

세계선도 중점학과 육성사업 결과보고서

소 속	분자의학 및 바이오제약 학과		
직 급	학생연구원	성명	이하경
승 인 여 행 기 간	2018. 11. 22 ~ 2018. 11. 23		
여 행 기 간	2018. 11. 22 ~ 2018. 11. 23		
여 행 국 (도 시 명)	대한민국(부산)		
여 행 목 적	2018 한국약제학회 국제학술대회 참석 및 포스터 발표		
주 요 방 문 일 정	<ul style="list-style-type: none"> ▪ 2018. 11. 22 : 학회 참석 및 포스터 발표 ▪ 2018. 11. 23 : 학회 참석 및 포스터 발표 		
활 동 내 용 (보 고 서 요 약)	<ul style="list-style-type: none"> ▪ 2018 한국약제학회 국제학술대회 참석 ▪ In vivo efficacy of combination therapy of caspase mediated prodrug 포스터 발표 및 논의 		
제 출 인	이하경		
첨 부	1. 발표 포스터 1부. 2. 국제점검기준표 1부. 끝.		

국제 학술대회 점검 기준표

소속 학과	분자의학 및 바이오제약학과		
학회일정	2018. 11. 22 ~ 2018. 11. 23	사업명	세계선도 중점학과 육성사업
학술회의명	2018 한국약제학회 국제학술대회	학회지(장소)	부산

1. 주관기관 : 한국약제학회

2. 총 참여 국가(발표자의 소속국가) : 7 개국

3. 총 발표 논문 수

구두발표 수	포스터 발표 수	총 발표 논문 수
33	100	70

4. 구두발표 논문 중 외국인 발표자 비율

한국인 비율 (건수)	외국인 비율 (건수)	전체 논문 비율 (건수)
66.7% (22)	33.3% (11)	34% (24)

*외국인 비율: 구두발표논문의 제1저자의 소속기관을 기준으로 산정.

- 제1저자가 논문을 제출할 때의 소속기관을 기준으로 함. 외국기관 소속 한국 국적의 사람일 경우 외국인 논문 비율에 포함. 한국 기관에 소속된 외국인은 외국인논문비율에 포함하지 않음

- 제1저자의 구분이 없는 경우, 저자 수의 50% 이상이 되는 저자 소속 기관의 국적으로 판정

5. 관련규정 : 과학기술(기초, 융복합)분야

- 4개국(대한민국 포함)이상 참여

- 총 구두발표 논문이 20건 이상

- 구두발표의 논문 발표자 중 외국기관 소속 외국인이 50% 이상

	지도교수	
결재		



In vivo efficacy of combination therapy of caspase mediated prodrug

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PURPOSE

Here we suggest a new effective strategy to overcome tumor heterogeneity for eradicating metastatic triple negative breast cancer (TNBC). We applied a combination therapy of caspase-3 mediated “targeting” (RGDEVD-DOX) and “maintaining” (EMC-DEVD-S-DOX) prodrugs, given in a sequential manner.

