

Bavachalcone targets transferrin receptor and sensitizes gemcitabine to affect bladder cancer progression

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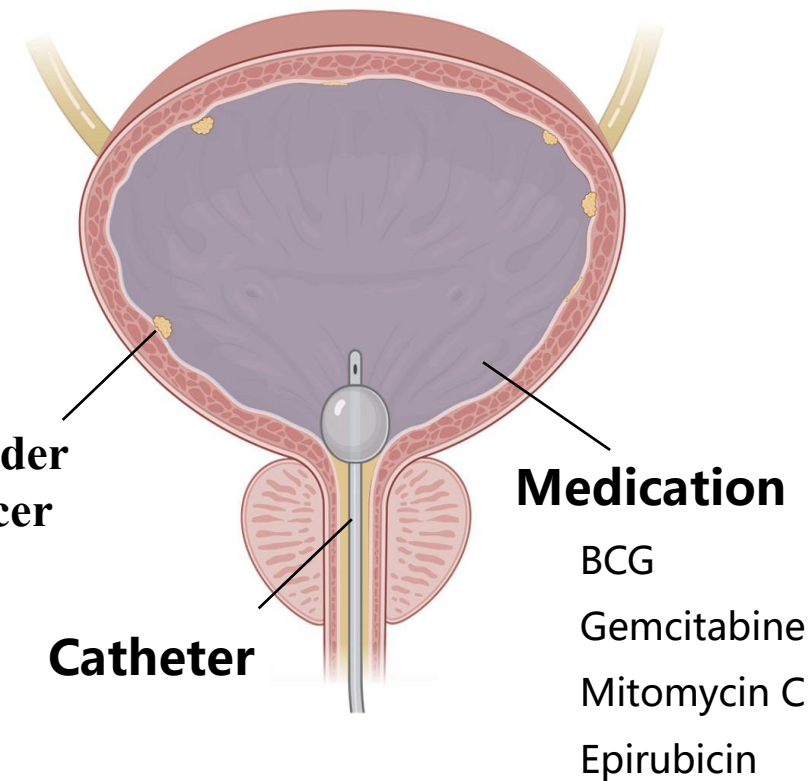


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Introduction

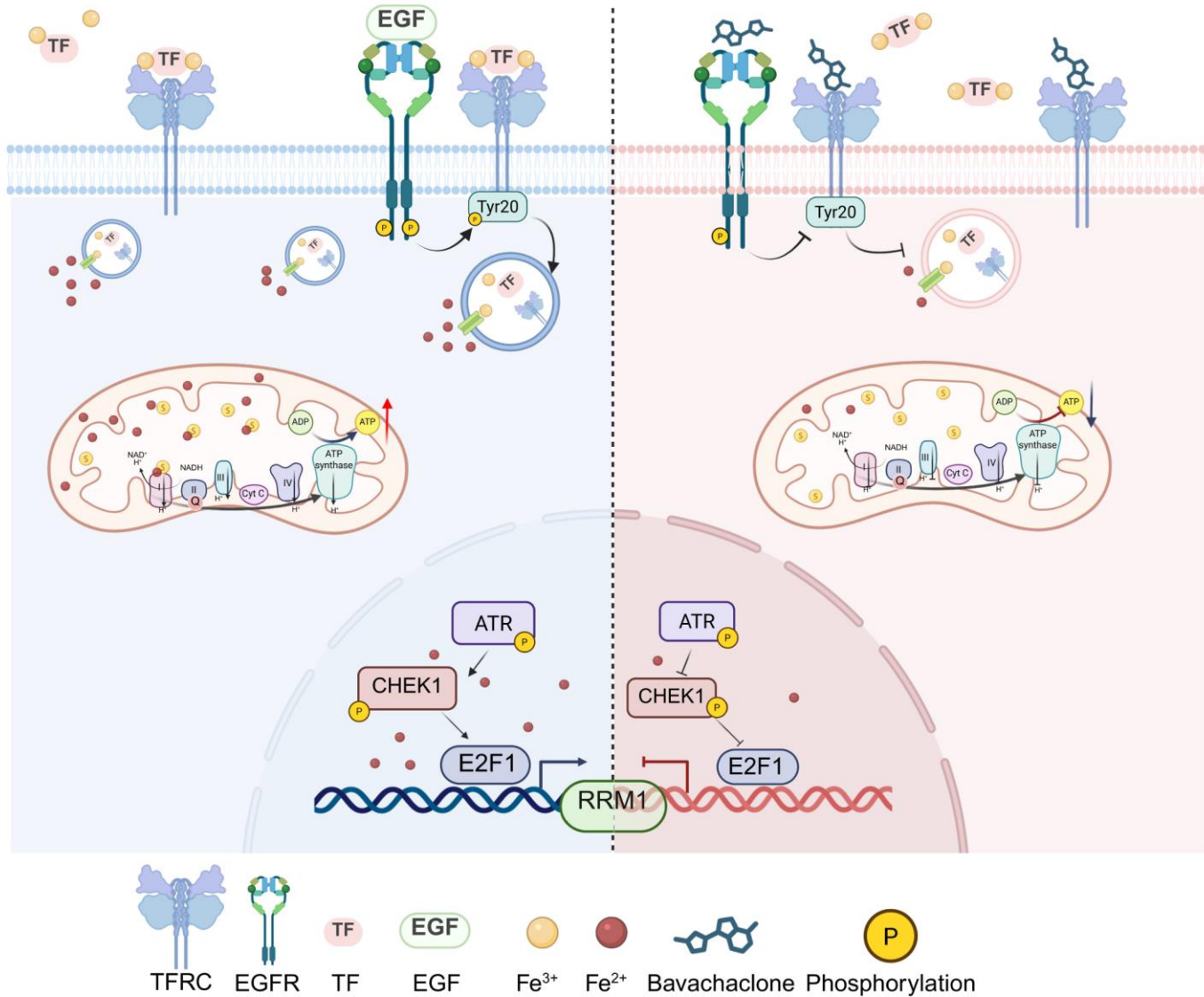
	Male			Female		
Estimated New Cases	Prostate	313,780	30%	Breast	316,950	32%
	Lung & bronchus	110,680	11%	Lung & bronchus	115,970	12%
	Colon & rectum	82,460	8%	Colon & rectum	71,810	7%
	Urinary bladder	65,080	6%	Uterine corpus	69,120	7%
	Melanoma of the skin	60,550	6%	Melanoma of the skin	44,410	4%
	Kidney & renal pelvis	52,410	5%	Non-Hodgkin lymphoma	35,210	4%
	Non-Hodgkin lymphoma	45,140	4%	Pancreas	32,490	3%
	Oral cavity & pharynx	42,500	4%	Thyroid	31,350	3%
	Leukemia	38,720	4%	Kidney & renal pelvis	28,570	3%
	Pancreas	34,950	3%	Leukemia	28,170	3%
All sites	1,053,250		All sites	988,660		
Estimated Deaths	Lung & bronchus	64,190	20%	Lung & bronchus	60,540	21%
	Prostate	35,770	11%	Breast	42,170	14%
	Colon & rectum	28,900	9%	Pancreas	24,930	8%
	Pancreas	27,050	8%	Colon & rectum	24,000	8%
	Liver & intrahepatic bile duct	19,250	6%	Uterine corpus	13,860	5%
	Leukemia	13,500	4%	Ovary	12,730	4%
	Esophagus	12,940	4%	Liver & intrahepatic bile duct	10,840	4%
	Urinary bladder	12,640	4%	Leukemia	10,040	3%
	Non-Hodgkin lymphoma	11,060	3%	Non-Hodgkin lymphoma	8,330	3%
	Brain & other nervous system	10,170	3%	Brain & other nervous system	8,160	3%
	All sites	323,900		All sites	294,220	



