

성공적인 학술연구비 신청의 이해

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보건복지부

2021년도 보건복지부 R&D 사업 통합 시행계획

□ 보건복지부 R&D 연도별 예산 현황('16~'20)

- (전체 규모) 최근 5년간 복지부 전체 R&D 예산은 연평균 3.8% 증가, 정부 전체 R&D 내 비중은 2.6 ~ 2.8% 수준 유지
- (주요 R&D) 복지부 주요 R&D 예산은 일몰제에 따라 '16년부터 일시적으로 정체하였으나, 전반적인 증가 추세(연평균 3.8%)

* (주요 R&D) 일반 R&D를 제외한 실제 과학기술 연구개발사업 투입 예산

* (일반 R&D) 본부 정책연구비, 질병청·국립정신병원 등 인건비 성격 예산

구분	2016년	2017년	2018년	2019년	2020년*	CAGR
정부 R&D	190,942	194,615	196,681	205,328	242,195	6.1
보건복지부 R&D	5,323	5,243	5,479	5,511	6,170	3.8
정부 R&D 대비 비중	2.79	2.69	2.79	2.68	2.55	
주요 R&D	4,608	4,496	4,657	4,669	5,278	3.5
진흥원	3,693	3,550	3,618	3,496	4,100	2.7
질병청	433	521	607	749	790	16.2
암센터	362	312	312	334	334	△2.0
첨복단지	82	74	73	36	-	-
재활원	38	39	47	54	54	9.2
일반 R&D	715	747	822	842	892	5.7

(단위 : 억 원, %)

* '20년 예산은 본예산 기준

□ 보건복지부 주요 R&D 분야별 예산 현황('16~'20)

○ (비중) 최근 5년간 분야별 예산 비중은 ① **질환극복·관리**, ② **신약·의료기기**, ③ **첨단의료기술**, ④ **연구기반조성**, ⑤ **기타**(한의약, 서비스 등) 順

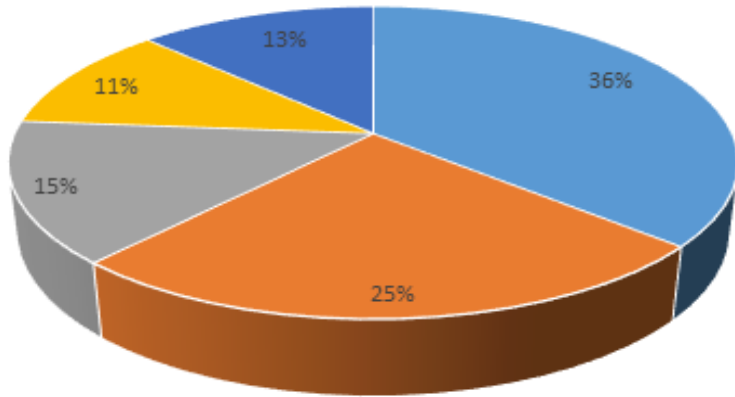
○ (추세) 모든 분야 예산이 증가세로, **연구기반조성** 분야에서 **가장 높은 증가율(11.5%)**을 보임

- 다수 사업의 **일몰*** 영향에도 불구하고, **감염병, 의료기기, 치매, 한의약** 분야 사업 **예타 통과****로 전반적 투자 규모 상승

* 첨단의료기술개발, 의료기기기술개발, 질환극복기술개발, 한의약선도기술개발 등

** 감염병 예방·치료 기술개발사업, 범부처 전주기 의료기기 연구개발사업, 치매극복 연구개발사업, 한의약혁신 기술개발사업

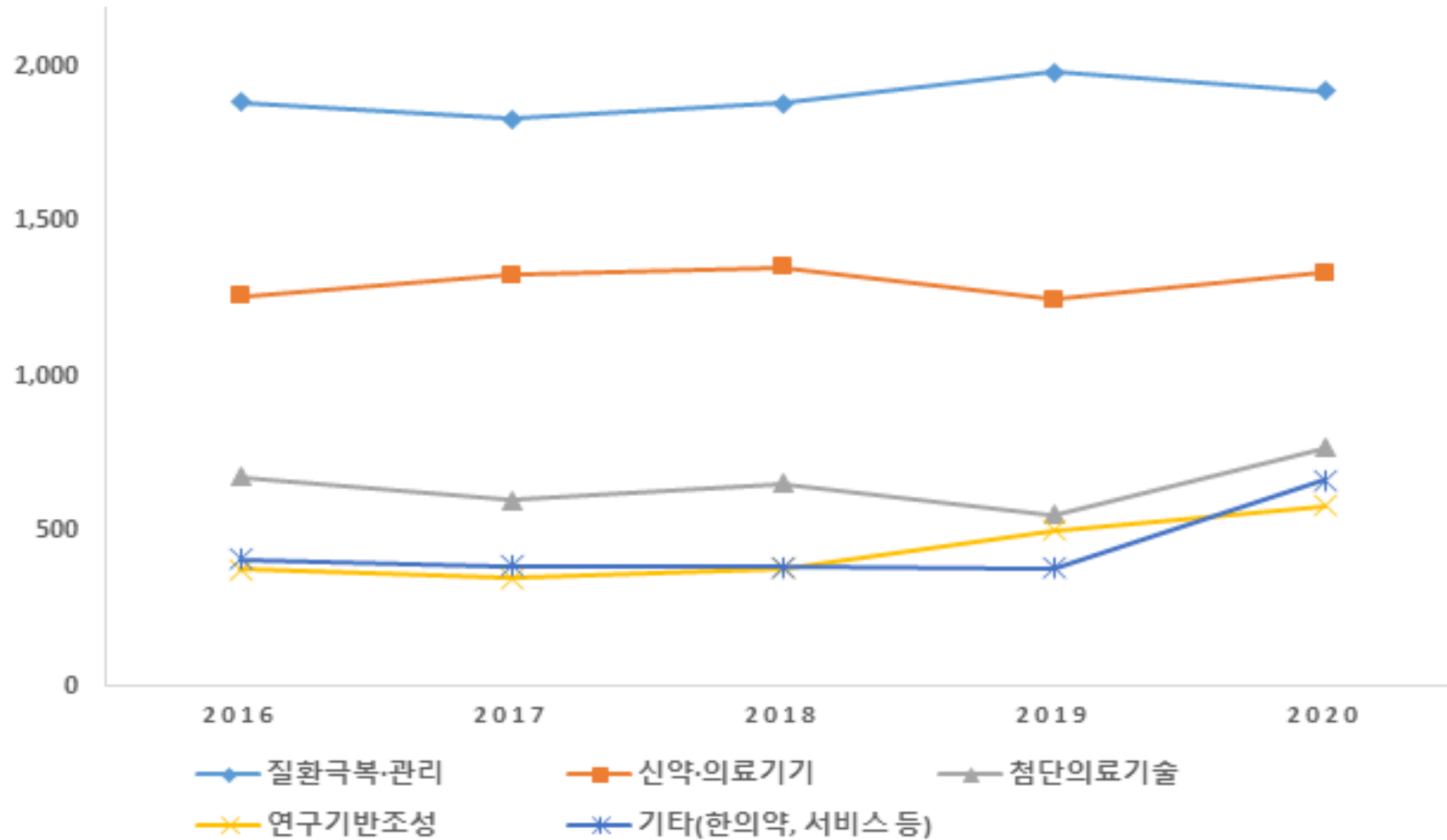
(단위: 억 원, %)



- 질환극복·관리
- 신약·의료기기
- 첨단의료기술
- 연구기반조성
- 기타(한의약, 서비스 등)

구분	2016년	2017년	2018년	2019년	2020년*	CAGR
주요 R&D	4,608	4,496	4,657	4,669	5,278	3.5
질환극복·관리	1,886 (41%)	1,832 (41%)	1,882 (40%)	1,983 (42%)	1,924 (36%)	0.5
신약·의료기기	1,259 (27%)	1,327 (30%)	1,353 (29%)	1,248 (27%)	1,334 (25%)	1.5
첨단의료기술	676 (15%)	602 (13%)	656 (14%)	554 (12%)	770 (15%)	3.3
연구기반조성	378 (8%)	349 (8%)	380 (8%)	502 (11%)	584 (11%)	11.5
기타 (한의약, 서비스 등)	409 (9%)	386 (9%)	385 (8%)	382 (8%)	666 (13%)	13.0

주요 R&D 분야별 투자 추이('16~'20) (단위: 억 원)



2021 보건복지부 R&D 추진방향

- ◇ 바이오헬스 분야 정부 R&D 투자를 '25년까지 4조원 이상으로 확대 추진
 - 기초연구·응용연구를 균형 있게 확대(바이오헬스산업 혁신전략, '19.5월)

2021년도 전략목표

공익적 R&D 투자 강화로 국민의 보건의료문제 해결,
첨단유망기술 육성을 통한 국가 주력산업으로의 도약

4대 전략별
중점 추진방향

<p>감염병 위기 대응 역량 강화</p>	<p>① 감염병 상시화에 대비한 예방·진단·치료기술 등 투자 강화</p>
<p>바이오헬스 첨단 유망기술 육성</p>	<p>② 재생의료 제도 완비 및 중점 지원 ③ 빅데이터, 인공지능 등 D.NA 기술 연계·활용 투자 ④ 신약·의료기기 등 차세대 유망기술 중점 지원</p>
<p>공익적 R&D 투자 강화</p>	<p>⑤ 사회문제 해결을 위한 취약계층 맞춤형 R&D 확대 ⑥ 치매·만성질환 등 고부담·난치성 질환 극복 중점 투자</p>
<p>의료현장 연계 R&D 지원</p>	<p>⑦ 병원 인프라를 연구 생태계 혁신거점으로 집중 육성</p>

'21년도 복지부 주요 R&D 예산 현황

(단위: 억 원, %)

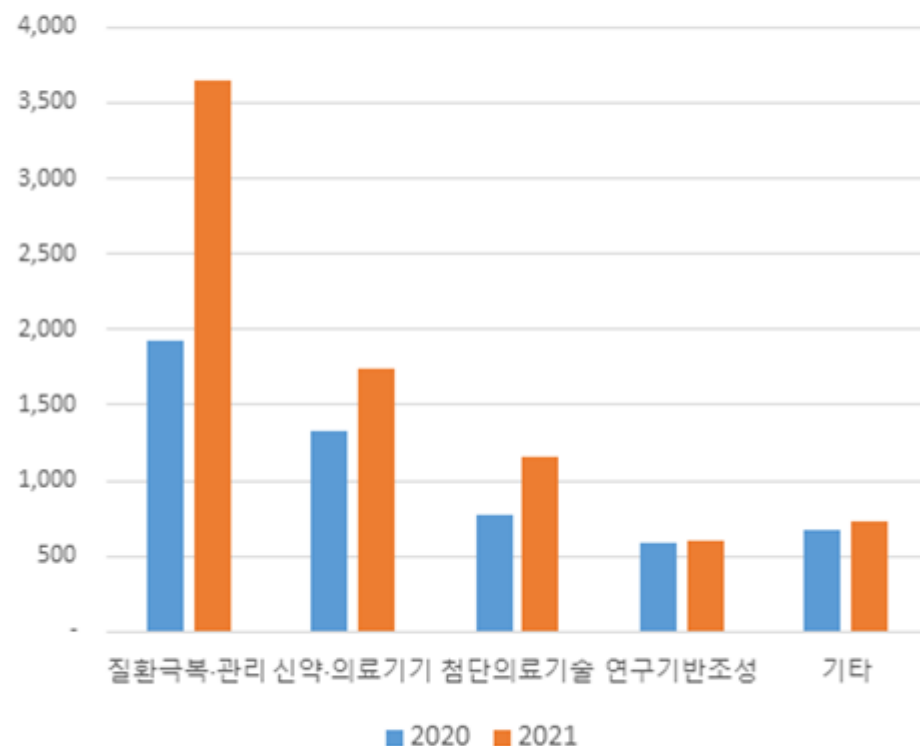
구분	2020년 (본예산)	2020년 (추경 포함)	2021년	증가율
복지부 주요 R&D	5,278	6,607	7,878	49.3
한국보건산업진흥원	4,100 (77.7%)	5,163 (78.1%)	6,362 (80.8%)	55.2
질병관리청	790 (15%)	1,056 (16.0%)	1,062 (13.5%)	34.4
국립암센터	334 (6.3%)	334 (5.1%)	360 (4.6%)	7.8
국립재활원	54 (1%)	54 (0.8%)	94 (1.2%)	74.1

주요 R&D 분야별 예산 현황('20~'21)

(단위: 억 원, %)

분야별	2020	2021	증감률
주요 R&D	5,278	7,878	49.3
질환극복·관리	1,924 (36.5)	3,653 (46.4)	89.9
신약·의료기기	1,334 (25.3)	1,744 (22.1)	30.7
첨단의료기술	770 (14.6)	1,151 (14.6)	49.5
연구기반조성	584 (11.1)	596 (7.6)	2.1
기타	666 (12.6)	736 (9.3)	10.5

(단위: 억 원)



주요 R&D 분야: 1. 신약, 의료기기 개발



(신약)			45,461	45,461	54,124	8,663	19.1
신규	일반	국가신약개발사업	-	-	15,051	15,051	순증
계속	일반	바이오헬스 투자인프라 연계형 R&D 사업	2,236	2,236	5,635	3,399	152
계속	일반	의료기술상용화지원센터(질환유효성평가지원센터)	3,750	3,750	7,500	3,750	100
계속	일반	국가 항암신약개발사업	12,156	12,156	3,306	△8,850	△72.8
계속	일반	스마트 임상시험 플랫폼 기반 구축사업	2,780	2,780	3,707	927	33.3
계속	일반	인공지능 신약개발 플랫폼 구축	2,778	2,778	3,000	222	8
일몰	일반	임상연구인프라조성(질환유효성평가기반구축등)	4,928	4,928	550	△4,378	△88.8
일몰	기금	첨단의료기술개발(신약개발지원, 제약산업특화지원)	16,333	16,333	15,375	-958	△5.9
종료	일반	범부처전주기신약개발사업(복지부)	500	500	-	△500	순감
(의료기기)			83,503	86,503	114,407	30,904	37.0
계속	일반	노인장애인 보조기기 연구개발사업	4,800	4,800	7,600	2,800	58.3
계속	일반	돌봄로봇 중개연구 및 서비스모델 개발	2,201	2,201	2,858	657	29.9
계속	일반	범부처전주기 의료기기 연구개발사업	30,189	30,189	60,200	30,011	99.4
계속	일반	의료기술상용화지원센터(의료기기혁신지원센터등)	2,700	5,700	9,495	6,795	251.7
계속	일반	치의학 의료기술 연구개발	2,008	2,008	3,157	1,149	57.2
계속	일반	마이크로의료로봇 실용화 기술개발 사업	8,704	8,704	10,143	1,439	16.5
계속	일반	인공지능바이오로봇 의료융합 기술개발(복지부)	2,800	2,800	2,200	△600	△21.4
일몰	일반	임상연구인프라조성(의료기기인프라지원)	6,333	6,333	3,667	△2,666	△42.1
일몰	기금	의료기기기술개발	23,768	23,768	15,087	△8,681	△36.5
(첨단의료복합단지 - 신약·의료기기 개발 인프라)			4,453	4,453	5,887	1,434	32.2
계속	일반	첨단의료복합단지 미래의료산업 원스톱 지원	4,453	4,453	5,887	1,434	32.2



NEOS Non-clinical Evaluation Center for Lung Disease

한국보건산업진흥원 의료기술상용화지원센터 산업
폐질환 유효성평가지원센터
Non-clinical Evaluation Center for Lung Disease

One Stop Solution Service 시스템 운영

질환유효성평가기반구축: 호흡기질환 특화 보건의료 T2B(Technology to business)기반구축사업

NCER National Center for Efficacy evaluation of Respiratory disease product

국가지정
호흡기질환 제품 유효성평가 연구단
호흡기질환 T2B 기반구축센터

: 4대 전략, 중점추진방향

주요 R&D 분야: 2. 첨단의료기술개발



(의료정보·빅데이터)			18,342	18,342	41,988	23,646	128.9
신규	일반	다부처국가생명연구자원선진화사업	-	-	2,510	2,510	순증
신규	일반	공익적의료기술연구사업(현장수요대응형환자안전연구개발등)	-	-	873	873	순증
신규	일반	디지털병리기반의 암전문AI분석 솔루션 개발 사업	-	-	7,170	7,170	순증
신규	일반	중환자 특화 빅데이터 구축 및 AI기반 CDSS 개발	-	-	7,064	7,064	순증
계속	일반	바이오 빅데이터구축 시범사업	4,267	4,267	7,250	2,983	69.9
계속	일반	의료데이터 보호·활용 기술개발	7,970	7,970	9,914	1,944	24.4
계속	일반	국가보건의료연구인프라구축(국가바이오빅데이터시범사업)	2,205	2,205	4,207	2,002	90.8
일몰	기금	첨단의료기술개발(인공지능정보의학)	3,900	3,900	3,000	△900	△23.1



(재생의료)			40,994	40,994	54,195	13,201	32.2
신규	일반	범부처 재생의료 기술개발사업	-	-	6,411	6,411	순증
일몰	일반	임상연구인프라조성(나노의학인프라, 화개난치성질환유전자치료)	1,407	1,407	333	△1074	△76.3
계속	일반	포스트게놈 신산업육성을 위한 다부처 유전체 사업	9,232	9,232	8,518	△714	△7.7
일몰	기금	첨단의료기술개발(출세포재생의료실용화, 융복합보건의료기술등)	30,355	30,355	38,933	8,578	28.3
(정밀의료)			17,710	17,710	18,868	1,158	6.5
계속	일반	CDM 기반 정밀의료 데이터 통합 플랫폼 기술개발	5,366	5,366	5,366	0	0
계속	일반	혁신성장동력프로젝트(복지부)	11,261	11,261	10,702	△559	△5.0
계속	기금	보건의료인재양성지원사업(국민건강증진기금)(교육훈련)	1,083	1,083	2,800	1,717	158.5

주요 R&D 분야: 3. 연구기반 조성 및 인재 양성



3] 연구기반 조성 및 인재 양성		58,410	58,410	59,551	1,141	2.0
계속	일반	연구중심병원육성	37,170	37,170	43,996	6,826 18.4
계속	일반	보건의료인재양성지원사업(일반회계)	16,300	16,300	13,505	△2,795 △17.1
계속	기금	보건의료인재양성지원사업(국민건강증진기금(글로벌 인재육성등))	1,820	1,820	1,270	△550 △30.2
일몰	기금	선도형특성화연구사업	3,120	3,120	780	△2,340 △75.0

주요 R&D 분야: 4. 질환 극복 및 관리 기술 개발



(감염병)			78,058	185,588	245,544	167,486	214.6
계속 일반	감염병 예방치료 기술개발사업		25,532	25,532	46,768	21,236	83.2
계속 일반	공공백신개발·지원센터 건립 및 운영		15,842	20,122	13,577	Δ2,265	Δ14.3
계속 기금	감염병 관리기술 개발연구		20,492	20,492	23,993	3,501	17.1
일몰 기금	감염병위기대응기술개발		16,192	16,192	6,973	Δ9,219	Δ56.9
계속 일반	감염병 방역기술개발		-	8,500	13,933	13,933	순증
계속 일반	감염병 의료기술근거생성 연구		-	750	1,500	1,500	순증
계속 일반	코로나19 치료제 임상지원 사업		-	45,000	62,700	62,700	순증
계속 일반	코로나19 백신 임상지원 사업		-	49,000	68,700	68,700	순증
신규 일반	코로나19 치료제 백신 비임상 지원 사업		-	-	7,400	7,400	순증



(만성병)			13,485	13,485	15,847	2,362	17.5
계속 기금	만성병 관리기술 개발연구		13,485	13,485	15,847	2,362	17.5



