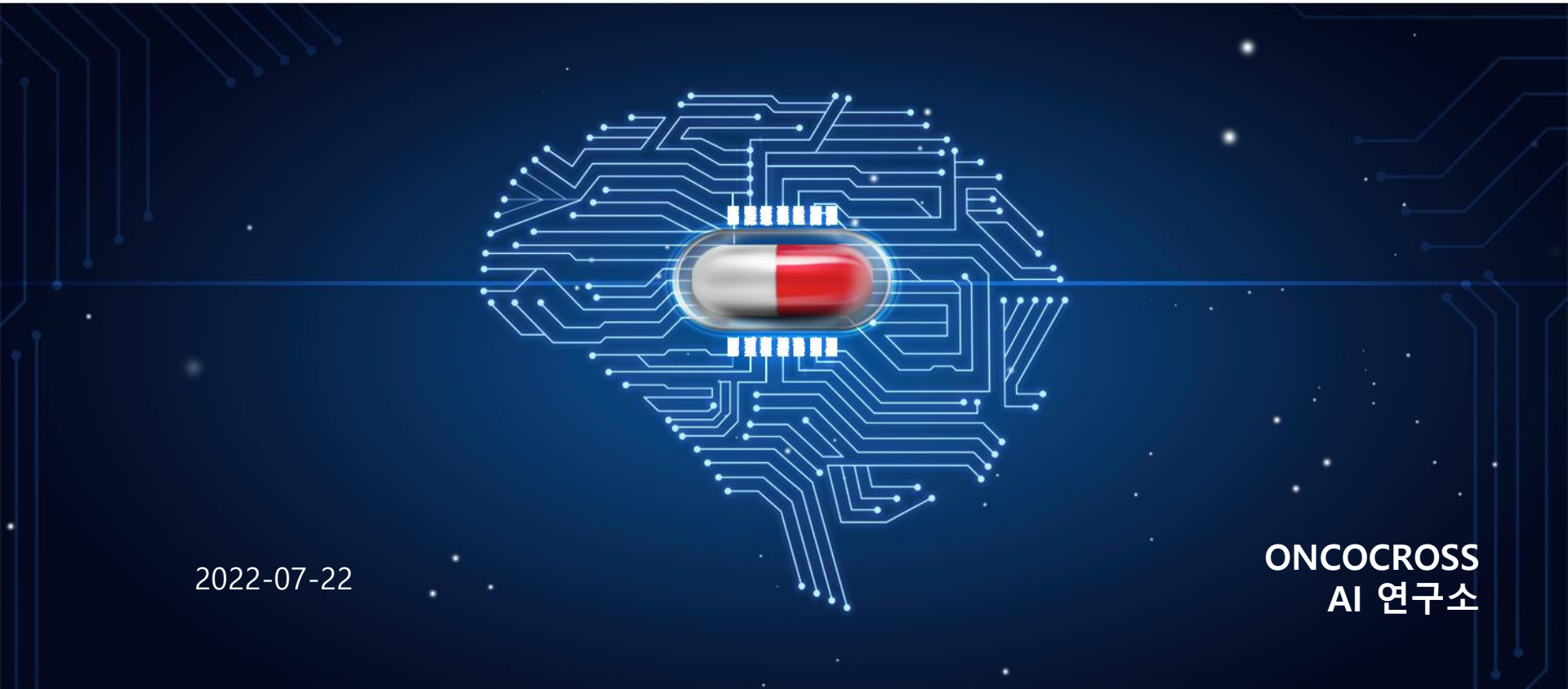
JW pharma [URC-102]

