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Global New Drug Development Company

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Healthy and Happy Life

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- 호중구감소증
- 구강점막염
- 급성방사선증후군
- 비알코올성지방간염
- 기타 염증성질환
  (류마티스관절염, 건선, 패혈증)

100조원 이상 시장 가능성

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- 거담제
- 항결핵제

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2000억원 시장 가능성

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Healthy
and
Happy Life

Ch.1

EC-18면역조절 플랫폼 기술

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EC-18 적응증 파이프라인

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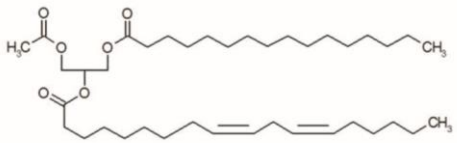
타겟 적응증	비임상	임상 1상	임상 2상	Note
비알콜성 지방간염 (NASH)				
전이암 (Metastatic Cancer)				
항암화학요법 유발 호중구 감소증 (CIN)				Breakthrough Therapy 지정 목표
항암화학 방사선요법 유발 구강 점막염 (CRIOM)				Fast Track 지정 (2018. 02)
급성방사선증후군 (ARS)				희귀의약품 지정 (2017. 12), Animal Rule (2상만으로 종료)
류마티스 관절염				
패혈증				
아토피 피부염				
건선				
천식				
만성 폐쇄성 폐질환 (COPD)				

암 염증성 질환

EC-18 면역조절 플랫폼 기술

암, 염증 질환에 대한 혁신적인 치료기술

전이암, 염증성 질환의 예방 및 치료를 위한 혁신적 치료기술

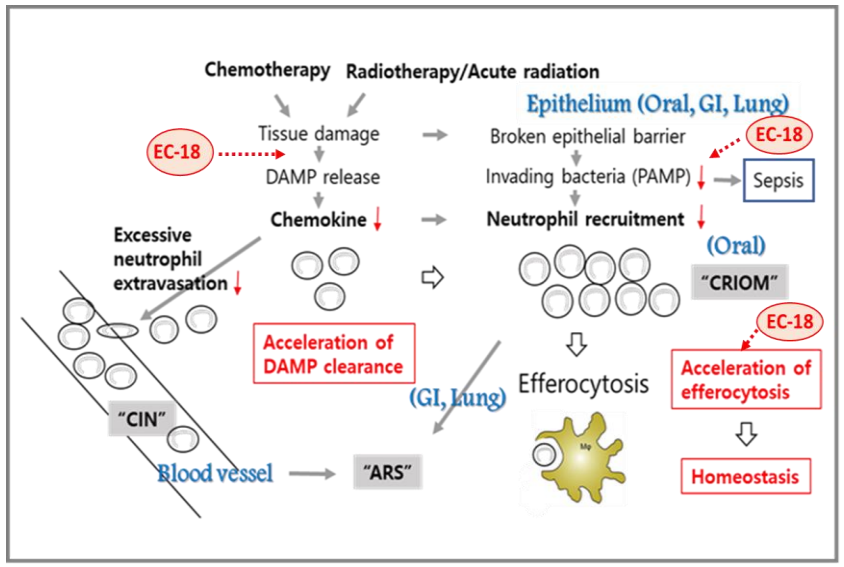


EC-18

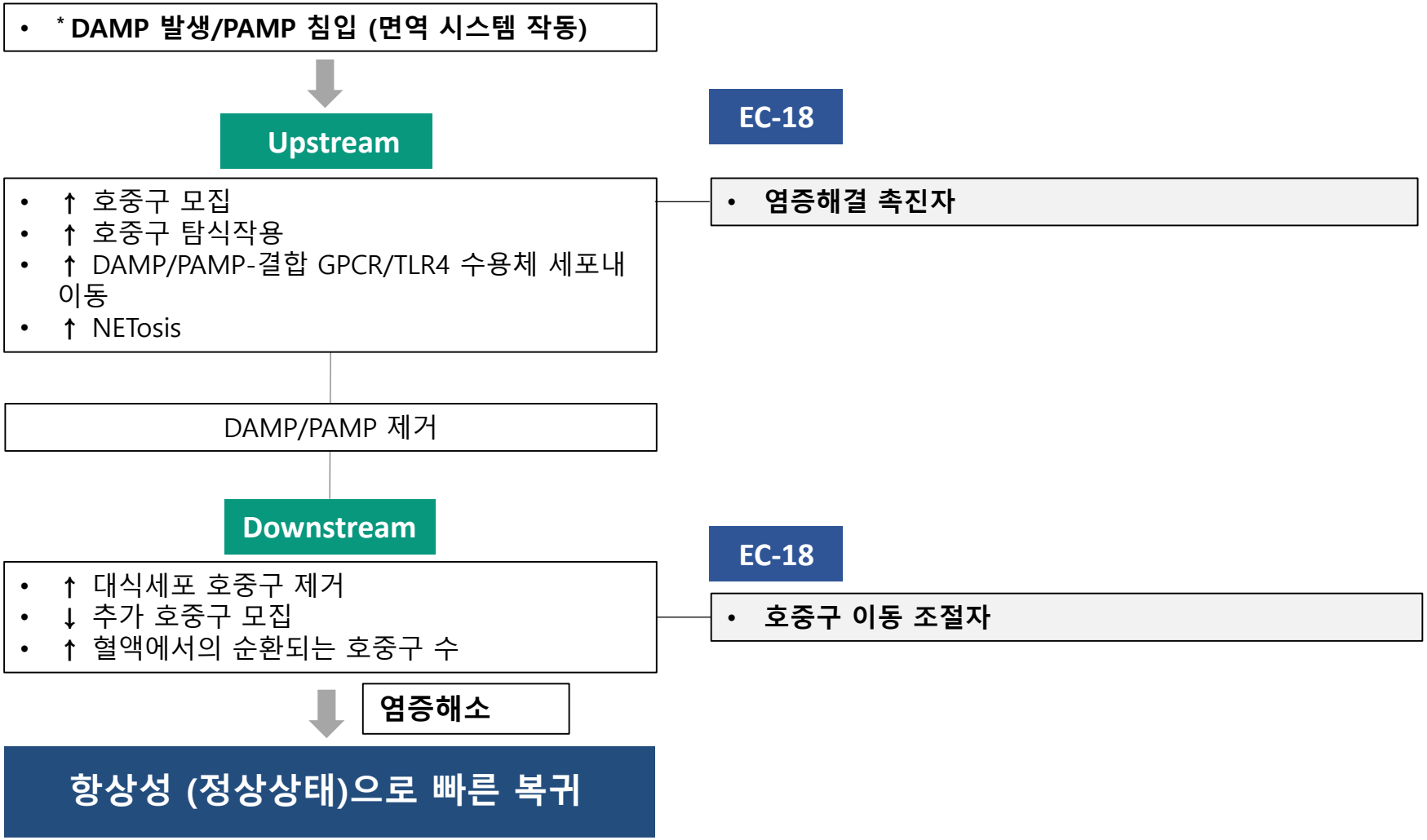
40년 이상 연구로 부터 개발된 혁신적 치료제 기술

EC-18은 안전하고, 경구투여, 지질기반의 저분자, first-in-class 글로벌 신약

- 지질기반 저분자 화합물 : 1-Palmitoyl-2-Linoleoyl-3-Aceltyl-rac-Glycerol (PLAG)
- 염증 종결 촉진자 (Immune Resolution Accelerator, IRA)
  호중구 이동 조절자 (Neutrophil Trafficking Modulator, NTM)
- 항암화학 요법에 의한 호중구 감소증 (CIN)과 항암화학 방사선요법에 의한 구강점막염 (CRIOM) 치료제 개발 글로벌 임상2상 시험 진행 중
- CRIOM에 대해 FDA로 부터 Fast Track 지정
- 급성방사선 증후군 (ARS)에 대해 FDA 로 부터 희귀의약품 지정
- ARS에 대해 FDA 신속심사 바우처 확보 및 판매를 통한 수익 실현 가능성



EC-18 작용기전


• *DAMP 발생/PAMP 침입 (면역 시스템 작동)
Upstream
• ↑ 호중구 모집
• ↑ 호중구 탐식작용
• ↑ DAMP/PAMP-결합 GPCR/TLR4 수용체 세포내 이동
• ↑ NETosis
EC-18
• 염증해결 촉진자
DAMP/PAMP 제거
Downstream
• ↑ 대식세포 호중구 제거
• ↓ 추가 호중구 모집
• ↑ 혈액에서의 순환되는 호중구 수
EC-18
• 호중구 이동 조절자
염증해소
항상성 (정상상태)으로 빠른 복귀

AACR Annual Meeting 2019, Atlanta

ENZYCHEM LIFESCIENCES

Poster No. 4586

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KRIBB Korea Research Institute of Bioscience & Biotechnology

PLAG enhances macrophage mobility for efferocytosis of active neutrophils via membrane re-distribution of P2Y2

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[1] Korea Institute of Bioscience and Biotechnology (KRIBB), Daejeon, Republic of Korea

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Abstract

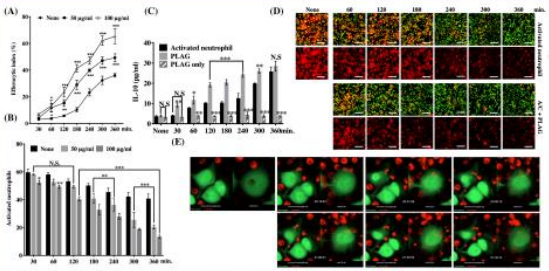
Neutrophil activity is prerequisite during chemotherapy. The DAMP (Damage Associated Molecular Pattern) molecules generated by chemotherapy could be effectively trapped by activated neutrophil called 'NETosis'. Efferocytosis of macrophages should remove most activated neutrophils including NETosis A timely removal of activated neutrophils is essential for the prevention of abnormal activation of immune response and metastatic activity of cancer cells induced by tumor microenvironment (TME). Particularly, appropriate clearance of the activated neutrophils by efferocytosis should be carried out because activated neutrophils have a detrimental effect on TME.

In this research, we investigated the effect of 1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol (PLAG) on efferocytosis and its underlying molecular mechanisms. In a co-culture of activated neutrophils with macrophages, PLAG increased the activity of efferocytosis for elimination of activated neutrophils. PLAG accelerated translocation of P2Y2 from lipid rafts to non-lipid-raft plasma membrane domains in macrophages. This repositioning of P2Y2 enables the polarization of the cytoskeleton by association of the receptor with cytoskeletal proteins such as α-tubulin and actin to improve the mobility of macrophages. Through these protein assemble, PLAG encouraged macrophage mobility toward the activated neutrophils. Formation of micelle including PLAG, chylomicron-like structures, was a prerequisite for induction of this macrophage activity. PLAG effect on this activity was not observed in the absence of GPIHBP1,micelle receptor.

Taken together, these data showed that PLAG triggered a prompt clearance of activated neutrophils through enhancement of efferocytosis activity. Subsequently, PLAG could have effects on modulation of TME. PLAG could be utilized as an effective lipid-based TME modulator via the prevention of abnormal activation induced by uncontrolled immune response during chemotherapy.