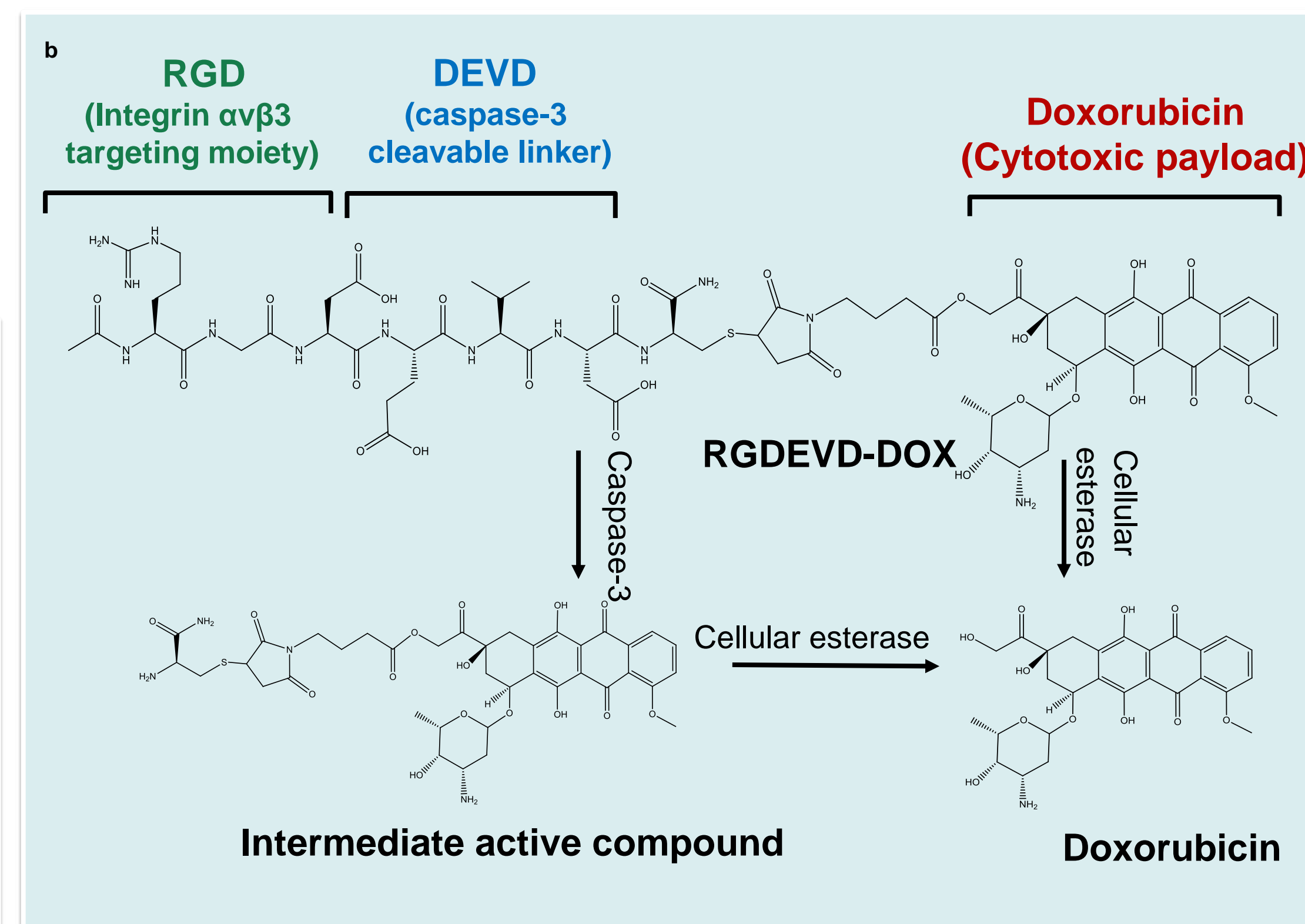
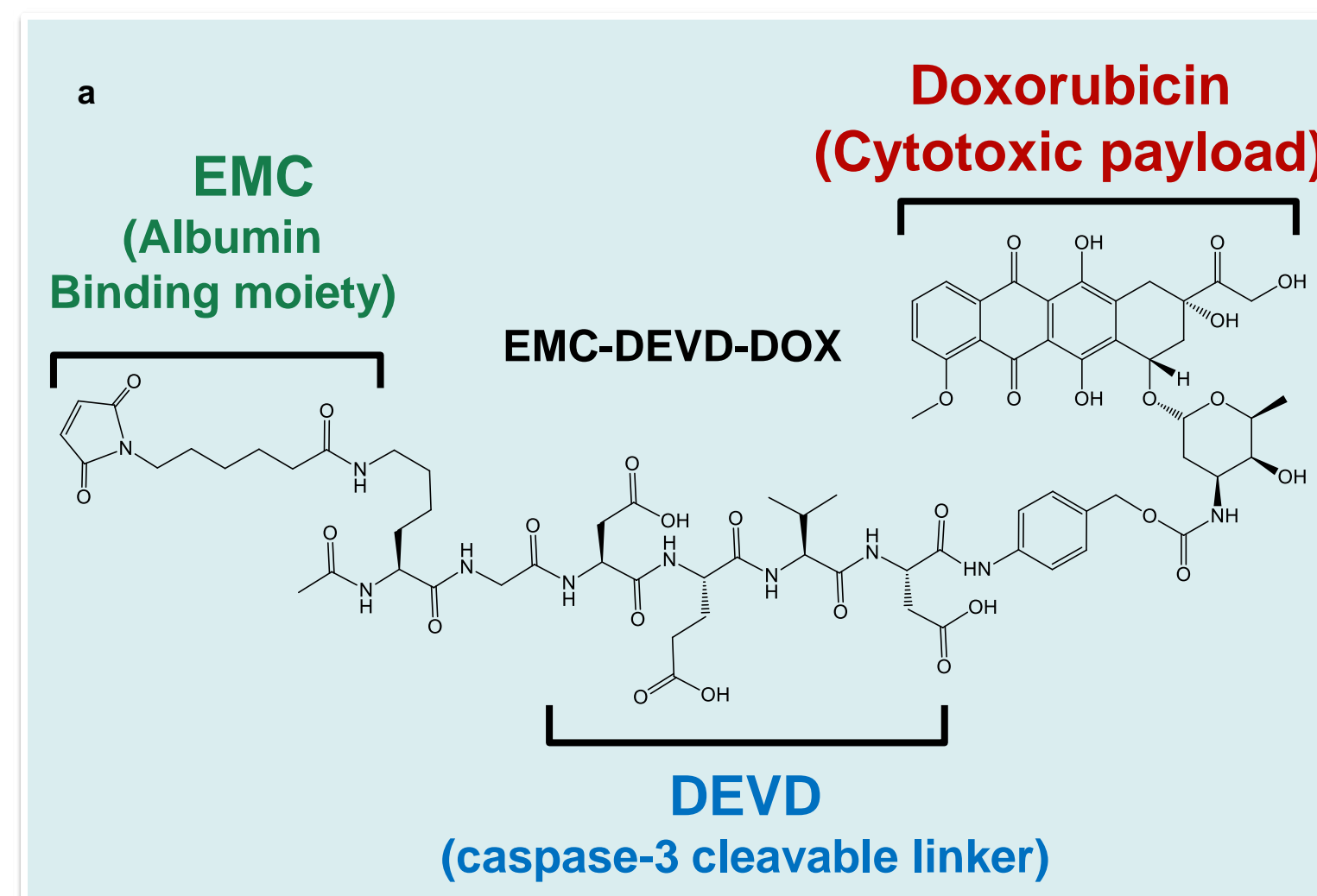
