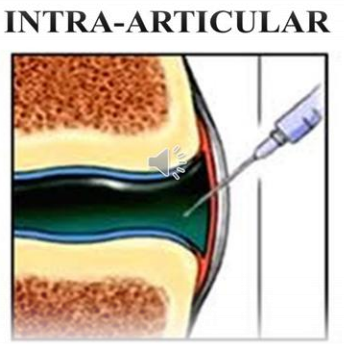
		Unweighted prevalence, % (95% CI)		Weighted prevalence, %	
	n	Model 1†	Model 2‡	Model 1†	Model 2‡
Overall	3364	5.8 (5.1–6.6)	14.3 (13.2–15.5)	4.7	11.0
By gender					
Female	1822	7.1 (6.0–8.4)	17.5 (15.8–19.3)	5.6	13.1
Male	1542	4.2 (3.3–5.3)	10.5 (9.1–12.1)	3.7	8.8
By age groups					
18–29 years	424	0.7 (0.2–2.1)	2.4 (1.3–4.3)	0.8	1.6
30–39 years	465	1.3 (0.6–2.8)	7.5 (5.5–10.3)	0.6	5.7
40–49 years	828	4.3 (3.2–6.0)	12.1 (10.0–14.5)	4.4	9.7
50–59 years	830	7.5 (5.9–9.5)	18.3 (15.8–21.1)	6.4	15.7
60–69 years	527	9.5 (7.3–12.3)	21.3 (18.0–24.9)	8.7	18.4
≥70 years	290	13.1 (9.7–17.5)	24.8 (20.2–30.1)	10.8	21.5
By age categories					



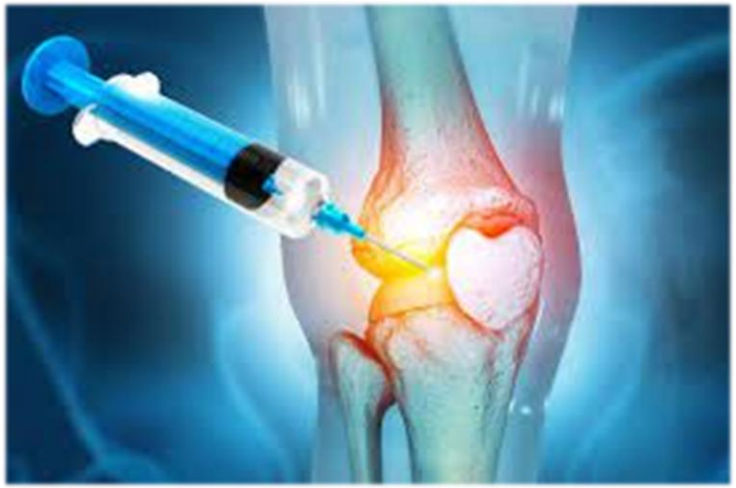
TREATMENT GOALS FOR OA:

- **AIM TO:**
  - ✓ REVERSE OA-ASSOCIATED JOINT DAMAGE
  - ✓ PREVENT PROGRESSION OF OA
  - ✓ ACHIEVE GOOD SYMPTOM CONTROL - PAIN AND STIFFNESS
  - ✓ ACHIEVE GOOD PATIENT-REPORTED FUNCTIONAL OUTCOMES (PRO) - WOMAC, HAQ, KOOS SCORES

INTRA-ARTICULAR THERAPY (IAT) FOR KNEE OSTEOARTHRITIS



- IA CORTICOSTEROIDS (IA CS)
- IA NSAIDS(Pareocoxib/Piroxicam)
- IA TRAMADOL



- IA HYALURONIC ACID (IAHA)

