

胃粘膜病变和胃癌的早诊早治

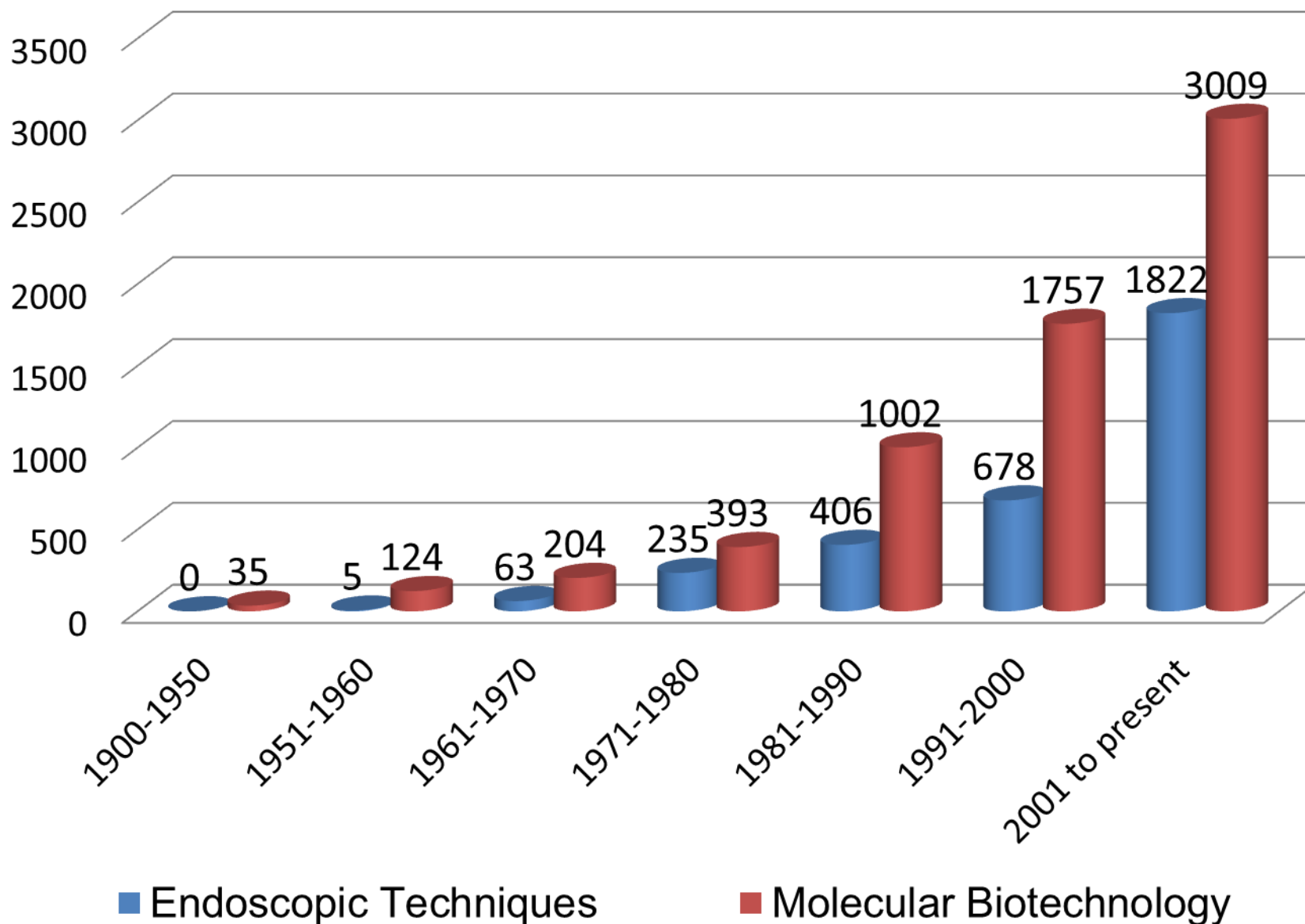
厦门大学附属中山医院消化内科

厦门大学消化疾病研究所

厦门市消化疾病中心

任建林

Early gastric cancer diagnosis and treatment



PROGRESSION TO GASTRIC ADENOCARCINOMA

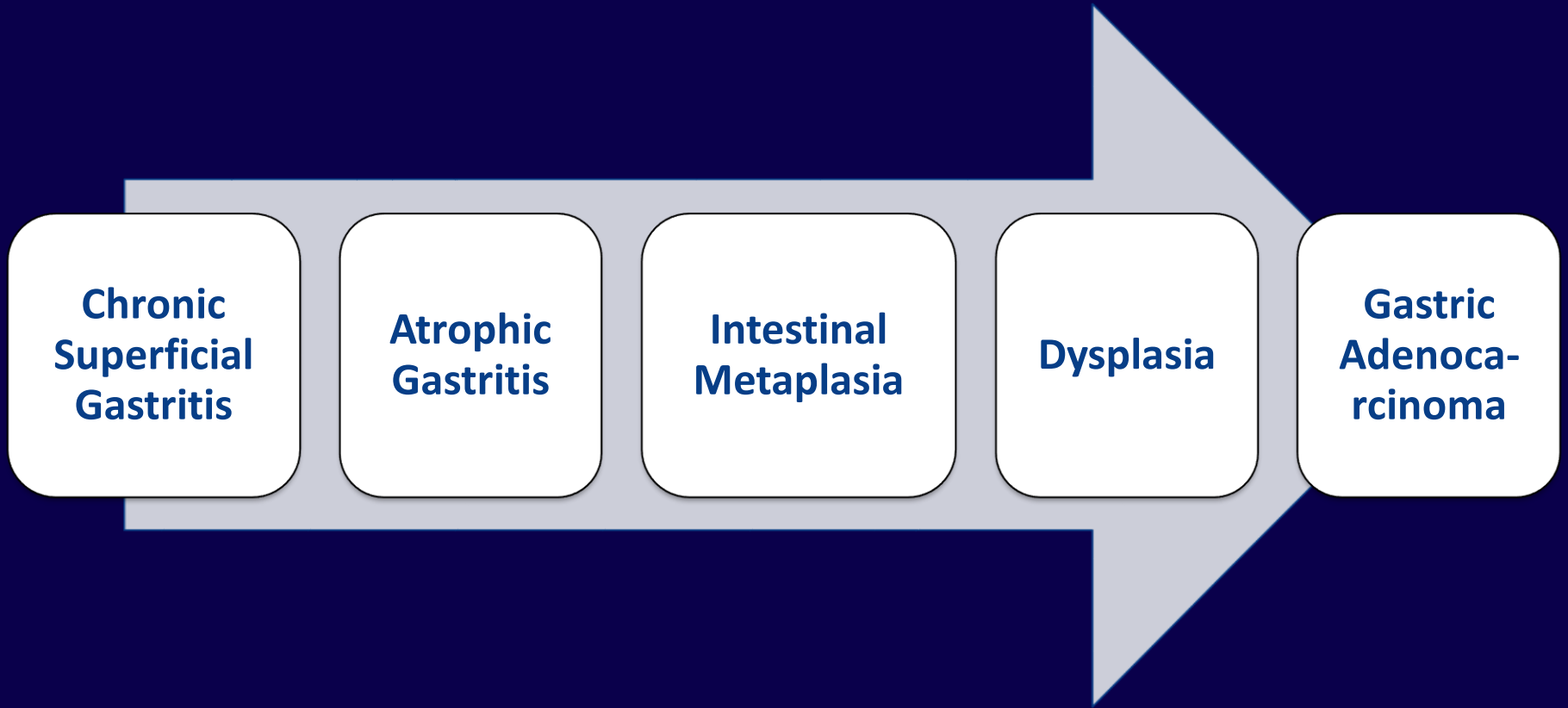
**Chronic
Superficial
Gastritis**

**Atrophic
Gastritis**

**Intestinal
Metaplasia**

Dysplasia

**Gastric
Adenoca-
rcinoma**



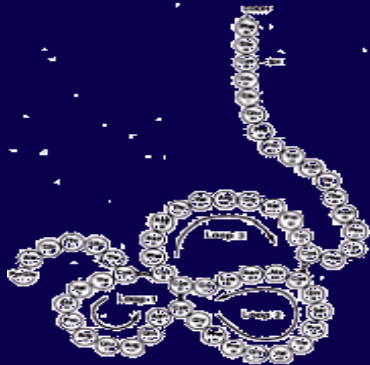
- ◆ ECHS1 acts as a novel HBsAg-binding protein enhancing apoptosis through the mitochondrial pathway in HepG2 cells. *Cancer Lett.* 2013 Mar 1;330(1):67-73.
- ◆ Distribution of bone-marrow-derived endothelial and immune cells in a murine colitis-associated colorectal cancer model. *PLoS One.* 2013 Sep 10;8(9):e73666.
- ◆ Silencing of Pokemon enhances caspase-dependent apoptosis via fas- and mitochondria-mediated pathways in hepatocellular carcinoma cells. *PLoS One.* 2013 Jul 17;8(7):e68981.
- ◆ Circulatory antigen processing by mucosal dendritic cells controls CD8(+) T cell activation. *Immunity.* 2013 Jan 24;38(1):153-65.
- ◆ Pyruvate kinase M2 plays a dual role on regulation of the EGF/EGFR signaling via E-cadherin-dependent manner in gastric cancer cells. *PLoS One.* 2013 Jun 28;8(6):e67542.

- ◆ miRNA423-5p regulates cell proliferation and invasion by targeting trefoil factor 1 in gastric cancer cells. *Cancer Lett.* 2014 May 28;347(1):98-104.
- ◆ Exome sequencing revealed novel germline mutations in Chinese Peutz-Jeghers syndrome patients. *Dig Dis Sci.* 2014 Jan;59(1):64-71.
- ◆ Piezo1 Is as a Novel Trefoil Factor Family 1 Binding Protein that Promotes Gastric Cancer Cell Mobility In Vitro. *Dig Dis Sci.* 2014 May 6. [Epub ahead of print]
- ◆ Fibrinogen Alpha Chain Acts as a HBsAg Binding Protein and their Interaction Promotes HepG2 Cell Apoptosis. *Current Proteomics.* 2014 Jan [Epub ahead of print]
- ◆ Serum TFF3 may be a pharmacodynamic marker of responses to chemotherapy in gastrointestinal cancers. *BMC Clinical Pathology.* 2014 Jul [Epub ahead of print]

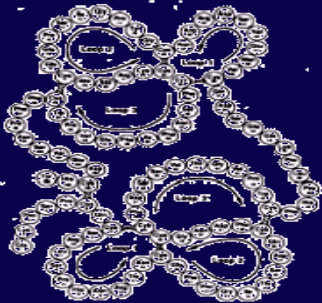
Defensive Factor

TFFs

TFF1



TFF2



TFF3



Interaction with mucin glycoprotein

Increased blood flow

Migration of cells

Restoration of barrier

Cell signaling pathways



Searching receptor
of TFFs ?

Piezo1 : 一种新的TFF1结合蛋白促进胃癌细胞迁移

Piezo1 is as a novel TFF 1 binding protein that promotes GC cell mobility in vitro

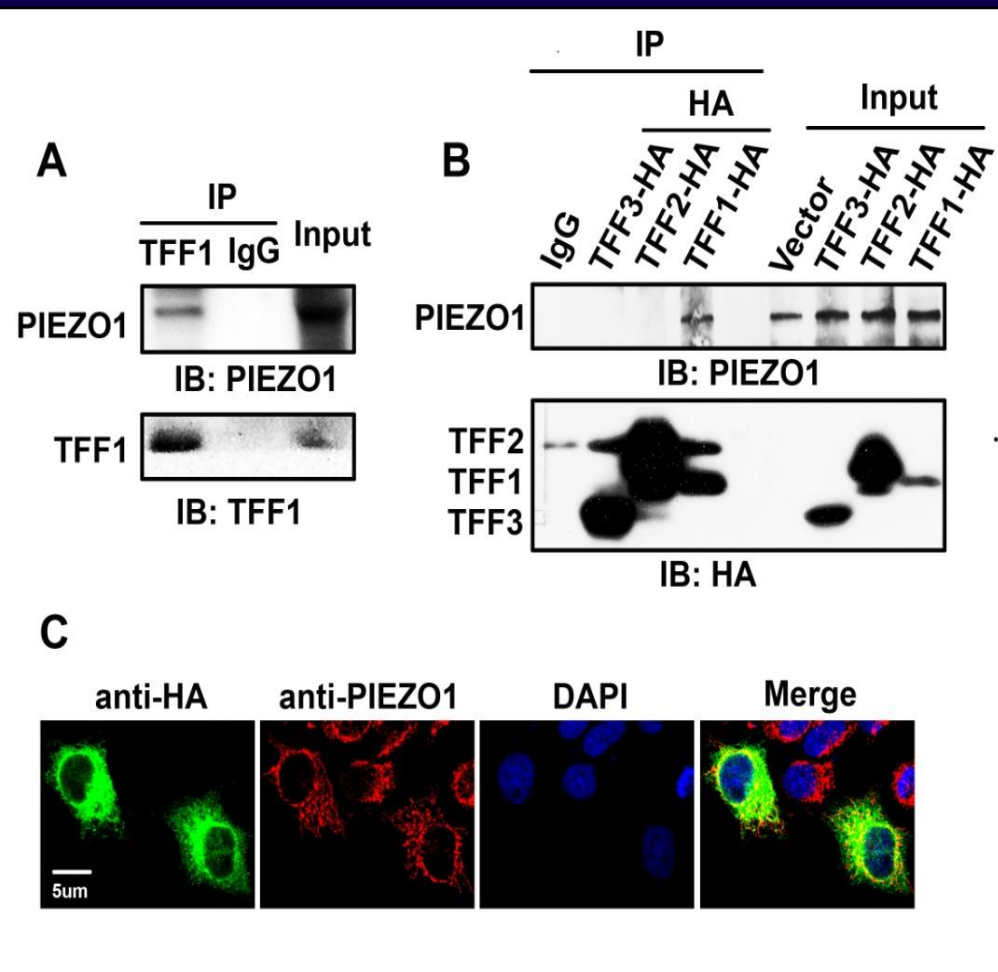


Fig. 1 TFF1与Piezo1结合验证

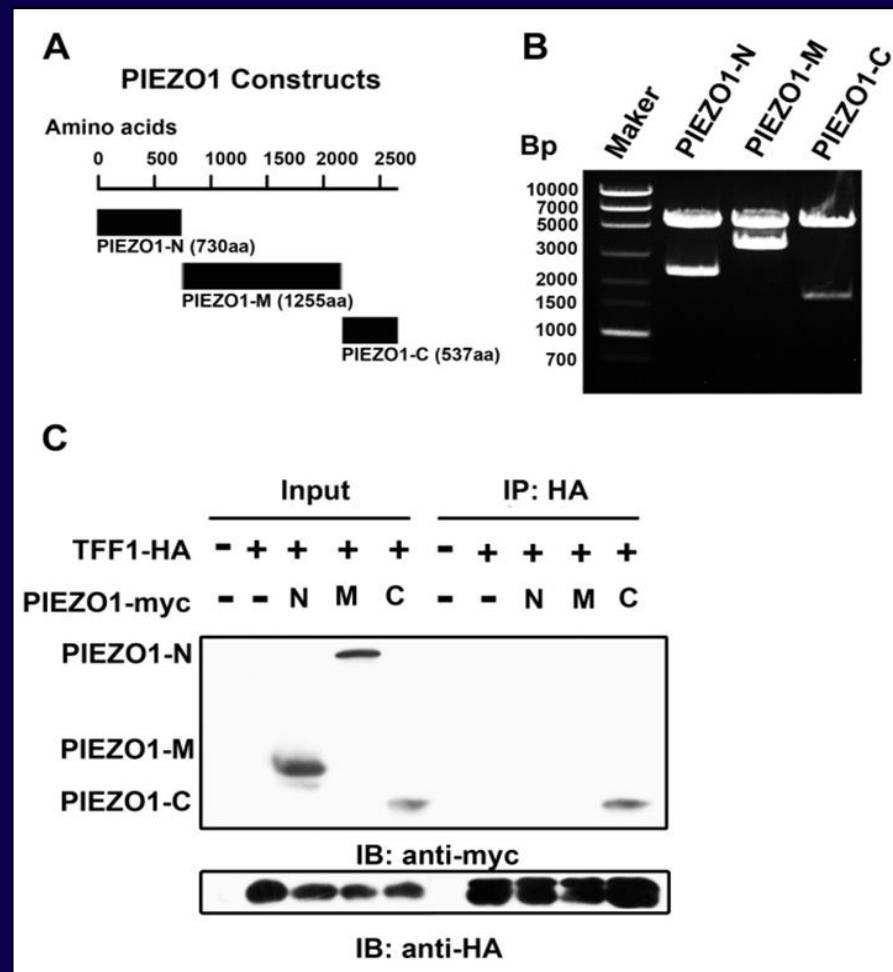


Fig. 2 TFF1与Piezo1 C端结合

Piezo1 : 一种新的TFF1结合蛋白促进胃癌细胞迁移

Piezo1 is as a novel TFF 1 binding protein that promotes GC cell mobility in vitro