Indication screening Result



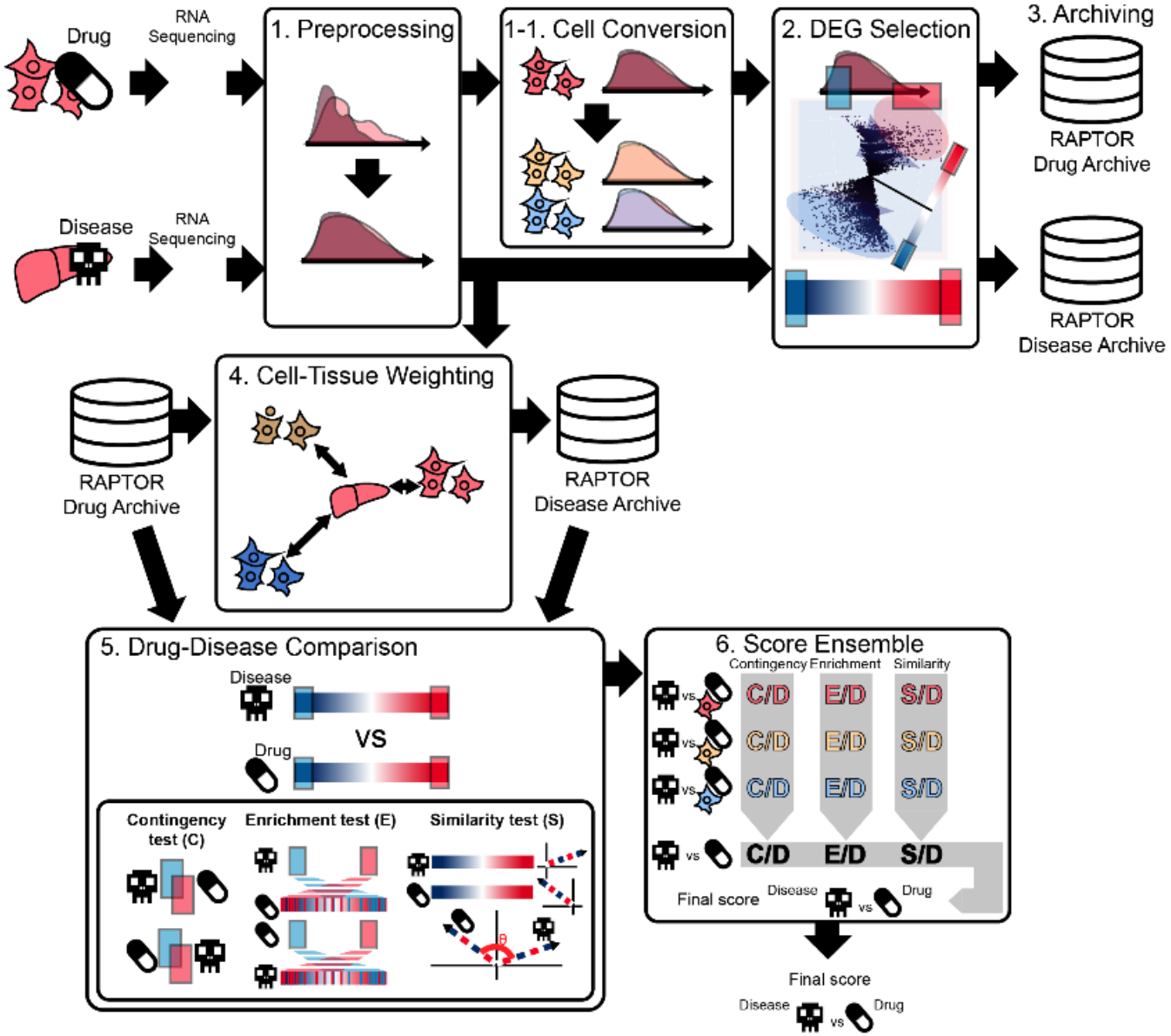
2022-07-22

ONCOCROSS
AI 연구소

Accelerate Drug Development with ONCOCROSS

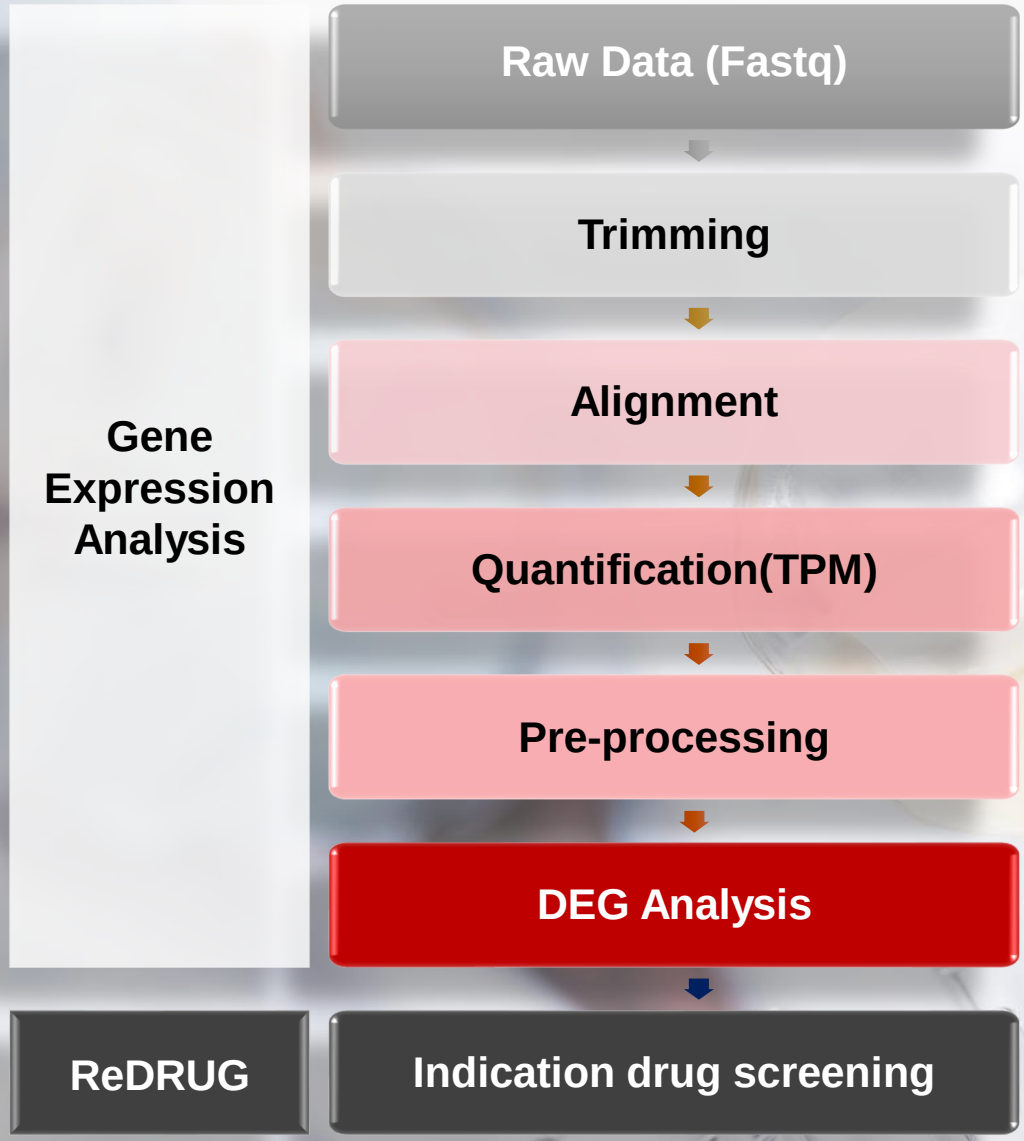
Contents

RAPTOR AI Process



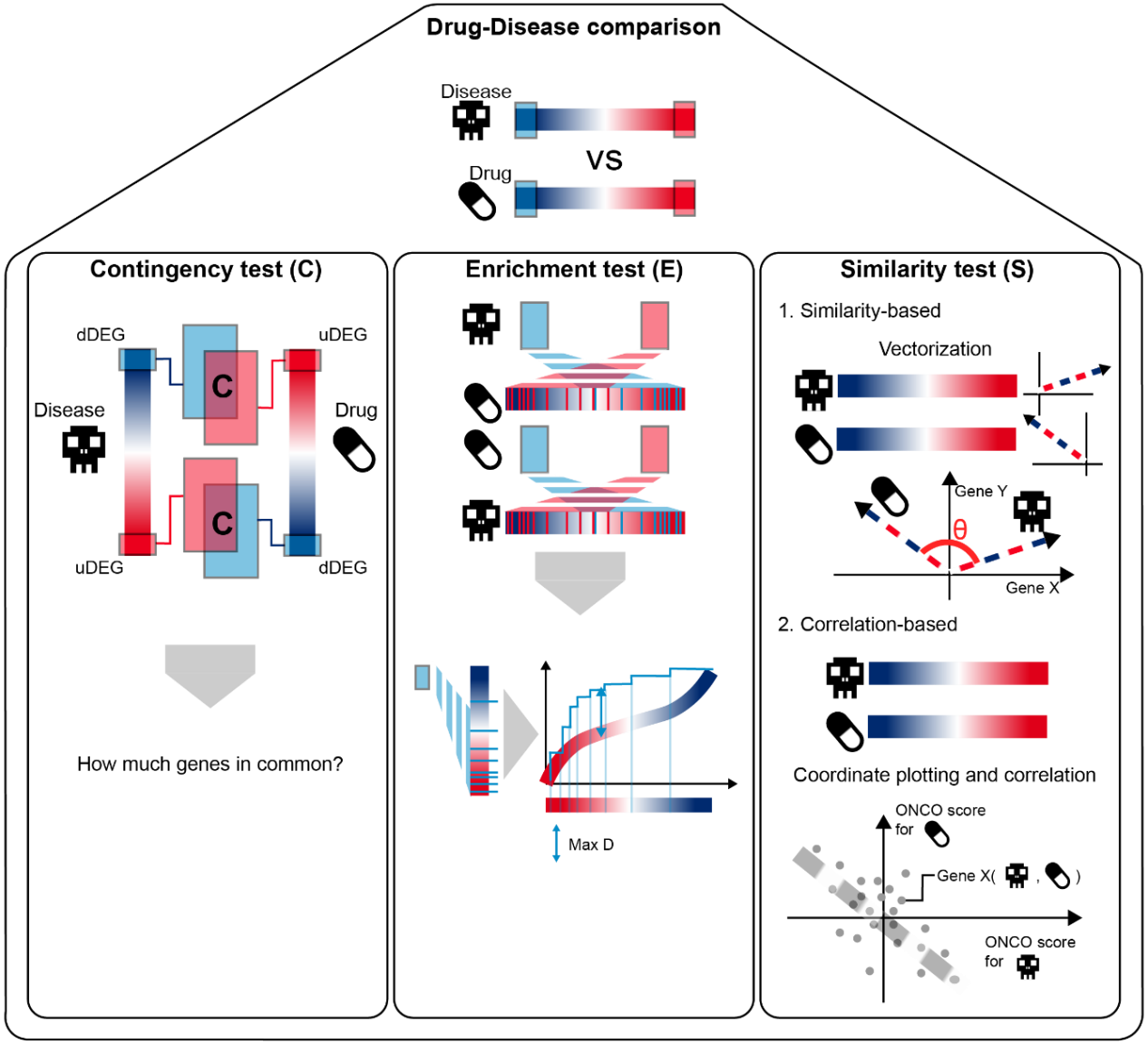
RAPTOR AI Data analysis workflow

ONCOCROSS



RAPTOR AI Ver 3.b.2	
Process	***Tools(version)***
Trimming	***Trimmomatic-0.39-1***
Alignment	***STAR-2.7.8a(GRCh38.105) RSEM-1.3.3***
Cell-Tissue Similarity	***UMAP-15D***