- **IA POLYNUCLEOTIDE (PN)**
- **IA MD COLLAGEN**

- **IA PRP +/- HA**
- **IA AUTOLOGOUS PROTEIN SOLUTION (APS)**
- COMBINATION IATs

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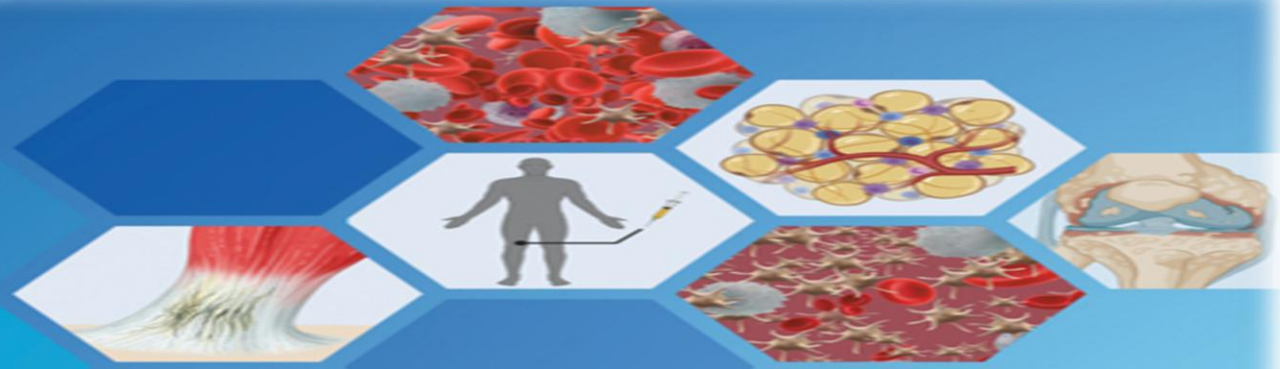