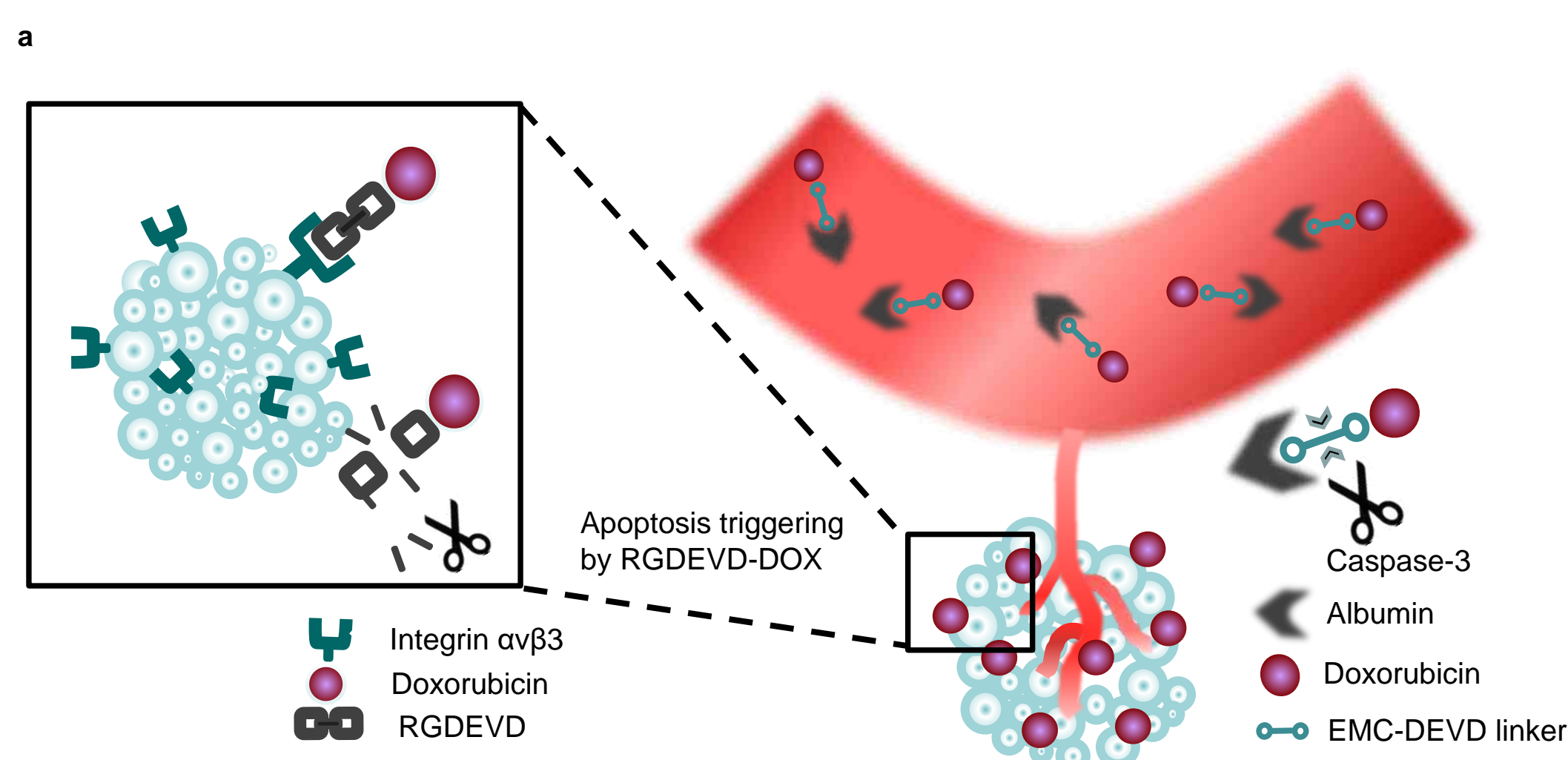