- ◆ Urothelial carcinoma is one of the common malignant tumors of the urinary system.
- ◆ Approximately 70%–75% of bladder cancer patients have non-muscle invasive bladder cancer.

- ◆ Postoperative intravesical instillation is an important intervention.

Highlights



- Using high-throughput drug screening and organoid models, we found that Bavachalcone can effectively increase the sensitivity of bladder cancer to gemcitabine.
- Bavachalcone can directly target TFRC and EGFR, inhibit iron influx and stabilize TFRC on the cell membrane.
- Bavachalcone inhibits the expression of RRM1, a key gemcitabine resistance protein, by suppressing the iron-dependent ATR-CHEK1-E2F1 signaling pathway.
- The PDX model and bladder cancer in situ model were used to verify that Bavachalcone combined with gemcitabine can effectively inhibit the malignant progression of bladder cancer.

Result

◆ Establishment of cell and PDO models for in vitro screening of Chinese medicine monomers

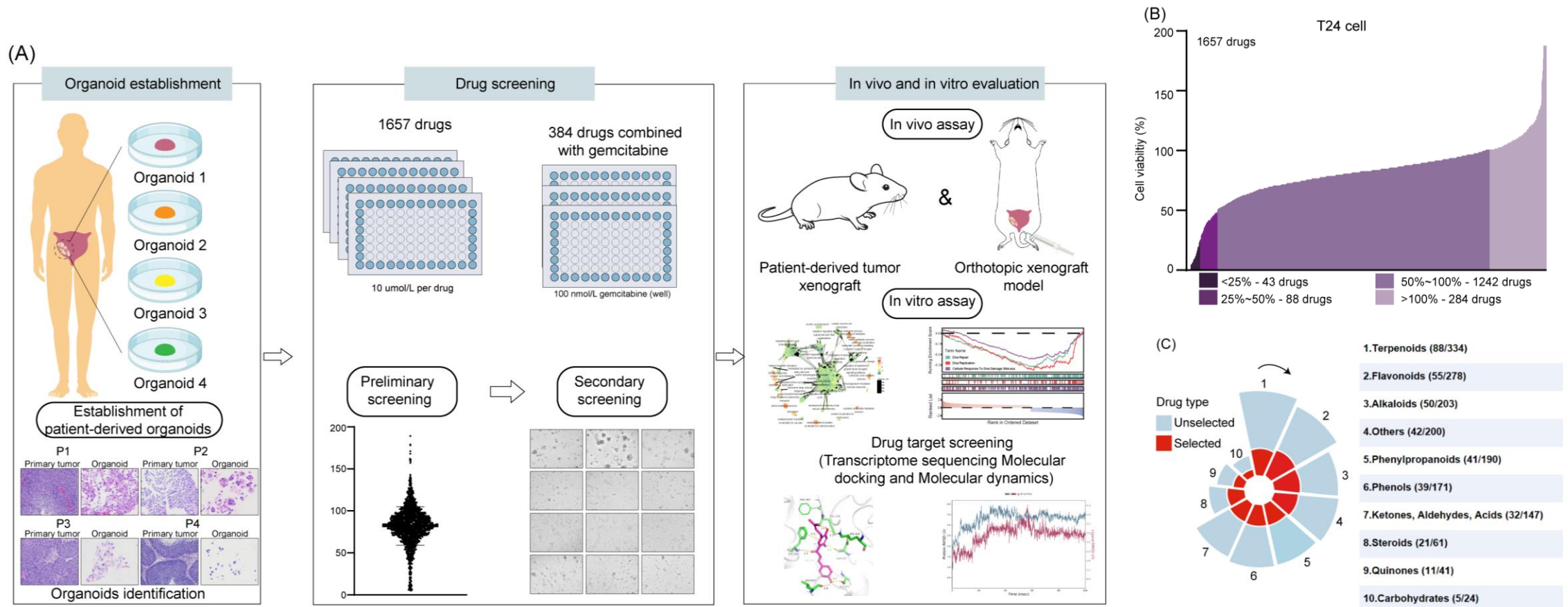
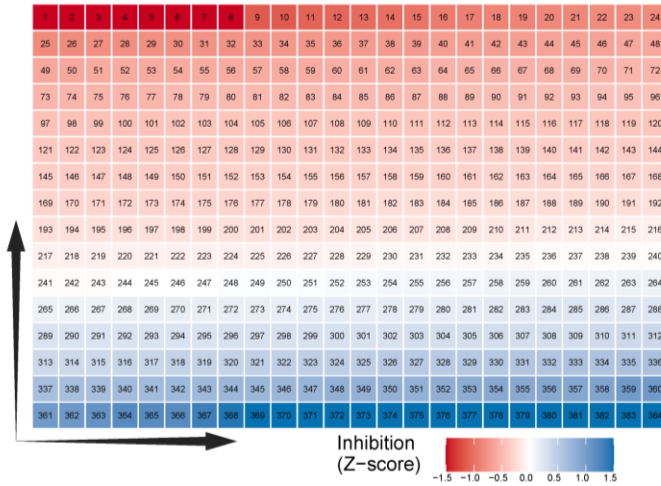


Figure 1 Drug screening based on bladder cancer cells and organoids.

