골관절염 세포유전자 치료제

인보사

2017.12.28

코오롱생명과학 김 수정

KOLON LIFE SCIENCE

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코오롱생명과학

설립일	2000년 TissueGene Asia 설립
	2006년 코오롱생명과학㈜으로 사명 변경
소재지	본사: 경기도 과천시
	연구소: 서울, 성남
	공장: 충주, 음성, 김천
상장	2009년 코스닥 상장
사업 분야	바이오 신약, 원료의약품, polymer
임직원수	480명

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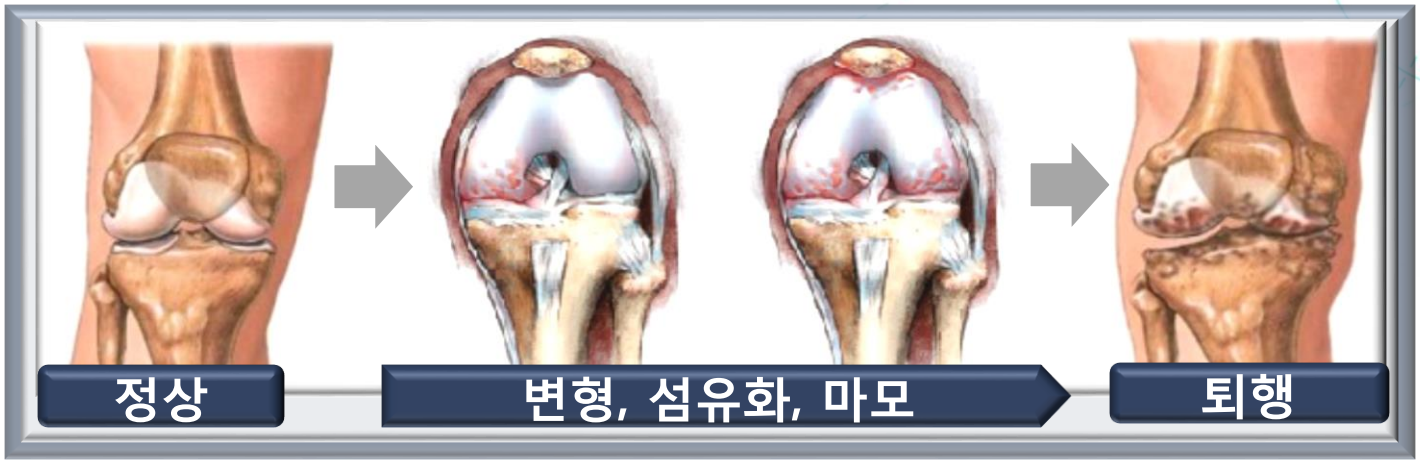
적응증: 골관절염 (Osteoarthritis)



[원인]

관절 내 연골 손상 및 염증기전 악순환에 의해 발생

[증상]

통증, 뻑뻑함, 관절 운동 범위 감소, 종창

현재 치료법 및 한계

퇴행성관절염 진행 :초기 중기 말기

생활습관 개선

물리 치료

진통제

- 장기 복용 X
- 부작용 발생

무릎 주사

- HA
- Steroid

"질병 계속 진행"

인공관절수술

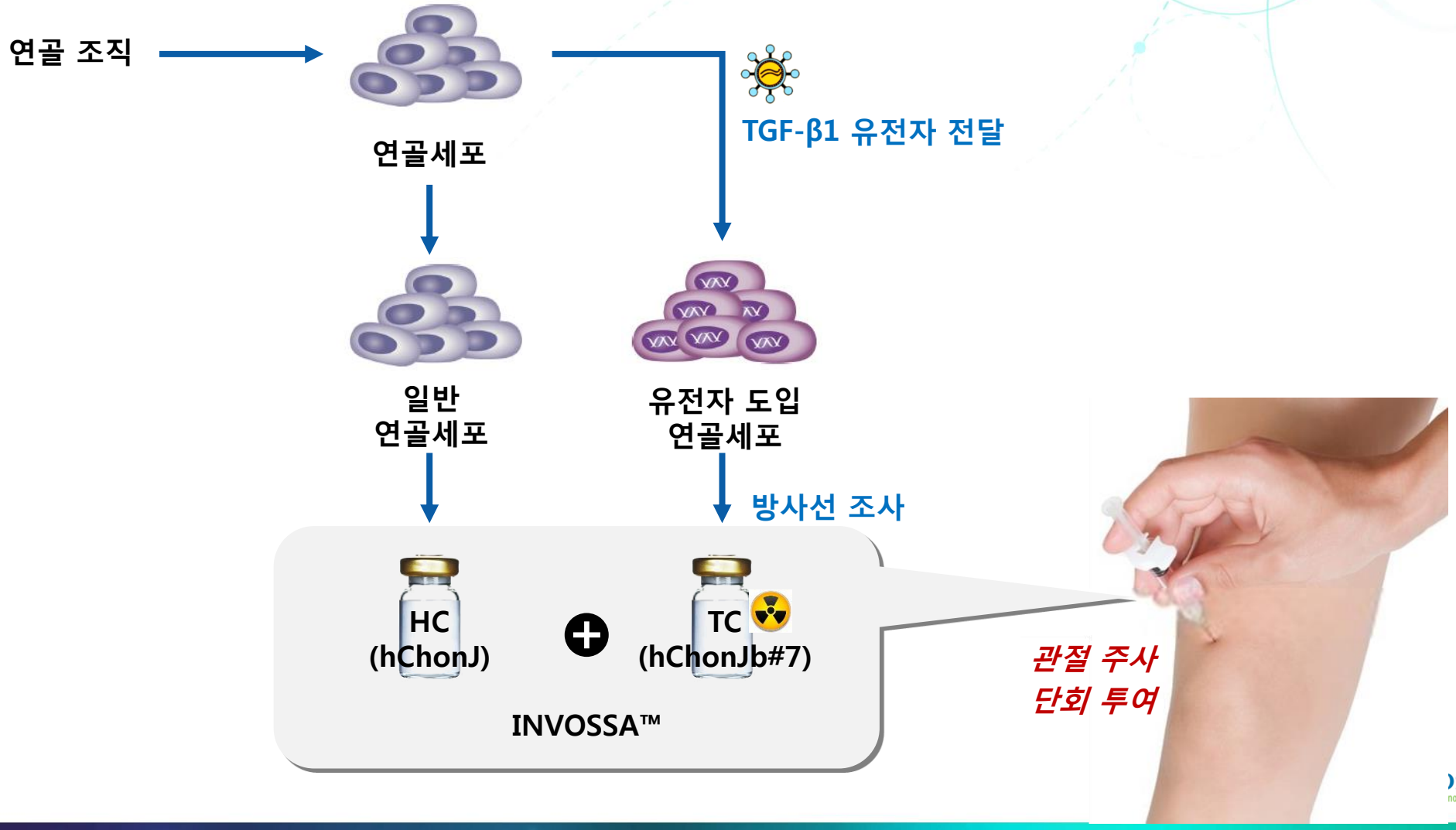
- 마취 부담
- 재수술 필요

치료법 Gap 존재

INVOSSA

인보사 (Invossa)

세계 최초 동종 세포유전자 치료제



허가 정보

+ 성분

이름	성분	용량
1액 (2 mL)	동종 연골세포 (HC)	1.35×10^7 세포
2액 (1 mL)	TGF-β1 유전자도입 동종 연골세포 (TC)	4.5×10^6 세포

+ 적응증

–3개월 이상의 보존적 요법(약물치료, 물리치료 등)에도 불구하고 증상이 지속되는 중등도 무릎 골관절염(Kellgren & Lawrence grade 3)의 치료

+ 용법용량

–무릎 관절강내 투여

INVOSSA tonogenconcel

투여 방법

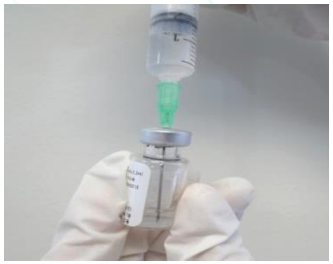
인보사-케이주 1 KIT

- **인보사-케이주 1 KIT :**
  - ① HC 1.35x10^7 cells/2mL
  - ② TC 0.45X10^7 cells/1mL
- **보관 조건 :**
  LN_2 tank (< -135℃)
- **유통 기한: 2년**

투약 과정

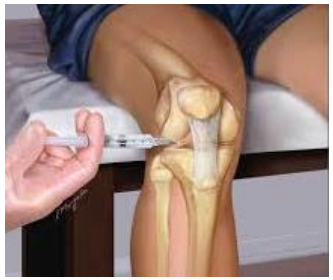
1 세포 해동 at 37℃

2 주사기 충진



3 가볍게 흔들어 혼합

4 주사



개발 History

1999년 연구 개시, 2017년 한국 품목허가

한국 임상

- 2006 임상 1상 승인 (승인번호 : 생물의약품안전팀 15942호)
- 2009 임상 2a상 승인
- 2011 임상 2b상 승인
- 2013 임상 3상 승인
- 2016 품목허가 신청
- 2017 품목허가

미국 임상

- 2006 임상 1상 승인
- 2010 임상 2상 승인
- 2015 임상 3상 승인 (SPA)

비임상 연구

- 약리 시험
- 독성 시험

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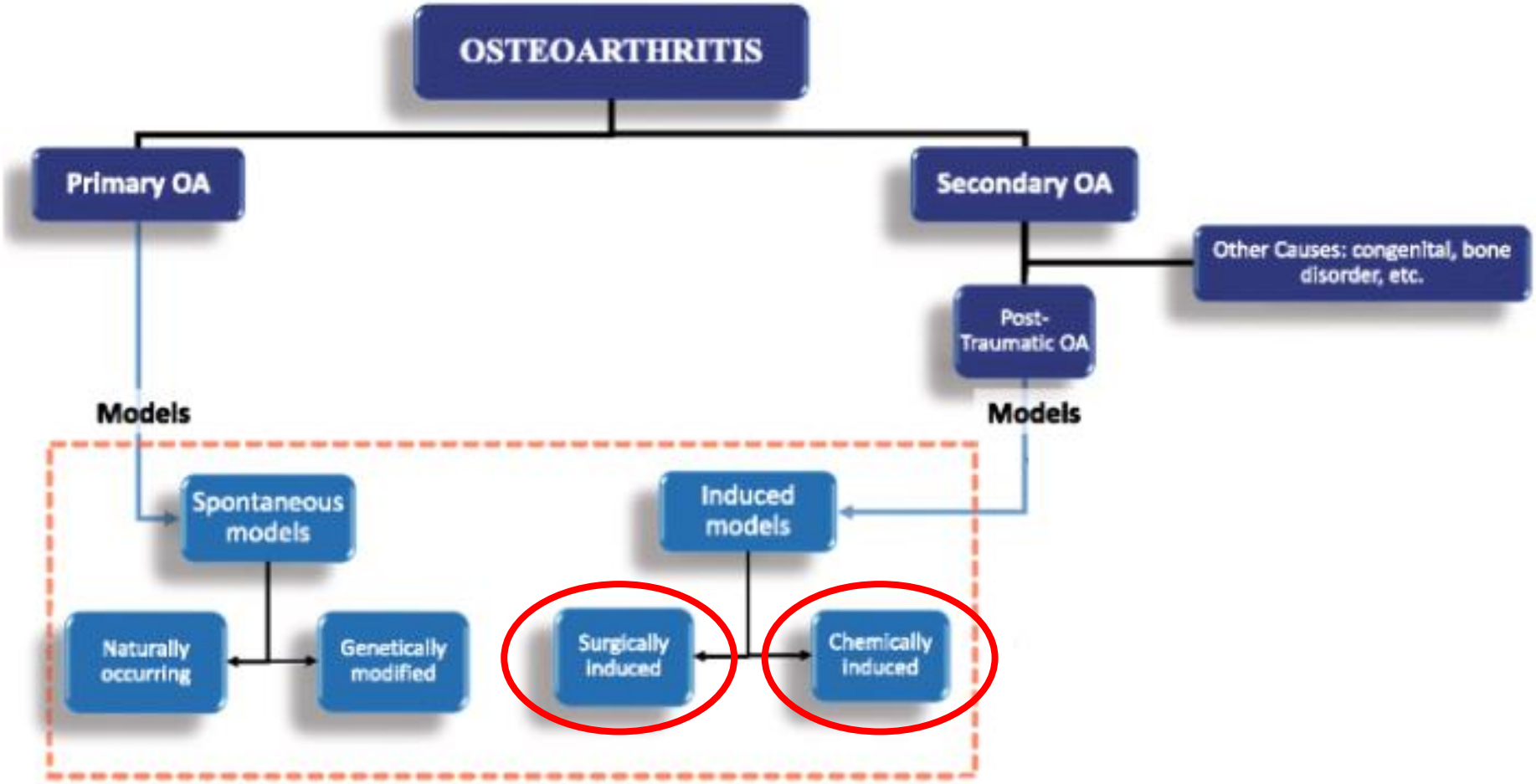
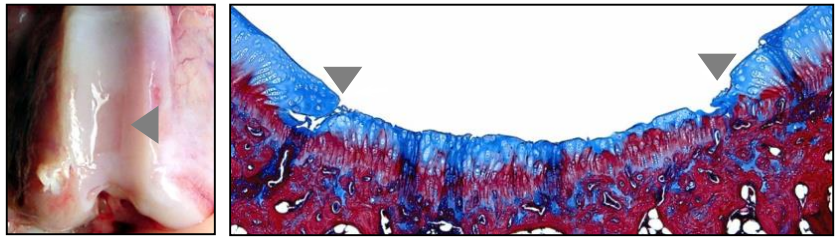
동물 모델