Figure 1. Mechanism of DEVD prodrug (a) Schematic description of combination therapy **Figure 2.** Structural depiction of caspase-3 prodrug system. The structure of (a) EMC-DEVD-DOX and (b) RGDEVD-DOX and active compound

METHOD

RGDEVD-DOX is designed to target integrin $\alpha v \beta 3$ and induce apoptosis specifically in tumor cells. EMC-DEVD-DOX binds to circulating albumin after administration to show enhanced half-life and accumulates at tumor site. In the apoptotic tumor tissue, caspase-3 releases free doxorubicin from the prodrug and this induces indiscriminate killing of surrounding tumor cells regardless of the integrin $\alpha v \beta 3$ expression, resulting in continuous activation of prodrug. In order to determine the efficacy of RGDEVD-DOX and EMC-DEVD-DOX combination, we performed *in vivo* efficacy test using two TNBC xenograft models. In case of MDA-MB-231 and 4T1 xenograft models, combination therapy showed 78% ($p=0.0006$) and 80% ($p<0.0001$) of tumor growth inhibition respectively compared the control group.

RESULT

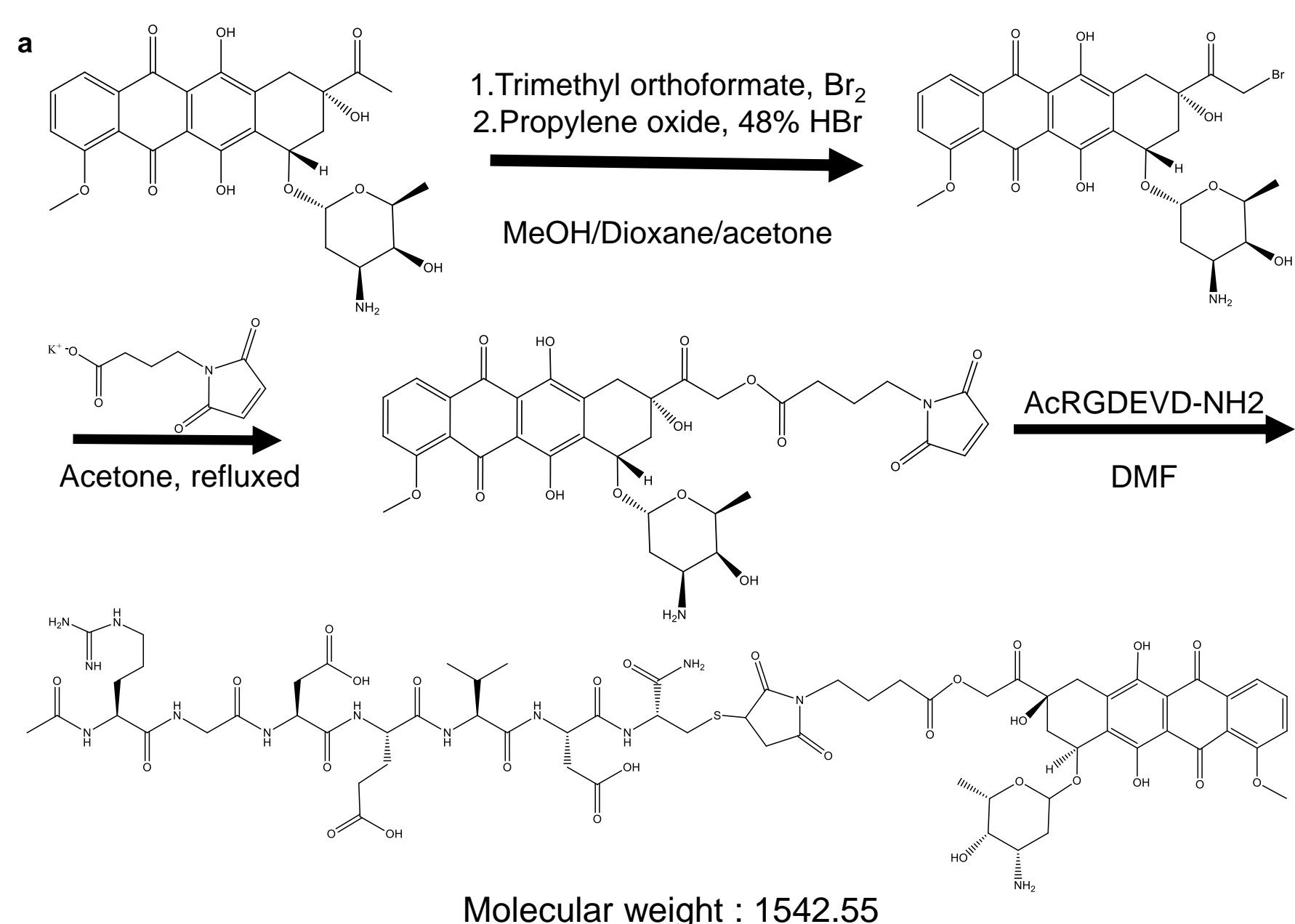


Figure 3. Synthesis of RGDEVD-DOX (a) Synthesis scheme of RGDEVD-DOX

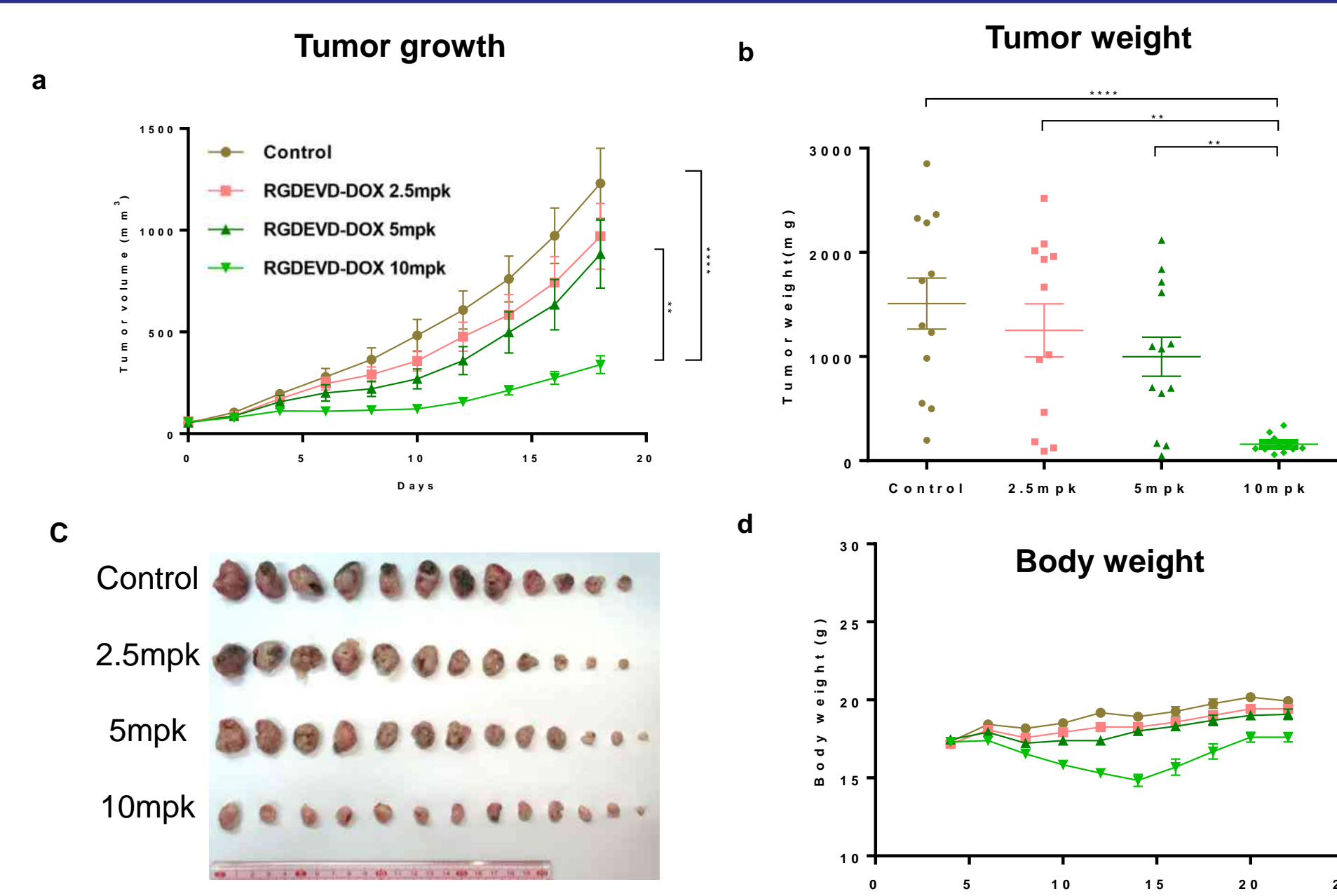


Figure 4. *In vivo* dose dependent antitumor efficacy of RGDEVD-DOX. (a) Tumor growth (b) tumor weight (c) images of 4T1 tumor and (d) body weight of 4T1 xenografted mice that received RGDEVD-DOX (2.5, 5, 10 mg/kg DOX-equivalent IV infusion, n=12-13) for 5 days