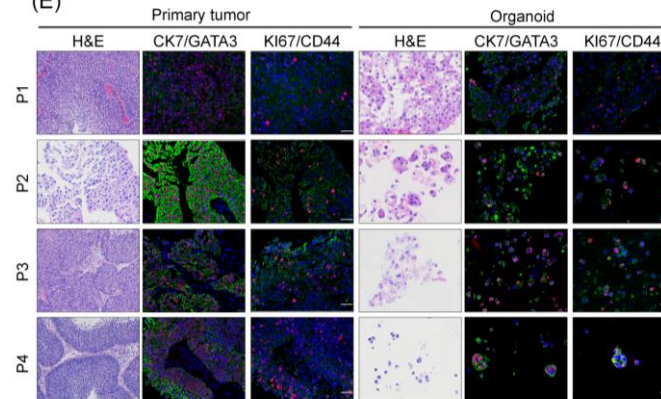
Result

◆ Establishment of cell and PDO models for in vitro screening of Chinese medicine monomers

(D)



(E)



(F)

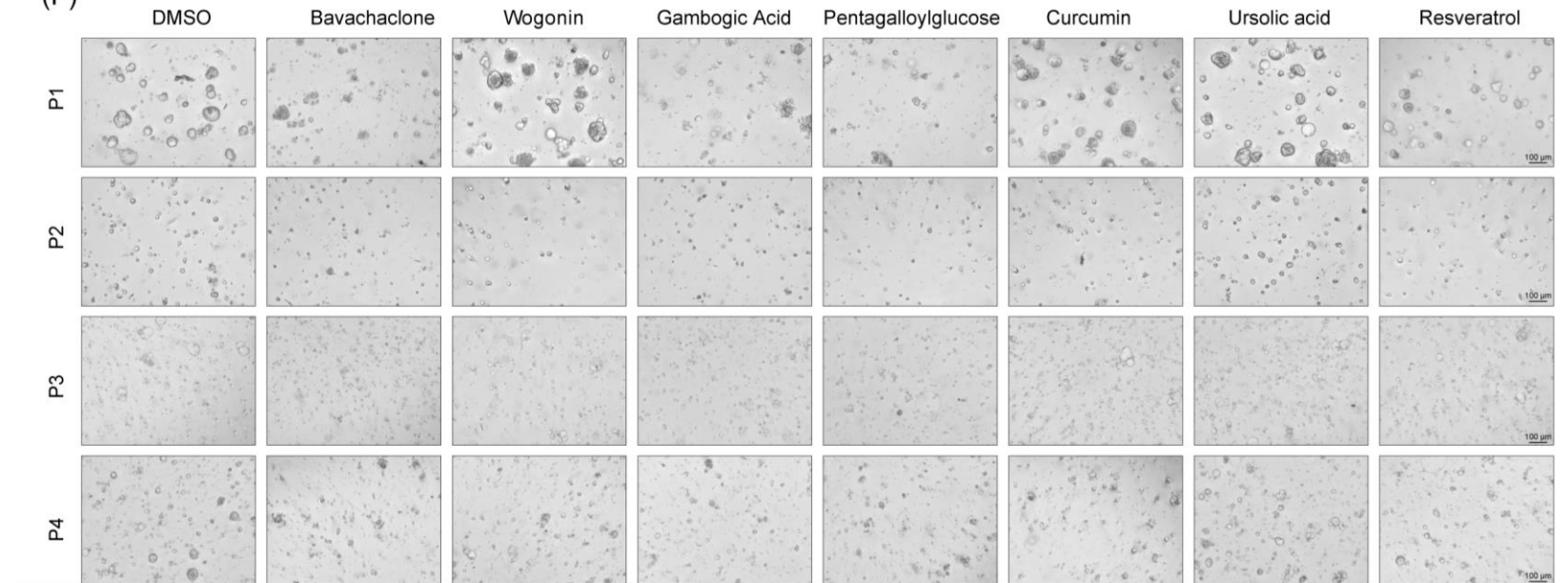


Figure 1 Drug screening based on bladder cancer cells and organoids.

Result

◆ Bavachalcone inhibits malignant progression of bladder cancer in vivo and in vitro

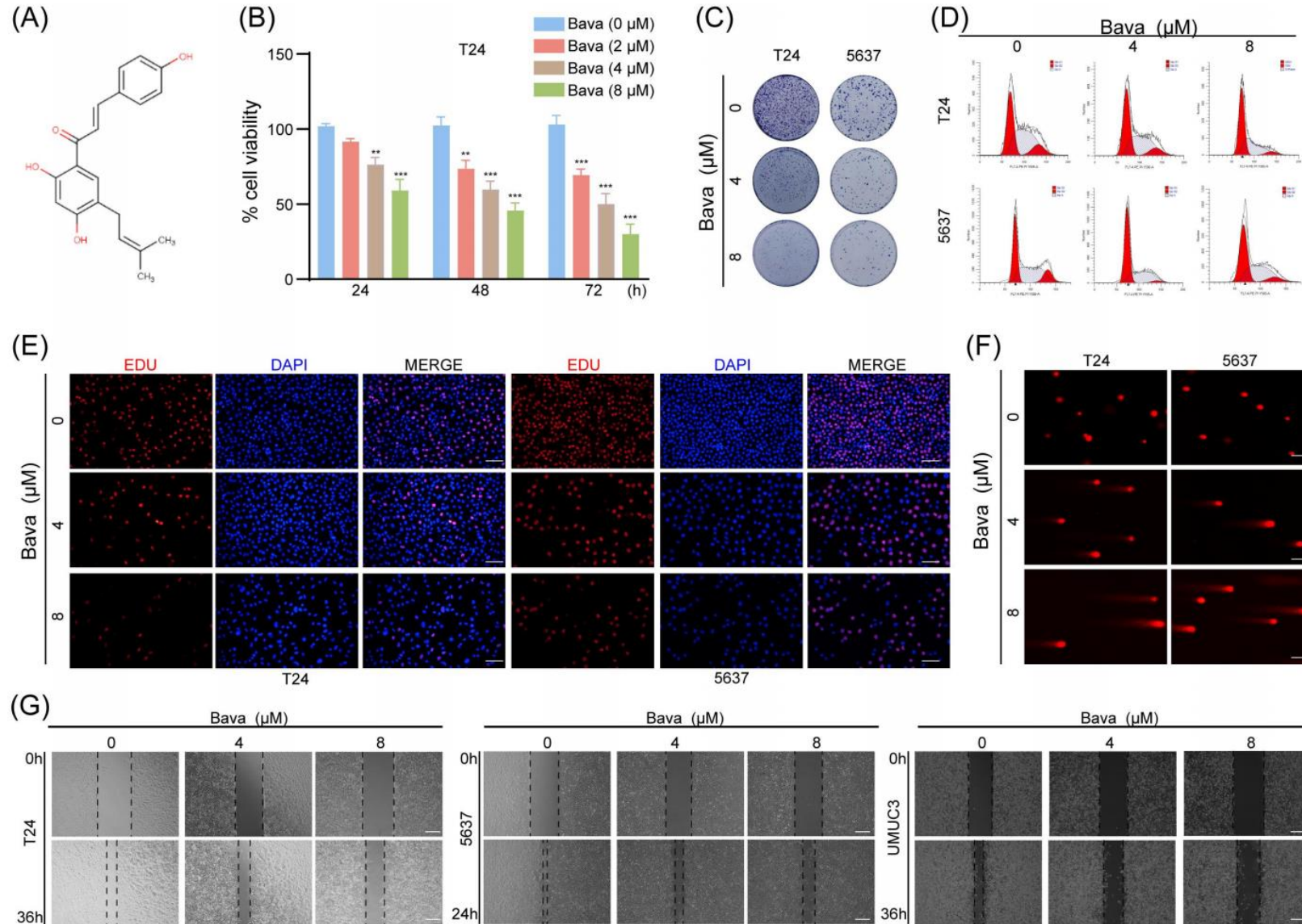


Figure 2 In vitro and vivo studies on the inhibition of bladder cancer by Bavachalcone.