OSTEOARTHRITIS
Primary OA
Secondary OA
Other Causes: congenital, bone disorder, etc.
Post-Traumatic OA
Models
Models
Spontaneous models
Induced models
Naturally occurring
Genetically modified
Surgically Induced
Chemically Induced

토끼 모델에서 연골 재생 확인

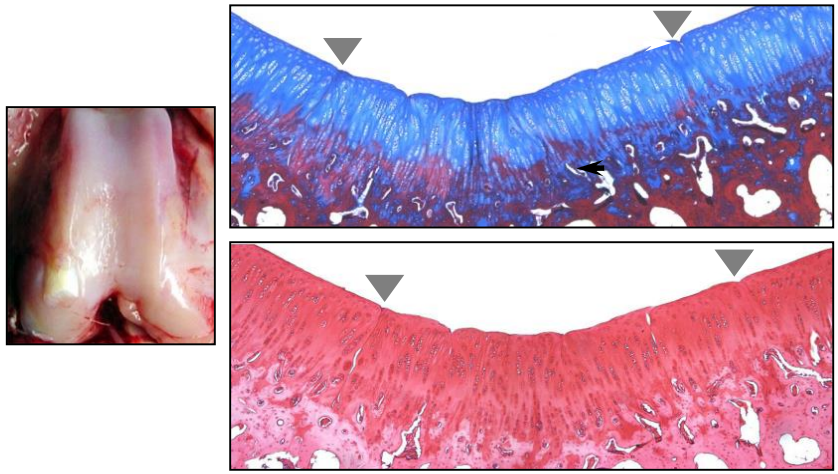
토끼 연골 손상 모델

대조군

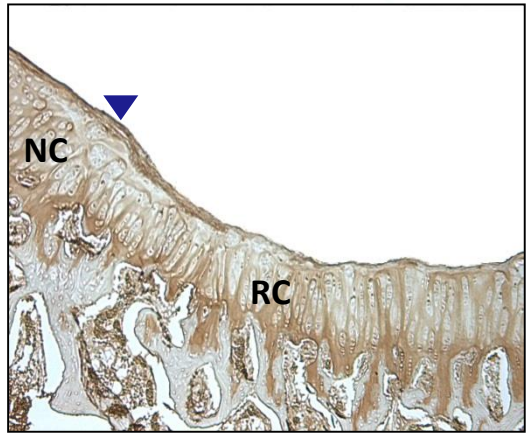


Masson's trichrome staining

Invossa



S/O staining



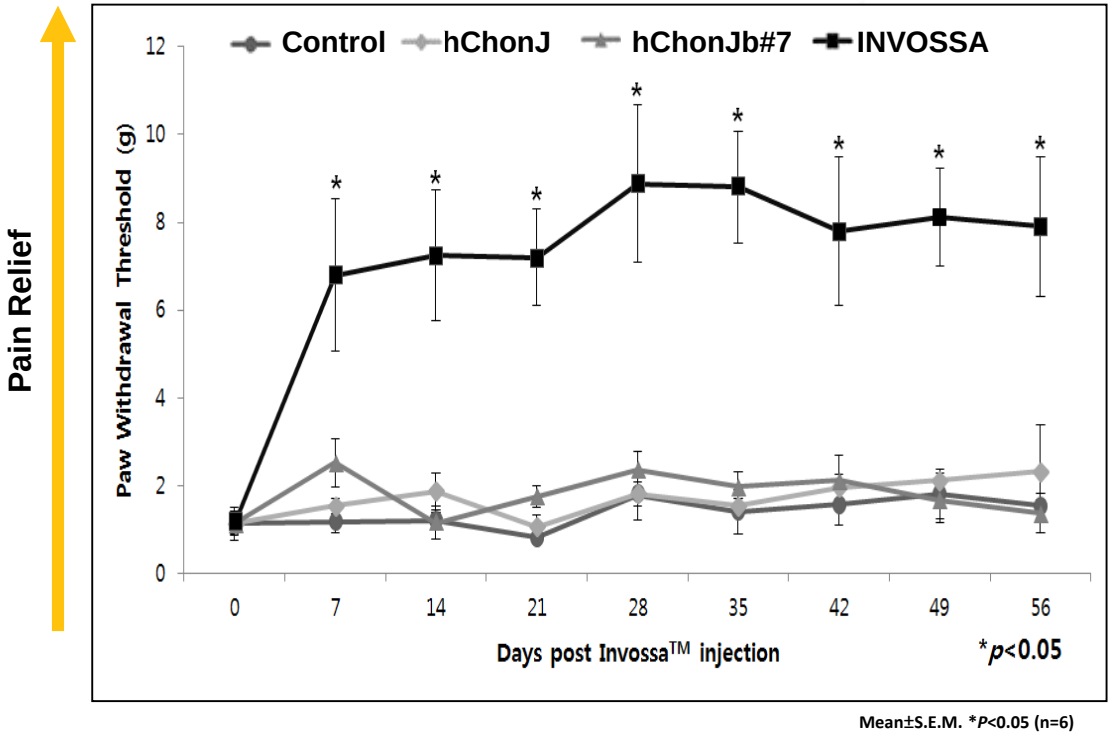
Type II collagen

NC: normal cartilage (정상연골)
RC: regenerated cartilage (재생연골)

Rat 모델에서 통증 개선 및 연골 재생 확인

Rat MIA model

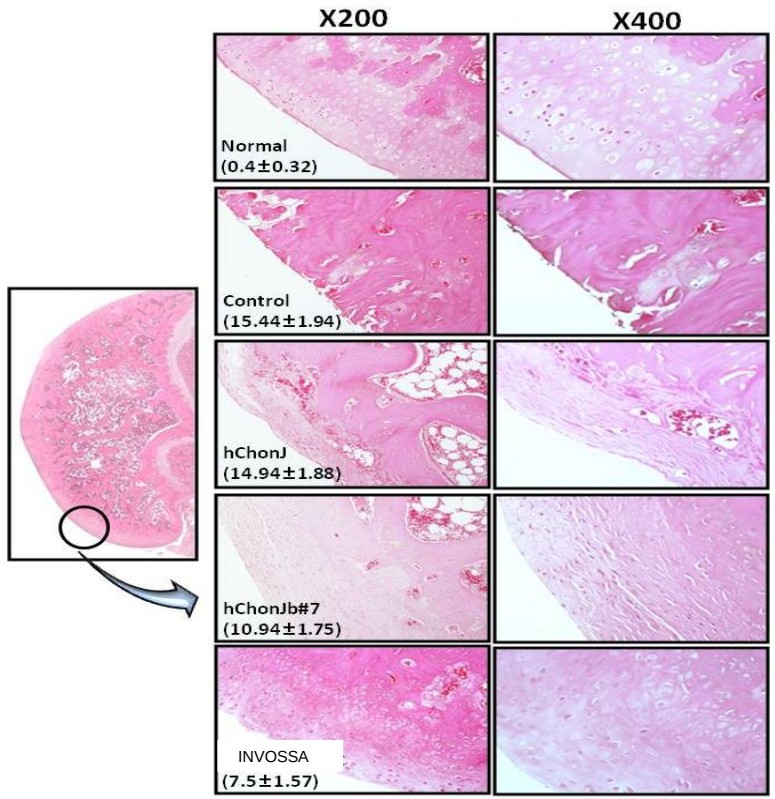
von Frey Filament test



Mean±S.E.M. *P<0.05 (n=6)

Control, CS-10; hChonJ, 9.0x10^5; hChonJb#7, 3.0x10^5;
INVOSSA®, 1.2x10^6

H&E Staining

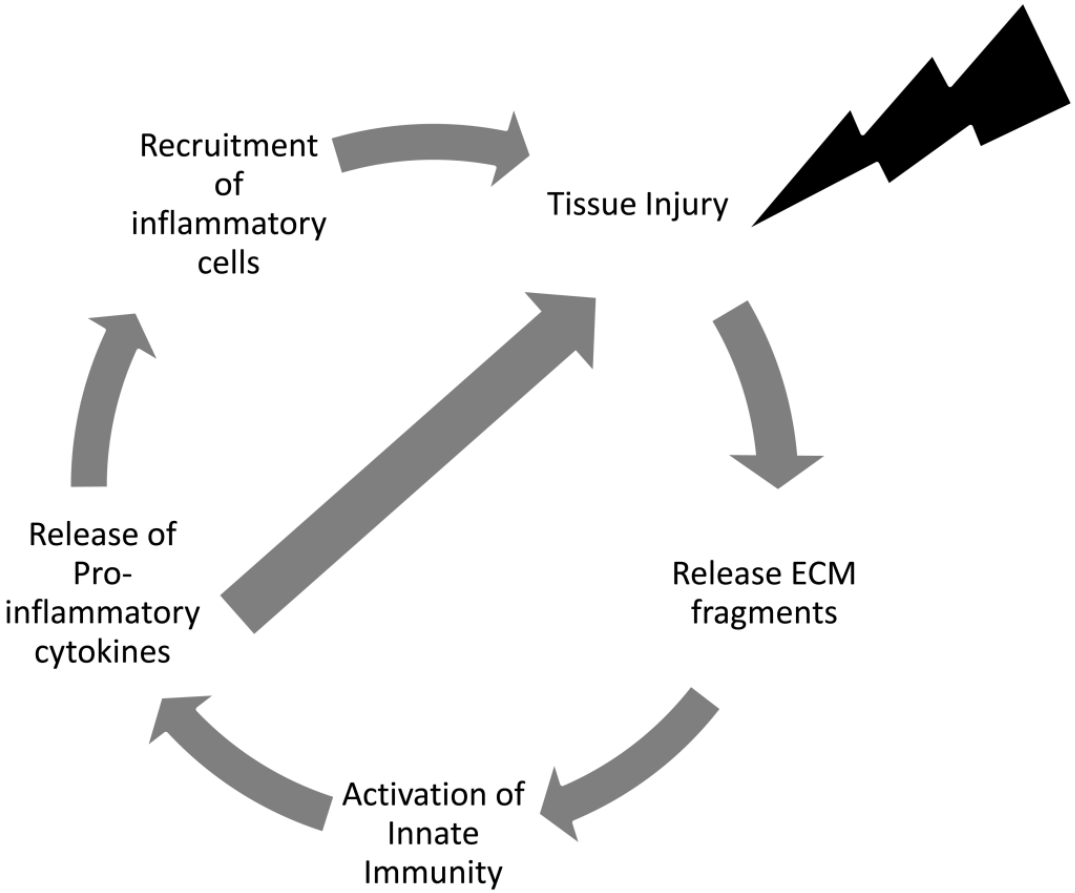


Harvested at day 56 post treatment

[1] MIA (Monosodium iodoacetate)

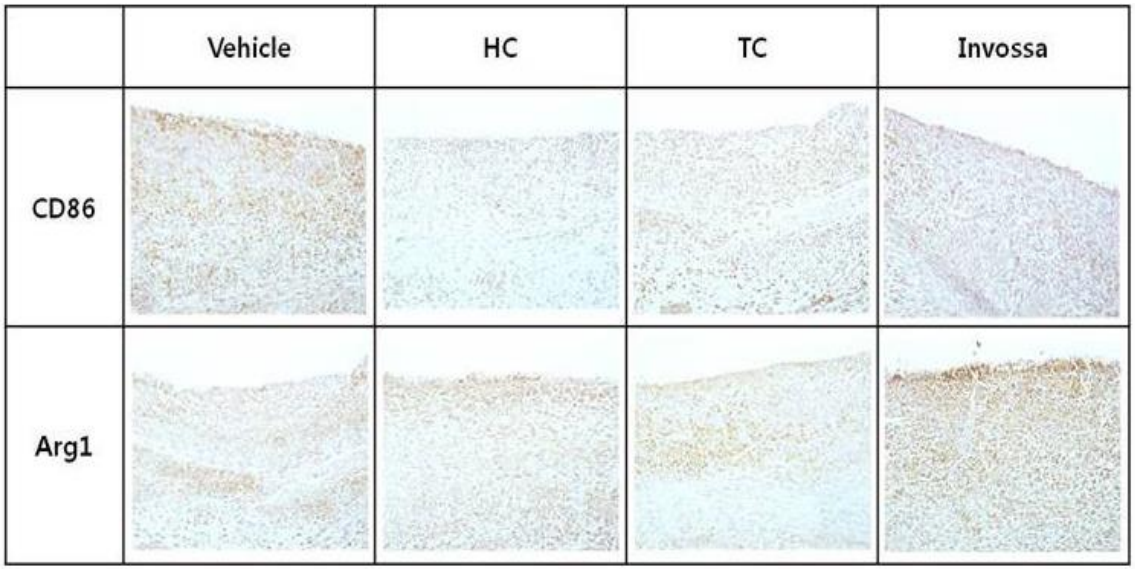
작용 기전은?