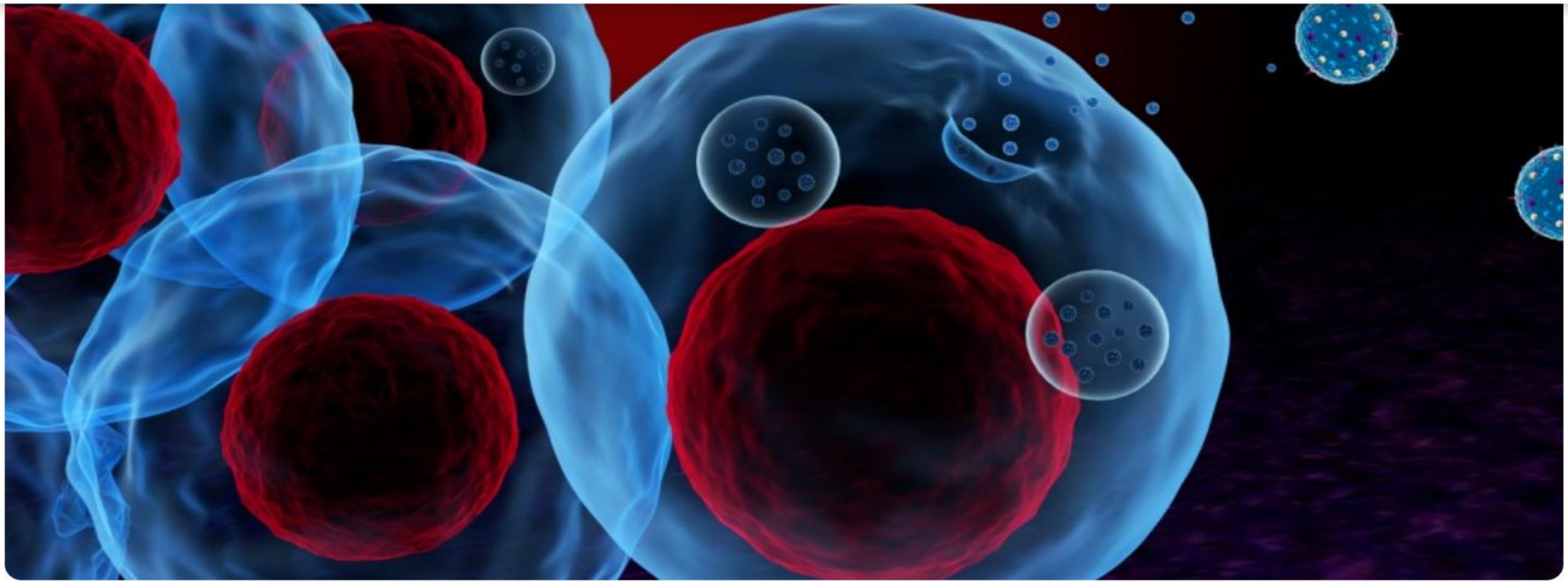
Orthobiologics

Injectable Therapies for the Musculoskeletal System

ISAKOS
International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine

ICRS
International Cartilage Regeneration & Joint Preservation Society

Springer



THE POTENTIAL ROLES OF EXOSOMES IN OSTEOARTHRITIS TREATMENT

Bone Research

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PMID: 32596023

Exosomes: roles and therapeutic potential in osteoarthritis

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Abstract

Go to: ▸

Exosomes participate in many physiological and pathological processes by regulating cell–cell communication, which are involved in numerous diseases, including osteoarthritis (OA). Exosomes are detectable in the human articular cavity and were observed to change with OA progression. Several joint cells, including chondrocytes, synovial fibroblasts, osteoblasts, and tenocytes, can produce and secrete exosomes that influence the biological effects of targeted cells. In addition, exosomes from stem cells can protect the OA joint from damage by promoting cartilage repair, inhibiting synovitis, and mediating subchondral bone remodeling. This review summarizes the roles and therapeutic potential of exosomes in OA and discusses the perspectives and challenges related to exosome-based treatment for OA patients in the future.

