INSTITUTE OF BIOPHYSICS
HEBEI UNIVERSITY OF TECHNOLOGY
IBP.HUT

Natural compounds targeting at ion channels are potential antitumor drugs

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CONTENTS

河北工業大学
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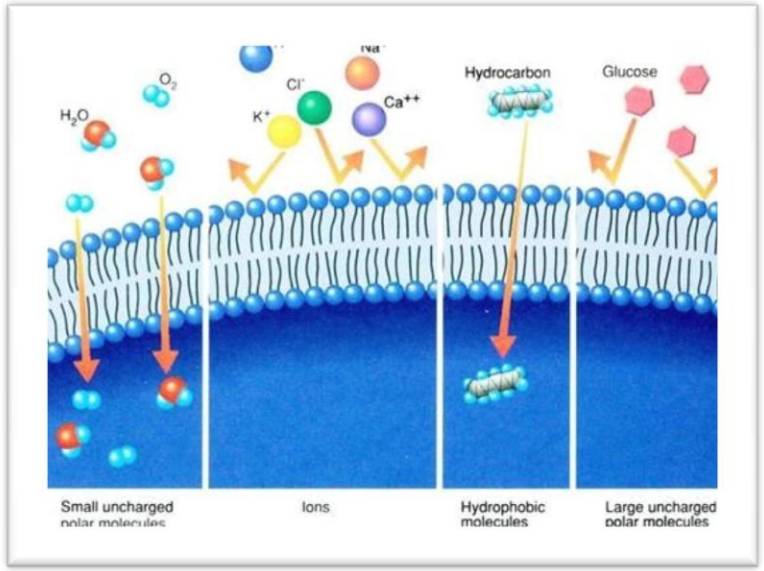
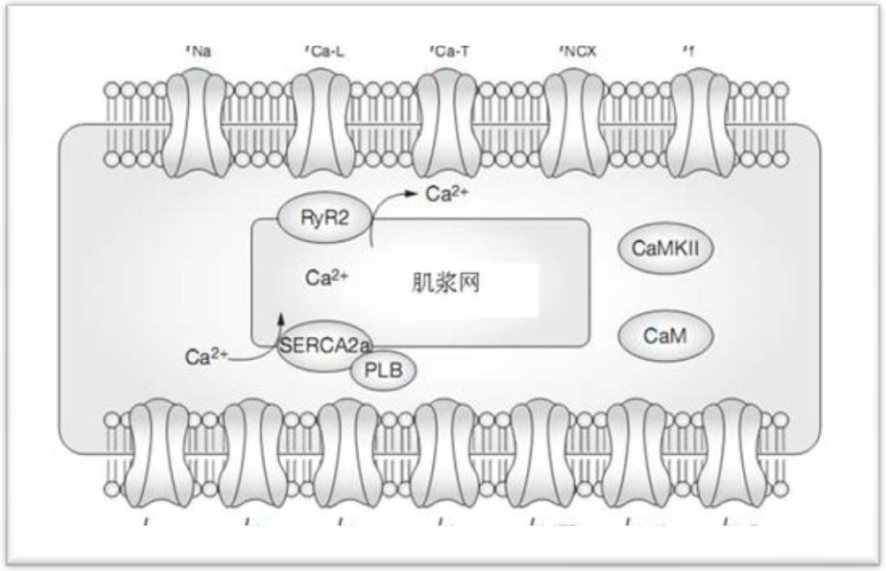
Ion channels and Membrane.



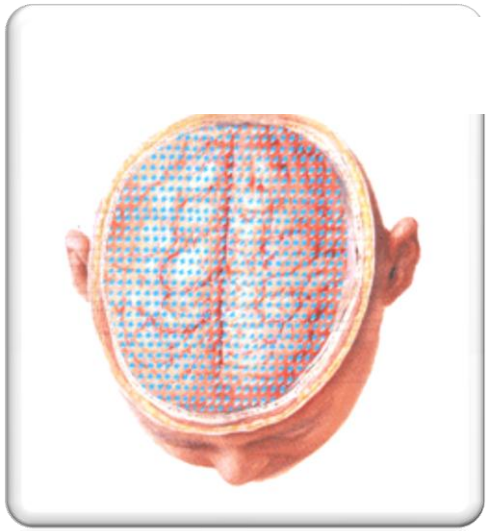
No ions can permeate membrane directly.



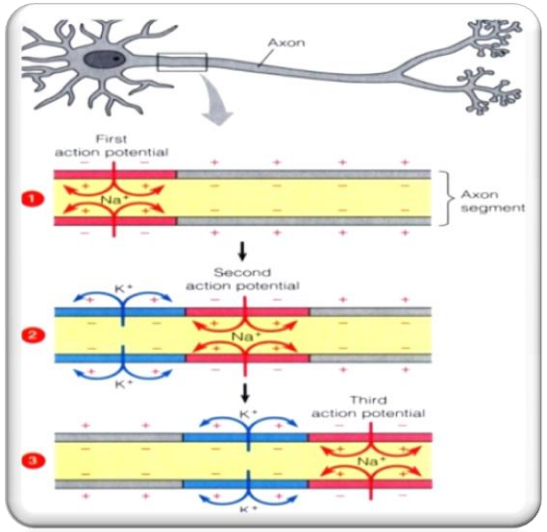
There are numerous ion channels implanting in the membrane.

Ion channel: the basis of electro-activities.

Heart rates



Brain signals

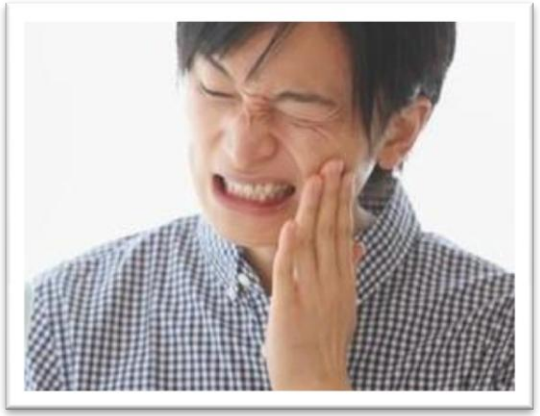


Neuro-signals

Ion channel: the basis of feelings.

sour

bitter

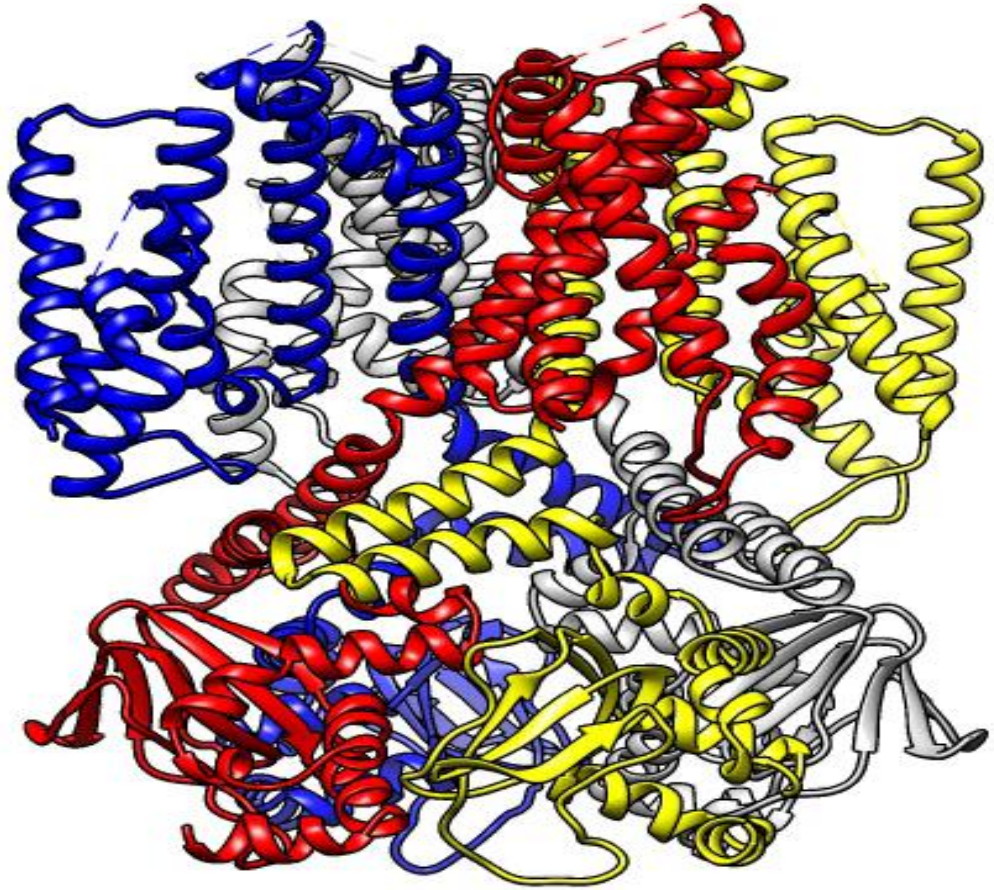


pain

hot

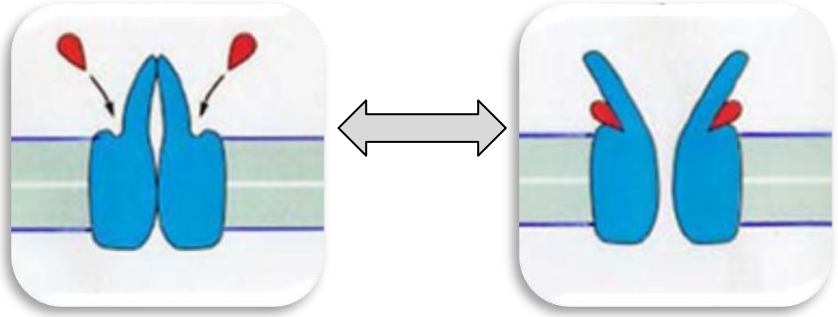
cold

Ion channels transit its conformation response to diverse stimuli.



Science, (2016), **353** 664-669.

Ion channel related diseases and targeted drugs design.



Binding with the ligands regulates the function of ion channels.

Ion channels represent the second largest target for existing drugs after G protein-coupled receptors.

