Literature Report 6

Fang Xiangning

2021.08.19

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Article

A Small Molecule Strategy for Targeting Cancer Stem Cells in Hypoxic Microenvironments and Preventing Tumorigenesis

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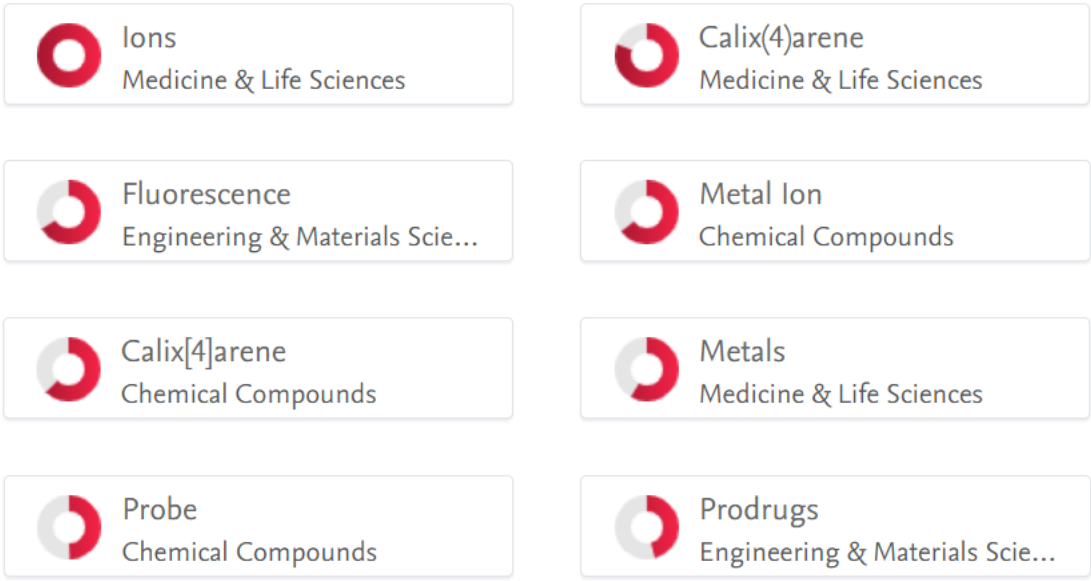
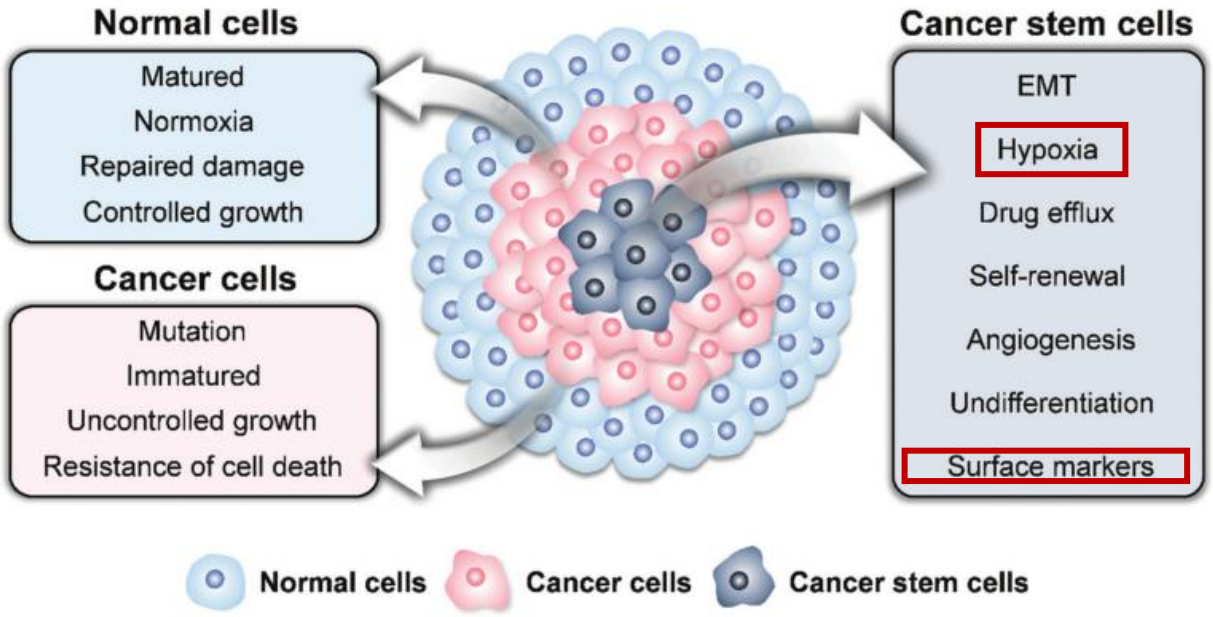
Highly Cited Researcher