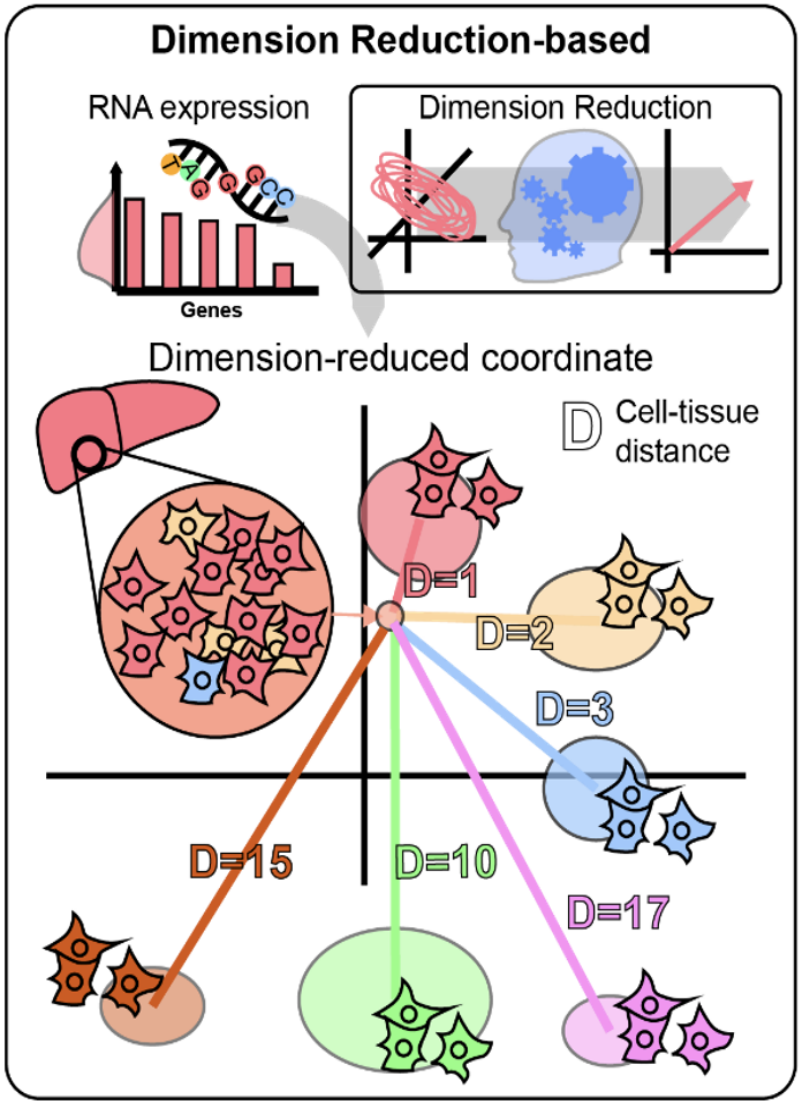
RAPTOR AI Drug-Disease comparison

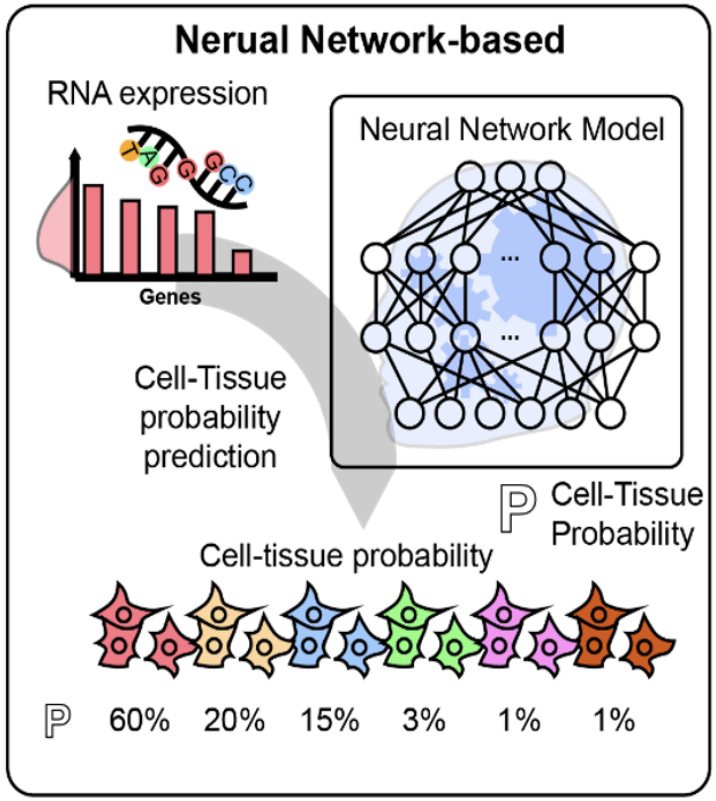


RAPTOR AI Cell - Tissue Similarity Analysis

ONCOCROSS

Cell line Integration method: v.ud.15





URC-102

Indication screening result

농도설정 [MTT Assay]

MTT Assay for Dose Selection

Tested Dose	Cell Lines
Set 1: 0.01/0.1/0.5/1/10/50/100/500 μM	PC3, MCF7, and HL60

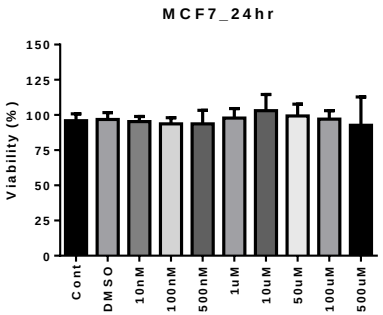
Final JSI-1187 Dose for RNA-seq: 8μM

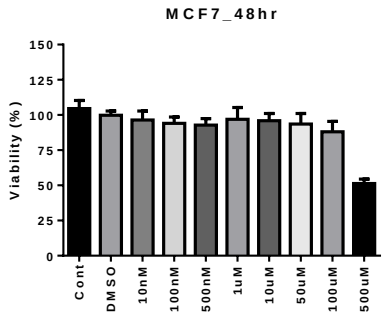
RNA Preparation (Triplicated Cell Culture)
(Negative Control group / Drug-treated group)

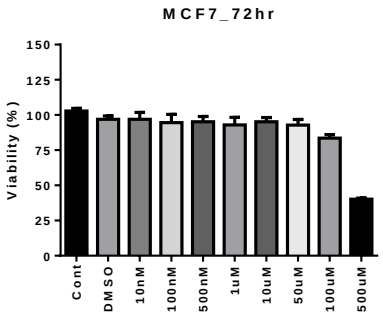
RNA sequencing
(Control group / Drug-treated group)

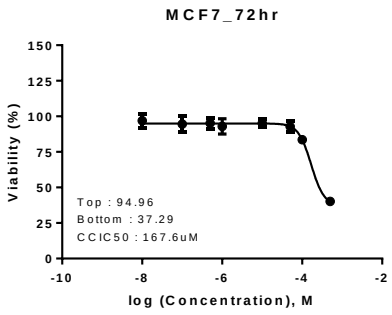
농도설정 [MTT Assay]

#1









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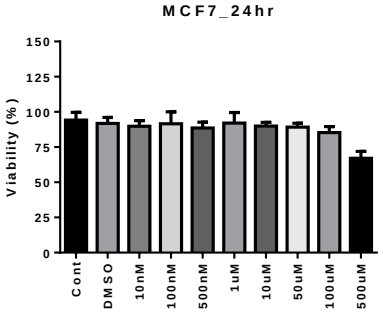

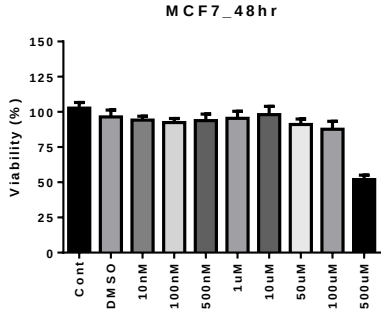

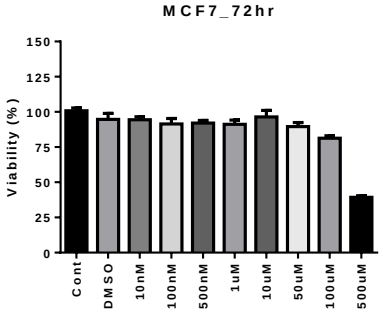

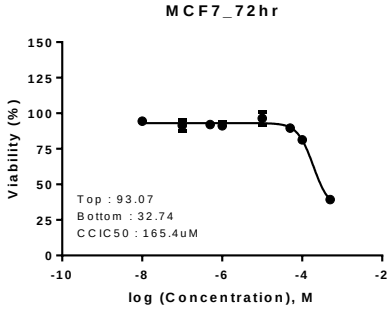

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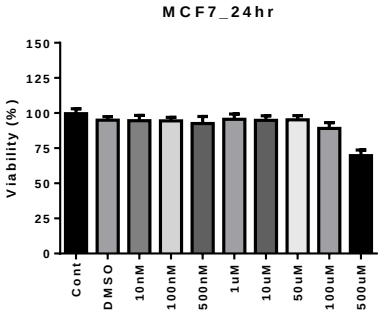

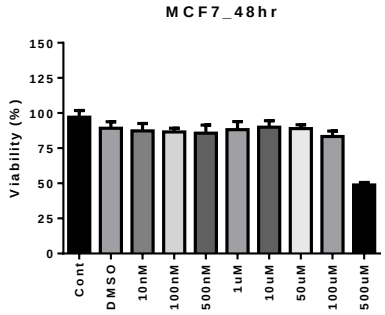

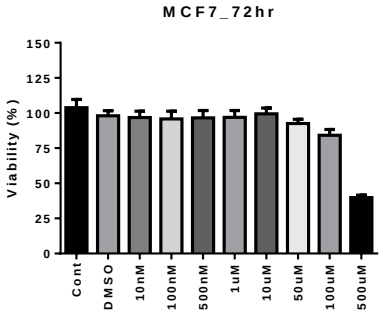

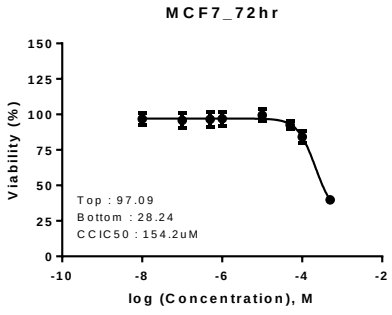

농도설정 [MTT Assay]