Result

◆ Bavachalcone inhibits malignant progression of bladder cancer in vivo and in vitro

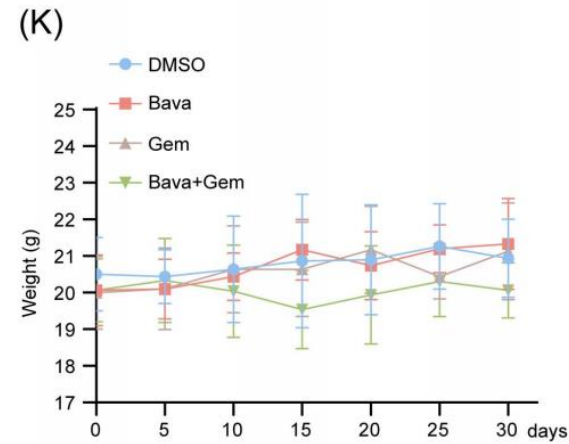
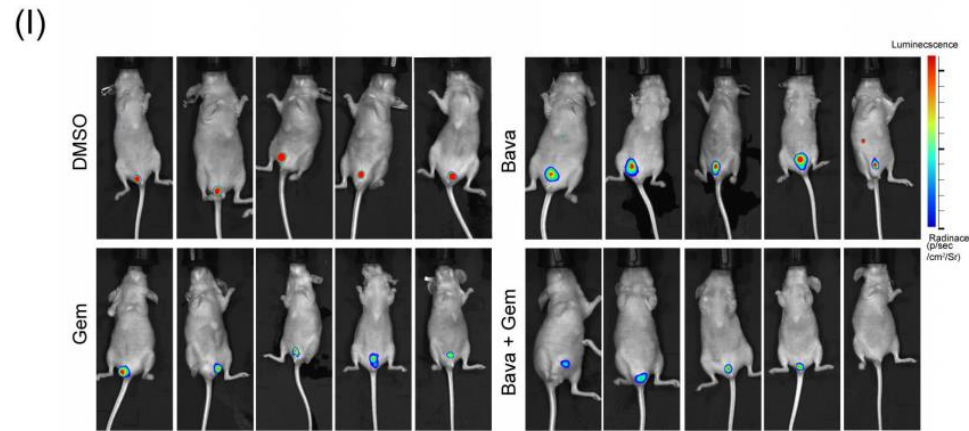
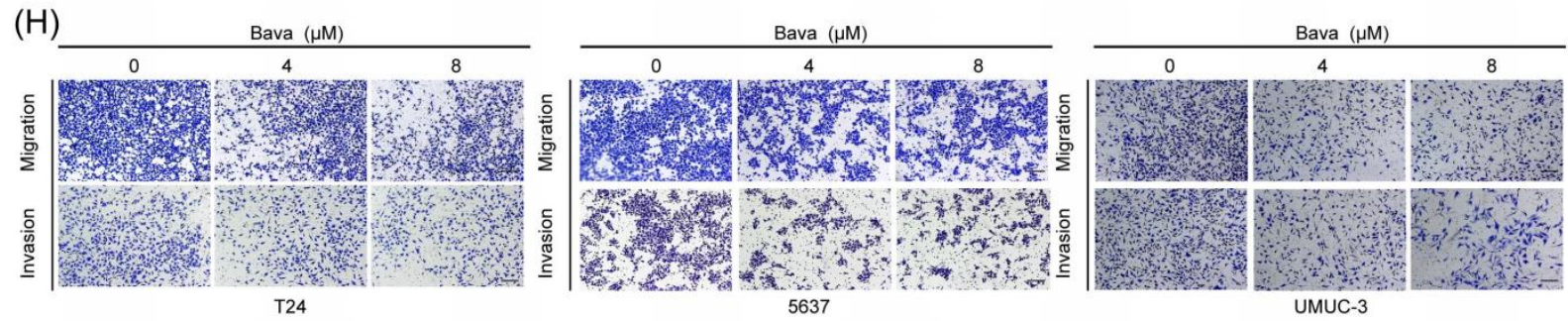
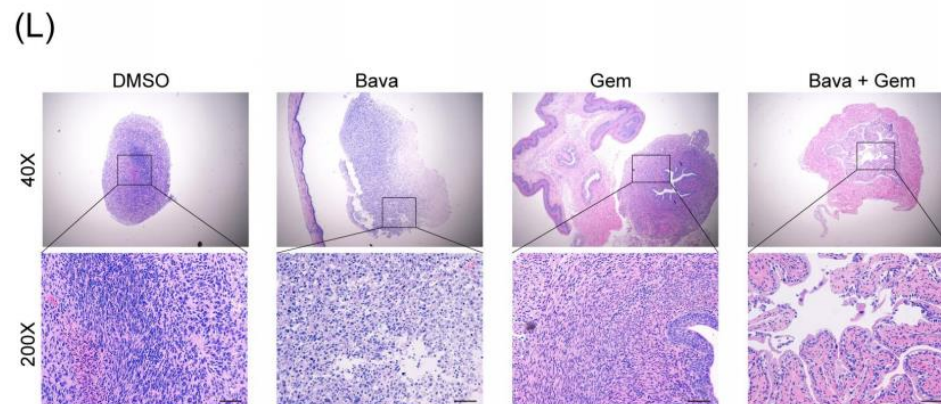
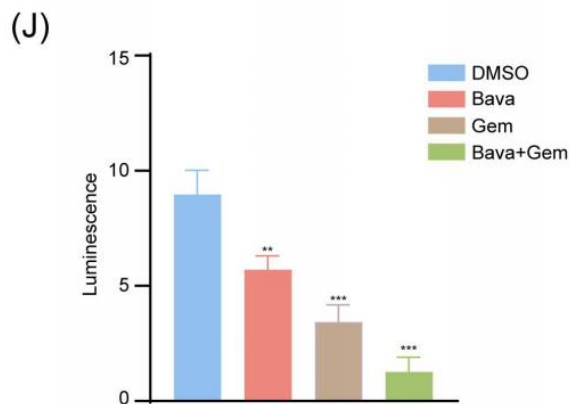


Figure 2 In vitro and vivo studies on the inhibition of bladder cancer by Bavachalcone.