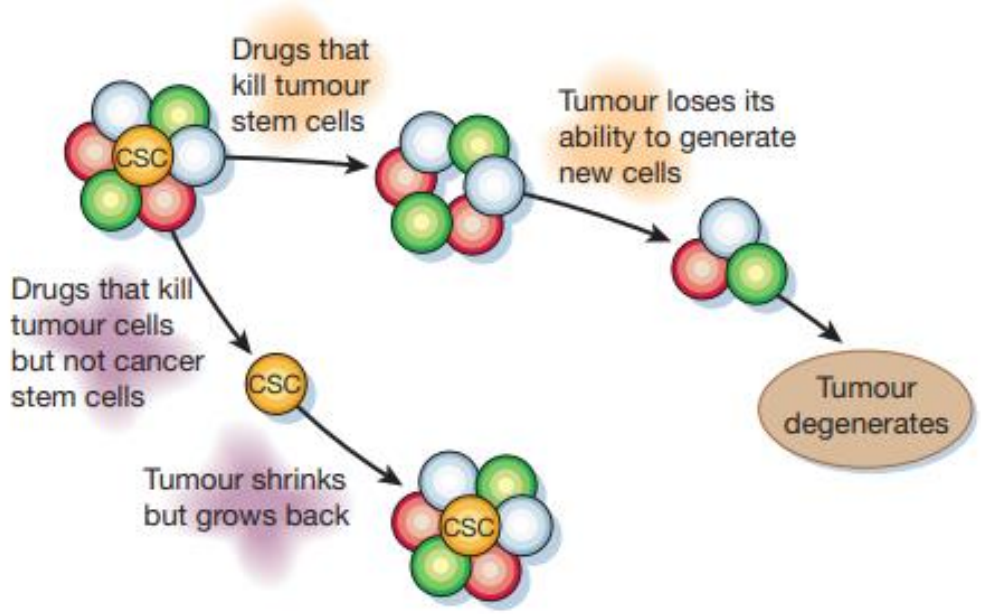


Background

癌症干细胞：cancer stem cells （CSCs）



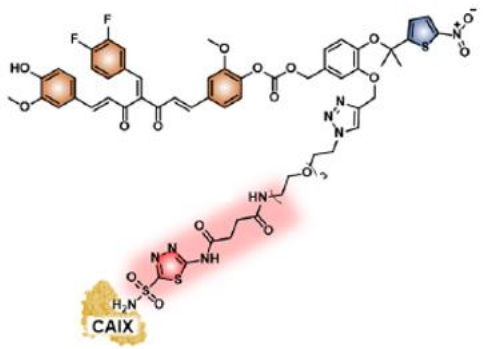
Chem. Soc. Rev., 2020, 49, 7856



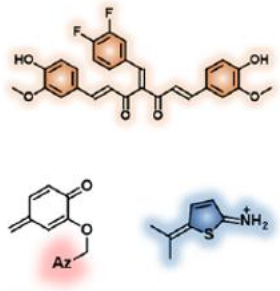
Nature, 2001, 414, 105

Probe Design

AzCDF
(Therapeutic Molecule)



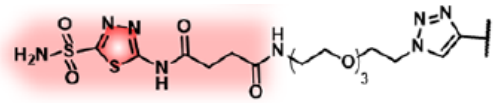
Hypoxia

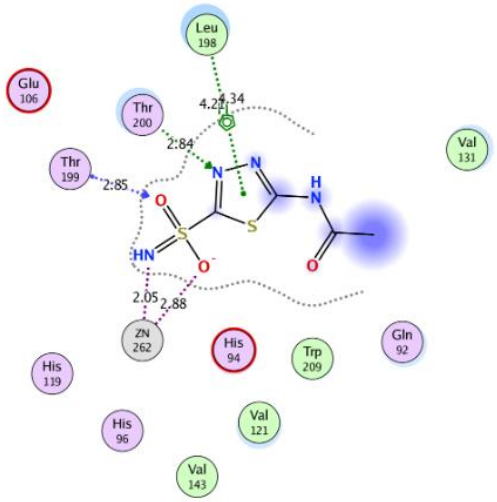


3,4-Difluorobenzylidene curcumin
[Anti-CSC drug]
CDF

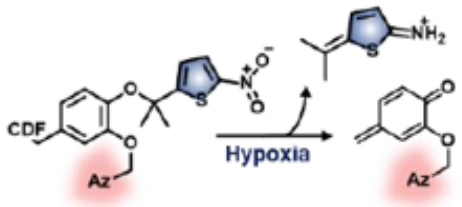
Dimethylnitrothiophene
[Hypoxic trigger]
Trigger

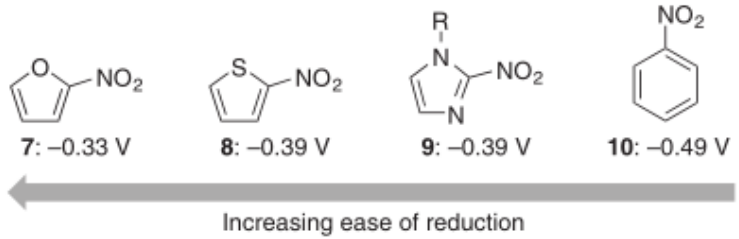
Acetazolamide
[CSC targeting]
Az



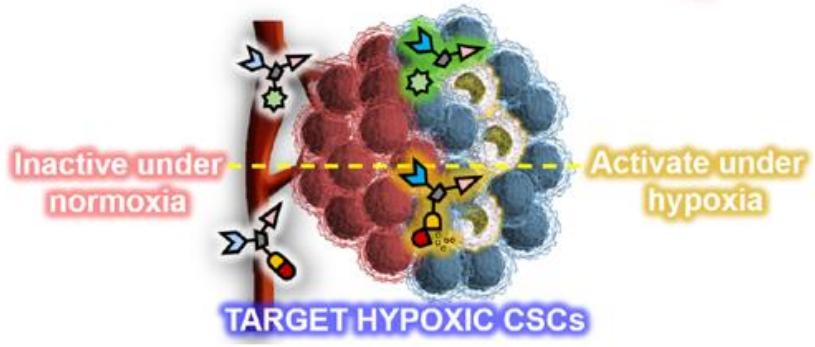


Bioorganic Chemistry, 2020, 95, 103514





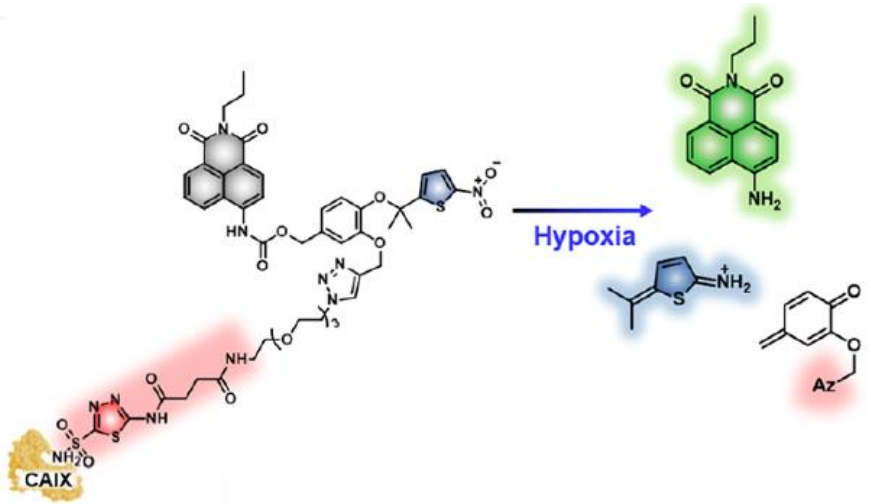
Nat Protoc, 2016, 781



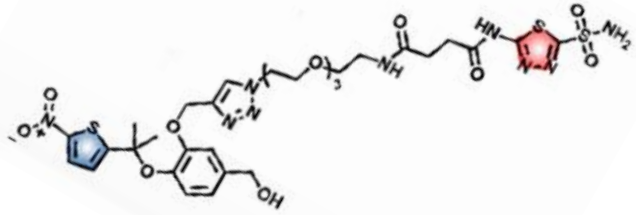
Normal cell
Cancer cell
Cancer stem cell