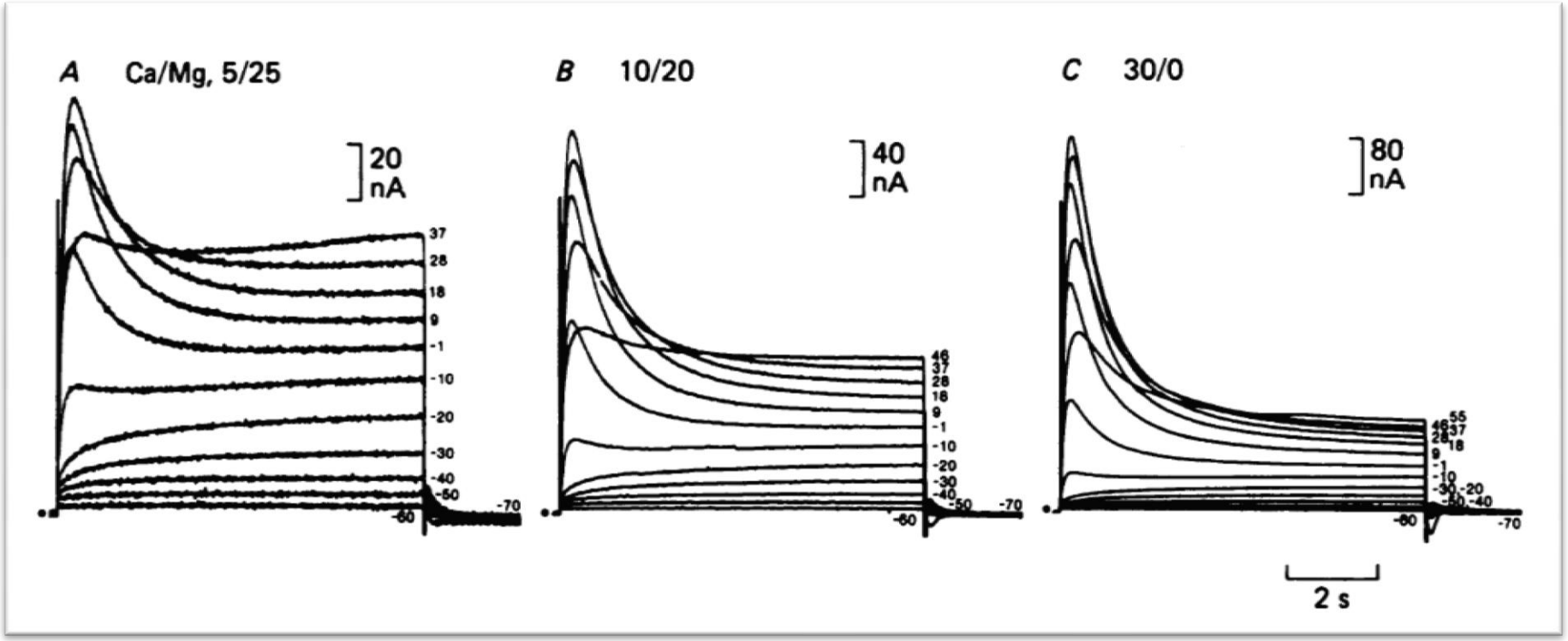
NO.	Ion channel	Cancer
1	Kv1.1	Macrophages[1]
2	Kv1.3	Blood cells[2] , Melanoma[3]
3	Kv1.5	Macrophages[1]
4	**Kv10.1**	**Breast[4-6],cervix[7],neuroblastoma[8],colon[9], ovary[10], head and neck, Sarcoma[11], AML[12]**
5	Kv10.2	Medulloblastoma[13]
6	Kv11.1	Thyroid[14], breast[15], Glioblastoma[16], gastric[17], colon[18], ovary[19], head and neck[20]
7	Kir1.1	Blood cells[21,22]
8	Kir3.4	Adrenal[23]
9	K2p5.1	Breast[24]
10	K2p9.1	Breast[25,26], neurons[27], lung[27], glioma[28], Ovary[29]
11	KCa1.1	Neurons[30], glioma[31-33],
12	KCa2.3	Breast[34]
13	KCa3.1	Glioma[33,35,36], Vascular smooth muscle[37], colon[38], breast[34]
14	Nav1.2	Mesothelioma[39], Cervix[40]
15	Nav1.5	Breast[41], non-small cell lung cancer[42], Lymphoma[43]
16	Nav1.6	Cervix[40]
17	Nav1.7	Prostate[44], Cervix[40]
18	Hv1	Colon[45], glioma[46]
19	Cav3.1	Glioma [47-49], Neuroblastoma[50], Breast[51], Retinoblastoma[52], Fibrosarcoma[53]
20	Cav3.2	Glioma[47-49], Breast[51], Prostate[54], Pheochromocytoma[55], Leukemogenesis[56,57]
21	TRPM1	Melanoma[58-60]
22	TRPM5	Melanoma[58]
23	TRPM7	Breast[61]
24	TRPM8	Prostate[62-64]
25	TRPV1	Prostate[65], bladder[66], colon[67], pancreas[68]
26	TRPV6	Prostate[69,70], breast[71], Colon[72]
27	CLC3	Glioma[73]
28	**Ano1**	**Breast[74], head and neck[75],lung[76], gastric cancer[77]**
29	Ano6	Breast[78]
30	Ano7	Prostate[79,80]

Focused issues by our lab.

- **Function and structure relations : Kir channels、CaCCs、Kv channels.**
- **Ion channel and disease : CaCCs and Kv channels with evolution of cancer.**
- **Drug screening and optimization targeting at ion channels.**

JBC (2012), JMB(2011, 2013, 2015, 2017×2 , 2018), JCAMD (2013, 2015), PLoS ONE (2014, 2017), Scientific Reports (2015), MNB(2016), EJP(2017), IJBM(2017), CPL(2015, 2016, 2017), Channels (2016), Proteins (2016), BJP(2011, 2014, 2015), JCP(2018×2).

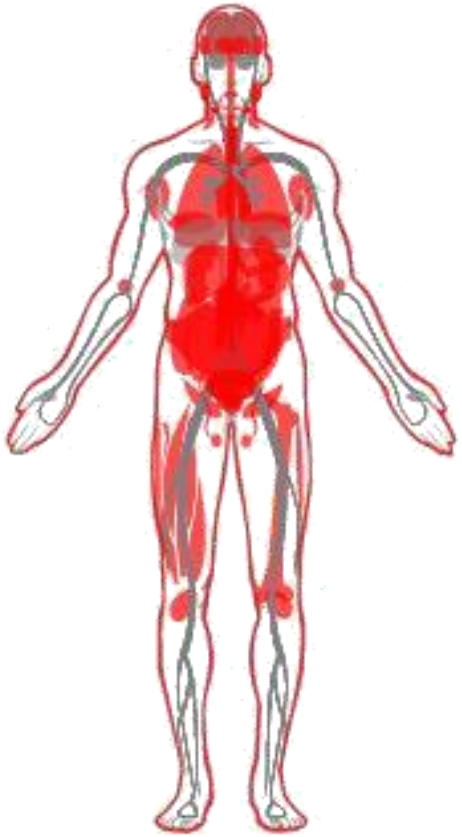
Currents mediated by calcium-activated chloride channels (CaCCs) were first observed in the early 1980's in *Xenopus* oocytes (1,2) and salamander photoreceptors (3).

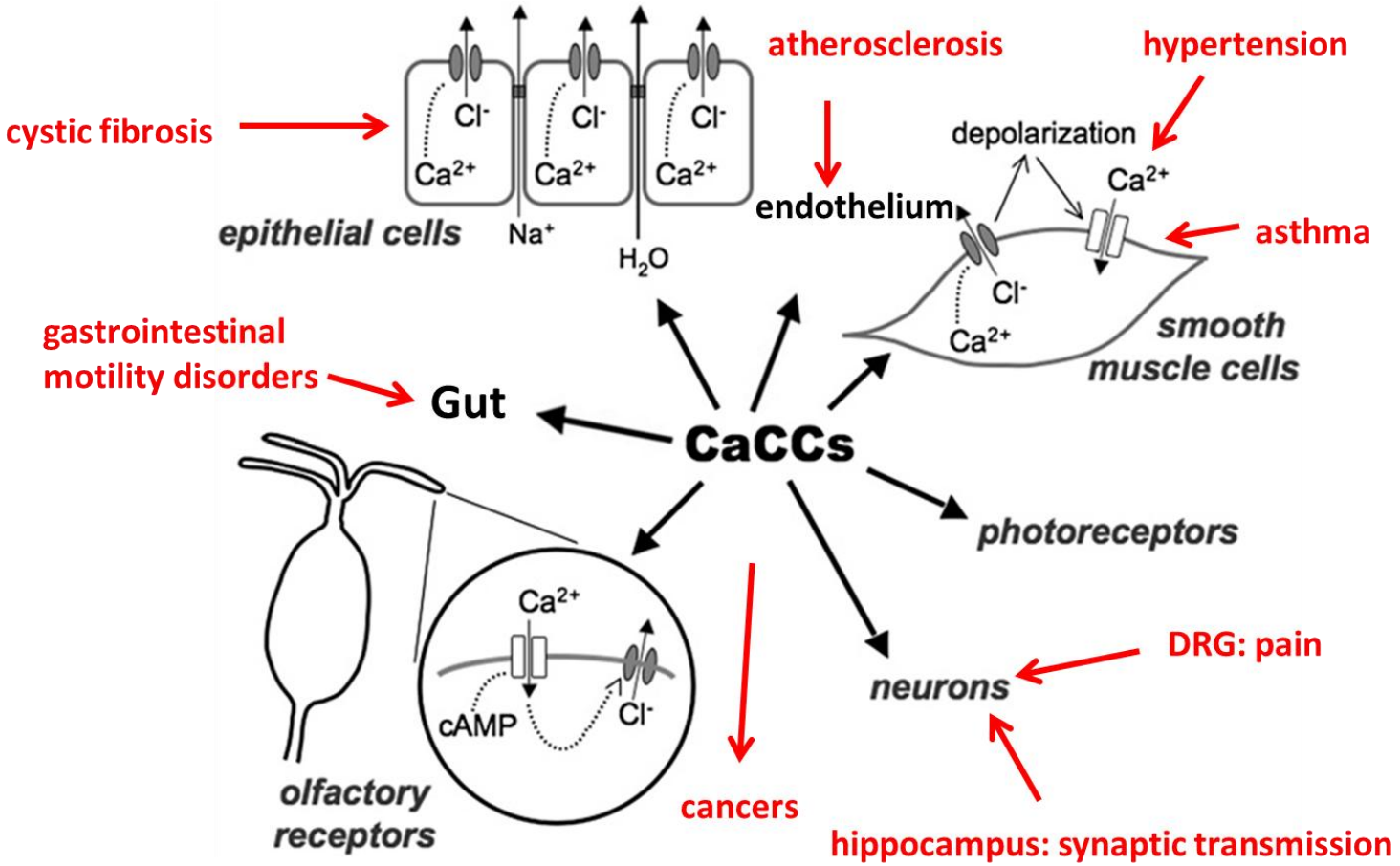


CaCCs were first recorded in oocytes.

Proc R Soc Lond B Biol Sci 1982, *J Physiol* 1983, *J Physiol* 1982.