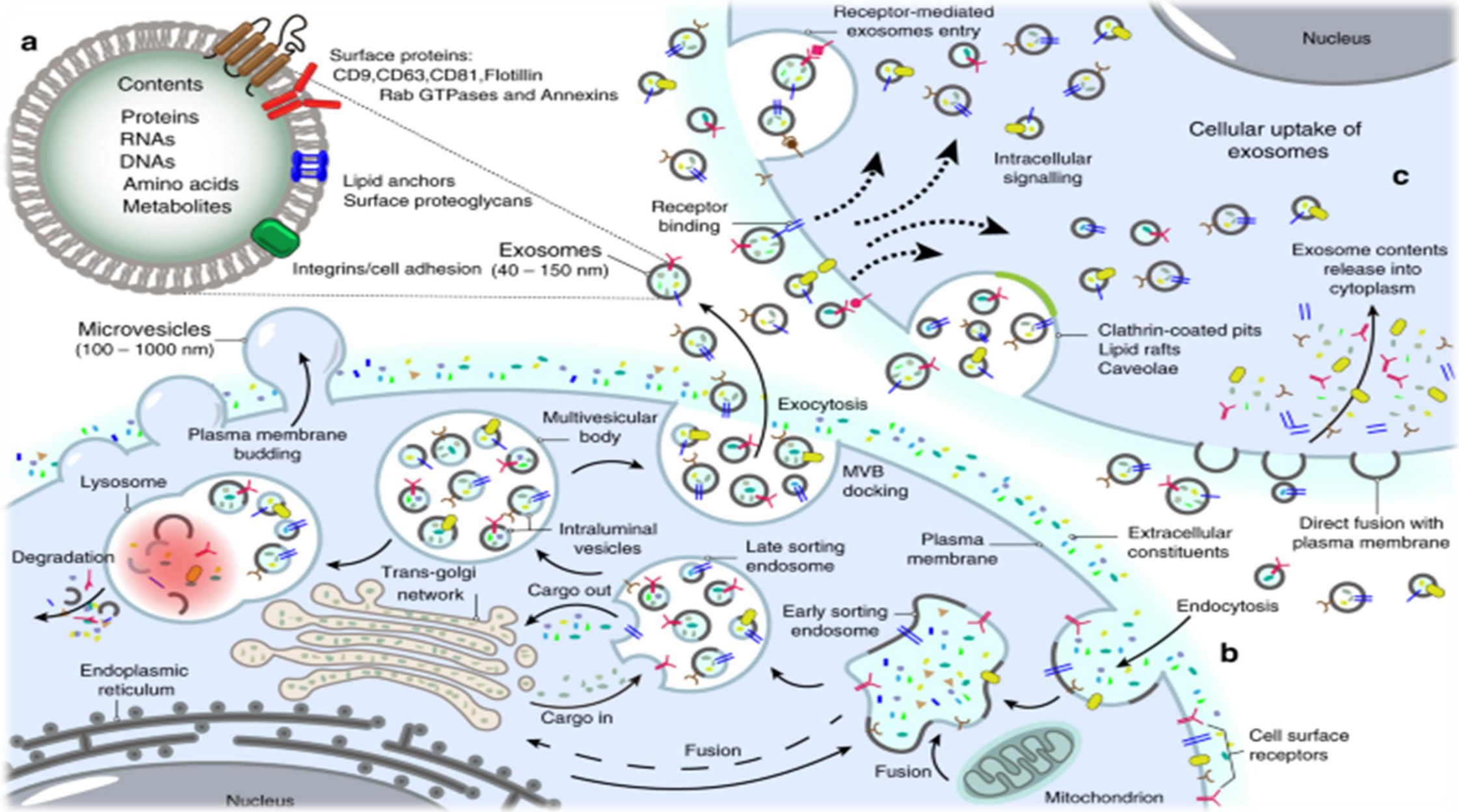
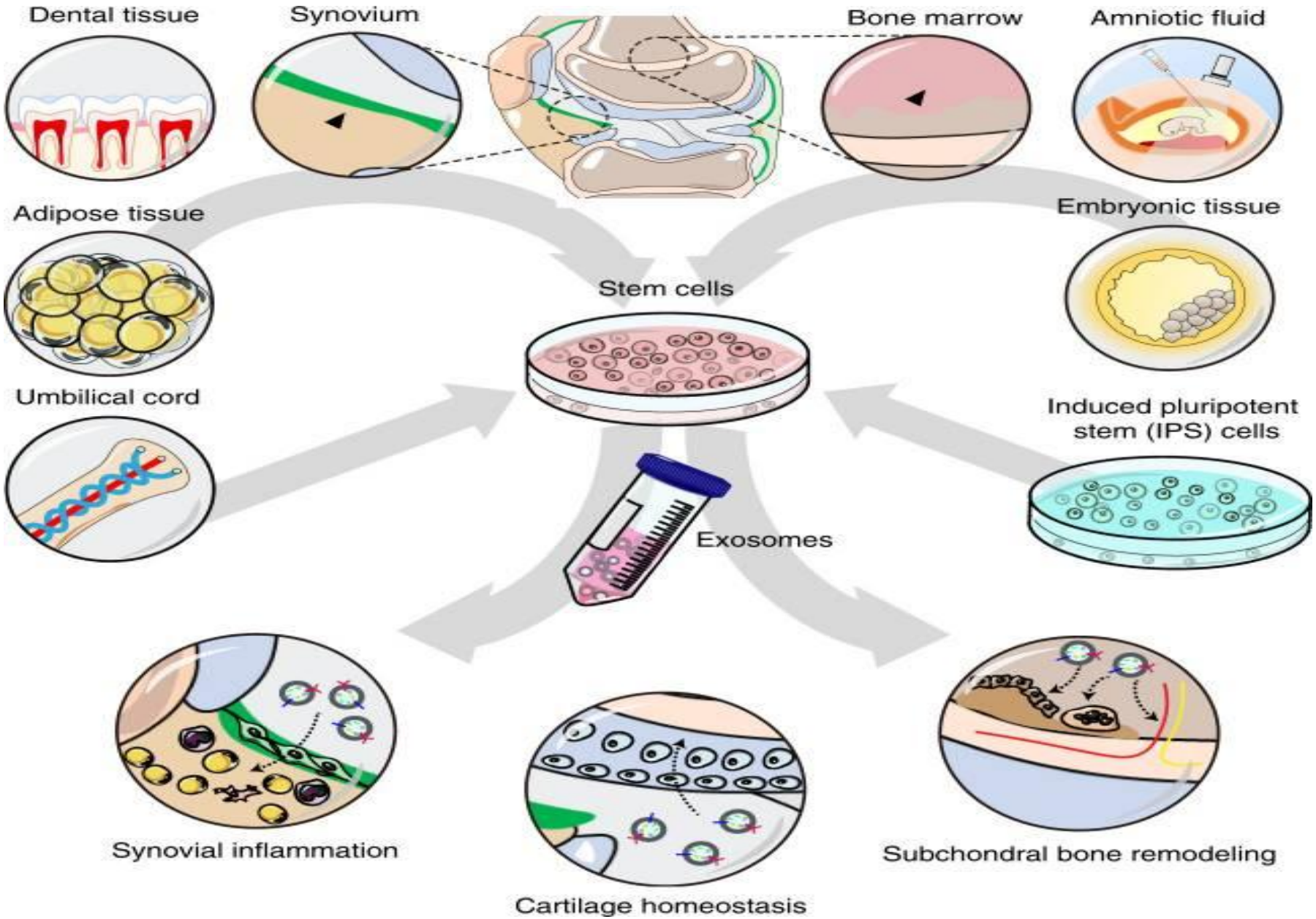