- **관절 내 염증 반응에 주목**
- **골관절염 진행에 면역반응이 중요한 역할**



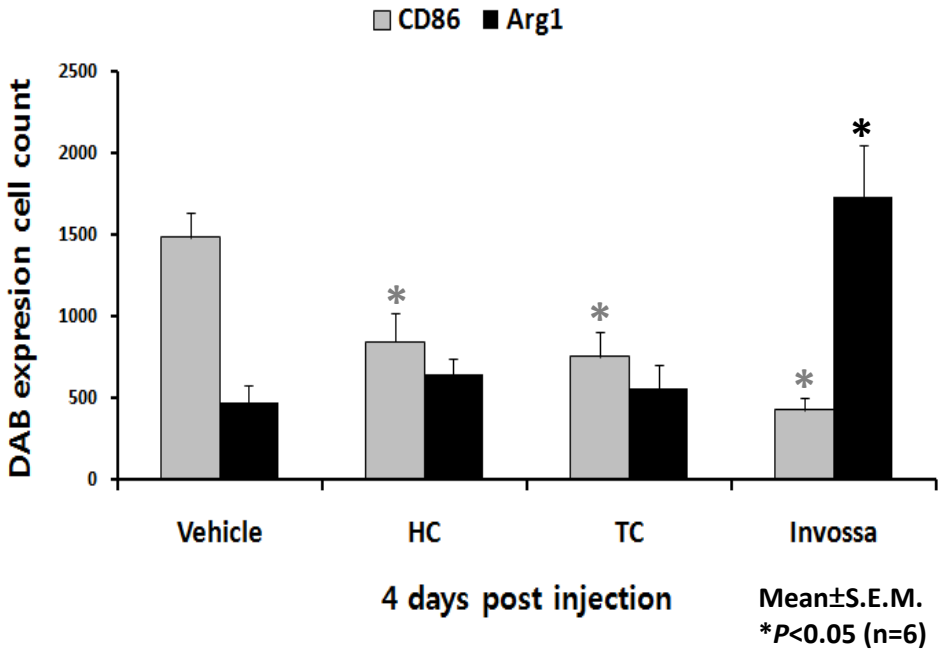
M2 Macrophage 유도

Immunohistochemistry (CD86/Arg1)



Synovial membrane, harvested at day 4 following treatment X200

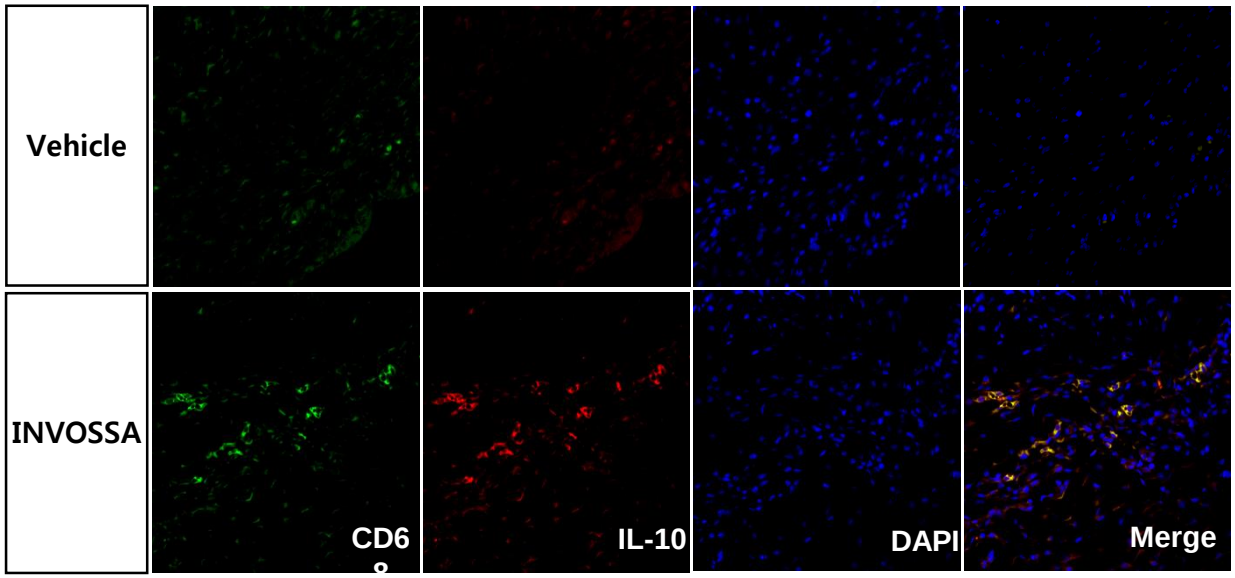
Macrophage polarization



Mean±S.E.M.
*P<0.05 (n=6)

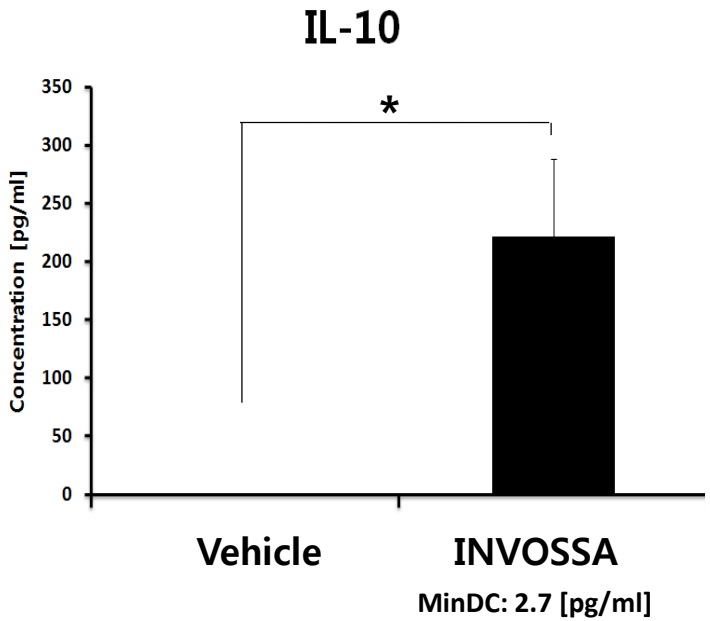
IL-10 분비 증가

Dual Immunofluorescence(CD68/IL-10)

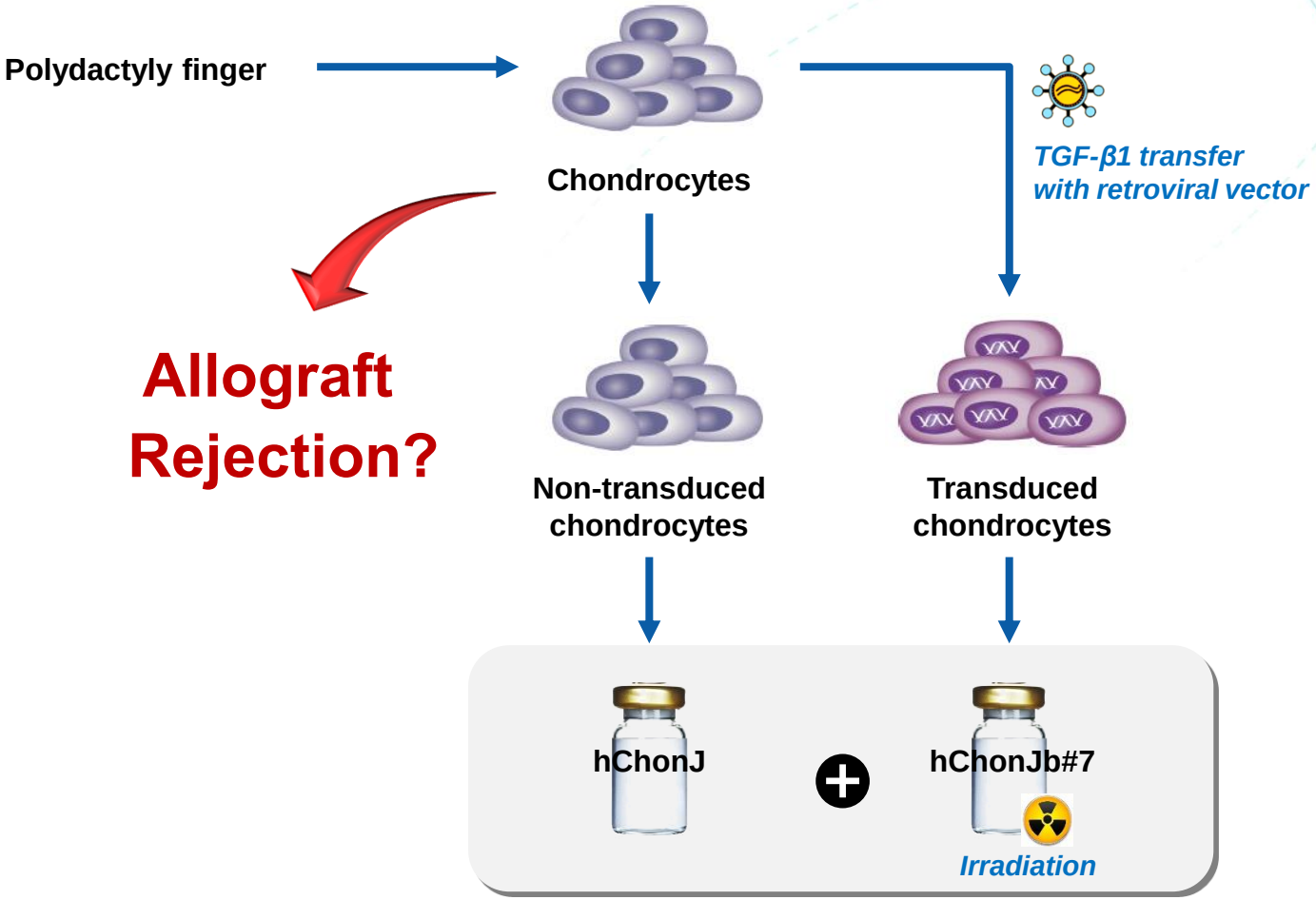


Synovial membrane, harvested at day 4 following treatment X400

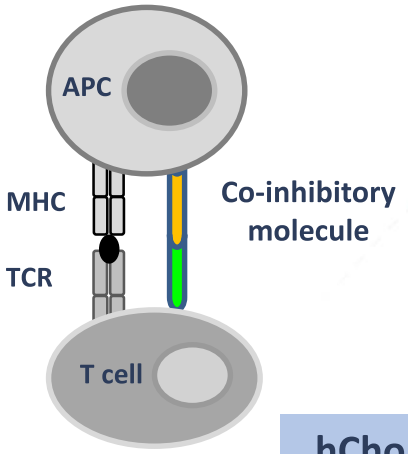
Multiplex Cytokine assay



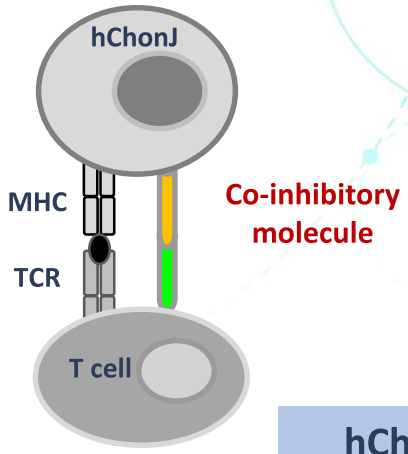
인보사의 면역원성


Polydactyly finger
Chondrocytes
TGF-β1 transfer
with retroviral vector
Allograft
Rejection?
Non-transduced
chondrocytes
Transduced
chondrocytes
hChonJ
hChonJb#7
Irradiation

hChonJ Expressing T Cell Co-Inhibitory Molecules



VS.