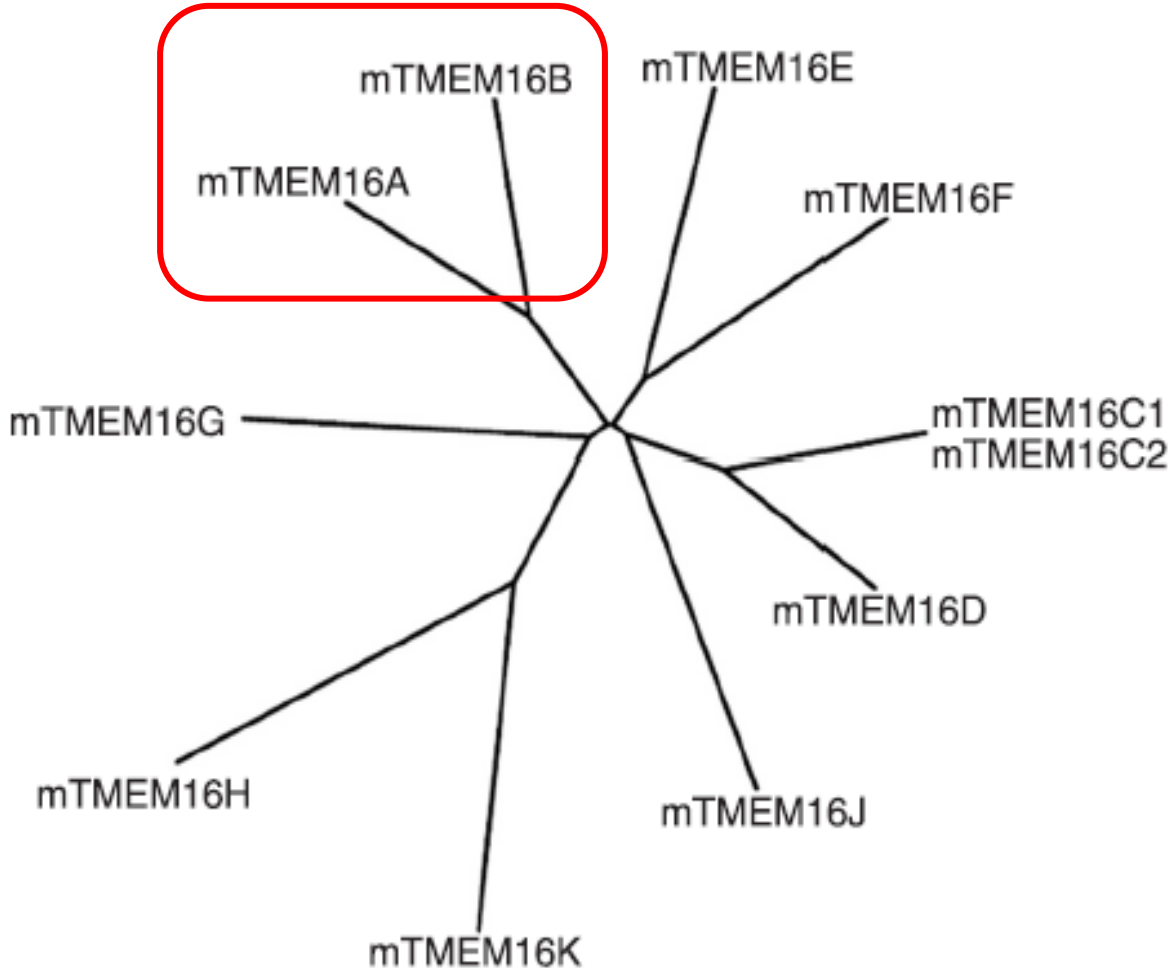
CaCCs (Calcium activated chloride currents) have been detected in variety of tissues in human bodies and play important roles in variety of physiological processes.





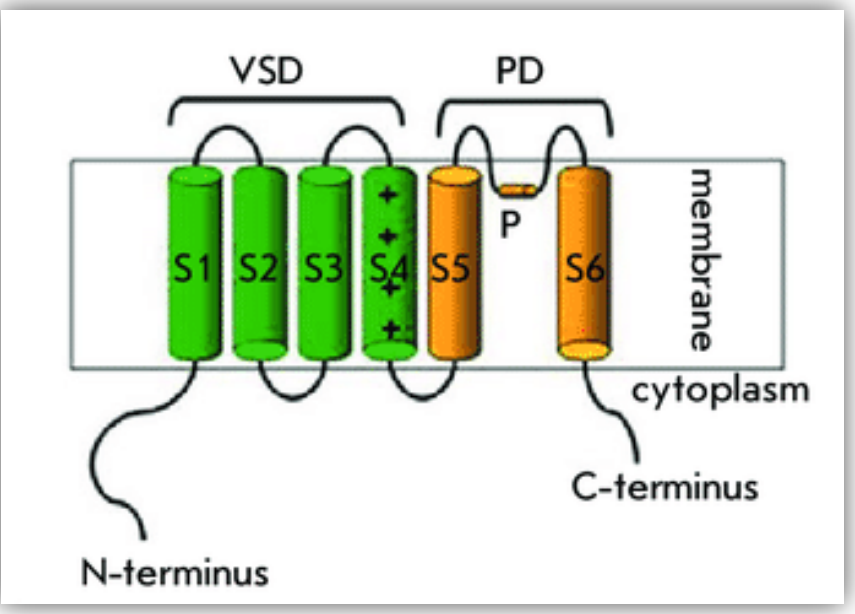
Pedemonte N, et al. *Physiological Reviews*, 2014, 94(2): 419-459.

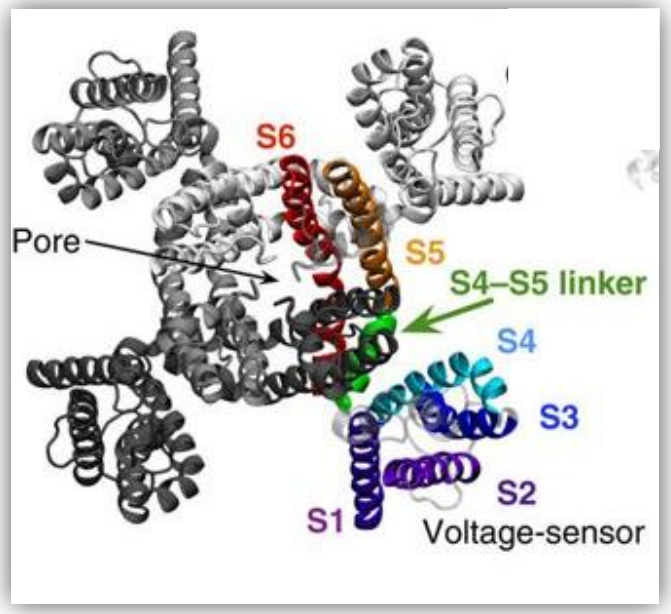
TMEM16A & B belonging to TMEM16 family are the molecular basis for CaCCs.

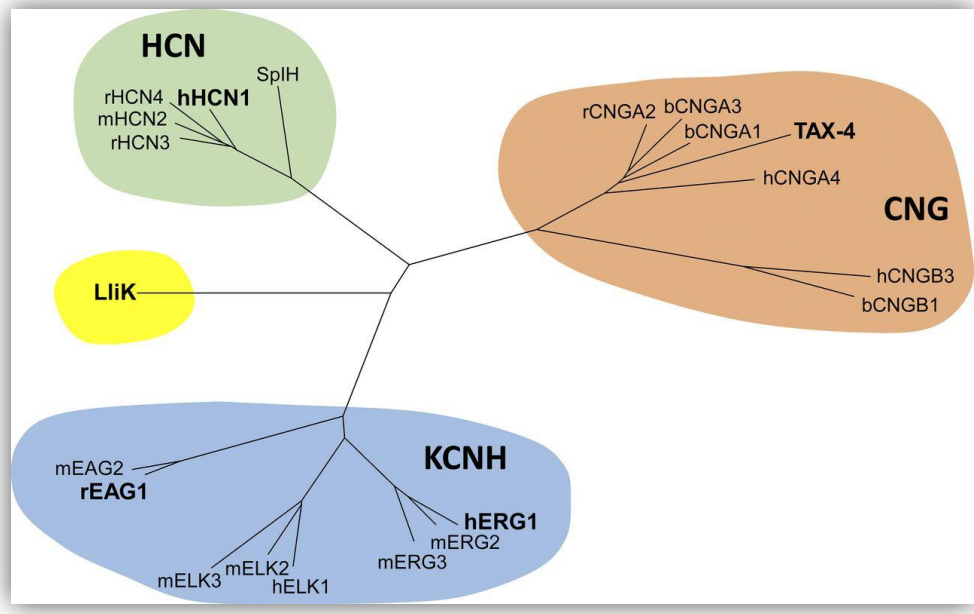


Cell, Nature and Science, 2008; PNAS, 2009.

Kv10.1 channel, a voltage dependent gating potassium channel, belongs to the EAG subfamily which has two members.







Unlike CaCCs, Kv10.1 channel is rarely discovered in normal tissues, no distribution in the heart, however, its dysfunction is associated with 12 malignancies - an ideal anti-tumor drug target.