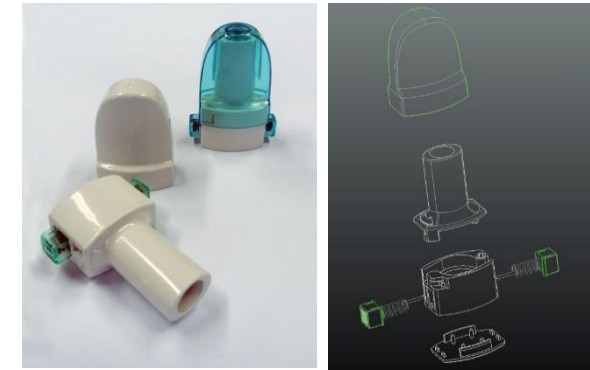
(심혈관계질환)			855	855	-	Δ855	순감
종료 일반	심혈관계질환 첨단의료기술 가상훈련시스템 기술개발		855	855	-	Δ855	순감



(암)			33,433	33,433	36,015	2,582	7.7
계속 일반	암연구소 및 국가암관리사업본부 운영(주요사업비)		33,433	33,433	36,015	2,582	7.7
(중개연구)			10,069	10,069	4,048	Δ6,021	Δ59.8
시규 일반	지방자치단체연구사업		-	-	3,663	3,663	순증



일몰 기금	질환극복기술개발(중개연구등)		2,485	2,485	385	Δ2,100	Δ84.5
종료 일반	연구자수도질병극복연구		7,584	7,584	-	Δ7,584	순감
(정신건강)			6,244	6,244	6,244	0	0
계속 일반	정신건강 문제해결 연구		6,244	6,244	6,244	0	0



최첨단 흡입제형 개발을 통한 난치성 천식 치료 기술 개발



주요 R&D 분야: 4. 질환 극복 및 관리 기술 개발

(질병관리본부 연구기반 구축)			22,869	45,199	41,473	18,604	81.4%
신규	일반	바이오위해평가 원팀 리노베이션사업	-	-	650	650	순증
계속	일반	국가 보건의료 연구인프라 구축	15,414	37,744	31,002	15,588	101.1
계속	기금	보건의료생물자원종합관리	5,249	5,249	7,653	2,404	45.8
계속	기금	형질분석연구	2,206	2,206	2,168	△38	△1.7
(치매)			16,040	16,040	7,877	△8,163	△50.9
계속	일반	치매극복연구개발사업	2,950	2,950	7,877	4,927	167.0
종료	일반	국가치매극복기술개발	13,090	13,090	-	△13,090	순감
(환경성질환)			4,062	4,062	4,602	540	13.3
계속	기금	미세먼지 기인 질병대응연구	4,062	4,062	4,602	540	13.3
(희귀난치성질환·저출산극복 등)			7,260	7,260	3,600	△3,660	△50.4
신규	일반	공익적의료기술연구사업(희귀질환극복연구,저출산극복연구)	-	-	3,300	3,300	순증
일몰	기금	질환극복기술개발(공공보건기술개발)	300	300	300	-	0
종료	일반	공익적 질병극복연구지원사업	6,960	6,960	-	△6,960	순감



주요 R&D 분야: 5. 기타



(건강관리 및 사회복지서비스기술개발 등)			46,120	46,120	51,717	5,597	12.1
신규	일반	노인천만시대 대비 고령친화서비스 연구개발	-	-	3,995	3,995	순증
신규	일반	지능형 재활운동 체육 중개연구사업	-	-	4,002	4,002	순증
계속	일반	국민건강 스마트관리 연구개발사업	2,966	2,966	4,815	1,849	62.3
계속	일반	환자중심 의료기술 최적화 연구사업	19,105	19,105	22,404	3,299	17.3
계속	일반	국립재활원 재활연구개발용역사업	5,395	5,395	5,401	6	0.1
계속	일반	라이프케어융합서비스개발사업	9,072	9,072	630	△8,442	△93.1
일몰	일반	사회서비스	150	150	150	0	0
계속	일반	피부과학 응용소재 선도기술 개발	7,740	7,740	10,320	2,580	33.3
종료	일반	100세 사회 대응 고령친화제품연구개발	1,692	1,692	-	△1,692	순감
(한의학 기술개발)			20,453	20,453	21,842	1,389	6.8
계속	일반	한의학기반융합기술개발	5,439	5,439	6,630	1,191	21.9
계속	일반	한의학혁신기술개발	7,779	7,779	10,177	2,398	30.8
일몰	기금	한의학선도기술개발	7,235	7,235	5,035	△2,200	△30.4



Our Research timeline

연도	주관기관(사업)
2002.	과학기술부 주관 MRC (Medical Science and Engineering Research Center) 알레르기성 면역질환 연구센터
2004-2010.	과학기술부 지원 국가지정연구실 선정(기도개형 제어기술개발 연구실)(5년)
2008-2013.	보건복지부 지정 병원특성화 연구센터 (폐 손상 치료제 개발 특성화 센터)
2012-현재.	국내 최초 보건복지부 지정 호흡기전문질환센터
2012-2020.	보건복지부 지원 임상 현장 발굴 국가 핵심 중개 연구 (최첨단 흡입 제형 개발을 통한 난치성 천식 치료 기술 개발)
2014-2019.	한국연구재단 개인기초연구(중견) (세포소기관 복합체 역할규명을 통한 중증 폐질환 발병 기전 연구)
2016-현재.	보건복지부 지정 질환 유효성평가기반구축사업 및 질환 유효성평가지원센터 (호흡기질환 특화 보건의료 T2B(Technology to business)기반구축사업, 폐질환 유효성평가지원센터)
2020-현재.	한국연구재단 개인기초연구(중견) (최첨단 기술을 통한 중증 상·하기도 통합기도질환의 심층 병태생리 규명 및 핵심 제어 기술 개발 연구)

Contribution of Vascular Endothelial Growth Factor to Airway Hyperresponsiveness and Inflammation in a Murine Model of Toluene Diisocyanate-Induced Asthma¹

Yong C. Lee,^{3*} Yong-Geun Kwak,[†] and Chang H. Song[‡]

Isocyanate chemicals, including toluene diisocyanate (TDI), are currently the most common causes of occupational asthma. Although considerable controversy remains regarding its pathogenesis, TDI-induced asthma is characterized by hyperresponsiveness and inflammation of the airways. One of the histological hallmarks of inflammation is angiogenesis, but the possible role of vascular endothelial growth factor (VEGF), a potent angiogenic cytokine, in TDI-induced asthma is unknown. We developed a murine model to investigate TDI-induced asthma by performing two courses of sensitization with 3% TDI and one challenge with 1% TDI using ultrasonic nebulization to examine the potential involvement of VEGF in that disease. These mice develop the following typical pathophysiological features: airway hyperresponsiveness, airway inflammation, and increased VEGF levels in the airway. Administration of VEGFR inhibitors reduced all these pathophysiological symptoms. These results suggest that VEGF is one of the major determinants of TDI-induced asthma and that the inhibition of VEGF may be a good therapeutic strategy. *The Journal of Immunology*, 2002, 168: 3595–3600.

Lee YC et al. J Immunol 2002

Lee YC et al. JACI 2004

Our Research timeline

연도	주관기관(사업)
2002.	과학기술부 주관 MRC (Medical Science and Engineering Research Center) 알레르기성 면역질환 연구센터
2004-2010.	과학기술부 지원 국가지정연구실 선정(기도개형 제어기술개발 연구실)(5년)
2008-2013.	보건복지부 지정 병원특성화 연구센터 (폐 손상 치료제 개발 특성화 센터)
2012-현재.	국내 최초 보건복지부 지정 호흡기전문질환센터
2012-2020.	보건복지부 지원 임상 현장 발굴 국가 핵심 중개 연구 (최첨단 흡입 제형 개발을 통한 난치성 천식 치료 기술 개발)
2014-2019.	한국연구재단 개인기초연구(중견) (세포소기관 복합체 역할규명을 통한 중증 폐질환 발병 기전 연구)
2016-현재.	보건복지부 지정 질환 유효성평가기반구축사업 및 질환 유효성평가지원센터 (호흡기질환 특화 보건의료 T2B(Technology to business)기반구축사업, 폐질환 유효성평가지원센터)
2020-현재.	한국연구재단 개인기초연구(중견) (최첨단 기술을 통한 중증 상·하기도 통합기도질환의 심층 병태생리 규명 및 핵심 제어 기술 개발 연구)

전북대병원 난치성폐질환 연구 최우수 등급 선정

이용철·김소리·정재석 교수 - 세포 소기관 기반 접근 향후 치료제 개발 새 지평

차원준 기자 승인 2020.09.15 14:01 댓글 1

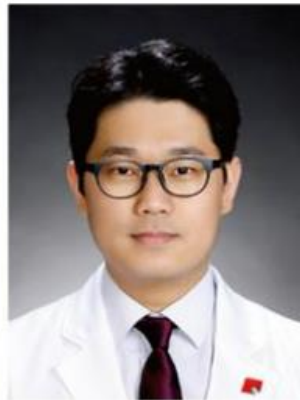
[의학신문·일간보사=차원준 기자] 전북대학교병원 호흡기알레르기내과 이용철·김소리·정재석 교수 연구팀의 중증 폐질환에 대한 연구 과제 결과가 최근 시행된 한국연구재단의 2020 연구과제 심사에서 최우수 등급의 과학적 성과에 선정되는 영예를 안았다.



이용철 교수



김소리 교수



정재석 교수

전북대병원은 한국연구재단의 지원을 받아 2014년부터 총 6년간 진행해 온 '세포 소기관 복합체의 역할 규명을 통한 중증 폐질환 발병 기전 연구'가 한국연구재단 심사위원단의 호평을 받아 최우수 등급(S등급)의 최종 평가를 받았다고 15일 밝혔다.

김소리 교수는 젊은 의과학자 육성을 목표로 시작된 **보건복지부 주관 세계선도 의생명 과학자 육성 사업 (Medi-star project)**의 주관 연구 책임자로 3년간 중증 천식에 대한 활발한 연구를 진행하고, 최종 평가에서 최우수등급(S 등급)을 받은 바 있다.

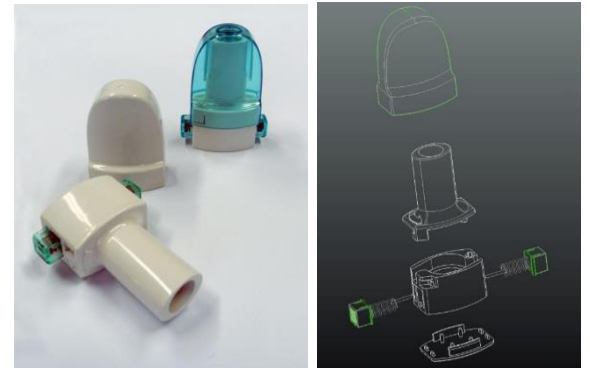
과학기술정보통신부 한국연구재단 개인연구사업(중견연구)

성장단계 지원유형	분야/군영	연구자의 성장단계	성숙/안정
개인연구 1 (연구역량)	학문후속세대지원 박사과정생 연구참여금지 박사후 국내외 연수 대통령포상 탈모우입	신진연구	우수연구
		중견연구	리더연구
		중견연구	리더연구
개인연구 2 (연구인턴)	학문균형발전지원 장외도전 연구지원	생애기초연구	생애기초연구
		생애기초연구	생애기초연구
		생애기초연구	생애기초연구
기반구축 집단연구	대학연구기반구축 기초과학 연구역량강화	집단연구	집단연구
		집단연구	집단연구
		집단연구	집단연구

기초연구



임상연구



최첨단 흡입제형 개발을 통한 난치성 천식 치료 기술 개발

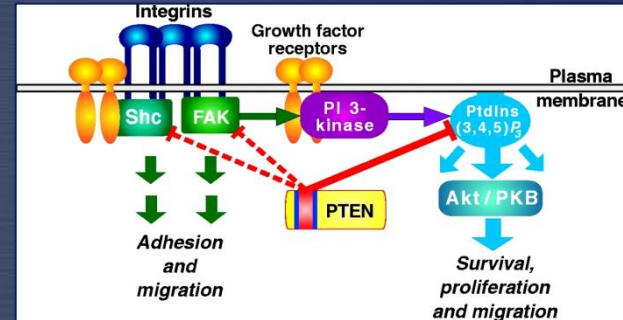
전임상연구

질환유효성평가기반구축: 호흡기질환 특화 보건의료 T2B(Technology to business)기반구축사업



연구팀의 PI3K 관련 기전 연구 업적

- 총괄 책임 연구자가 세계 최초로 PI3K 저해제가 천식에 효과를 보임을 확인한 연구 결과를 발표함



Involvement of PTEN in airway hyperresponsiveness and inflammation in bronchial asthma

Yong-Geun Kwak,
Kyung S. Lee,⁵ and

¹Department of Pharmacology,
²Department of Anatomy,
³Department of Pediatrics,
⁴Department of Biochemistry,
⁵Department of Internal Medicine,
Chonbuk National University School of Medicine, Chonju, South Korea

Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene that encodes a protein that acts as a phosphatase and is involved in the regulation of cell growth and differentiation. In a mouse model of bronchial inflammation, PTEN was found to be involved in the regulation of airway hyperresponsiveness and inflammation. However, this involvement was not observed in mice challenged with allergen. The increased IL-4 and IL-5 levels in the airway after OVA inhalation were significantly reduced in PTEN-deficient mice. Adenovirus-mediated overexpression of PTEN remarkably reduced bronchial inflammation and airway hyperresponsiveness. These findings indicate that PTEN may play a pivotal role in the pathogenesis of the asthma phenotype.

J. Clin. Invest. 111:1083-1092 (2003). doi:10.1172/JCI200316440.

Journal of Clinical Investigation
2003;111:1083-92.(IF:16.915)

PTEN Levels Tied to Asthma Symptoms in Mice

REUTERS HEALTH INFORMATION

similar means, is expressly liable for any errors or omissions and the Reuters sphere of influence extends to all companies around the world.

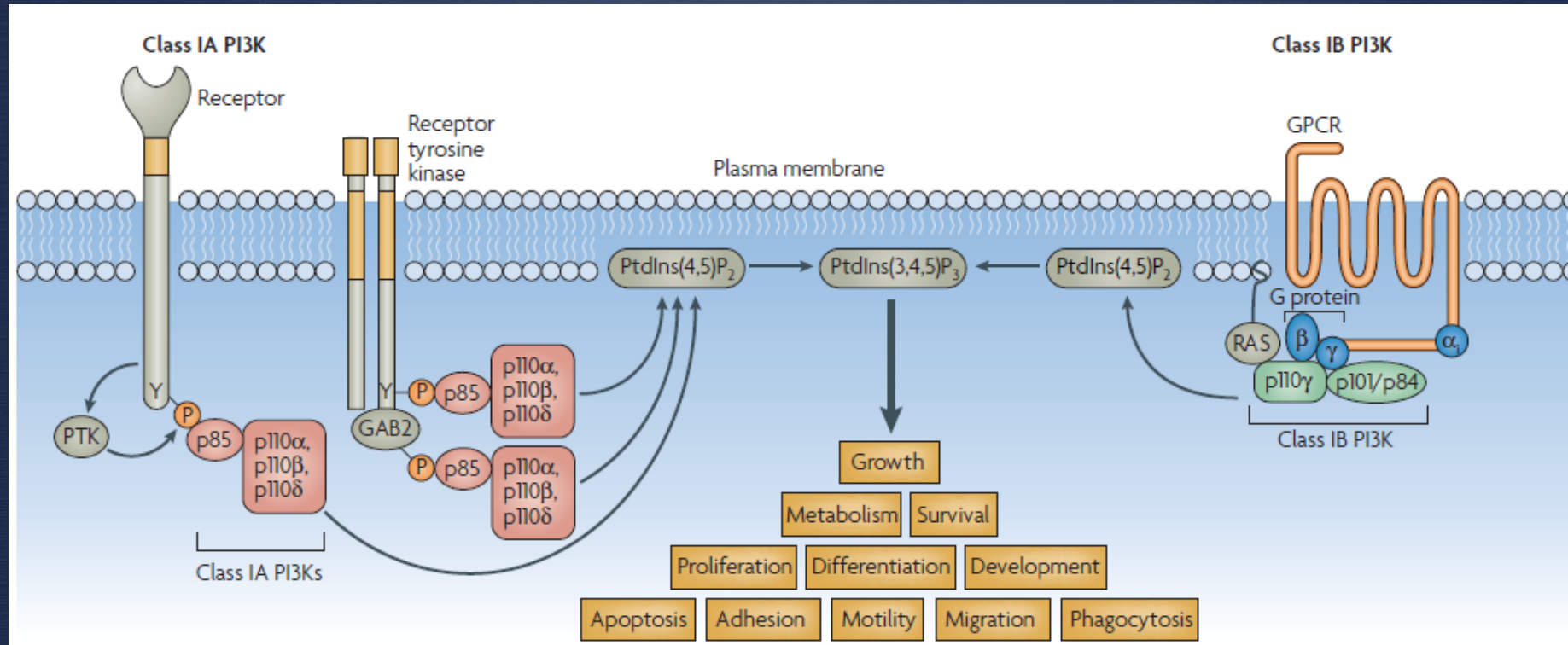
or PTEN appears to play a role in the regulation of airway hyperresponsiveness and inflammation. However, this involvement was not observed in mice challenged with allergen. The increased IL-4 and IL-5 levels in the airway after OVA inhalation were significantly reduced in PTEN-deficient mice. Adenovirus-mediated overexpression of PTEN remarkably reduced bronchial inflammation and airway hyperresponsiveness. These findings indicate that PTEN may play a pivotal role in the pathogenesis of the asthma phenotype.

Furthermore, Dr. Lee told Reuters Health that as part of their ongoing investigations in this field, "we have also demonstrated that PTEN expression is diminished in airway inflammatory cells of patients with bronchial asthma."