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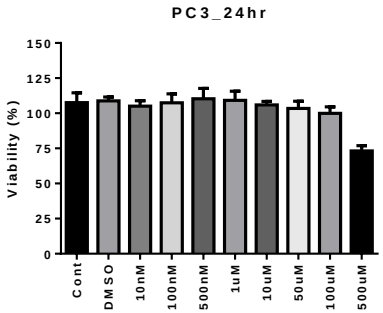

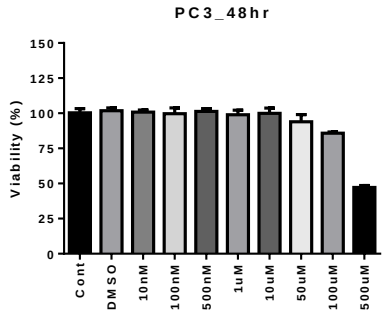

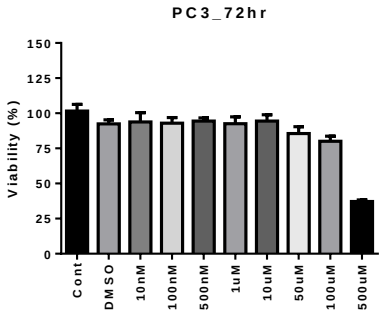

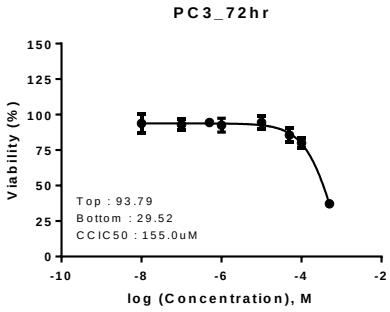

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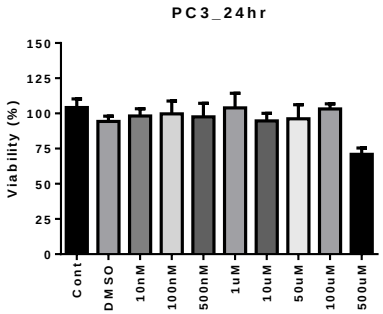

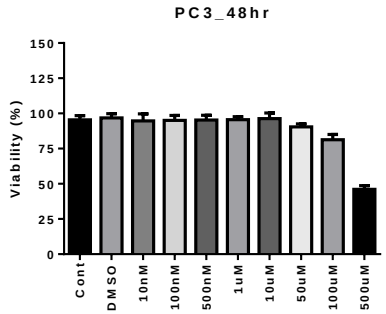

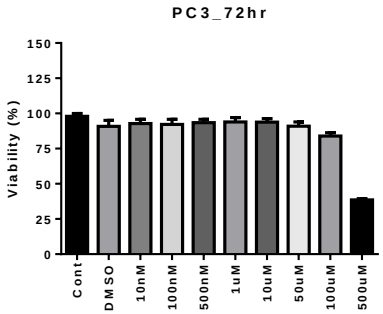

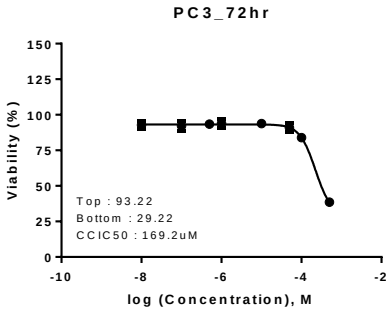

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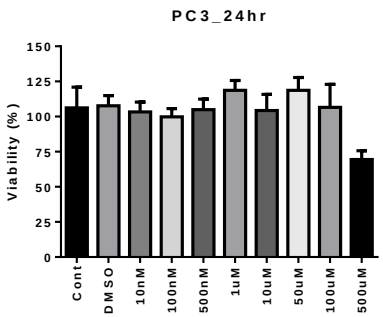

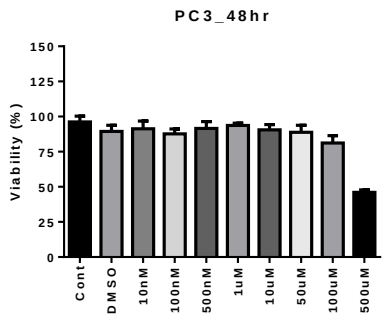

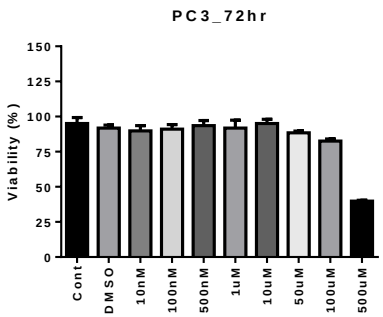

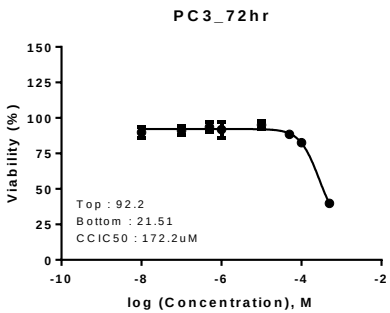

농도설정 [MTT Assay]

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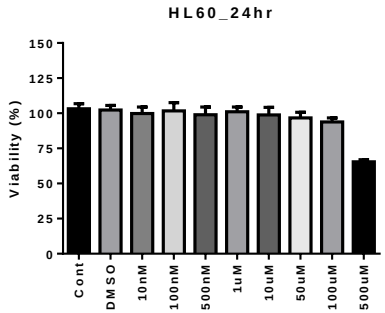

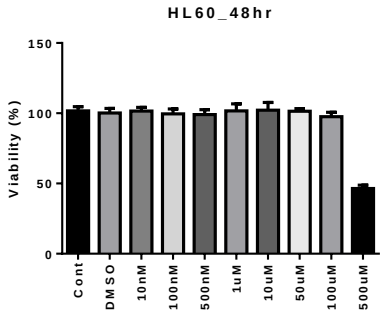

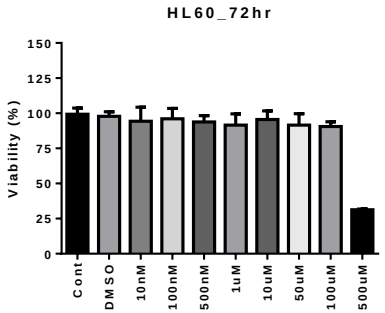

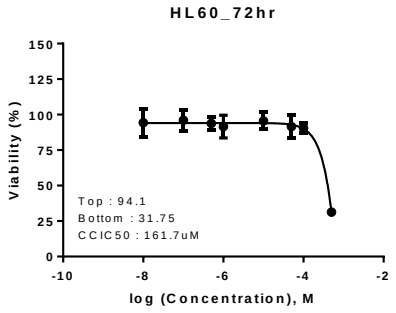

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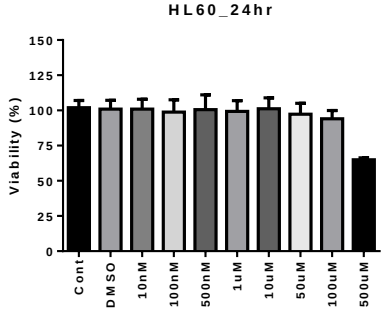

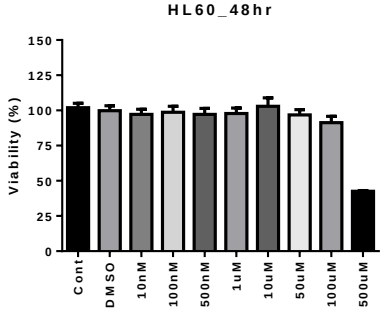

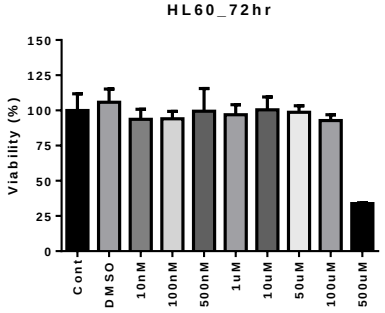

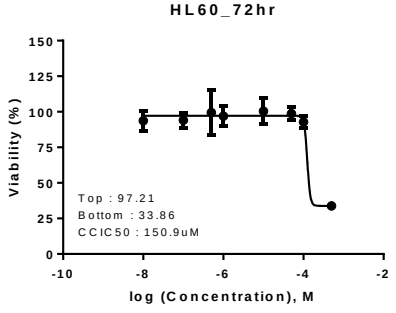

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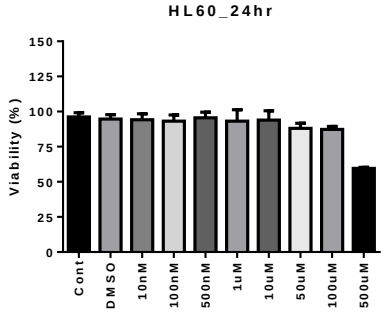