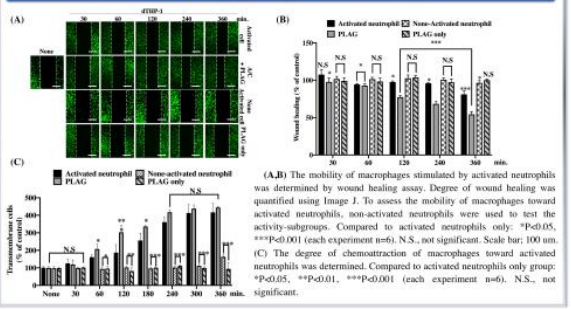
Result

Effect of PLAG on the induction of activated neutrophil efferocytosis



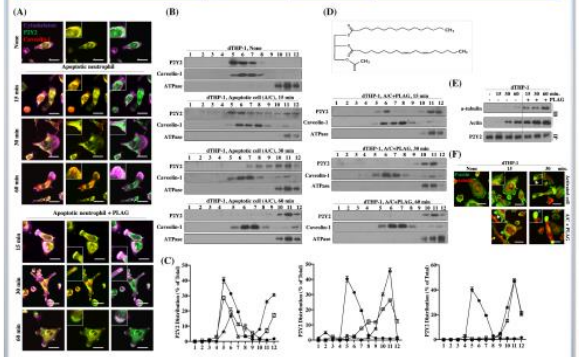
Differentiated THP-1 cells were pre-treated with PLAG for 1 h and then stimulated by activated neutrophils. **(A)** Efferocytotic index was calculated by FACS. Compared to activated neutrophil only group: *P<0.05, **P<0.01, ***P<0.001 (each experiment n=6). **(B)** Number of un-engulfed activated neutrophils was quantitated by FACS. Compared to control: *P<0.05, **P<0.01, ***P<0.001 (each experiment n=6). **(C)** Changes in IL-10 cytokine levels in the culture medium were determined by ELISA. Compared to control: *P<0.05, **P<0.01, ***P<0.001 (each experiment n=6). N.S., not significant. **(D)** The degree of clearance of apoptotic neutrophils was confirmed using confocal microscopy. Activated neutrophils were tagged with red fluorescence and macrophages tagged in green fluorescence. Scale bar; 100 um. **(E)** Efferocytosis of macrophages was visualized in real time.

Increase of macrophage mobility on the PLAG treated cells



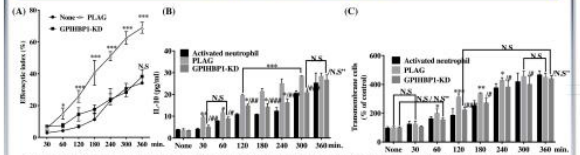
(A,B) The mobility of macrophages stimulated by activated neutrophils was determined by wound healing assay. Degree of wound healing was quantified using Image J. To assess the mobility of macrophages toward activated neutrophils, non-activated neutrophils were used to test the activity-subgroups. Compared to activated neutrophils only: *P<0.05, ***P<0.001 (each experiment n=6). N.S., not significant. Scale bar; 100 um. **(C)** The degree of chemoattraction of macrophages toward activated neutrophils was determined. Compared to activated neutrophils only group: *P<0.05, **P<0.01, ***P<0.001 (each experiment n=6). N.S., not significant.

Enhanced movement of P2Y2 receptor from the lipid raft to non-lipid raft in the PLAG treated cells

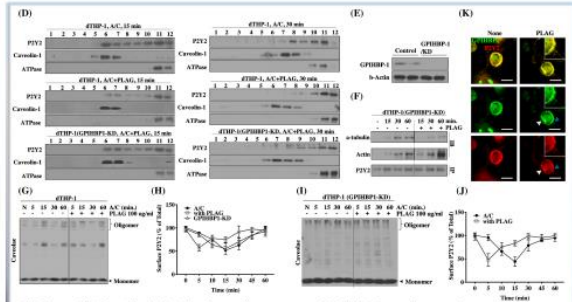


(A) Co-localization shift of P2Y2 and co-binding with cytoskeleton by membrane distribution change were confirmed by confocal. White arrow indicated that P2Y2 were co-localization with caveolin-1 and blue arrow indicate that P2Y2 were co-localization with cytoskeleton. Scale bar; 20 um. **(B)** The membrane distribution change of P2Y2 was determined by the lipid raft fractionation method. Caveolin-1 was used as a lipid raft marker. **(C)** The distribution of P2Y2 in each band was quantified and plotted. ●: None, □:Apoptotic neutrophil, △: PLAG. **(D)** The simple structure of PLAG. **(E)** The binding of P2Y2 with proteins related to polarization of the cytoskeleton was detected by immunoprecipitation. **(F)** The degree of cytoskeletal polarization and colocalization with actin protein was determined by confocal microscopy. Scale bar; 20 um

Promoted movement of P2Y2 receptor to non-lipid raft by structural PLAG was dependent on GPIHBP1, vesicle recognizing receptor

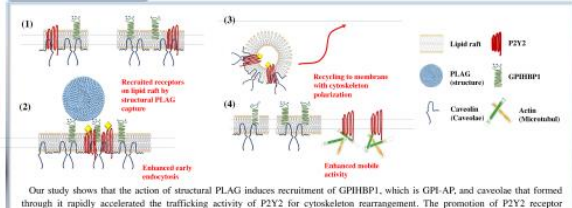


The effect of PLAG was examined in macrophages with GPIHBP-1 knock-down via siRNA transfection. **(A)** Efferocytotic index was calculated by FACS. Compared to activated neutrophil only group: *P<0.05, ***P<0.001 (each experiment n=6). N.S., not significant.

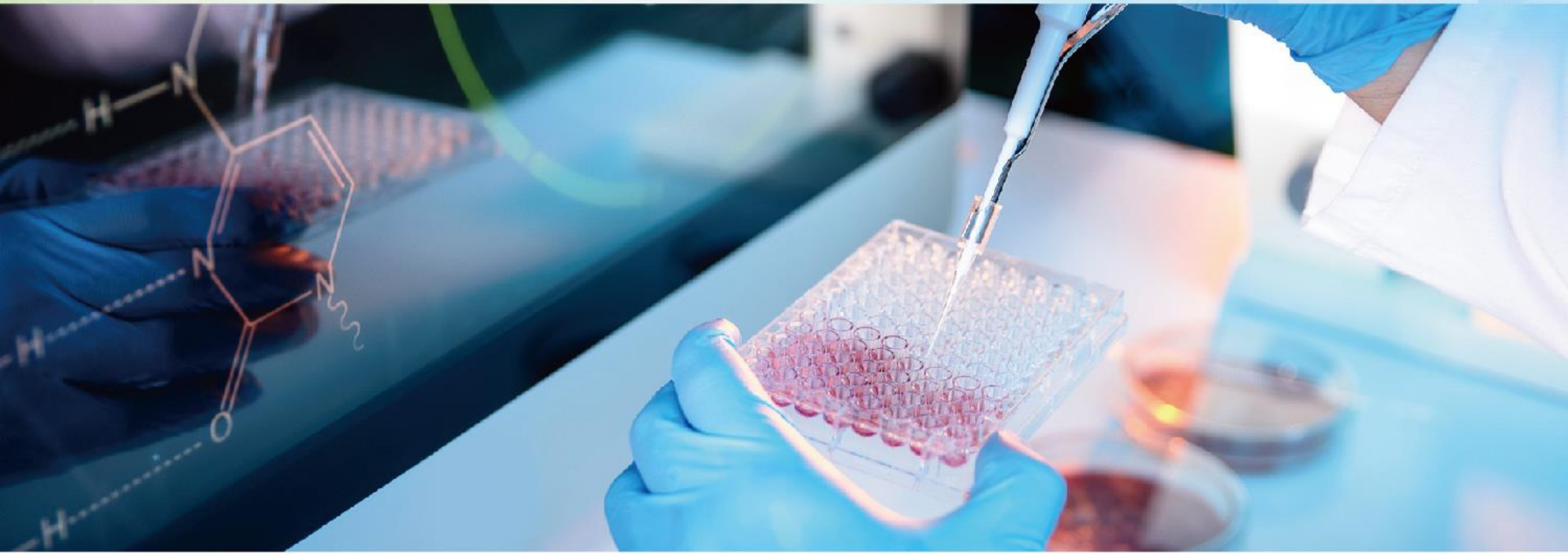


(B) Changes of IL-10 cytokine levels in the culture medium were measured by ELISA. Compared to apoptotic neutrophil only group: *P<0.05, **P<0.01, ***P<0.001 (each experiment n=6). Compared to PLAG group: #P<0.05, ##P<0.01, ###P<0.001 (each experiment n=6) N.S., not significant (Compared to apoptotic neutrophil only group). N.S.", not significant (Compared to PLAG group). **(C)** The degree of chemoattraction of macrophages toward apoptotic neutrophils was determined. Compared to apoptotic neutrophil only group: *P<0.05, **P<0.01, ***P<0.001 (each experiment n=6). Compared to PLAG group: #P<0.05, ##P<0.001 (each experiment n=6) N.S., not significant (Compared to apoptotic neutrophil only group). N.S.", not significant (Compared to PLAG group). **(D)** The membrane distribution change of P2Y2 in GPIHBP-1 knock-down cells was confirmed by the lipid raft fraction method. Change of P2Y2 distribution by PLAG treatment was quantified at the same time. **(E)** Knock-down of GPIHBP-1 via siRNA transfection was confirmed. **(F)** Co-immunoprecipitation of P2Y2 with proteins related to polarization of the cytoskeleton. **(G,I)** The changes of caveolae formation in Lipid raft over time were confirmed by Western blotting. **(H,J)** The surface membrane expression of P2Y2 (Trafficking) over time was quantitated using FACS. **(K)** The co-localization and polarization changes of GPIHBP1 and P2Y2 by structural PLAG treatment were confirmed by Confocal Scale bar; 20 um.

Conclusion



Our study shows that the action of structural PLAG induces recruitment of GPIHBP1, which is GPI-AP, and caveolae that formed through it rapidly accelerated the trafficking activity of P2Y2 for cytoskeleton rearrangement. The promotion of P2Y2 receptor translocation by PLAG provides more rapid movement of macrophages toward nucleotides generated by activated neutrophils, allowing the macrophages to rapidly eliminate the activated neutrophils.



Healthy
and
Happy Life

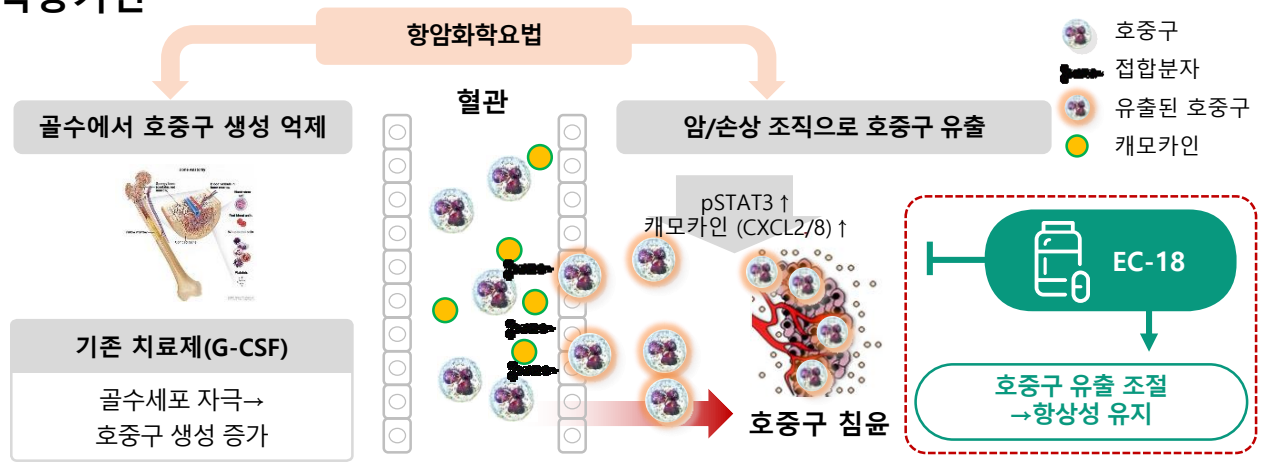
Ch.2
호중구감소증(CIN)

ENZYCHEM
LIFESCIENCES

개요 및 목표시장 _ 호중구감소증 치료제

∴ 호중구감소증 개요 및 EC-18 작용기전

- 항암치료에 의해 발생되는
  - ① 골수 내 호중구 생성 억제
  - ② 혈관으로부터 호중구 유출에 의한 혈액 내 호중구 수 감소
- 바이러스 및 세균 감염 위험 증가, 500cells/㎕ 미만 시 중증 감염 발생
- 항암치료 연기 또는 G-CSF 투여



∴EC-18의 목표 시장

시장 규모

Amgen G-CSF 판매액
+ 바이오시밀러
+ 기타 시장

7.7조원

환자 규모 (미국)