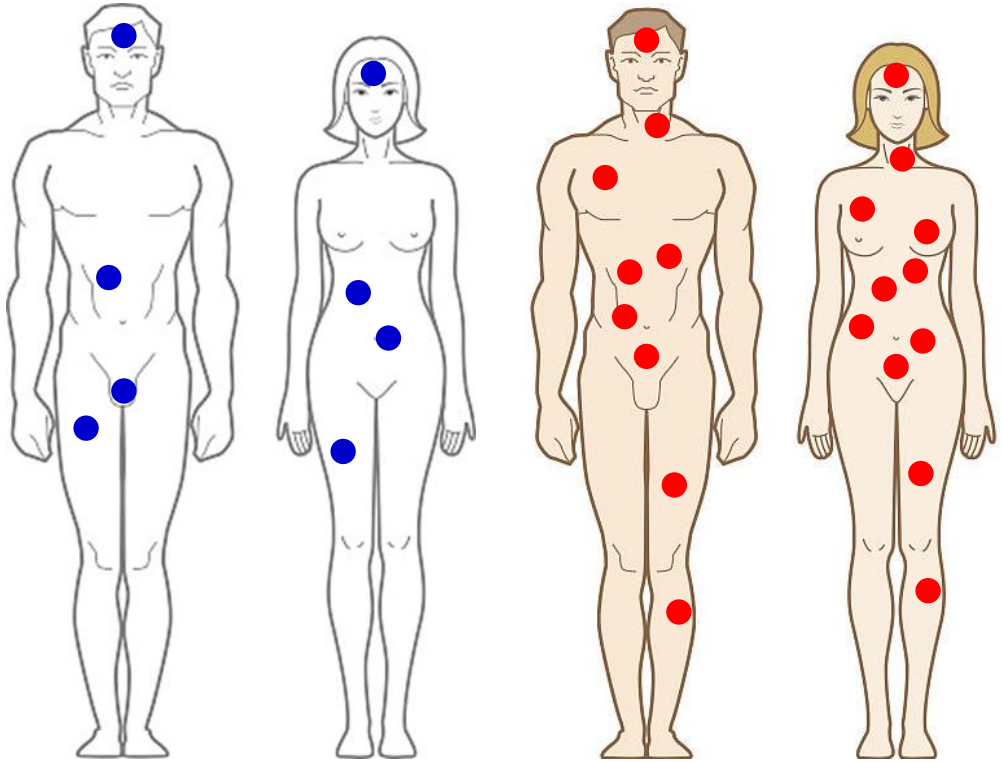
Brain

Adrenal gland

Placenta

Testis

Myoblasts



Normal human body

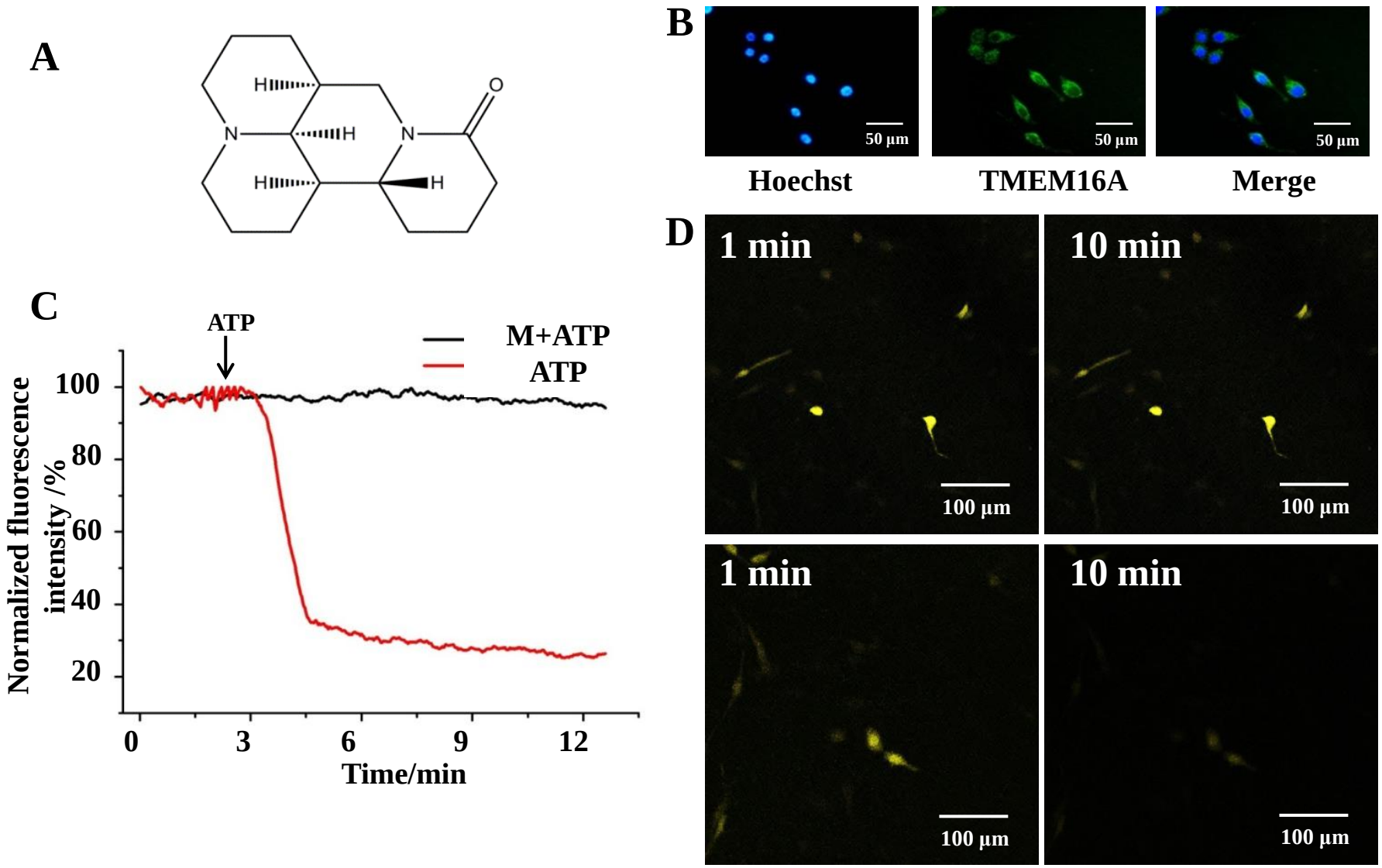
Cancer patients

Gliomas
Head and neck cancer
Lung cancer
Breast cancer
Gastric cancer
liver cancer
Colon cancer
Ovarian cancer
Cervical cancer
Prostate cancer
Leukemia
Sarcoma

[1] Sensors, 2012, 12(5), 5986-5995.
[2] Cancer Research, 2004, 64(19), 6996-7001.
[3] Embo Journal, 1999, 18(20), 5540-5547.
[4] Pflügers Archiv - European Journal of Physiology, 2016, 468(5), 751-762.
[5] Diagnostic pathology,2010 5(1), 78.

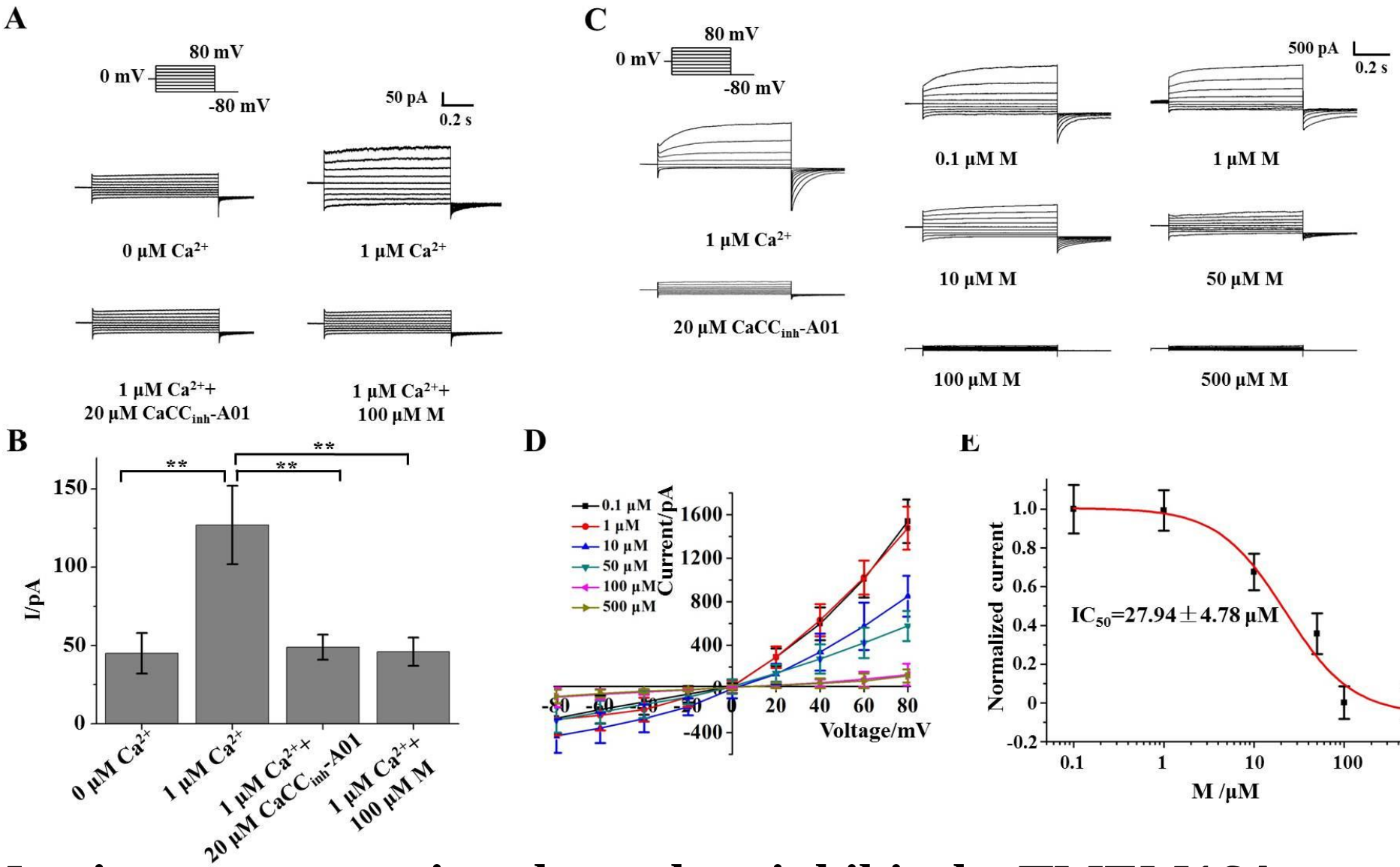
Anti-tumor drug screening Targeting at CaCCs