a
Contents
Proteins
RNAs
DNAs
Amino acids
Metabolites
Surface proteins:
CD9,CD63,CD81,Flotillin
Rab GTPases and Annexins
Lipid anchors
Surface proteoglycans
Integrins/cell adhesion
Exosomes
(40 – 150 nm)
Receptor-mediated
exosomes entry
Nucleus
Intracellular
signalling
Cellular uptake of
exosomes
c
Receptor
binding
Exosome contents
release into
cytoplasm
Clathrin-coated pits
Lipid rafts
Caveolae
Microvesicles
(100 – 1000 nm)
Plasma membrane
budding
Exocytosis
Multivesicular
body
MVB
docking
Lysosome
Degradation
Intraluminal
vesicles
Trans-golgi
network
Late sorting
endosome
Cargo out
Plasma
membrane
Extracellular
constituents
Direct fusion with
plasma membrane
Endocytosis
Early sorting
endosome
b
Endoplasmic
reticulum
Cargo in
Fusion
Fusion
Cell surface
receptors
Nucleus
Mitochondrion

Table 2

The therapeutic effects and underlying mechanisms of exosomes derived from stem cells on OA

Exosomes	Separation method	Mechanisms of actions	Biological effects
BMSCs-derived exosomes	Ultracentrifugation and Ultrafiltration	• Prevent OA chondrocytes from apoptosis by p38, ERK, and akt signaling pathways.[182,183]	• Reduce the damage of articular cartilage.[182,185]
		• Regulate catabolism and anabolism in chondrocytes.[182]	• Abrogate the degradation of subchondral bone.[182,185]
		• Maintain mitochondrial membrane potential and inhibit mitochondrial dysfunction.[183,184]	• Inhibit aberrant nerve invasion and abnormal formation of H-type vessel in subchondral bone.[185]
		• Suppress osteoclast activity in subchondral bone via RANKL-RANK-TRAF6 pathway.[185]	• Relieve pain in OA model.[185]
		• Inhibit proliferation and enhance apoptosis in synovial fibroblasts via microRNA-26a-5p/ PTGS2 pathway.[186]	• Decrease the infiltration of inflammatory cells, down-regulate the level of inflammatory factor and alleviate pathological changes of synovium.[186]
			• Inhibit the activation of


Dental tissue
Synovium
Bone marrow
Amniotic fluid
Adipose tissue
Embryonic tissue
Stem cells
Umbilical cord
Induced pluripotent stem (IPS) cells
Exosomes
Synovial inflammation
Cartilage homeostasis
Subchondral bone remodeling