암 환자수	연간 발병수
500만명	168만명

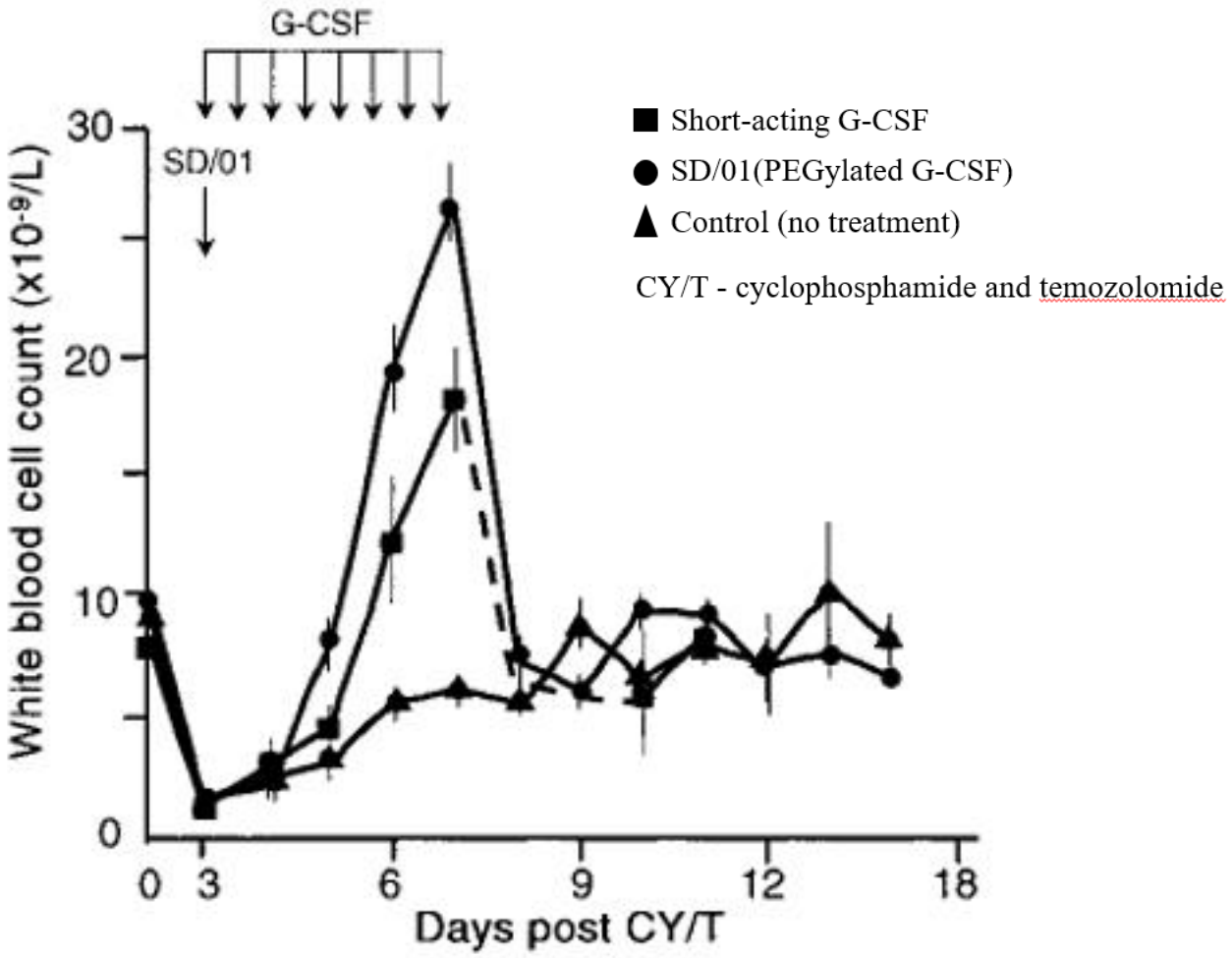
Target Market

미충족 의학적 수요

- G-CSF 반응없는 환자
- 방사선 치료 대상 환자
- 혈핵암 환자

약 **20**만명 | 약 **3조**원

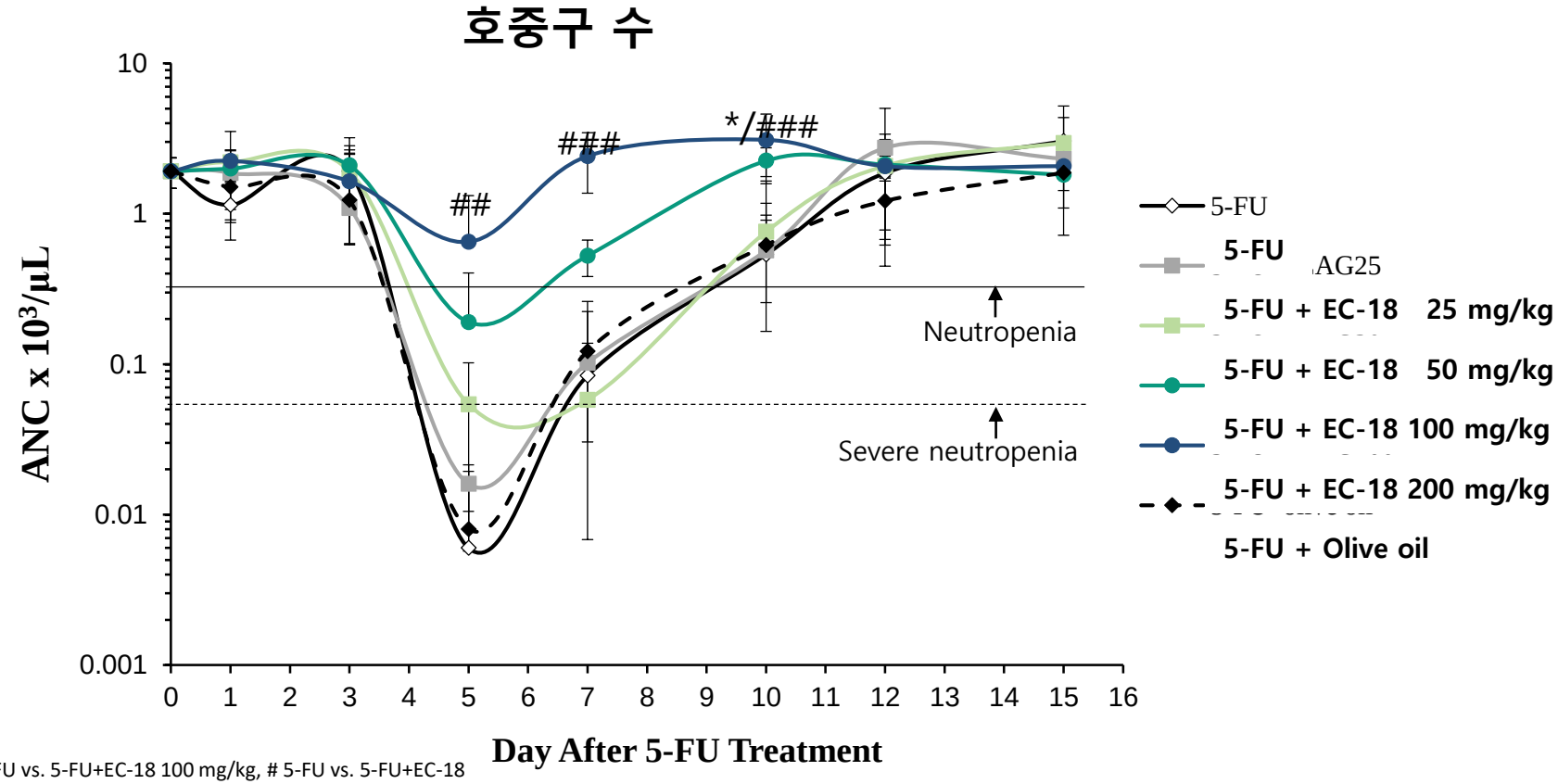
호중구감소증 기존 치료제 작용 (G-CSF)



Clinical Cancer Research, 2001;7:2085–2090

호중구감소증 비임상 효능

- **Balb/c**: 7주, 매 5마리의 수컷 쥐
- **Anti-cancer agent**: 5-Fluorourasil (5-FU) 100mg/kg , I.P. 1일 1회 주사
- **EC-18**: 1일부터 15일까지 매일 250 mg/kg 경구 투여
- **Check point**: CBC 분석



* 5-FU vs. 5-FU+EC-18 100 mg/kg, # 5-FU vs. 5-FU+EC-18 200 mg/kg; */#P<0.05, **/##P<0.01 and ***/###P<0.001.

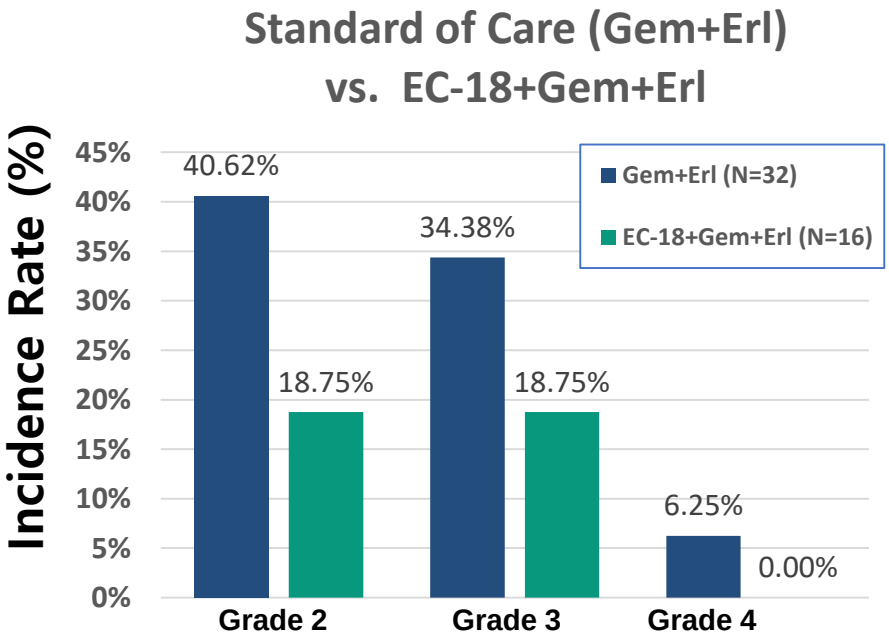
AACR Annual Meeting 2019; Abstract 360

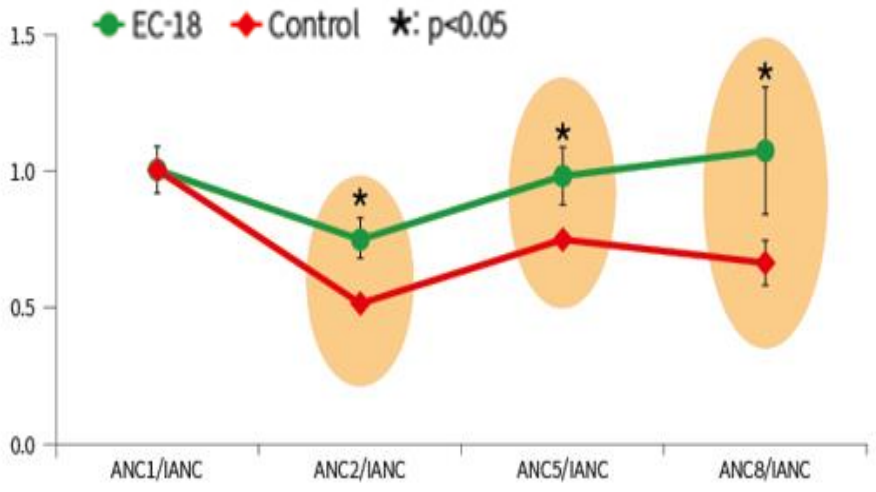
EC-18은 농도의존적으로 중증 호중구감소증의 발병율과 발병기간을 줄임

췌장암 환자 대상 파일럿 임상에서 호중구감소증 효과

ENZYCHEM LIFESCIENCES

젬시타빈 요법으로 치료받는 췌장암 환자대상 EC-18을 통한 CIN 예방 효과 연구





항암화학 요법 12주 간 정상 호중구 수 범위 유지
호중구의 과도한 증가 없음

World J Oncol 6(4):410-415, 2015

2-4등급의 호중구 감소증 환자의 수는 EC-18 투여를 통해 44.7% 감소

AACR Annual Meeting 2019, Atlanta

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Saving Lives One at A Time

ENZYCHEM LIFESCIENCES | KRIBB Korea Research Institute of Bioscience & Biotechnology

360

Therapeutic potential of EC-18 as a chemotherapy adjuvant for 5-fluorouracil-induced neutropenia

Yong-Jae Kim[1], Jinseon Jeong[1,2,3], Ki-Young Sohn[1], Do Young Lee[1], Sun Young Yoon[1], and Jae Wha Kim[2,3]

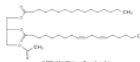
[1]Enzychem Lifesciences, Jecheon, Republic of Korea. [2]Korea Research Institute of Bioscience and Biotechnology, Daejeon, Republic of Korea. [3] University of Science and Technology, Daejeon, Republic of Korea.