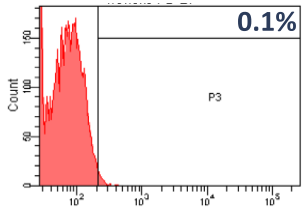
hChonJ (Resting)

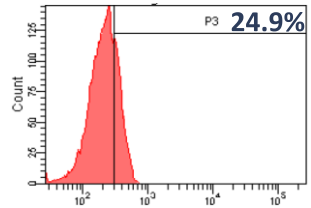
hChonJ (Stimulated)

hChonJ

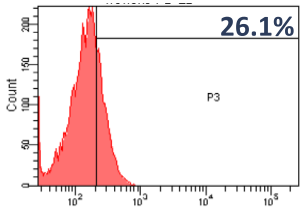
IFN-r treated hChonJ

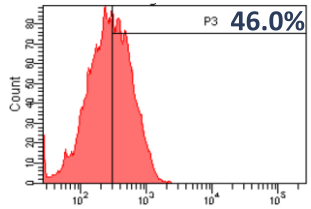
PD-L1





PD-L2

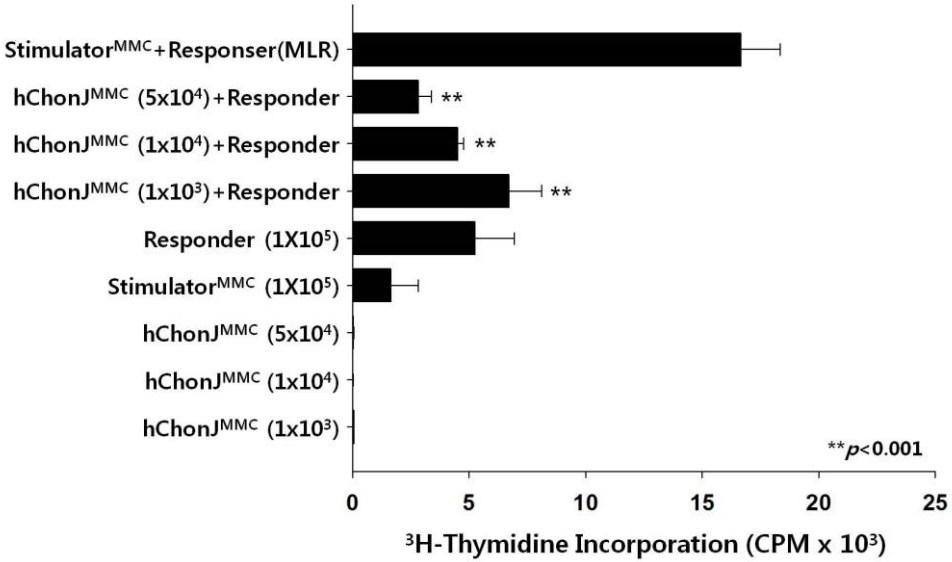




hChonJ Not Stimulating, but Inhibiting MLR

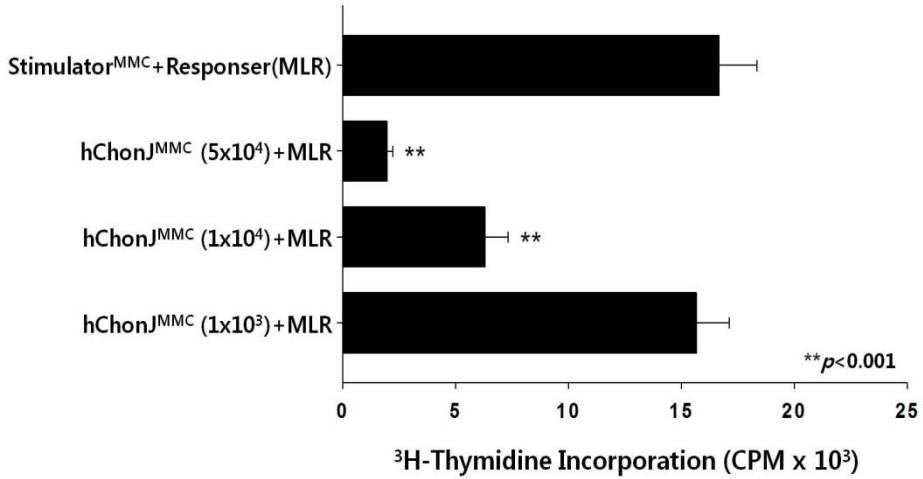
Mixed Lymphocyte Reaction Assay

No stimulation of Immune Reaction



**p<0.001 vs. the MLR group.

Inhibition of Immune Reaction

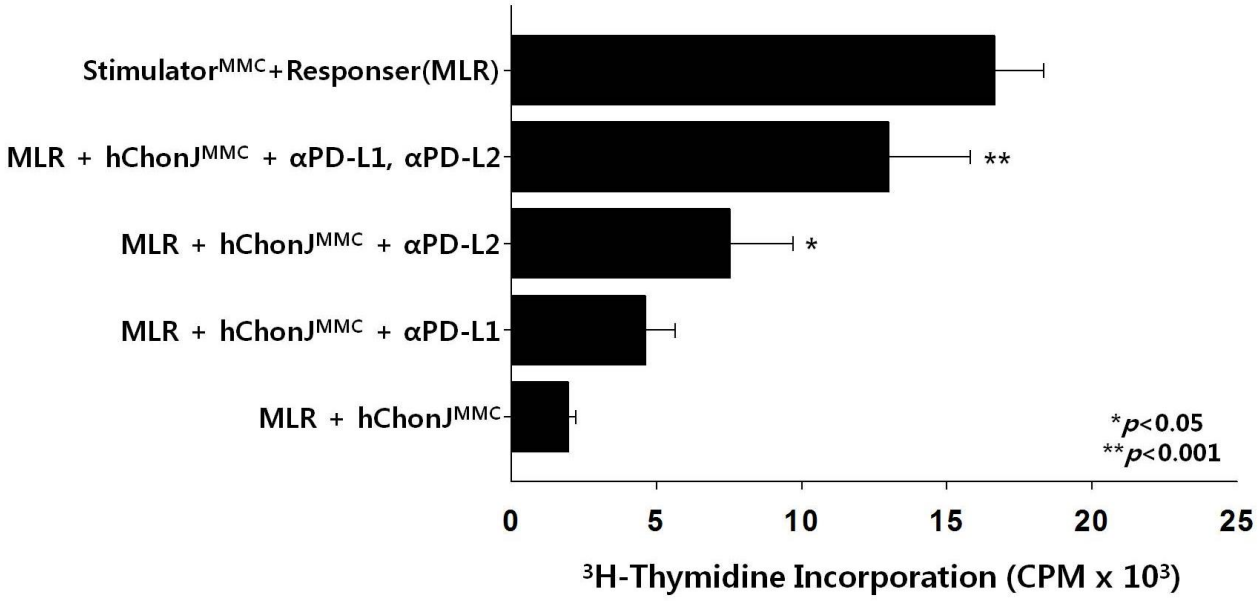


**p<0.001 vs. the MLR group.

1 MMC(Mitomycin): Inhibit proliferation of cell

hChonJ Suppressing Immune Response through PD-L1 & PD-L2

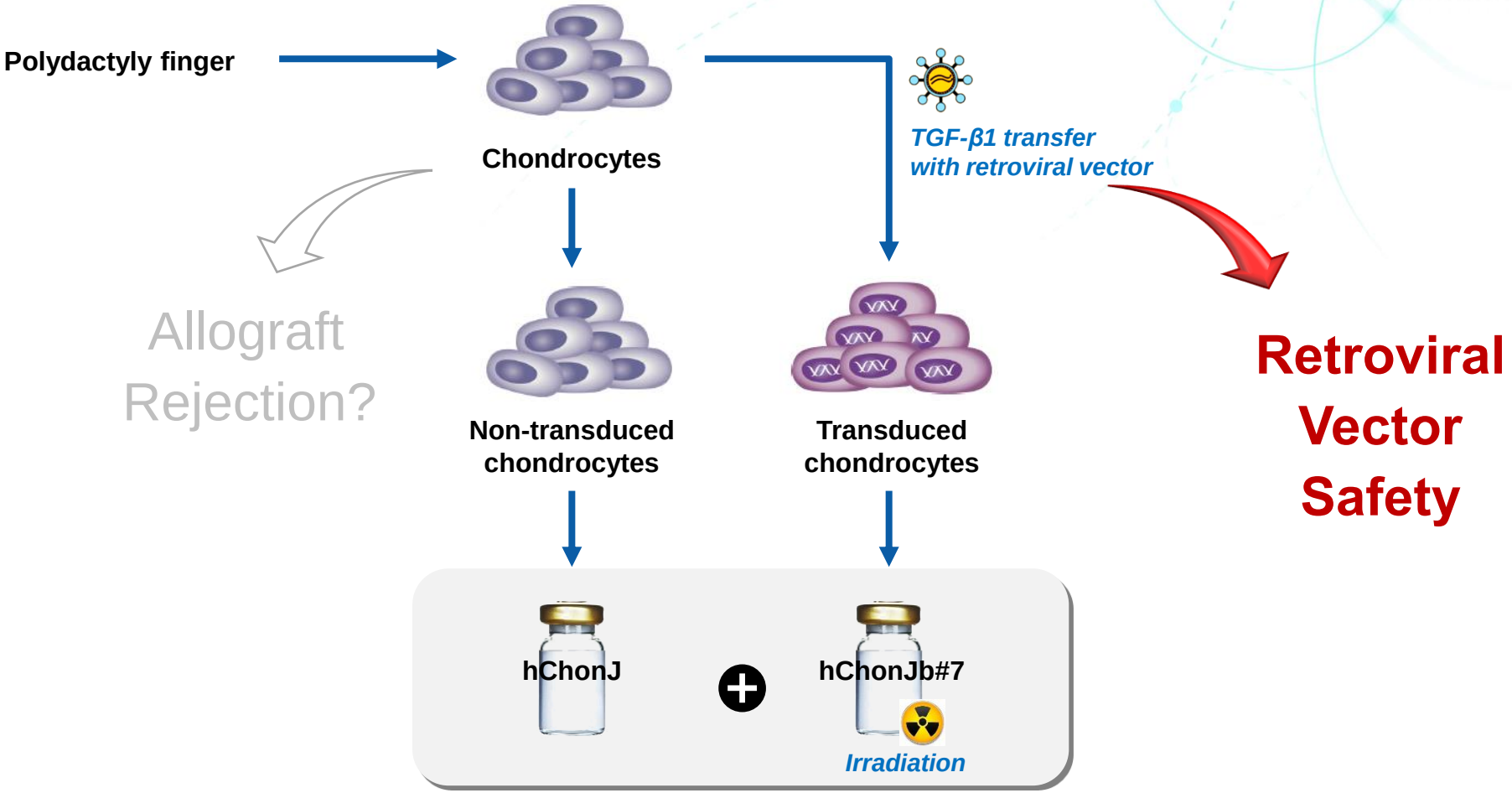
Mixed Lymphocyte Reaction Assay with antibodies against PD-L1 & PD-L2