2. CaCCs/TMEM16A inhibitor discovery--Matrine



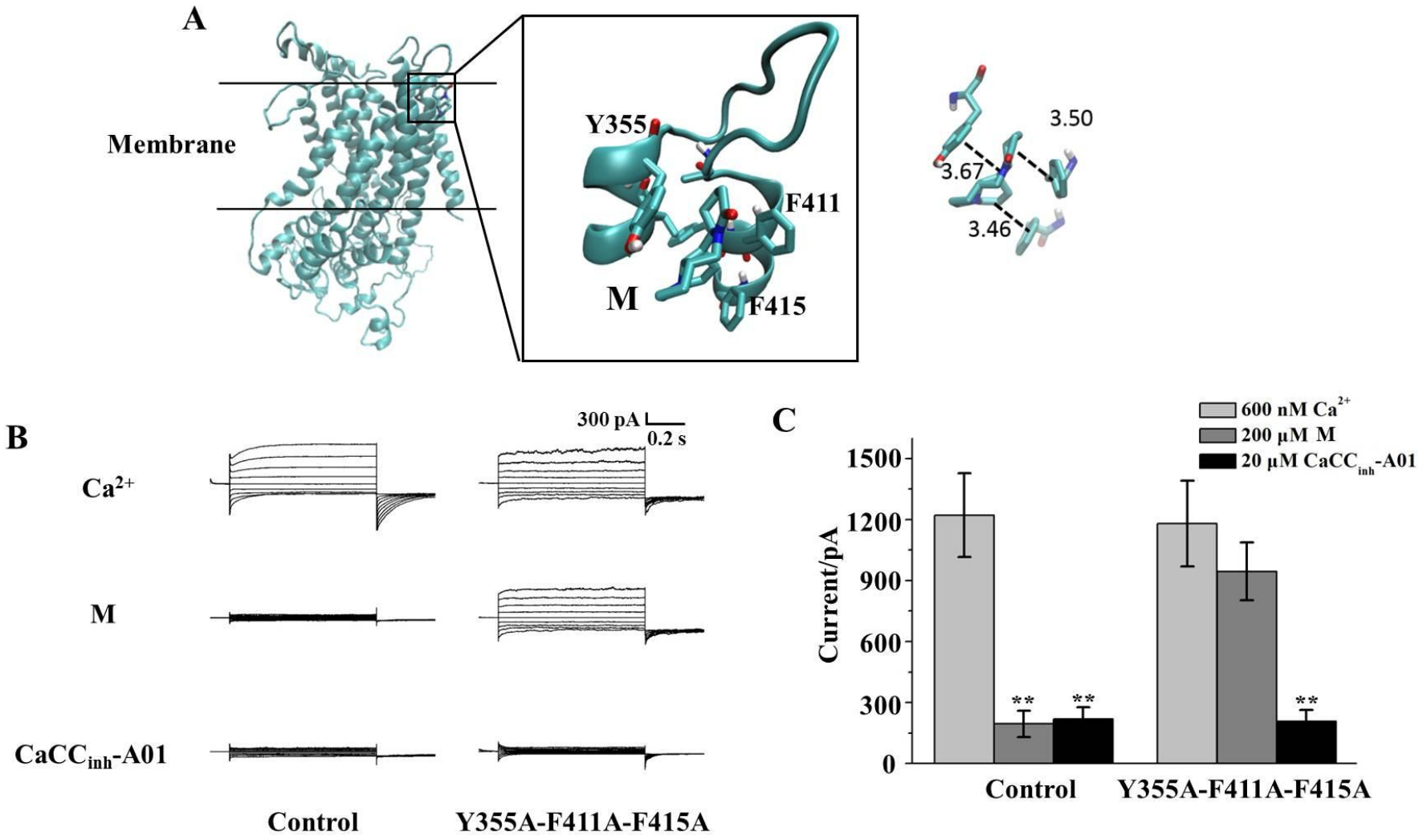
Matrine can inhibit TMEM16A channel

2. CaCCs/TMEM16A inhibitor discovery---Matrine



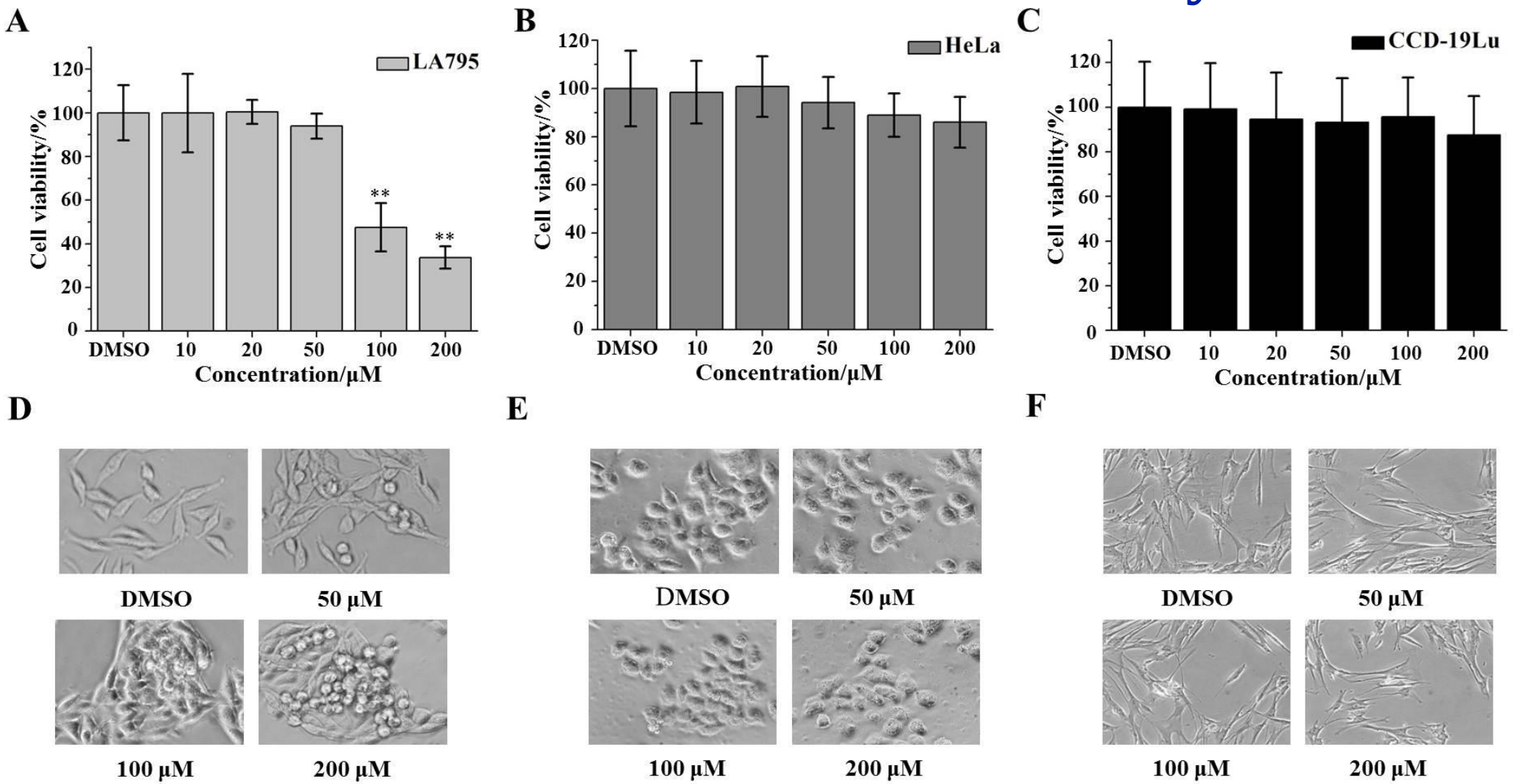
Matrine concentration-dependent inhibit the TMEM16A currents

2. CaCCs/TMEM16A inhibitor discovery---Matrine



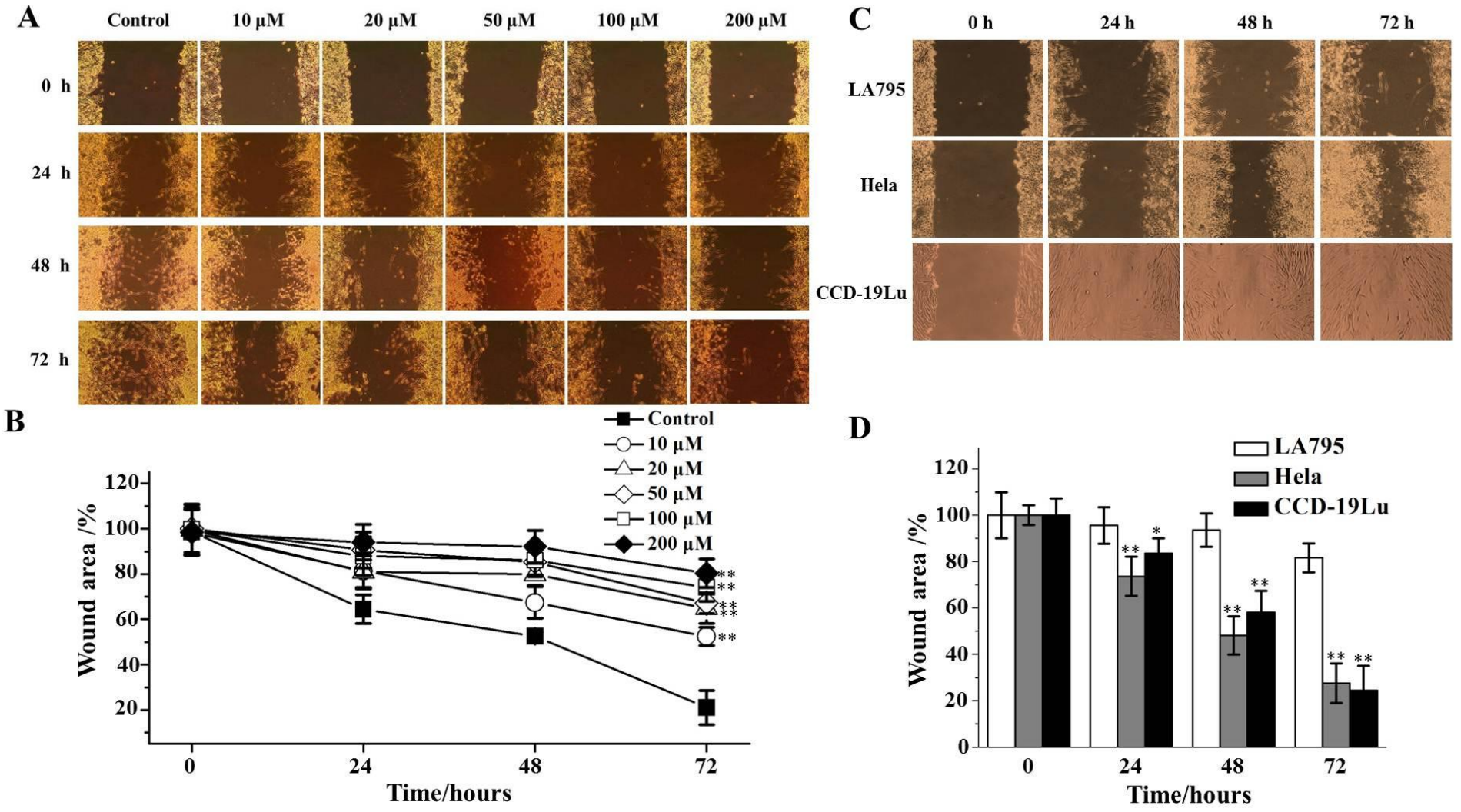
Determination of binding site of Matrine with TMEM16A