The Involvement of PTEN in Airway Hyper-responsiveness and Inflammation in Bronchial Asthma,
The Journal of Clinical Investigation

Citation: 350 times

Class I Phosphoinositide 3-kinase (PI3K) family

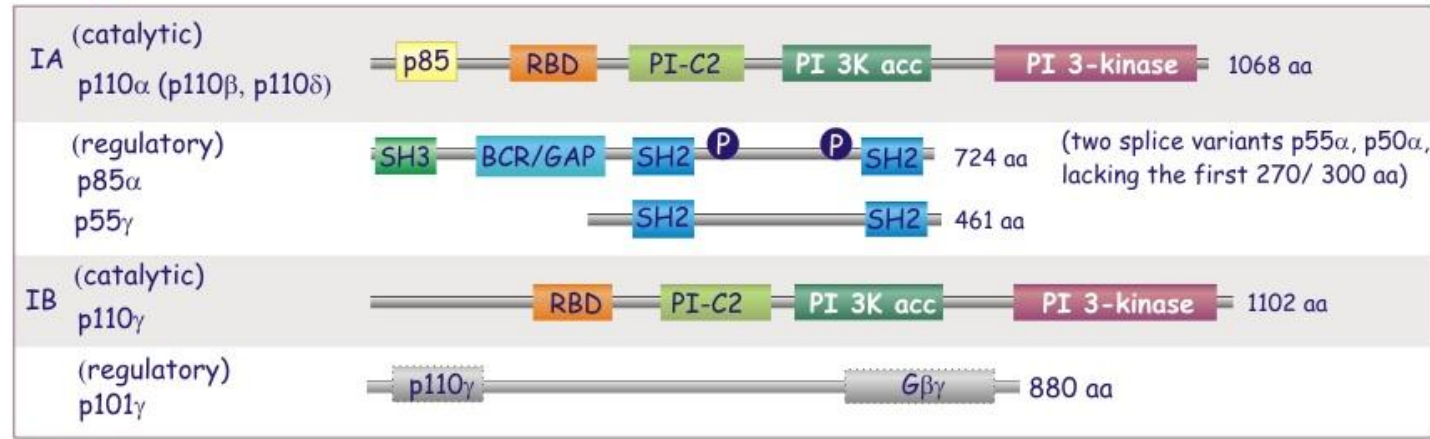


- Class IA isoforms, PI3K $\alpha/\beta/\delta$, interact with tyrosine kinases such as growth factor receptor tyrosine kinases
- Class IB member PI3K γ interacts with G-protein-coupled receptors

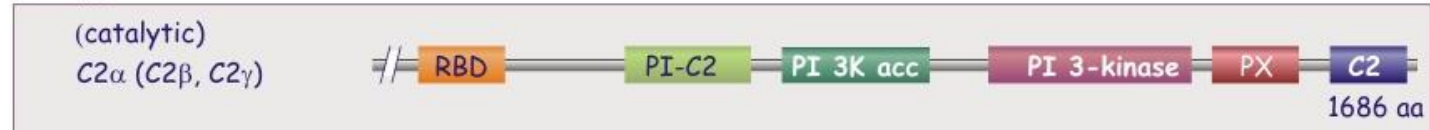
Rommel et al. Nat. Rev. Immunology 2007;7:191-201

Isoforms of phosphoinositide 3-kinase

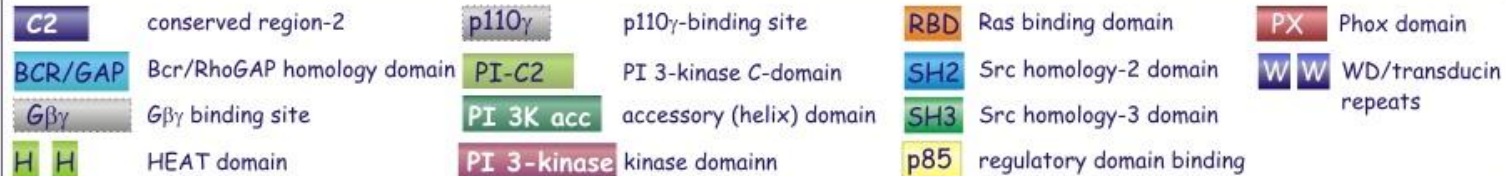
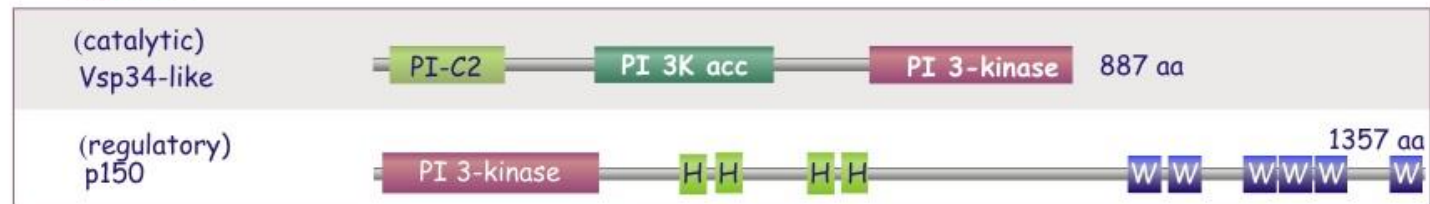
type I



type II



type III



연구팀의 PI3K 관련 기전 연구 업적

Inhibition of phosphoinositide 3-kinase δ attenuates allergic airway inflammation and hyperresponsiveness in murine asthma model

Kyung S. Lee,* Ho K. Lee,* Joel S. Hayflick,[†] Yong C. Lee,*¹ and Kamal D. Puri^{1†}

*Department of Internal Medicine, Research Center for Allergic Immune Diseases, Chonbuk National University Medical School, Jeonju, South Korea; and [†]ICOS Corporation, Bothell, Washington, USA

ABSTRACT PI10 δ phosphoinositide 3-kinase (PI3K) plays a pivotal role in the recruitment and activation of certain inflammatory cells. Recent findings revealed that the activity of p110 δ also contributes to allergen-IgE-induced mast cell activation and vascular permeability. We investigated the role of p110 δ in allergic airway inflammation and hyperresponsiveness using IC87114, a selective p110 δ inhibitor, in a mouse asthma model. BALB/c mice were sensitized with OVA and, upon OVA aerosol challenge, developed airway eosinophilia, mucus hypersecretion, elevation in cytokine and chemokine levels, up-regulation of ICAM-1 and VCAM-1 expression, and airway hyperresponsiveness. Intratracheal administration of IC87114 significantly ($P < 0.05$) attenuated OVA-induced influx into lungs of total leukocytes, eosinophils, neutrophils, and lymphocytes, as well as levels of IL-4, IL-5, IL-13, and RANTES in a dose-dependent manner. IC87114 also significantly ($P < 0.05$) reduced the serum levels of total IgE and OVA-specific IgE and LTC₄ release into the airspace. Histological studies show that IC87114 inhibited OVA-induced lung tissue eosinophilia, airway mucus production, and inflammation score. In addition, IC87114 significantly ($P < 0.05$) suppressed OVA-induced airway hyperresponsiveness to inhaled methacholine. Western blot analyses of whole lung tissue lysates shows that IC87114 markedly attenuated the OVA-induced increase in expression of IL-4, IL-5, IL-13, ICAM-1, VCAM-1, RANTES, and eotaxin. Furthermore, IC87114 treatment markedly attenuated OVA-induced serine phosphorylation of Akt, a downstream effector of PI3K signaling. Taken together, our findings implicate that inhibition of p110 δ signaling pathway may have therapeutic potential for the treatment of allergic airway inflammation.—Lee, K. S., Lee, H. K., Hayflick, J. S., Lee, Y. C., Puri, K. D. Inhibition of phosphoinositide 3-kinase δ attenuates allergic airway inflammation and hyperresponsiveness in murine asthma model. *FASEB J*. 20, 455–465 (2006)

CHRONIC INFLAMMATION, mucus hypersecretion, elevated serum IgE levels, and airway hyperresponsiveness (AHR) are fundamental characteristics of allergic asthma. T helper type 2 (Th2) cells, together with other inflammatory cells such as mast cells, B cells, and eosinophils, are proposed to play critical roles in the initiation, development, and chronicity of this disease (1–6). Upon activation, these inflammatory cells contribute to the production of Th2 cytokines (IL-4, IL-5, and IL-13) and chemokines (eotaxin and RANTES), which are found at elevated levels in asthmatic lungs. Th2 cytokines are pivotal for B cell maturation, IgE synthesis, airway eosinophilia, mucus secretion, and ultimately AHR. The importance of Th2 cytokines in the pathogenesis of allergic asthma has been demonstrated by specific gene knockout and antibody neutralization studies in mouse asthma models (7–9). In addition, RANTES and eotaxin are central to the recruitment of eosinophils to the airways, which is regulated by the interaction of adhesion molecules such as VLA-4 and its ligand VCAM1 (10, 11). AHR is thought to result from the combination of submucosal edema, infiltration of airway epithelium by leukocytes, damage to epithelial cells, followed by the direct effect of mediators derived from inflammatory cells (1, 6, 12).

Class I phosphoinositide 3-kinases (PI3Ks) play a key role in induction of the Th2 responses (13–16). Structurally, these kinases exist as heterodimeric complexes in which a catalytic p110 subunit (designated as α , β , γ , or δ) is in association with a particular regulatory subunit (designated p85, p55, p50, or p101) (17, 18). Functionally, all class I PI3Ks catalyze the phosphorylation of phosphatidylinositol (4, 5)-bisphosphate (PIP₂) to form phosphatidylinositol (3, 4, 5)-trisphosphate (PIP₃) in response to activation of either receptor tyrosine kinase (RTK) or G-protein-coupled receptors (GPCRs), which ultimately regulate cell growth, differ-

¹ Correspondence: K.D.P., ICOS Corporation, 22021 20th Ave. SE, Bothell, WA 98021, USA. E-mail: kpuri@icos.com or

기관지 천식에서 PI3K- δ 아형 억제제의 역할을 규명한 최초 연구 발표 Dr. Kamal D. Puri와 co-work

The screenshot shows a web page from the Faculty of 1000 Biology. The article title is "Inhibition of phosphoinositide 3-kinase delta attenuates allergic airway inflammation and hyperresponsiveness in murine asthma model." by Lee KS, Lee HK, Hayflick JS, Lee YC, Puri KD. The article is from FASEB J 2006 Mar 20(3):455-65. It has been selected by Santa Jeremy Ono and evaluated on 10 Mar 2006. A faculty comment from Santa Jeremy Ono states: "This study confirms the seminal findings from the Vanhaesebroeck group (1) that show that the phosphoinositide 3-kinase (PI-3K) delta subunit is critical for type 1 hypersensitivity reactions. The work shows a clear attenuation of late phase leukocyte recruitment as well as decreases in total and allergen-specific IgE levels. The work further supports targeting of this subunit as a therapeutic modality in allergy." (1) Ali et al. Nature 2004, 431:1007-11 [PMID:15496927].

- 이 분야 전문가들이 꼭 읽어야 할 논문 등급인 '추천 (Recommended)' 등급, 논문의 가치를 '중요한 결론 (Important Confirmation)'으로 평가

FASEB J 2006;20:455-465

Expanding role of PI3K δ isoform in bronchial asthma

: Corticosteroid resistance

Inhibition of phosphoinositide 3-kinase δ attenuates allergic airway inflammation and hyperresponsiveness in murine asthma model

Kyung S. Lee,* Ho K. Lee,* Joel S. Haylick,[†] Yong C. Lee,*¹ and Kamal D. Puri^{†,1}

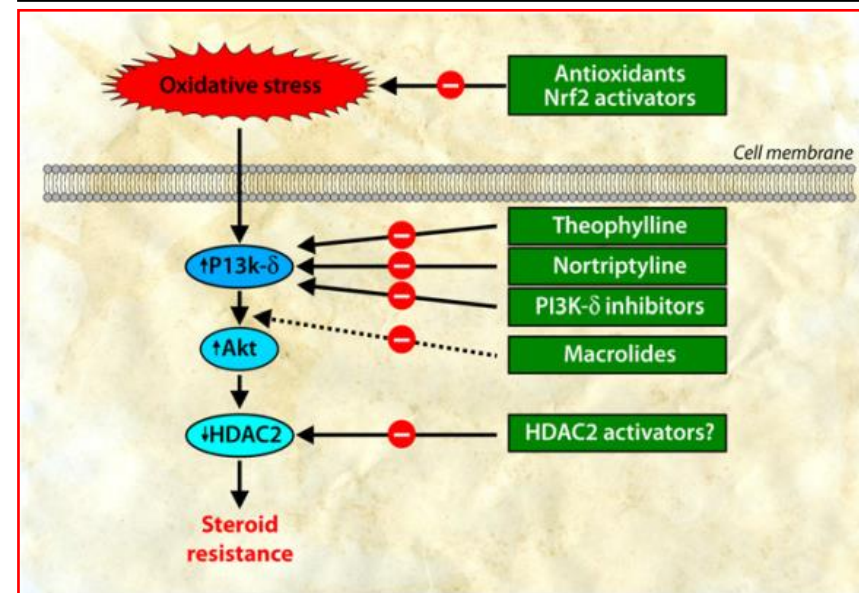
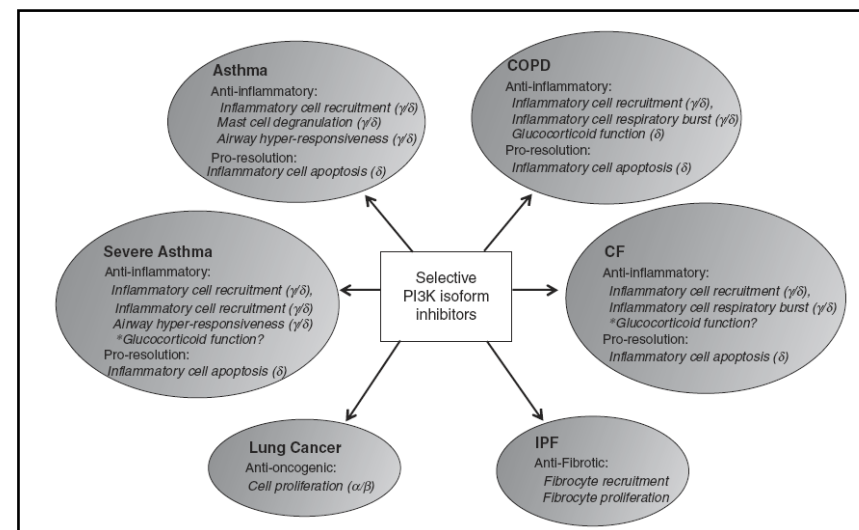
*Department of Internal Medicine, Research Center for Allergic Immune Diseases, Chonbuk National University Medical School, Jeonju, South Korea; and [†]ICOS Corporation, Bothell, Washington, USA

ABSTRACT PI10 δ phosphoinositide 3-kinase (PI3K) plays a pivotal role in the recruitment and activation of certain inflammatory cells. Recent findings revealed that the activity of p110 δ also contributes to allergen-IgE-induced mast cell activation and vascular permeability. We investigated the role of p110 δ in allergic airway inflammation and hyperresponsiveness using IC87114, a selective p110 δ inhibitor, in a mouse asthma model. BALB/c mice were sensitized with OVA and, upon OVA aerosol challenge, developed airway eosinophilia, mucus hypersecretion, elevation in cytokine and chemokine levels, up-regulation of ICAM-1 and VCAM-1 expression, and airway hyperresponsiveness. Intratracheal administration of IC87114 significantly ($P < 0.05$) attenuated OVA-induced influx into lungs of total leukocytes, eosinophils, neutrophils, and lymphocytes, as well as levels of IL-4, IL-5, IL-13, and RANTES in a dose-dependent manner. IC87114 also significantly ($P < 0.05$) reduced the serum levels of total IgE and OVA-specific IgE and LTC₄ release into the airspace. Histological studies show that IC87114 inhibited OVA-induced lung tissue eosinophilia, airway mucus production, and inflammation score. In addition, IC87114 significantly ($P < 0.05$) suppressed OVA-induced airway hyperresponsiveness to inhaled methacholine. Western blot analyses of whole lung tissue lysates shows that IC87114 markedly attenuated the OVA-induced increase in expression of IL-4, IL-5, IL-13, ICAM-1, VCAM-1, RANTES, and eotaxin. Furthermore, IC87114 treatment markedly attenuated OVA-induced serine phosphorylation of Akt, a downstream effector of PI3K signaling. Taken together, our findings implicate that inhibition of p110 δ signaling pathway may have therapeutic potential for the treatment of allergic airway inflammation.—Lee, K. S., Lee, H. K., Haylick, J. S., Lee, Y. C., Puri, K. D. Inhibition of phosphoinositide 3-kinase δ attenuates allergic airway inflammation and hyperresponsiveness in murine asthma model. *FASEB J.* 20, 455–465 (2006)

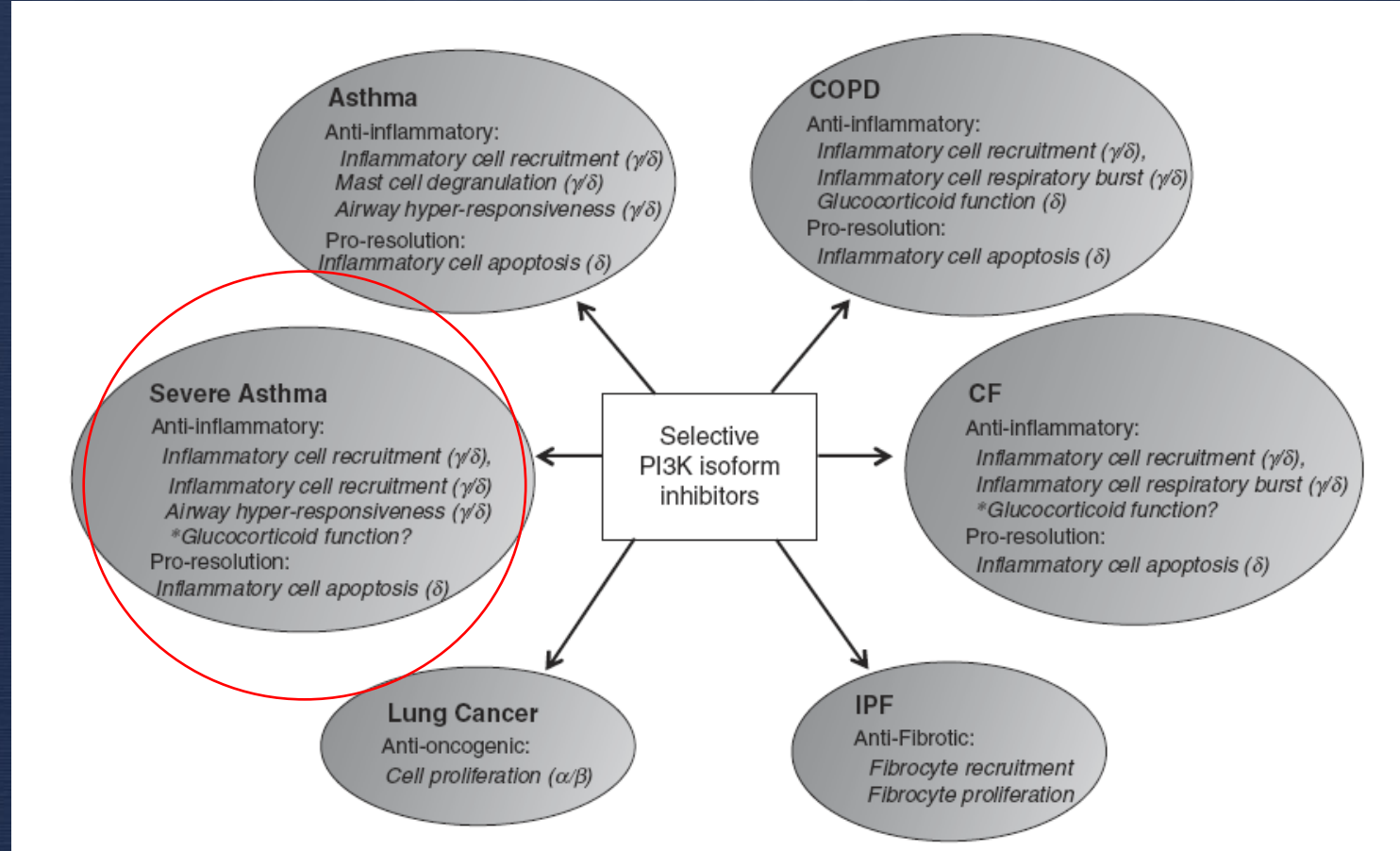
CHRONIC INFLAMMATION, mucus hypersecretion, elevated serum IgE levels, and airway hyperresponsiveness (AHR) are fundamental characteristics of allergic asthma. T helper type 2 (Th2) cells, together with other inflammatory cells such as mast cells, B cells, and eosinophils, are proposed to play critical roles in the initiation, development, and chronicity of this disease (1–6). Upon activation, these inflammatory cells contribute to the production of Th2 cytokines (IL-4, IL-5, and IL-13) and chemokines (eotaxin and RANTES), which are found at elevated levels in asthmatic lungs. Th2 cytokines are pivotal for B cell maturation, IgE synthesis, airway eosinophilia, mucus secretion, and ultimately AHR. The importance of Th2 cytokines in the pathogenesis of allergic asthma has been demonstrated by specific gene knockout and antibody neutralization studies in mouse asthma models (7–9). In addition, RANTES and eotaxin are central to the recruitment of eosinophils to the airways, which is regulated by the interaction of adhesion molecules such as VLA-4 and its ligand VCAM-1 (10, 11). AHR is thought to result from the combination of submucosal edema, infiltration of airway epithelium by leukocytes, damage to epithelial cells, followed by the direct effect of mediators derived from inflammatory cells (1, 6, 12).