*p<0.05 and **p<0.001 vs. the MLR + hChonJ^{MMC} group

1 MMC(Mitomycin): Inhibit proliferation of cell

Retroviral Vector Safety of Invossa



Retroviral Vector Safety of Invossa

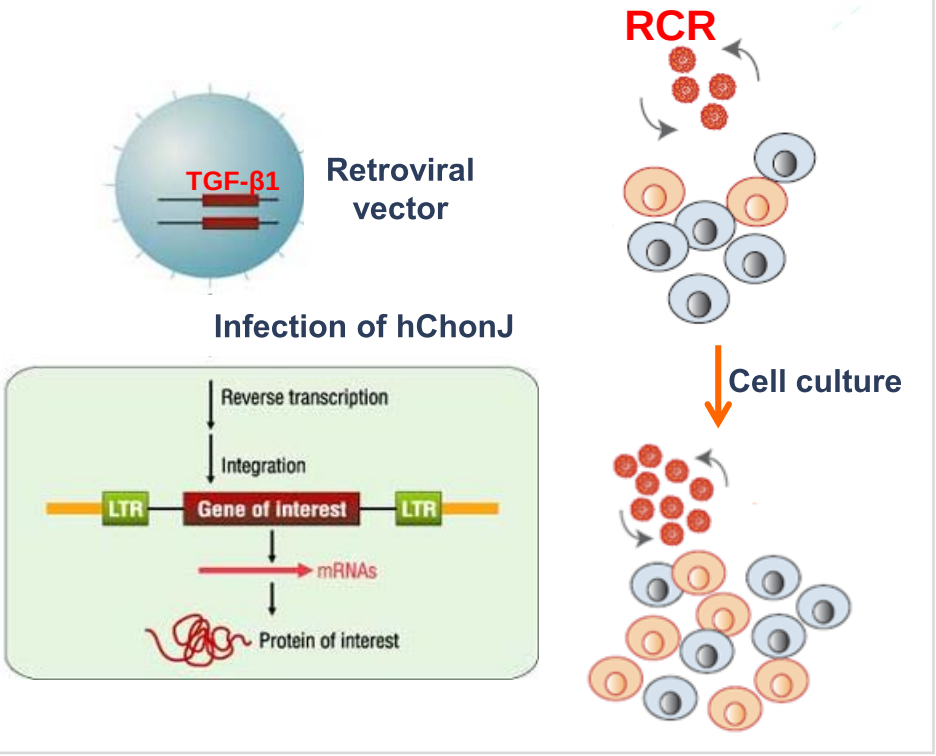
1.Replication competent retrovirus (RCR) test

2. Insertion site analysis of integrated DNA

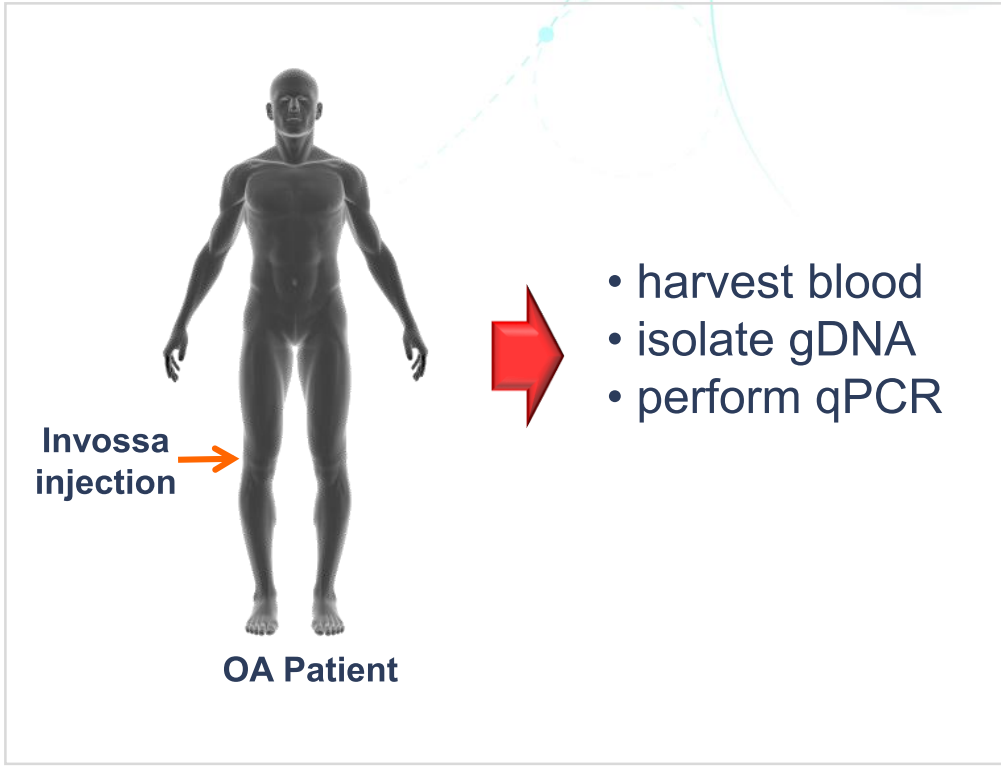
3. Irradiation

No RCR Detected

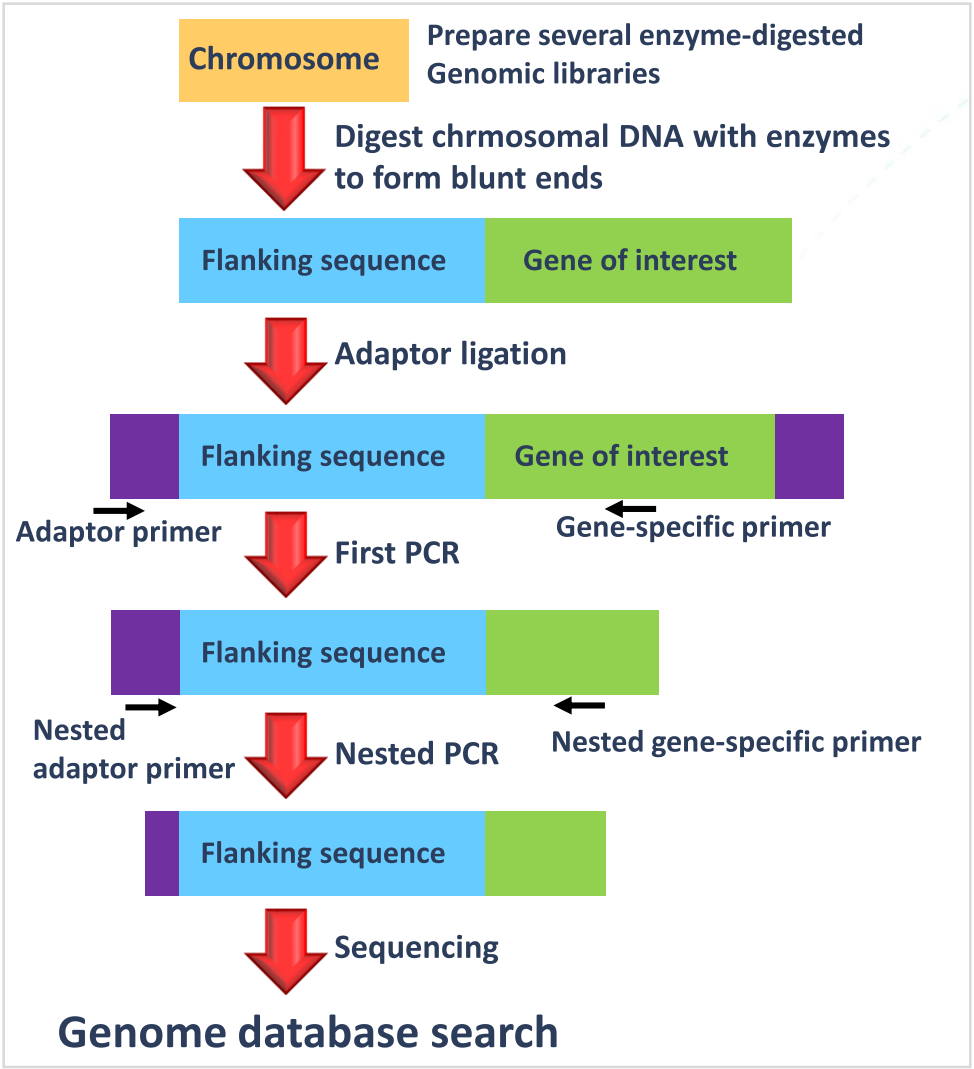
Post Cell Production



Post Patient Dosing



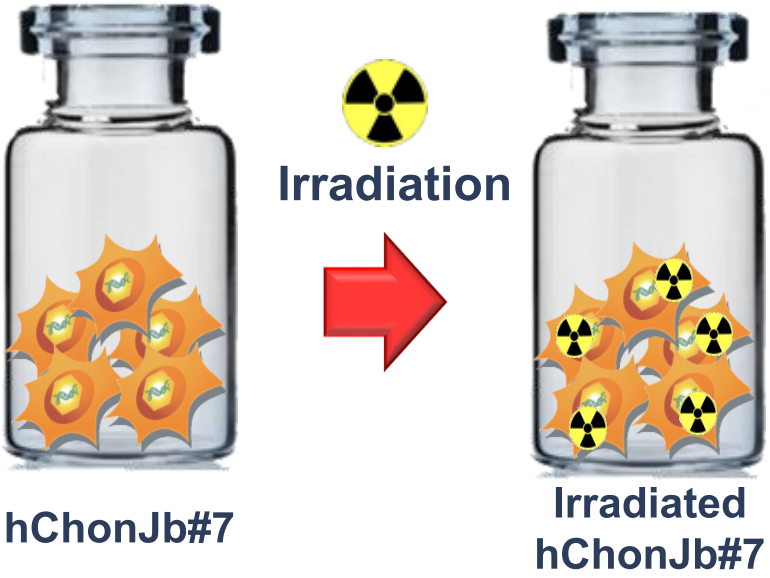
No oncogenes Near All Integration Sites

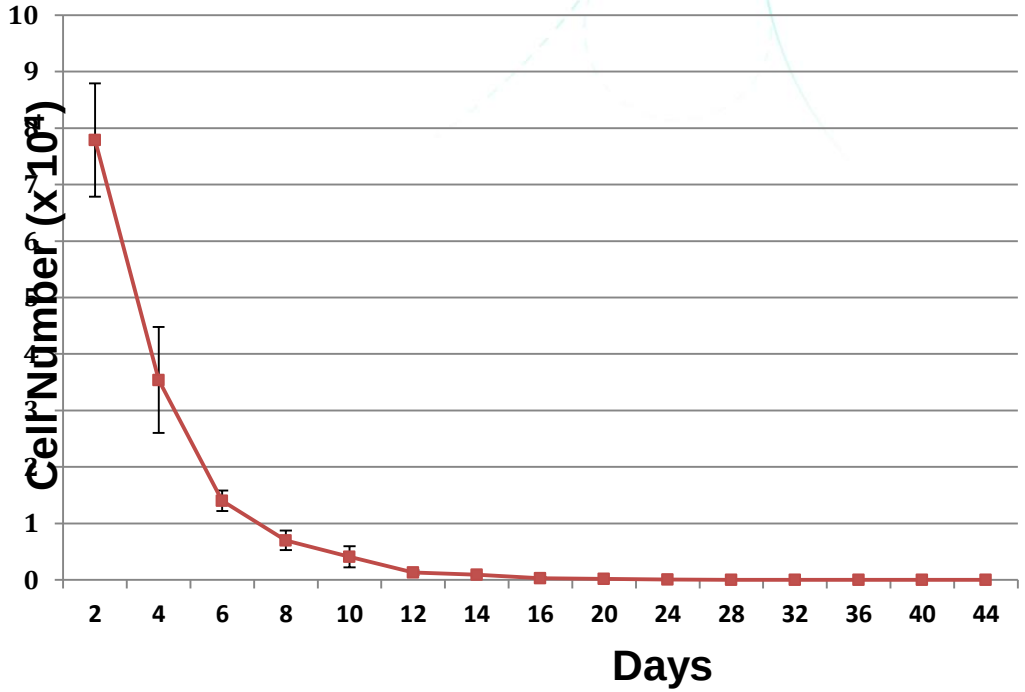


No	Insertion Chr. (Accession no.)	Insertion site	Transcriptional change
1	X Chromosome (L78810)	• ADP/ATP carrier protein(ANT-2)	No
2	Chromosome 12 (AC012085)	• Suppressor of cytokine signaling2 (SOCS2)	Up regulation
3	Chromosome 3 (AC117515)	• Similar to Roundabout homologus 2(RH2)	N/A
4	Chromosome 20 (AL035652)	• 2nd intron of the Topoisomerase I (TOP1)	No
5	Chromosome 1 (AL954711)	• profilin 1(PFN1) pseudogene • peptidylprolyly isomerase A(PPIA) pseudogene	N/A N/A
6	Chromosome 10 (AL356608)	• 1st intron of Cyclin M2(CNNM2)	No
7	X Chromosome (AC002349)	• putative transcription factor XPRF	N/A No
8	Chromosome 2 (AC012595)	• non-coding sequence	N/A
9	Chromosome 9 (AL162733)	• Last intron of Protein tyrosine phosphatase, non-receptor type 3(PTPN3)	No
10	Chromosome 16 (AC009065)	• RNA binding protein S(RNPS1) • DC1 • Hypothetical protein (LOC388204)	No No N/A
11	Chromosome 10 (AL157892)	• non-coding sequence	N/A
12	Chromosome 1 (AL590422)	• 2nd intron of RGL1 (Ral ganine nucleotide dissociation)	No
13	Chromosome 16 (AC135050)	• hypothetical protein(FLJ13479) • zinc finger protein(KIAA0296) • vitamin K epoxide reductase(VKORC1) • brandched chain alpha-ketoacid dehydrogenase(BCKDK) • syntaxin 4A placental(STX4A)	N/A N/A No No No
14	Chromosome 18 (AP005210)	• hypothetical protein	N/A