Result

◆ Bavachalcone targets TFRC and EGFR

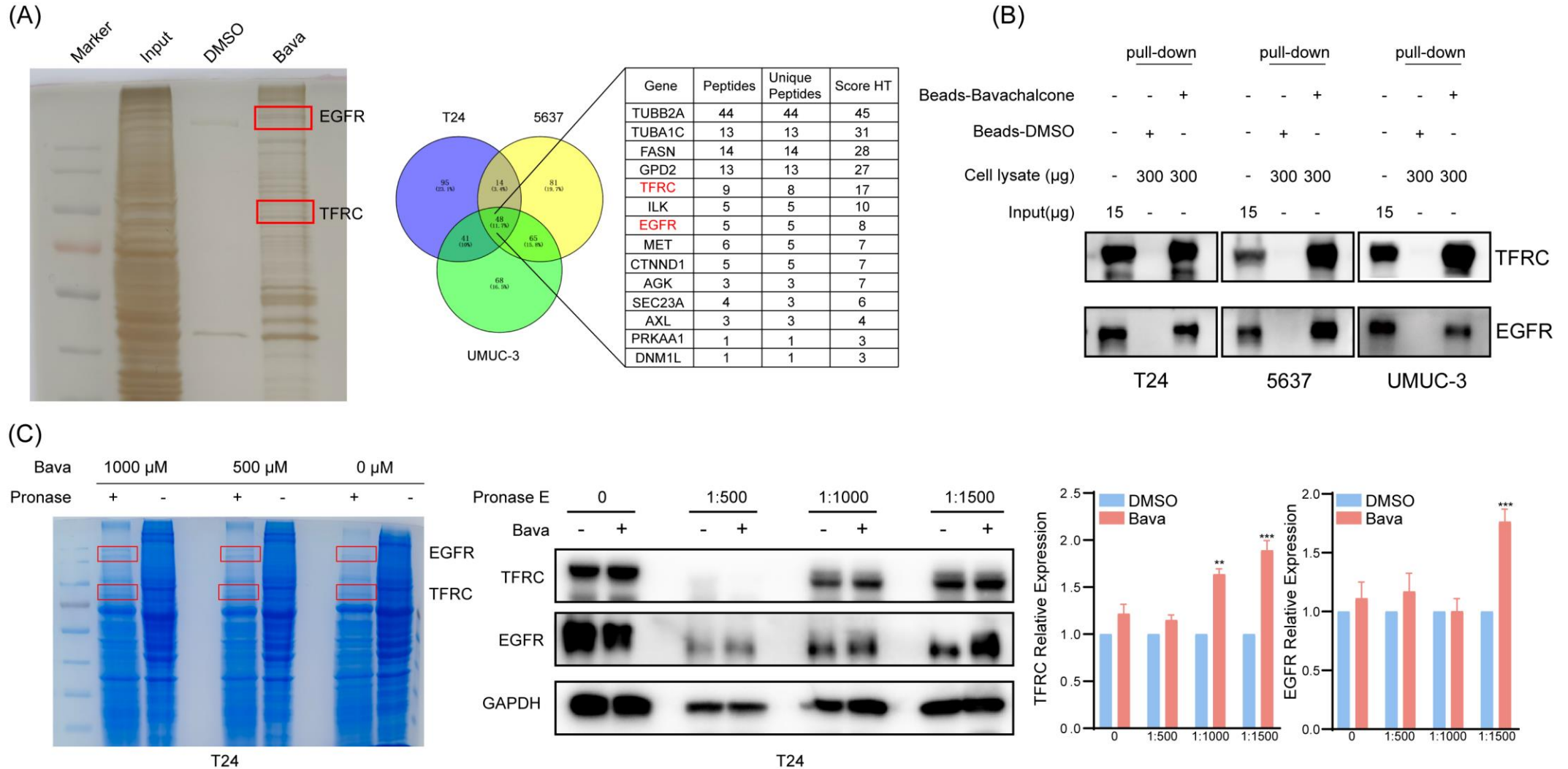
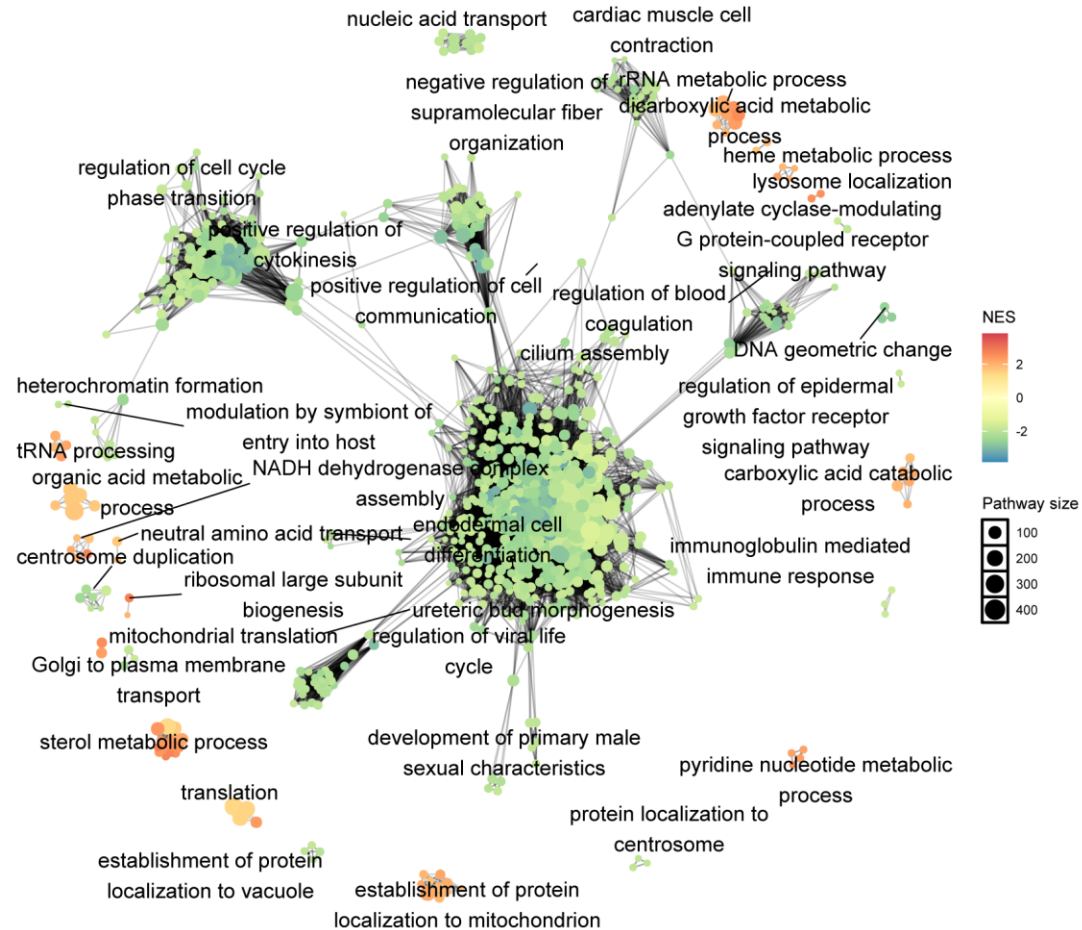


Figure 3. Bavachalcone directly targets TFRC and EGFR and competes with TF for TFRC binding.