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PI3K 아형의 호흡기계 질환에 대한 치료적 적용 시도



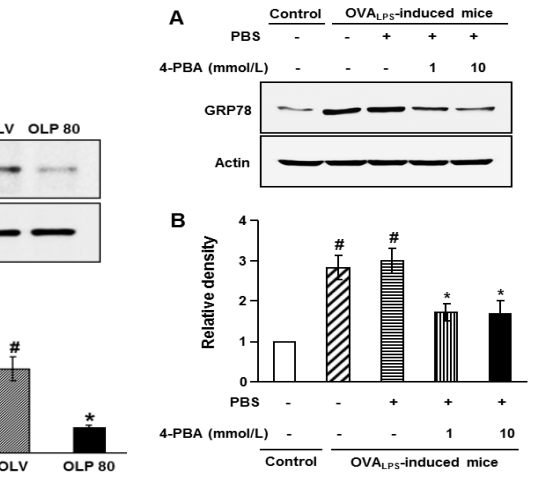
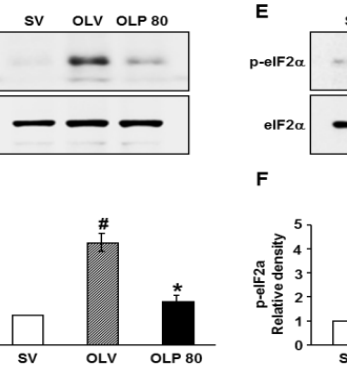
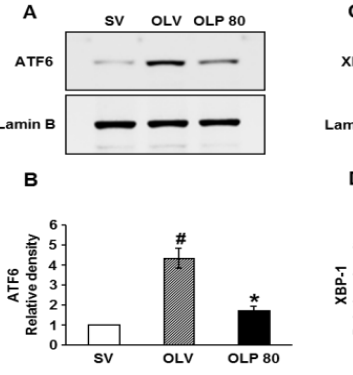
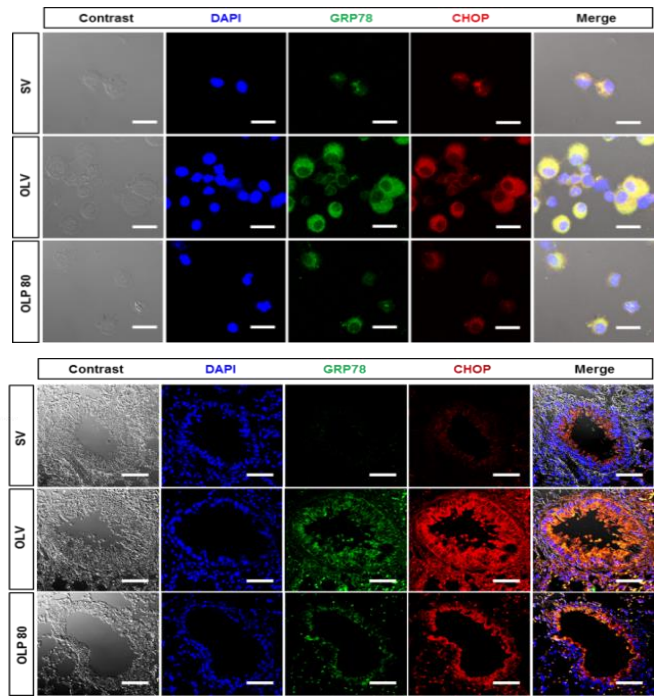
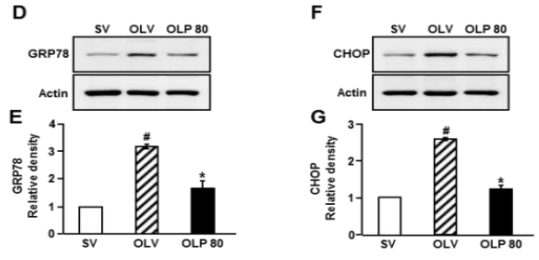
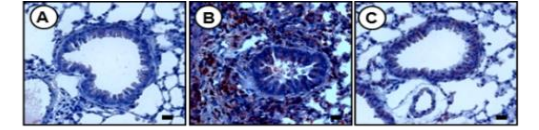
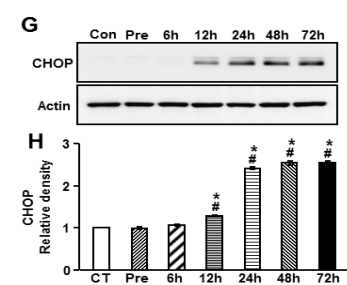
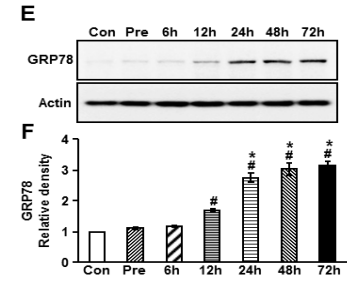
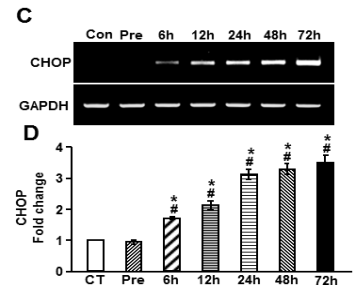
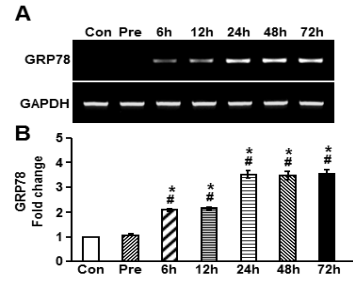
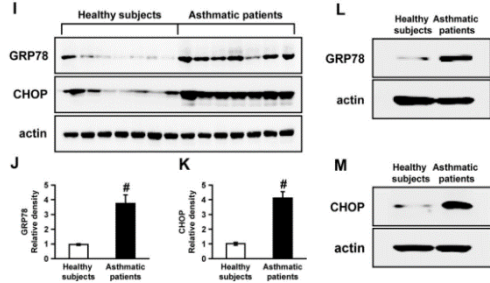
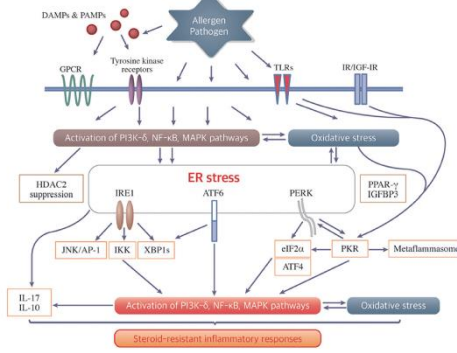
Ther Adv Respir Dis 2010; 4: 19-34

Endoplasmic reticulum stress influences bronchial asthma pathogenesis by modulating nuclear factor κ B activation

So Ri Kim, MD, PhD,* Dong Im Kim, MS,* Mi Ran Kang, BS, Kyung Sun Lee, PhD, Seung Yong Park, MD, PhD, Jae Seok Jeong, MD, and Yong Chul Lee, MD, PhD Jeonju, Korea

ER Stress

- Corticosteroid-resistant severe Neutrophilic asthma





Phosphoinositide 3-kinase- δ regulates fungus-induced allergic lung inflammation through endoplasmic reticulum stress

Kyung Sun Lee,¹ Jae Seok Jeong,² So Ri Kim,^{1,3} Seong Ho Cho,⁴ Narasaiah Kolliputi,⁴ Yun Hee Ko,^{1,3} Kyung Bae Lee,^{1,3} Suk Chul Park,^{1,3} Hae Jin Park,^{1,3} Yong Chul Lee^{1,3}

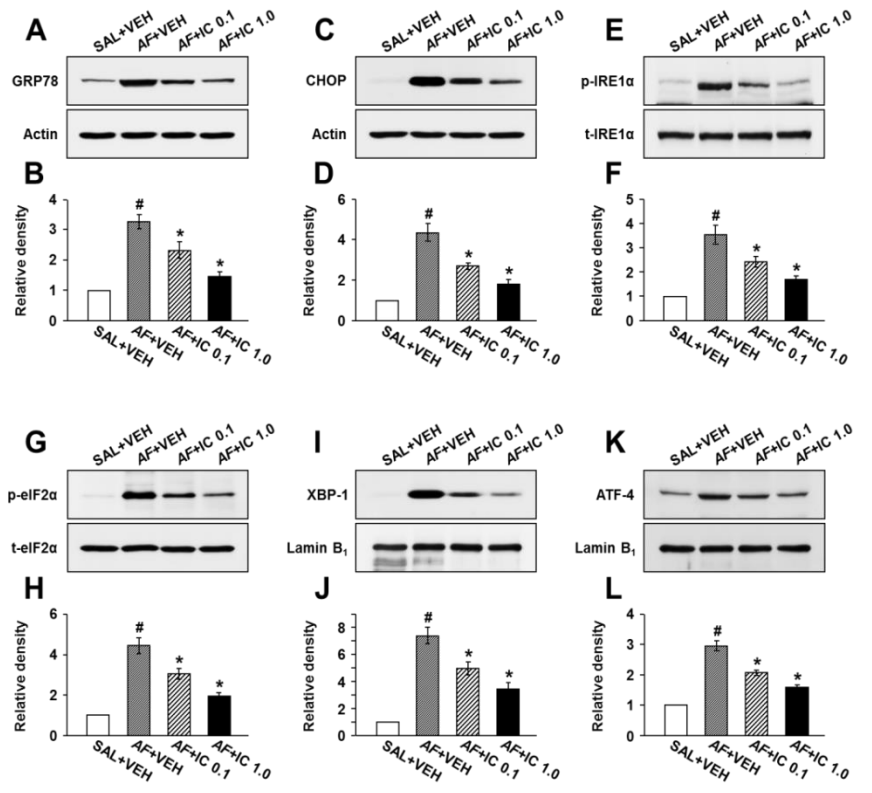
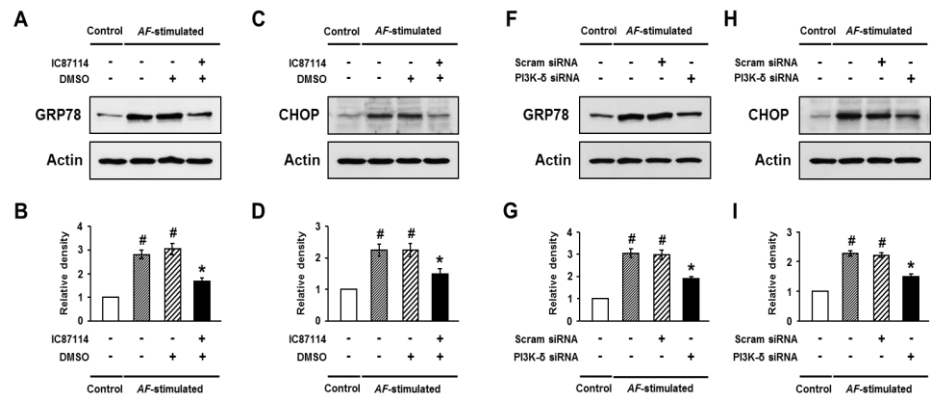
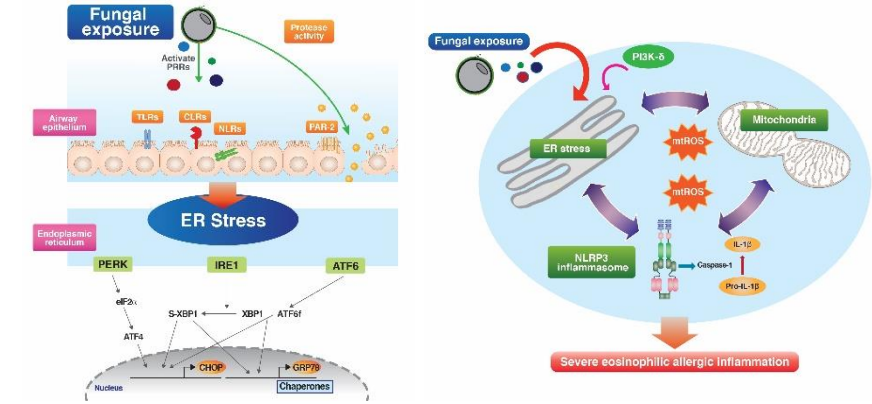
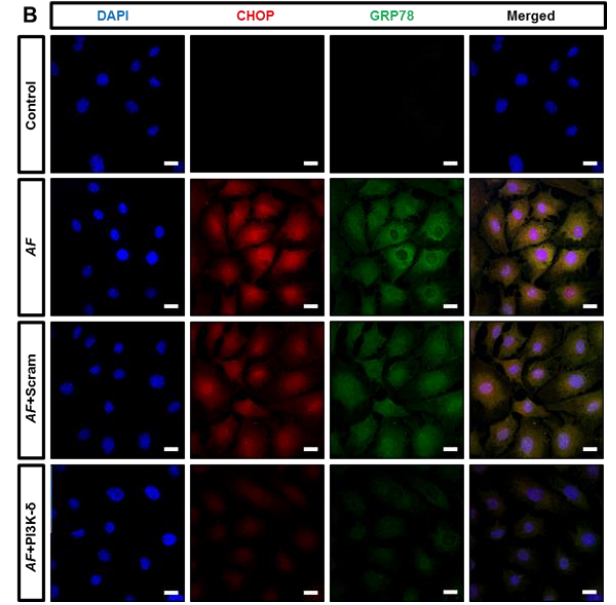
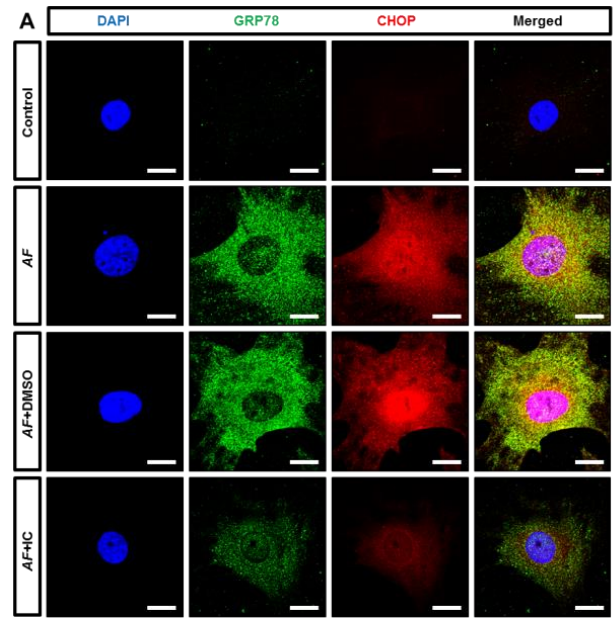
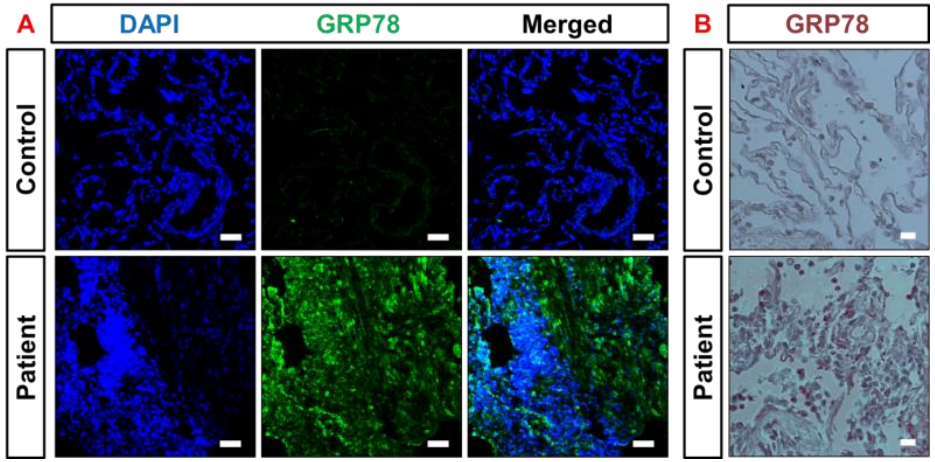
ABSTRACT

Background Sensitisation with *Aspergillus fumigatus* (AF) is known to be associated with severe allergic lung inflammation, but the mechanism remains to be clarified. Phosphoinositide 3-kinase (PI3K)- δ and

Key messages

What is the key question?

Corticosteroid-resistant severe eosinophilic asthma



Severe asthma with fungal sensitization (SAFS) ; PI3K- δ regulates fungus-induced allergic lung inflammation through ER stress

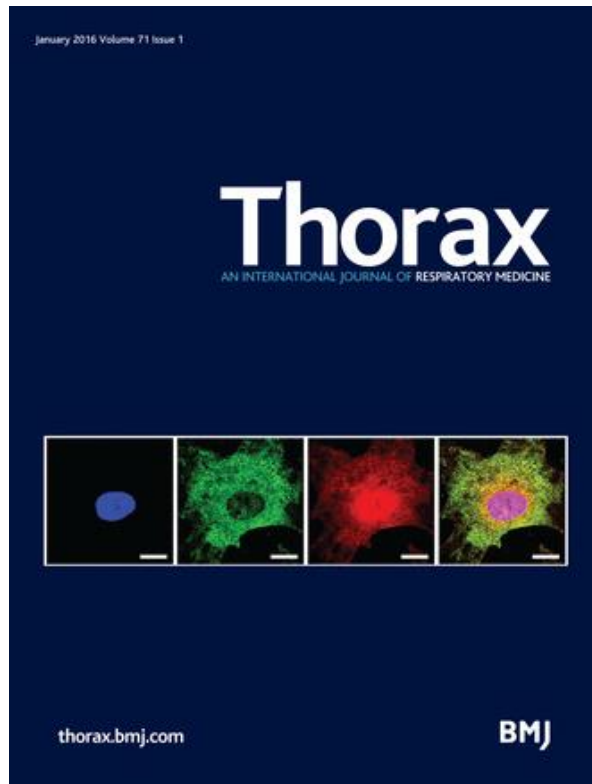
Thorax cover image (January 2016, Volume 71, Issue 1)



ORIGINAL ARTICLE

Phosphoinositide 3-kinase- δ regulates fungus-induced allergic lung inflammation through endoplasmic reticulum stress

Kyung Sun Lee,¹ Jae Seok Jeong,² So Ri Kim,^{1,3} Seong Ho Cho,⁴ Narasaiah Kolliputi,⁴ Yun Hee Ko,^{1,3} Kyung Bae Lee,^{1,3} Suk Chul Park,^{1,3} Hae Jin Park,^{1,3} Yong Chul Lee^{1,3}



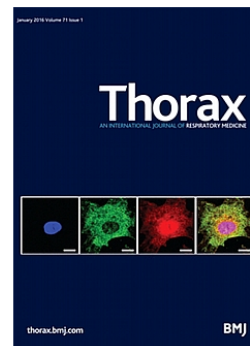
학회·학술 전 북대병원 이용철 교수, Thorax 신년표지 장식
중증천식기관지 세포 - 우주 망원경을 통해 관찰한 듯 아름다워
차원론 기자 (chamed17@bosa.co.kr) 다른 기사 보기

송고시간 : 2016-01-04 12:16

프린트 이메일 기사목록



“이 이미지는 허블 우주 망원경을 통해 얻은 소행성과 주변의 위성이 반짝이는 것처럼 보이지만 사실은 중증 천식 동물 모델의 기관지 세포를 공초점 레이저 현미경으로 관찰한 형광 사진이다”



이는 전북대학교병원 호흡기전문질환센터 이용철 교수팀의 연구 결과가 세계적인 학술지인 흉부학 저널 'Thorax'의 2016년 1월 신년호 표지를 장식하고 'Thorax' 지 편집위원이 설명한 내용이다.

기초의학 결과는 어렵고 멀게만 느껴왔던 사람들에게도 표지 사진 속 이미지는 실제 우주 여행 중 한 장면처럼 기억되기에 충분히 아름답고 생생해 보인다.

이 이미지는 이용철 교수팀의 새로운 논문의 연구 결과로 중증 천식 환자에서 생체 내 발현이 증가되는 소포체 스트레스 (Endoplasmic Reticulum Stress, ER stress)의 표지자에 형광 발색을 일어나게 처리하고 이를 공초점 레이저 현미경을 이용해 촬영한 사진이다.