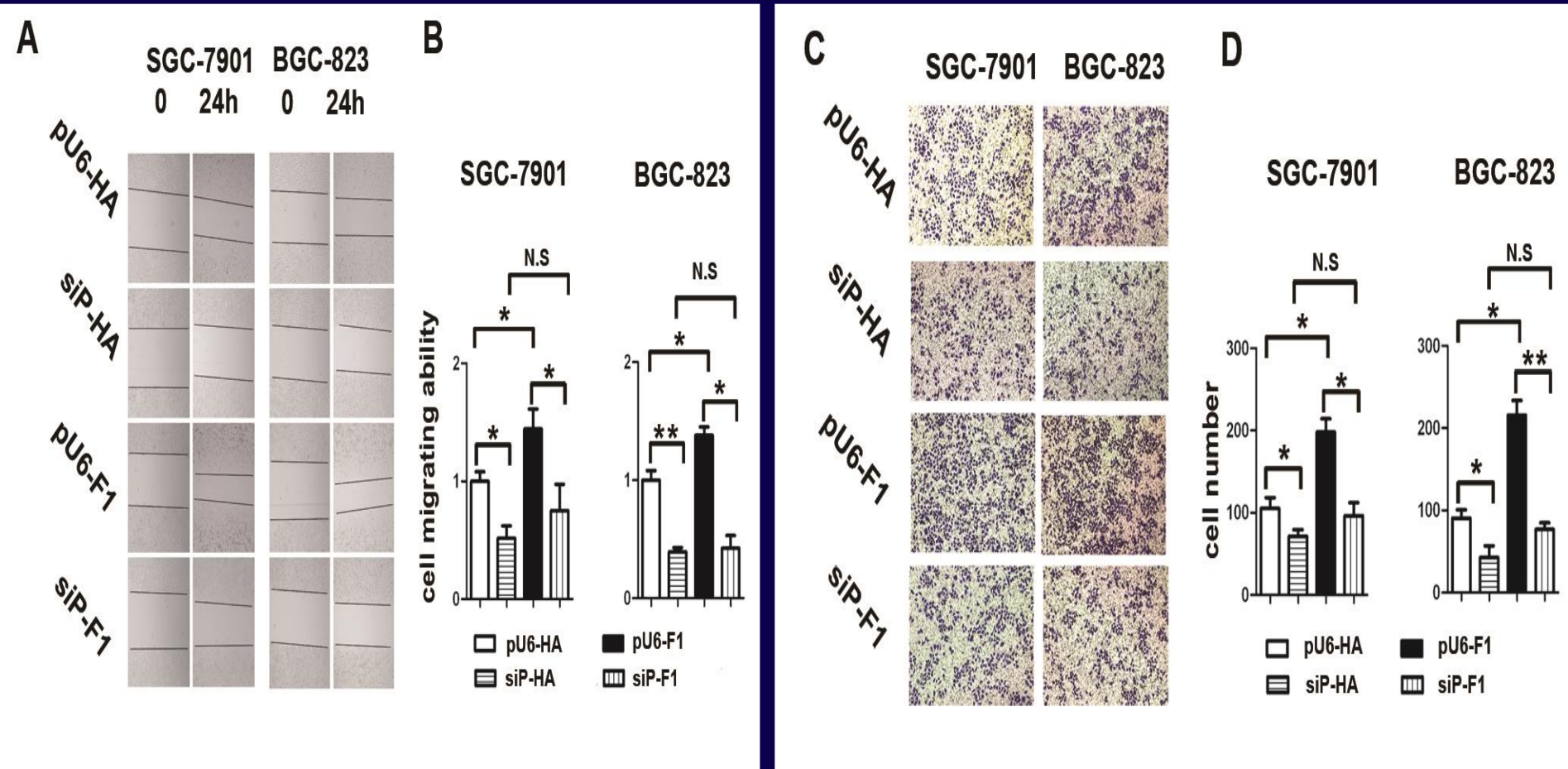


Fig. 3 胃癌细胞中干扰Piezo1 表达降低细胞迁移能力

miRNA423-5p regulates cell proliferation and invasion by targeting TFF1 in GC cells

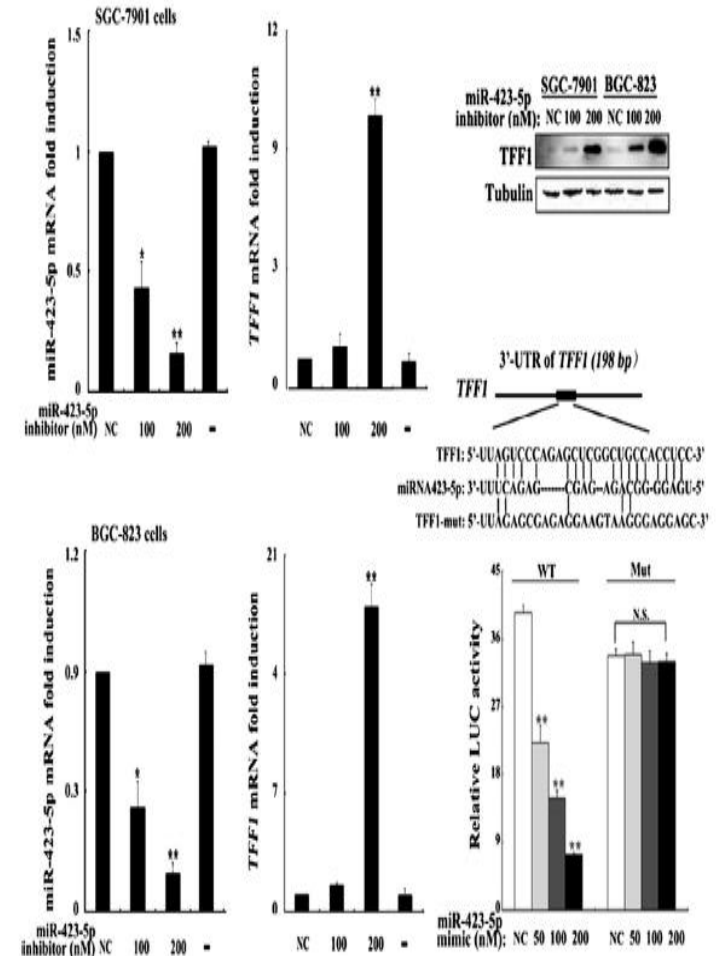
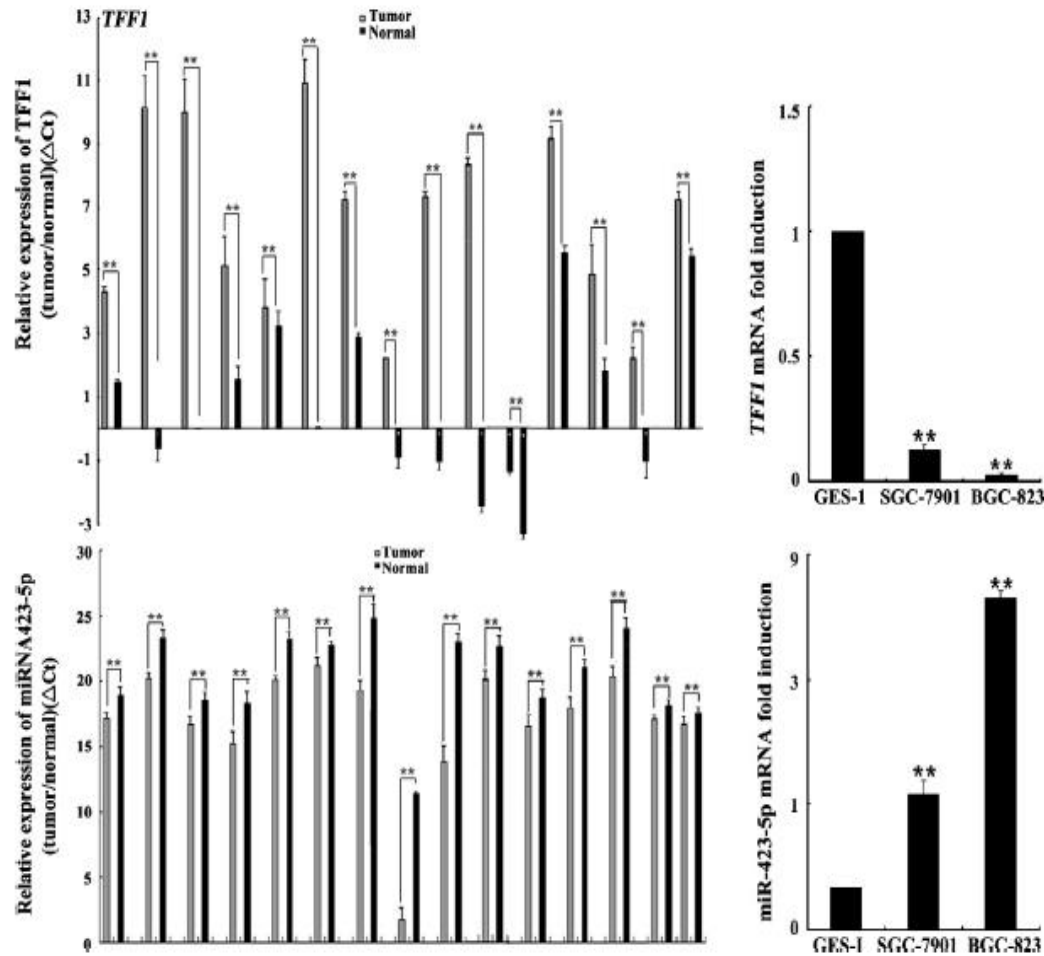
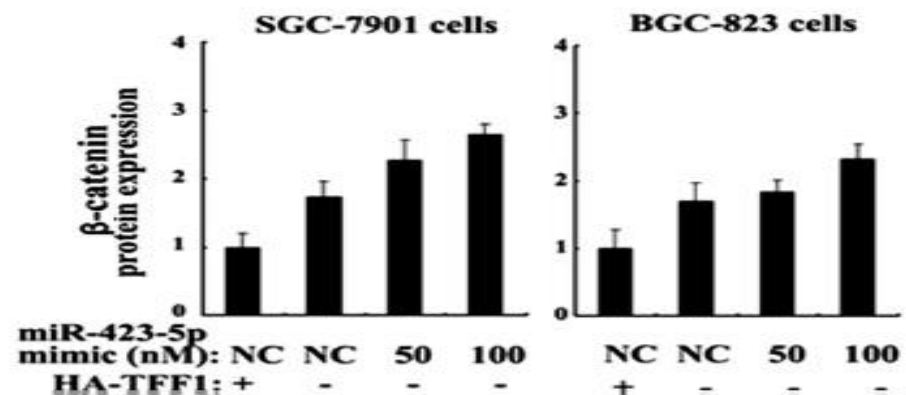
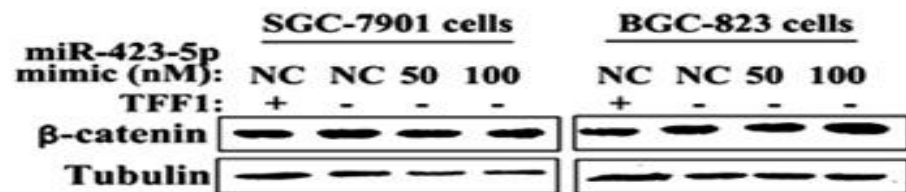
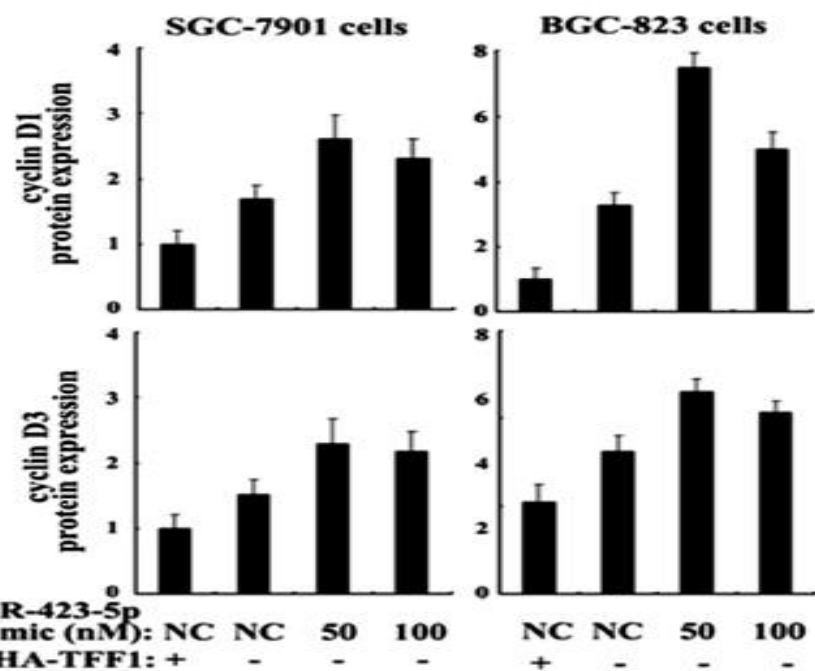
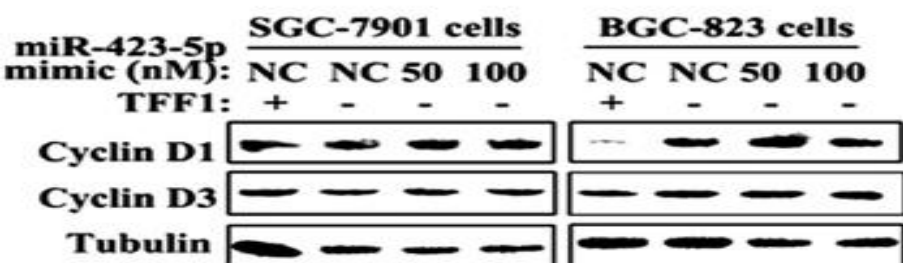


Fig. 1 TFF1与miRNA-423-5p在胃癌、癌旁正常组织及胃癌细胞株中的表达呈负相关

Fig. 2 miRNA-423-5p通过结合于3'URT 下调TFF1表达

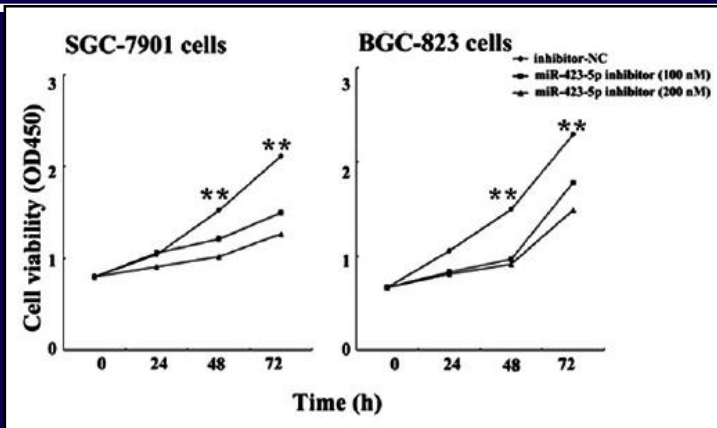
miRNA-423-5p通过靶基因TFF1调控胃癌细胞增殖与侵袭

miRNA423-5p regulates cell proliferation and invasion by targeting TFF1 in GC cells

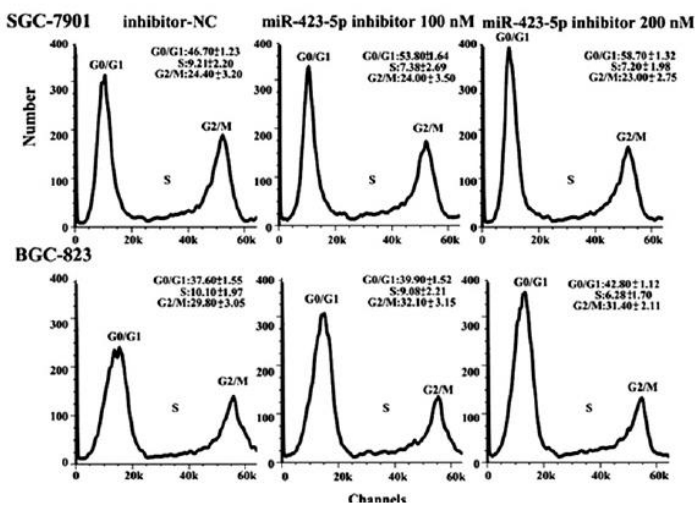


miRNA-423-5p通过靶基因TFF1调控胃癌细胞增殖与侵袭

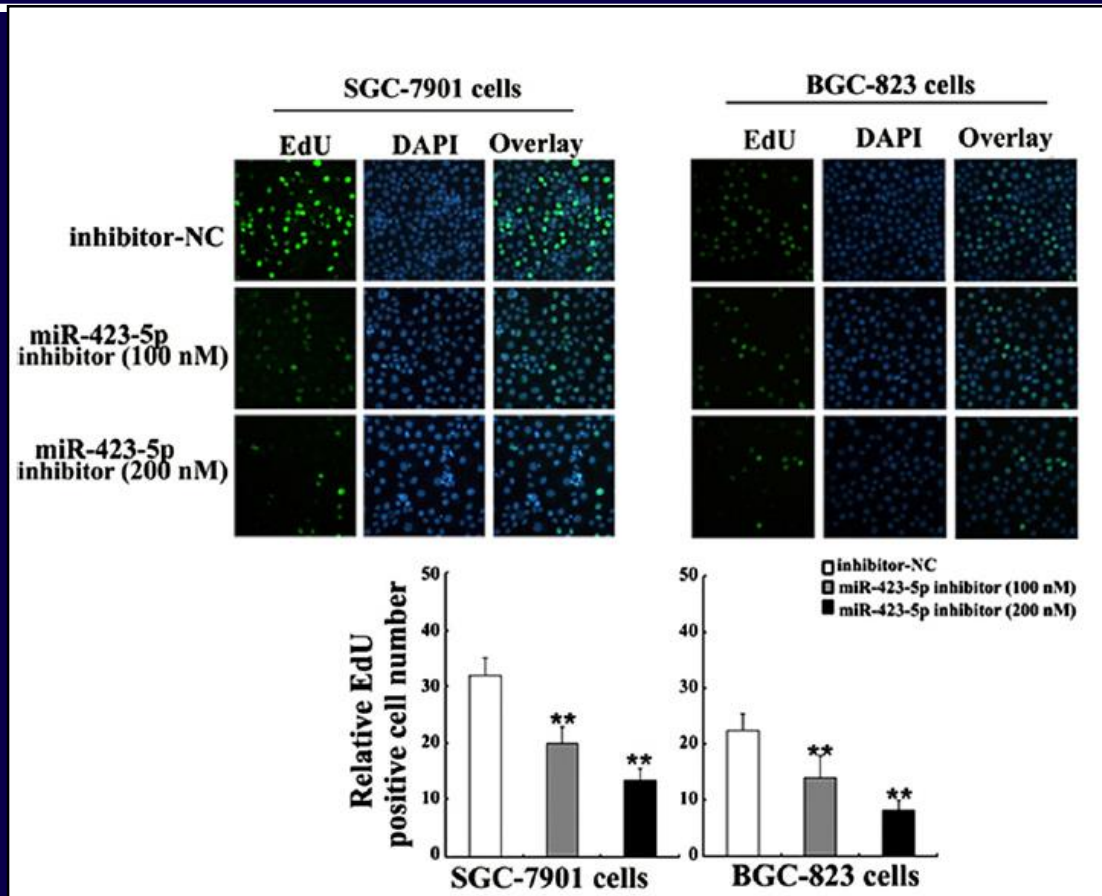
miRNA423-5p regulates cell proliferation and invasion by targeting TFF1 in GC cells