- EXOSOMES DERIVED PROTEIN PEPTIDES FROM HEALTHY BONE MARROW DONORS FROM JAPAN

INTRARTICULAR EXOSOMES INJECTION FOR SEVERE KNEE OSTEOARTHRITIS

- **KINTARO EXOSOMES** IS A BIO-REVITALIZANT THAT IS A VITAL PRODUCT OF BONE MARROW DERIVED MESENCHYMALSTEM CELLS (MULTIPOTENT MESENCHYMAL STROMAL CELLS) FROM YOUNG HEALTHY JAPANESE DONORS(AGE 18-26) AFTER CAREFUL SCREENING AT THE JAPANESE CELL BANK.
- **KINTARO EXOSOMES** CONTAINS GROWTH FACTORS, CYTOKINES, ANGIOGENIC SUBSTANCES, ANTI-INFLAMMATION AND ANTI-APOPTOTIC FACTORS AND IMMUNOMODULATORS.

INTRARTICULAR EXOSOMES INJECTION FOR SEVERE KNEE OSTEOARTHRITIS

- THIS PRODUCT HAS BEEN IN USED IN JAPAN SINCE 2011 WITH MORE THAN A THOUSAND TREATMENTS GIVEN, AND WAS INTRODUCED ONLY IN AUG 2023 TO SINGAPORE.
- I VIAL OF KINTARO EXOSOMES CONTAINS 10MLS OF WATER SOLUBLE BIO-REVITALIZANT. EACH KNEE WAS INJECTED WITH 5 TO 10MLS OF KINTARO EXOSOMES

- HAS BEEN GIVEN AS PERIARTICULAR INJECTIONS
- **WE ARE THE FIRST IN ASIA TO DO INTRAARTICULAR KINTARO EXOSOMES KNEE INJECTIONS**

METHODS:

- ALL THE PATIENTS WHO RECEIVED IA EXOSOMES (KINTARO) FROM AUG 2023 TO FEB 2024 IN OUR CLINIC WERE REVIEWED AND ANALYSED.
- THE PATIENTS DEMOGRAPHIC DATA AND CLINICAL PRESENTATION AND TREATMENT OUTCOMES WERE SUMMARISED AND COLLATED AND ANALYSED

RESULTS:

- **45** PATIENTS WHO RECEIVED IA EXOSOMES FOR KNEE OA TREATMENT WERE REVIEWED: WITH 20 MALES AND 25 FEMALES, WITH 42 CHINESE PATIENTS.
- AGE RANGE: 51-89 YEARS OLD.
- MAJORITY HAD SEVERE DISEASE GRADE 3 (15) GRADE 4 (16).
- DURATION OF DISEASE **1-15 YEARS**.
- ALL HAD FAILED VARIOUS IAT INCLUDING STEROIDS, NSAIDS, HYALURONIC ACID & POLYNUCLEOTIDE.

RESULTS OF IA EXOSOMES

- IMPROVEMENT IN KNEE SYMPTOMS WAS SEEN IN **67% OF PATIENTS**
- WITH DURATION OF EFFECT RANGING FROM **1-14 MTHS**.
- **7** HAD NO RESPONSE AND **8** WERE LOST TO FOLLOW-UP.
- **NO ADVERSE EFFECTS WERE SEEN**

PATIENT PRESENTATION 1

- KSG/86/CHI/F
- MILD DM, OSTEOPOROSIS, MULTI-JOINT OA OF SPINE, SHOULDERS AND KNEES.
- **SEVERE OA KNEES SINCE 2018. GRADE 4 DISEASE.**
- VARIOUS TREATMENTS GIVEN INCLUDING IA HAs/IA STEROIDS/NSAID/MBST CARTILAGE REGENERATION MAGNETIC THERAPY.
- 2023 – RECURRENT KNEE PAIN AND SYNOVITIS.