BEAUTIFUL IMAGES OF ALLERGIC INFLAMMATION

...“The elegant images in figures 2 and 6 could be from the Hubble space telescope but are in fact confocal laser immunofluorescence photomicrographs”...
Editors-in chief, *Highlights from this issue*

“Journal articles read most by allergists & immunologists last month”
by Medscape Allergy

Medscape ALLERGY

Top Journal Articles

Journal articles read most by Allergists & Immunologists last month:

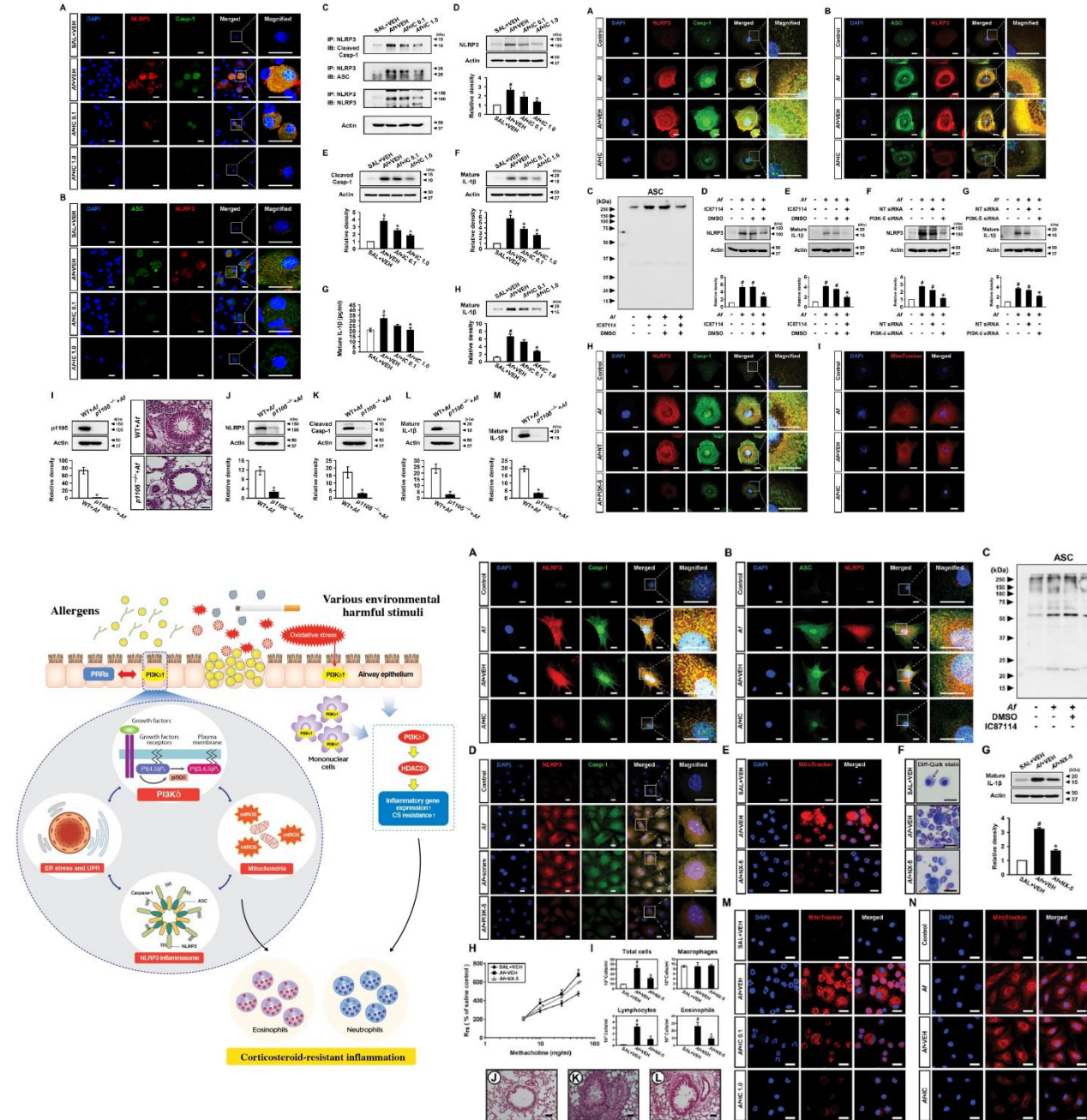
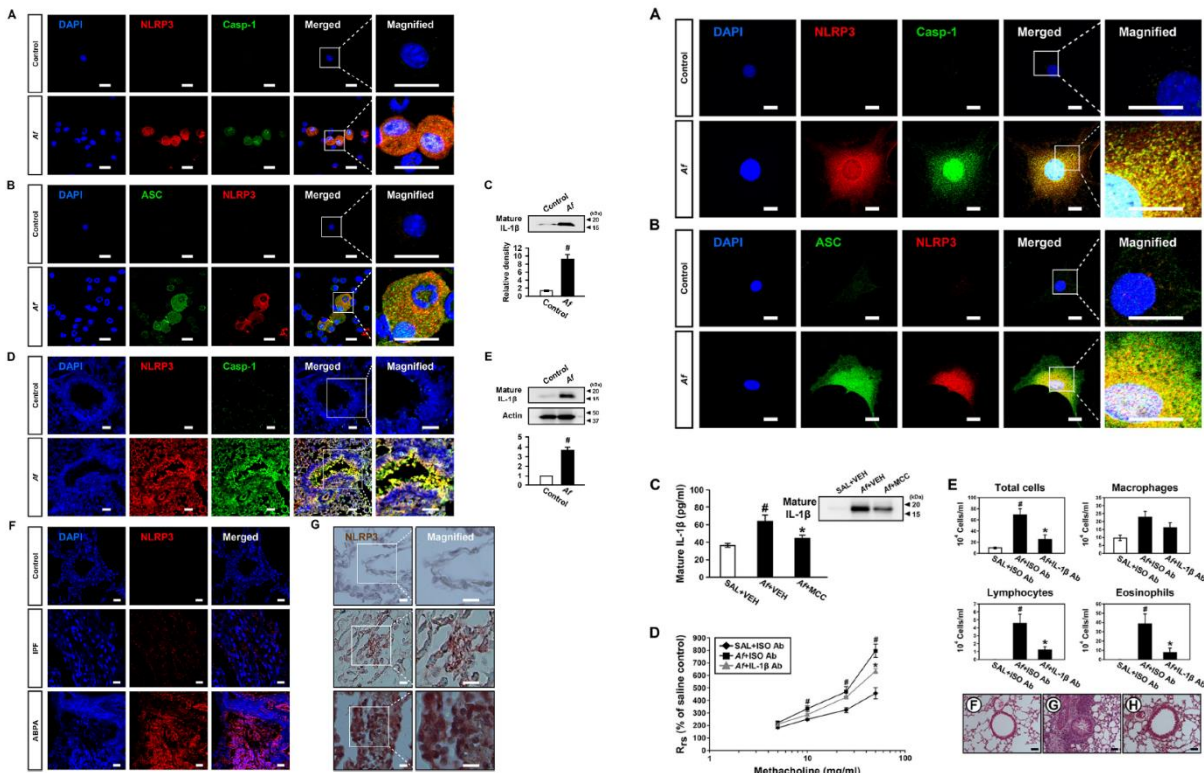
- 1. Phosphoinositide 3-Kinase-Delta Regulates Fungus-Induced Allergic Lung Inflammation Through Endoplasmic Reticulum Stress**
Thorax. 2016;71(1):52-63. © 2016 BMJ Publishing Group Ltd & British Thoracic Society
- 2. New Inhaled Formulations for the Treatment of Asthma in Children and Adolescents**
Pediatr Pharm. 2015;21(12) © 2015 University of Virginia
- 3. Pathogenesis and Prevention Strategies of Severe Asthma Exacerbations in Children**
Curr Opin Pulm Med. 2016;22(1):25-31. © 2016 Lippincott Williams & Wilkins
- 4. Prenatal Tobacco Smoke Exposure Increases Hospitalizations for Bronchiolitis in Infants**
Respiratory Research. 2015;16(152) © 2015 BioMed Central, Ltd.



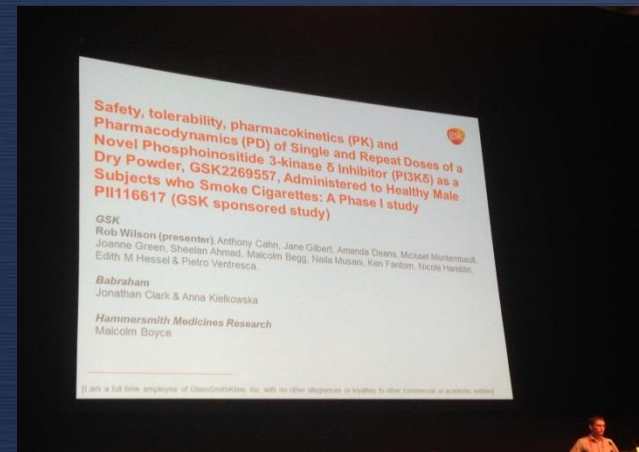
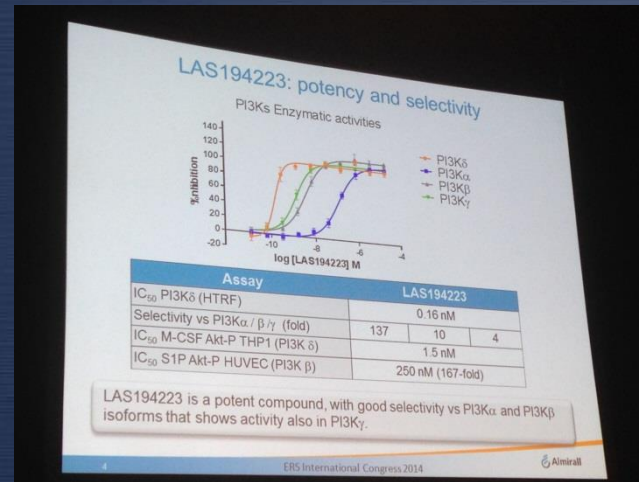
ORIGINAL ARTICLE

Airway epithelial phosphoinositide 3-kinase- δ contributes to the modulation of fungi-induced innate immune response

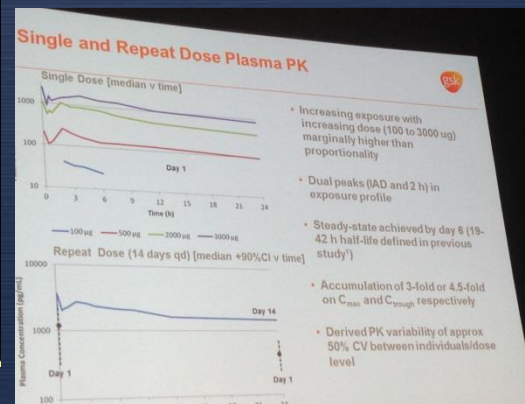
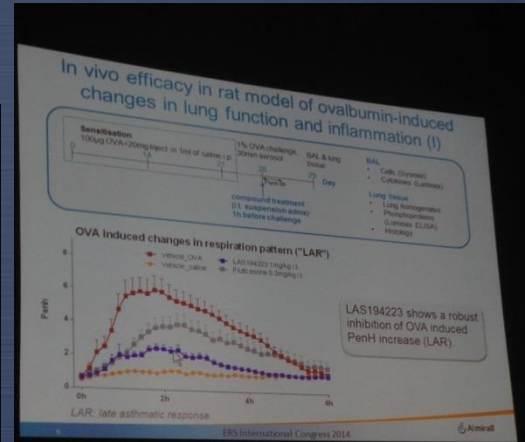
Jae Seok Jeong,¹ Kyung Bae Lee,¹ So Ri Kim,^{1,2} Dong Im Kim,¹ Hae Jin Park,¹ Hern-Ku Lee,³ Hyung Jin Kim,^{2,4} Seong Ho Cho,⁵ Narasaiah Kolliputi,⁵ Soon Ha Kim,⁶ Yong Chul Lee^{1,2}



글로벌 제약 연구소 최근 동향: -PI3K- δ 아형에 대한 치료적 적용 노력



2014-2016 ERS congress



글로벌 제약 연구소 최근 동향:

- PI3K- δ 아형에 대한 치료적 적용 노력

Study #	Abbreviated Title	
115117	FTIH study for GSK2269557	Concluded
115119	GSK2269557/PBO, Ph2A, COPD pts, 14 day RD (DPI), Safety&Tolerability, PK, PD, PGx	Concluded
115120	Proof of Concept for GSK2269557	Cancelled Before Active
115568	GSK2269557 PK bridging study in patients	Cancelled Before Active
116190	Pi3Kd treatment in COPD using GSK2269557 - PoM	Cancelled Before Active
116191	GSK2269557 for Pi3Kd in viral challenge - PoM	Cancelled Before Active
116617	GSK2269557 Dry Powder PK/Safety Study	Concluded
116678	GSK2269557, PBO, Ph2a, COPD pts, 12 weeks RD, Efficacy, Safety, PD, PK, PGx	러시아 포함 4개국진행중 2상
201543	GSK2269557, Placebo, Ph2a, Asthmatic pts, 2-period crossover, 28 day RD (DPI)	50명 목표, 독일단독진행
201544	GSK2269557, Ph1, HV, SD, RD, Ellipta, PK	30명 목표, 소규모, 미/영 단독진행
201928	GSK2269557, Ph2a, COPD patients with exacerbation, RD inhaled, sputum induction	35명 목표, 소규모, 캐나다단독진행
202092	asthma enabling study	Concluded
204655	Efficacy of PI3Kdelta in asthma patient samples	Created in error
204745	A PH2a Study to investigate Safety, PK and PD of GSK2269557 in A PDS/PASLI Pts	4명 목표, 영국단독진행
205192	Pilot study for study 201928 (no IMP)	Cancelled Before Active

Our Research timeline

연도	주관기관(사업)
2002.	과학기술부 주관 MRC (Medical Science and Engineering Research Center) 알레르기성 면역질환 연구센터
2004-2010.	과학기술부 지원 국가지정연구실 선정(기도개형 제어기술개발 연구실)(5년)
2008-2013.	보건복지부 지정 병원특성화 연구센터 (폐 손상 치료제 개발 특성화 센터)
2012-현재.	국내 최초 보건복지부 지정 호흡기전문질환센터
2012-2020.	보건복지부 지원 임상 현장 발굴 국가 핵심 중개 연구 (최첨단 흡입 제형 개발을 통한 난치성 천식 치료 기술 개발)
2014-2019.	한국연구재단 개인기초연구(중견)(세포소기관 복합체 역할규명을 통한 중증 폐질환 발병 기전 연구)
2016-현재.	보건복지부 지정 질환 유효성평가기반구축사업 및 질환 유효성평가지원센터 (호흡기질환 특화 보건의료 T2B(Technology to business)기반구축사업, 폐질환 유효성평가지원센터)
2020-현재.	한국연구재단 개인기초연구(중견) (최첨단 기술을 통한 중증 상·하기도 통합기도질환의 심층 병태생리 규명 및 핵심 제어 기술 개발 연구)

연구과제 최종 성과 및 실적

- 전임상 IND 및 기술 이전 필요 자료 확보

약효 약동학 연구

- 약동학연구 1: 약물 흡수 연구, 각 조직 및 장기 분포 연구, 배설 연구
- 약동학연구 2: 대사경로 연구, 예상 대사체 연구
- 약효연구: 동물모델 약효 연구

안전성 연구

- 비설치류 흡입독성연구: 비글개 DES/2주 DRF, 4주 반복투여 독성
- 안전성약리 연구: 호흡기계, 중추신경계, 심혈관계 영향 평가

제제 연구

- 임상시험용 제제 연구: 임상시험용 제제 연구 및 상용 DPI Device 검토, Device 평가
- 제제안정성 연구: 임상시험용 제제의 안정성 연구

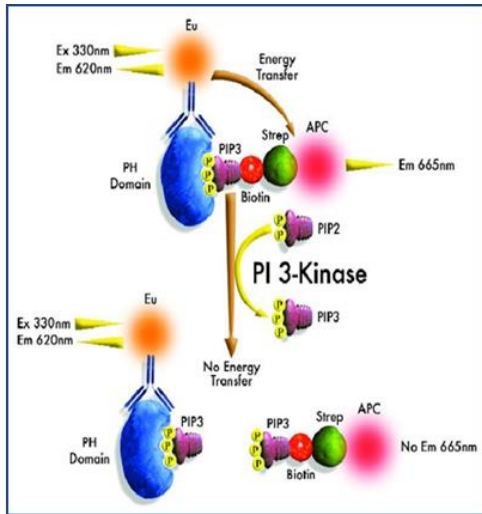
원료 및 제제연구

- 전임상 연구자료 IND filing:
IND 및 기술이전에 필요한 보고서 관리, 자료 요약 및 정리

연구과제 최종 성과 및 실적

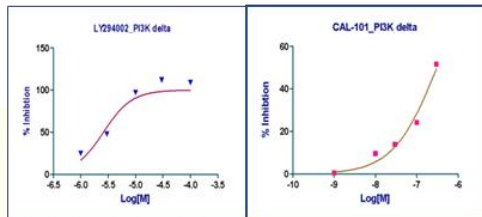
- 연구내용: PI3K isoform inhibitor 개발을 위한 Hit 도출

Assay set up & validation



HTRF assay 원리

[From Merck Millipore]

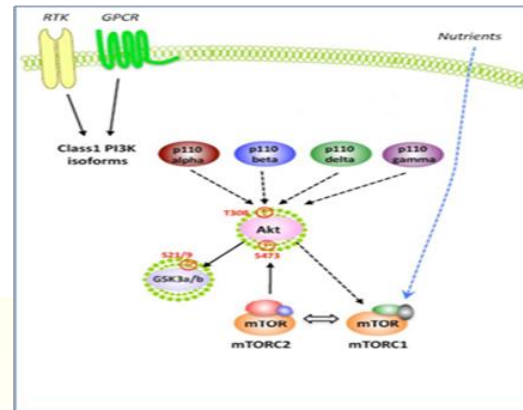


Validation

HTS & PI3K-oriented library screening



HTS system

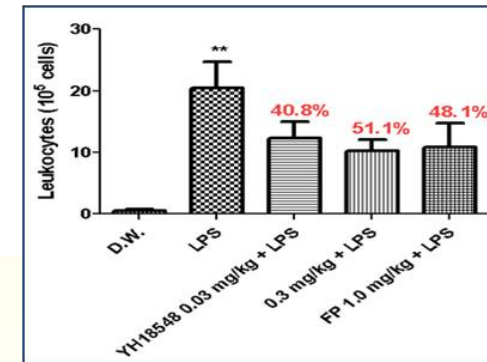


Focused screening

Hit 도출 & modification

	YH18548 (α/γ)	YH20008 (α/γ)	YH21067 (γ)
PI3K γ	5	3	3
PI3K α	6	11	304
PI3K β	> 50,000	> 50,000	> 10,000
PI3K δ	> 50,000	> 50,000	> 10,000

Anti-inflammatory effect of YH18548 in LPS-induced lung inflammation



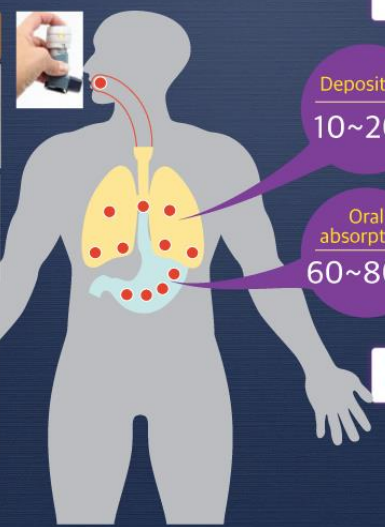
Novel drug development

추진도



성과

- 1200종 이상 신규 NCE 합성 완료
PI3K inhibitor library 구축
효능(SAR), 흡입제형(SPR), 독성(STR) 반영한 화합물 설계
- In vitro Enzyme assay
Cell based assay (pAKT)
hERG assay, Ames test
In vitro ADME (MMS, CYP, Papp)
- LPS 동물 모델 평가
흡입독성용 시료 대량생산
물성, 결정형, 안정성 평가
우수 선도물질군 도출 완료
- 전임상후보물질
YH25487
도출 완료



PI3K- δ inhibitor (YH25487) | Inhaled formulation (Mist)

* NB-2N를 이용한 발생법 확립: 품질의 적용 목적에 따른 입자 크기 조절 및 발생 농도 조절

NB-2N

중량농도 "0"

완전용액

현탁-Sterile

내불리이저를 목적으로 mist 제형 확립
약물의 particle size 조절 및 발생농도 조절 기술 확립

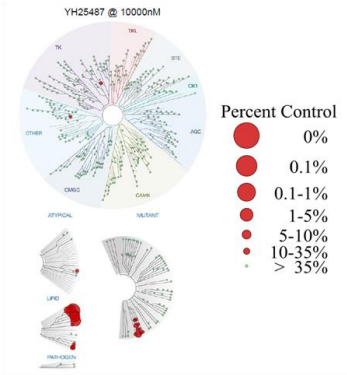
Chamber

10 분간포집 (mg/m³)

30 분간포집 (mg/m³)

Nebulizer 방식에 적용 가능한 mist 제형 확립

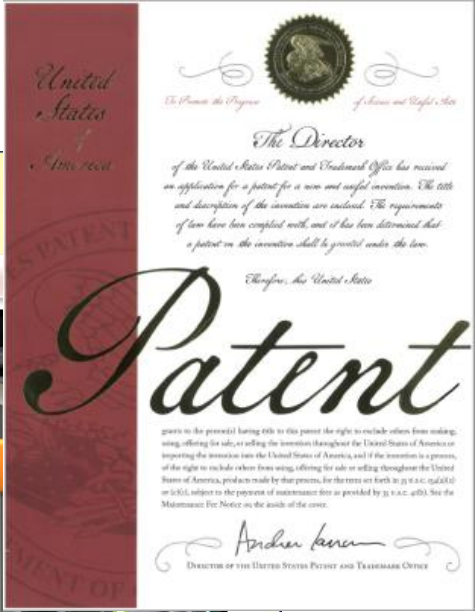
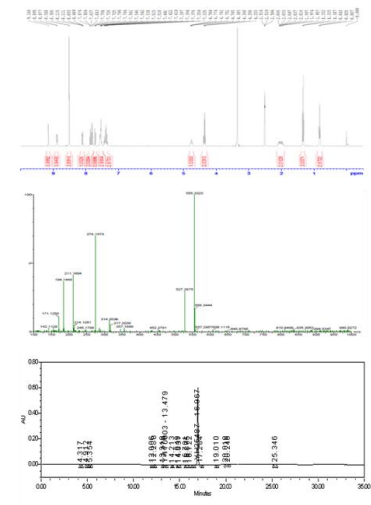
◆ YH25487 kinase selectivity



◆ YH25487 toxicity study

시험항목	위탁연구기관	진행상황	완료예정일
조제물분석법 확립 및 검증	Envigo	진행중	2018. 1.
생체시료분석법 확립 및 검증	Envigo	진행중	2018. 1.
2주 DRF/DES 흡입독성	Envigo 유력	계획	2018. 4.
4주 반복 흡입독성	Envigo 유력	계획	2018. 9.
Safety Pharmacology	Envigo 유력	계획	2018. 9.