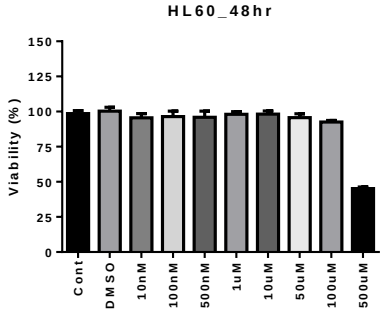

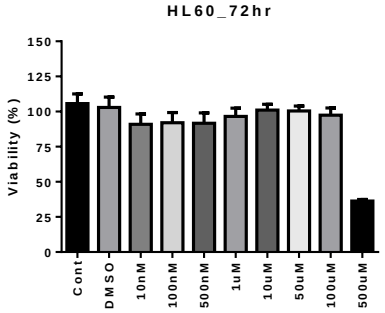

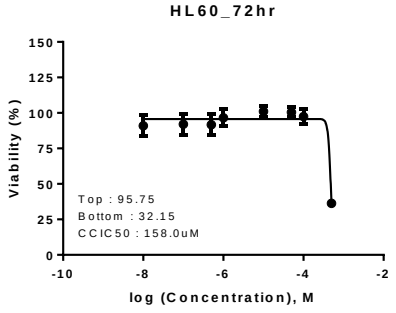

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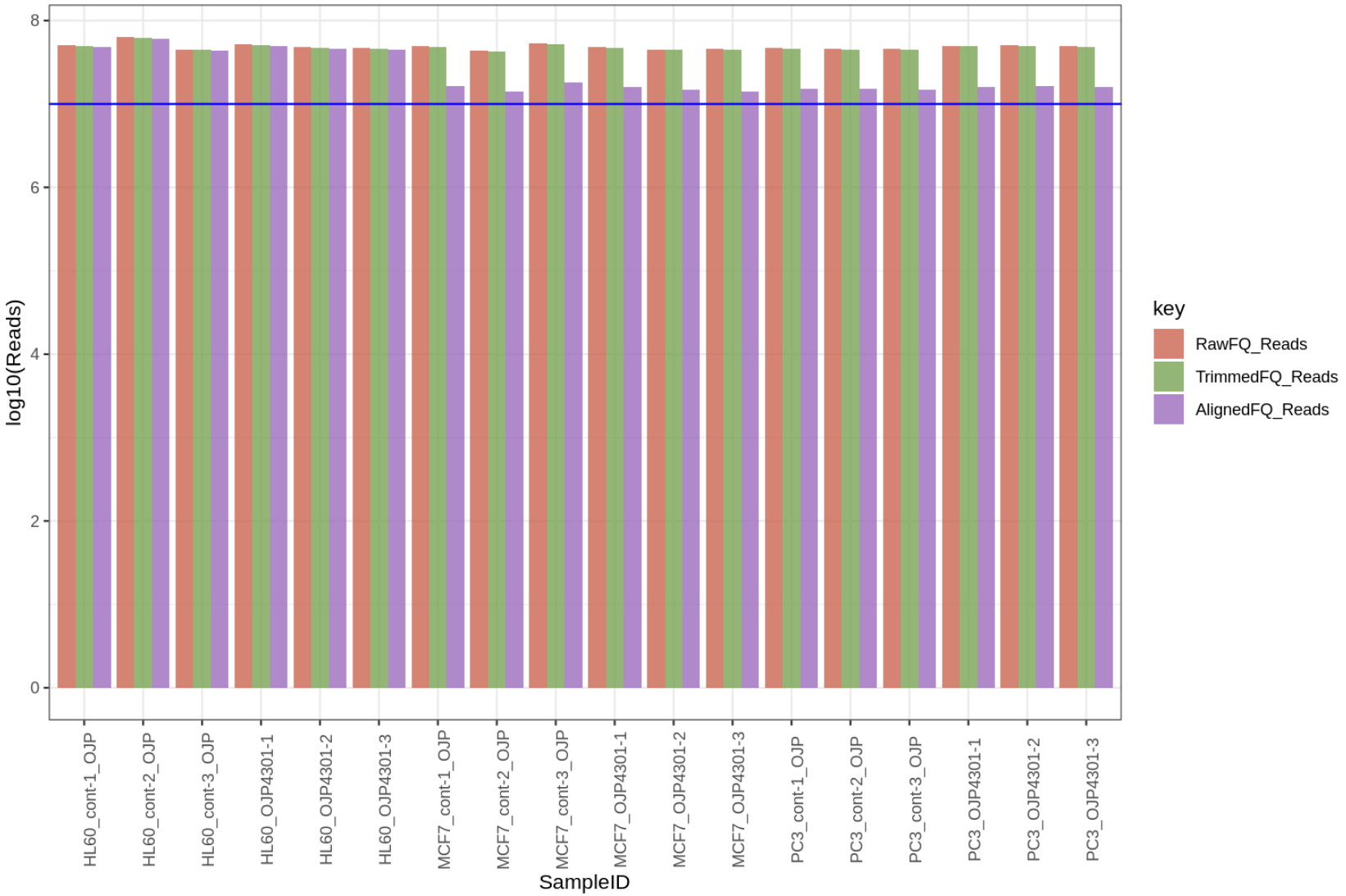
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6
4
2
0
HL60_cont-1_OJP
HL60_cont-2_OJP
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HL60_OJP4301-2
HL60_OJP4301-3
MCF7_cont-1_OJP
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MCF7_OJP4301-2
MCF7_OJP4301-3
PC3_cont-1_OJP
PC3_cont-2_OJP
PC3_cont-3_OJP
PC3_OJP4301-1
PC3_OJP4301-2
PC3_OJP4301-3
SampleID
key
RawFQ_Reads
TrimmedFQ_Reads
AlignedFQ_Reads

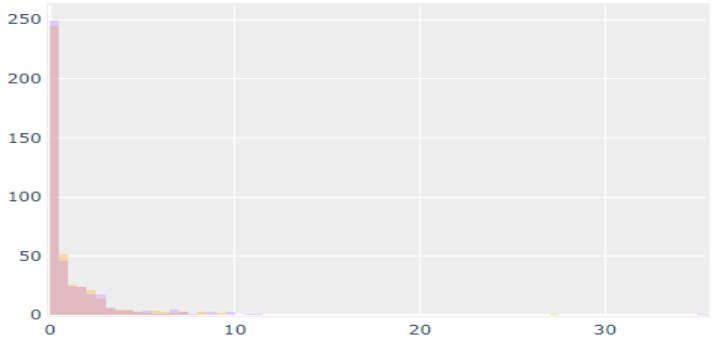
RAPTOR AI Score Distribution

ONCOCROSS

Cell line Integration method: v.ud.15

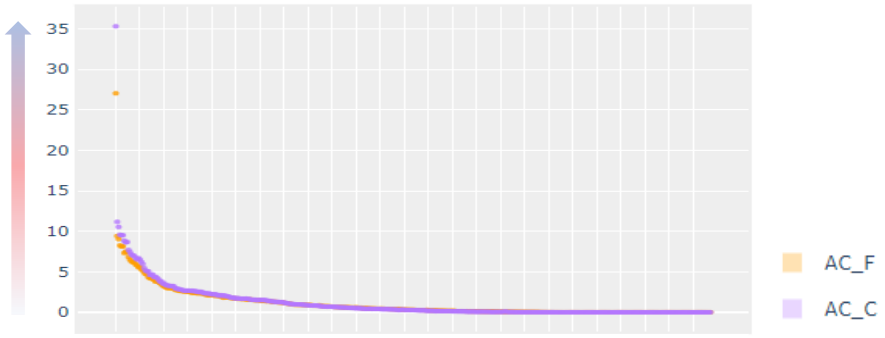
Result - METHOD (1) SCORE DISTRIBUTION Anti-common test