Abstract

Chemotherapy-induced neutropenia (CIN) is a complication that arises during cancer treatment and necesstates dose reduction. Preventing CIN and maintaining absolute neutrophil counts (ANC) is critical for successful chemotherapy because a rapid decline of neutrophils increases susceptibility to infection. Here, we investigated whether administration of EC-18 has therapeutic effects on the treatment of CIN in 5-fluorouracil (5-FU)-induced neutropenia mouse model. A single injection of 5-FU 100mg/kg reduced the ANC in the control, EC-18 125 and EC-18 250mg/kg-treated cohort from pre-injection values to <500 cells/μL by 5.2±0.45, 5.8±0.45 and 5.8±0.45 days, respectively. The administration of EC-18 in 5-FU-injected mice resulted in significant reduction in the duration of neutropenia and the time to recovery of ANC >1000 cells/μL. EC-18 125 or 250mg/kg significantly reduced the duration of neutropenia from 7.4±1.14 days to 2.6±0.55, 3.0±0.71 days, respectively. Moreover, the ANC of all individuals in the control cohort fell to severely neutropenic range (ANC <100 cells/ μL), while only 20% of individuals in both EC-18 125 and 250mg/kg-treated cohorts experienced severe neutropenia. EC-18 also reduced the duration of severe neutropenia from 5.2±1.48 days to 2 days. EC-18 125 or 250mg/kg administration significantly increased the mean nadir after 5-FU injection from 2.0±4.47 cells/μL to 236±4.47 or 158±11.32 cells/μL, respectively. The time of recovery to an ANC > 500 or 1000 cells/μL was significantly reduced in EC-18 125 and 250mg/kg-treated cohorts. Besides neutropenia, a single treatment of 5-FU induced the reduction of blood monocytes and eosinophils, similar to the pattern of the decrease of neutrophil counts. The administration of EC-18 125 or 250mg/kg in 5-FU-injected mice remarkably prevented the reduction of blood monocytes and eosinophils. In this study, thrombocytopenia is defined as a 50% or greater reduction in platelet count from baseline, and 2-fold or greater increase of platelet count from baseline for thrombocytosis. 5-FU treatment induced the moderate thrombocytopenia from 4 to 6 days and followed by a more pronounced and prolonged rebound thrombocytosis. EC-18 significantly reduced the extreme change in platelet counts, thus preventing 5-FU-induced thrombocytopenia and thrombocytosis. Moreover, EC-18 effectively prevented a constant reduction of red blood cell (RBC) count induced by 5-FU treatment. Based on the observations in this study, we concluded that EC-18 has therapeutic potential as a chemotherapy adjuvant for the treatment of 5-FU-induced CIN as well as chemotherapy-associated other hematologic disorders.

Introduction

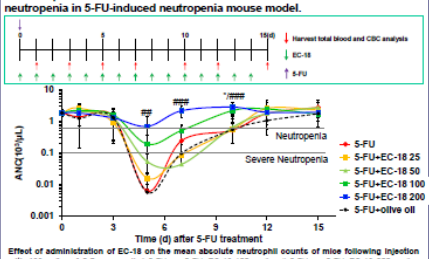
- Chemotherapy-induced neutropenia (CIN) is a complication that arises during cancer treatment and necessitates dose reduction. **Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Cancer 2005;103:1916-24.**
- Preventing CIN and maintaining absolute neutrophil counts is critical for sucoessful chemotherapy because a rapid decline of neutrophils increases susceptibility to infection. **Santolaya ME, Alvarez AM, Becker A, Cofre J, Enriquez N, O'Ryan M, *et al.* J Clin Oncol 2001;19:3415-21**
- In previous study, EC-18 attenuated gemcitabine-induced neutropenia via regulation of neutrophil extravasation. **Jeong *et al.* Cell Biosci. 2019; 9: 4. (Published online 2019 Jan 3. doi: 10.1186/s13578-018-0266-7).**



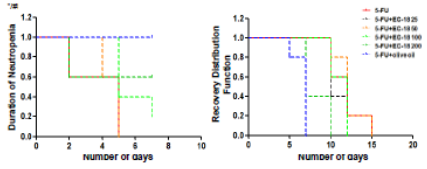
EC-18 (PLAG: 1-Palmitoyl-2-Linoleoyl-3-Acetyl-rac-Glycerol)

Results

1. Therapeutic effect of administration of EC-18 on the treatment of neutropenia in 5-FU-induced neutropenia mouse model.



Effect of administration of EC-18 on the mean absolute neutrophil counts of mice following injection with 100mg/kg of 5-fluorouracil. * 5-FU vs. 5-FU+EC-18 100 mg/kg, # 5-FU vs. 5-FU+EC-18 200 mg/kg; */#



Effect of administration of EC-18 on the duration of neutropenia and on time to recovery to ANC <500 cells/μL.

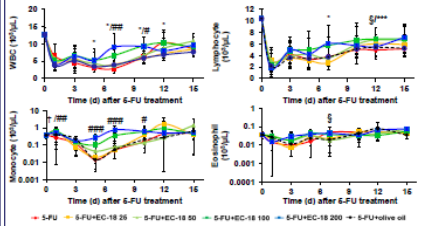
Treatment	Mean First Day Neutropenia (± SE, range)	Mean Duration of Neutropenia in Days (± SE, range)	Number of Individuals of Severe Neutropenia	Mean Duration of Severe Neutropenia in Days (± SE, range)
Control	4.8±0.4 (3-6)	6.8±0.76 (5-8)	6/6	3.8±0.7 (2-5)
EC-18 25mg/kg	3.8±0.48 (3-5) (*P* = NS)	8.4±1.17 (6-12) (*P* = NS)	6/6	4.8±0.2 (4-5)
EC-18 50mg/kg	6.0±0.0 (6-6) (*P* = NS)	6.2±0.80 (6-7) (*P* = NS)	4/6	5.6±0.5 (5-7)
EC-18 100mg/kg	6.4±0.4 (6-7) (*P* = NS)	2.8±0.80 (2-5) (*P* = 0.0031)	2/6	2.0±0.0 (2-2)
EC-18 200mg/kg	4.8±0.4 (3-5) (*P* = NS)	2.0±0.0 (2-2) (*P* = 0.001778)	0/6	N/A
Olive oil	5.0±0.0 (5-5) (*P* = NS)	6.8±0.48 (6-7) (*P* = NS)	5/6	3.8±0.7 (2-5)

Table 1. Mean First Day of Neutropenia (ANC <500 cells/μL), Mean Duration of Neutropenia, Number of Individuals of Severe Neutropenia (ANC <100 cells/μL), and Mean Duration of Severe Neutropenia in Control, and EC-18 25, 50, 100, 200 and olive oil-treated mice injected with 5-FU 100mg/kg

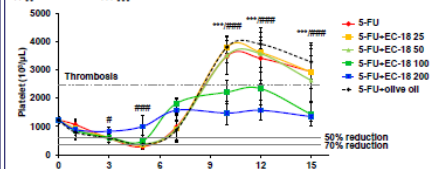
Treatment	Nadir of ANC (cells/μL)	Mean Number of Days to Recovery – ANC ≥500/μL (± SE, range)	Mean Number of Days to Recovery – ANC ≥1000/μL (± SE, range)
Control	6±0.0	11.8±0.9 (10-16)	12.8±0.8 (12-16)
EC-18 25mg/kg	14±2.4 (*P* = NS)	12.2±0.8 (10-16) (*P* = NS)	12.2±0.8 (10-16) (*P* = NS)
EC-18 50mg/kg	42±22.9 (*P* = NS)	11.2±0.6 (10-12) (*P* = NS)	10.0±0.0 (10-10) (*P* = 0.0081)
EC-18 100mg/kg	168±76.0 (*P* = NS)	8.2±0.7 (7-10) (*P* = 0.0166)	10.0±0.0 (10-10) (*P* = 0.0081)
EC-18 200mg/kg	368±52.2 (*P* = 0.0002)	6.8±0.4 (6-7) (*P* = 0.0008)	7.2±0.8 (6-10) (*P* = 0.0008)
Olive oil	6±0.7 (*P* = NS)	10.8±0.6 (10-12) (*P* = NS)	12.8±1.0 (10-16) (*P* = NS)

Table 2. Mean Nadir and Recovery from Neutropenia in Control, EC-18 25, 50, 100, 200 and olive oil-Treated mice injected with 5-FU 100mg/kg

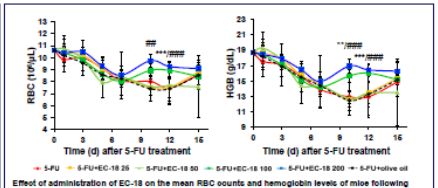
2. Therapeutic effect of administration of EC-18 on other hematologic indicators in 5-FU-treated mouse model



Effect of administration of EC-18 on the mean WBC, lymphocyte, monocyte and eosinophil counts of mice following injection with 100mg/kg of 5-fluorouracil. †§-FU vs. 5-FU+EC-18 25 mg/kg, §§-FU vs. 5-FU+EC-18 50 mg/kg,* 5-FU vs. 5-FU+EC-18 100 mg/kg, # 5-FU vs. 5-FU+EC-18 200 mg/kg; †/§/*/#P<0.05, ††/§§/**/##P<0.01 and †††/§§§/***/###P<0.001.

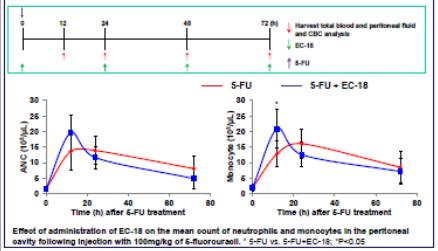


Effect of administration of EC-18 on the mean platelet counts of mice following injection with 100mg/kg of 5-fluorouracil. * 5-FU vs. 5-FU+EC-18 100 mg/kg, # 5-FU vs. 5-FU+EC-18 200 mg/kg; */#P<0.05, **/##P<0.01 and ***/###P<0.001.



Effect of administration of EC-18 on the mean RBC counts and hemoglobin levels of mice following injection with 100mg/kg of 5-fluorouracil. * 5-FU vs. 5-FU+EC-18 100 mg/kg, # 5-FU vs. 5-FU+EC-18 200 mg/kg; */#P<0.05, **/##P<0.01 and ***/###P<0.001.

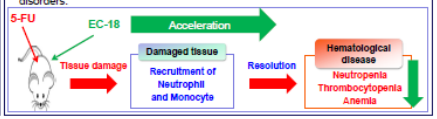
3. Effect of EC-18 administration on leukocyte recruitment in 5-FU-treated mouse model



Effect of administration of EC-18 on the mean count of neutrophils and monocytes in the peritoneal cavity following injection with 100mg/kg of 5-fluorouracil. * 5-FU vs. 5-FU+EC-18; *P<0.05

Conclusion

- Under 5-FU-induced neutropenic condition, EC-18 significantly increased the ANC and reduced the duration of neutropenia and time of recovery.
- EC-18 also effectively prevented other hematologic disorders induced by 5-FU treatment, such as the reduction of blood monocytes and eosinophils, thrombocytopenia, thrombocytosis and anemia.
- Based on the observations in this study, we concluded that therapeutic administration of EC-18 could be developed as a chemotherapeutic adjuvant for the treatment of CIN as well as chemotherapy-associated other hematologic disorders.