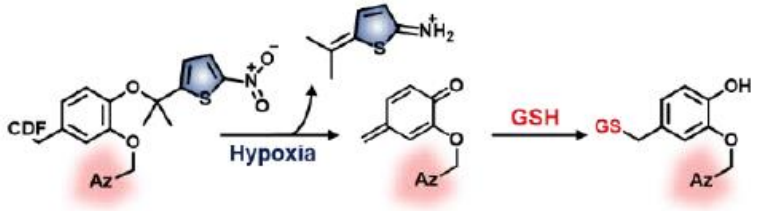
Probe Design

AzNap
(Imaging Molecule)

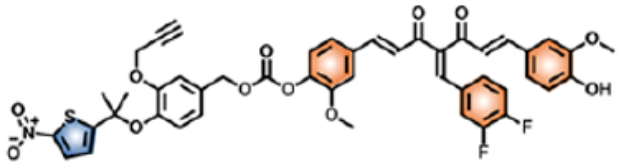


R-Az
(No Drug)



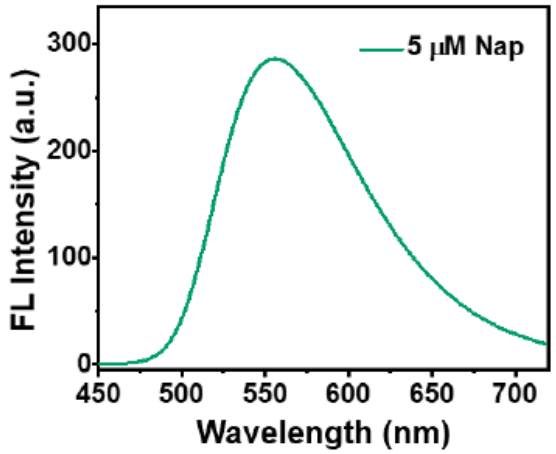


R-CDF
(No targeting)

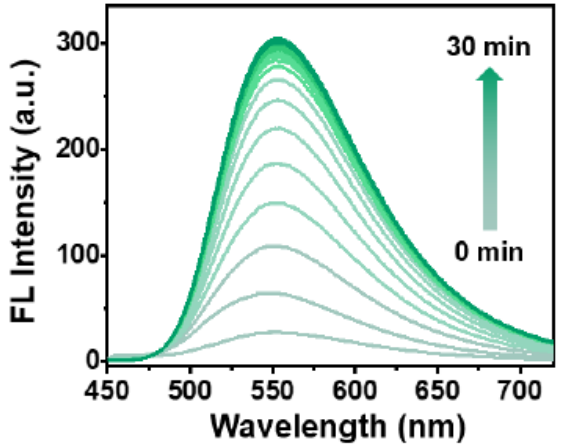


In Vitro Reductive Activation of AzNap and AzCDF

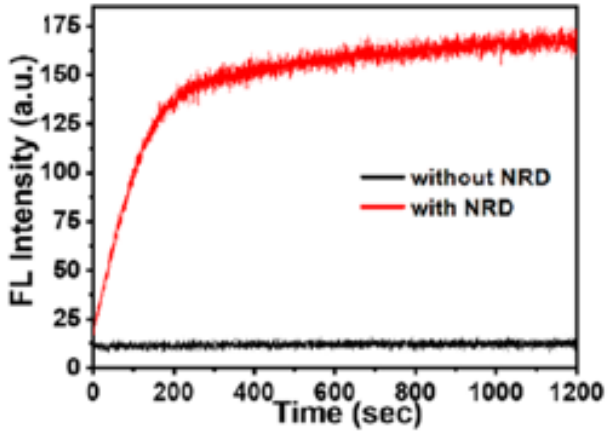
AzNap



Fluorescence spectrum of the naphthalimde fluorophore (5 μM).

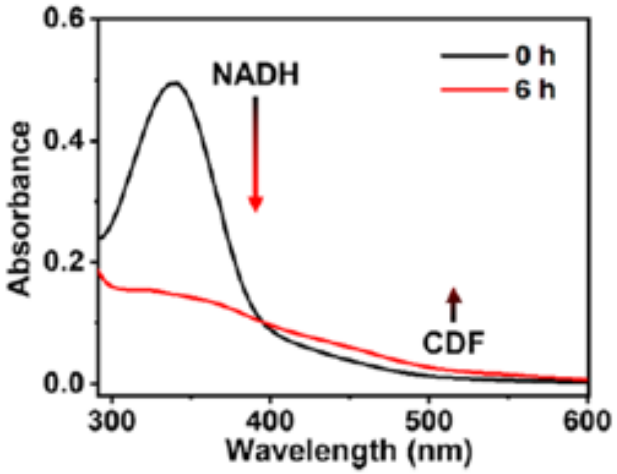


Time-dependent fluorescence of **AzNap** (5 μM) recorded after incubating with nitroreductase (10 μg/mL) and NADH (50 μM) for 30 min in PBS (pH 7.4) at 37°C.

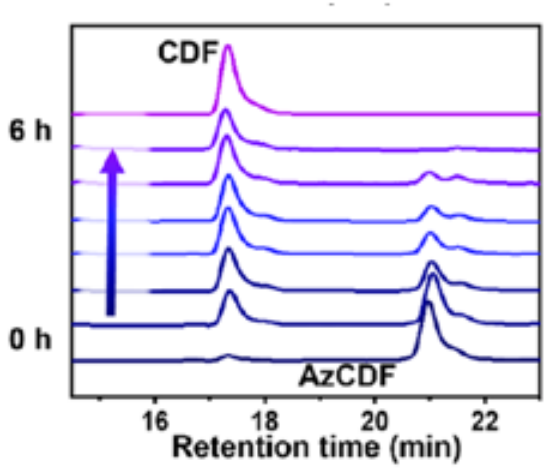


Time-dependent fluorescence of 5 μM AzNap with and without nitroreductase (λem = 550 nm).

AzCDF

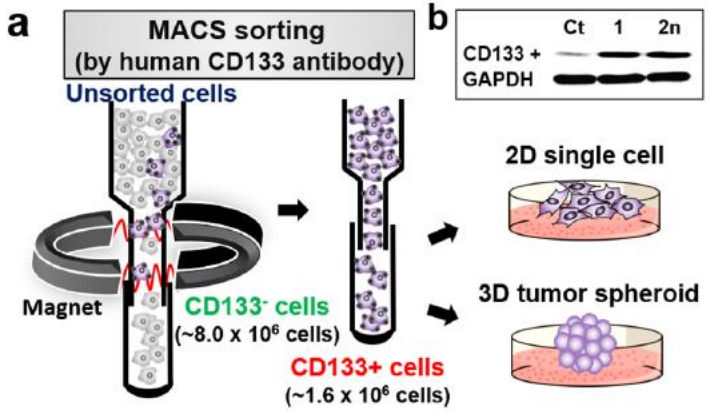


UV/vis spectrum of AzCDF (5 μM) before and after the addition of 10 μg/mL nitroreductase and NADH (50 μM).