Result

◆ Bavachalcone regulates intracellular iron homeostasis and mitochondrial metabolism and inhibits DNA damage repair

(A)



(B)

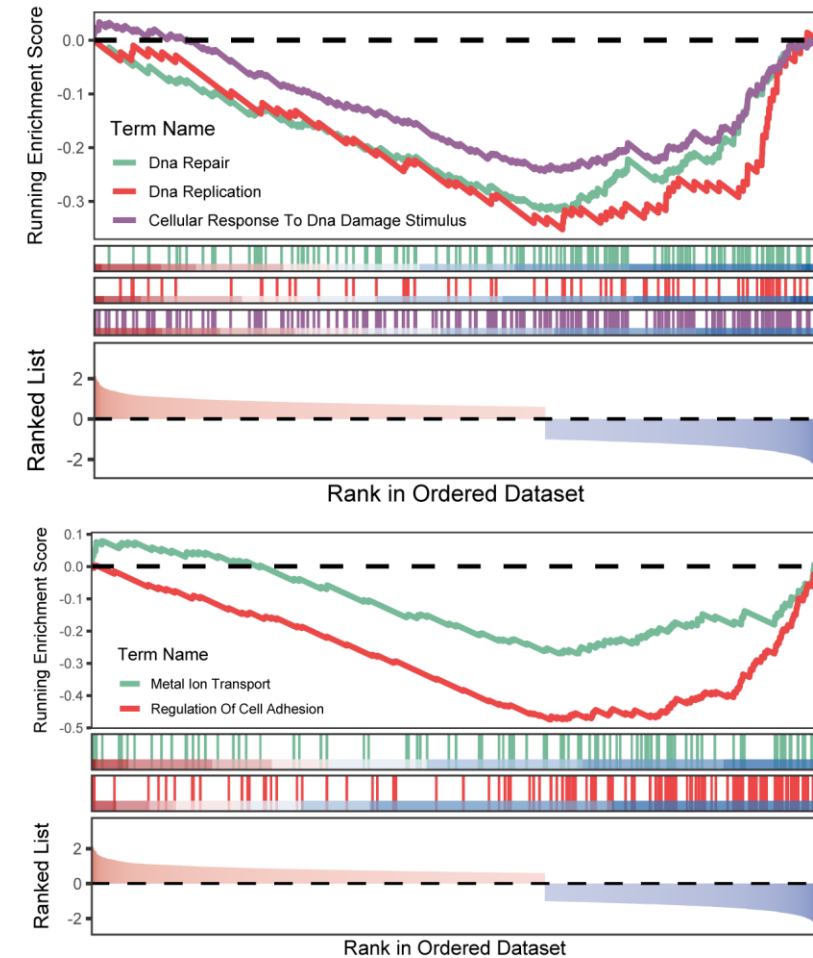


Figure 4 Bavachalcone inhibits DNA damage repair in bladder cancer by suppressing the iron-dependent ATR-CHEK1-E2F1 signaling pathway.

Result

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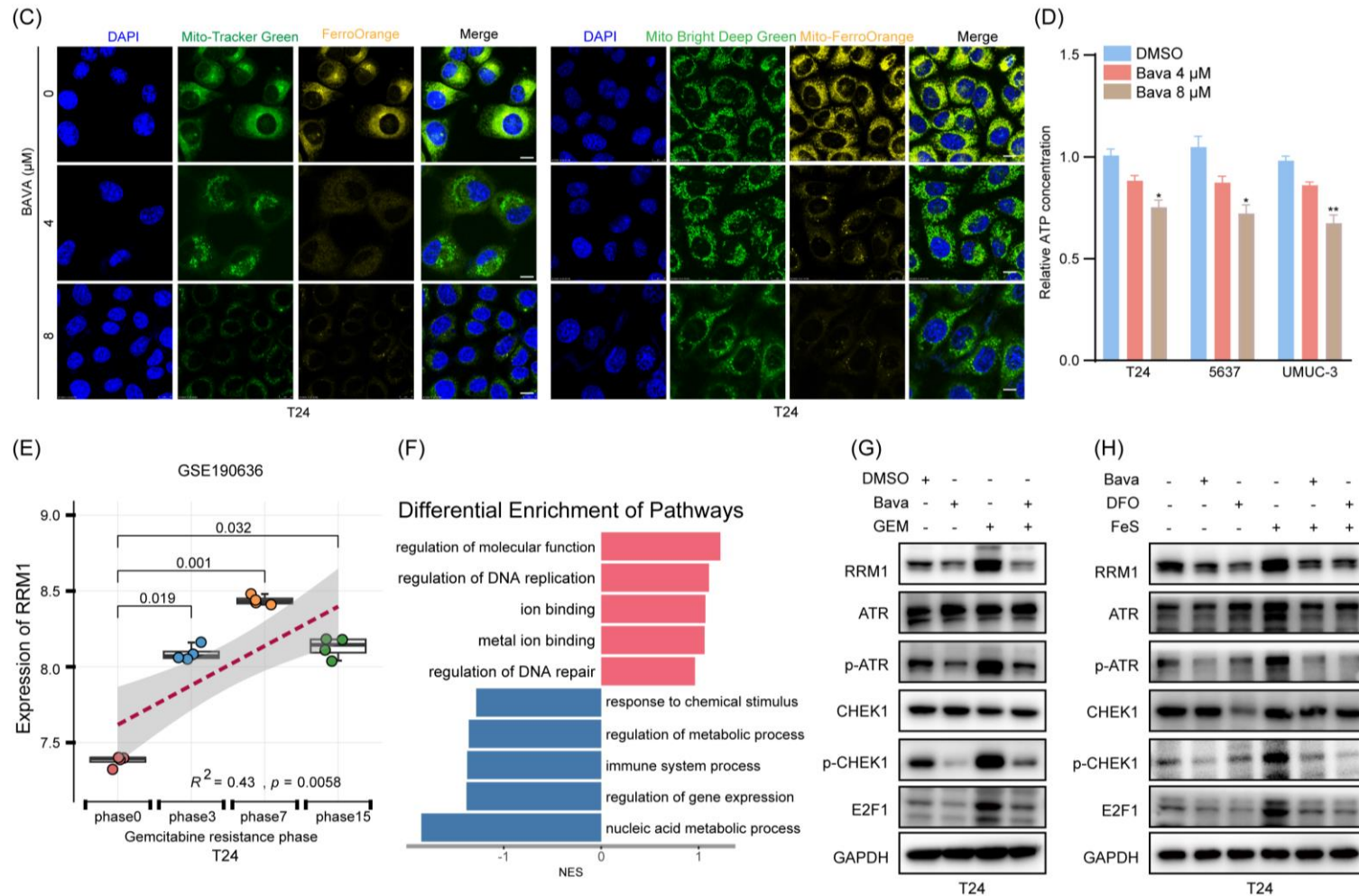


Figure 4 Bavachalcone inhibits DNA damage repair in bladder cancer by suppressing the iron-dependent ATR-CHEK1-E2F1 signaling pathway.