A. MTT检测细胞增殖



C. 流式细胞分析细胞周期



B. EDU检测细胞增殖

Fig. 3 miRNA-423-5p促进胃癌细胞增殖，抑制迁移、侵袭，诱导细胞周期G0/G1-S转换

转录因子SP3调控TFF2表达

The regulation of trefoil factor 2 expression by the transcription factor Sp3

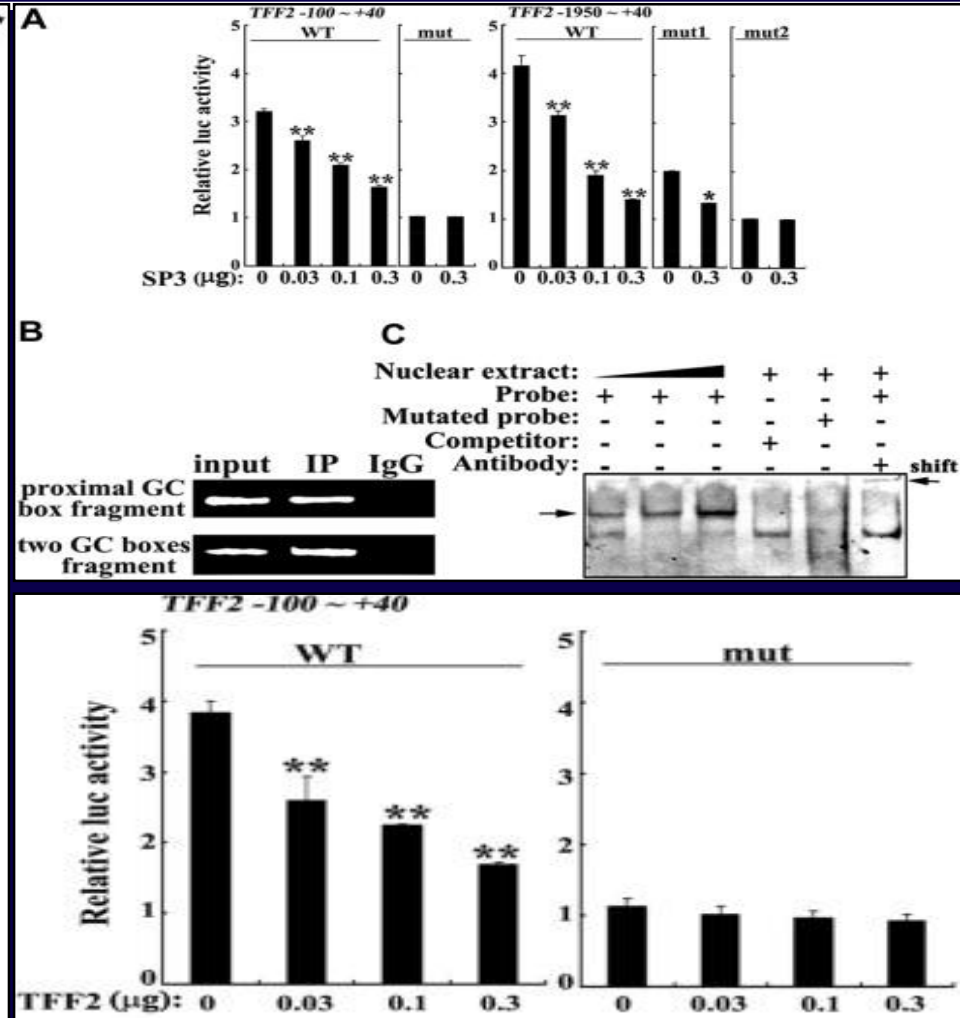
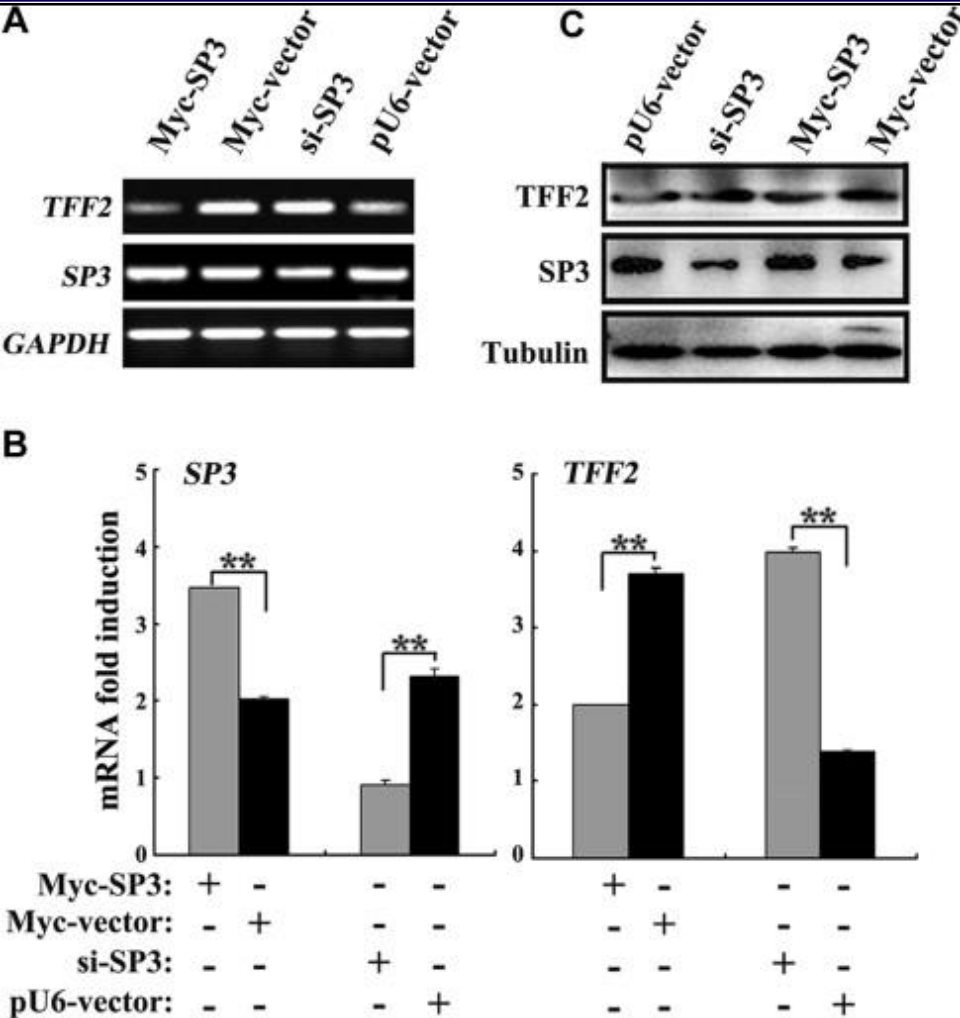
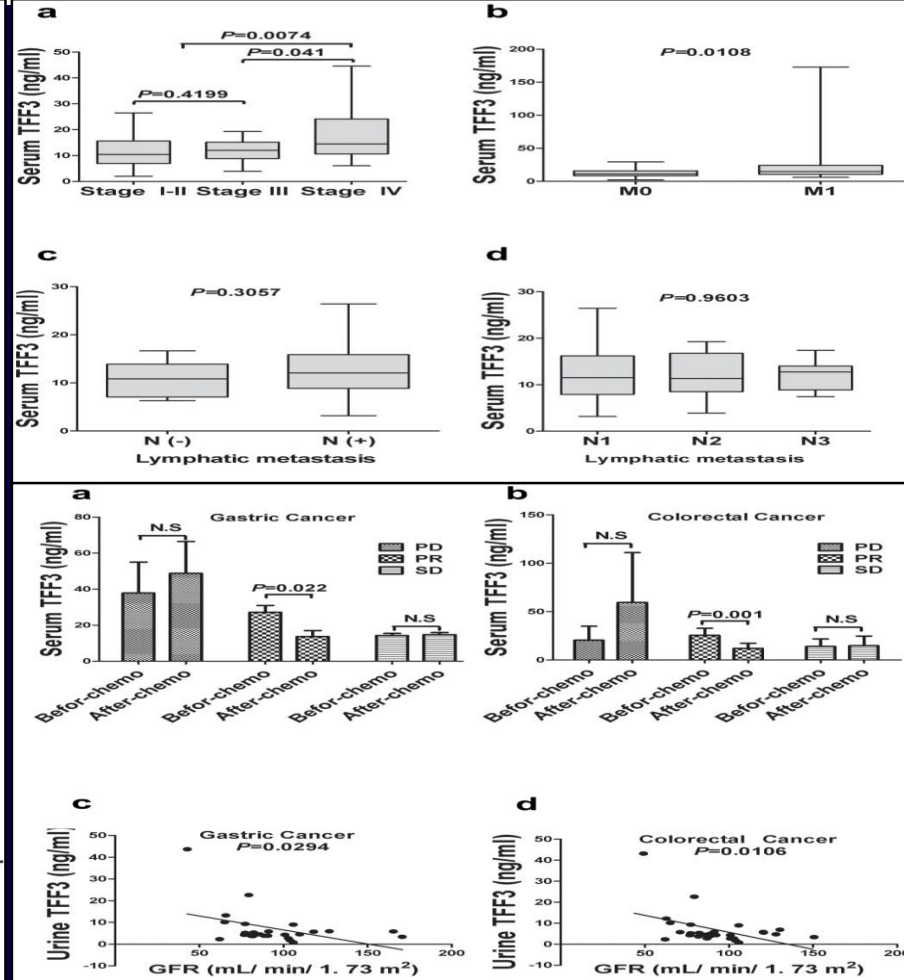
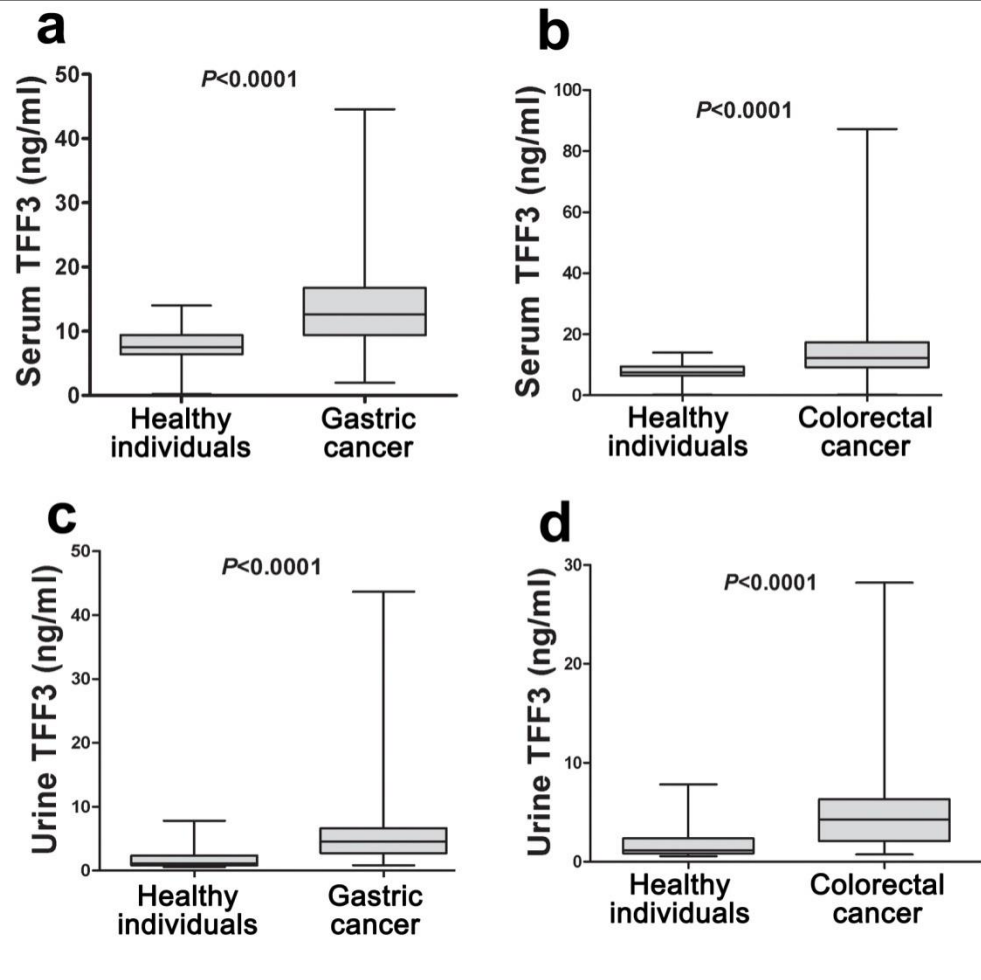


Fig. 1 胃粘膜上皮细胞GES-1中SP3负向调控TFF2表达

Fig. 3 TFF2剂量依赖性抑制SP3转录活性

血清及尿液TFF3 检测在胃肠道肿瘤诊断及化疗监测中的意义

Clinical significance in diagnosis and chemotherapy monitoring in patients with gastrointestinal cancer with tests for serum and urine levels of TFF3



胃癌与结直肠癌患者血清、尿液TFF3水平明显高于健康人群，血清TFF3水平可用于监测进展期胃癌和结直肠癌化疗疗效

Li Xiao, Yun-Peng Liu, Jian-Lin Ren et al.
BMC gastroenterology

缺氧条件下胃癌细胞株SGC-7901中TFF3诱导VEGF表达

TFF3 mediated induction of VEGF via hypoxia in human gastric cancer SGC-7901 cells

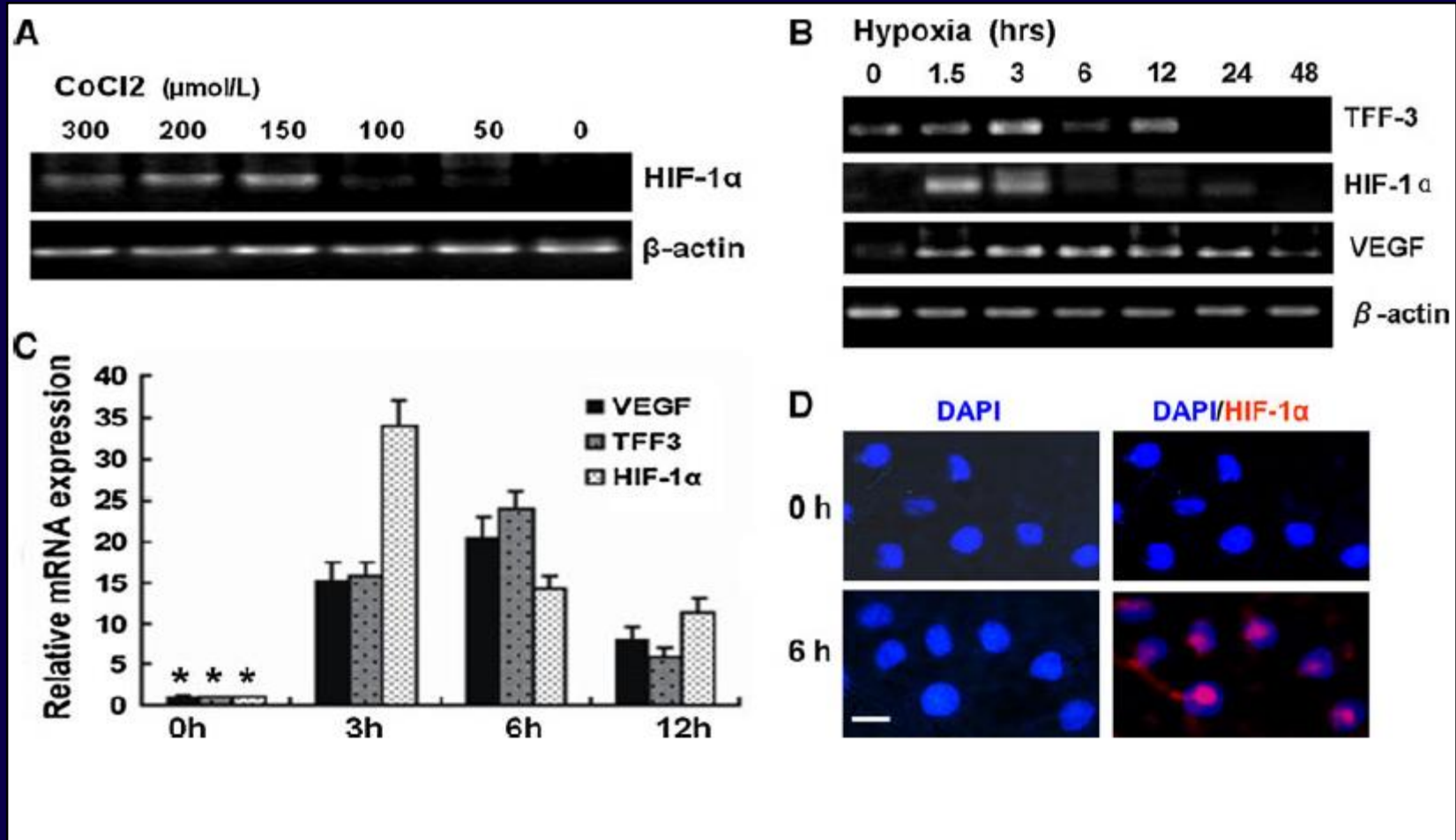


Fig.1 CoCl₂诱导缺氧条件下SGC-7901中HIF-1α、TFF3、VEGF表达升高

Guleng B, Han J, Ren JL et al. *Mol Biol Rep.* 2012;39:4127-4134

缺氧条件下胃癌细胞株SGC-7901中TFF3诱导VEGF表达

TFF3 mediated induction of VEGF via hypoxia in human gastric cancer SGC-7901 cells