◆ 원료 규격 설정 및 특성 연구



BIO International Convention BIO USA 2019. 06

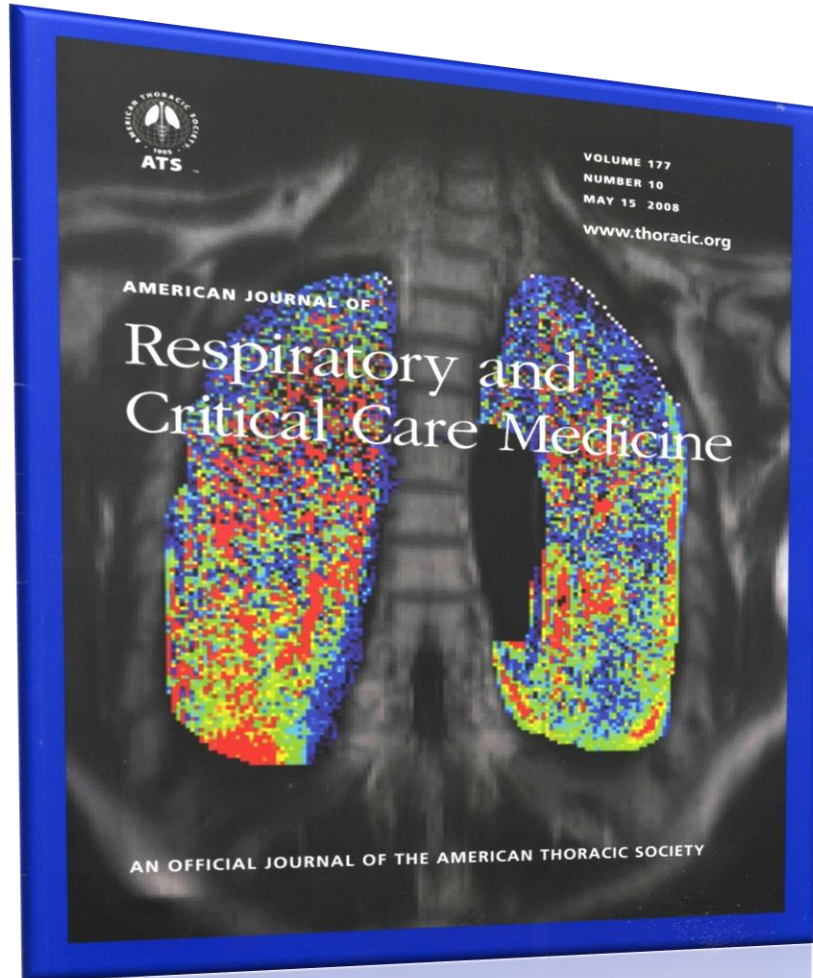


Confidential

YH25487, a potent and selective PI3K δ inhibitor,
as a new promising inhalation drug for asthma

June. 2019
Yuhan Corporation

THE WORKS OF RESEARCH: PAPERS



Am J Respir Crit Care Med (IF: 15.239)

AN OFFICIAL JOURNAL OF THE AMERICAN THORACIC SOCIETY

Vascular Endothelial Growth Factor Modulates Matrix Metalloproteinase-9 Expression in Asthma

Kyung Sun Lee*, Kyung Hoon Min*, So Ri Kim, Seoung Ju Park, Hee Sun Park, Gong Yong Jin, and Yong Chul Lee

Department of Internal Medicine, Department of Radiology, Airway Remodeling Laboratory, Chonbuk National University Medical School, Chonbuk National University, Chonbuk, Korea

Mast Cells Can Mediate Vascular Permeability through Regulation of the PI3K-HIF-1 α -VEGF Axis

Kyung Sun Lee^{1*}, So Ri Kim^{1*}, Seoung Ju Park¹, Kyung Hoon Min¹, Ka Young Lee¹, Yeong Hun Choe¹, Seung Yong Park¹, Ok Hee Chai², Xin Zhang², Chang Ho Song², and Yong Chul Lee¹

¹Department of Internal Medicine and Airway Remodeling Laboratory and ²Department of Anatomy, Chonbuk National University Medical School, Jeonju, South Korea

Rationale: Bronchial inflammation is usually accompanied by increased vascular permeability. Mast cells release a number of mediators that act directly on the vasculature, resulting in vasodilatation, increased permeability, and subsequent plasma protein extravasation. Vascular endothelial growth factor (VEGF) has been implicated to contribute to asthmatic tissue edema through its effect on vascular signaling in allergic airway disease are not clearly understood.

Objectives: An aim of the present study was to investigate the role of mast cells on VEGF-mediated signal transduction in allergic airway disease.

Methods: We used genetically mast cell-deficient $WBB6F_1-Ki\epsilon^{W/W^v}$ (W/W^v) mice and the congenic normal $WBB6F_1^{+/+}$ mouse model for allergic airway disease to investigate the role of mast cells on VEGF-mediated signal transduction in allergic airway disease, more specifically in vascular permeability.

Measurements and Main Results: Our present study, with ovalbumin (OVA)-sensitized without adjuvant and OVA-challenged mice, revealed the following typical pathophysiologic features of allergic airway diseases: increased inflammatory cells of the airways, airway hyperresponsiveness, increased vascular permeability, and increased levels of VEGF. However, levels of VEGF and plasma exudation in W/W^v mice after OVA inhalation were significantly lower than levels in W/W^+ mice. Moreover, mast cell-reconstituted W/W^v mice restored vascular permeability and VEGF levels similar to those of the $WBB6F_1^{+/+}$ mice. Our data also showed that VEGF expression was regulated by hypoxia-inducible factor-1 α (HIF-1 α) activation through the phosphatidylinositol 3-kinase (PI3K)-HIF-1 α pathway in allergic airway disease.

Conclusions: These results suggest that mast cells modulate vascular permeability by the regulation of the PI3K-HIF-1 α -VEGF axis.

Keywords: mast cells; vascular permeability; vascular endothelial

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

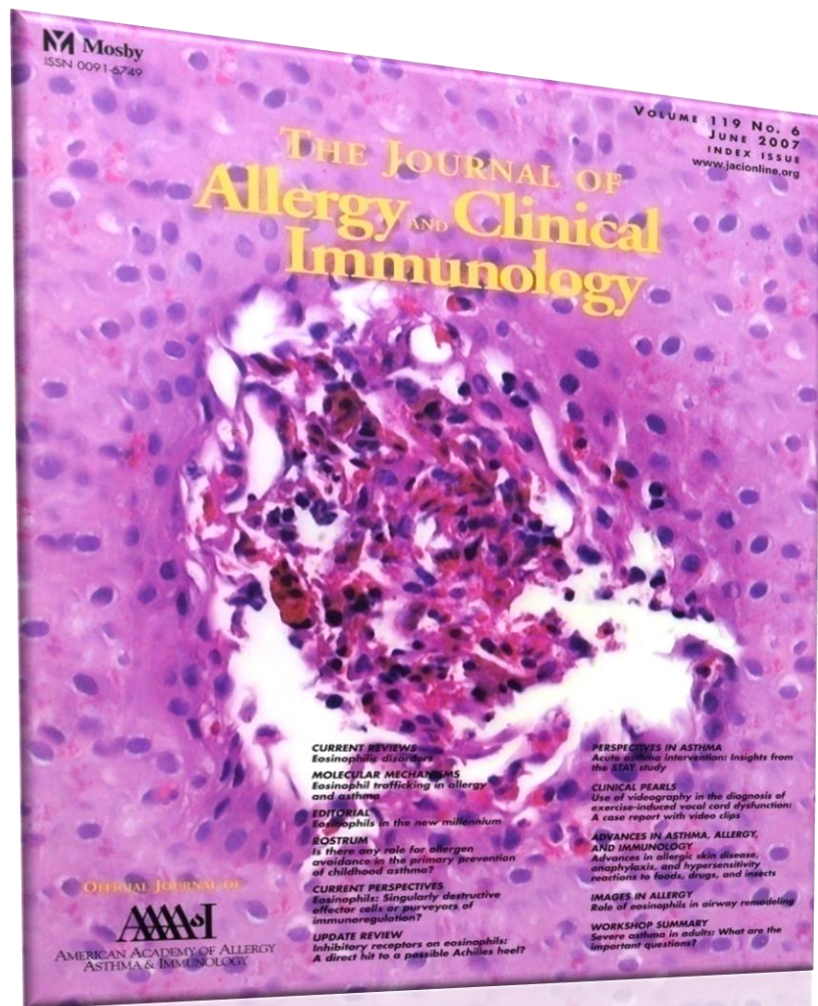
Mast cells are believed to contribute to the development of allergic airway disease accompanied by increased vascular permeability and plasma exudation.

What This Study Adds to the Field

Mast cells can regulate vascular leakage, at least in part via modulation of the PI3K-HIF-1 α -VEGF axis in mice.

resulting in plasma exudation (1). Changes in vascular permeability are crucial to the development and perpetuation of the inflammatory response. Increased vascular permeability causes secretion of intravascular components, which contribute to airway obstruction and hyperresponsiveness (2, 3). Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogenic peptide and plays a key role in vasculogenesis and angiogenesis (4). VEGF also stimulates vascular permeability, which leads to airway inflammation (3, 5, 6). Recently, we demonstrated that VEGF is implicated in the pathogenesis of asthma, and thus the inhibition of VEGF receptor may be a good therapeutic strategy (3, 6, 7). In addition, VEGF is a mediator of vascular and extravascular remodeling and inflammation that enhance antigen sensitization and is crucial in adaptive T-helper type 2 (Th2) cell-mediated inflammation (5).

THE WORKS OF RESEARCH: PAPERS



J Allergy Clin Immunol
(IF: 12.485)

Phosphoinositide 3-kinase- δ inhibitor reduces vascular permeability in a murine model of asthma

Kyung Sun Lee, PhD,^{a,b,c} Seoung Ju Park, MD, PhD,^{a,b,c}

Cysteinyl leukotriene upregulates IL-11 expression in allergic airway disease of mice

Kyung Sun Lee, PhD, So Ri Kim, MD, PhD, Hee Sun Park, MD, PhD,

Mechanisms of allergy and clinical immunology

Involvement of sirtuin 1 in airway inflammation and hyperresponsiveness of allergic airway disease

So Ri Kim, MD, PhD,^{a,b,c} Kyung Sun Lee, PhD,^{a,c*} Seoung Ju Park, MD, PhD,^{a,c*} Kyung Hoon Min, MD, PhD,^{a,c} Yeong Hun Choe, MD,^{a,c} Hee Moon, MD,^{a,c} Wan Hee Yoo, MD, PhD,^{a,c} Han-Jung Chae, PhD,^{b,c} Myung Kwan Han, PhD,^d and Yong Chul Lee, MD, PhD^{a,c} Jeonju, South Korea

Background: Bronchial asthma is a chronic inflammatory disorder of the airways characterized by increased expression of multiple inflammatory genes. Acetylation of histones by histone acetyltransferases is associated with increased gene transcription, whereas hypoacetylation induced by histone deacetylases is associated with suppression of gene expression. Sirtuin 1 (SIRT1) is a member of the silent information regulator 2 family that belongs to class III histone deacetylase. **Objective:** This study aimed to investigate the role of SIRT1 and the related molecular mechanisms in the pathogenesis of allergic airway disease.

Methods: By using a murine model of ovalbumin (OVA)-induced allergic airway disease and murine tracheal epithelial cells, this study investigated the involvement of SIRT1 and its signaling networks in allergic airway inflammation and hyperresponsiveness.

Results: In this study with mice after inhalation of OVA, the increased levels of SIRT1, hypoxia-inducible factor 1 α (HIF-1 α), and vascular endothelial growth factor protein in the lungs after OVA inhalation were decreased substantially by the administration of a SIRT1 inhibitor, sirtinol. We also showed that the administration of sirtinol reduced significantly the increased numbers of inflammatory cells of the airways: airway hyperresponsiveness; increased levels of IL-4, IL-5, and IL-13; and increased vascular permeability in the lungs after OVA inhalation. In addition, we have found that inhibition of SIRT1 reduced OVA-induced upregulation of HIF-1 α in airway epithelial cells.

Conclusions: These results indicate that inhibition of SIRT1

hyperresponsiveness through the modulation of vascular endothelial growth factor expression mediated by HIF-1 α in mice. (J Allergy Clin Immunol 2010;125:449-60.)

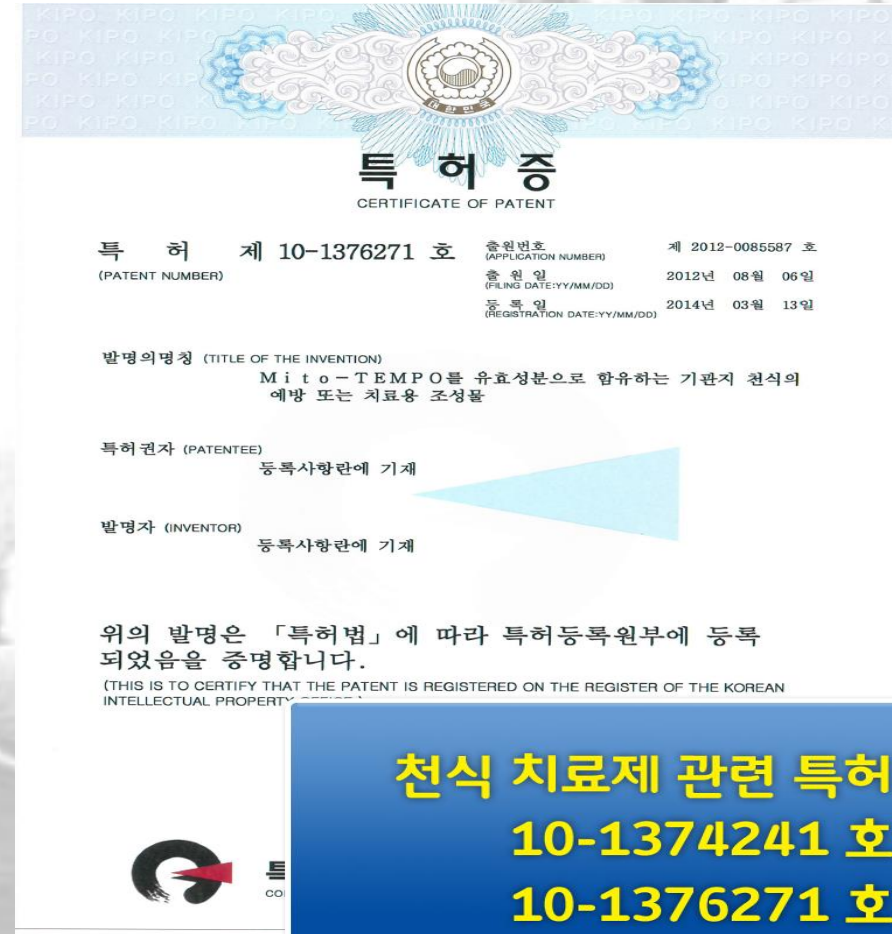
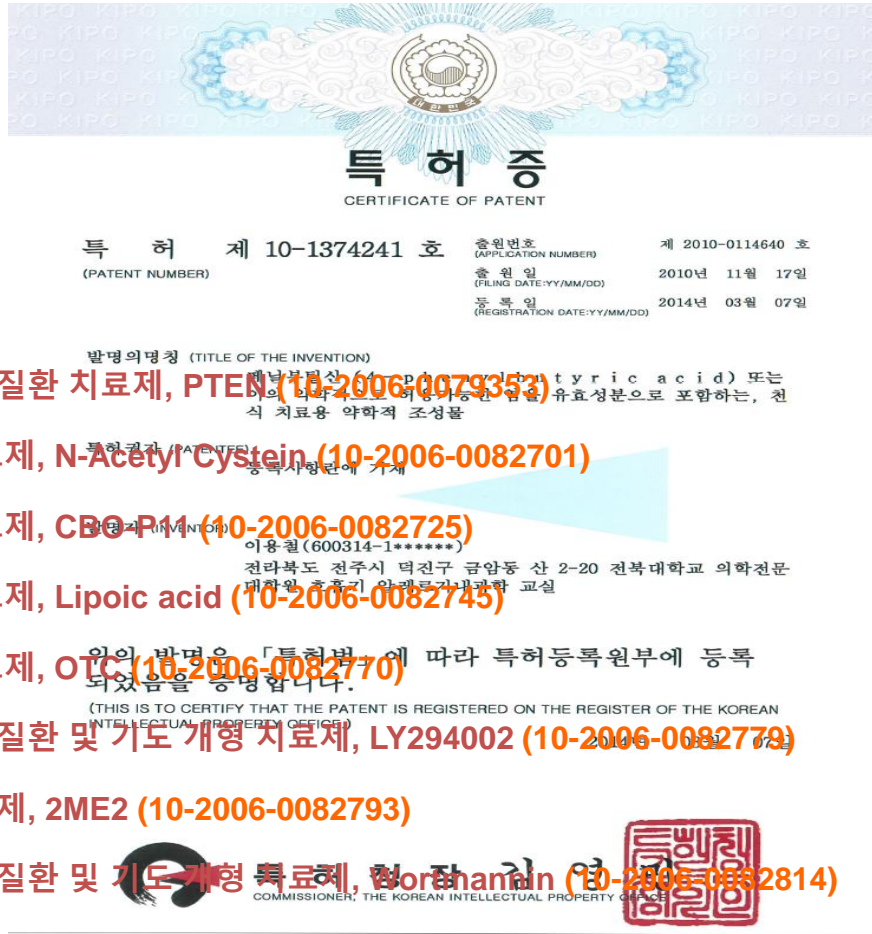
Key words: Allergic airway disease, histone deacetylase, hypoxia-inducible factor 1 α , sirtuin 1, sirtinol, vascular endothelial growth factor

Bronchial asthma is a chronic inflammatory disorder of the airways characterized by an associated increase in airway hyperresponsiveness.¹ Th2 cells participate in asthma pathogenesis by stimulating B cells that produce allergen-specific IgE, as well as cells into the airways.^{2,3} Cytokines produced by Th2 cells, including IL-4, IL-5, and IL-13, exacerbate airway inflammation.⁴