Frequency distribution for Anti-common test of drug-disease pair



No significant → *Significant*

Top 1000 Drug-Disease pairs with Anti-common test score



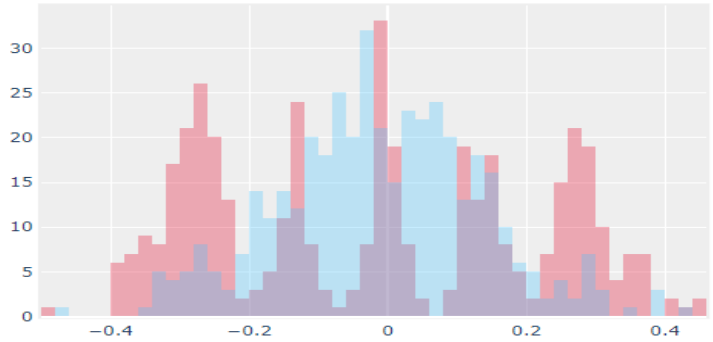
RAPTOR AI Score Distribution

ONCOCROSS

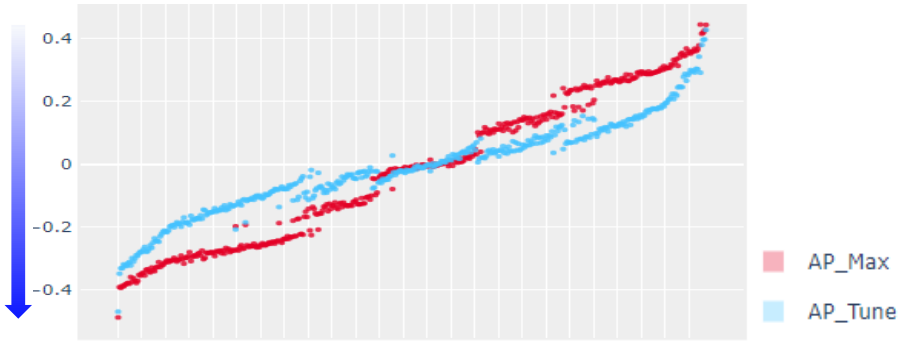
Cell line Integration method: v.ud.15

Result - METHOD (2) SCORE DISTRIBUTION Anti-projection test

Frequency distribution for Anti-projection test of drug-disease pair



Top 1000 Drug-Disease pairs with Anti-projection test score



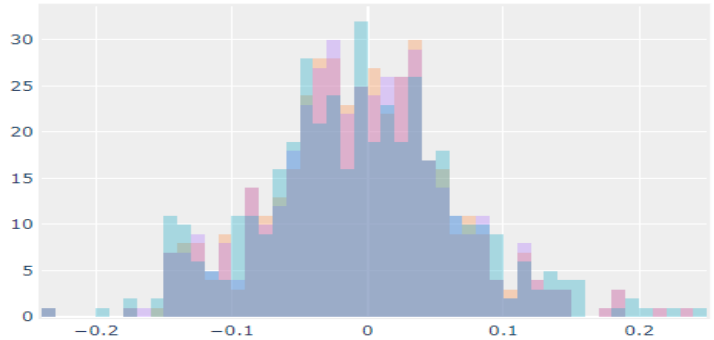
RAPTOR AI Score Distribution

ONCOCROSS

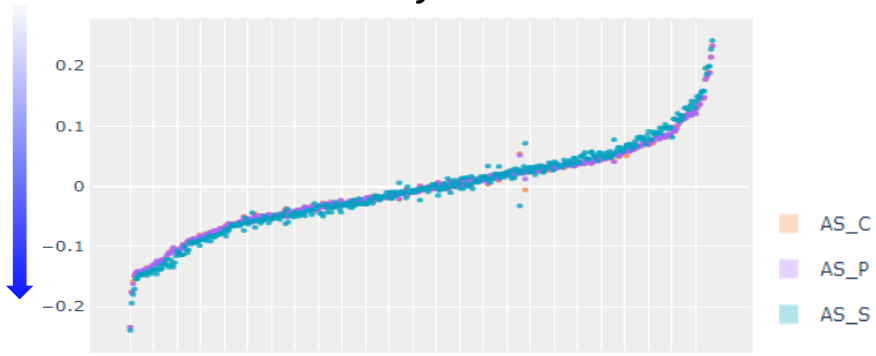
Cell line Integration method: v.ud.15

Result - METHOD (3) SCORE DISTRIBUTION Anti-Similarity test

Frequency distribution for Anti-Similarity test of drug-disease pair



Top 1000 Drug-Disease pairs with Anti-Similarity test score



URC-102 (URAT1 inhibitor)

Indication screening (Top 20)

ONCOCROSS

Cell line Integration method: v.ud.15.ranked

Rank Mean (total : 421)	Disease name	TISSUE	Cohort number	description
1	Dravet syndrome	blood	DravetSyndrome_v1	An early infantile epileptic encephalopathy that has_material_basis_in heterozygous mutation in the SCN1A gene on chromosome 2q24.
2	Aging	brain_cerebellar_hemisphere	GTEx_2030s_vs_6070s	Aging, Biological aging, Scenescence (MeSH Unique ID D000375, Tree Number(s) G07.345.124)
3	isolated elevated serum creatine phos phokinase levels	myotube	GSE44874	An inherited metabolic disorder characterized by elevated serum creatine kinase levels in the absen ce of muscle weakness or other symptoms that has_material_basis_in in some cases in heterozygo us mutation in CAV3 on chromosome 3p25.3.
4	asthma	airway_epithelium	GSE67472	A bronchial disease that is characterized by chronic inflammation and narrowing of the airways, whi ch is caused by a combination of environmental and genetic factors. The disease has_symptom rec urring periods of wheezing (a whistling sound while breathing), has_symptom chest tightness, has_s ymptom shortness of breath, has_symptom mucus production and has_symptom coughing. The sy mptoms appear due to a variety of triggers such as allergens, irritants, respiratory infections, weath er changes, exercise, stress, reflux disease, medications, foods and emotional anxiety.
5	membranous glomerulonephritis	kidney_tubulointerstitium	GSE108113	deposition of immune complexes on the glomerular basement membrane (GBM) with GBM thickening. Cause is usually unknown, although secondary causes include drugs, infections, autoimmune disorders, and cancer.
6	membranous glomerulonephritis	kidney_glomeruli	GSE108113	deposition of immune complexes on the glomerular basement membrane (GBM) with GBM thickening. Cause is usually unknown, although secondary causes include drugs, infections, autoimmune disorders, and cancer.
7	lipoid nephrosis	kidney_tubulointerstitium	GSE108113	minimal change nephropathy
8	vasculitis	kidney_tubulointerstitium	GSE108113	A vascular disease that is characterized by inflammation of the blood vessels.
9	vasculitis	kidney_glomeruli	GSE108113	A vascular disease that is characterized by inflammation of the blood vessels.
10	focal segmental glomerulosclerosis	kidney_glomeruli	GSE108113	a histopathologic finding of scarring (sclerosis) of glomeruli and damage to renal podocytes.
11	focal segmental glomerulosclerosis	kidney_tubulointerstitium	GSE108113	a histopathologic finding of scarring (sclerosis) of glomeruli and damage to renal podocytes.
12	focal segmental glomerulosclerosis	kidney_glomeruli	GSE104066	a histopathologic finding of scarring (sclerosis) of glomeruli and damage to renal podocytes.
13	lipoid nephrosis	kidney_glomeruli	GSE108113	minimal change nephropathy
14	retinal detachment	retina	GSE28133	a disorder of the eye in which the retina peels away from its underlying layer of support tissue.
15	cryptorchidism	testicular	GSE25518	the absence of one or both testes from the scrotum.
16	atopic dermatitis	skin_non_lesion	GSE32924	An allergic contact dermatitis that is a chronically relapsing inflammatory allergic response located_i n the skin that causes itching and flaking.
17	coronary artery disease	peripheral_blood	GSE71226	An artery disease that is characterized by plaque building up along the inner walls of the arteries of t he heart resulting in a narrowing of the arteries and a reduced blood supply to the cardiac muscles.
18	cryptorchidism	testicular	GSE16191	the absence of one or both testes from the scrotum.
19	type 2 diabetes mellitus	arterial	GSE13760	A diabetes mellitus that involves high blood glucose resulting from cells fail to use insulin properly.
20	uremia	whole_blood	GSE37171	the term for high levels of urea in the blood. Urea is one of the primary components of urine.

관련 자료 조사

* URAT1 inhibition -> hyperuricemia 에 의한 kidney disease 에 대한 효능 가능성

› Phytomedicine. 2021 Jul;87:153585. doi: 10.1016/j.phymed.2021.153585. Epub 2021 May 24.