2. CaCCs/TMEM16A inhibitor discovery---Matrine



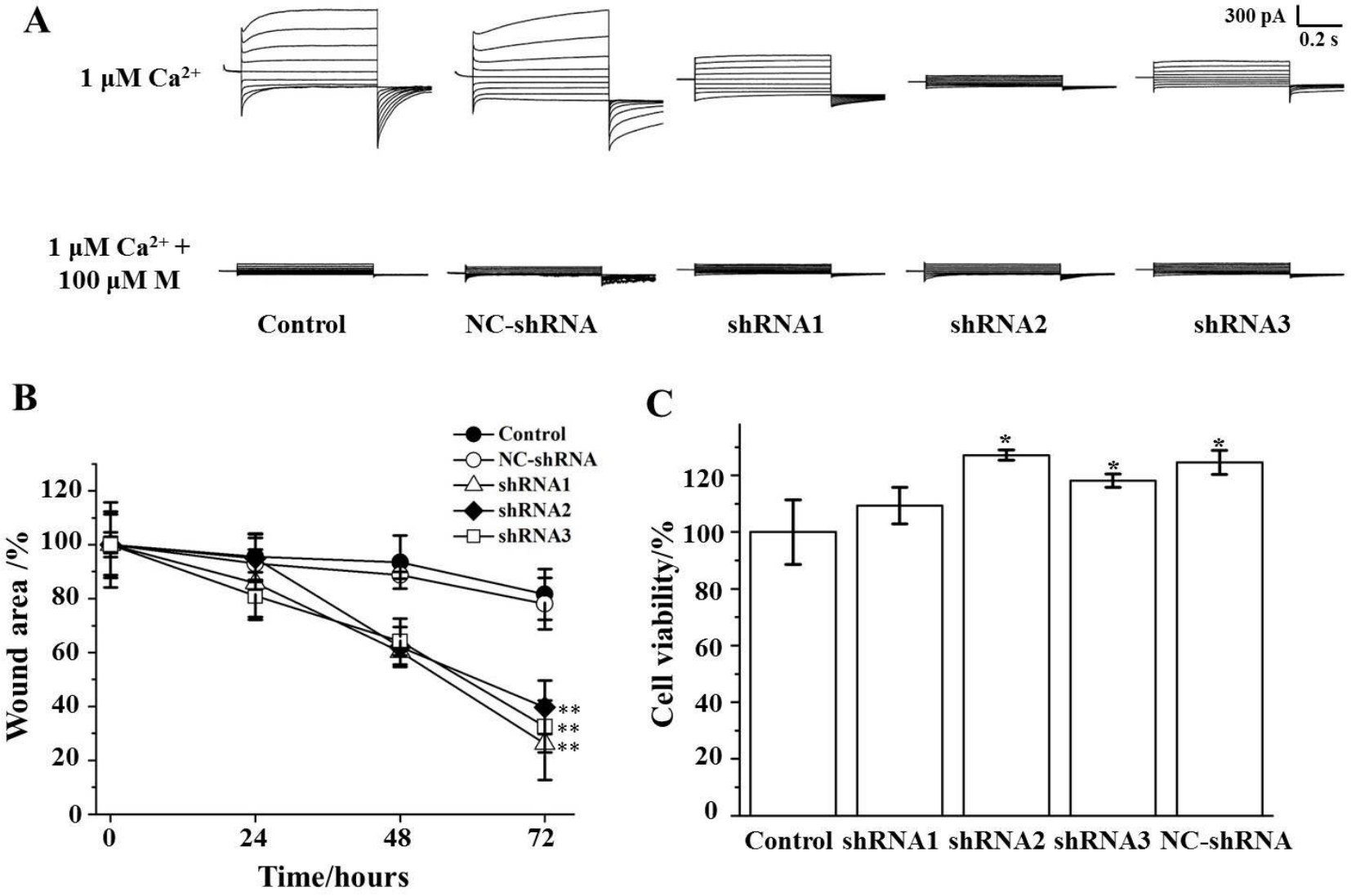
Matrine inhibited the proliferation of LA795 cells by inhibiting TMEM16A

2. CaCCs/TMEM16A inhibitor discovery---Matrine



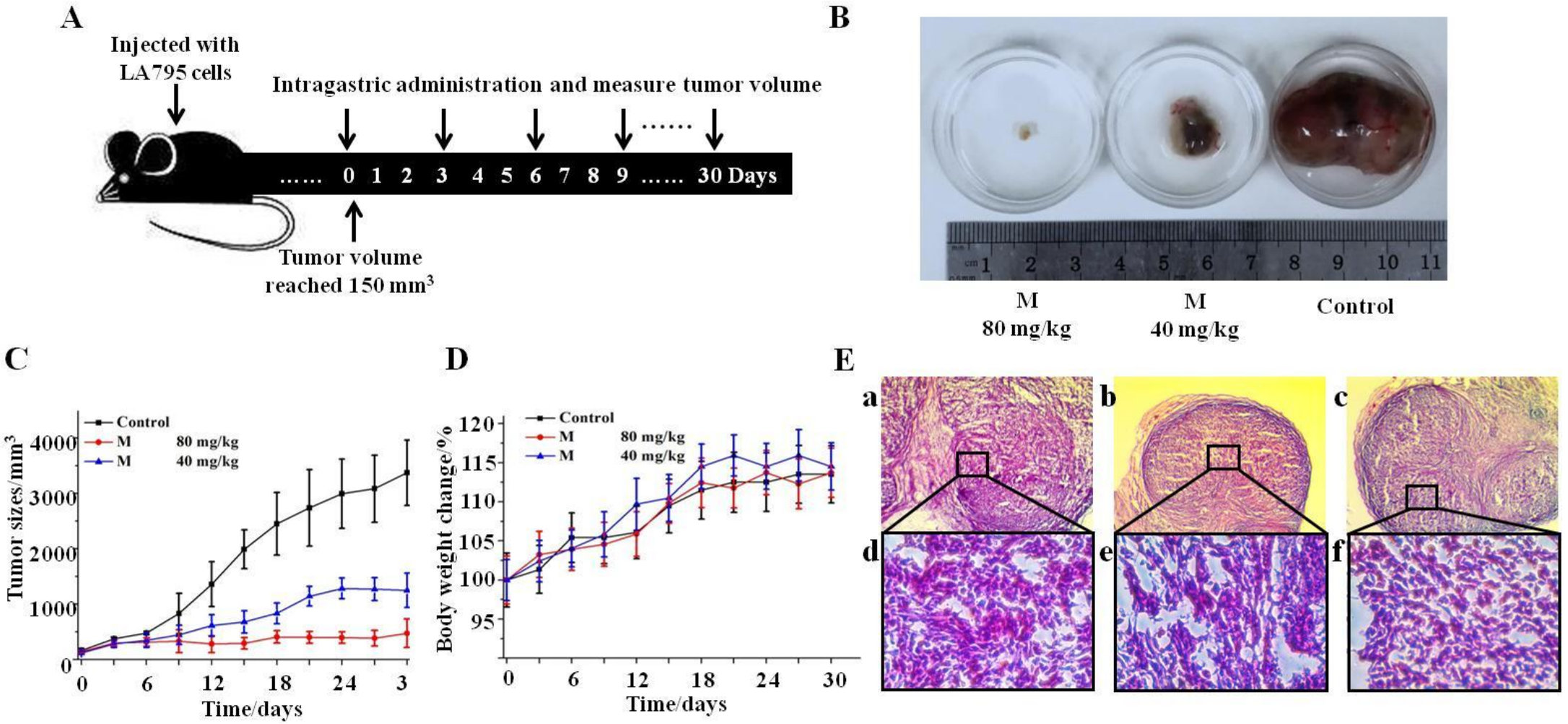
Matrine inhibited the migration of LA795 cells by inhibiting TMEM16A

2. CaCCs/TMEM16A inhibitor discovery---Matrine



The effect of Matrine disappeared when TMEM16A were knocked out

2. CaCCs/TMEM16A inhibitor discovery---Matrine

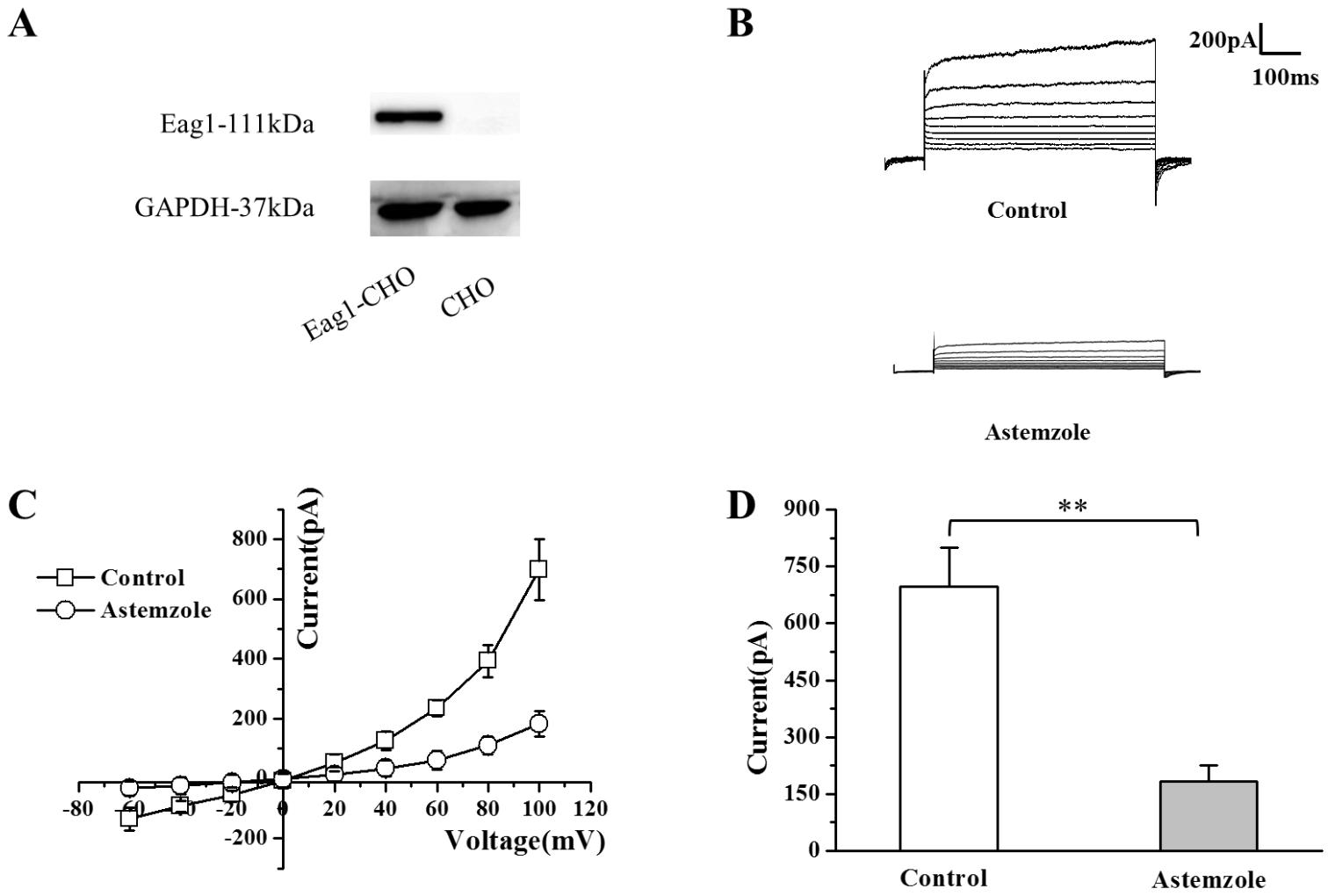


Matrine inhibits lung tumor growth by inhibiting TMEM16A to induce cell apoptosis