PATIENT PRESENTATION 1

- 2023 – FROM JAN – MAY :HAD IA HA MTHLY + IA STEROID/NSAID/TRAMADOL
- JUN-JULY : – IA CONJURAN PN X 2 TO BOTH KNEES
- **RECURRENT KNEE PAIN DUE TO INFLAMAGING/SYNOVITIS-DRIVEN OA KNEES**
- **8/23 – HAD IA KINTARO 5MLS EXOSOMES TO BOTH KNEES.**
- RESPONDED WELL AND WAS MUCH IMPROVED.
- DID NOT REQUIRE FURTHER IA TILL **DEC/JAN'24, 4-5 MTHS LATER.**

RESPONSE TO IA EXOSOMES

DATE	RIGHT KNEE		LEFT KNEE	
	VAS	WOMAC	VAS	WOMAC
15/8	7	44	7	44
17/8	1	10	1	11
24/8	0	7	3	6

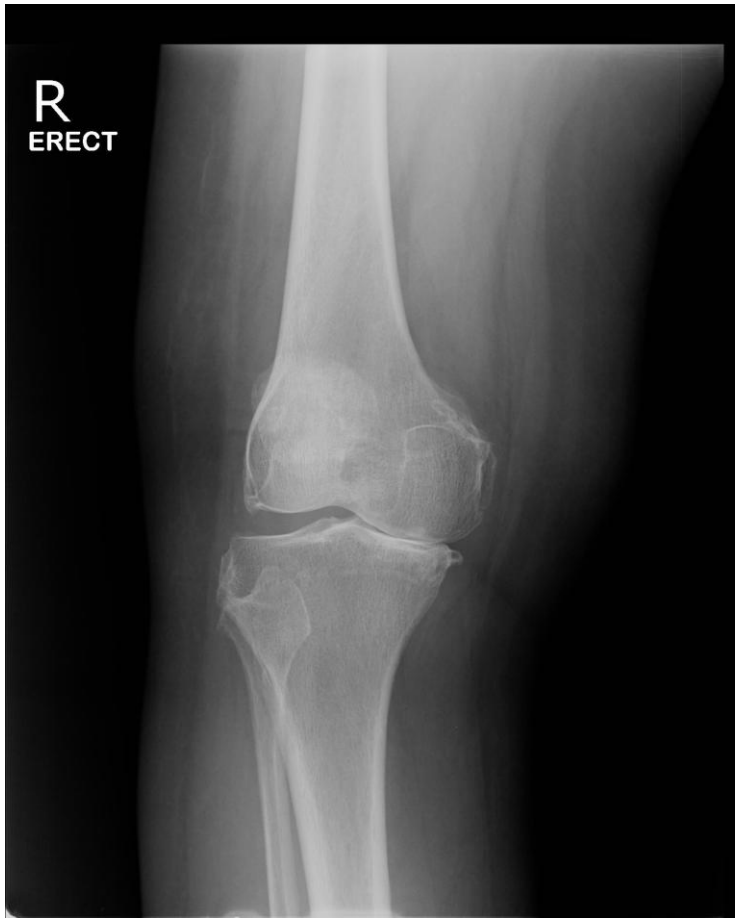
PATIENT PRESENTATION 2

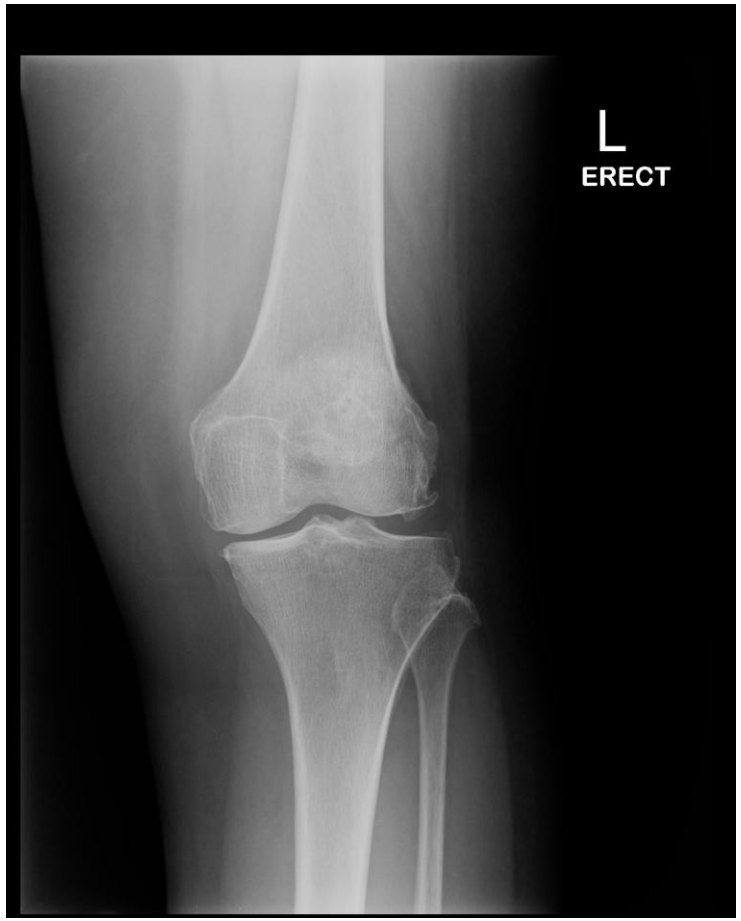
- **TMC, 83/CHI/F, OA KNEES FOR 9 YEARS.**
- HA IA SYNVISC 2016 TO BOTH KNEES
- IA HYMOVIS 2020 TO BOTH KNEES
- MBST THERAPY TO LEFT KNEE 2020 DUE TO RESIDUAL KNEE PAIN, WHICH IMPROVED AFTER THE THERAPY.
- RECURRENT RIGHT KNEE PAIN 2022
- HAD IA TRIAMCINOLONE/PIROXICAM/SYNOLISVA COMBINATION IAT
- MBST THERAPY TO RIGHT KNEE WITH IMPROVEMENT

PATIENT PRESENTATION 2

- RECURRENT KNEE PAIN IN **2023**
- U/S KNEE - EFFUSION ++ SYNOVITIS++ OSTEOPHYTES+++ REDUCED JOINT SPACE G3 OA