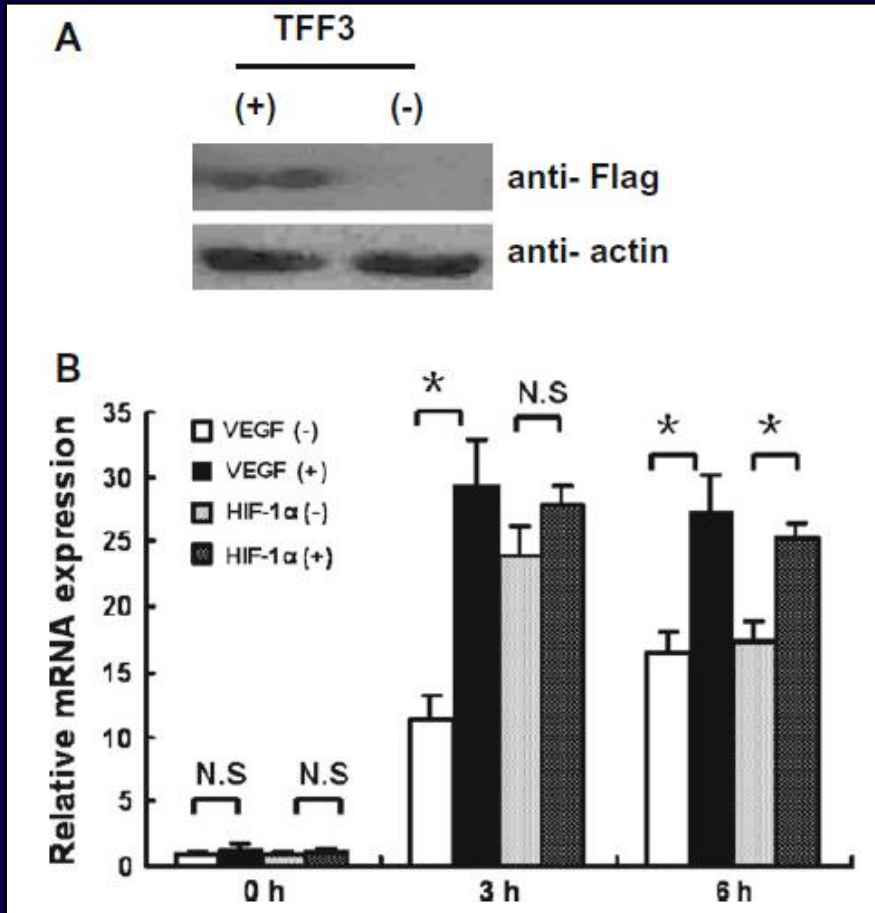


Fig. 2 缺氧条件下在SGC-7901中过表达TFF3增加VEGF、HIF-1α mRNA表达

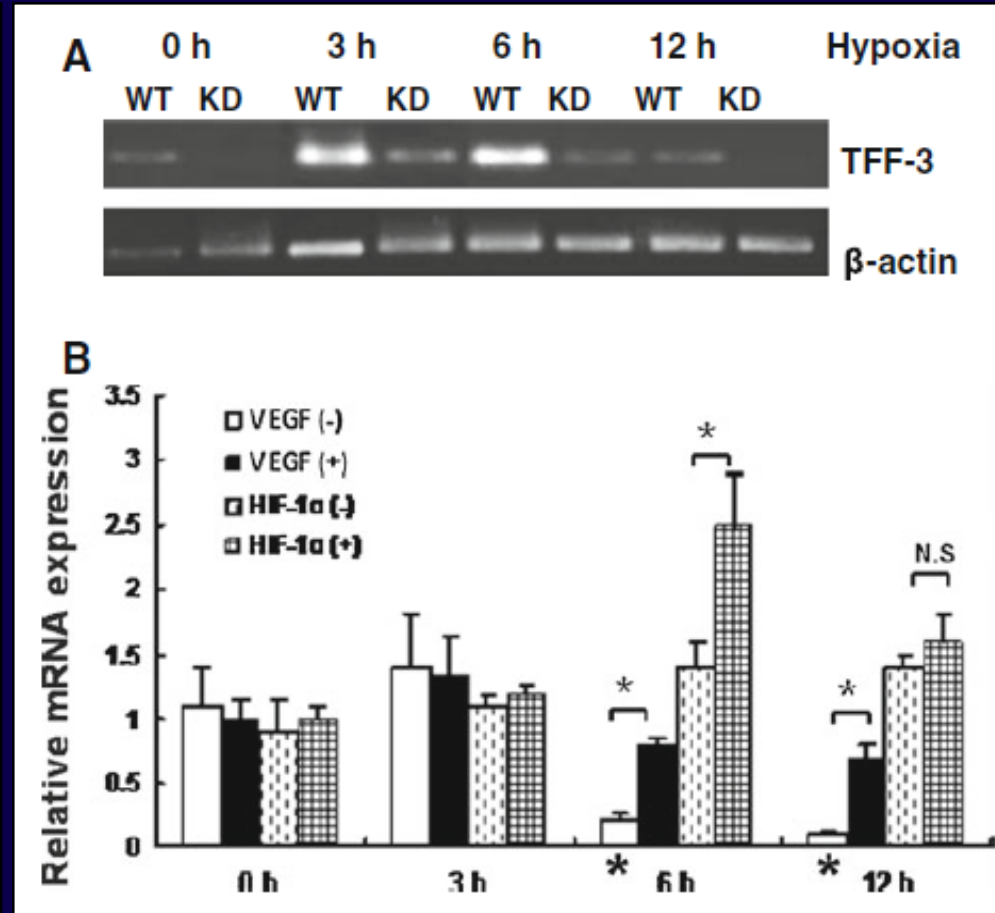
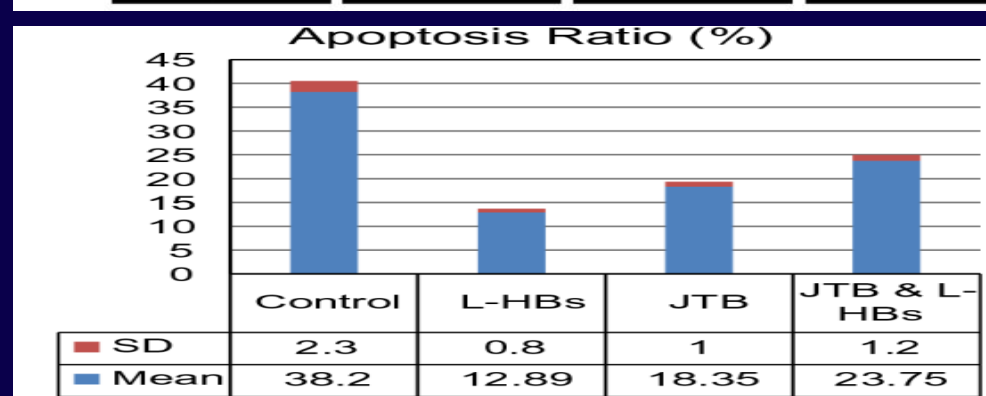
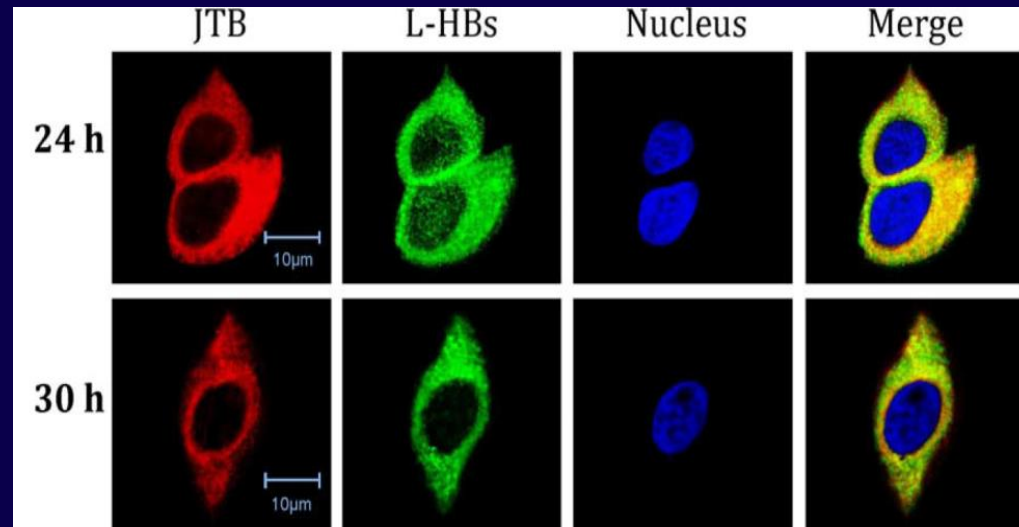
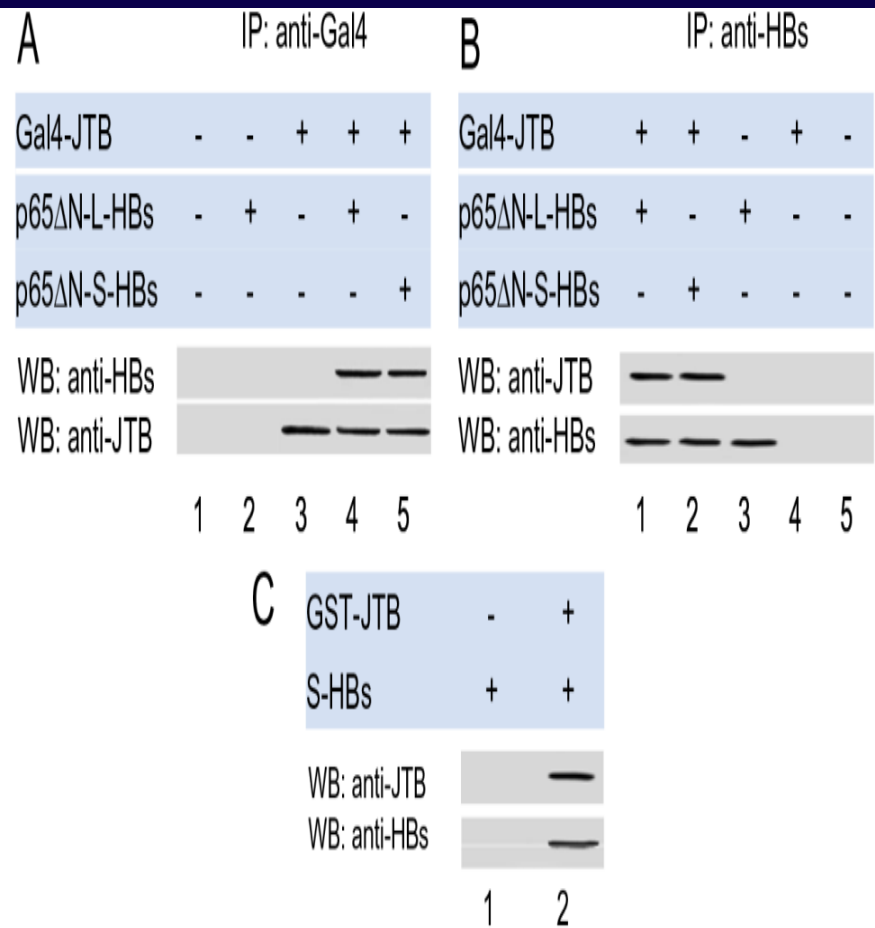


Fig. 3 缺氧条件下在SGC-7901中干扰TFF3减少VEGF、HIF-1α mRNA表达

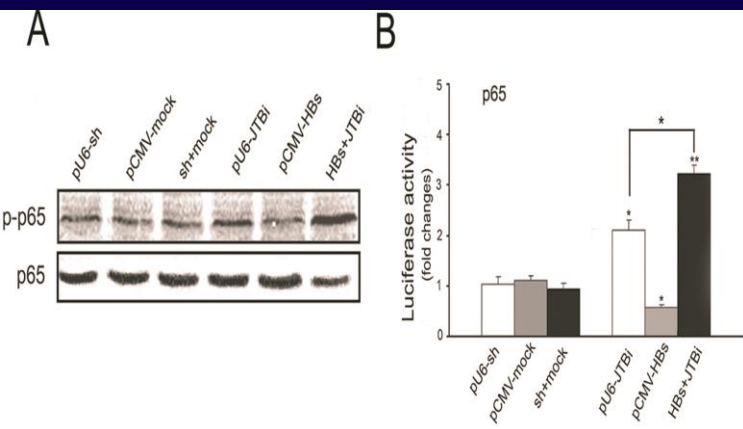
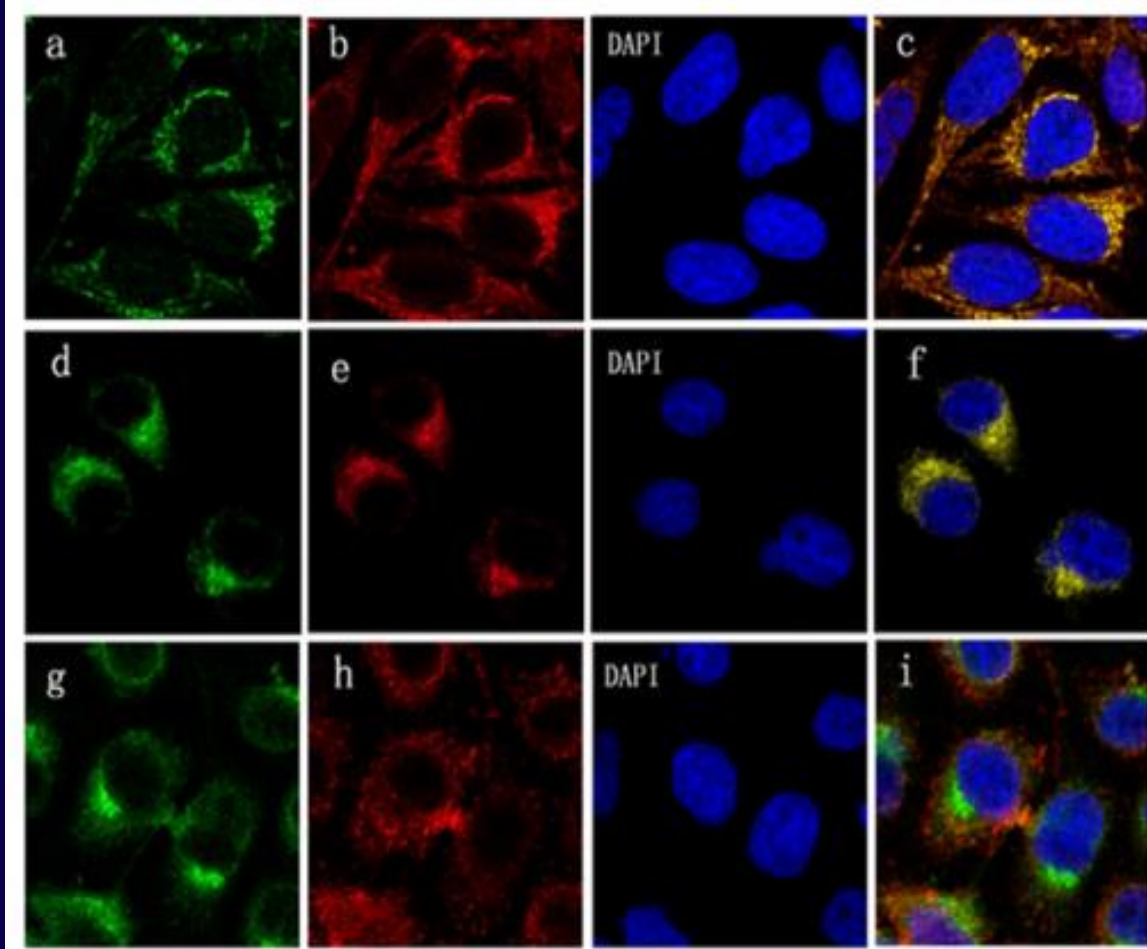
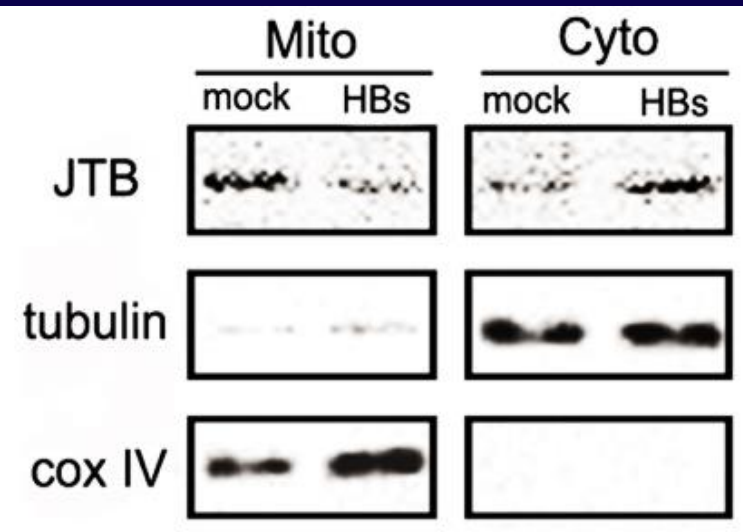
JTB与HBsAg相互结合的验证



免疫共沉淀实验显示外源表达HBsAg蛋白和JTB蛋白后，经过免疫共沉淀的正向和反向验证均证明HBsAg与JTB存在共结合现象。

Liu YP, Ren JL et al. HBsAg inhibits the translocation of JTB into mitochondria in HepG2 cells and potentially plays a role in HCC progression, PLoS One 7 (2012) e36914