Healthy
and
Happy Life

Ch.3
구강점막염(CRIOM)

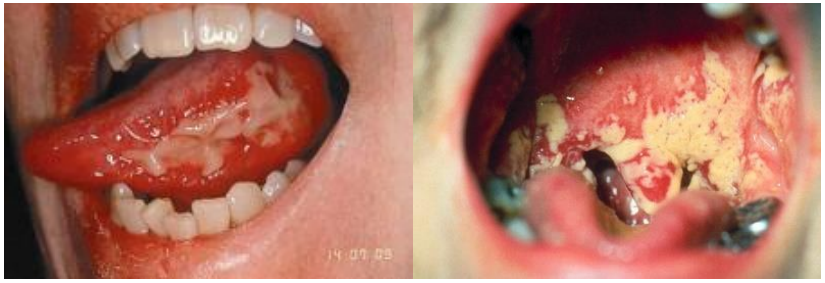
ENZYCHEM
LIFESCIENCES

개요 및 목표시장 _ 구강점막염 치료제

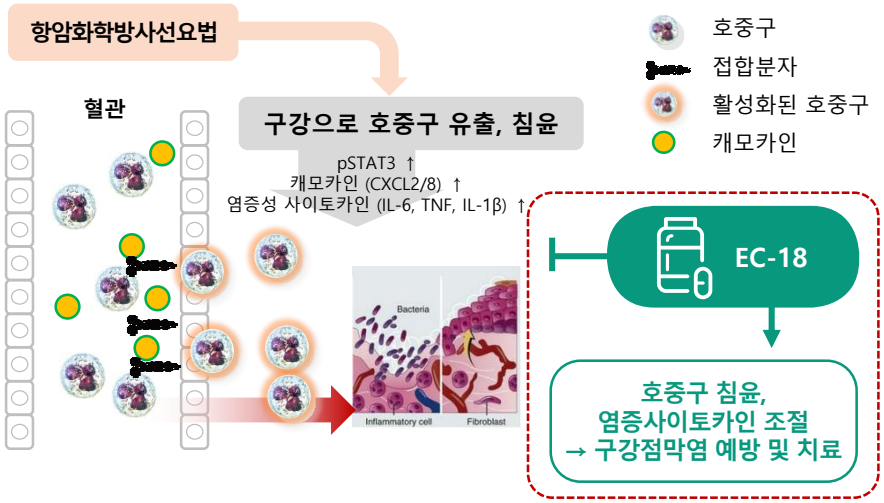
ENZYCHEM LIFESCIENCES

항암화학방사선 치료 중 발생하는 구강 염증 또는 궤양

∴구강점막염 개요 및 EC-18 작용기전



- 항암치료 중에 발생하는 입안의 염증 또는 궤양
- 고통으로 인한 식사 불가로, 영양결핍과 체력 고갈로 직결
- 세균 침투에 의한 패혈증 위험 4배 증가
- 고형암에 대한 항암치료 중 발생하는 구강점막염 치료제 부재



∴EC-18의 목표 시장

50만명
연간 발병 수 (미국)

25만명
방사선 치료 암환자 수 (미국)

16.7만명
궤양성 구강점막염
환자 수 (미국)

80-100%
두경부암 환자의
궤양성 구강점막염 발전 비율

목표 시장

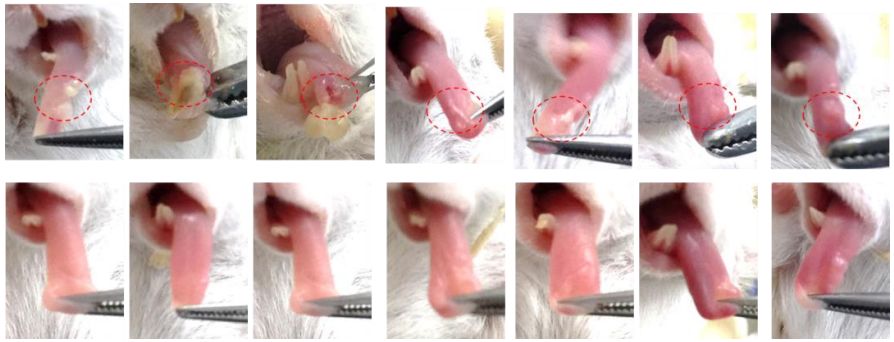
약 **17만 명**

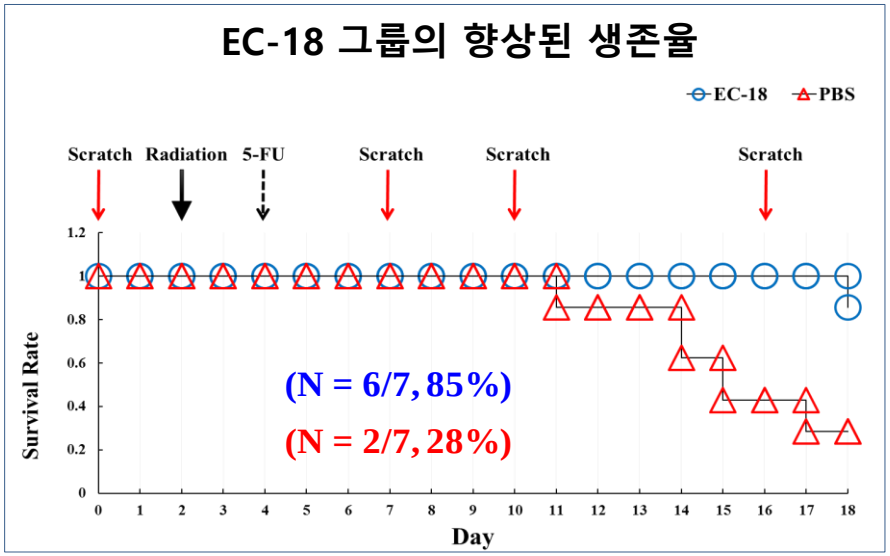
약 **2.6조원**

구강점막염 비임상 효능 (항암화학방사선 모델)

ENZYCHEM LIFESCIENCES

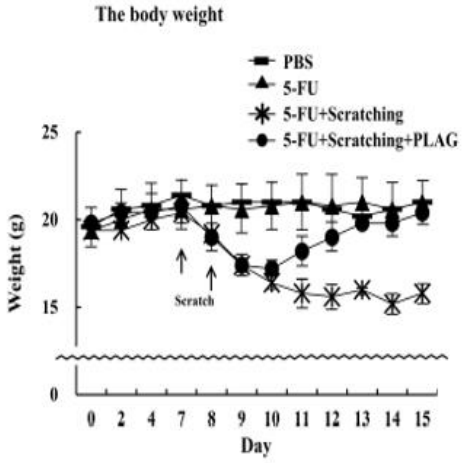
- 고형암 환자에게 발생하는 구강점막염 예방을 위한 특정 치료법 현재 없음
- 5-FU 유발 및 항암화학 방사선 요법 유발 구강점막염 동물 모델에서 EC-18 (PLAG)의 치료 효과 연구
- EC-18 매일 250mg/kg 투여
- EC-18 투여로 5-FU 유발 구강점막염 감소
- 조직학적 분석 결과 또한 EC-18 투약군에서 구강점막염의 회복을 보여줌

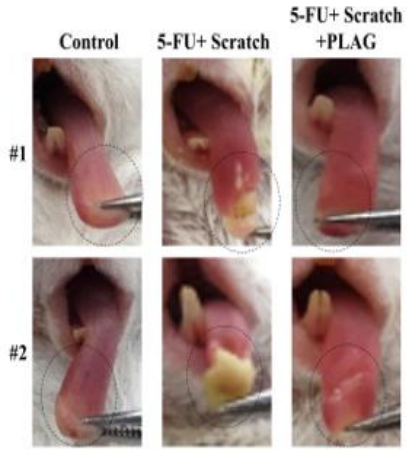


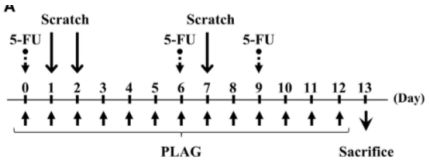


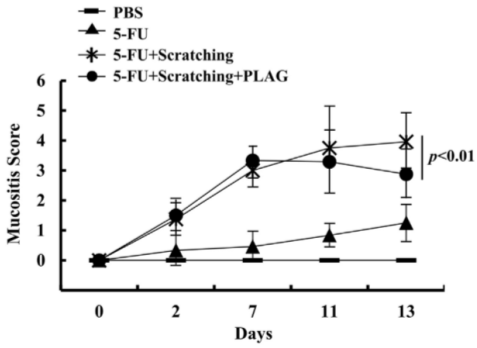
구강점막염 비임상 효능 (항암화학 모델)

- EC-18(PLAG)을 투약한 군에서 감소되었던 체중의 회복이 관찰
- EC-18(PLAG) 투약은 5-FU 유발 구강점막염으로 인한 체중감소를 막는 중요한 효과를 보여 줌
- EC-18은 5-FU로 인해 발생한 구강점막염의 회복을 촉진하며, 항암화학 요법을 받는 환자들에게 빈번히 발생하는 점막염과 근감소증과 같은 부작용인 효과가 있을 가능성이 있음









Frontiers in Oncology 6:209, 2016

Healthy
and
Happy Life

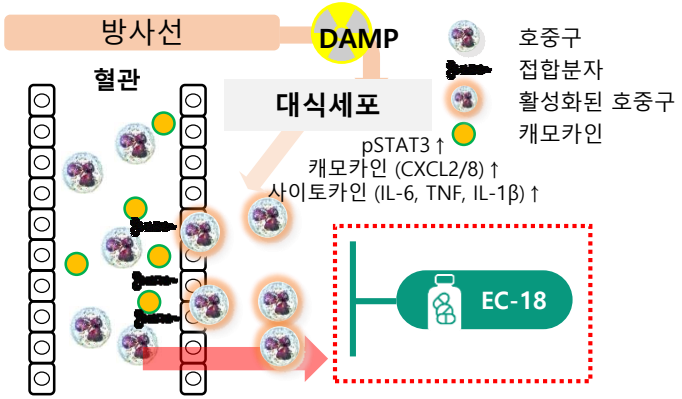
Ch.4
급성방사선증후군(ARS)

ENZYCHEM
LIFESCIENCES

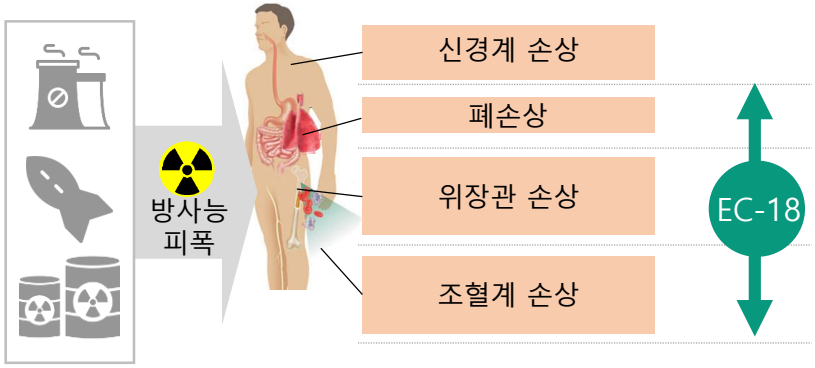
개요 및 목표시장 _ 급성방사선증후군 치료제

ENZYCHEM LIFESCIENCES

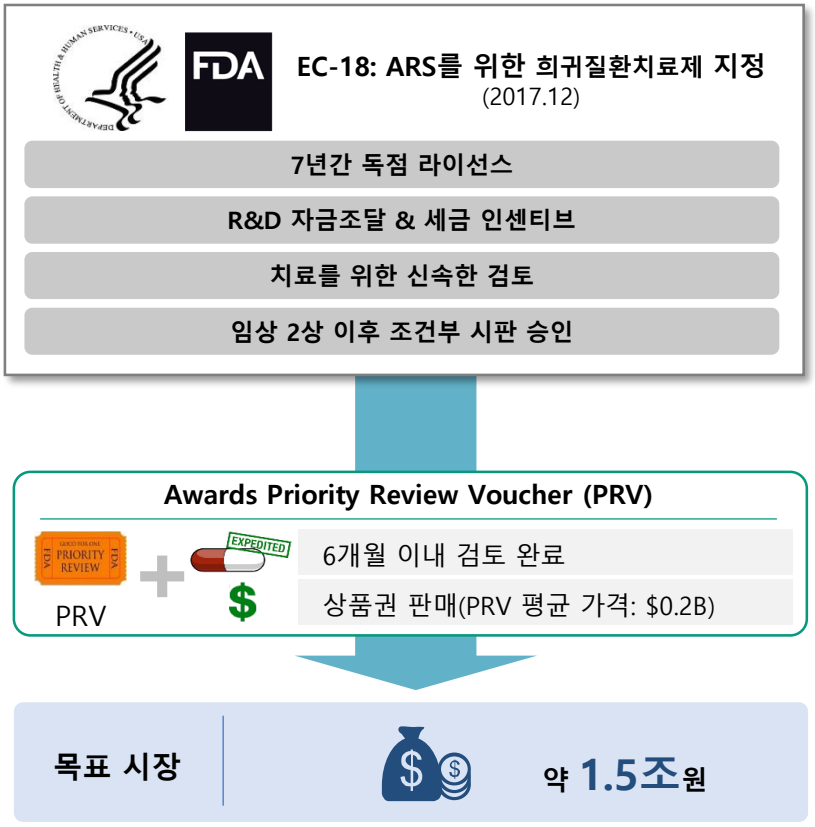
∴ 작용기전



∴ 급성방사선증후군(ARS) 개요



∴ 급성방사선증후군(ARS)을 위한 희귀질환치료제 지정



급성방사선증후군 비임상 효능 (동시투약)