The status of histone acetylation is associated with the transcriptional regulation of genes and is controlled with the reversible covalent modifying enzymes histone acetyltransferase and histone deacetylase (HDAC).⁵ HDACs are divided into 2 classes. Class I members (HDACs 1, 2, 3, 8, and 11) are transcriptional corepressors homologous to yeast RPD3.⁶ Class II members (HDACs 4, 5, 6, 7, 9, and 10) have domains similar to yeast histone deacetylase 1.⁷ Class III HDACs are distinct from class I and II HDACs and are homologues of the yeast silent information regulator 2 (Sir2).⁸ Mammalian sirtuin 1 (SIRT1; Sir2 α) is a member of the Sir2 family. Sir2 has been implicated in caloric restriction, aging, and inflammation.⁹

SIRT1 deacetylates several transcription factors that govern metabolism, endocrine signaling, and inflammation, including

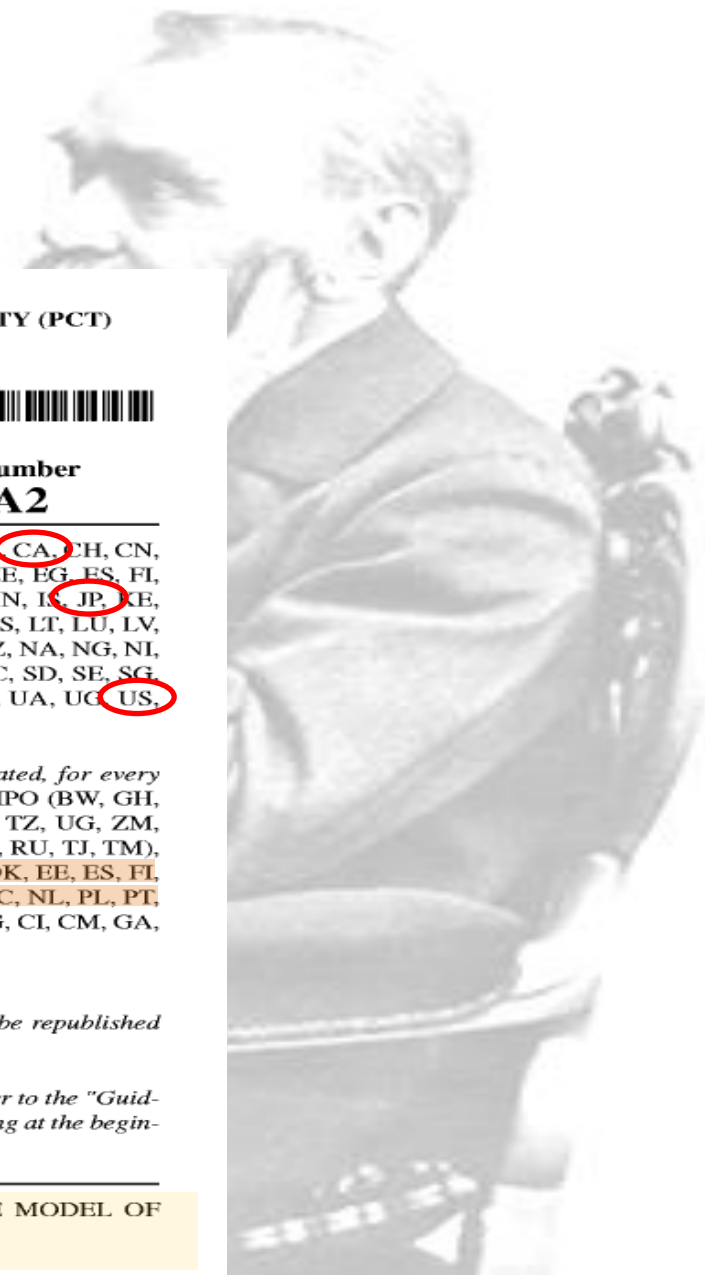
THE WORKS OF RESEARCH: PATENT



- 알레르기성 기도 질환 치료제, PTEN (10-2006-0079353)
- 급성 폐 손상 치료제, N-Acetyl Cystein (10-2006-0082701)
- 급성 폐 손상 치료제, CBO-P11 (10-2006-0082725)
- 급성 폐 손상 치료제, Lipoic acid (10-2006-0082745)
- 급성 폐 손상 치료제, OTC (10-2006-0082770)
- 알레르기성 기도 질환 및 기도 개형 치료제, LY294002 (10-2006-0082779)
- 기관지 천식 치료제, 2ME2 (10-2006-0082793)
- 알레르기성 기도 질환 및 기도 개형 치료제, Worchamanin (10-2006-0082814)
- Blockade of airway hyperresponsiveness and inflammation in a murine model of asthma by insulin-like growth factor binding protein-3 (IGFBP-3) (06727569.3-1223-I)
- 급성 폐 손상 치료제, COMP-Ang1 (10-2008-0046344)

천식 치료제 관련 특허 등록
10-1374241 호
10-1376271 호

THE WORKS OF RESEARCH: PATENT



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau



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(71) Applicant (for all designated States)
BIO-TECH
Office Tel, 187-1 Gumi-Dong, Bundang-Gu, Seong-Nam-City, Kyunggi-Do (KR).

(71) Applicant (for US only): **LEE, Yong, Chul** [KR/KR];
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South Korea (KR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

IGFBP-3 관련 공개 특허

- 미국 US 2008152623A2
- 유럽연합 EP 1853323A2
- 캐나다 CA 2600755A1
- 일본 JP 2008-530081A
- 대한민국 KR 2008-0015775A

Y, BZ, CA, CH, CN,
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E, CG, CI, CM, GA,
TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BLOCKADE OF AIRWAY HYPERRESPONSIVENESS AND INFLAMMATION IN A MURINE MODEL OF ASTHMA BY INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3 (IGFBP-3)



THE WORKS OF RESEARCH: PATENT



United States of America



To Promote the Progress of Science and Useful Arts

The Director

of the United States Patent and Trademark Office has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this United States

Patent

grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America, and if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States of America, products made by that process, for the term set forth in 35 U.S.C. 154(a)(2) or (c)(1), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b). See the Maintenance Fee Notice on the inside of the cover.

Ander Lane
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

(12) **United States Patent**
Lee et al.

(10) **Patent No.:** US 10,292,969 B2
(45) **Date of Patent:** May 21, 2019

- (54) **COMPOSITION FOR PREVENTION OR TREATMENT OF BRONCHIAL ASTHMA COMPRISING PKR INHIBITOR AS ACTIVE INGREDIENT**
- (71) Applicants: **INDUSTRIAL COOPERATION FOUNDATION CHONBUK NATIONAL UNIVERSITY**, Jeonju-si, Jeollabuk-do (KR); **CHONBUK NATIONAL UNIVERSITY HOSPITAL**, Jeonju-si, Jeollabuk-do (KR)
- (72) Inventors: **Yong Chul Lee**, Jeonju-si (KR); **So Ri Kim**, Jeonju-si (KR)
- (73) Assignee: **Industrial Cooperation Foundation Chonbuk National University**, Jeonju (KR)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 35 days.

- (52) **U.S. CL**
CPC **A61K 31/429** (2013.01); **A23L 29/00** (2016.08); **A23L 33/10** (2016.08); **A23L 2002/00** (2013.01)
- (58) **Field of Classification Search**
CPC . A61K 31/429; A61K 31/4178; A61K 31/428
See application file for complete search history.

- (56) **References Cited**
U.S. PATENT DOCUMENTS
8,329,646 B2* 12/2012 Tisdale A61K 31/198 514:21.91
- FOREIGN PATENT DOCUMENTS**
WO 2000035920 6/2000
WO 2009070378 6/2009
WO 2012072269 6/2012
- OTHER PUBLICATIONS**

Jammi, N. V. et al., "Small molecule inhibitors of the RNA-dependent protein kinase", *Biochemical and Biophysical Research Communications*, vol. 308, 2003, pp. 50-57.
* cited by examiner

Primary Examiner — Kendra D Carter
(74) *Attorney, Agent, or Firm* — Hunton Andrews Kurth LLP

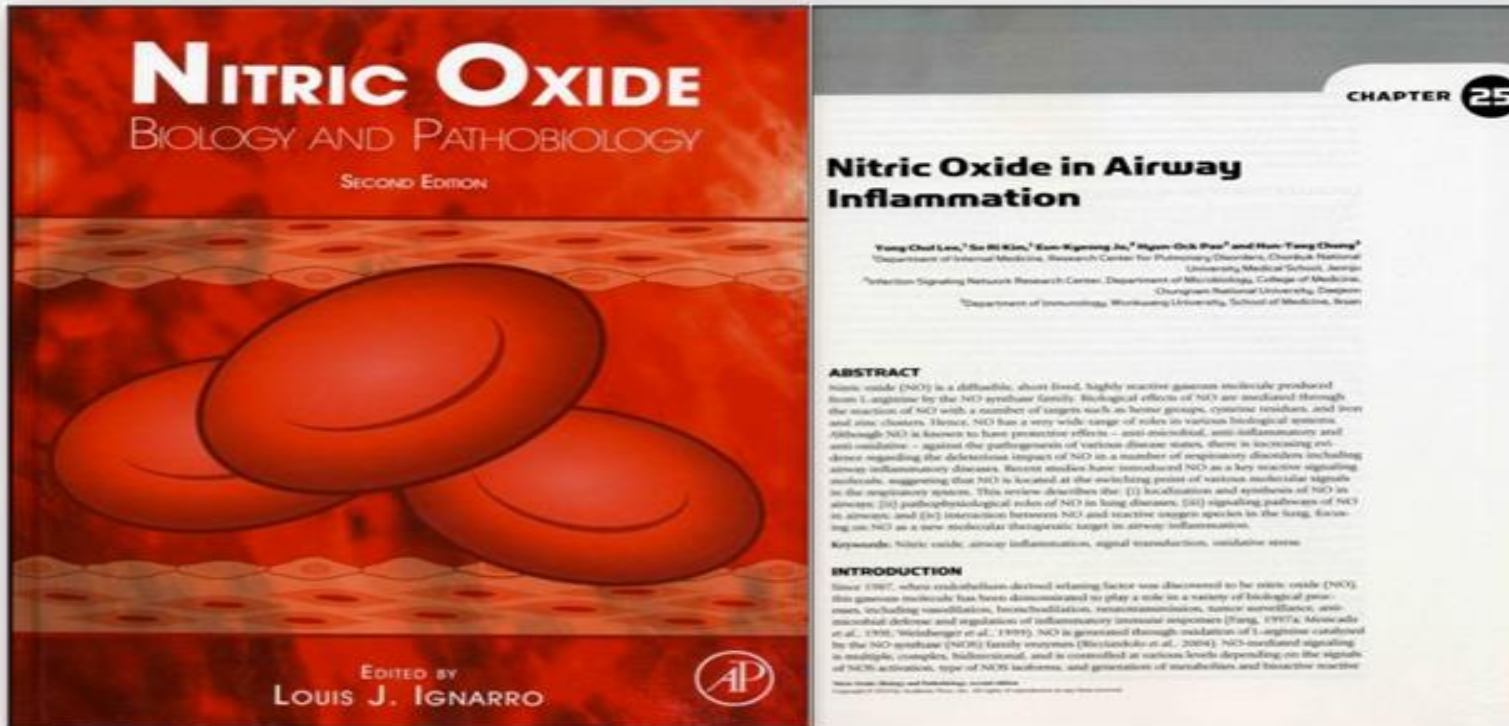
(57) **ABSTRACT**
The present invention relates to a composition for prevention or treatment of bronchial asthma comprising a PKR inhibitor as an active ingredient. The PKR inhibitor and derivatives thereof according to the present invention can be used as a pharmaceutical for prevention, amelioration or treatment of bronchial asthma and as a supplementary health food because the PKR inhibitor and derivatives thereof reduce the total counts of inflammatory cells, eosinophils, neutrophils and lymphocytes in bronchoalveolar lavage fluid of neutrophilic severe asthma-induced mice, reduce airway inflammation and airway hyper-responsiveness, and reduce inflammatory mediators.

4 Claims, 7 Drawing Sheets

- (21) Appl. No.: **15/547,030**
- (22) PCT Filed: **Dec. 16, 2015**
- (86) PCT No.: **PCT/KR2015/013791**
§ 371 (c)(1),
(2) Date: **Jul. 27, 2017**
- (87) PCT Pub. No.: **WO2016/129802**
PCT Pub. Date: **Aug. 18, 2016**
- (65) **Primary Publication Data**
US 2018/0000794 A1 Jan. 4, 2018
- (30) **Foreign Application Priority Data**
Feb. 12, 2015 (KR) 10-2015-0021423
- (51) **Int. CL**
A61K 31/429 (2006.01)
A61K 31/4178 (2006.01)
A61K 31/428 (2006.01)
A23L 33/10 (2016.01)
A23L 29/00 (2016.01)

THE WORKS OF RESEARCH: PUBLICATIONS

- 주관연구책임자인 이용철 교수는 1998년 노벨생리의학상을 수상하는 등 세계 최고 권위자인 루이스 이그나로(Louis J. Ignarro) UCLA 의과대학 교수와 저서 '**Nitric Oxide; Biology and Pathobiology**'을 함께 출간함.



THE WORKS OF RESEARCH: PUBLICATIONS

국제 전문 학술 서적 출판사
Springer 의뢰 천식 관련 서적 집필

The screenshot shows the Amazon product page for the book "Severe Asthma: Toward Personalized Patient Management" (1st ed., 2018 Edition) edited by Yong Chul Lee, So Ri Kim, and Seong Ho Cho. The book cover is displayed on the left, featuring a colorful abstract design. The right side of the page shows the price as \$109.00 for the hardcover, with a pre-order option. The page also includes navigation links, a search bar, and a "prime student" discount banner.

The book cover is primarily blue with a vertical green stripe on the left side. The title "Severe Asthma" is written in large white letters, with the subtitle "Toward Personalized Patient Management" below it. The editors' names, "Lee · Kim · Cho Eds.", are listed at the top. The Springer logo is at the bottom right. The back cover (left side) contains a detailed description of the book's content, focusing on the state-of-the-art knowledge on severe asthma, its clinical significance, and the role of biomarkers in diagnosis and treatment. The ISBN 978-981-10-1997-5 is printed at the bottom left.

This book presents state of the art knowledge on severe asthma with the aim of providing readers with a clear understanding of, first, the heterogeneity of the condition and of patients' symptom profiles and responses to therapy and, second, the future implications of this heterogeneity for individualized patient care. After an opening section that offers an overview of severe asthma, including its clinical significance, the pathogenesis, available diagnostic approaches, and treatment options are described in detail. The sections on diagnosis and treatment cover the role of biomarkers, the use of radiologic diagnostic modalities, and both pharmacologic and non-pharmacologic therapies, including emerging options that will address hitherto unmet needs of patients. The outcomes of cutting-edge preclinical and clinical research are carefully documented and numerous useful tips provided on patient management. The inclusion of many informative schematic figures will assist readers in grasping the contents easily. The book will be of high value for medical students, researchers, general physicians, specialists, and paramedical staff.

Lee · Kim · Cho
Eds.
Severe Asthma
Toward Personalized
Patient Management

Severe Asthma
Toward Personalized
Patient Management

Springer

Internal Medicine
ISBN 978-981-10-1997-5
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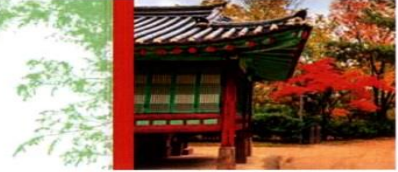
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THE WORKS OF RESEARCH: AWARD

WAC XXIV World Allergy Congress
14-17 October 2015
2015 *Seoul, Korea*



제 7회 화이자 의학상 임상의학상 수상



Abstract

Pawankar

Pawankar
Allergy and Immunology Past-President
and International Committee Chair

연구과제 최종 성과 및 실적

- 논문 및 저서

ORIGINAL ARTICLE

Phosphoinositide 3-kinase- δ regulates fungus-induced allergic lung inflammation through endoplasmic reticulum stress

Kyung Sun Lee,¹ Jae Seok Jeong,² So Ri Kim,^{1,3} Seong Ho Cho,⁴ Narasaiah Kolliputi,⁴ Yun Hee Ko,^{1,3} Kyung Bae Lee,^{1,3} Suk Chul Park,^{1,3} Hae Jin Park,^{1,3} Yong Chul Lee^{1,3}

ABSTRACT
Background Sensitisation with *Aspergillus fumigatus* (Af) is known to be associated with severe allergic lung inflammation, but the mechanism remains to be clarified. Phosphoinositide 3-kinase (PI3K)- δ and

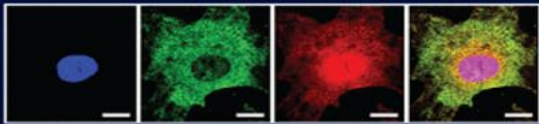
Key messages

What is the key question?

BEAUTIFUL IMAGES OF ALLERGIC INFLAMMATION
...“The elegant images in figures 2 and 6 could be from the Hubble space telescope but are in fact confocal laser immunofluorescence photomicrographs”...
Editors-in chief, *Highlights from this issue*

January 2016 Volume 71 Issue 1

Thorax
AN INTERNATIONAL JOURNAL OF RESPIRATORY MEDICINE



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BMJ

PI3K- δ 의 호산구성 중증 천식에서의 새로운 역할 규명

This book presents state of the art knowl-
available diagnostic approaches, and treatment options are described in detail. The sections on diagnosis and treatment cover the role of biomarkers, the use of radiologic diagnostic modalities, and both pharmacologic and non-pharmacologic therapies, including emerging options that will address hitherto unmet needs of patients. The outcomes of cutting-edge preclinical and clinical research are carefully documented and numerous useful tips provided on patient management. The inclusion of many informative schematic figures will assist readers in grasping the contents easily. The book will be of high value for medical students, researchers, general physicians, specialists, and paramedical staff.