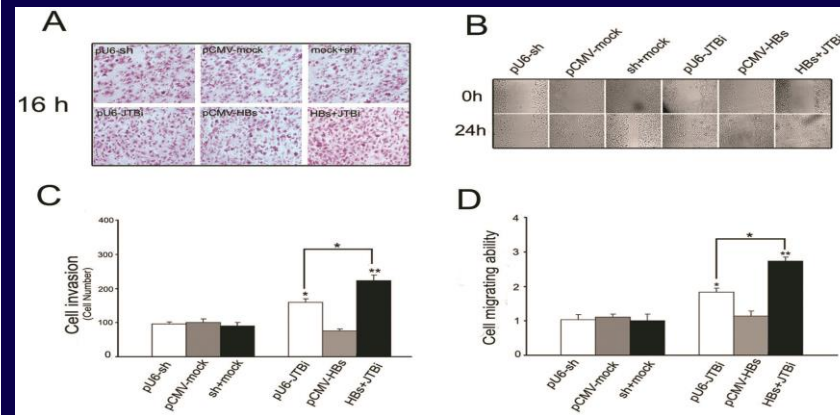
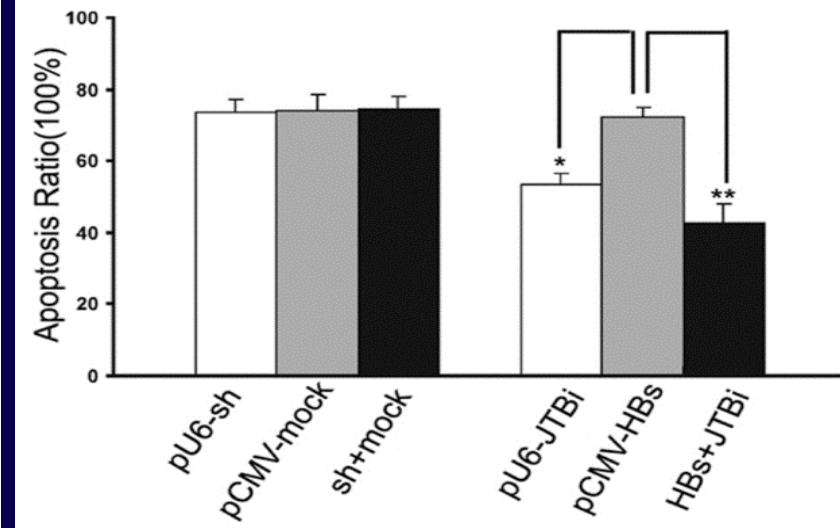
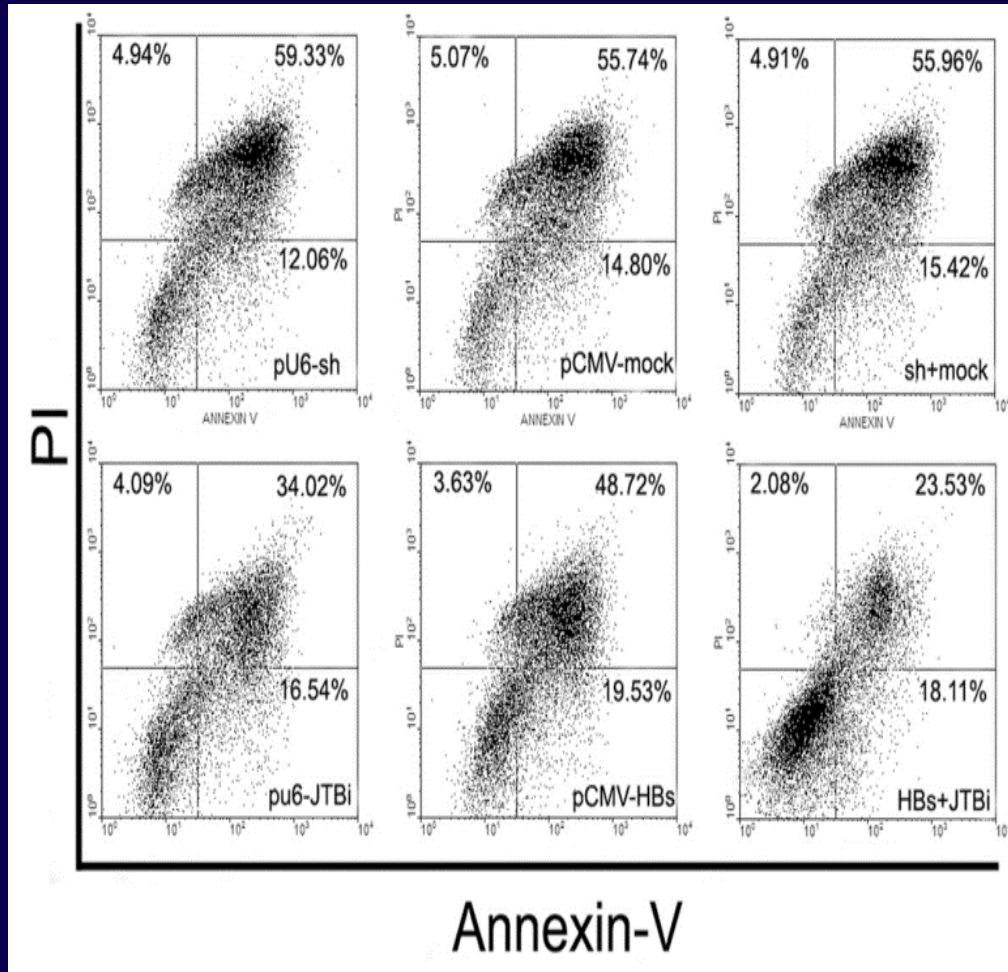
JTB与HBsAg相互作用促进肝癌细胞恶性进展



左图显示当细胞外源表达HBsAg时，JTB的细胞定位发生改变，线粒体中德JTB含量逐渐减少而细胞之中的JTB含量逐渐增多，说明HBsAg可以抑制JTB的线粒体定位过程。右图通过免疫荧光共聚焦的方法证明HBsAg的过表达可以使JTB与线粒体的共定位效应消失。验证了HBsAg对JTB的结合可以抑制JTB的线粒体定位。

Liu YP, Ren JL et al. HBsAg inhibits the translocation of JTB into mitochondria in HepG2 cells and potentially plays a role in HCC progression, PLoS One 7 (2012) e36914

JTB与HBsAg相互作用促进肝癌细胞恶性进展

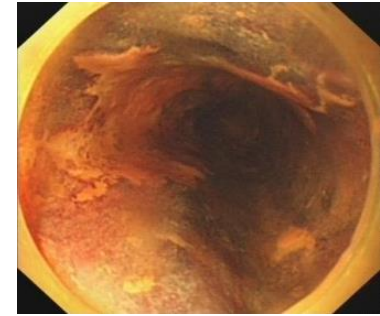
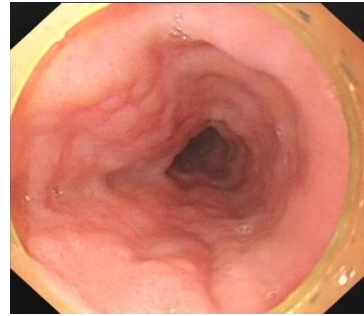


JTB与HBsAg的相互作用抑制氧化应激诱导的肝癌细胞凋亡，基因沉默JTB时细胞抗凋亡作用有所增强，当外源表达HBsAg的同时再基因沉默JTB时，抗凋亡能力明显增强。证明JTB与HBsAg均有协同作用。

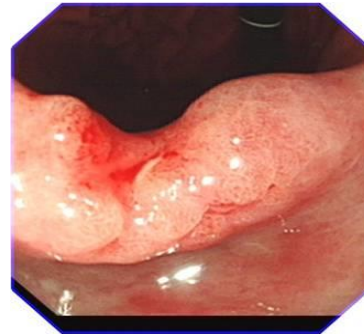
Liu YP, Ren JL et al. HBsAg inhibits the translocation of JTB into mitochondria in HepG2 cells and potentially plays a role in HCC progression, PLoS One 7 (2012) e36914

早癌诊断手段—染色内镜

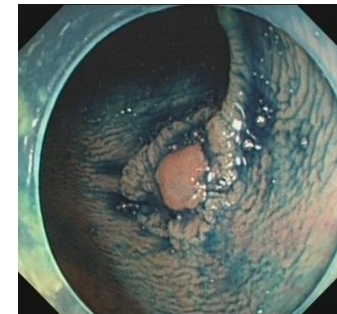
食管：Lugol`s碘染色



胃角：靛胭脂染色

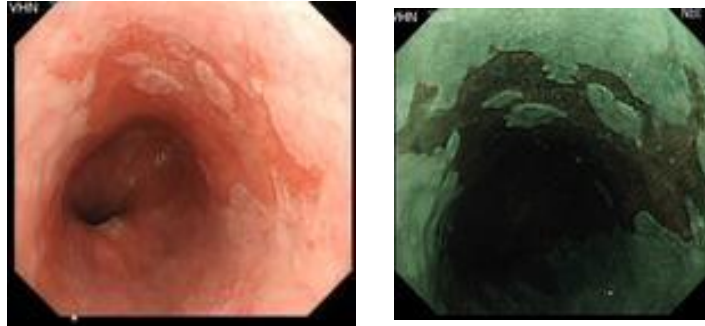


结肠：靛胭脂染色

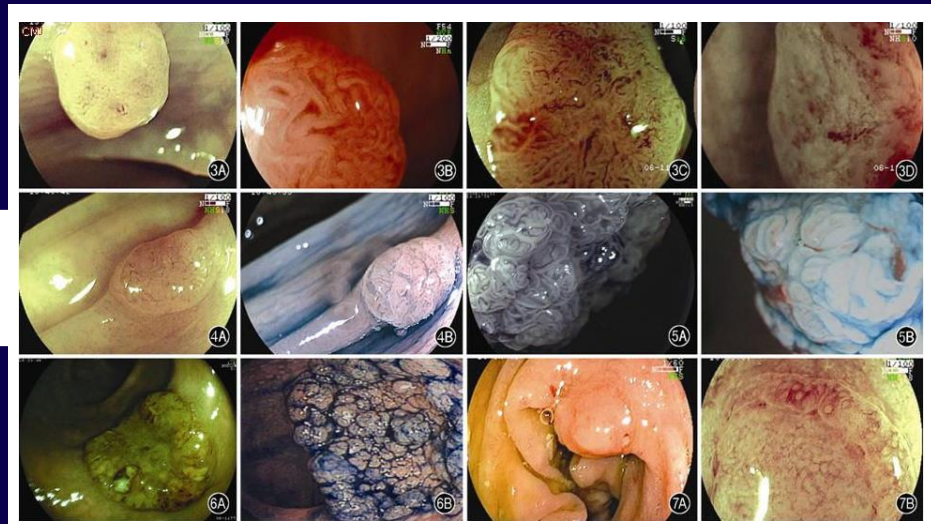


早癌诊断手段——电子染色内镜

NBI

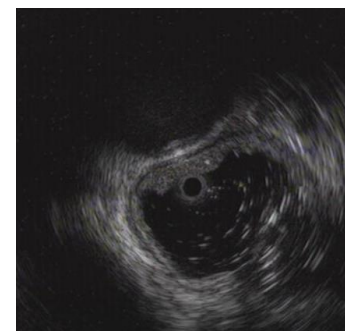
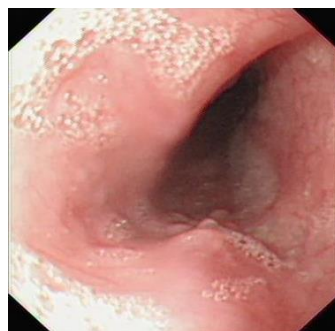


FICE

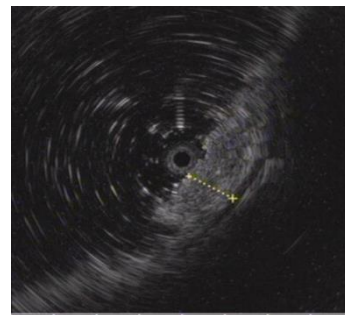


早癌诊断手段——超声内镜

食管早癌



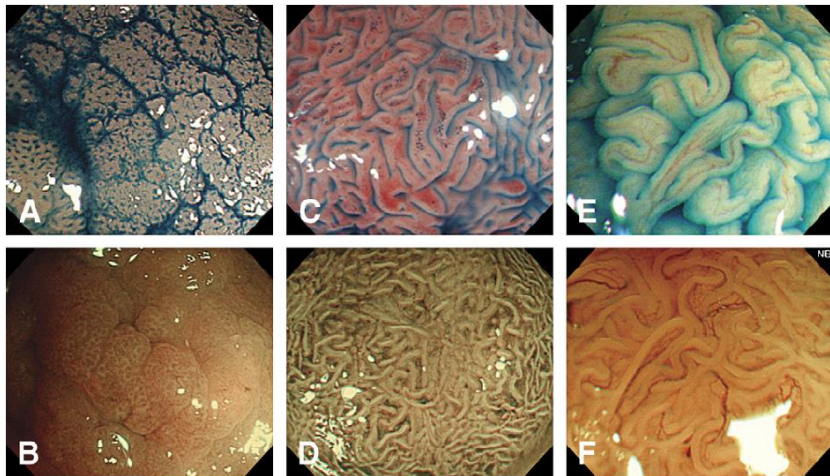
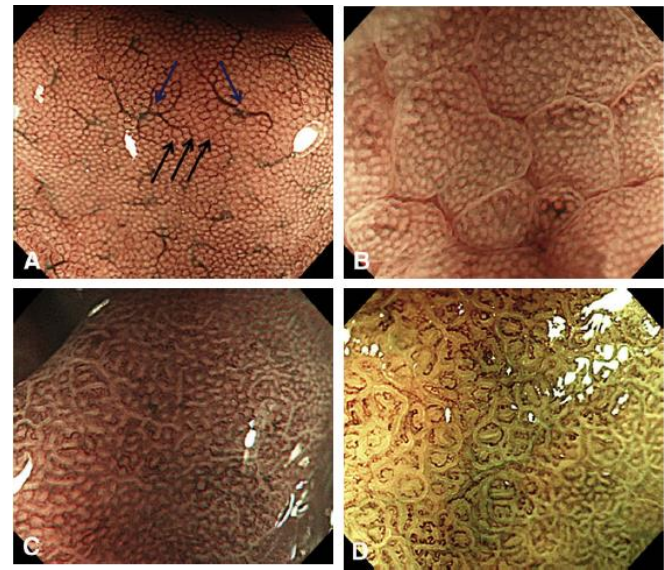
胃早癌



早癌诊断手段——放大内镜

胃早癌
(放大结合NBI)

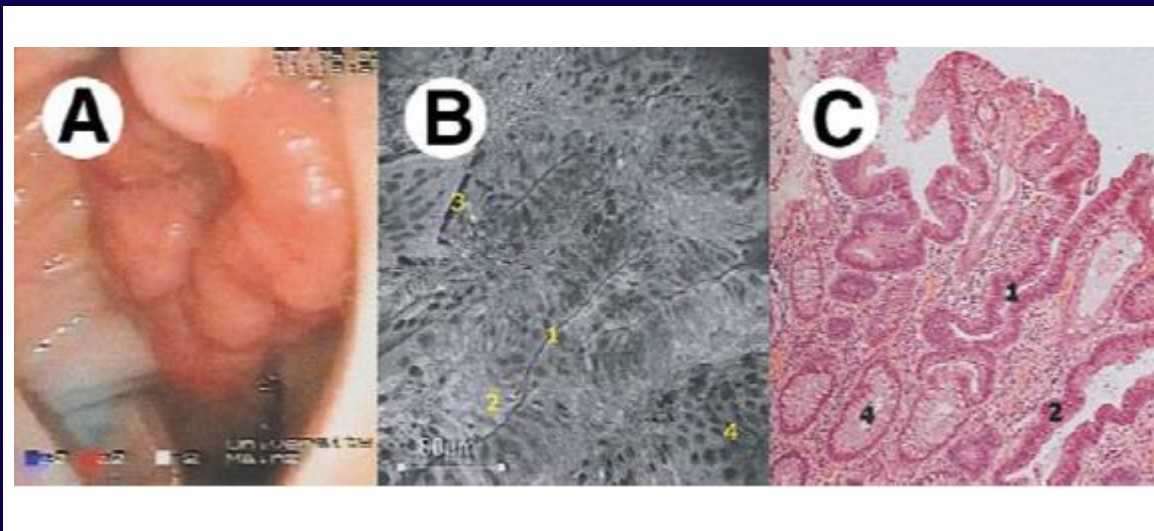
正常胃	异常1
异常2	异常3胃



II	III _L	IV
V	III _S	III _S

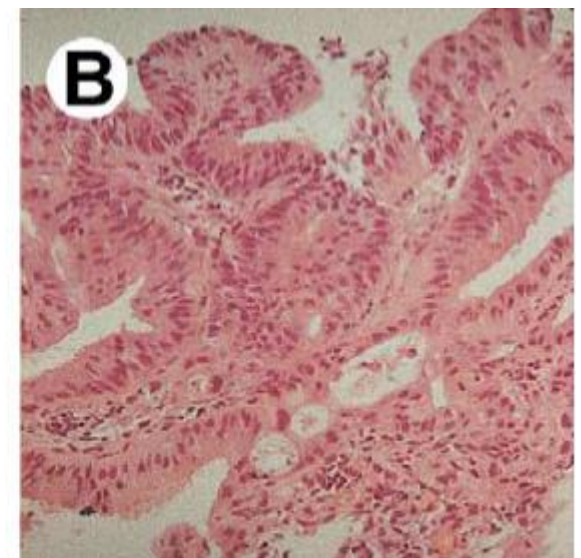
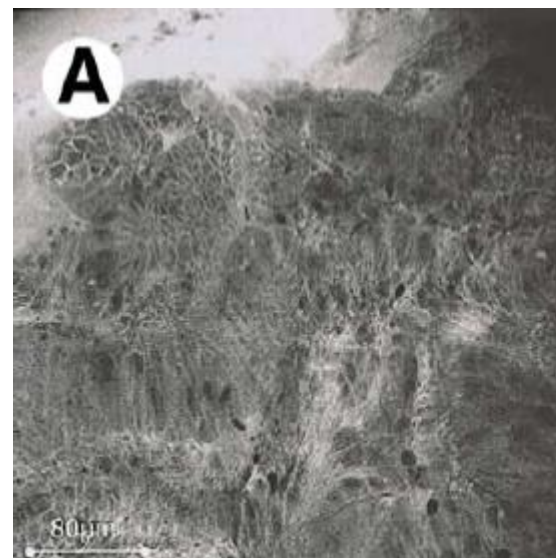
结肠病灶
(染色结合放大)

早癌诊断手段—激光共聚焦



腺瘤
(高级别上皮内瘤变)

肠癌



早期内镜治疗方法

- 激光治疗
 - Nd:YAG 激光治疗
 - 钬激光治疗
- 微波凝固治疗
- 光动力学疗法 (Photodynamic Therapy, PDT)
- 氩离子血浆凝固术 (Argon Plasma Coagulation, APC)
- 内镜黏膜切除术 (Endoscopic Mucosal Resection, EMR)
- 内镜黏膜下剥离术 (Endoscopic Submucosal Dissection, ESD)
- 射频消融 (Radiofrequency Ablation, RFA)