- ANOTHER COURSE OF IA SYNOLISVA INJECTIONS X 3.
- **2/2024**
- RECURRENT KNEE PAIN ON WALKING 6 WEEKS AFTER LAST IA HA INJECTION.
- XRAY DONE - **G4 OA KNEE (R) G3 ON LEFT**

PATIENT PRESENTATION 2





PATIENT PRESENTATION 2

- AGREEABLE FOR IA EXOSOMES INJECTION
- RIGHT KNEE EFFUSION
- ASPIRATION DONE 18 MLS OF FLUID.
- IA BETAMETHASONE GIVEN
- IA HIGH CONC KINTARO 5MLS GIVEN TO THE RIGHT KNEE
- KNEE : VAS 8 WOMAC 45

PATIENT PRESENTATION 2

- FOLLOW-UP VISITS
- 4/24
- 1/25
- REMAINS WELL. NO KNEE PAIN
- TELECONSULT FOLLOW-UP 7/25
- **MILD PAIN AFTER 1.5 YEARS**
- WILL COME FOR ANOTHER IA WHEN SHE GOES TRAVELLING

CONCLUSIONS:

- **IA EXOSOMES IS A PROMISING NEW IA THERAPEUTIC AGENT** THAT DESERVES FURTHER EVALUATION AND FOLLOW-UP STUDY FOR THE TREATMENT OF SEVERE KNEE OA.
- THIS IS AN EXPANDING FIELD OF INTEREST FOR THOSE TREATING MODERATE TO ADVANCED KNEE OA WHO HAVE FAILED OTHER MORE COMMONLY AVAILABLE IAT.


UNVEILING THE FUTURE OF
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