Irradiation Ensuring Proliferation Incompetent

< 2 weeks survival after irradiation





임상시험

- 한국 3상
- 미국 2상

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한국 임상3상

Study design

위약 대조, 이중 눈가림, 무작위배정, 다기관 공동 제 3상 임상 시험

<table>
<tr><td>목적</td><td colspan="3">대조군 대비 안전성 및 유효성 평가</td></tr>
<tr><td>대상자 선정 기준</td><td colspan="3">무릎 퇴행성관절염 환자, K&L Grade 3, ICRS Grade 3 or 4, 병변 크기 6cm^2 이하
<table>
<tr><th>그룹</th><th>시험약</th><th>대상자 수</th></tr>
<tr><td>시험군</td><td>INVOSSA™ (1.8 x 10^7 cells/knee, 3.0mL)</td><td>78</td></tr>
<tr><td>대조군</td><td>Placebo (Normal Saline, 3.0mL)</td><td>78</td></tr>
</table></td></tr>
<tr><td>투여/관찰기간</td><td colspan="3">무릎 관절강 내 1회 투여
투여 후 12개월 관찰</td></tr>
<tr><td>평가 변수</td><td colspan="3">1차 : IKDC, VAS
2차 : WOMAC, KOOS, X-Ray (Joint Space Width), MRI</td></tr>
<tr><td>시험 참여 기관</td><td colspan="3">서울대병원, 서울아산병원, 삼성서울병원, 인하대병원, 울산대병원, 경북대병원, 이화여대 목동병원, 전북대병원, 한양대병원, 서울성모병원, 충북대병원, 인제대 백병원</td></tr>
</table>

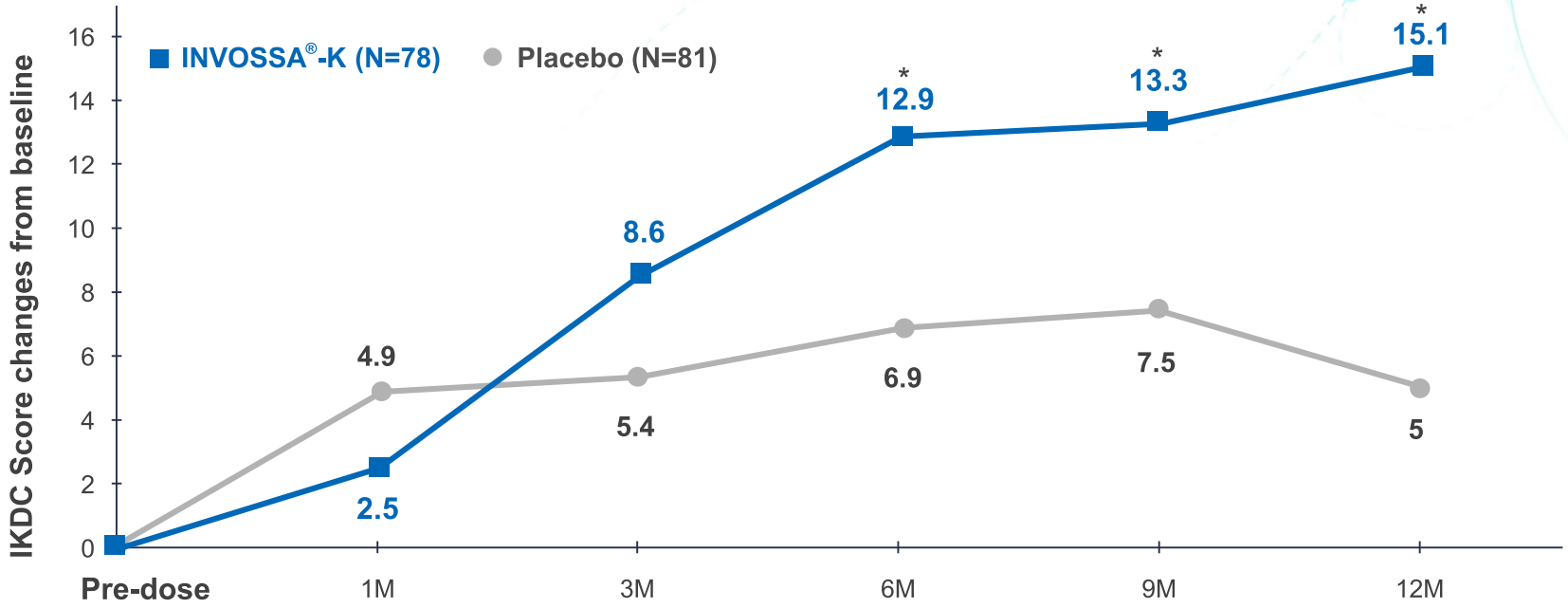
Patients Population

두 군간 유의한 차이 없음

Parameter	Statistic	INVOSSA®-K (N=78) N (%)	Placebo (N=81) N (%)	Total (N=159) N (%)	*P* -value
Gender	Male	18 (23.1)	11 (13.6)	29 (18.2)	0.1211
	Female	60 (76.9)	70 (86.4)	130 (81.8)	
Age (year)	Mean (range)	61.6 (31-79)	61.5 (44-77)	61.5 (31-79)	0.6117
	30~40	1 (1.3)	0 (0.00)	1 (0.63)	0.2801
	40~50	5 (6.4)	4 (4.9)	9 (5.7)	
	50~60	20 (25.7)	30 (37.0)	50 (31.5)	
	60~70	42 (53.9)	33 (40.7)	75 (47.2)	
	70~80	10 (12.8)	14 (17.3)	24 (15.1)	
Body Mass Index (kg/m^2)	Mean (range)	25.4 (19.8-29.9)	25.7 (21.0-29.9)	25.6 (19.8-30.0)	0.4694
Lesion	Left knee	42 (55.1)	39 (48.2)	82 (51.6)	0.3786
	Right knee	35 (44.9)	42 (51.9)	23 (48.4)	
Disease duration (year)		5.7	5	5.3	0.5485

골관절염 증상 개선

+ 12개월까지 IKDC score 개선



[Baseline] INVOSSA®-K : 40.3 / Placebo : 39.6

Statistical Analysis (within group): paired *t*-test (*ITT Population*)

*Between treatment group: two-sample *t*-test, *p*-value<0.05;

IKDC (International Knee Documentation Committee): Symptom, sports activity and function

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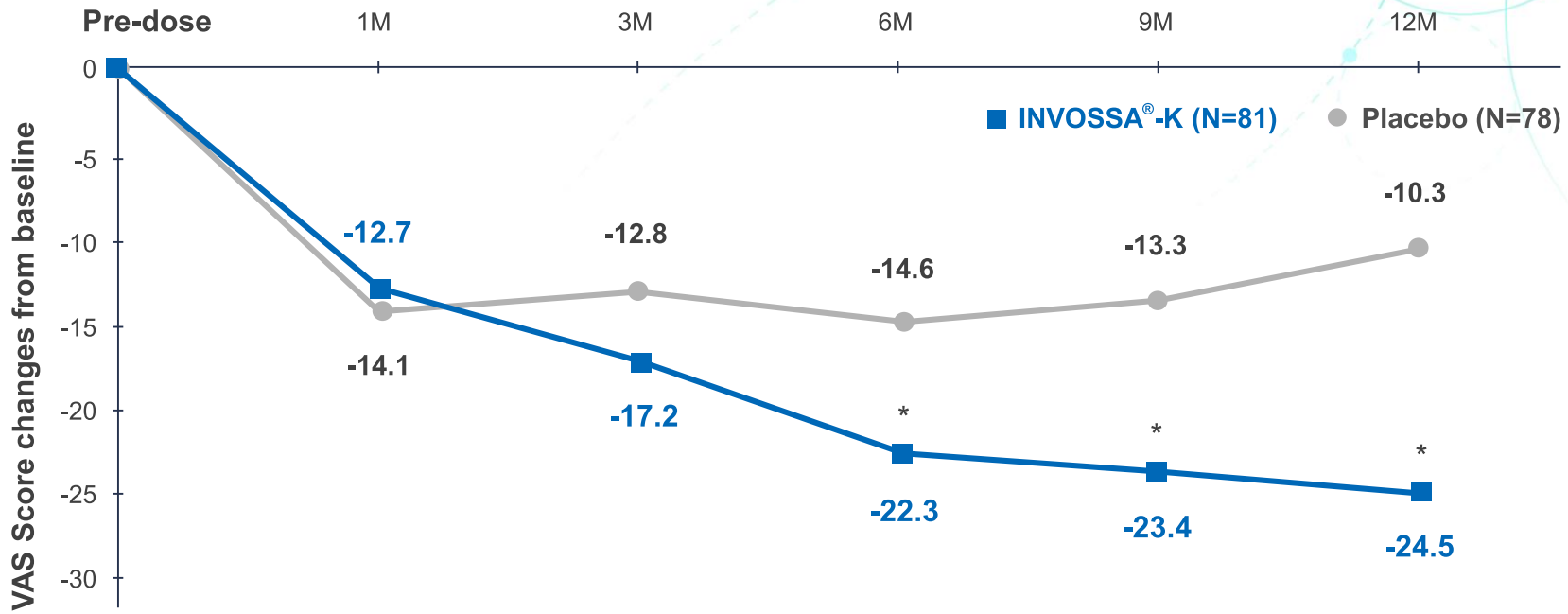
통증 완화

+ 12개월까지 VAS 개선



[Baseline] INVOSSA® -K : 60.0 / Placebo : 62.3

Statistical Analysis (within group): paired *t*-test (*ITT Population*)
*Between treatment group: two-sample *t*-test, *p*-value<0.05;
100mm VAS (Visual Analogue Scale): 0 being no pain and 100 being intolerable pain

163명의 퇴행성 무릎 골관절염 환자를 대상으로 인보사®-케이와 위약을 1회 투여 후 12개월 추적 관찰한 (한국) 제3상 임상시험

1) Jung Jong Cho, INVOSSA®-K (TissueGene-C) in patients with osteoarthritis: A phase III trial. OARSI 2016 World congress; Poster No. 322
2) Data on file. 퇴행성관절염 환자를 대상으로 세포매개성 유전자치료제인 '티슈진-C'의 유효성 및 안전성 평가를 위한 위약대조, 양측눈가림, 무작위배정, 평행군, 다기관 공동 제3상 임상시험. Protocol No. KS-TGC-01-3. CSR v1.0. 2016