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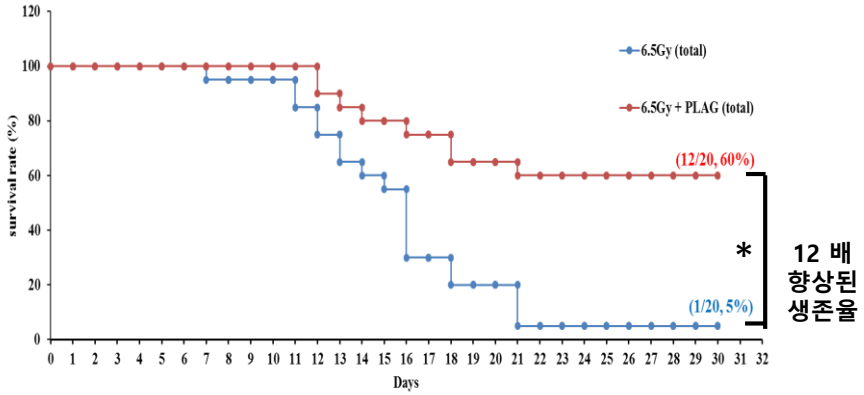
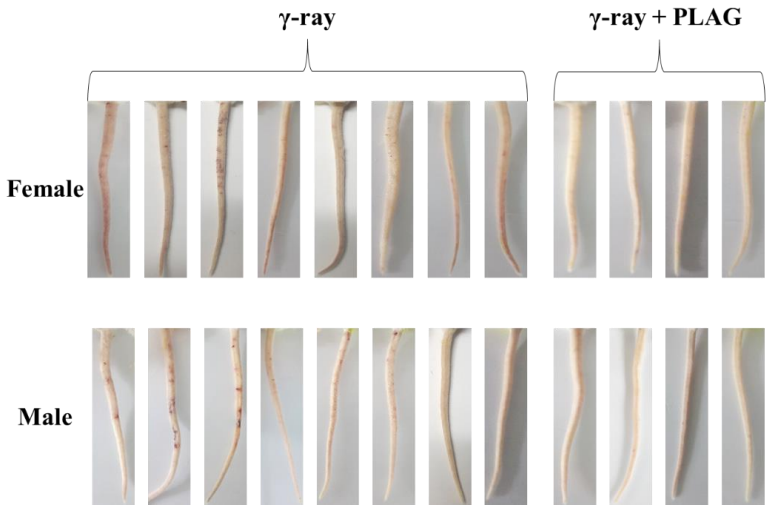
∴생쥐를 이용한 ARS 동물 연구_ 30일간 생존율



11 weeks Balb/c mice_6.5 Gy γ-irradiation to whole body
Each group: n= 20 (10 male & 10 female)
PLAG (EC-18) treatment: 250 mpk

Radiation only vs PLAG (EC-18) (250mpk) co-treatment, * *P* < 0.001;

∴홍반 또는 자반 (또는 심한 피멍)의 유무



EC-18은 방사선 조사 마우스에서 생존 및 혈액응고 장애에 효능

급성방사선증후군 비임상 효능 (24/48/72 시간 후 투약)

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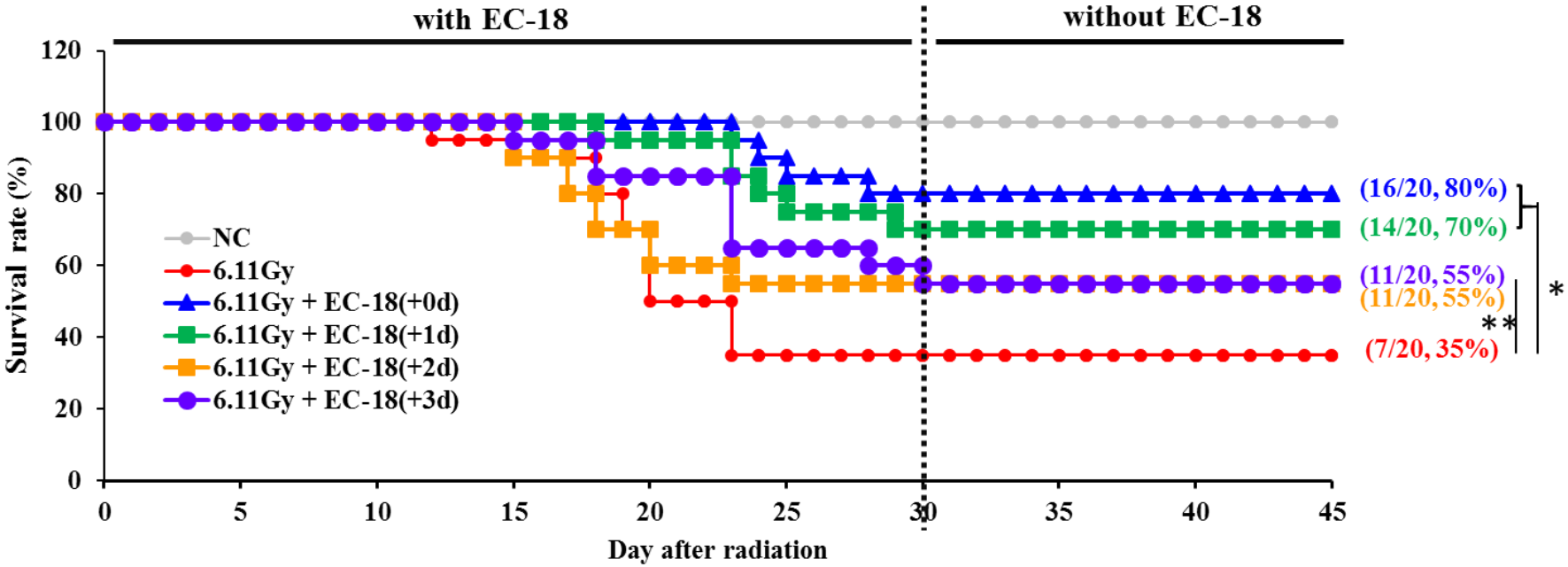
LD70/30 방사선 양에서 24시간, 48시간 또는 72시간 지연 치료 (30일 생존)에 대한 완화 효과

- **Balb/c**: 11 weeks, **20 mice** (10 female and 10 male) per group
- **Radiation**: 6.11 Gy γ-radiation, TBI once on Day 0
- **EC-18**: 250 mg/kg daily oral administration from Day 0, Day 1, Day 2, Day 3 to Day 30
- **Check point**: Survival during EC-18 administration; Survival monitoring for 15 consecutive days without EC-18 administration

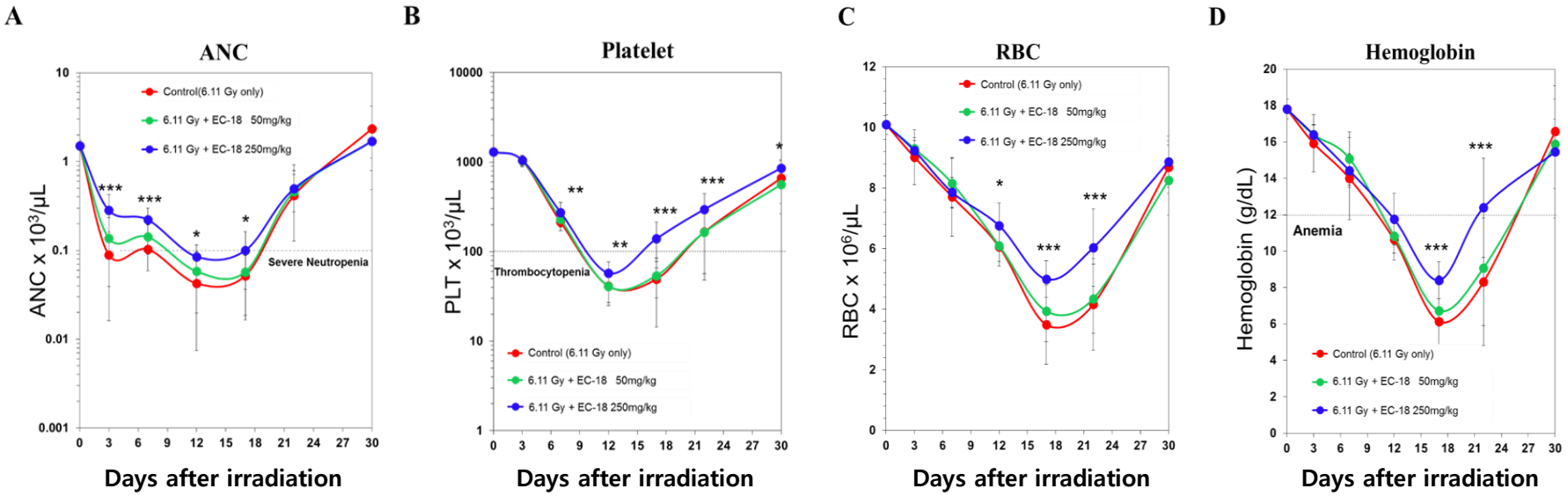


Radiation only vs EC-18 (250mpk) co-treatment, * $P < 0.001$; Radiation only vs EC-18 24h post-IR, * $P < 0.001$; Radiation only vs EC-18 48h post-IR, ** $P < 0.01$; Radiation only vs EC-18 72h post-IR, ** $P < 0.01$

72시간 방사선 조사 후 투약 치료 모델에서도 생존율에 효능

동물 효능 : H-ARS 모델의 CBC 분석

- **Balb/c**: 11주령 그룹당 20 마리 (암수 각 10 마리) 및 정상 대조군 20 마리의 쥐 (암수 각 10 마리)
- **Radiation**: 6.11 Gy γ-radiation, Day 0에 TBI
- **EC-18**: Day 1부터 Day 30까지 1일당 50 ~ 250 mg/kg 경구 투여
- **Check point**: CBC 분석
- **Blood collection:** 매 5일마다 수집**(**Day 3, 7, 13, 17, 23 and 30)



*6.11 Gy vs 6.11 Gy + EC-18 250 mg/kg, N≤20
*, $P < 0.05$
**, $P < 0.01$
***, $P < 0.001$

EC-18은 방사선 조사 24시간 후 치료모델에서 호중구감소증, 혈소판감소증 및 빈혈 개선에 효능

AACR Annual Meeting 2019, Atlanta

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3730

1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol mitigates the hematopoietic syndrome of lethal acute radiation syndrome in mice

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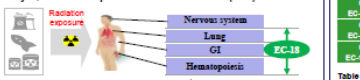
[1]Enzychem Lifesciences, Jecheon, Republic of Korea. [2]Korea Research Institute of Bioscience and Biotechnology, Daejeon, Republic of Korea. [3] University of Science and Technology, Daejeon, Republic of Korea.