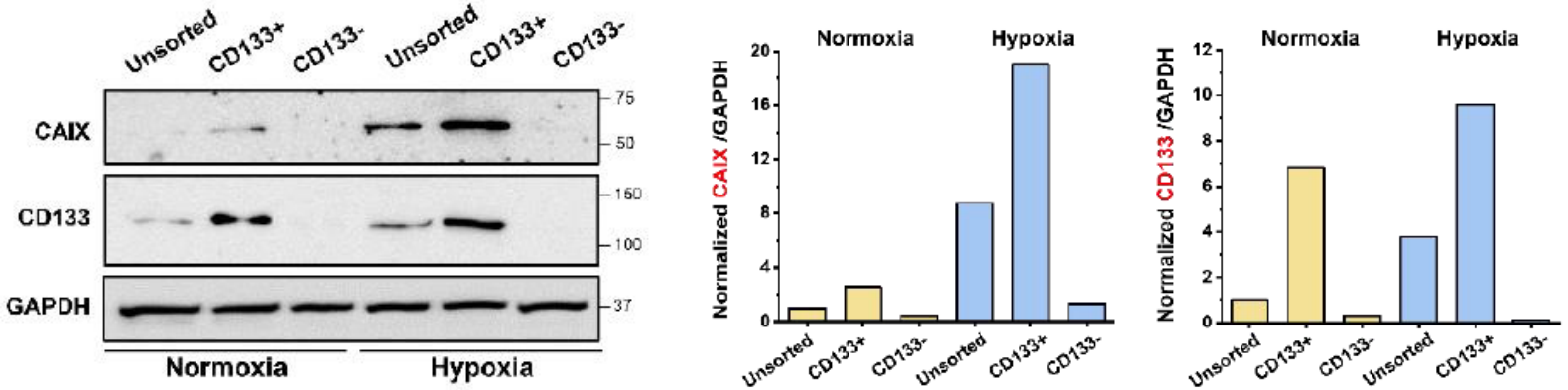


HPLC analysis (absorbance at 365 nm) of 5 μM AzCDF incubated with 10 μg/mL nitroreductase and 50 μM NADH at 37 °C for the indicated times.

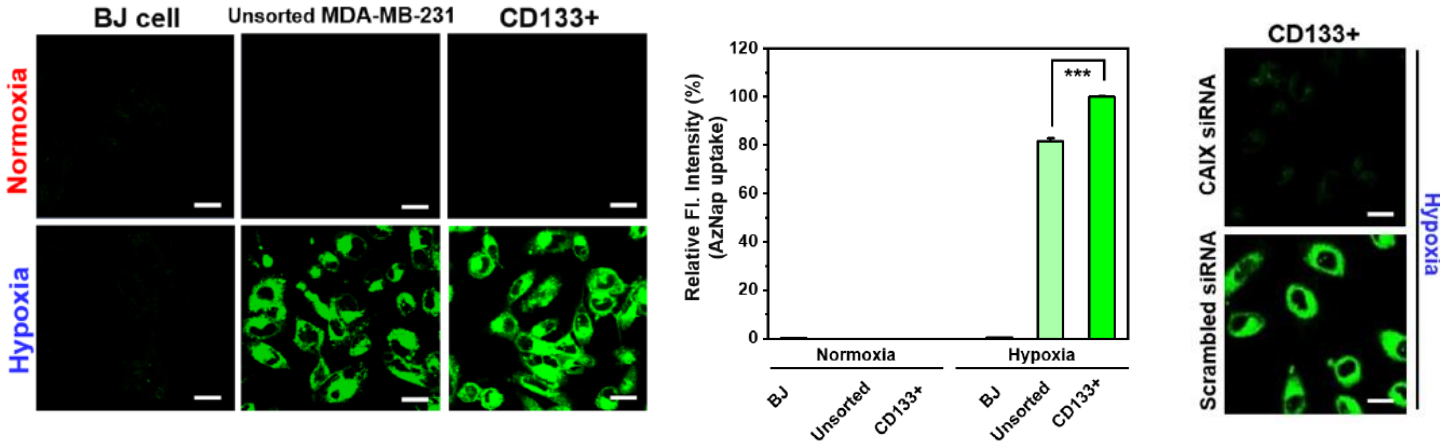
AzNap and AzCDF Activation in Hypoxic CSCs