Apigenin ameliorates hyperuricemic nephropathy by inhibiting URAT1 and GLUT9 and relieving renal fibrosis via the Wnt/β-catenin pathway

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Affiliations + expand

PMID: 34044255 DOI: 10.1016/j.phymed.2021.153585

Abstract

Background: Hyperuricemia (HUA) is characterized by abnormal serum uric acid (UA) levels and demonstrated to be involved in renal injury leading to hyperuricemic nephropathy (HN). Apigenin (API), a flavonoid naturally present in tea, berries, fruits, and vegetables, exhibits various biological functions, such as antioxidant and anti-inflammatory activity.

Purpose: To investigate the effect of API treatment in HN and to reveal its underlying mechanisms.

Methods: The mice with HN were induced by potassium oxonate intraperitoneally and orally administered for two weeks. The effects of API on renal function, inflammation, fibrosis, and uric acid (UA) metabolism in mice with HN were evaluated. The effects of API on urate transporters were further examined in vitro.

Results: The mice with HN exhibited abnormal renal urate excretion and renal dysfunction accompanied by increased renal inflammation and fibrosis. In contrast, API reduced the levels of serum UA, serum creatinine (CRE), blood urea nitrogen (BUN) and renal inflammatory factors in mice with HN. Besides, API ameliorated the renal fibrosis via Wnt/β-catenin pathway suppression. Furthermore, API potently promoted urinary UA excretion and inhibited renal urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9) in mice with HN. In vitro, API competitively inhibited URAT1 and GLUT9 in a dose-dependent manner, with IC_{50} values of 0.64 ± 0.14 μM and 2.63 ± 0.69 μM, respectively.

Conclusions: API could effectively attenuate HN through co-inhibiting UA reabsorption and Wnt/β-catenin pathway, and thus it might be a potential therapy to HN.

Review › Nat Rev Nephrol. 2019 Dec;15(12):767-775. doi: 10.1038/s41581-019-0174-z. Epub 2019 Jul 11.

The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD

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Affiliations + expand

PMID: 31296965 DOI: 10.1038/s41581-019-0174-z

Abstract

Hyperuricaemia is common among patients with chronic kidney disease (CKD), and increases in severity with the deterioration of kidney function. Although existing guidelines for CKD management do not recommend testing for or treatment of hyperuricaemia in the absence of a diagnosis of gout or urate nephrolithiasis, an emerging body of evidence supports a direct causal relationship between serum urate levels and the development of CKD. Here, we review randomized clinical trials that have evaluated the effect of urate-lowering therapy (ULT) on the rate of CKD progression. Among trials in which individuals in the control arm experienced progressive deterioration of kidney function (which we define as ≥4 ml/min/1.73 m² over the course of the study - typically 6 months to 2 years), treatment with ULT conferred consistent clinical benefits. In contrast, among trials where clinical progression was not observed in the control arm, treatment with ULT was ineffective, but this finding should not be used as an argument against the use of uric acid-lowering therapy. Although additional studies are needed to identify threshold values of serum urate for treatment initiation and to confirm optimal target levels, we believe that sufficient evidence exists to recommend routine measurement of serum urate levels in patients with CKD and consider initiation of ULT among those who are hyperuricaemic with evidence of deteriorating renal function, unless specific contraindications exist.

International Urology and Nephrology
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NEPHROLOGY - ORIGINAL PAPER

Hyperuricemia and hypertriglyceridemia indicate tubular atrophy/interstitial fibrosis in patients with IgA nephropathy and membranous nephropathy

Bingman Liu[1] · Liangyu Zhao[1] · Qingqing Yang[1] · Dongqing Zha[1] · Xiaoyun Si[1]

Received: 10 October 2020 / Accepted: 22 March 2021

Abstract

Purpose Hyperuricemia (HUA) and hypertriglyceridemia (HTG) were very common in chronic kidney disease (CKD) and associated with accelerated progression of CKD. This was a retrospective, cross-sectional study which aimed to explore the relationship between serum uric acid levels or triglyceride levels and tubular atrophy/interstitial fibrosis (proven by renal biopsy).

Methods The present study enrolled 229 CKD individuals who included 127 biopsy-proven primary IgA nephrology (IgAN) patients and 102 biopsy-proven primary membranous nephropathy (MN) patients. The baseline characteristics at the time of the kidney biopsy were collected. According to the serum uric acid (UA) or triglyceride (TG) whether it exceeds the normal reference range, patients were divided into non-HUA ($n = 127$), HUA ($n = 102$), non-HTG ($n = 119$), and HTG group ($n = 110$). Based on the extent of tubular atrophy/interstitial fibrosis, patients were divided into no/mild injury (T0, $n = 127$), moderate injury (T1, $n = 102$). Multivariable logistic regression for factors predicting moderate tubular atrophy/interstitial fibrosis was performed.

Results There were 127 IgAN and 102 MN cases among 229 patients in the present study. The prevalence of HUA was 44.5% ($n = 102$), 40.9% ($n = 52$), and 49.0% ($n = 50$) in all patients, IgAN patients and MN patients, respectively ($P = 1.49$). The prevalence of HTG was 48.0% ($n = 110$), 29.9% ($n = 38$), and 70.6% ($n = 72$) ($P < 0.001$), respectively, as well. Multivariate logistic regression analysis showed that HUA and HTG were independent risk factors for moderate tubular atrophy/interstitial fibrosis (HUA OR = 2.335, 95% CI = 1.147–4.755, $P = 0.019$; HTG OR = 2.646, 95% CI = 1.289–5.432, $P = 0.008$). The area under curve (AUC) of model 1 (HUA + eGFR + HTG + age + serum globulin + 24 h urinary protein, AUC = 0.876) was larger than the other two models; however, there was no significant difference among these models (all $P > 0.05$).

Conclusions Hyperuricemia and hypertriglyceridemia, which were prevalent in CKD patients, were the independent risk factors for moderate tubular atrophy/interstitial fibrosis. HUA together with HTG could improve the value of diagnosis for moderate tubular atrophy/interstitial fibrosis to some extent.

관련 자료 조사

Asthma/Atopy

제품명	리자벤캡슐 Rizaben Cap.
성분 / 함량	Tranilast 트라닐라스트 100mg (동일성분 의약품)
첨가제	결정셀룰로오스 스테아르산칼슘 카르복시메틸셀룰로오스칼슘 (첨가제 더보기)
도핑금지 약물정보	경기기간중 : 허용 경기기간외 : 허용 (상세정보 확인) ※ 상세정보는 반드시 한국도핑방지위원회 홈페이지를 통해 확인해주세요.
전문 / 일반	전문 / 단일 / 복합 / 단일
제조 / 수입사	제이더블유중외제약
제형	경질캡슐 / 투여경로 / 경구(내용고형)
성상	담황색 분말이 들어있는 상하단 흰색의 캡슐제
허가일	1983년 03월 11일

키세이 제약
회사
KISSEI

Kissei(일본) 개발(Brandname: Rizaben)
일본, 한국에서 허가된 의약품.
염증 및 알러지 반응 억제작용으로 천식, 아토피 적응증으로 사용되고 있으며,
URAT1 억제 작용으로 혈중 요산 감소 기능 연구됨

PRP Pharmacology Research & Perspectives
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ORIGINAL ARTICLE

Uricosuric targets of tranilast

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[3]Renal Division, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Keywords
Benzbromarone, GLUT9, gout, hyperuricemia, tranilast, URAT1, uric acid

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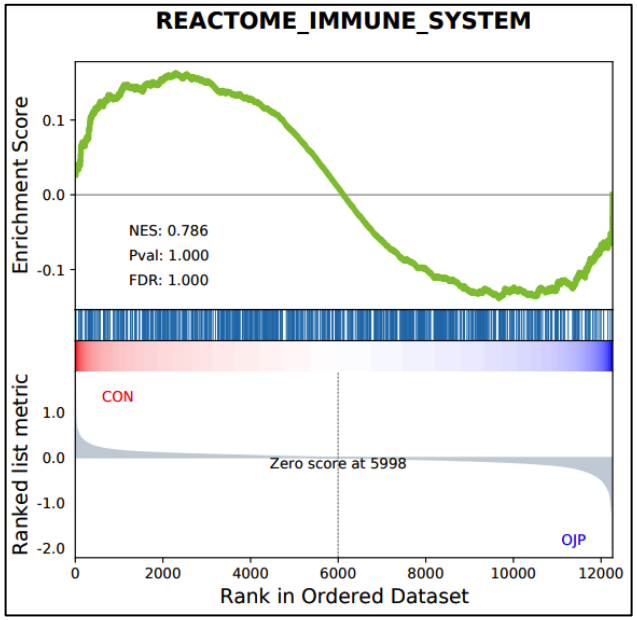
Abstract