Lee · Kim · Cho *Eds.*

Severe Asthma
Toward Personalized Patient Management

Yong Chul Lee
So Ri Kim
Seong Ho Cho
Editors

Choi
Editors
Severe Asthma
Toward Personalized Patient Management

Internal Medicine
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Springer

PI3K- δ 아형 관련 중증 천식 기전 연구 결과 내용을 기반한 저서 출간

PI3K delta could be a biomarker for eosinophilic nasal polyps

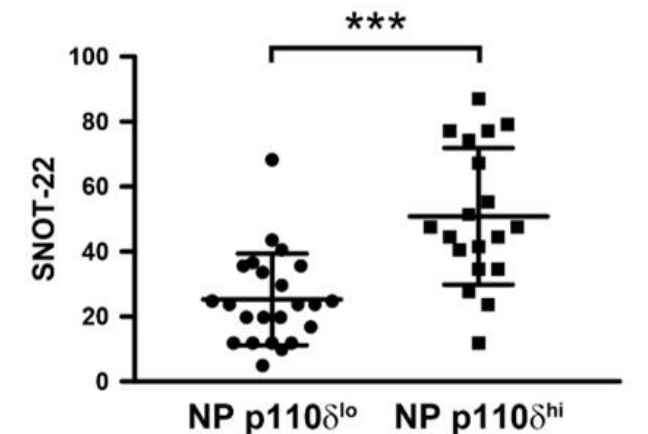
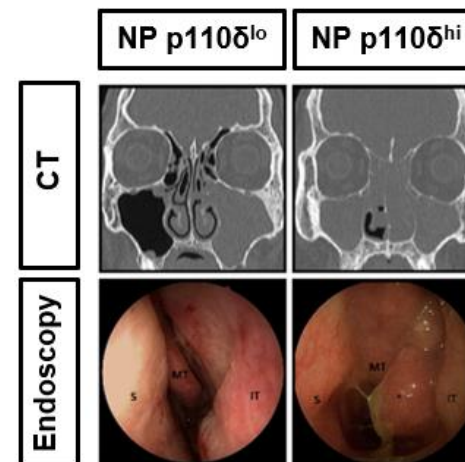
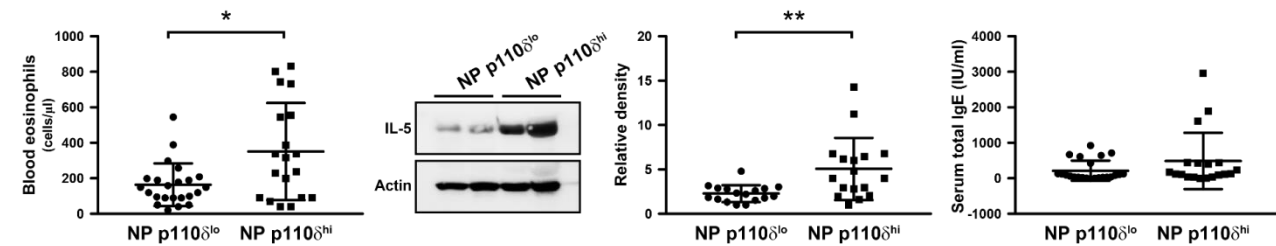
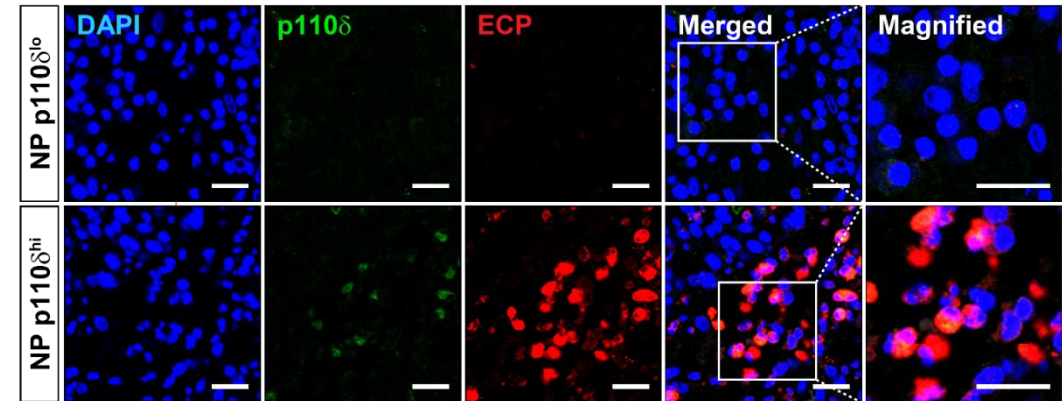
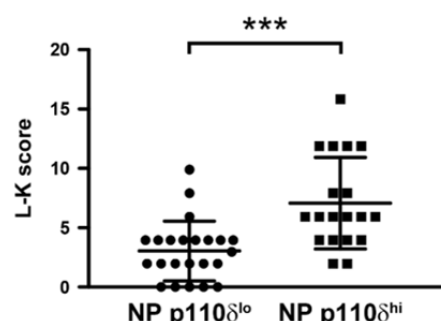
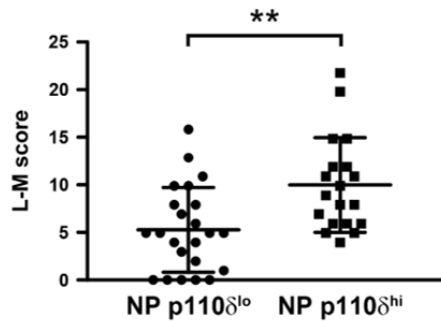
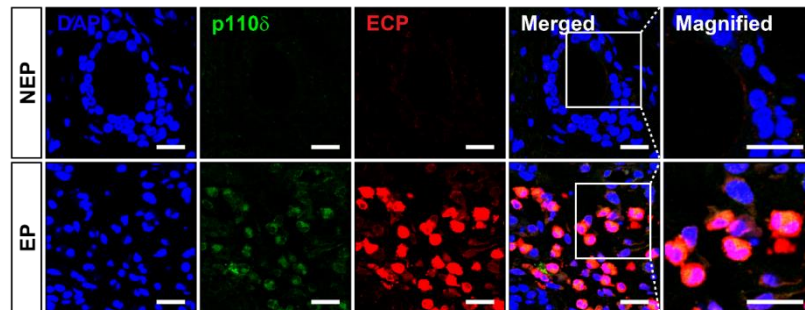
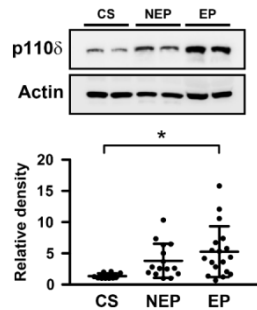
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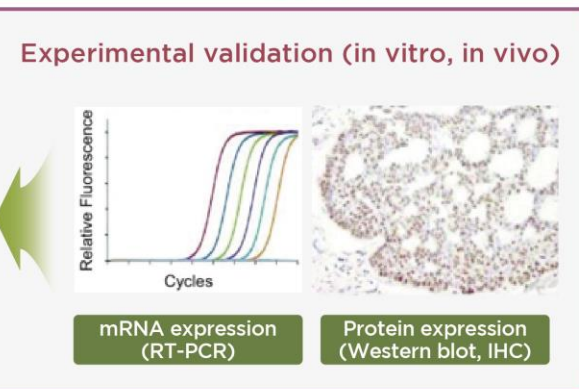
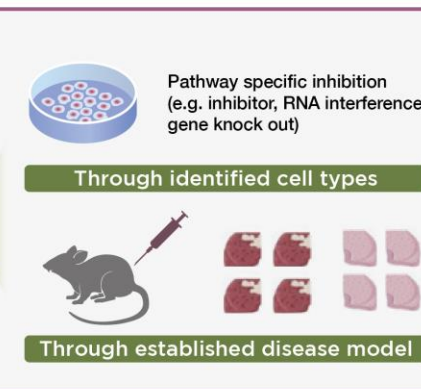
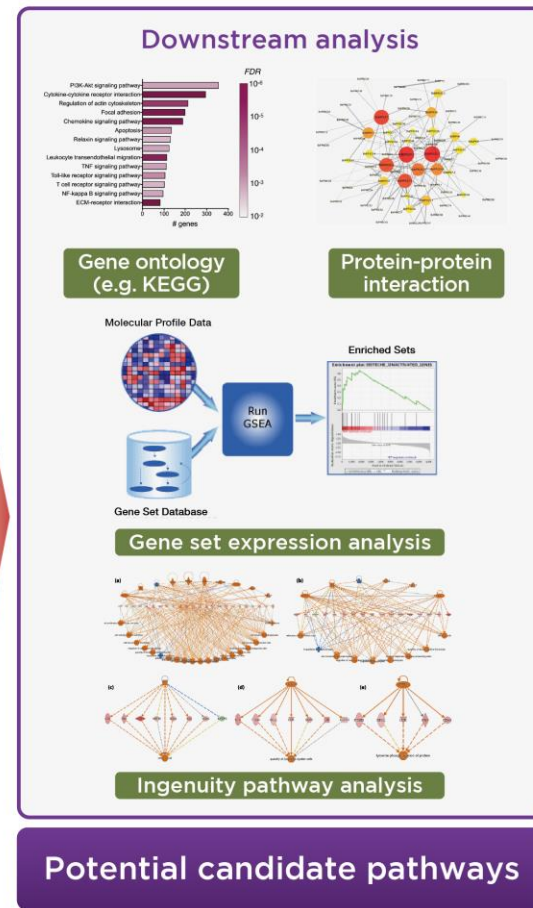
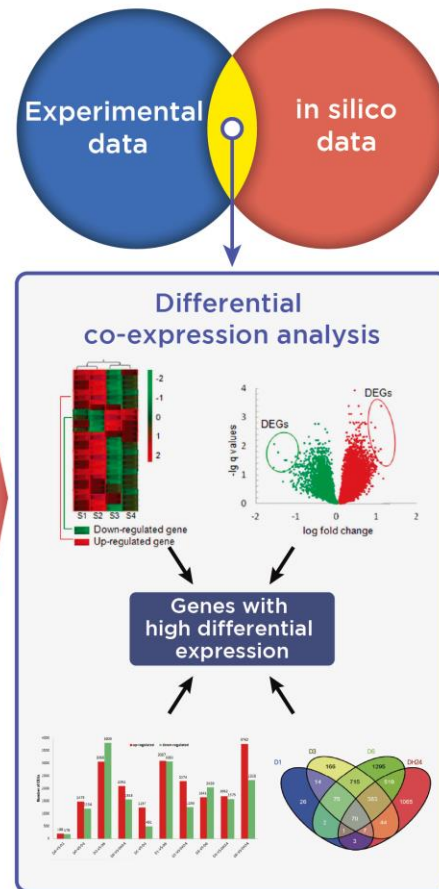
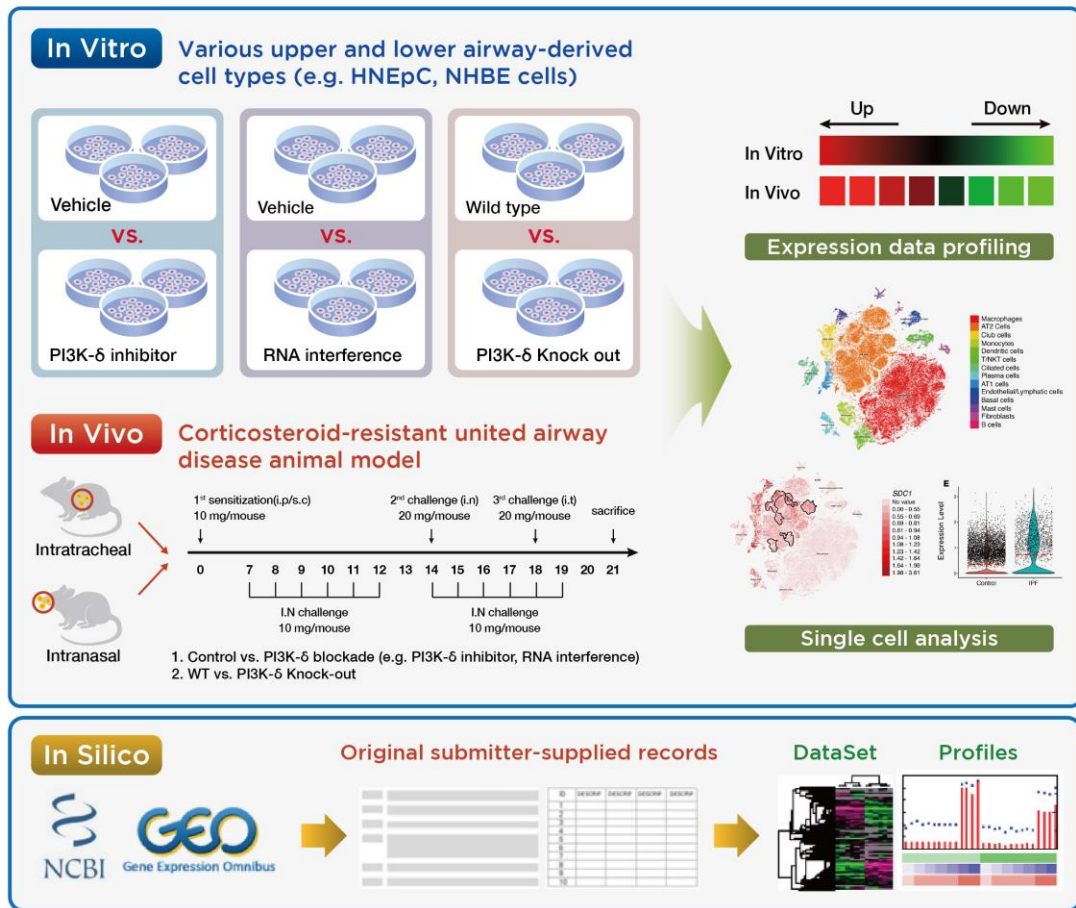
Phosphoinositide 3-kinase-delta could be a biomarker for eosinophilic nasal polyps

Jong Seung Kim^{1,3}, Jae Seok Jeong², Kyung Bae Lee², So Ri Kim^{2,3}, Yeong Hun Choe², Sam Hyun Kwon^{1,3}, Seong Ho Cho⁴ & Yong Chul Lee^{2,3}

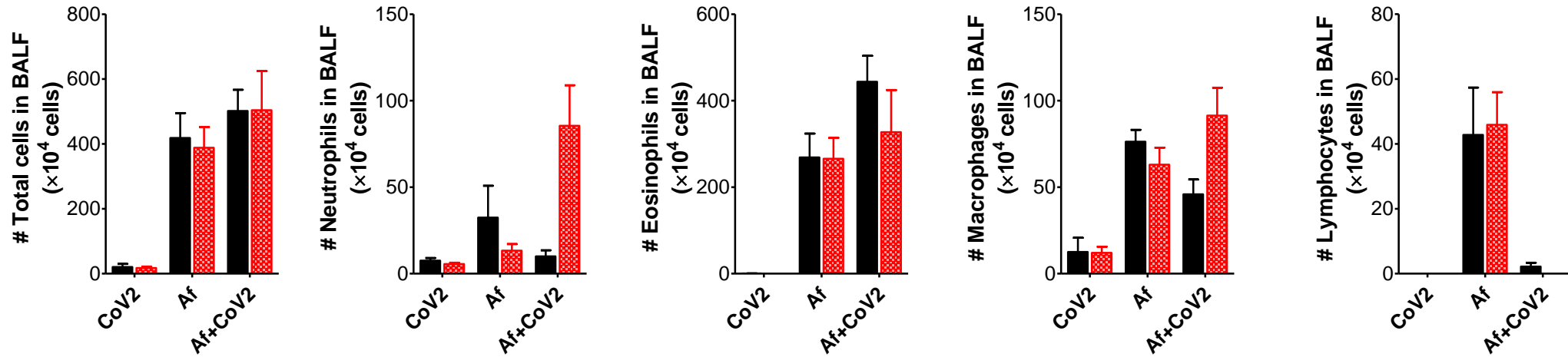
Nasal polyps (NP) cause diverse clinical symptoms of chronic rhinosinusitis (CRS). Chronic inflammation of sinonasal mucosa is known to be crucial in NP formation. We aimed to define the implications of phosphoinositide 3-kinase (PI3K)- δ in nasal inflammation associated with NP by analyzing NP tissue obtained from CRS patients. Results showed that expression of p110 δ , a regulatory subunit of PI3K- δ , in NP tissue was increased compared to control tissue. Increased p110 δ expression was closely correlated with more severe CRS features. Interestingly, p110 δ expression was increased in eosinophilic NP, which are closely related to more complicated clinical courses of the disease. Furthermore, CRS patients possessing NP with higher p110 δ expression displayed more eosinophils in NP tissue and blood, higher levels of IL-5 in NP tissue, and more severe features of the disease. Therefore, PI3K- δ may contribute to the formation of NP, especially eosinophilic NP associated with more severe clinical presentations and radiological features.

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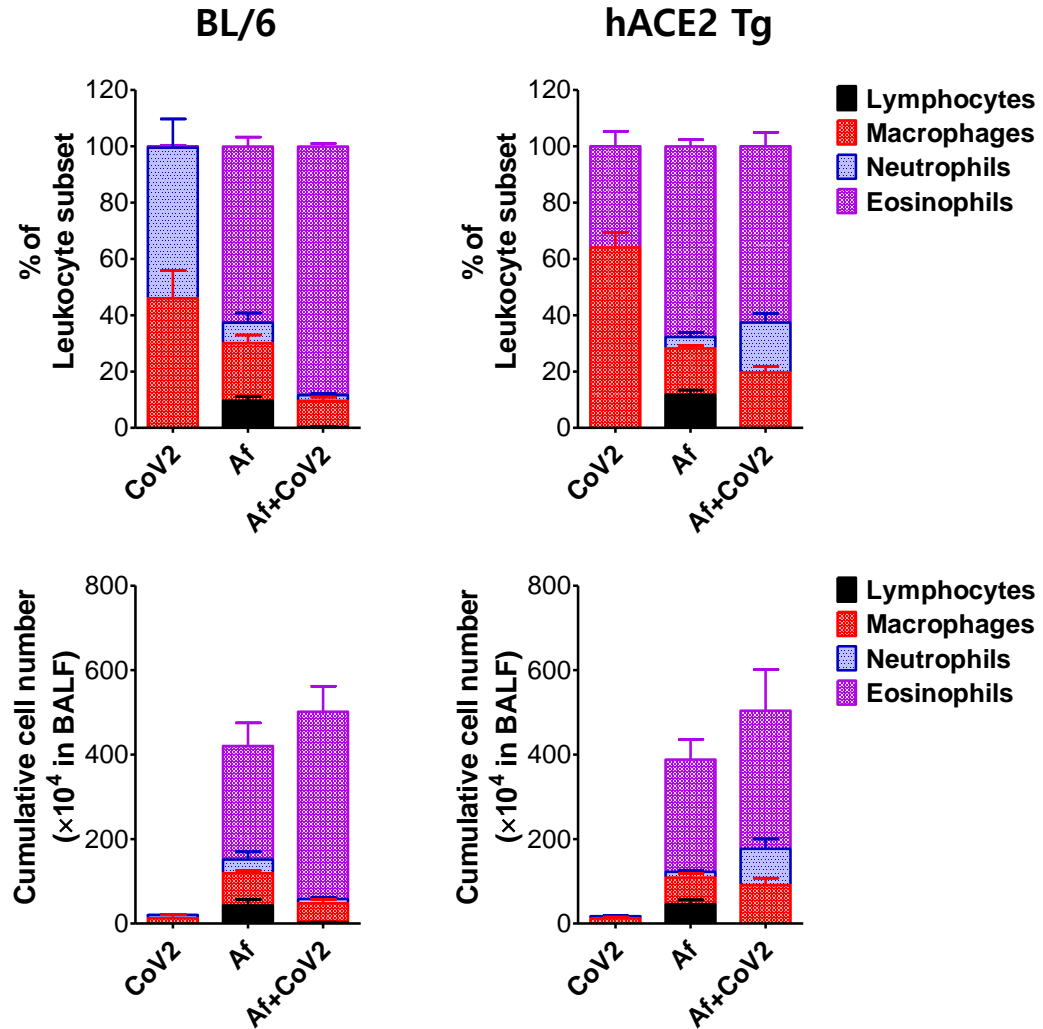
SARS-CoV2 infection facilitates the accumulation of neutrophils in Af-induced eosinophilic asthma



완벽하게 구사된 실험은 아니지만 특수시설내에서 BALF harvest시 오랜기간 작업을 하다보니 BALF내 세포가 damage를 받았음. 그러나, Wright's Giemsa staining에 의하여 eosinophil의 형태는 분명히 볼 수 있었으며, neutrophil과 macrophage의 구분 또한 세포의 전체적 윤곽과 damage를 파악하여 count하였으나, lymphocyte와 macrophage의 구분이 확연하지 않음으로 lymphocyte의 수는 부정확할 수 있음을 유념하여 두시기 바랍니다.

결과를 살펴보면 BL/6는 SARS-CoV2에 의하여 감염이 일어나지 않음으로 eosinophil이 증가되는 현상을 보여주지만 hACE2 Tg mouse는 SARS-CoV2감염에 의하여 eosinophil의 변화는 없고 유의적으로 neutrophil이 증가되는 현상으로 나타나는 것으로 보여짐

SARS-CoV2 infection facilitates the accumulation of neutrophils in Af-induced eosinophilic asthma



전 슬라이드의 내용을 바탕으로 다르게 표시하는 것으로 각 leukocyte의 % 또는 전체 leukocyte의 accumulated total number를 표시한 그림입니다.

앞서 이야기한 것처럼 hACE2 Tg mouse에서 SARS-CoV2의 감염에 의하여 neutrophil이 증가되는 현상이 관찰되는 것으로 보여짐

Take home messages

- 임상의로로서 의학 연구의 궁극적인 목표는 **난치성 질병에 대한 새로운 병태생리 규명 및 이를 통한 치료제** 개발
- 개인의 **연구 주기**마다의 고유 역할이 있음 (능력배양기, 확장기, 성숙기)
- 각 주기에 맞는 적절한 **연구주제** 설정 및 **인적 네트워크** 구축이 필요
- **연구 결과의 확장**을 통한 **새로운 질병개념의 설정/확립** 및 심화 연구(반복)

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Inhalation Toxicology Center,
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Kyu Hong Lee



Morsani College of Medicine,
University of South Florida,
Tampa, FL, USA

Seong Ho Cho,

Closing

“I have a dream of taking our nation’s science to a whole new level and I hope that these scientific developments return to the patients”