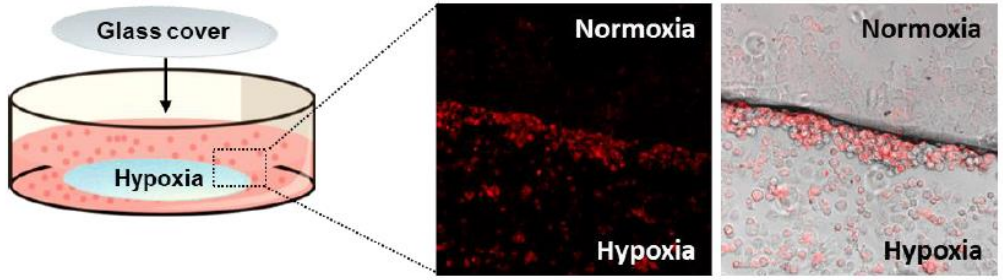
CD133：癌症干细胞生物标志物
利用磁激活细胞分选筛选CD133⁺细胞



CD133⁺细胞在肿瘤组织中特异性表达CAIX

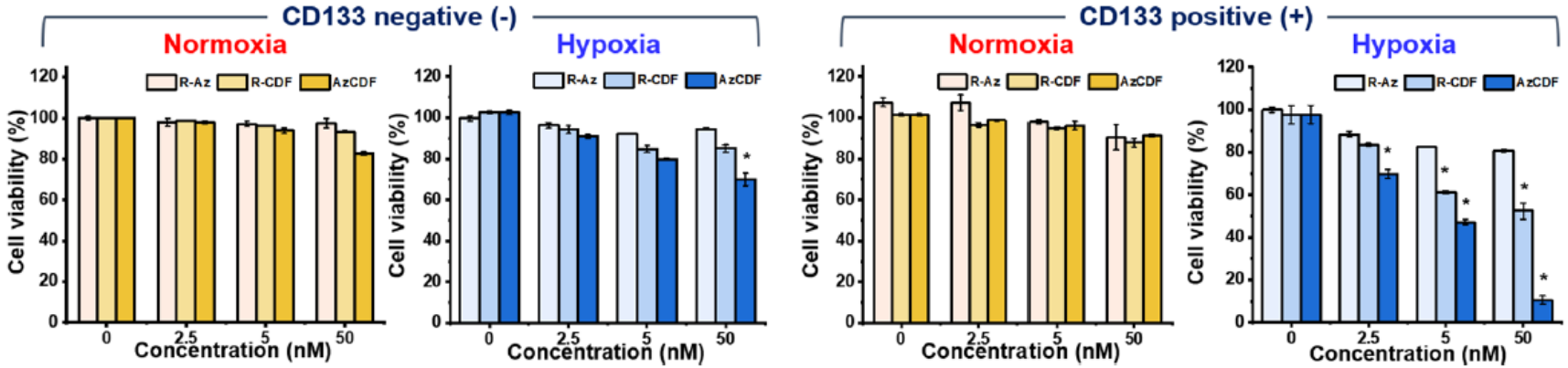


CAIX促进AzNap摄取



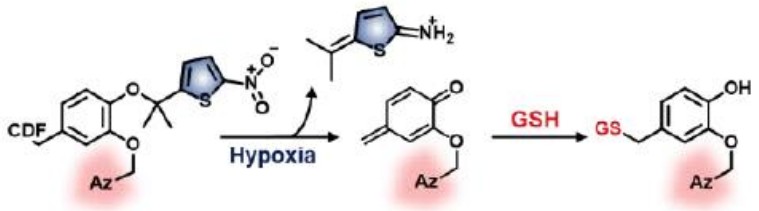
AzNap的激活仅限于低氧环境

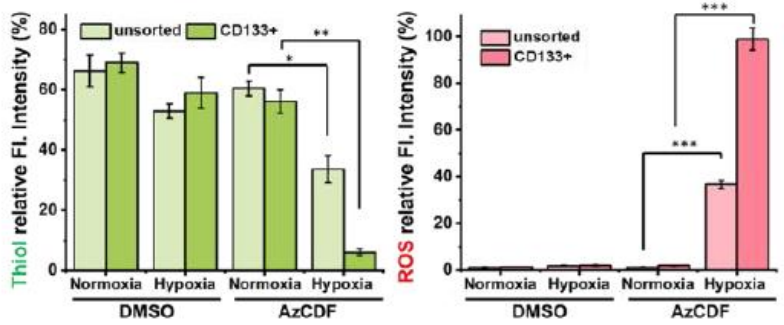
AzNap and AzCDF Activation in Hypoxic CSCs

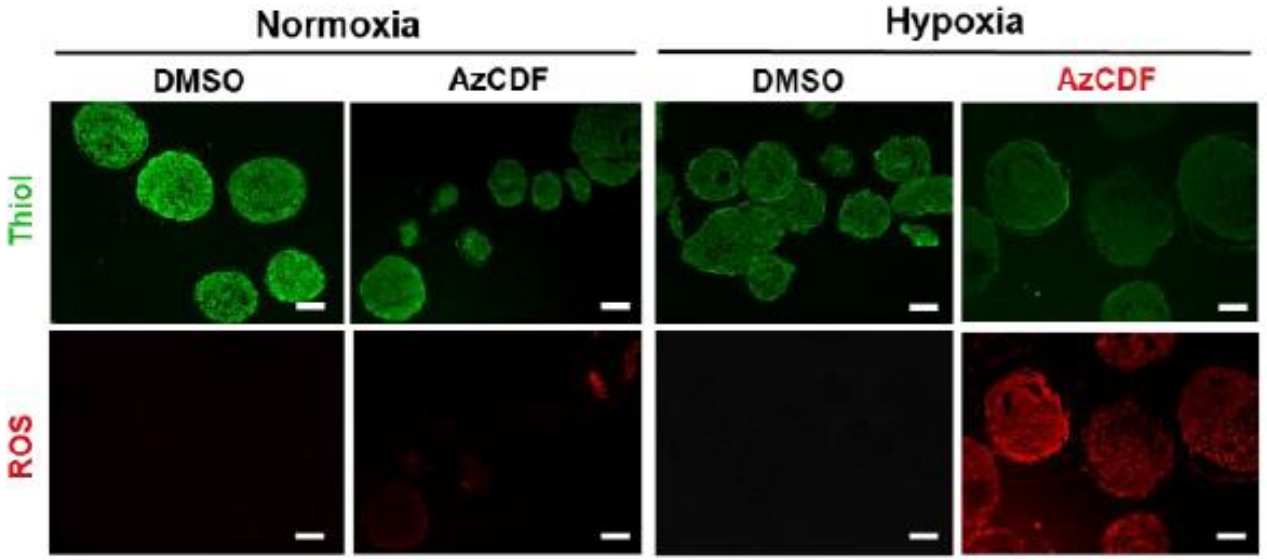


AzCDF仅在缺氧条件下有很强的细胞毒性

Cytotoxicity (MTT assay) of CD133− and CD133+ cells under normoxia and 3% O_2, incubated for 24 h with AzCDF