海峡两岸消化系肿瘤早期诊断和治疗基地

海峡两岸医药卫生交流协会消化病学专家委员会
厦门大学附属中山医院
新加坡国立大学医院
台湾大学附设台大医院
高雄医学大学附设医院
香港中文大学威尔斯亲王医院

拉曼内镜的研发及临床应用

- 厦门大学消化疾病研究所
厦门市消化疾病中心
- 厦门大学化学化工学院
- 新加坡国立大学医院
新加坡国立大学生物工程系

整合拉曼光谱内镜图谱

ATLAS OF HOLISTIC INTEGRATIVE
RAMAN SPECTROSCOPIC ENDOSCOPY

整合拉曼光谱内镜图谱

ATLAS OF HOLISTIC INTEGRATIVE
RAMAN SPECTROSCOPIC ENDOSCOPY



主审 | 樊代明 沈祖尧 (香港) 李兆申
主编 | 任建林 何克裕 (新加坡) 黄志伟 (新加坡)



人民卫生出版社

Confocal Raman probe

Excitation
fiber



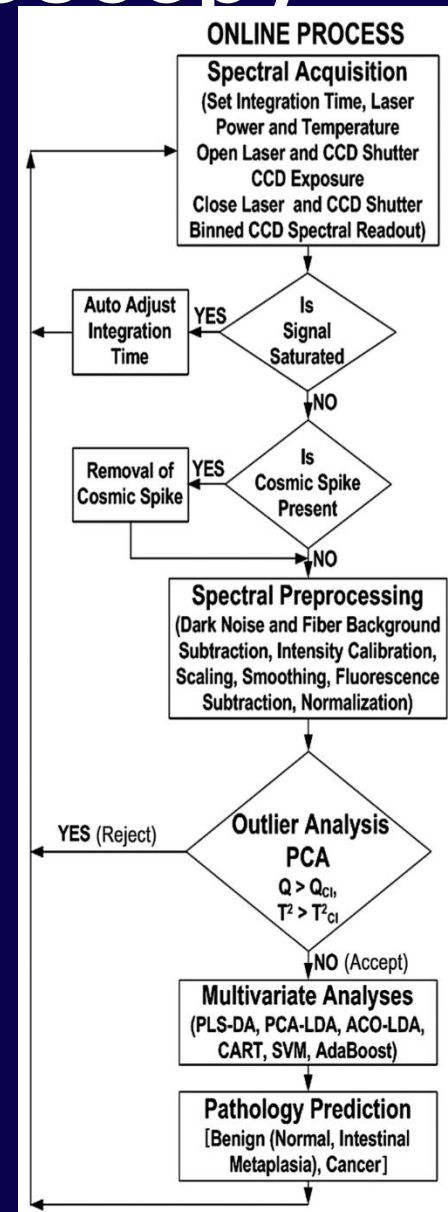
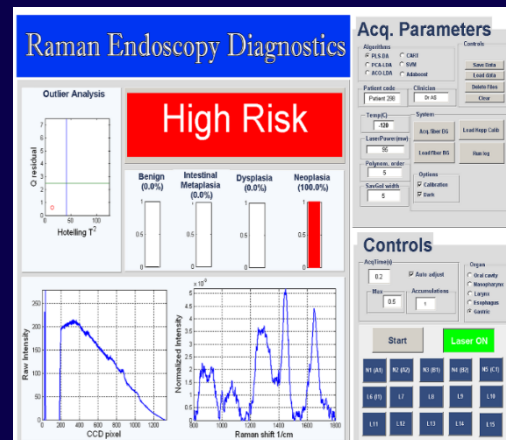
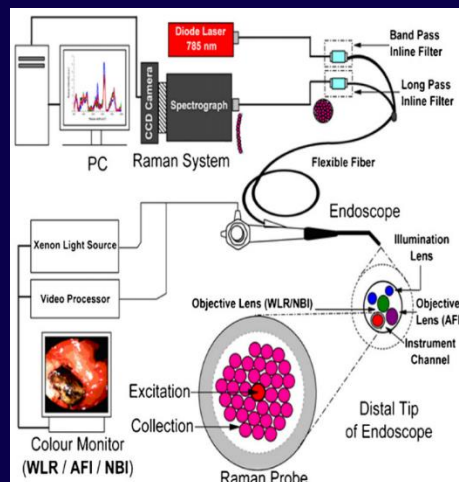
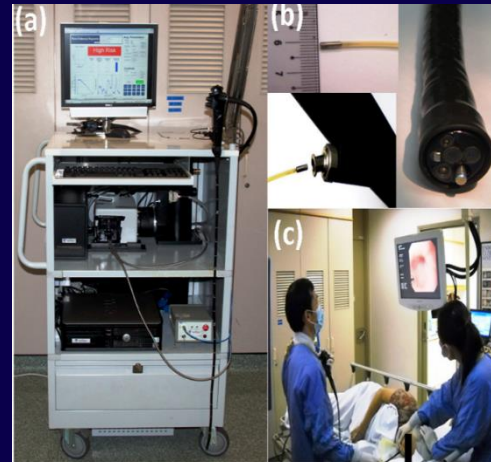
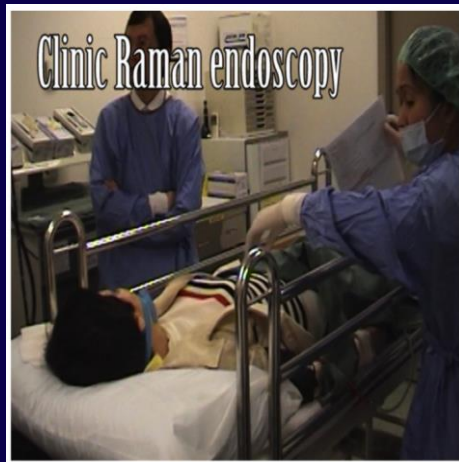
人民卫生出版社
PEOPLE'S MEDICAL PUBLISHING HOUSE

Epithelium
Stroma

AFT WLR/NBI

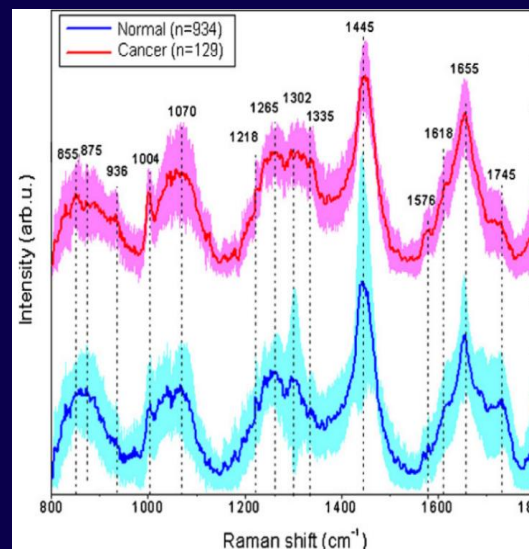
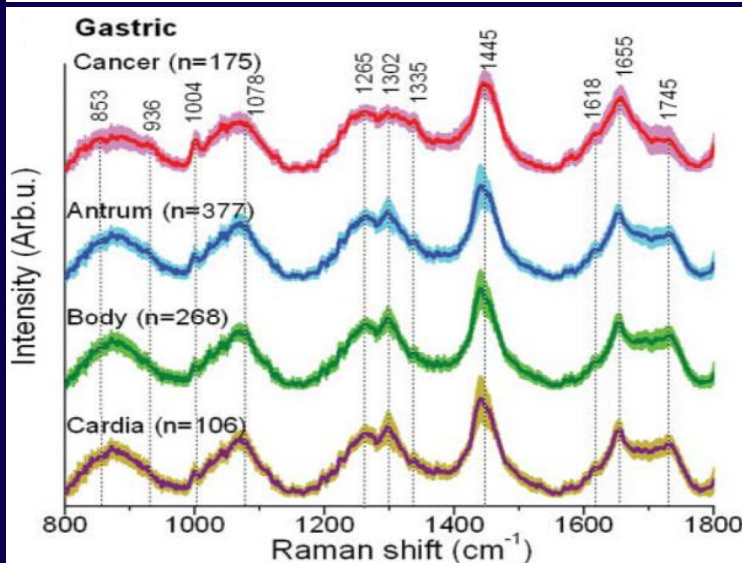
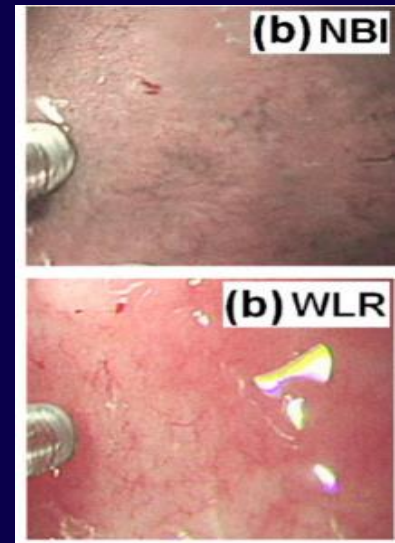
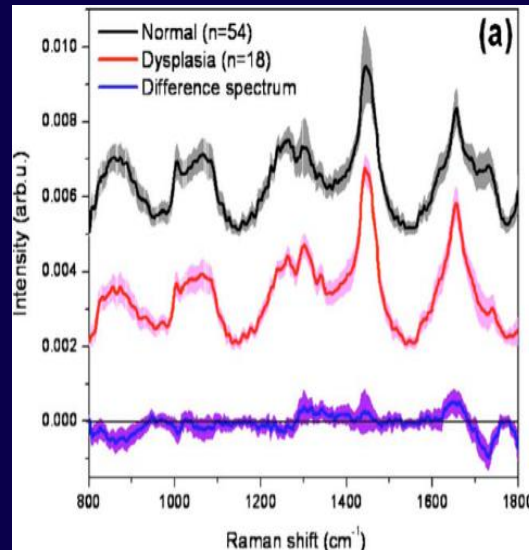
Distal tip of
endoscope

Clinic Raman endoscopy



Raman endoscopy and Gastric Cancer

853	ν (C-C)	proteins (collagen)
936	ν (C-C) in α conformation	proteins
1004	ν_s (C-C) breathing	proteins (phenylalanine)
1078	ν (C-C)	lipids
1265	Amide III ν (C-N) δ (N-H)	proteins
1302	δ (CH ₂)	proteins/lipids
1335	CH ₃ CH ₂ wagging mode	DNA/proteins
1445	δ (CH ₂)	lipids/proteins
1618	ν (C = C)	porphyrins
1655	Amide I ν (C = O)	proteins/lipids
1745	ν (C = O)	lipids

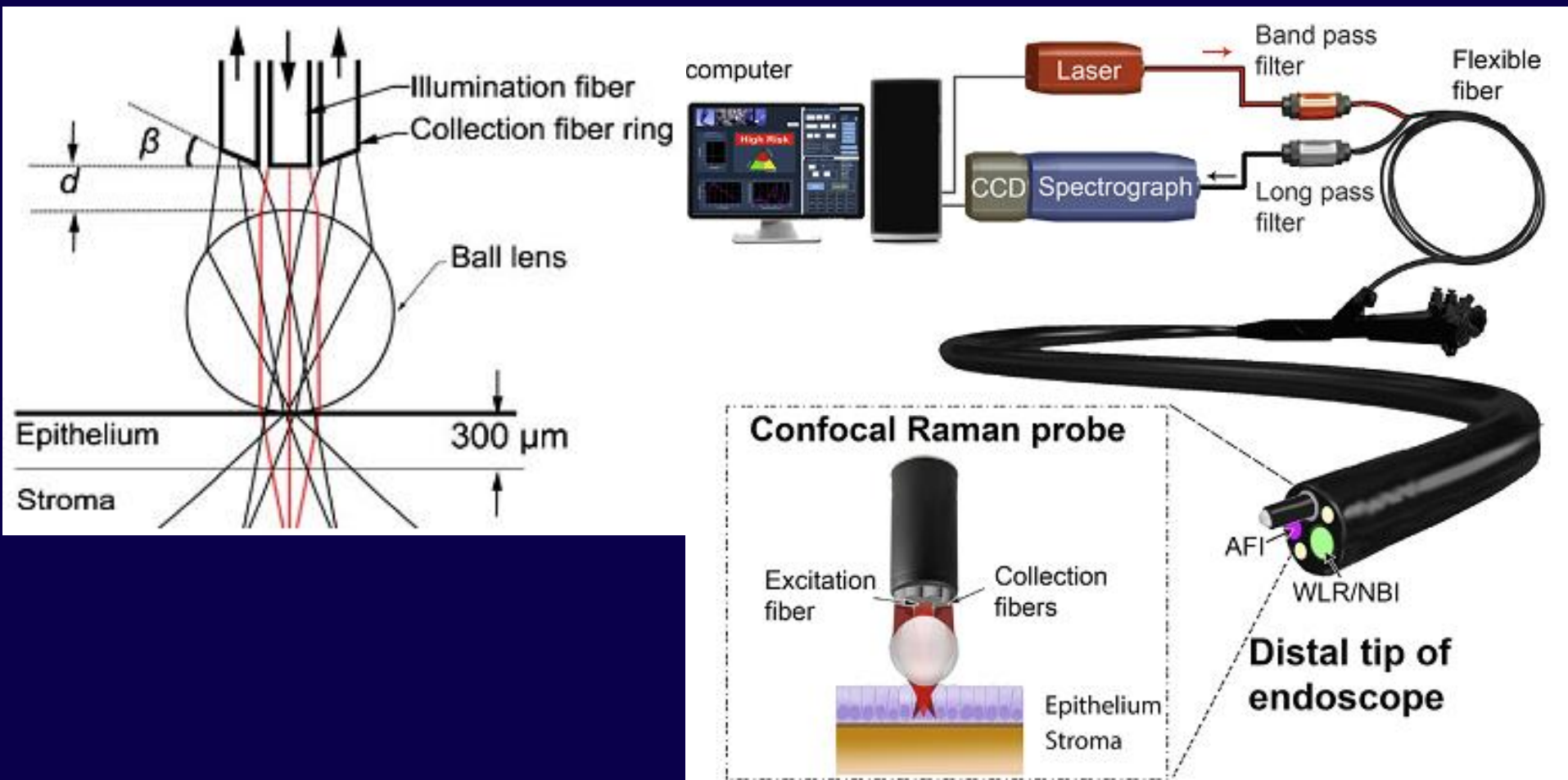


Journal of Biomedical Optics 16(2011)
Journal of Biomedical Optics 153(2010)

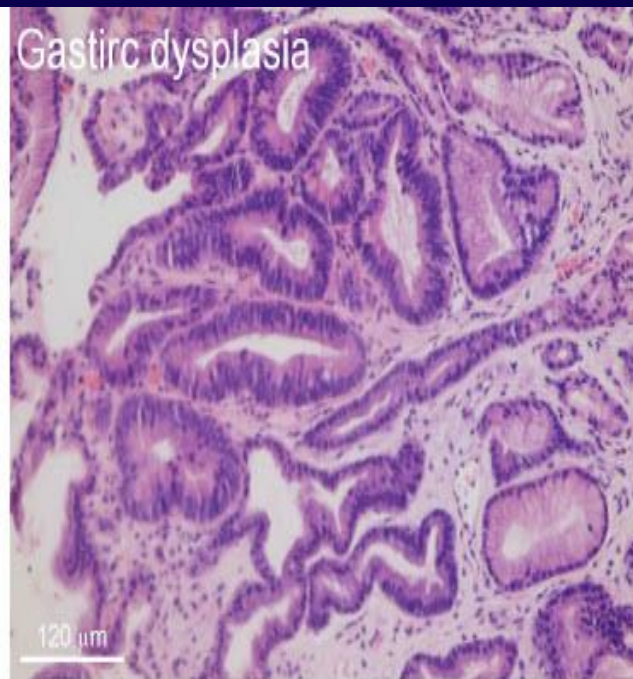
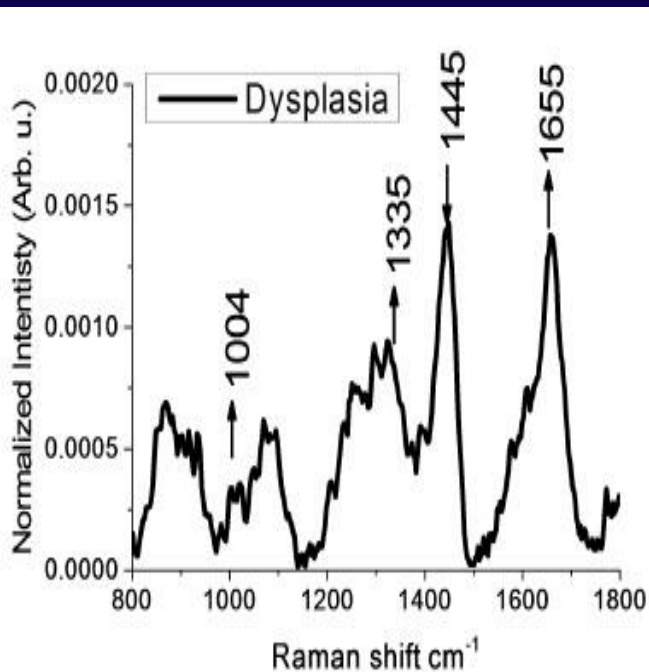
Biosensors and Bioelectronics 26 (2010)

Confocal Raman Spectroscopy

- Near-infrared diode laser (785 nm)
- Raman spectrum range 800 - 1800 cm^{-1} , Spectral resolution $\sim 9 \text{ cm}^{-1}$
- Raman probe comprises 9 x 200 μm filter-coated fibers, beveled angle (β) $\sim 20^\circ$, NA = 0.22
- Sapphire ball lens ($d = 1.0 \text{ mm}$, NA = 1.78)



Raman endoscopy and Gastric Cancer



In vivo Raman spectrum of gastric dysplasia. Dysplastic tissue shows relative increase protein (1004cm^{-1} (ν_s (C-C) ring breathing of phenylalanine) 1655cm^{-1} (amide I ν (C=O) of proteins)) and DNA content (1335cm^{-1} (adenine, guanine)) and decreased lipid content (1445cm^{-1} (δ (CH_2) deformation of lipids),)

胃异型增生的活体拉曼光谱。由拉曼光谱变化可知，异型增生组织的蛋白质（ 1004cm^{-1} ：苯环对称 C-C 键呼吸振动； 1655cm^{-1} ：蛋白质酰胺 I C=O 键振动）和 DNA（ 1335cm^{-1} ：核酸，腺嘌呤，鸟嘌呤）成分增加，同时脂质成分（ 1445cm^{-1} ：蛋白质和脂质的 CH_2 弯曲振动形变）减少。