Result

◆ Bavachalcone inhibits the growth of bladder cancer PDX and enhances the sensitivity of tumors to gemcitabine

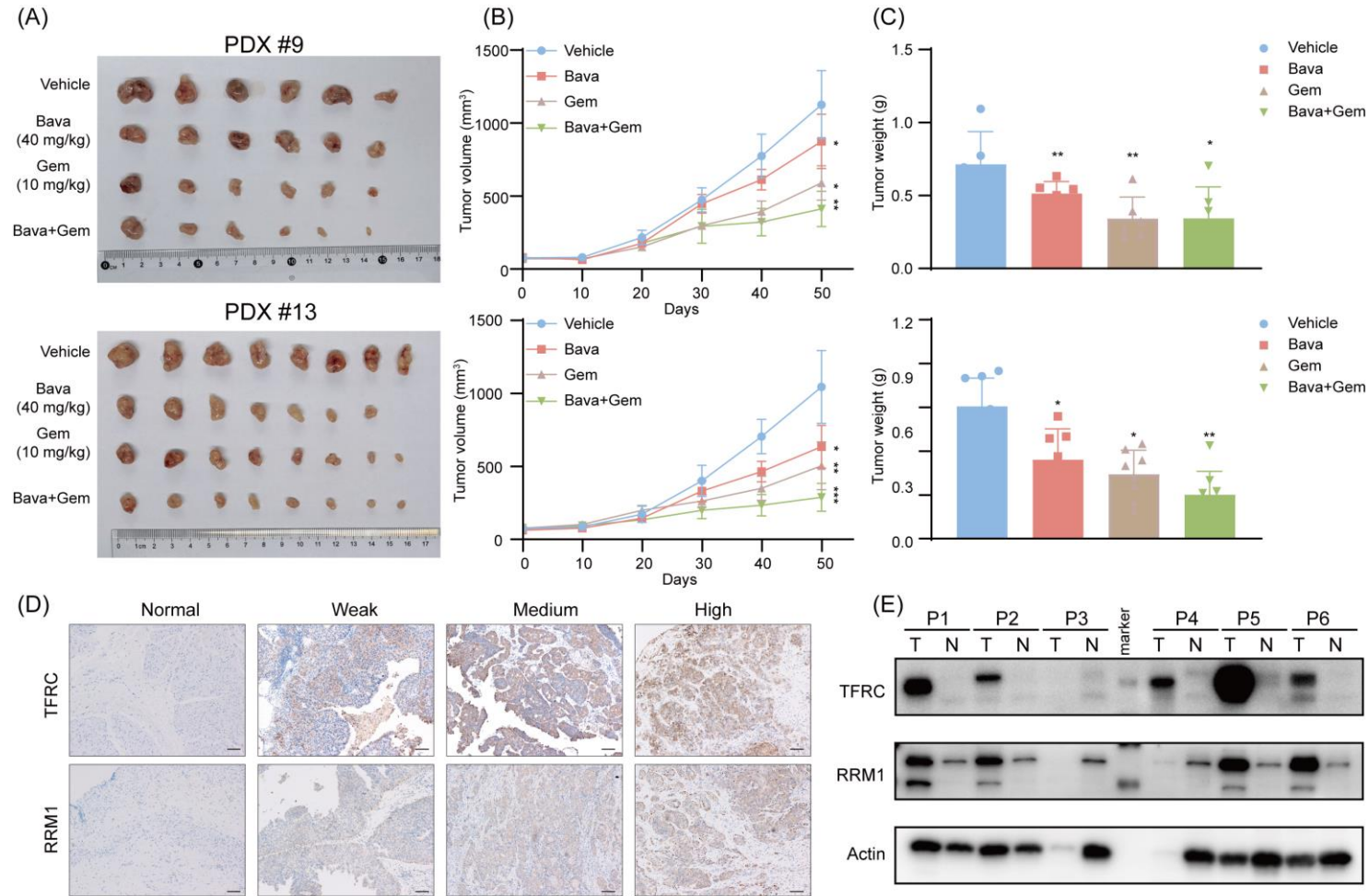


Figure 5 Bavachalcone treatment suppresses bladder tumor growth in PDX models and links TFRC/RRM1 expression to disease progression and patient prognosis.

Result

◆ Bavachalcone inhibits the growth of bladder cancer PDX and enhances the sensitivity of tumors to gemcitabine