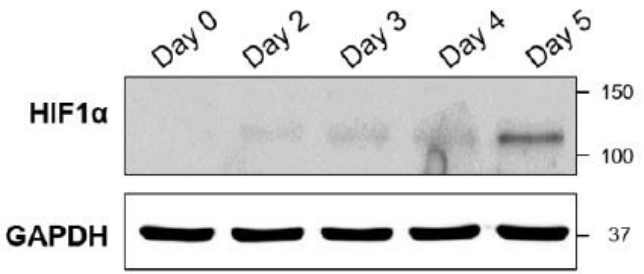


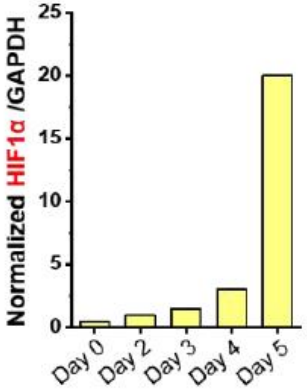


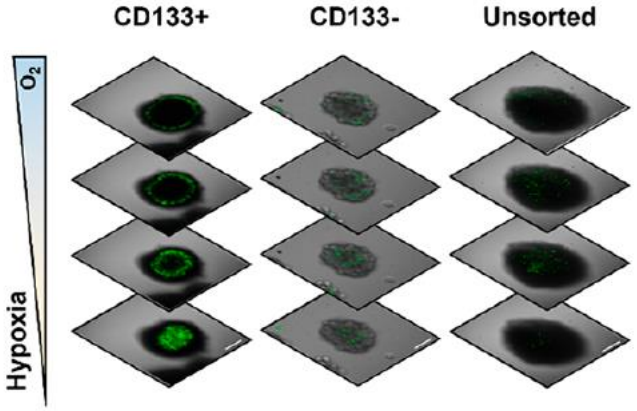


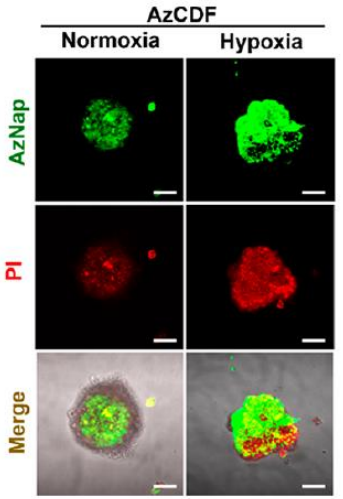
AzNap and AzCDF Activation in 3D Tumor Spheroids