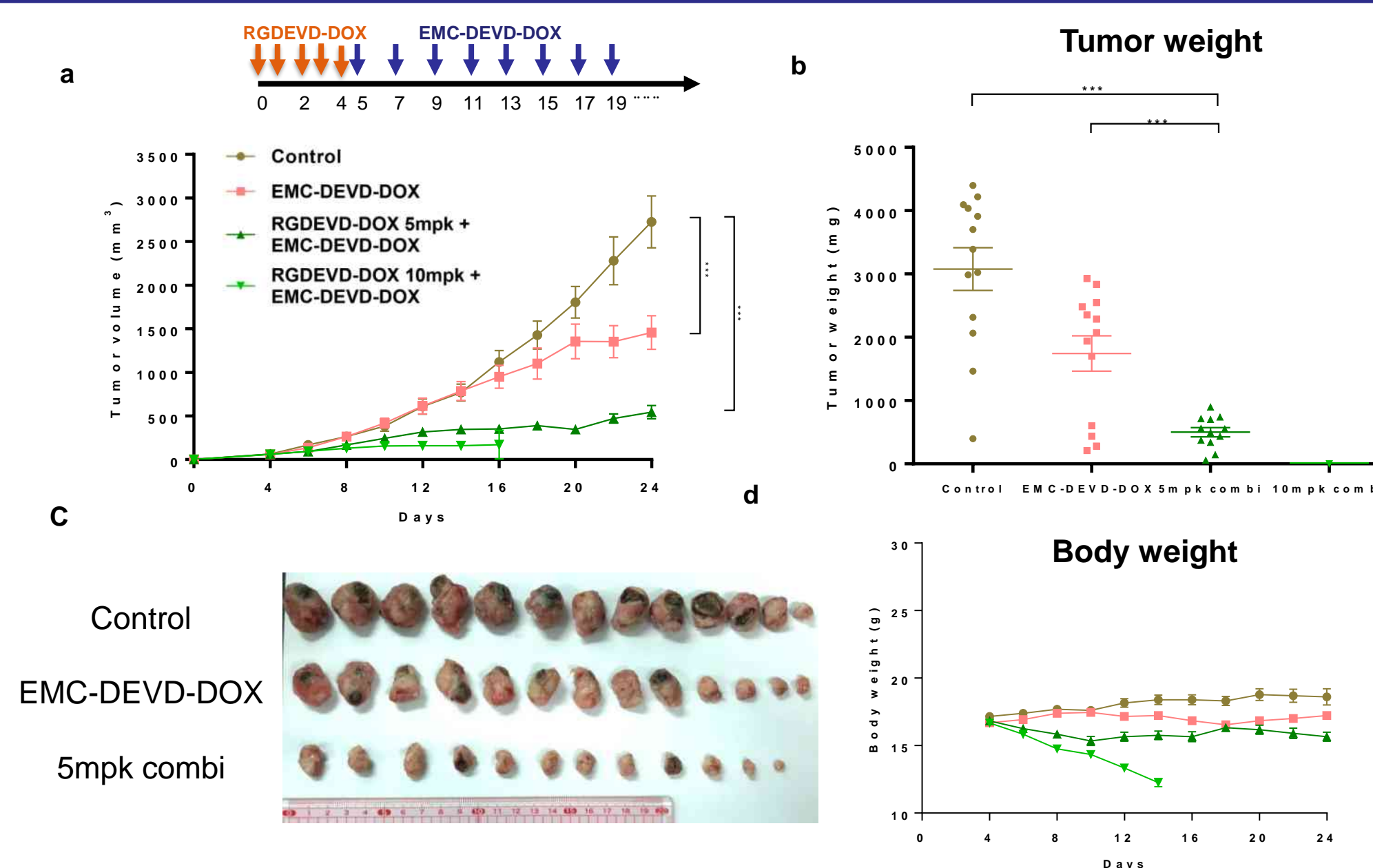


Figure 5. *In vivo* antitumor efficacy of combination therapy. (a) Tumor growth (b) tumor weight (c) images of 4T1 tumor and (d) body weight of 4T1 xenografted mice that received RGDEVD-DOX (5 or 10 mg/kg DOX-equiv, IV) for first 5 days and treatment is switched to EMC-DEVD-DOX (5mg/kg DOX-equiv, every other day IV, n=13) until day 24 or EMC-DEVD-DOX monotherapy (n=13)