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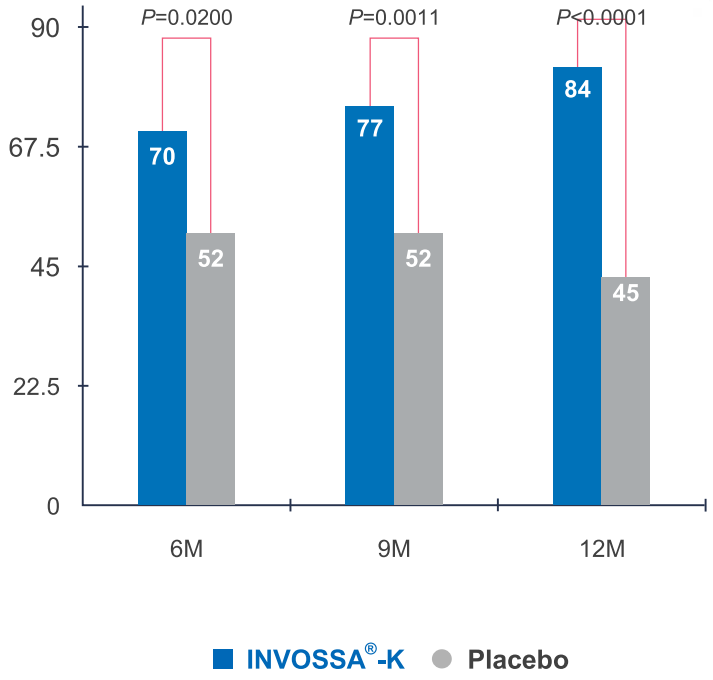
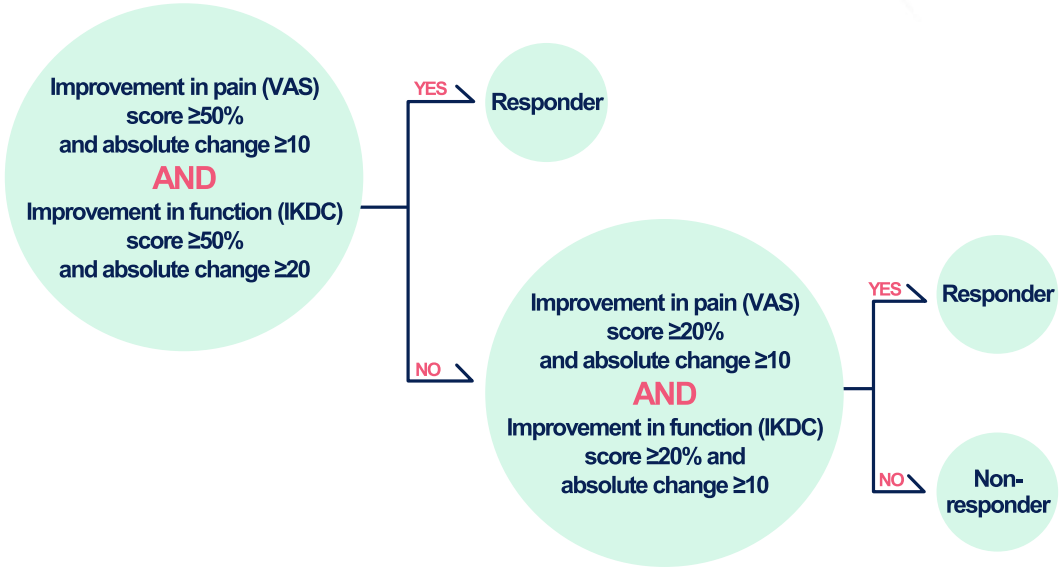
높은 반응률

+ 12개월차 반응률 84%

Response Rate (%)



OMERACT-OARSI responder criteria[1]



*OMERACT-OARSI response rate

1. Jung Jong Cho, INVOSSA (TissueGene-C) in patients with osteoarthritis: A phase III trial. OARSI 2016 World congress; Poster No. 322 퇴행성관절염 환자를 대상으로 세포매개성 유전자치료제인 '티슈진-C'의 유효성 및 안전성 평가를 위한 위약대조, 양측눈가림, 무작위배정, 평행군, 다기관 공동 제3상 임상시험.

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안전성

대부분 투여 부위 국소 반응

body system / preferred term	INVOSSA®-K (N=78)	Placebo (N=81)
	N (%)	N (%)
Total	27 (34.6)	10 (12.4)
General disorders and administration site conditions	15 (19.2)	2 (2.5)
Musculoskeletal and connective tissue disorders[1)]	7 (9.0)	6 (7.4)
Arthralgia	3 (3.9)	2 (2.5)
Joint Stiffness	1 (1.3)	1 (1.2)
Joint Swelling	5 (6.4)	3 (3.7)
Muscle Tightness	1 (1.3)	0
Spondylolisthesis	0	1 (1.2)
Skin and subcutaneous tissue disorders	3 (3.9)	0 (0.0)
Renal and urinary disorders (Hypertensive Nephropathy, etc.)	1 (1.3)	1 (1.2)
Gastrointestinal disorders (Diarrhea)	1 (1.3)	1 (1.2)
Infections and infestations (Cystitis, Tonsillitis)	1 (1.3)	1 (1.2)
Metabolism and nutrition disorders (Diabetes Mellitus, Hyperlipidaemia)	2 (2.6)	0 (0.0)
Nervous system disorders (Facial Spasm)	0 (0.0)	1 (1.23)

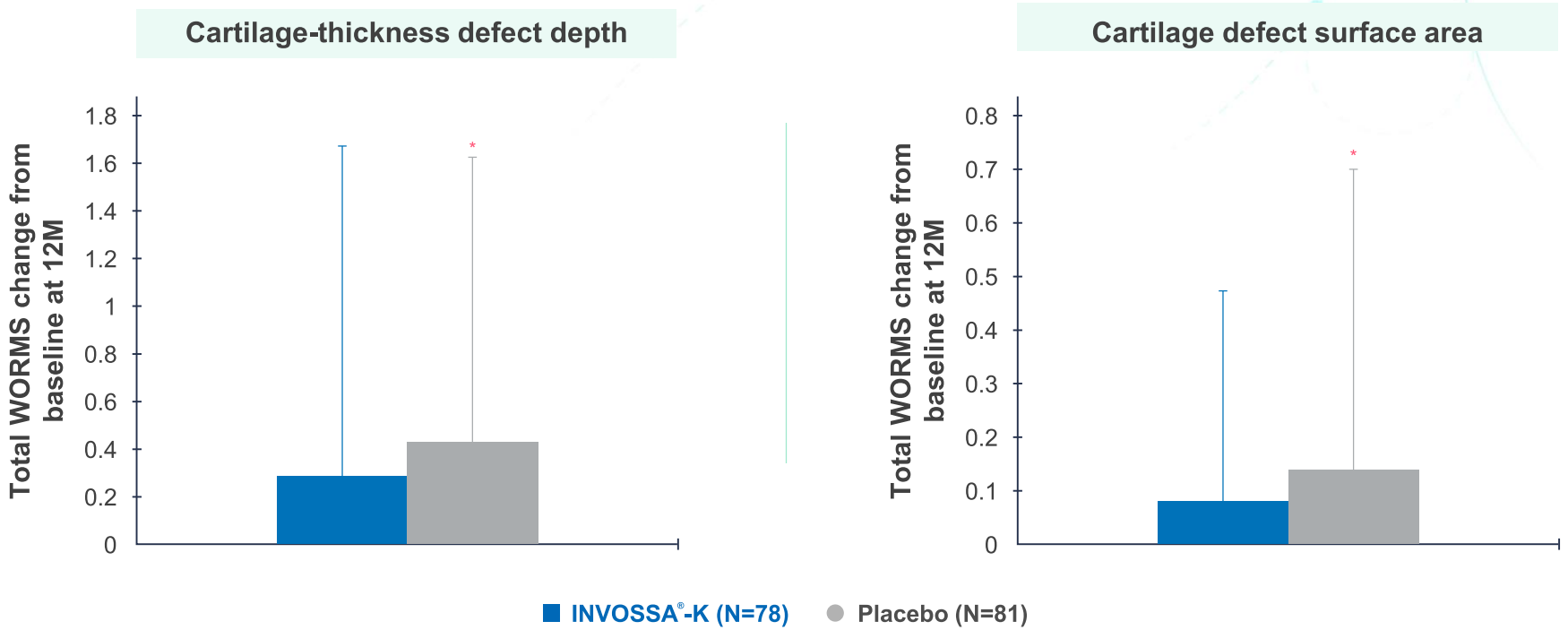
Biomarker 분석

Measurements	Evaluation	CRO
X-ray (SynaFlexer™)	Joint Space Width	Bioclinica(Synarc) (USA)
MRI (3T)	WORMS[1)] Quantitative	Qmetrics (USA) Imorphics (UK)
ELISA	Liquid biomarkers (Serum and urine)	Nordic Bioscience (Denmark)

1 Whole-Organ Magnetic Resonance Imaging Score

Cartilage defect changes in WORMS

+ 인보사 투여군에서는 투여 전 후 Cartilage defect score의 차이가 없음
+ 대조군에서는 투여 전 대비 투여 후 total cartilage defect score가 유의하게 증가함

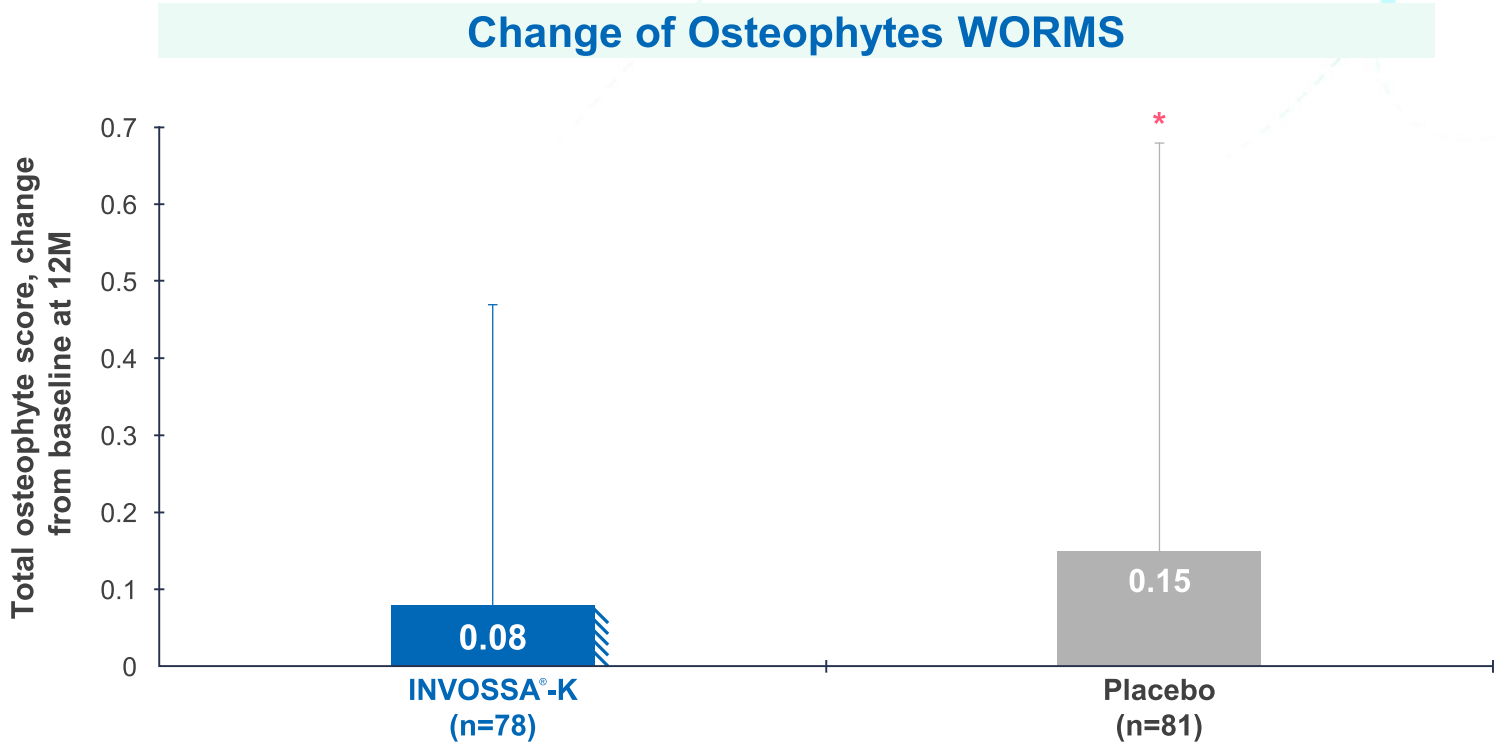


Total WORMS : [Medial(Tibia+WB Femur+Posterior condyle)] + [Trochlea+Patella], [Lateral(Tibia+WB Femur+Posterior condyle)]

Statistical analysis, Wilcoxon signed rank test, within group *$p < 0.05$
Cartilage-thickness defect depth WORMS: from 0 (normal) to 6 (worst possible score)
Cartilage defect surface area WORMS:from 0 (normal) to 5 (worst possible score)