Abstract

The acute radiation syndrome (ARS) is a broad term used to describe a range of signs and symptoms that reflect severe damage to specific organ systems and that can lead to death within hours to several months after exposure. In this study, we investigated the efficacy of EC-18 for the development of a medical countermeasure for ARS by analyzing ionizing radiation (IR)-induced mortality and morbidity. First, we established a murine model of the ARS by exposing eleven week old male and female BALB/c mice to 6.0-6.5Gy doses of total body irradiation (TBI; γ-ray, ^{60}Co, 153R/min), and assessed for 30 day survival, mean survival time and lethality dose (LD). The $LD_{70/30}$ with confidence interval (CI) was 6.11Gy (5.98-6.22Gy). To determine the efficacy of EC-18 in IR-induced mortality, we exposed BALB/c mice to a 6.11Gy dose ($LD_{70/30}$) of TBI and orally administered 10-250 mg/kg/day of EC-18, starting one day after irradiation. As a result, 6.11Gy of γ-radiation caused the death of 80% of the animals of positive control group within 23days, with an average life span (ALS) of 17.9days. The percentages of survival of the irradiated mice with EC-18 10, 50, and 250mg/kg were 20%, 40%, and 80% with ALS of 19.3, 22.3, and 28.2days, respectively. Moreover, the LD70/30 dose of γ-ray irradiation caused a substantial decrease in the body weight of the mice. The administration of EC-18 effectively prevented severe weight loss induced by irradiation. Next, we investigated the efficacy of EC-18 for hematopoietic ARS (H-ARS) by analyzing the kinetics of white blood cells (WBC), red blood cells (RBC), and platelets. A single whole body exposure of γ-radiation (6.11Gy) rapidly exhausted all kinds of WBC counts, and the administration of EC-18 significantly attenuated γ-radiation-induced depletion of WBCs in the irradiated mice. Especially, the administration of EC-18 substantially reduced γ-radiation-induced reduction of the absolute neutrophil counts (ANC). The mean first day of neutropenia (ANC<500cells/μL) of control and EC-18-treated cohorts was 1.8±1.09 and 2.2±1.09 days, respectively. Although EC-18 did not protect the irradiated mice from experiencing severe neutropenia, it effectively reduced the duration of severe neutropenia from 13.0 days to 7.2±1.79days. In addition, EC-18 significantly increased the mean nadir of ANC after γ-ray irradiation from 4.0±5.48 cells/μL to 20.0±10.00 cells/μL. In addition, the administration of EC-18 in the irradiated mice remarkably attenuated the rapid reduction of RBCs and hemoglobin. When exposed to a supra-lethal dose (8Gy) of γ-radiation, the two of five mice in the control cohort experienced severe skin discoloration and edema formation on the front right feet and hemorrhagic telangiectasia on the tales on day10. EC-18 remarkably improved γ-radiation-induced skin damage in the irradiated mice. Based on the observations in this study, we concluded that EC-18 has potential as a medical countermeasure for ARS.

Introduction

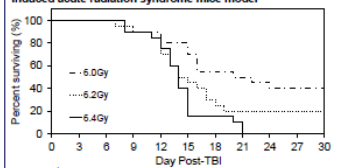
- The acute radiation syndrome (ARS) is a broad term used to describe a range of signs and symptoms that reflect severe damage to specific organ systems and that can lead to death within hours or up to several months after exposure. The ARS occurs after whole-body or significant partial-body irradiation of greater than 1 Gy, over a short time period (high dose rate). **López, Martín, and Margarita Martín. Reports of Practical Oncology & Radiotherapy 16.4 (2011): 138-146.**
- Since the risk of exposure to radiation continues to increase, there has also been an increasing interest in the search of ways of protection against the effects of acute irradiation by ionizing radiation in accidental condition. **Aminin, Dmitry L., et al. Natural product communications 6.5 (2011): 587-592.**



Overview of ARS and Symptoms

Results

1. Determination of Lethal Dose (LD)XX/30 in γ-radiation-induced acute radiation syndrome mice model

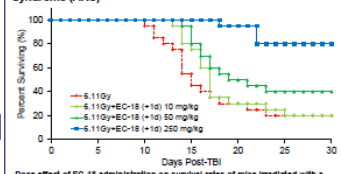


Survival rates of BALB/c mice. BALB/c mice (11 week old, male and female) exposed to ^{60}Co source of γ-radiation. Kaplan-Meier survival curves showing the proportion of mice surviving at each time points for each radiation dose of γ-ray.

LD XX/30	LD estimate (Gy)	Lower 95% CI (Gy)	Upper 95% CI (Gy)
LD30/30	5.31	4.98	5.56
LD50/30	5.79	5.59	5.96
LD70/30	6.11	5.98	6.22
LD95/30	6.39	6.30	6.48

Table 1. Estimated lethal dose in BALB/c mice after ^{60}Co γ-radiation.

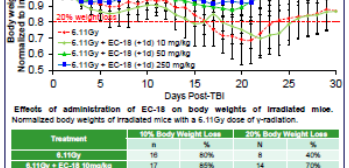
2. Dose effect relationship of EC-18 on the survival rate and body weight loss under γ-ray-induced acute radiation syndrome (ARS)



Dose effect of EC-18 administration on survival rates of mice irradiated with a dose of 6.11Gy of γ-radiation.; $^{*}P<0.0011$, 6.11Gy + EC-18 50mg/kg versus 6.11Gy; $^{\#}P<0.0001$, 6.11Gy + EC-18 250mg/kg versus 6.11Gy (Log rank test)

Treatment	Mice Survived /total	Survival rate	Mean survival time (days)	Median Survival (days)	Log-rank test P^{*}
6.11Gy	4/20	20%	17.9	15	
6.11Gy + EC-18 10mg/kg	4/20	20%	19.3	17	0.4425
6.11Gy + EC-18 50mg/kg	8/20	40%	22.3	20	0.0464
6.11Gy + EC-18 250mg/kg	16/20	80%	28.2	30	<0.0001

Table 2. Dose effect relationship of EC-18 on survivability and average life duration of irradiated mice

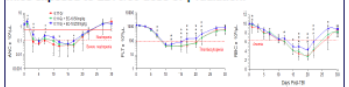


Effects of administration of EC-18 on body weights of irradiated mice. Normalized body weights of irradiated mice with a 6.11Gy dose of γ-radiation.

Treatment	10% Body Weight Loss		20% Body Weight Loss	
	n	%	N	%
6.11Gy	16	80%	8	40%
6.11Gy + EC-18 10mg/kg	17	85%	14	70%
6.11Gy + EC-18 50mg/kg	11	55%	7	35%
6.11Gy+ EC-18 250mg/kg	3	15%	3	15%

Table 3. PLAG significantly mitigates body-weight loss in mice exposed to the LD70/30 dose of γ-radiation.

3. PLAG mitigates the depletion of ANC, PLT, RBC, HGB in mice exposed to LD70/30 dose of γ-radiation.



EC-18 showed efficacy in improving neutropenia, thrombocytopenia and anemia in 24 h-delayed treatment model.

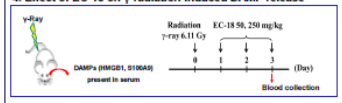
Treatment	Severe Neutropenia (ANC < 10^3 cells/μL)		Thrombocytopenia (PLT<10^5 cells/μL)		Anemia (HGB < 12 g/dL)	
	Mean First Day (±SE, range)	Mean Duration in Days (±SE, range)	Mean First Day (±SE, range)	Mean Duration in Days (±SE, range)	Mean First Day (±SE, range)	Mean Duration in Days (±SE, range)
6.11Gy	5.6±0.9 (3-17)	14.5±1.6 (4-23)	11.7±0.2 (7-12)	11.6±1.3 (5-18)	11.3±0.6 (3-17)	16.4±1.1 (10-18)
6.11Gy + EC-18 50mg/kg	9.0±1.1 (3-17) ($P = 0.0271$)	11.4±1.4 (4-19) (P = NS)	12.0±0.0 (12-12) (P = NS)	12.5±1.3 (P = NS)	12.5±0.3 (12-17) (P = NS)	15.1±1.5 (5-18) (P = NS)
6.11Gy + EC-18 250mg/kg	12.1±0.8 (3-17) ($P < 0.0001$)	8.8±0.7 (5-14) ($P = 0.0025$)	12.0±0.0 (10-12) (P = NS)	6.0±0.5 (5-10) ($P < 0.0001$)	14.5±0.6 (12-17) ($P = 0.0005$)	9.1±1.0 (5-18) ($P = 0.0004$)

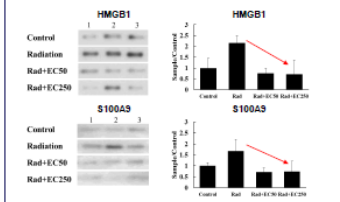
Table 4. Mean first day and mean duration of severe neutropenia (ANC <100 cells/μL), thrombocytopenia (PLT <100 x 10^3 cells/μL) and nemia (HGB <12 g/dL) in control and EC-18-treated mice exposed to lethal radiation dose

Treatment	Nadir of ANC (cells/μL)	Mean Number of Days to recovery ANC ≥ 500cells/μL (±SE, range)	Nadir of platelet (10^3 cells/μL)	Mean Number of Days to recovery platelet ≥ 10^4cells/μL (±SE, range)	Nadir of RBC (10^6 cells/μL)	Mean Number of Days to recovery RBC ≥ 6.3 x 10^6 cells/μL (±SE, range)
6.11Gy	29.0±4.3	25.2±1.9 (22-30)	35.4±3.7	29.2±1.3 (17-30)	3.8±0.4	26.0±1.3 (22-30)
6.11Gy + EC-18 50mg/kg	42.0±8.3 (P = NS)	25.4±1.1 (22-30) (P = NS)	38.0±3.5 (P = NS)	24.5±1.3 (17-30) (P = NS)	3.7±0.2 (P = NS)	29.1±0.9 (22-30) (P = NS)
6.11Gy + EC-18 250mg/kg	72.5±5.2 ($P < 0.0001$)	26.2±0.9 (22-30) (P = NS)	58.5±4.2 ($P = 0.0002$)	18.0±0.5 (17-22) ($P = 0.0002$)	4.8±0.2 ($P = 0.0225$)	25.3±1.0 (22-30) (P = NS)

Table 6. Mean nadir and mean number of days to recovery of ANC, platelets and RBCs in control and EC-18-treated mice exposed to lethal radiation dose

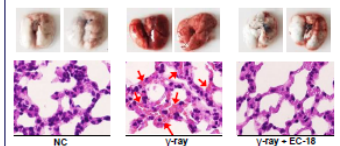
4. Effect of EC-18 on γ-radiation-induced DAMP release





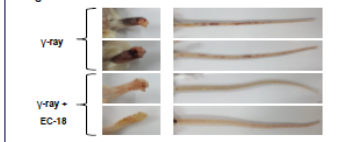
Effect of EC-18 administration on the release of HMGB1 and S100A9 in blood of mice irradiated with a dose of 6.11Gy of γ-radiation.

5. Effect of EC-18 on γ-radiation-induced lung injury.



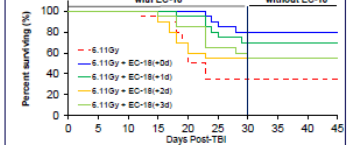
Effect of EC-18 administration on vascular leakage in lung of mice irradiated with a dose of 6.11Gy of γ-radiation.

6. Effect of EC-18 on γ-radiation-induced hemorrhagic telangiectasia and edema.



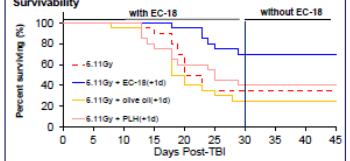
Effect of EC-18 administration on skin discoloration and edema formation of mice irradiated with a dose of 8Gy of γ-radiation.

7. Delayed administration effect of EC-18 on Survivability



Radiation only vs. EC-18 (250mpk) co-treatment, *** $P < 0.001$; Radiation only vs EC-18 24h post-IR, *** $P < 0.001$; Radiation only vs EC-18 48h post-IR, ** $P < 0.01$; Radiation only vs EC-18 72h post-IR, ** $P < 0.01$

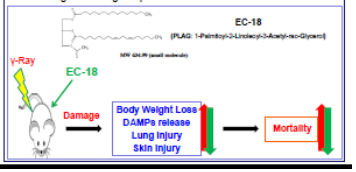
8. Comparison of EC-18 with olive oil and PLH on Survivability



Olive oil (same oalorie) and palmitic linoleic hydroxyl glycerol (PLH) showed little effect on survival in 24h delayed treatment. EC-18 has a distinctive mechanism of action for improving survivability in γ-radiation-induced ARS.