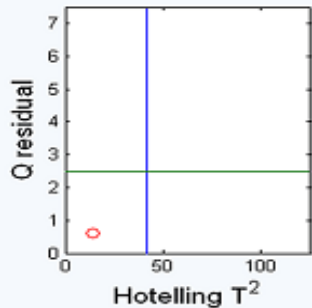
Confocal Raman Spectroscopy

Software for real-time data acquisition and diagnosis

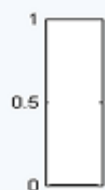
Raman Endoscopy Diagnostics

High Risk

Outlier Analysis



Benign
(0.0%)



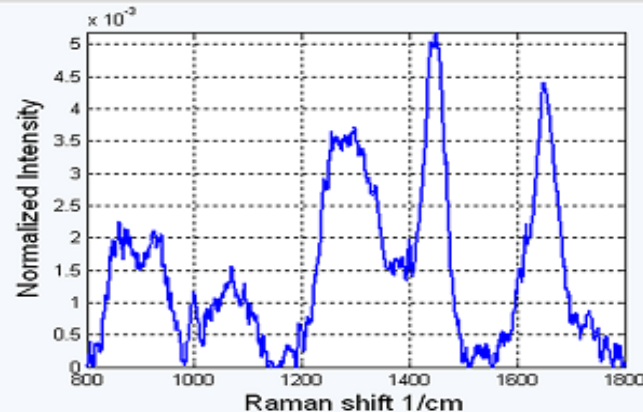
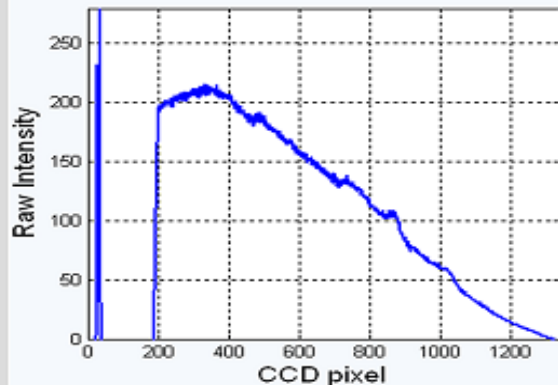
Intestinal
Metaplasia
(0.0%)



Dysplasia
(0.0%)



Neoplasia
(100.0%)



Acq. Parameters

Algorithms

- PLS-DA CART
 PCA-LDA SVM
 ACO-LDA Adaboost

Controls

- Save Data
Load data
Delete Files
Clear

Patient code

Patient 298

Clinician

Dr AS

Temp(C)

-120

LaserPower(mw)

95

Polynom. order

5

SavGol width

5

System

Acq. fiber BG

Load Kopp Calib

Load fiber BG

Run log

Options

- Calibration
 Dark

Controls

AcqTime(s)

0.2

Auto adjust

Max

0.5

Accumulations

1

Organ

- Oral cavity
 Nasopharynx
 Larynx
 Esophagus
 Gastric

Start

Laser ON

N1 (A1)

N2 (A2)

N3 (B1)

N4 (B2)

N5 (C1)

L6 (I1)

L7

L8

L9

L10

L11

L12

L13

L14

L15

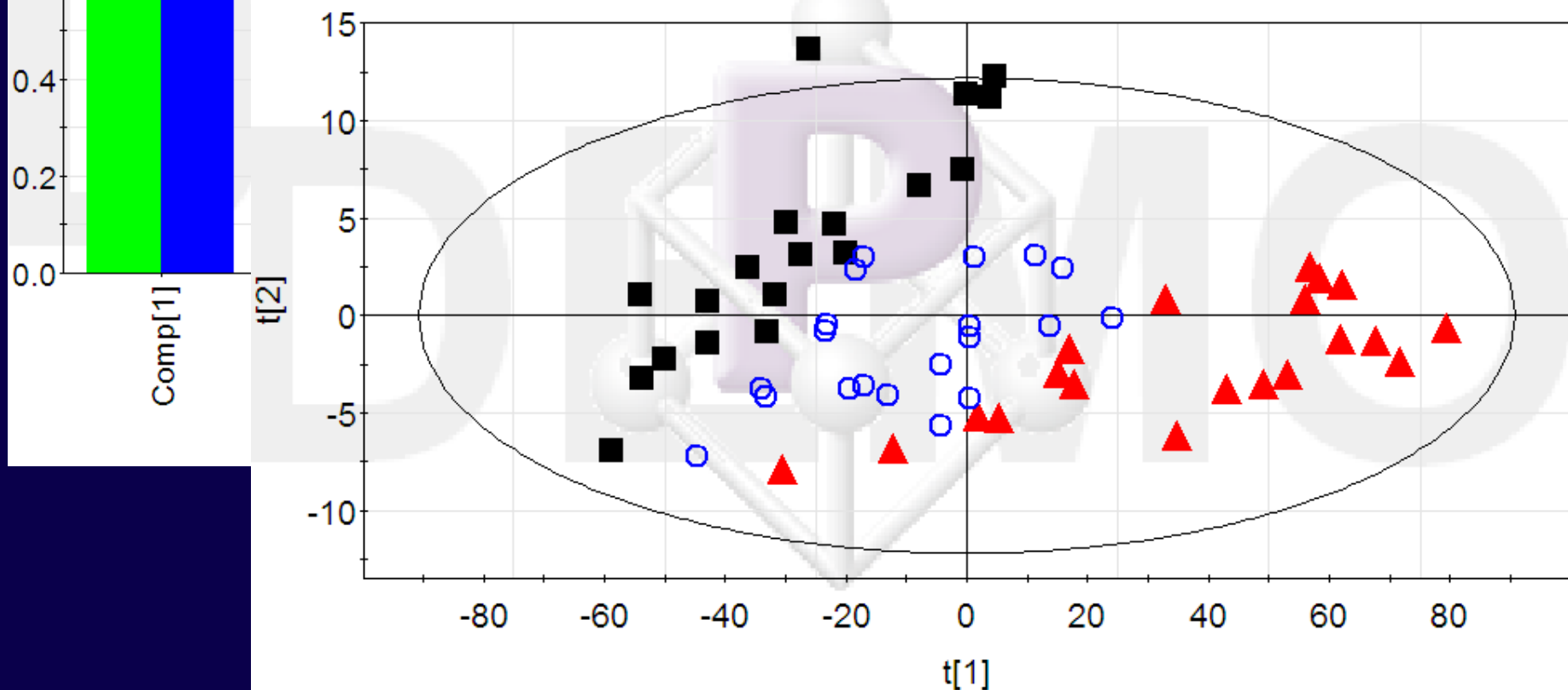
1127.M1 (PCA-X)

R2X(cum)
Q2(cum)

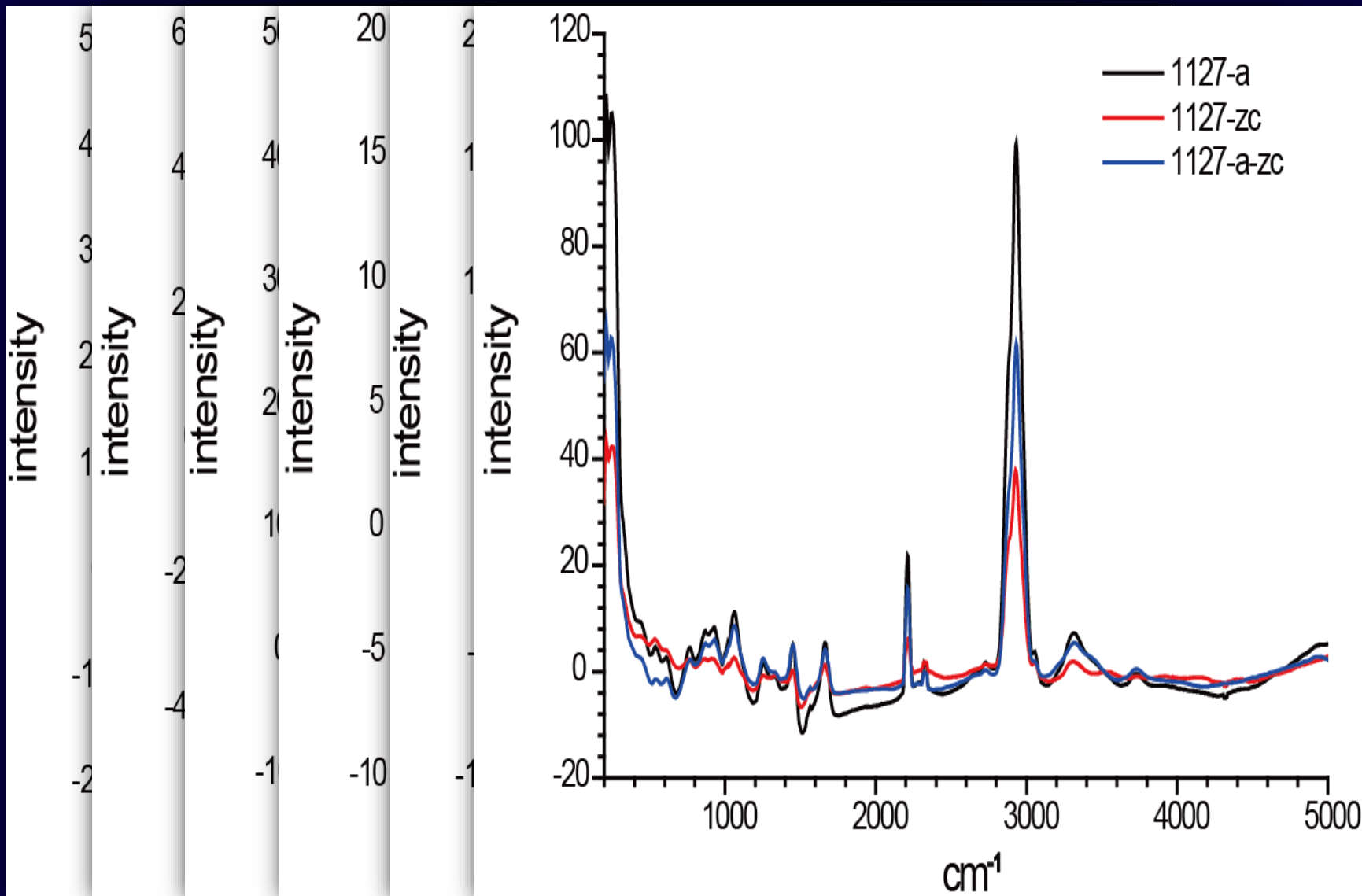


1127.M1 (PCA-X)

■ 1127-c
▲ 1127-n
○ 1127-nnc



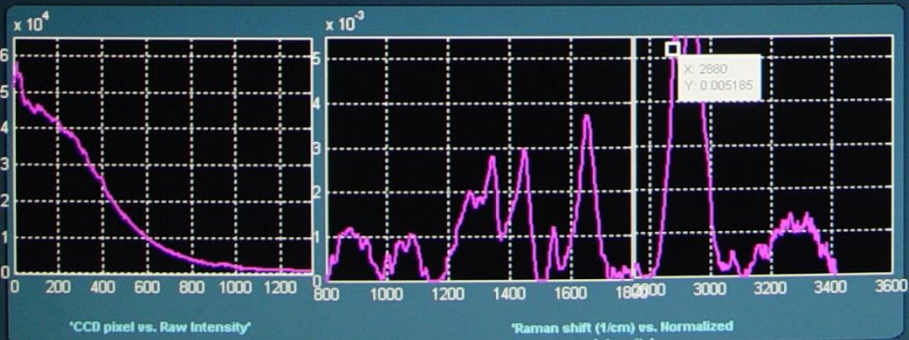
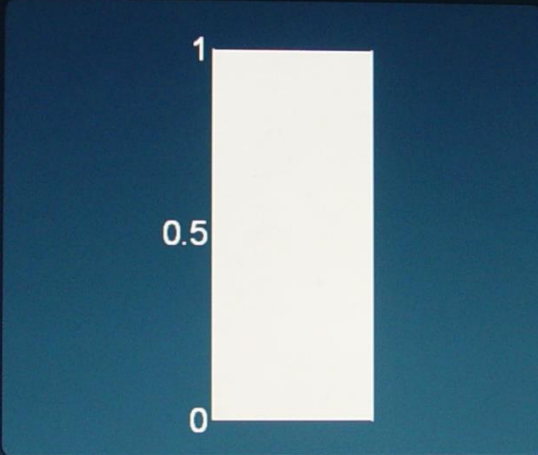
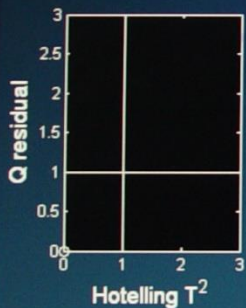
RAMAN IMAGING AND HISTOLOGICAL CHANGES





Normal

CONTACT VERIFICATION



PARAMETERS

XCRR004 43 m

Clinician: Xu **Endoscope RoomNo:** EG-450MR5 2

LaserPower(mw): 51 **Temp(C):** -70.5

Analysis:
 PLS-DA 3 class
 PLS-DA 2 class
 Custom

Diagnosis:
 ON
 OFF

Controls: Spec

Save Data
Load Data
Delete Spec
Clear Files
ProcessData
Load Dark
System Calibration

CONTROLS

AcqTime(s): 0.634024 Auto adjust

Max: 0.7 **Accumulations:** 1

ORGAN:

- Oral cavity Colon
- Nasopharynx Cervix
- Larynx Bladder
- Esophagus
- Gastric

Stop Laser ON

Site 1	Site 2	Site 3	Site 4	Site 5
Site 6	Site 7	Site 8	Site 9	Site 10
Site 11	Site 12	Site 13	Site 14	Site 15



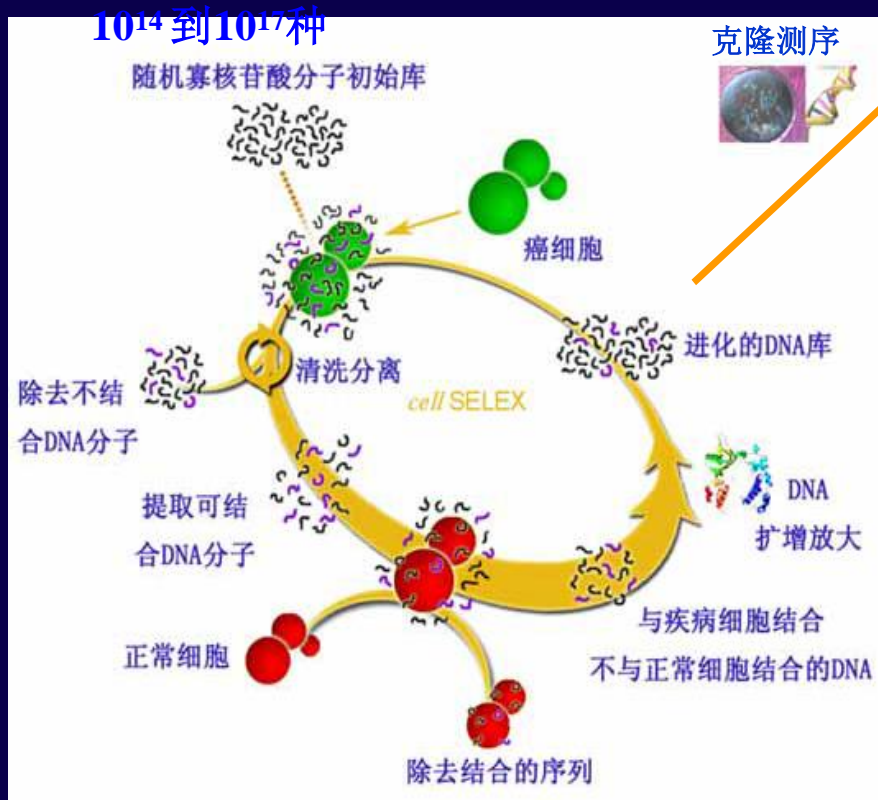
Patients and Sites number

- 175 patients recruited (in 6 weeks)
- 404 tissue sites measured (~4500 spectra)

Histopathology		Patient	Site
Normal (N)		<u>72</u>	168
Intestinal metaplasia (IM)		<u>52</u>	108
	Mild	32	
	Moderate	12	
	Severe	8	
Dysplasia (D)		<u>39</u>	92
	Atypical Hyperplasia (ATH)	28	
	Low-grade (LGIN)	8	
	High-grade (HGIN)	3	
Cancer (CA)		<u>12</u>	36

特异性核酸适体的合成筛选

指数级富集的配体系统进化法 (SELEX)



ATCG.....
核酸适体

癌变组织



◆ 针对不同癌细胞的核酸适体筛选

◆ 胃癌、肠癌、肝癌等

◆ 针对普适性肿瘤标志物的筛选

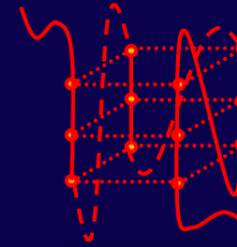
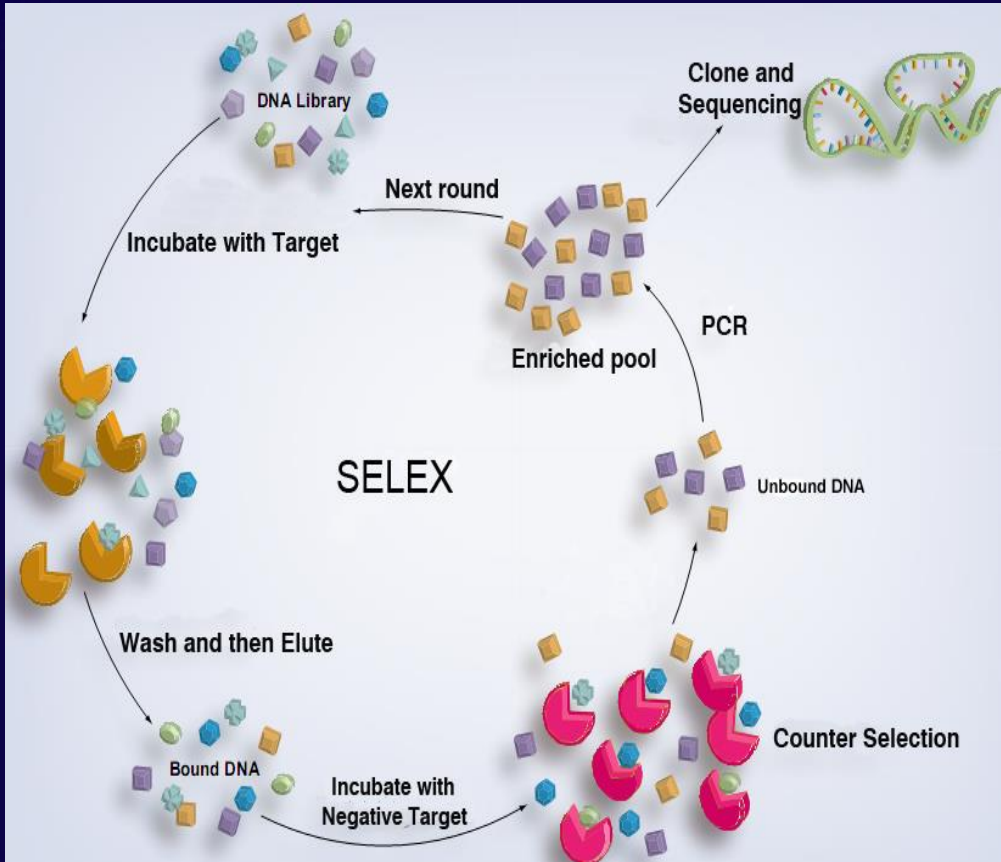
◆ 上皮细胞粘附分子EpCAM