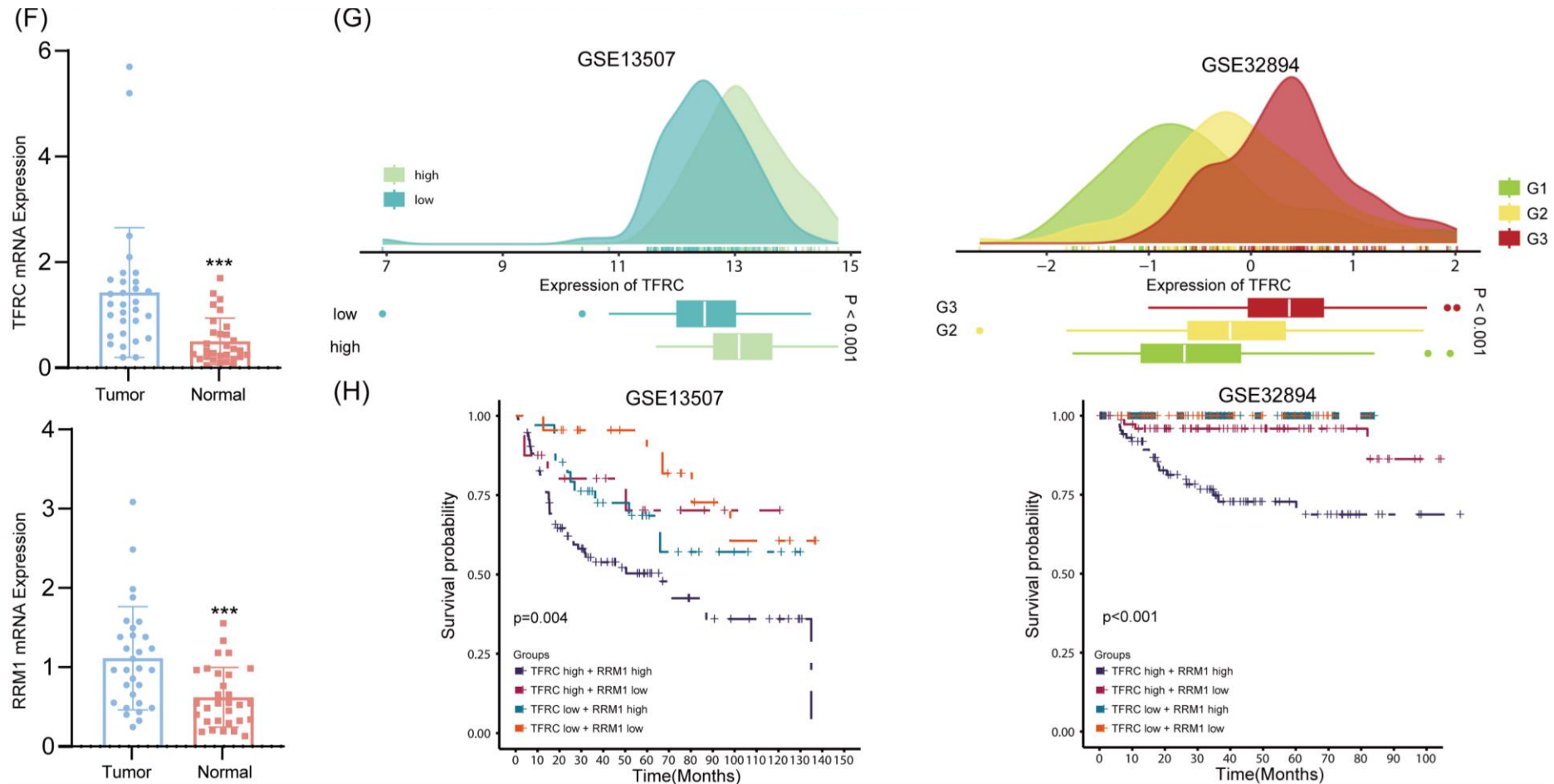
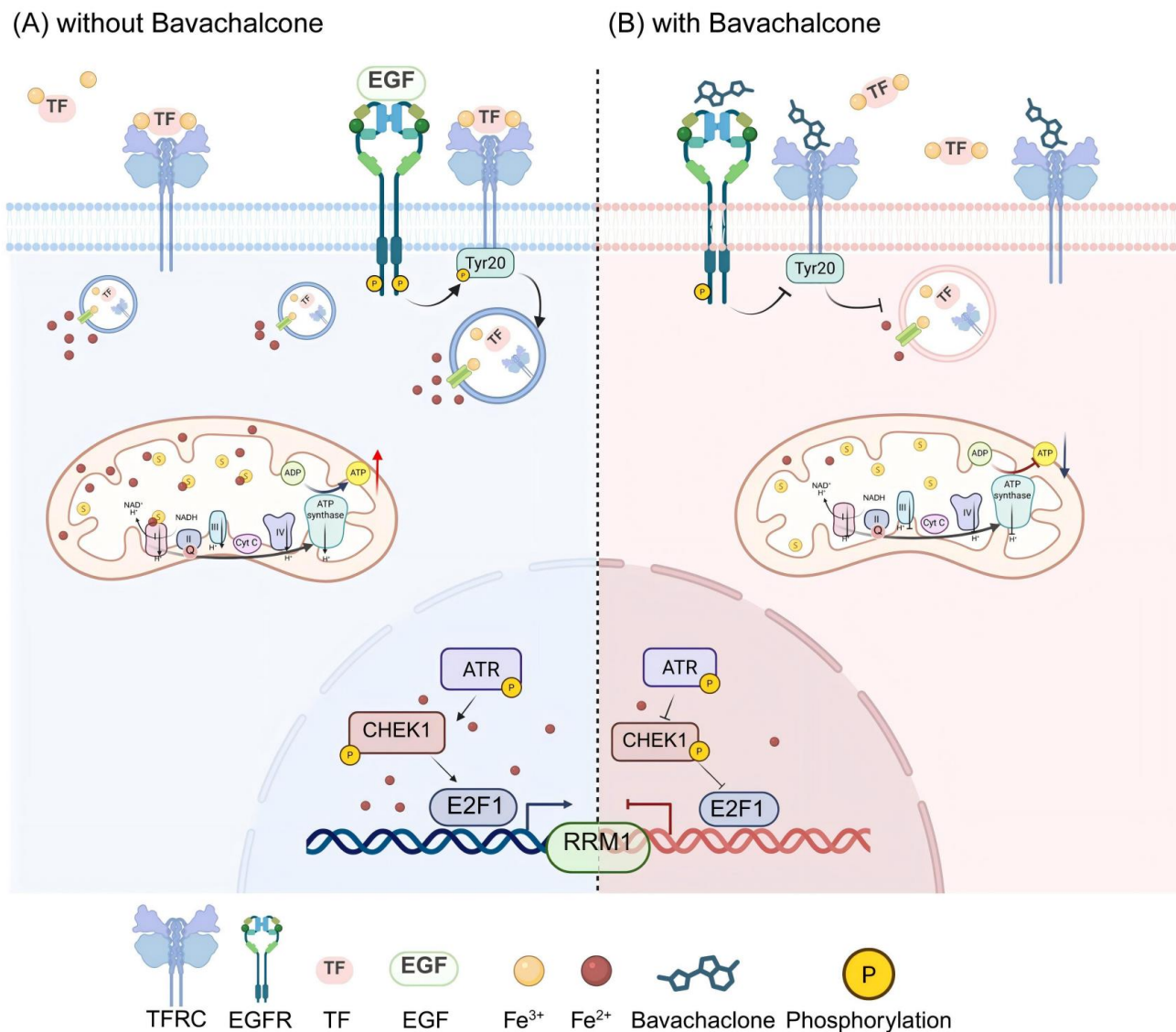


Figure 5 Bavachalcone treatment suppresses bladder tumor growth in PDX models and links TFRC/RRM1 expression to disease progression and patient prognosis.



Result

Working model



(A) Transferrin (Tf) binds extracellular Fe³⁺ to form a Tf-Fe³⁺ complex, which then engages the transferrin receptor (TFRC) on the cell surface and is internalized via endocytosis. The released Fe²⁺ enters mitochondria, where it combines with sulfur to assemble iron-sulfur clusters that support electron transport chain activity and ATP production. A portion of Fe²⁺ also translocates to the nucleus, participating in DNA replication and repair, thereby activating the ATR-CHEK1 signaling pathway and promoting RRM1 transcription.

(B) Bavachalcone blocks Tf-TFRC binding, preventing TFRC endocytosis and causing its retention on the plasma membrane, which inhibits iron influx. This reduction in intracellular iron impairs mitochondrial respiratory chain function and ATP synthesis, leading to attenuation of ATR-CHEK1 signaling and suppression of RRM1 transcription.



Summary

- ❑ Bavachalcone sensitizes bladder cancer cells to gemcitabine.
- ❑ The combination of bavachalcone and gemcitabine effectively inhibits malignant progression.
- ❑ Bavachalcone targets TFRC and EGFR, thereby blocking iron influx.
- ❑ Bavachalcone suppresses RRM1 transcription by inhibiting the iron-dependent ATR–CHEK1 signaling pathway.

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