Guo S, Chen Y, Pang C, et al. J Cell Physiol. 2018;1–11. https://doi.org/10.1002/jcp.27529

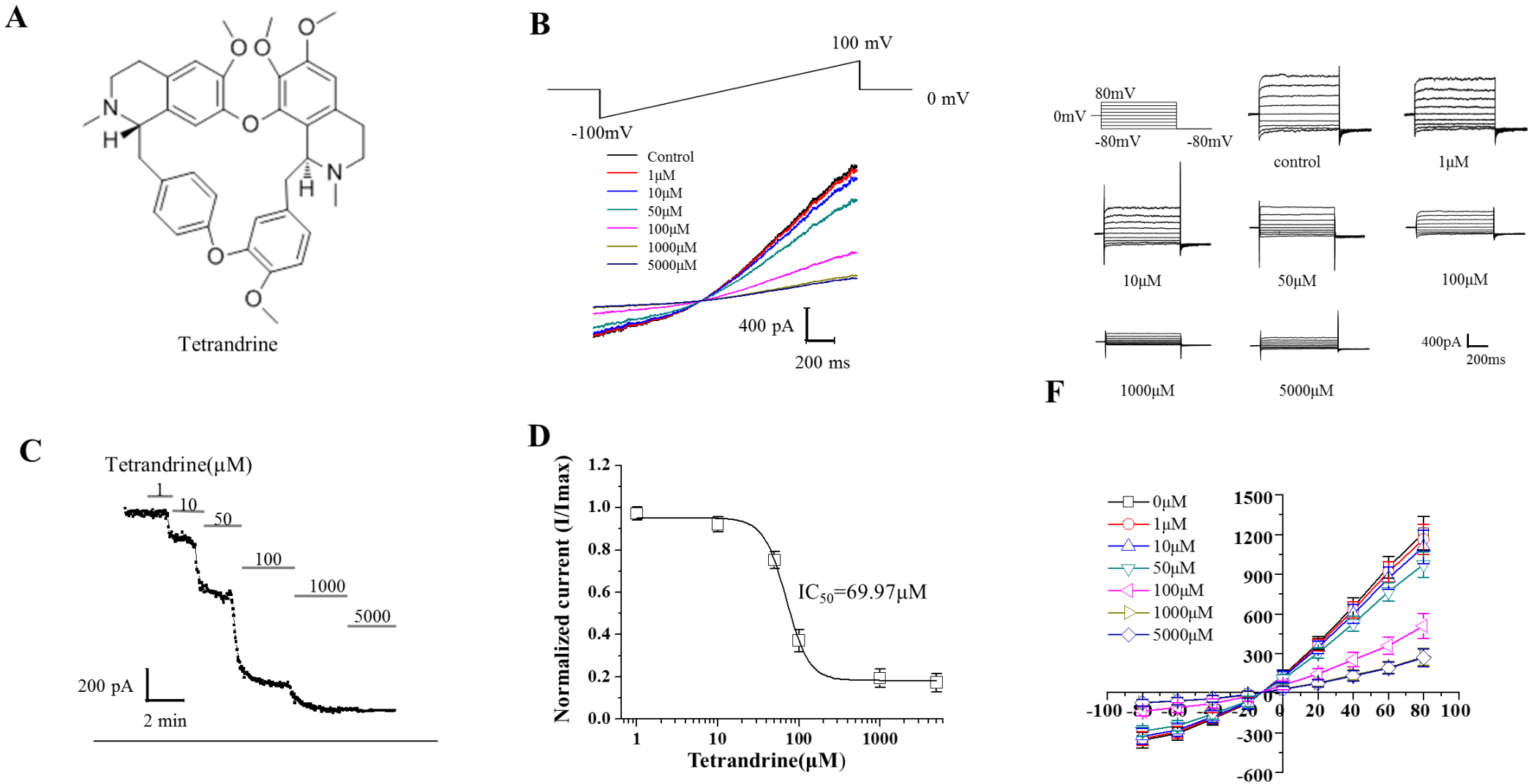
Anti-tumor drug screening targeting at Kv10.1

3. Anti-tumor drug screening targeting at Kv10.1.



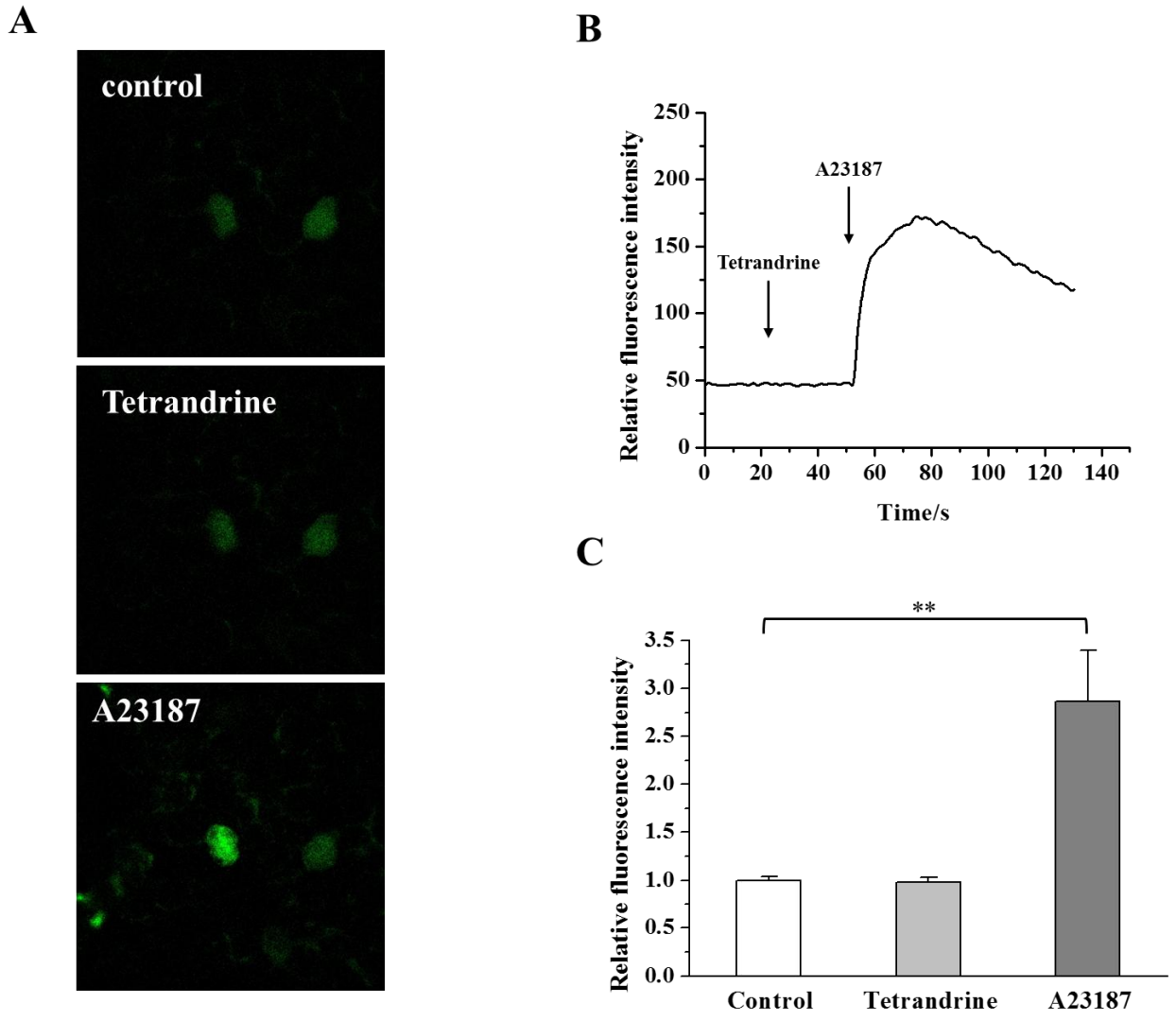
Characterization of Eag1 currents in stably transfected CHO cells.

3. Anti-tumor drug screening targeting at Kv10.1.



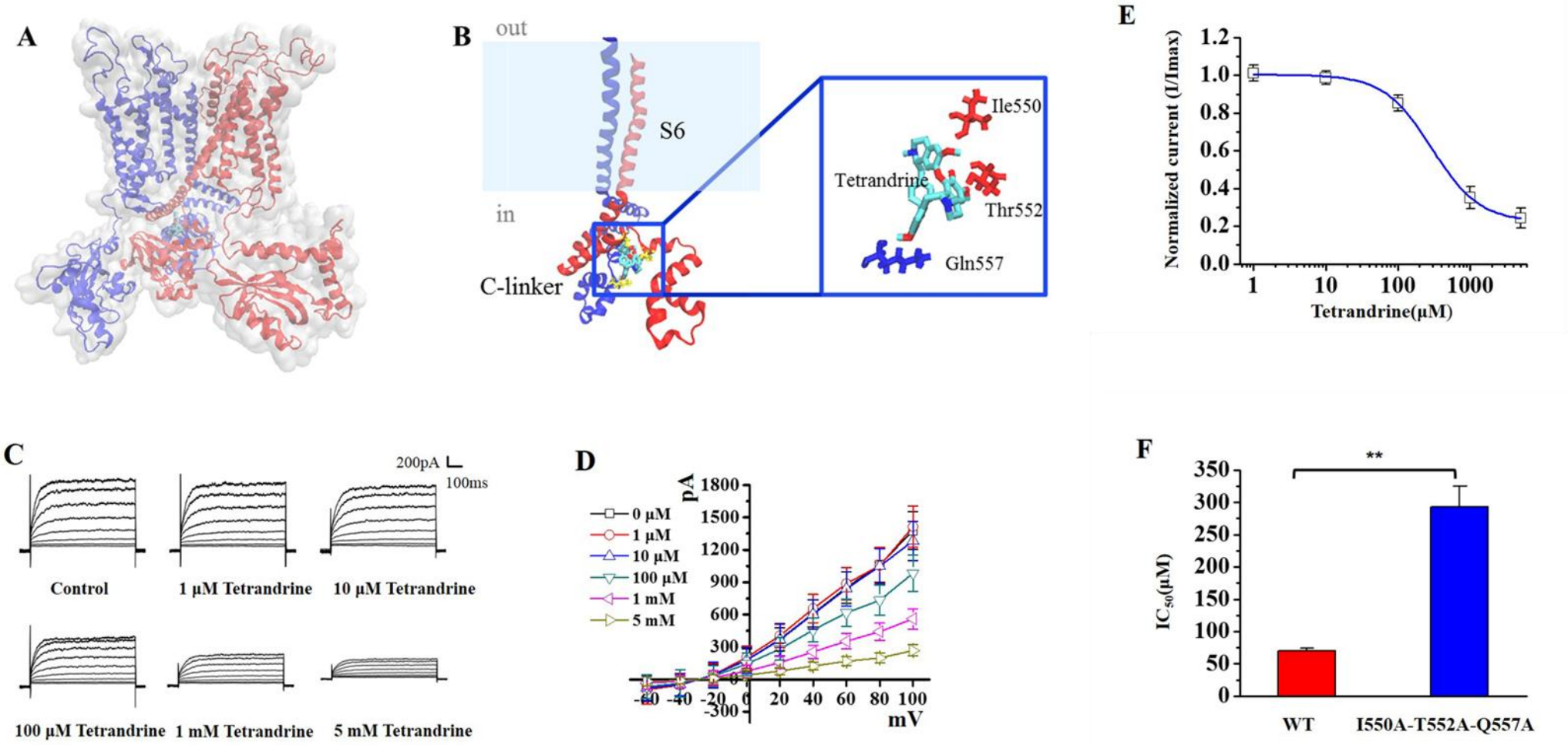
Currents inhibited by various concentrations of tetrandrine in CHO cells stably expressing Eag1