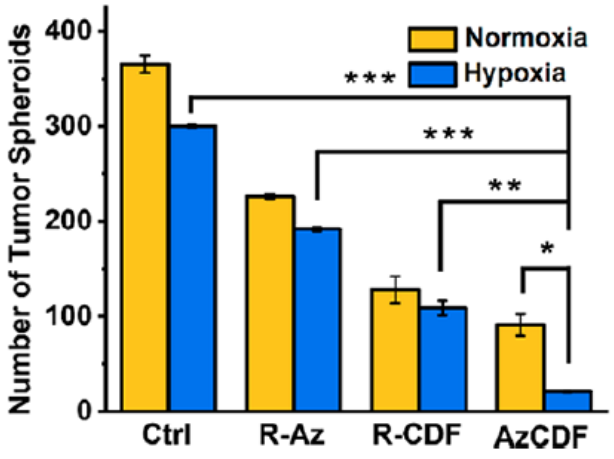
三维肿瘤球体：具有低氧内核，模拟肿瘤微环境

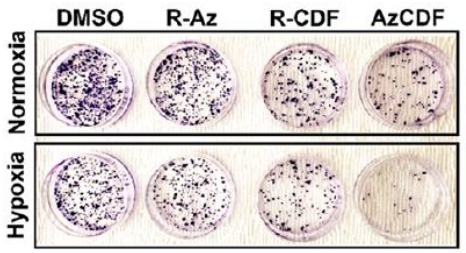


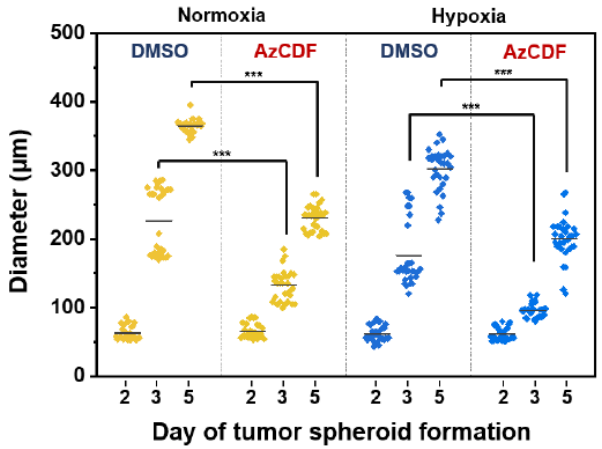


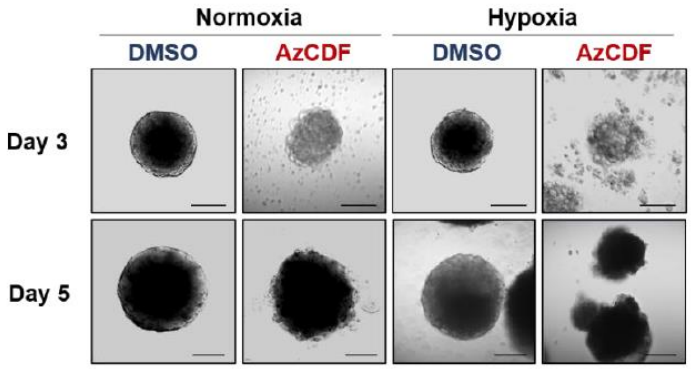






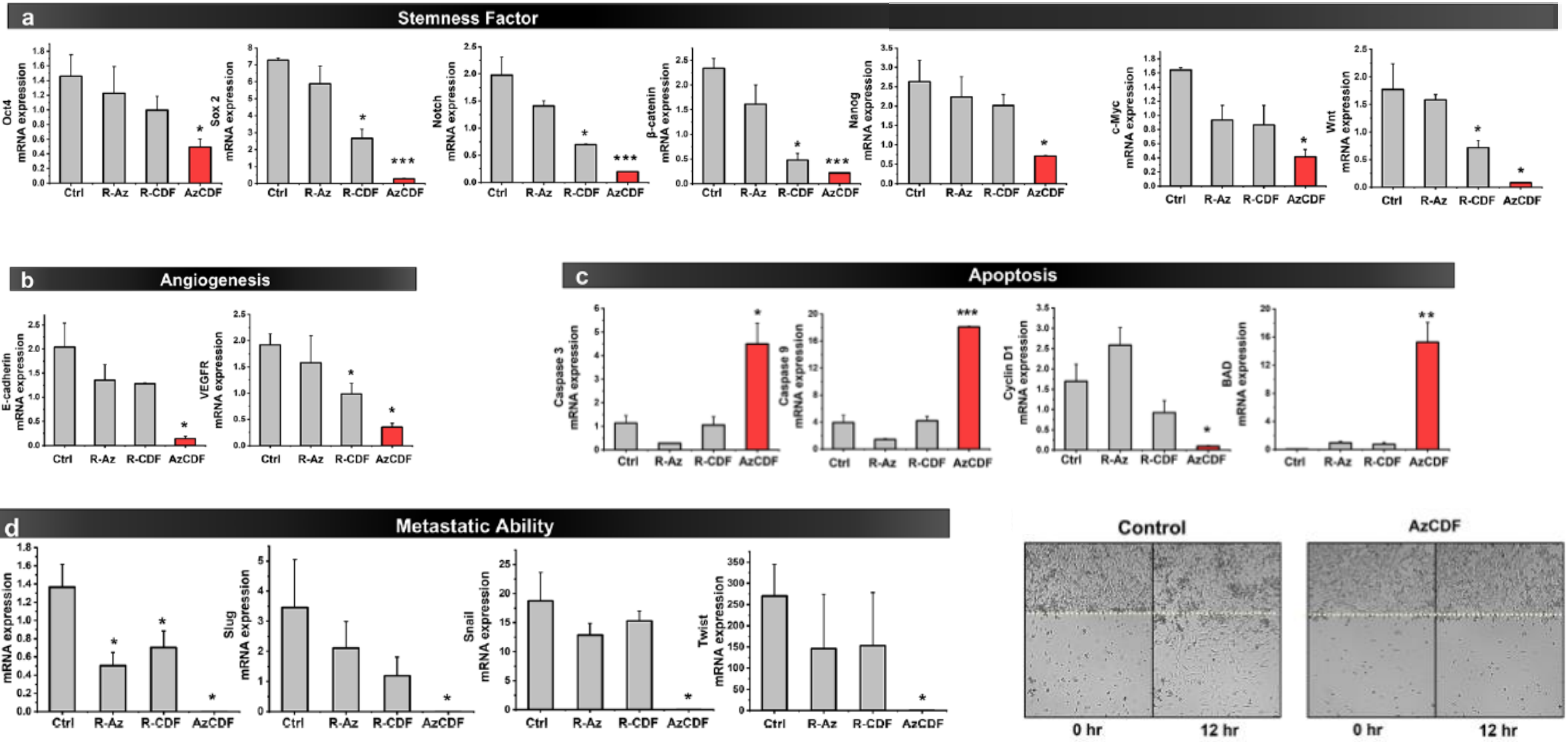






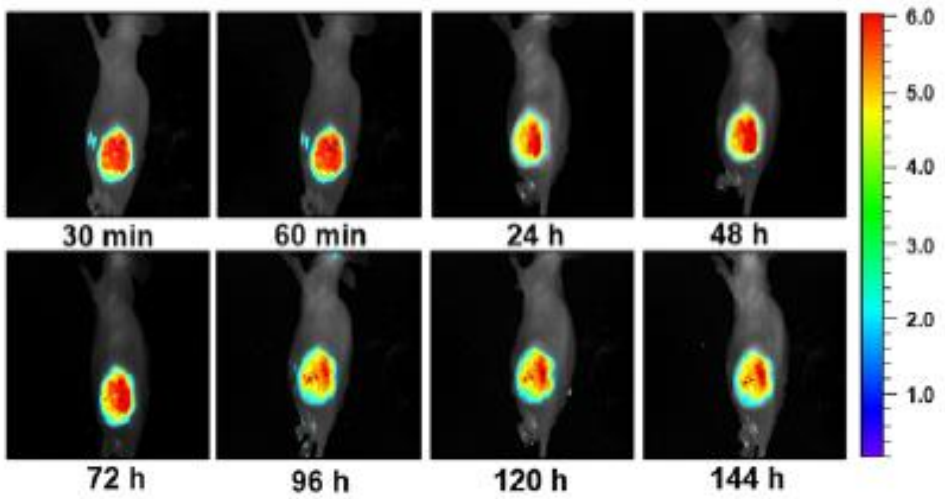
AzCDF抑制肿瘤生长，导致肿瘤干细胞起始特性下调

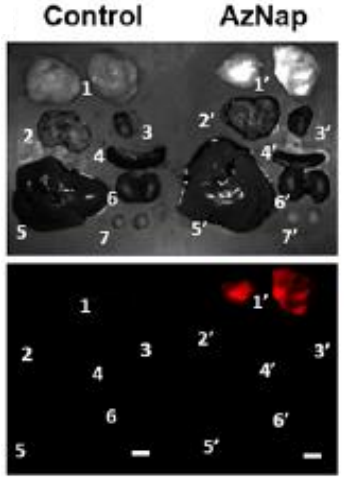
Mechanisms of AzCDF Suppresses Stemness in CD133+ CSCs