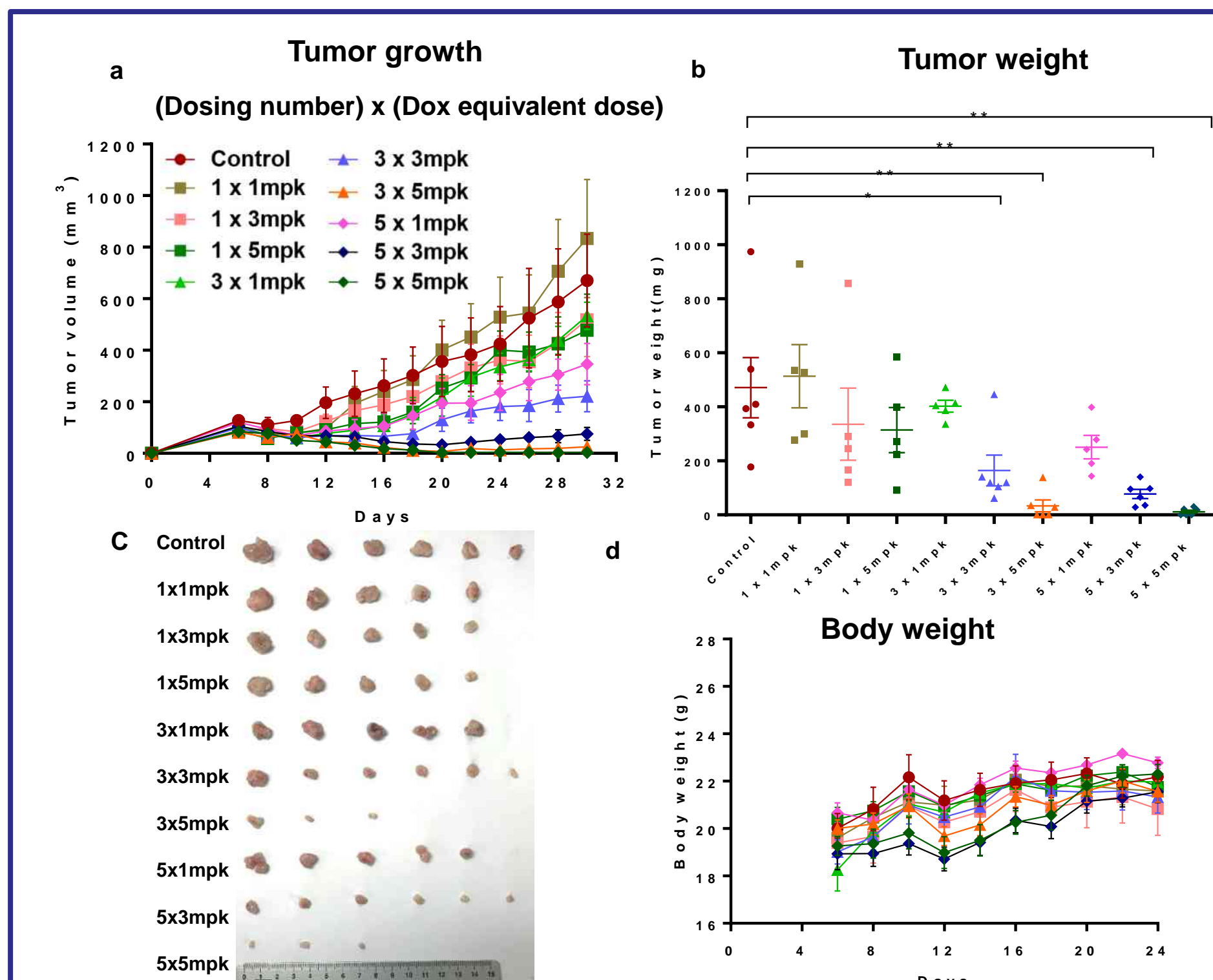


Figure 6. *In vivo* dose dependent antitumor efficacy of RGDEVD-DOX. (a) Tumor growth (b) tumor weight (c) images of MDA-MB-231 tumor and (d) body weight of MDA-MB-231 xenografted mice that received RGDEVD-DOX (1, 3, 5 mg/kg x 1, 3, 5 days IV, n=5)

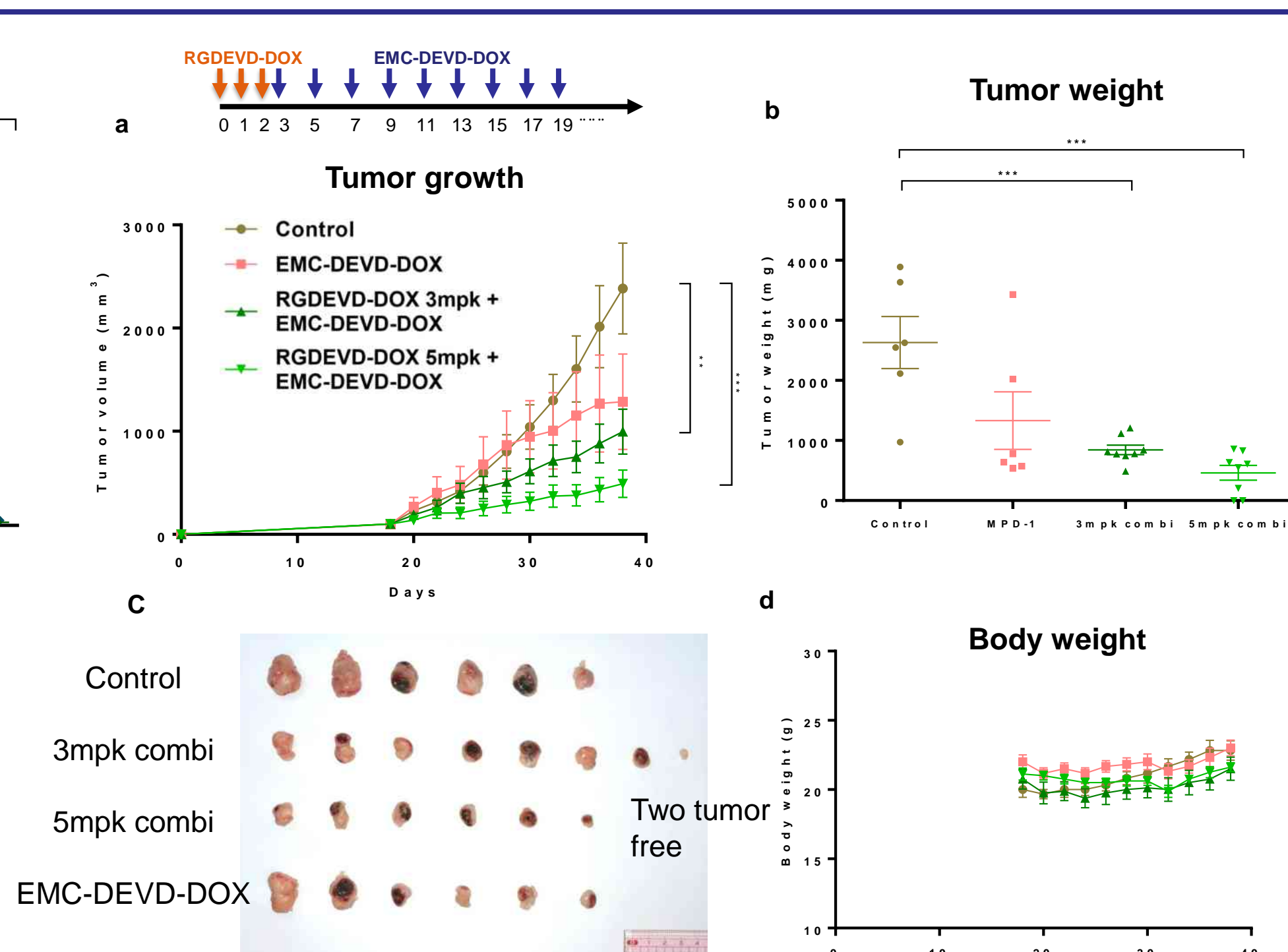


Figure 7. *In vivo* antitumor efficacy of combination therapy (a) Tumor growth (b) tumor weight (c) images of MDA-MB-231 tumor and (d) body weight of MDA-MB-231 xenografted mice that received RGDEVD-DOX (3 or 5 mg/kg IV, n=8) for first 3 days and treatment is switched to EMC-DEVD-DOX (5mg/kg every other day IV, n=8) or EMC-DEVD-DOX monotherapy (n=6)