Osteophyte change in WORMS

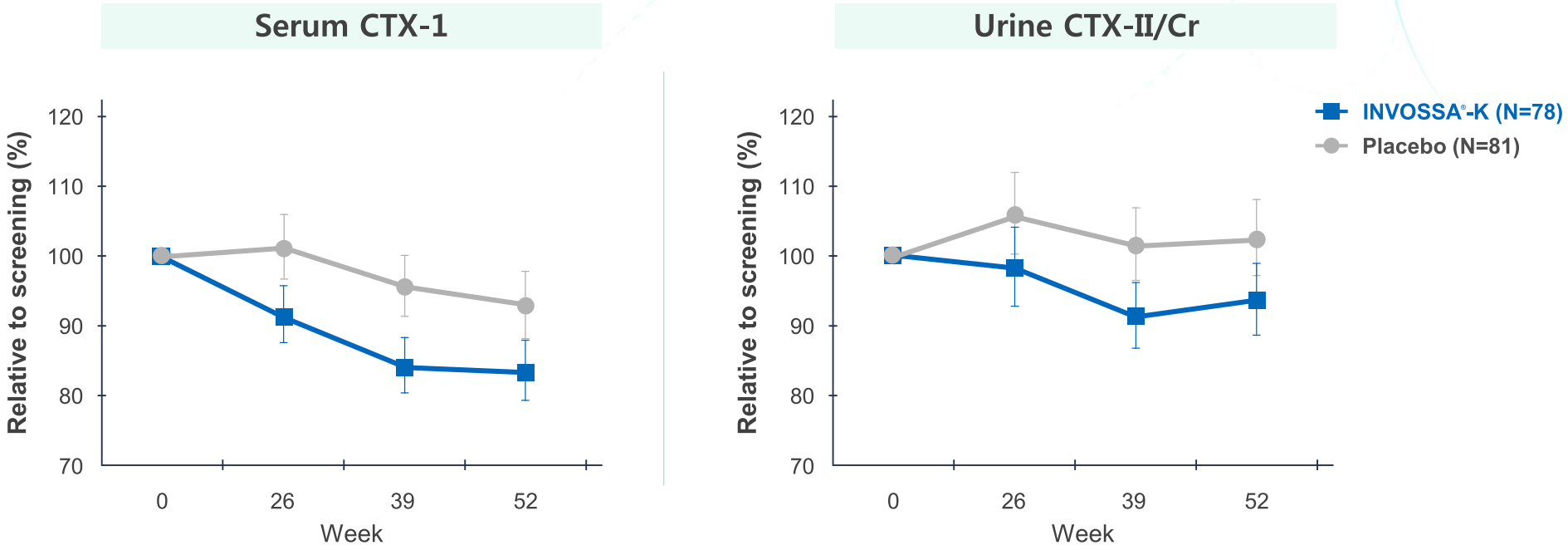
+ 인보사 투여군에서는 투여 전 후 Osteophyte score 차이가 없음
+ 대조군에서는 투여전 대비 투여 후 total osteophyte score가 유의하게 증가함



Statistical analysis, Wilcoxon signed rank test, $^{*}p < 0.05$
Osteophyte WORMS: from 0 (normal) to 4 (worst possible score)
* Osteophyte (total WORMS score) : [Medial (Tibia+WB Femur+Posterior condyle)] + [Trochlea+Patella], [Lateral (Tibia+WB Femur+Posterior condyle)]

Liquid biomarker 분석

+ serum CTX-I and urine CTX-II/Cr

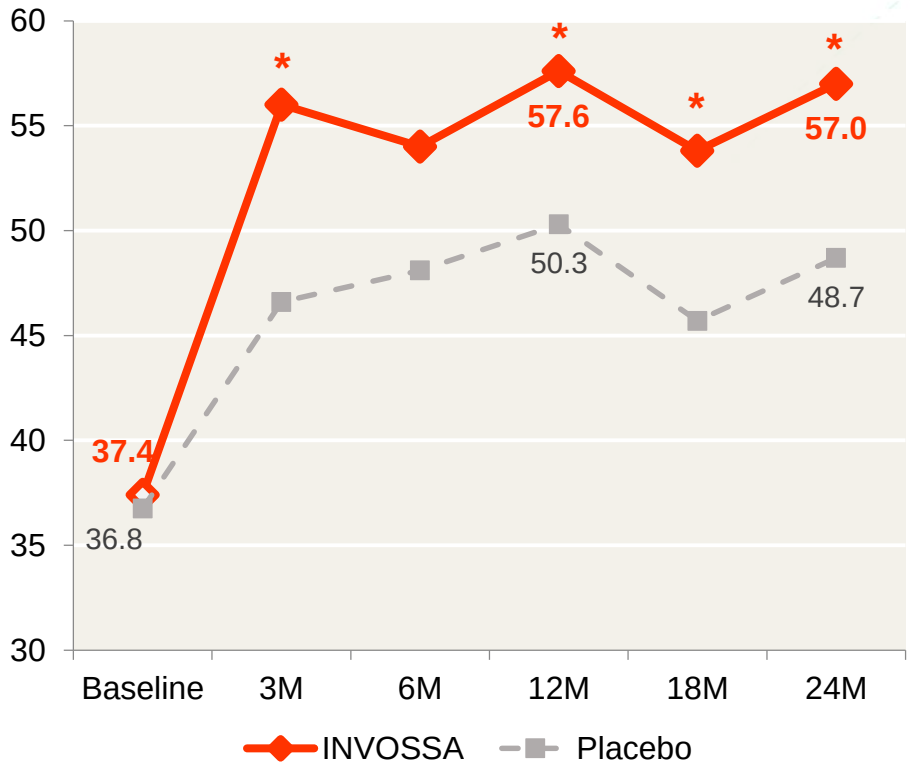


Assay and analysis performed at Nordic Bioscience Lab
CTX-I (C-terminal telopeptide of type I collagen): Serum biomarker of MMP-generated fragment released during bone degradation
CTX-II (C-terminal telopeptide of type II collagen): Urine biomarker of MMP-generated fragment released during cartilage degradation
CTX-II is reported as a normalized ratio to urinary creatinine in order to account for variations in urine flow rate
* Between treatment group *p* -value<0.05

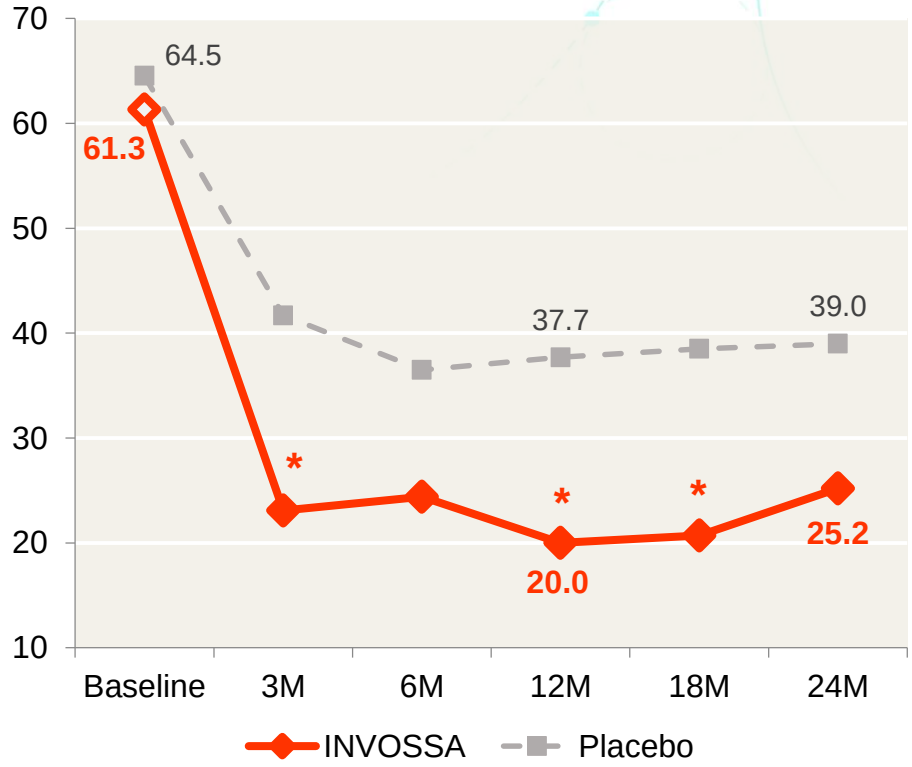
IKDC & VAS 개선

+ 24개월까지 IKDC & VAS 개선

IKDC[1] Score



VAS[2] Score



Statistical Analysis: Linear mixed model (ITT Population)

Between treatment group p-value<0.05; Within group p-value<0.05; Within group p-value>0.05

1 IKDC (International Knee Documentation Committee): Symptom, sports activity and function

2 VAS (Visual Analogue Scale): 0 being no pain and 100 being intolerable pain

시장 규모

환자 수

글로벌
1억5천만명

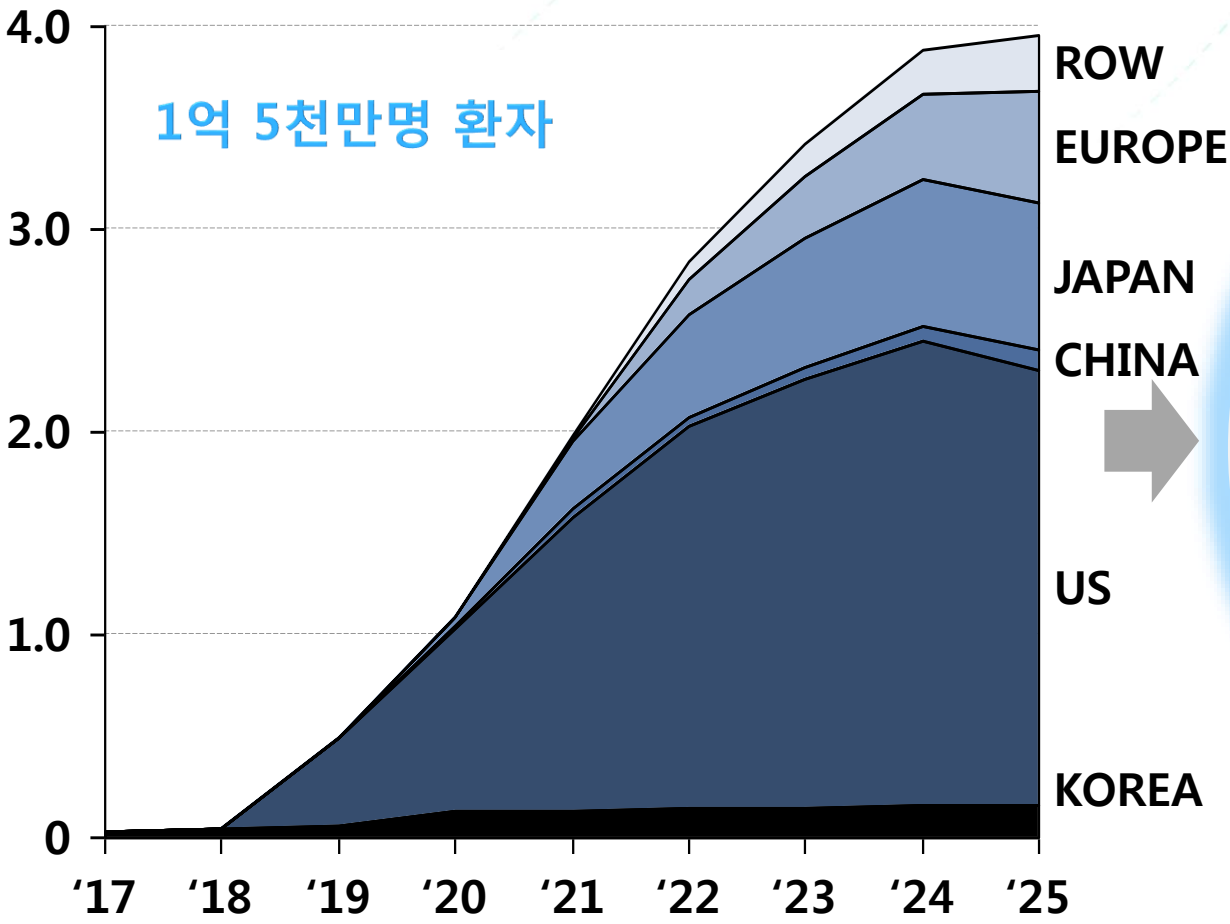
미국
2,700만명

국내
500만명

증가율: 13.5%

글로벌 예상 매출

(단위 : 조원)



INVOSSA
글로벌 매출
3.9조 원

INVOSSA
tonogenconcel

요약 및 결론

기존 약물에 반응하지 않지만 수술 받기 이른 환자들에게 새로운 치료옵션 제공

→ Treatment gap을 커버하며 질병 진행을 지연

단회 투여로 2년 이상 통증 완화 및 활동성 개선

기존 치료에 반응하지 않는 환자에게서 80% 이상의 반응률 확인

DMOAD 치료제로서의 가능성 제시

THANK YOU

KOLON

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