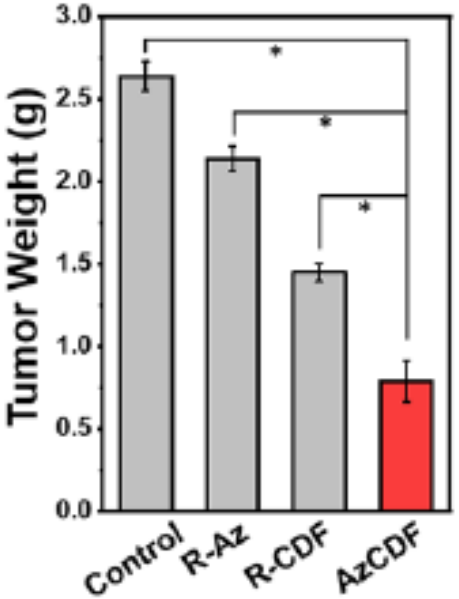
AzCDF导致CSCs生长抑制和凋亡，抑制血管生成，阻止肿瘤转移

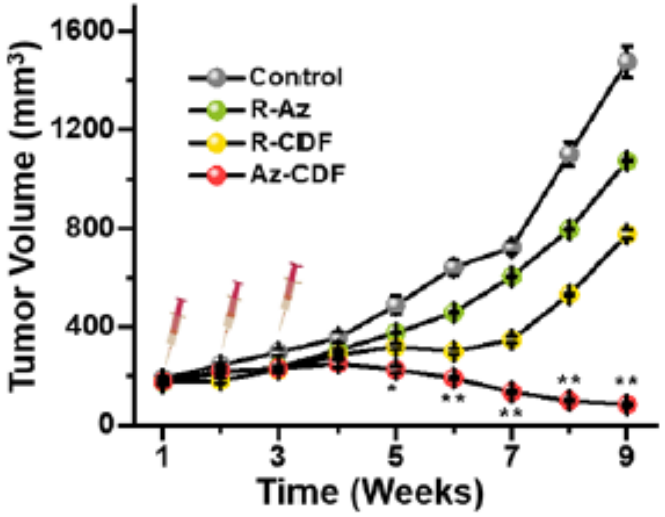
Selective Fluorescence Imaging of AzNap

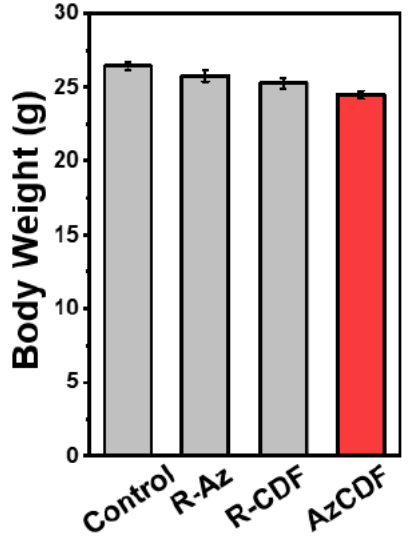




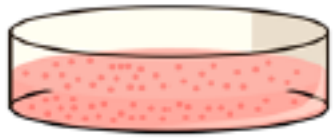
In Vivo Therapeutic Effect of AzCDF







Assessment of the ability of AzCDF to prevent tumorigenesis in vivo

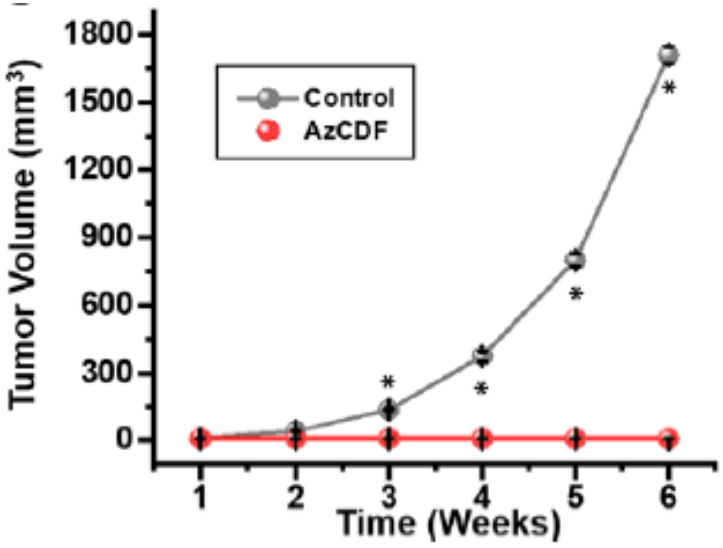


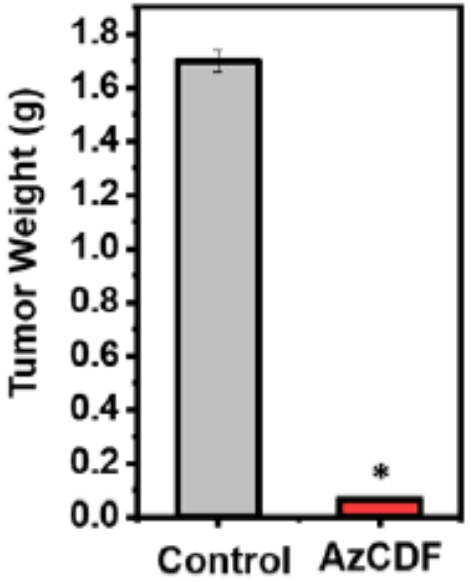
CD133⁺
MDA-MB-231

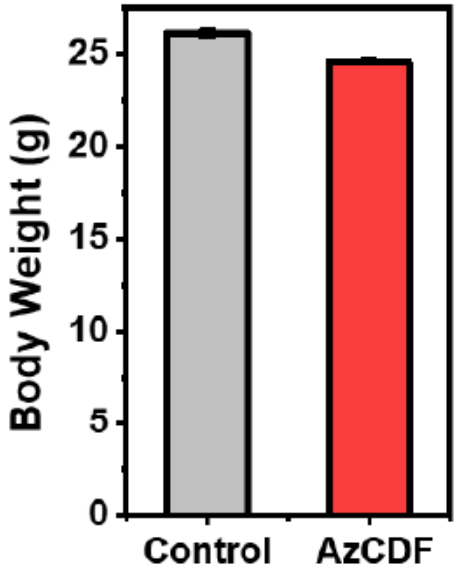
1. Treat with AzCDF or DMSO (control) under hypoxia

2. After 6 h, count the live cells and inject the same number of live cells each

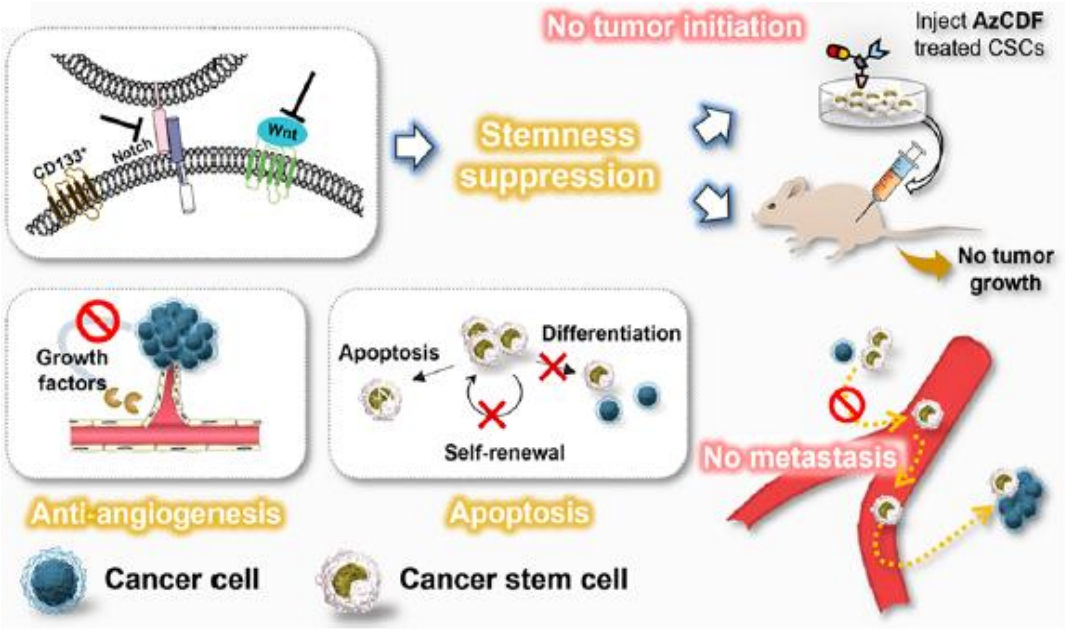
Inoculate with cells







Summary



- 针对癌症干细胞生物标志物CAIX、缺氧的特点设计了AzCDF（治疗）、AzNap（诊断）
- AzCDF仅在缺氧条件下存在肿瘤干细胞毒性，可有效抑制肿瘤生长、迁移
- AzNap可进行高度侵袭性癌症的早期诊断