◆ 肿瘤标志蛋白AGR2

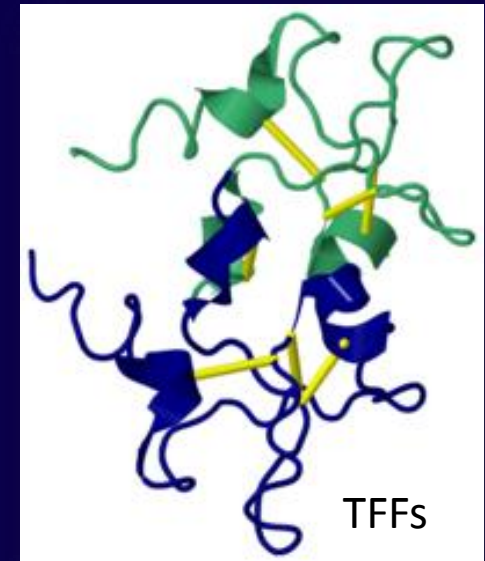
◆ 肝癌标志物GPC3

Defensive Factor

TFFs



Structure of aptamer



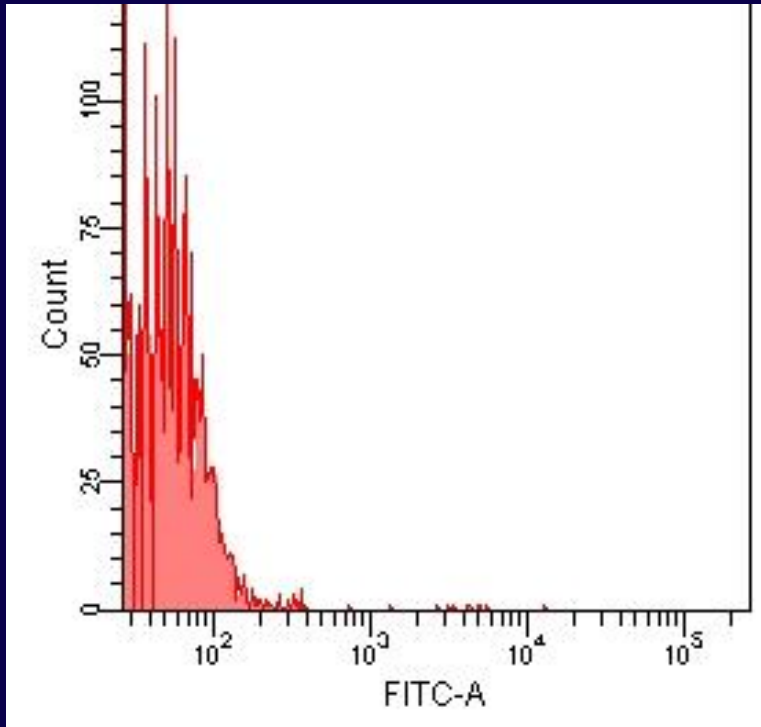
TFFs

Early molecular diagnosis

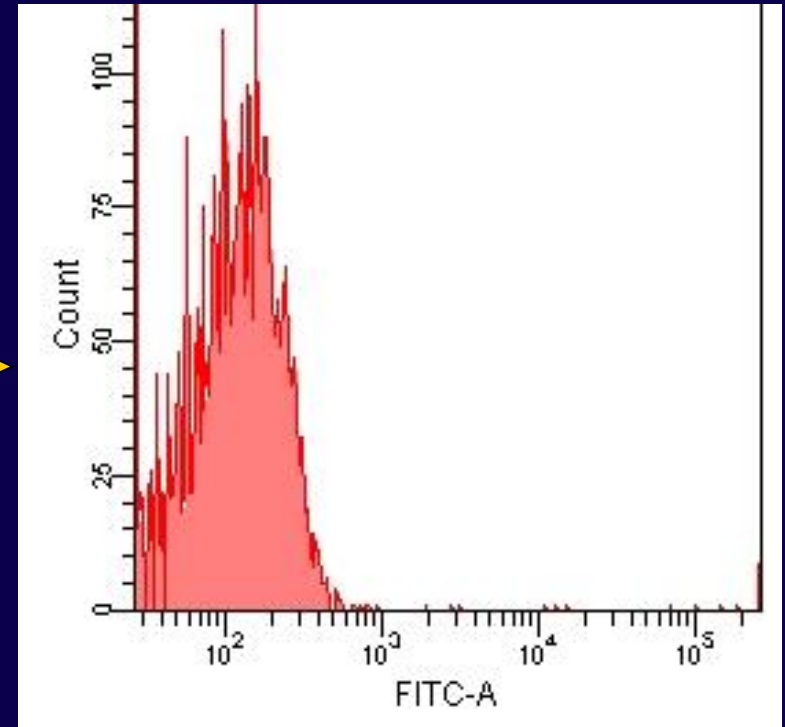
Targeted therapy

Defensive Factor

TFFs



0 cycle



15th

Screening of TFF3 aptamer

微生物生态与人类健康

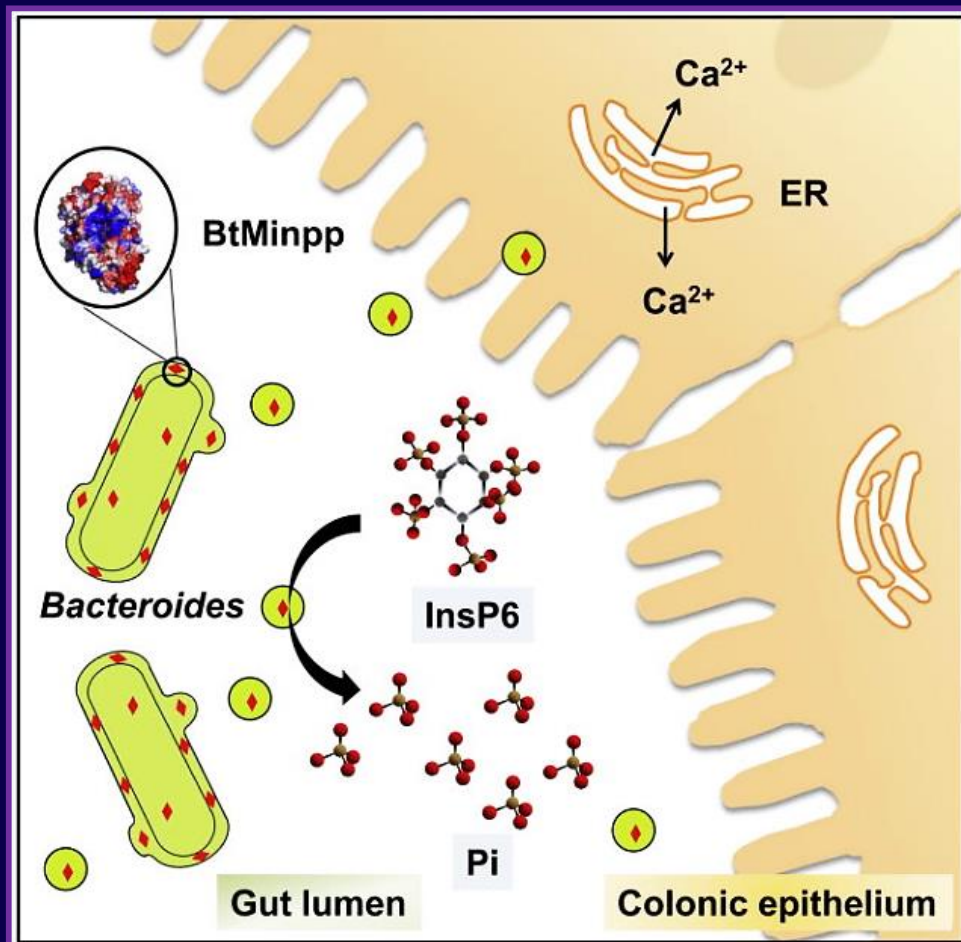
- 胃肠粘膜与胃肠微生物生态
- 粪菌移植
- 消化系分子影像
- 3D打印—消化系统

厦门大学化工学院

厦门大学分子影像中心

厦门大学材料学院

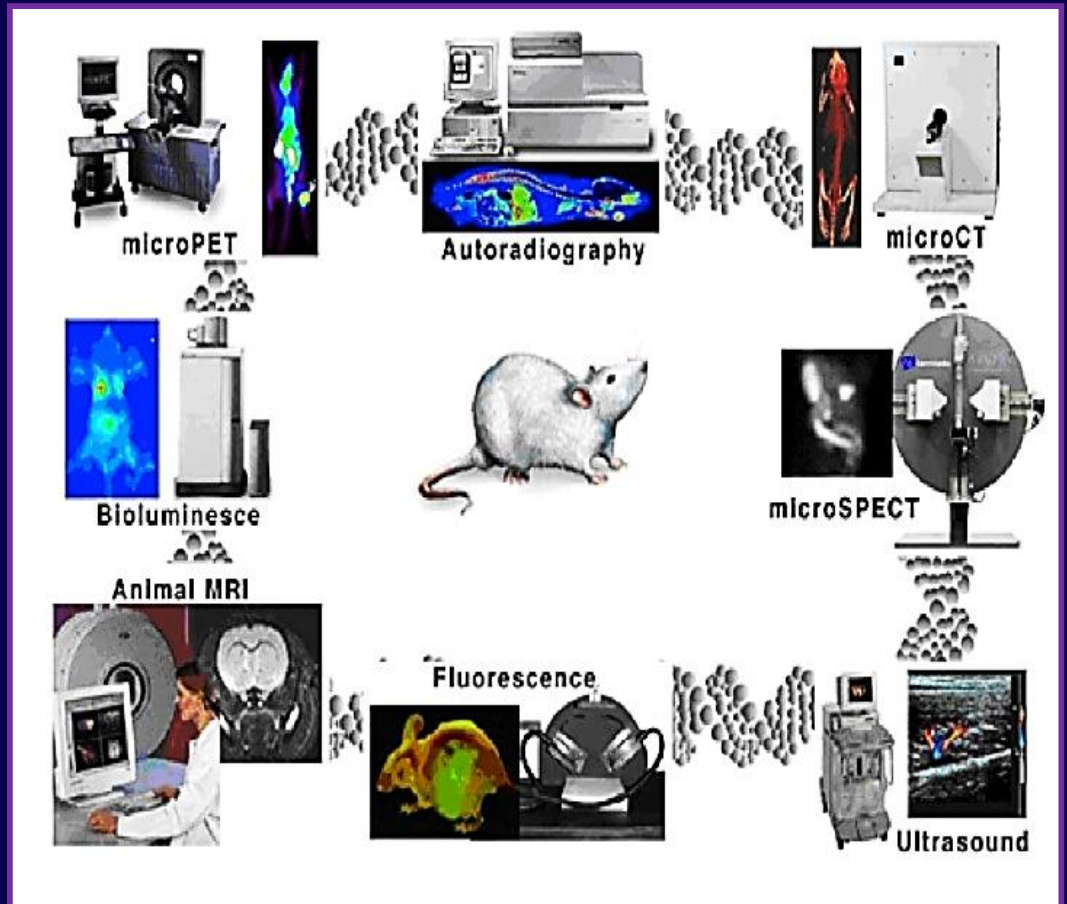
生命的信使—化学分子



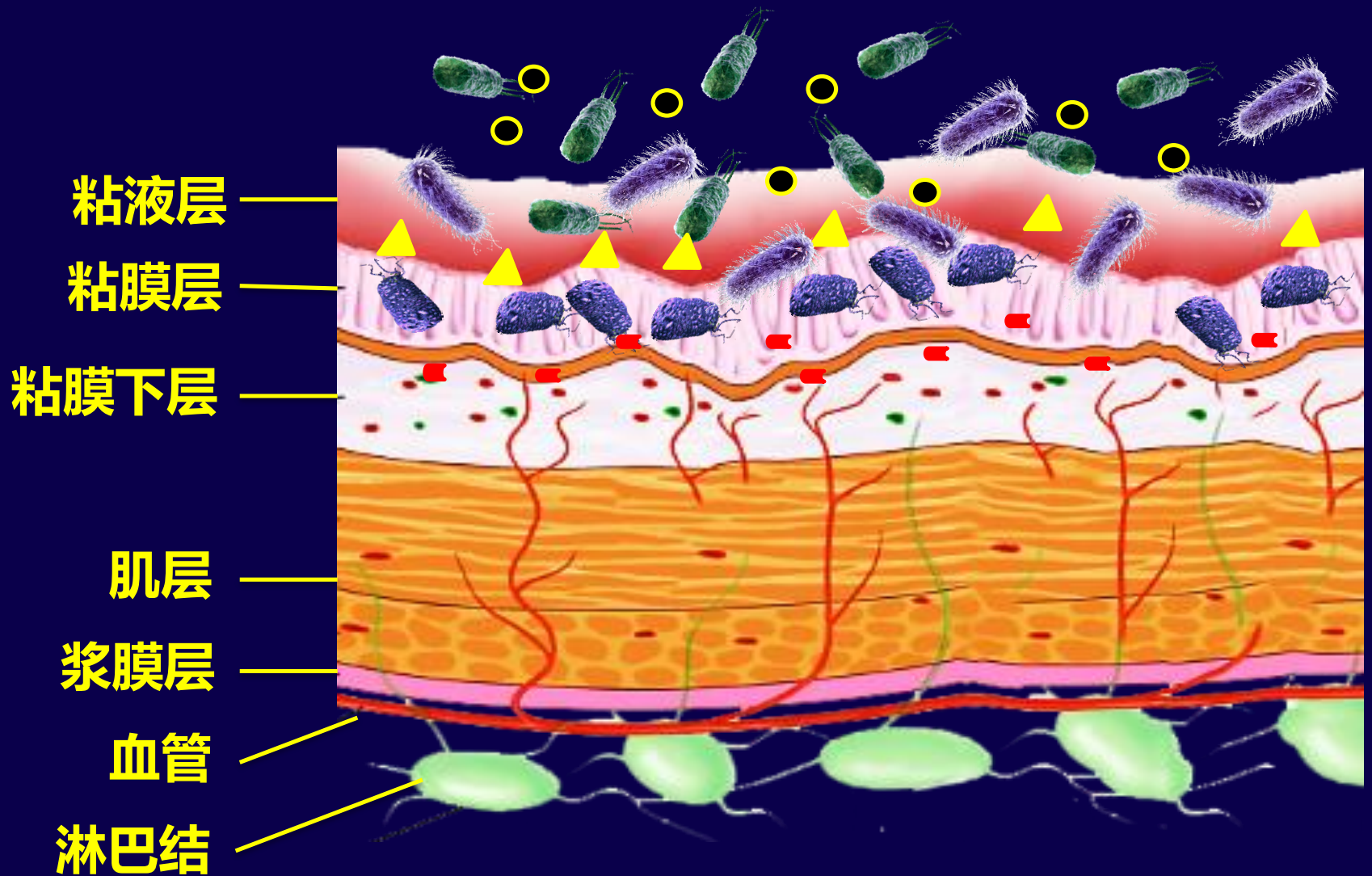
- ◆ 细菌与细菌之间的信号传递
- ◆ 细菌与胃肠道粘膜细胞交流
- ◆ 如何研究肠道菌群同机体细胞之间交流的分子机制？

分子影像

- 遗传基因信息、生物化学与新的成像探针进行综合，由精密的成像技术来检测，再通过一系列的图像后处理技术，达到显示活体组织在分子和细胞水平上的生物学过程的目的。



3D打印在胃肠道的未来.....







第四届海峡两岸消化论坛暨世界华人消化高峰论坛

2013年11月21日-24日·厦门



海峡两岸医药卫生交流协会
消化病学专家委员会成立

合影留念 2013.11.22 厦门



第五届海峡两岸消化论坛 暨世界华人消化高峰论坛 第二届世界华人消化青年论坛

The Fifth Cross-Straits Digestive Forum
and The World Chinese Digestive Summit
The Second World Chinese Digestive Youth Forum

厦门国际会议中心

2015年11月6-8日

第一轮通告 First Announcement

主办:

海峡两岸医药卫生交流协会消化病学专家委员会
两岸关系和平发展协同创新中心
台湾消化系医学会、消化系内镜医学学会
香港消化病学会、消化系内镜学会
厦门市医学会

协办:

西京消化病医院
北京协和医院
中山大学附属第一医院
台湾中山医学大学附设医院
四川大学附属华西医院
首都医科大学附属北京友谊医院
北京大学人民医院
澳门镜湖医院
《J Dig Dis》
《中华消化杂志》

承办:

厦门大学附属中山医院
台湾大学医学院附设医院
香港中文大学威尔斯亲王医院

新加坡国立大学医院
第二军医大学附属长海医院
上海交通大学医学院附属仁济医院
上海交通大学医学院附属瑞金医院
台湾高雄医学大学附设医院
南方医科大学附南方医院
长庚大学林口长庚医院
海峡消化网 (www.hxxhw.com)
《Clinical update:Gastroenterology and Hepatology》
《中华消化内镜杂志》

美丽的厦门欢迎您！



非机动车道
NO MOTOR VEHICLES
NO MOTOR VEHICLES

红色路面为
自行车和人行道
THE RED SURFACE IS FOR
BICYCLES AND PEDESTRIANS