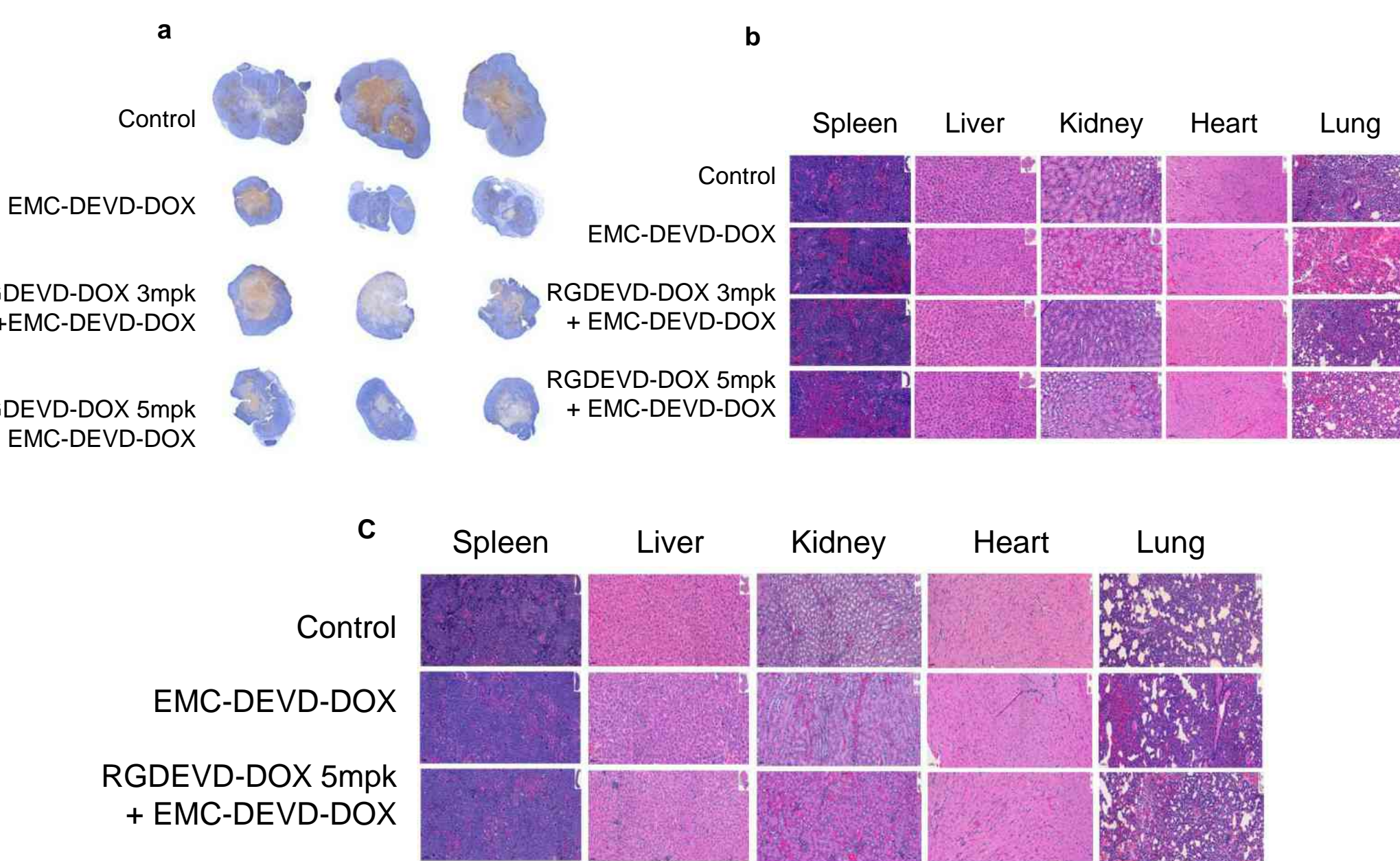


Figure 8. Evaluation of caspase-3 in tumor tissue and toxicities of the prodrug. (a) Immunohistochemical staining of caspase-3 in tumors (b) Histopathological analysis of spleen, liver, kidney, heart and lung of MDA-MB-231 xenograft mice received combination therapy in Figure 7 (c) Histopathological analysis of 4T1 xenograft mice received combination therapy in Figure 5

CONCLUSION

In conclusion, we verified that combination therapy of RGDEVD-DOX with EMC-DEVD-S-DOX showed synergistic effect in TNBC mouse model. We demonstrate that the sequential combination therapy of RGDEVD-DOX and EMC-DEVD-DOX successively reduces the incidence of metastasis and prolongs survival in TNBC model. Collectively, we propose that RGDEVD-DOX is a promising caspase-3 mediated prodrug in respect of overcoming tumor heterogeneity, which can synergize the efficacy of EMC-DEVD-DOX.