Conclusion

- Under γ-radiation-induced ARS condition, the administration of EC-18 significantly attenuated the radiation-associated mortality and loss of body weight in a dose-dependent manner.
- γ-radiation induced the rapid exhaustion of all kinds of blood cells, which is defined by γ-radiation-induced hematopoietic injury. The administration of EC-18 significantly attenuated γ-radiation-induced reduction of ANC, PLT and RBC counts.
- Based on the observations in this study, we concluded that EC-18 has therapeutic potential for improving survivability and reducing hematological damage in γ-radiation-induced ARS.



ARS: 미국 정부 R&D 프로그램 진행

ENZYCHEM LIFESCIENCES

Program	Funding Available	Status	Comments
NIH/NIAID/RNCP/PDSS	Cost of MTA non-clinical study covered by NIH	Study protocol (SRI) reviewing by Enzychem for the project start	ARS indication; SRI international leads the NIAID non-clinical program
NIH/NIAID/CCRP	Cost of MTA non-clinical study covered by NIH	Study protocol (Battelle) reviewing by Enzychem for the project start	Chemical (sulfur mustard) indication; Battelle is the agency's chosen lab
BARDA/Techwatch	BARDA MTA leading to non-clinical study funded by USG	White paper preparing for funding approval by Enzychem	BARDA will select an approved vendor lab to perform the work per the BARDA RTOR system
NIH/NIAID/BAA	$5,943K	Submitted the business & technical proposal for NHP study	ARS indications;
BARDA/ASPR/DRIVe	$749K	Submitted the study proposal for Sepsis	

Healthy and Happy Life

Appendix

EC-18 임상개발 적응증

ENZYCHEM LIFESCIENCES

항암화학요법 유발 호중구감소증 (CIN)

- 빈번한 항암치료의 부작용으로 종종 입원이 필요함
- 미국 기준 연간 150만 명 이상의 환자
- 입원 환자 14명 중 1명 사망 (사망률: 7.2 %)
- EC-18은 G-CSF에 반응 없는 환자, 혈액 암 환자, 항암화학 방사선 치료 환자를 대상으로 함.
- 독특하고 차별화 된 MOA

Target : 3조원 시장

항암화학 방사선요법 유발 구강점막염 (CRIOM)

- 항암화학방사선 치료 중 발생하는 심한 구강 염증
- 미국 기준 연간 약 17만 명의 궤양성 구강점막염 환자
- 암 환자의 치료 및 생존에 중요한 영향을 끼침
- 고형암 환자에게 사용 가능한 CRIOM 승인 의약품 부재
- 거대한 미충족 의학적 요구
- FDA 신속 심사 (Fast Track) 지정

Target : 2.6조원 시장

급성방사선증후군 (ARS)

- 다량의 방사선 노출로 인한 치명적 질환으로 세포 수준의 저하, 다양한 장기의 손상 및 사망 야기
- 인구가 2백만명 도시에서 27만 명 이상의 환자 발생
- EC-18은 조혈-ARS, 위장관-ARS, 폐-ARS 등 미국 정부기관의 의약대응조치 (MCM)에 필요한 다양한 질환에 효과
- FDA 희귀 의약품 지정

Target : 1.5조원 시장

EC-18 기회 극대화 전략

ENZYCHEM LIFESCIENCES

개발 전략	• 미충족 의학적 요구가 높은 적응증을 타겟 • 항암 분야 적응증에 우선적으로 집중 • FDA Breakthrough Therapy 지정 잠재력 • 빅파마에 기술라이센싱 및 협력개발 추진 • ARS에 대해 미국 정부 R&D 펀드 지원 프로그램 선정
지적 재산권	• 강력한 IP 포트폴리오 • 신약 개발을 위한 등록 특허 84건 • API 사업 등록 특허 11건 • 조영제 사업 등록 특허 1건 • 67건의 신약 개발 특허 추가 출원
규제과학	• ARS, 미국 FDA로부터 희귀의약품 지정 확보 • ARS를 위한 우선권 검토 바우처의 획득 목표 • CRIOM, 미국 FDA로부터 Fast Track 지정 확보 • CIN 과 CRIOM, 미국 FDA로부터 Breakthrough Therapy 지정 가능성

상업 생산 GMP 제조 시설

제1 GMP 생산 설비

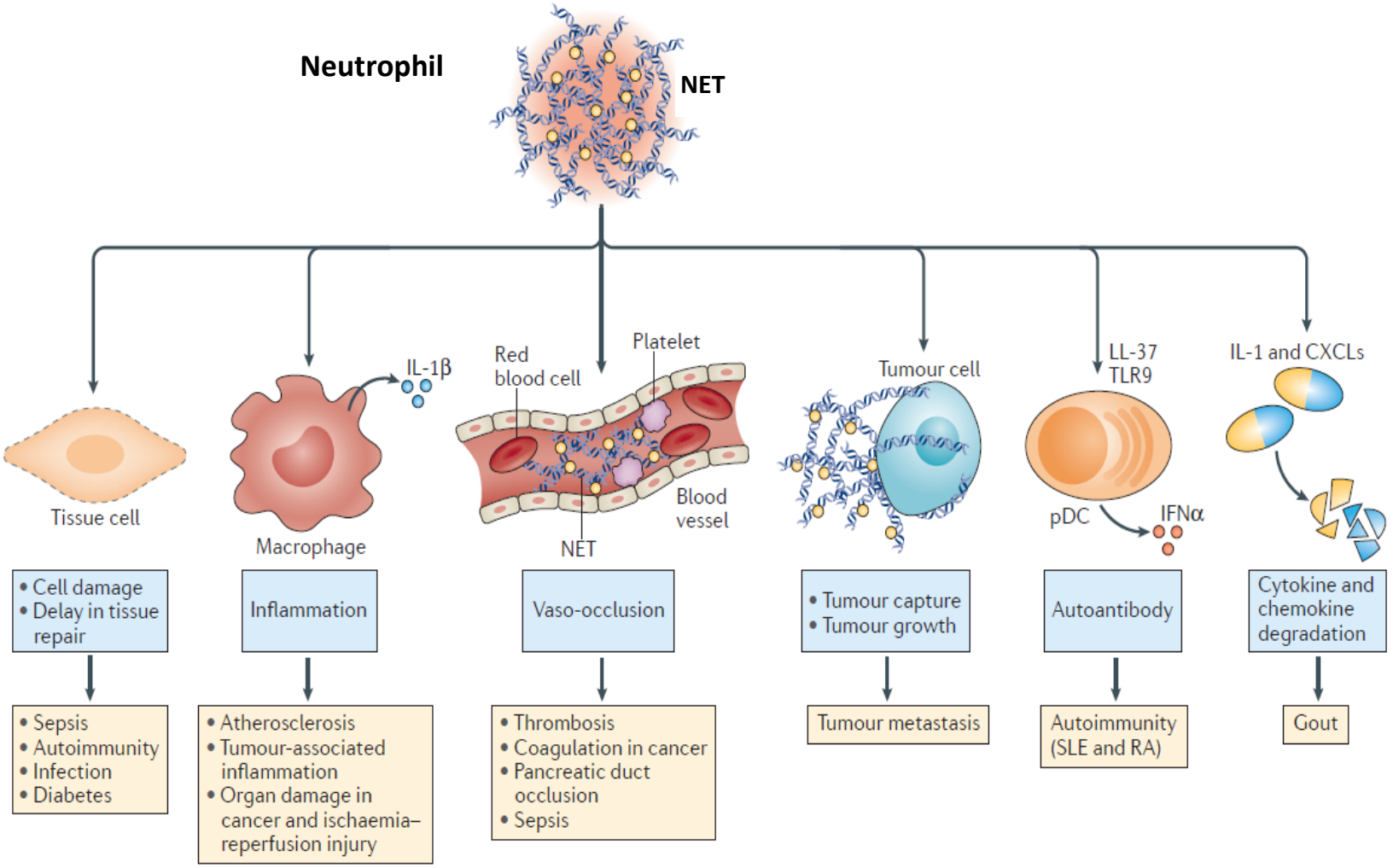
- 생산: 항생제 (Cephalosporin)
- GMP 승인: 2008년 4월 (2018년 갱신)
- 건물 면적: 21,000 ft²
- 연간 생산 능력: 250 tons
- PMDA GMP 자격 승인 (2015)

제2 GMP 생산 설비

- 생산: EC-18, Non-Cephalosporin API, 조영제
- GMP 승인: 2013년 1월 (2018년 갱신)
- 건물 면적: 19,000 ft²
- 연간 생산 능력: 200 tons (EC-18 10 tons)
- EU GMP 인증 (2019년 2월)

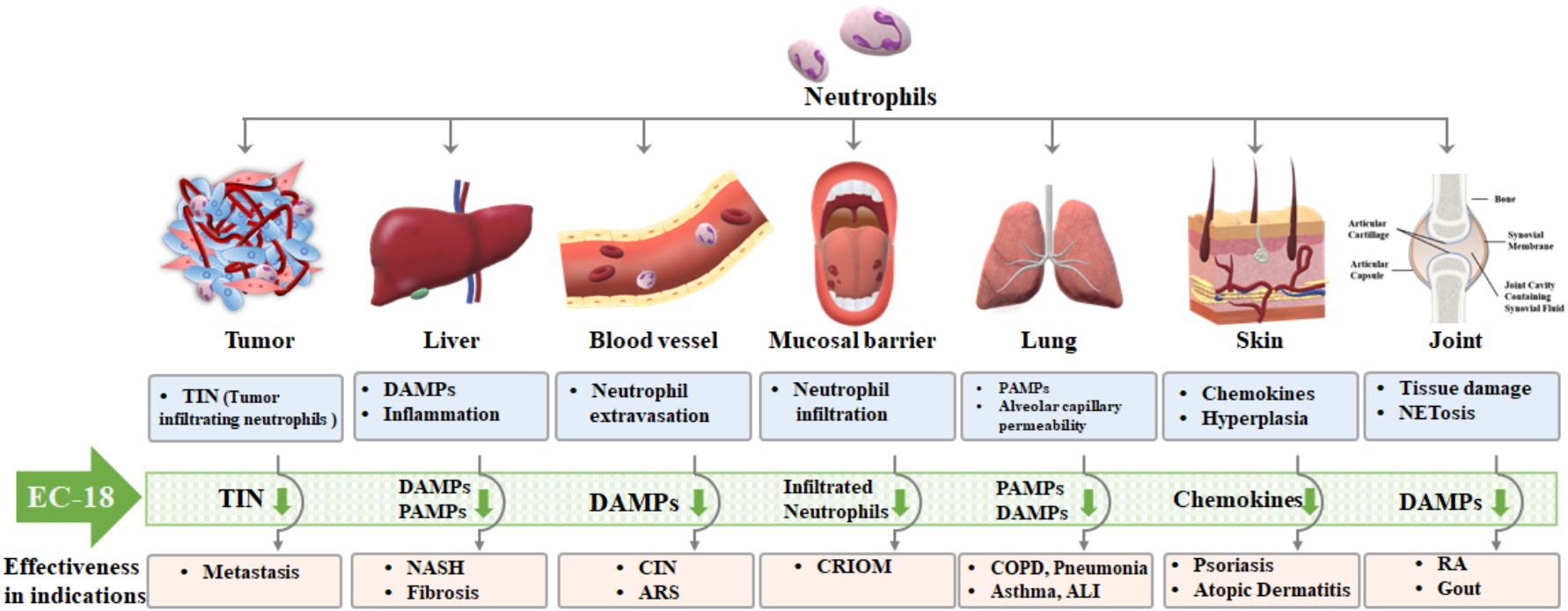
제2 공장 EC-18 생산 cGMP 추진

Neutrophil-mediated pathology



Nat Rev Immunol 2018; 18: 134

EC-18's efficacy in the neutrophil related diseases




Thank You