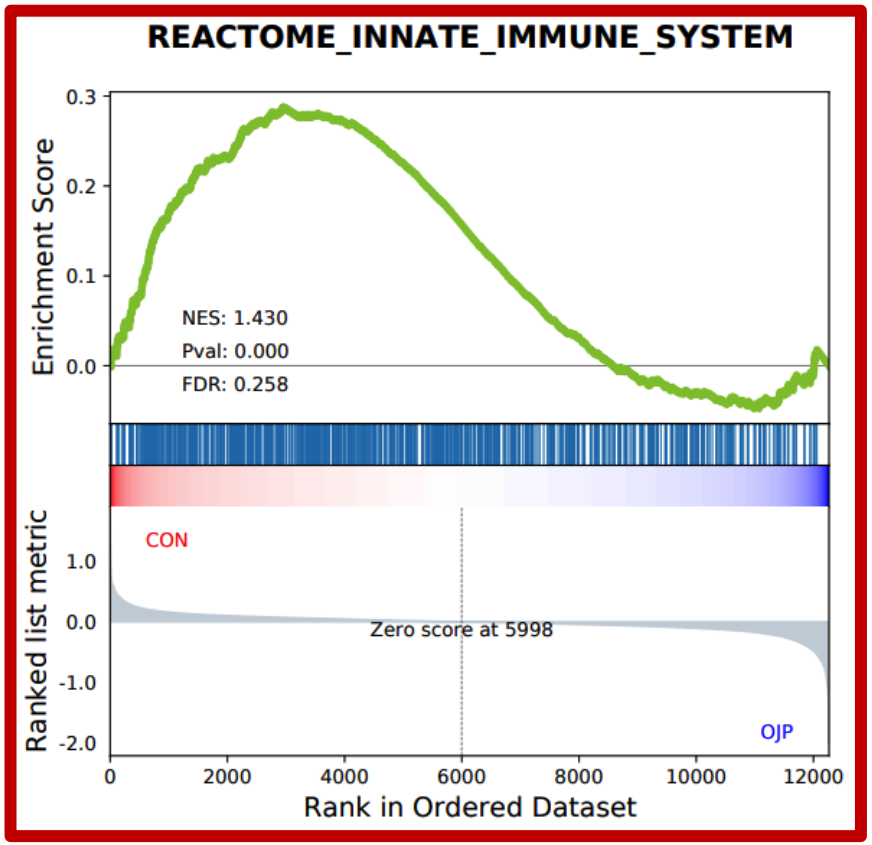
Uric acid, generated from the metabolism of purines, has both proven and emerging roles in human disease. Serum uric acid in humans is determined by production and by the net balance of reabsorption and secretion in kidney and intestine. In the human kidney, epithelial reabsorption dominates over secretion, such that in normal subjects there is at least 90% net reabsorption of filtered urate resulting in a fractional excretion of <10%. Tranilast, an anti-inflammatory drug with pleiotropic effects, has a marked hypouricemic, uricosuric effect in humans. We report here that tranilast is a potent inhibitor of [^{14}C]-urate transport mediated by the major reabsorptive urate transporters (URAT1, GLUT9, OAT4, and OAT10) in *Xenopus* oocytes; this provides an unequivocal molecular mechanism for the drug's uricosuric effect. Tranilast was found to inhibit urate transport mediated by URAT1 and GLUT9 in a fully reversible and noncompetitive (mixed) manner. In addition, tranilast inhibits

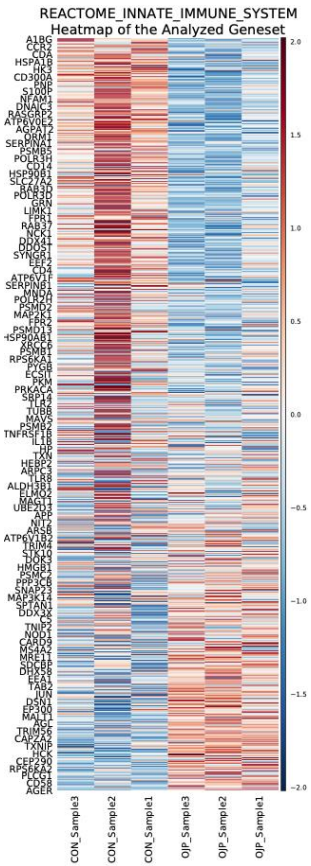
관련 자료 조사

Asthma/Atopy



*두집단 간 차이 없음





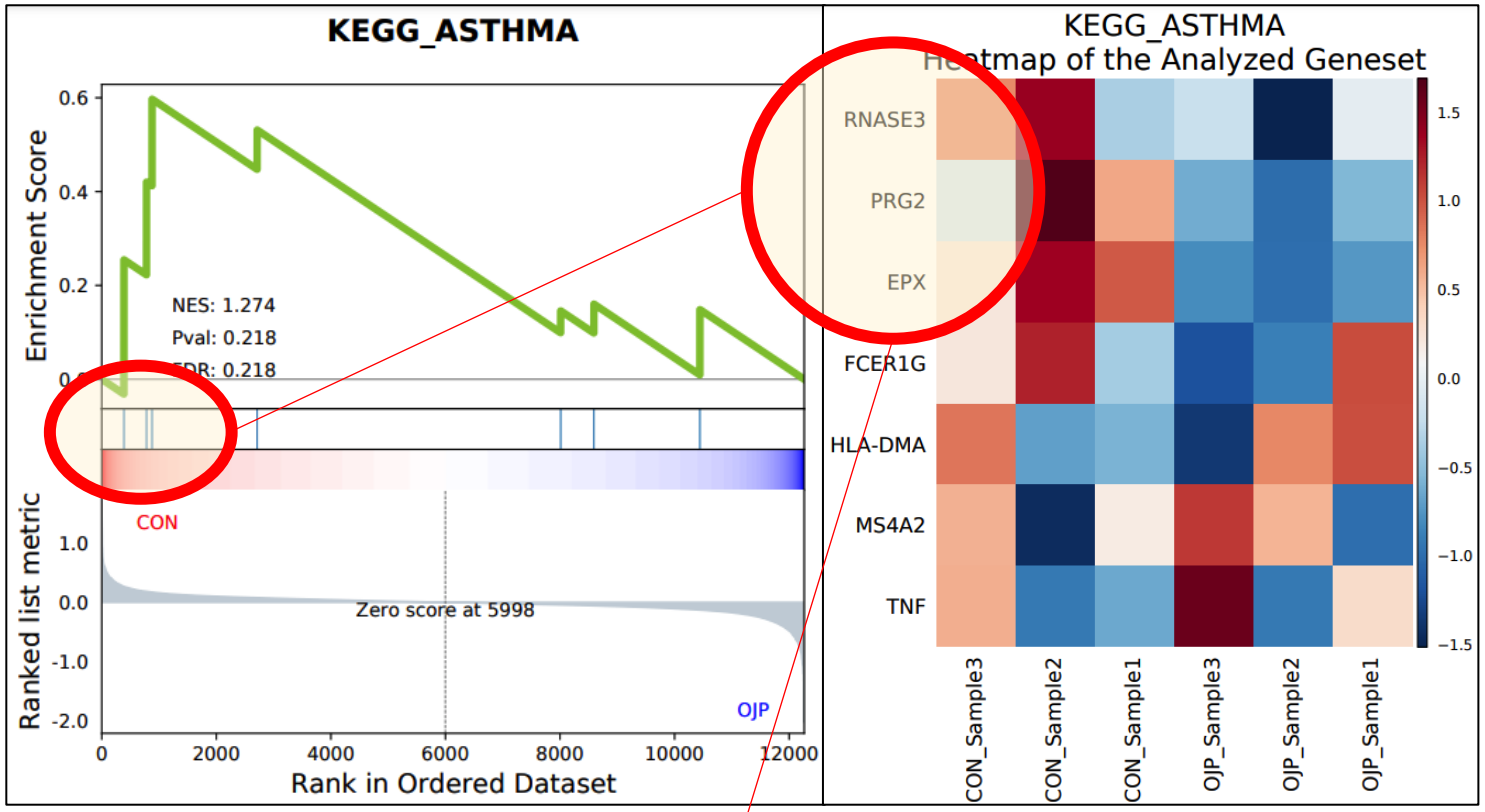
*Control 군에서 높음

Innate immune system 관련 유전자들의 발현이 약물군에서 비교적 낮은 경향(Cell line: HL60)

>> Asthma, Atopy 와 같은 면역 질환에 효능 가능성

관련 자료 조사

Asthma



* Cell line: HL60

Eosinophil, Asthma 와 더 직접적으로 연관성 있는 유전자가 투약군에서 낮음
>> Asthma 에 대한 효능 가능성

Thank you