3. Anti-tumor drug screening targeting at Kv10.1.



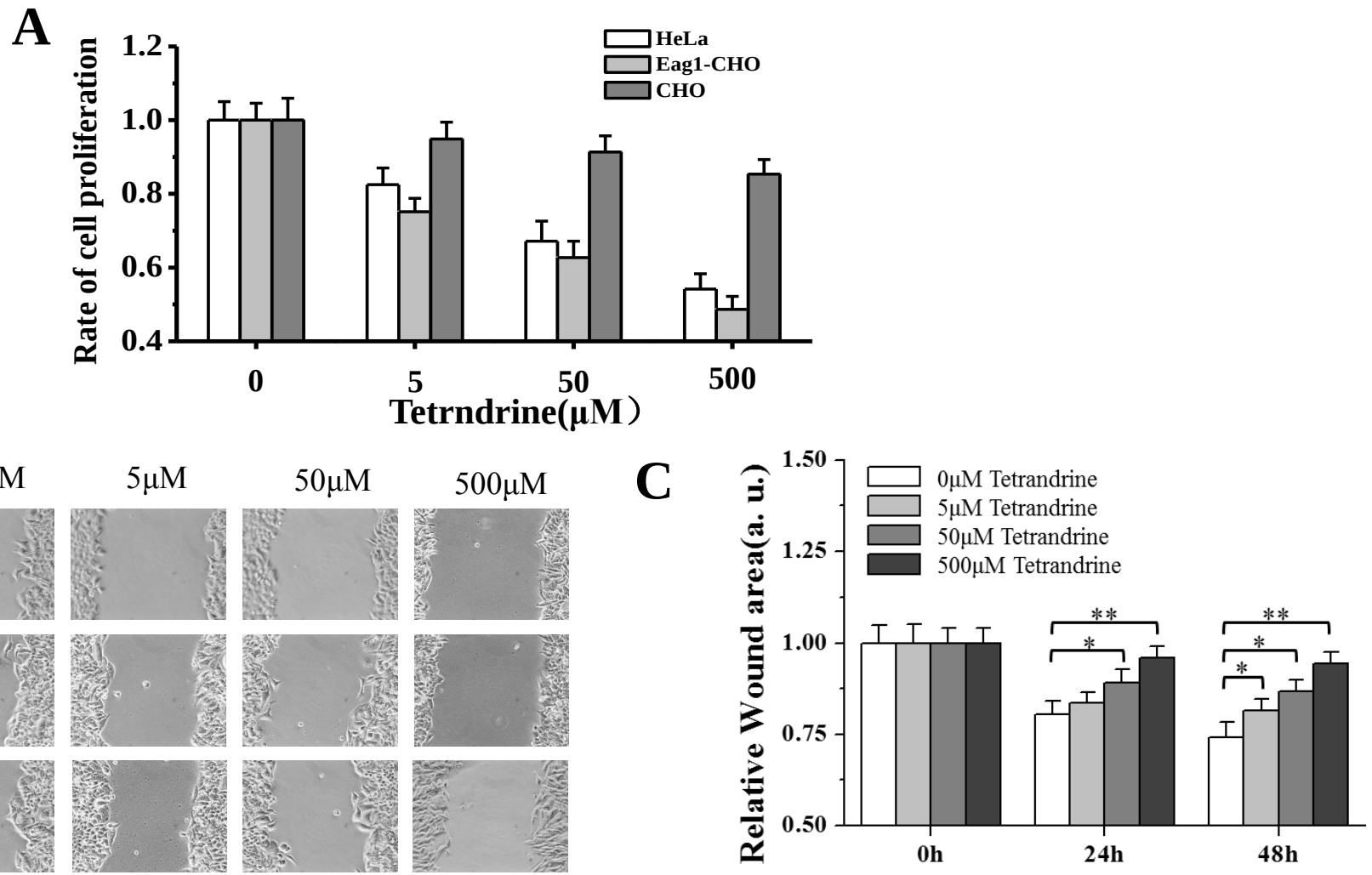
Inhibition mechanism of Eag1 by tetrandrine that includes no $[Ca^{2+}]i$ changes.

3. Anti-tumor drug screening targeting at Kv10.1.



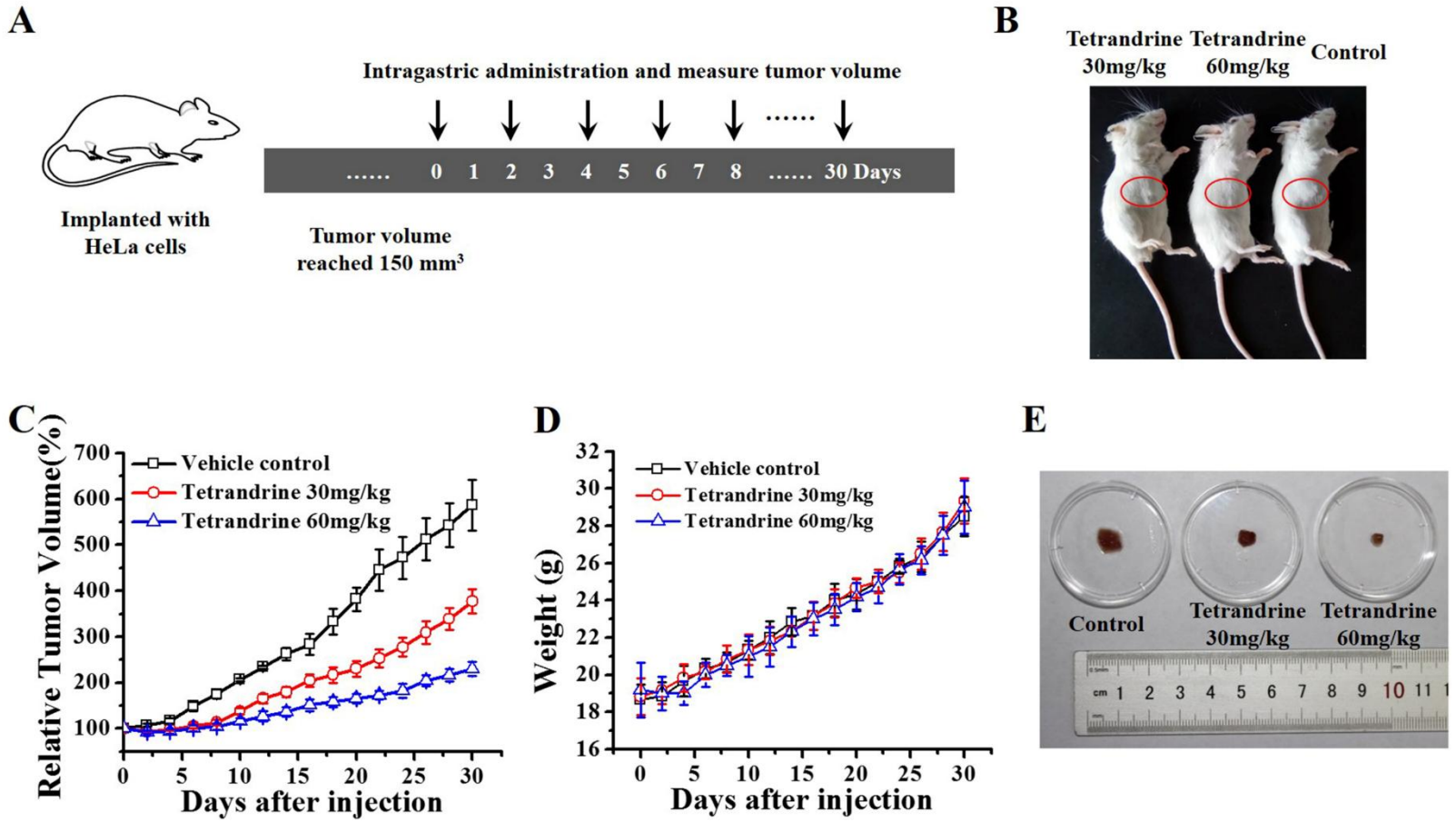
Molecular determination of tetrandrine sensitivity.

3. Anti-tumor drug screening targeting at Kv10.1.



Effects of different concentrations of tetrandrine on CHO cells stably expressing Eag1 and HeLa cells.

3. Anti-tumor drug screening targeting at Kv10.1.



The Eag1 inhibitor tetrandrine reduces tumour growth *in vivo*.

Wang X, Chen Y, Li J, et al. J Cell Physiol.2018;1–13. https://doi.org/10.1002/jcp.27470

致　谢

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IICC-5
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第五届国际离子通道大会
June 26 – June 30, 2015 Luzhou, China

Thanks for your attention.

河北工业大学文件

校政字〔2016〕317 号　　签发人：张建畅

关于印发《河北工业大学“元光学者计划”实施办法（试行）》的通知

人才层次	岗位名称	学科建设经费	住房补贴及安家费（万元）	（元/月）或高层次人才周转住房	工资	元光学者津贴（万元/年）	备注
一层次	卓越岗	2000 （可面议）	500 （可面议）	4000	基本工资 + 绩效工资	100	年薪≥150 万元
二层次	领军岗 A	理工科 800-1000 人文社科或经管类 300-500	300	3000		60	年薪≥90 万元
	领军岗 B	理工科 600-800 人文社科或经管类 200-300	250			45	
三层次	特聘岗 A	理工科 300-500 人文社科或经管类 100-200	200	2500		40	年薪≥60 万元
	特聘岗 B	理工科 150-400 人文社科或经管类 50-100	150			25	
四层次	启航岗 A	理工科 100-200 人文社科或经管类 30-50	100	2000		15	
	启航岗 B	理工科:30-50 人文社科或经管类:10-30	80			8	