CLDN18.2丨肿瘤免疫治疗赛道的黑马

CLDN18.2 (Claudin18.2)是一种胃特异性膜蛋白，是目前研究得最为透彻的Claudin家族蛋白。该靶点在胃癌和胰腺癌这两种癌种中表达上调，目前靶向CLDN18.2靶点的研究中多以胃癌为主。南模生物可提供CLDN18.2基因人源化的MC38和CT26的结肠癌细胞系。

近日，国内两款靶向CLDN18.2的产品接连获批临床，这一进展，让CLDN18.2靶点再次引起了人们的瞩目。CLDN18.2 (Claudin18.2)是一种胃特异性膜蛋白，是目前研究得最为透彻的Claudin家族蛋白。该靶点在胃癌和胰腺癌这两种癌种中表达上调，目前靶向CLDN18.2靶点的研究中多以胃癌为主。

Claudins

1998年，日本京都大学的研究人员Mikio Furuse和Shoichiro Tsukita首次发现并命名了Claudins。Claudins是存在于上皮细胞和内皮细胞紧密连接中的整合素膜蛋白，构成了细胞旁屏障和孔，控制上皮细胞间细胞间空间分子的流动。它们有四个跨膜结构域，其中N端和C端都在细胞质中。

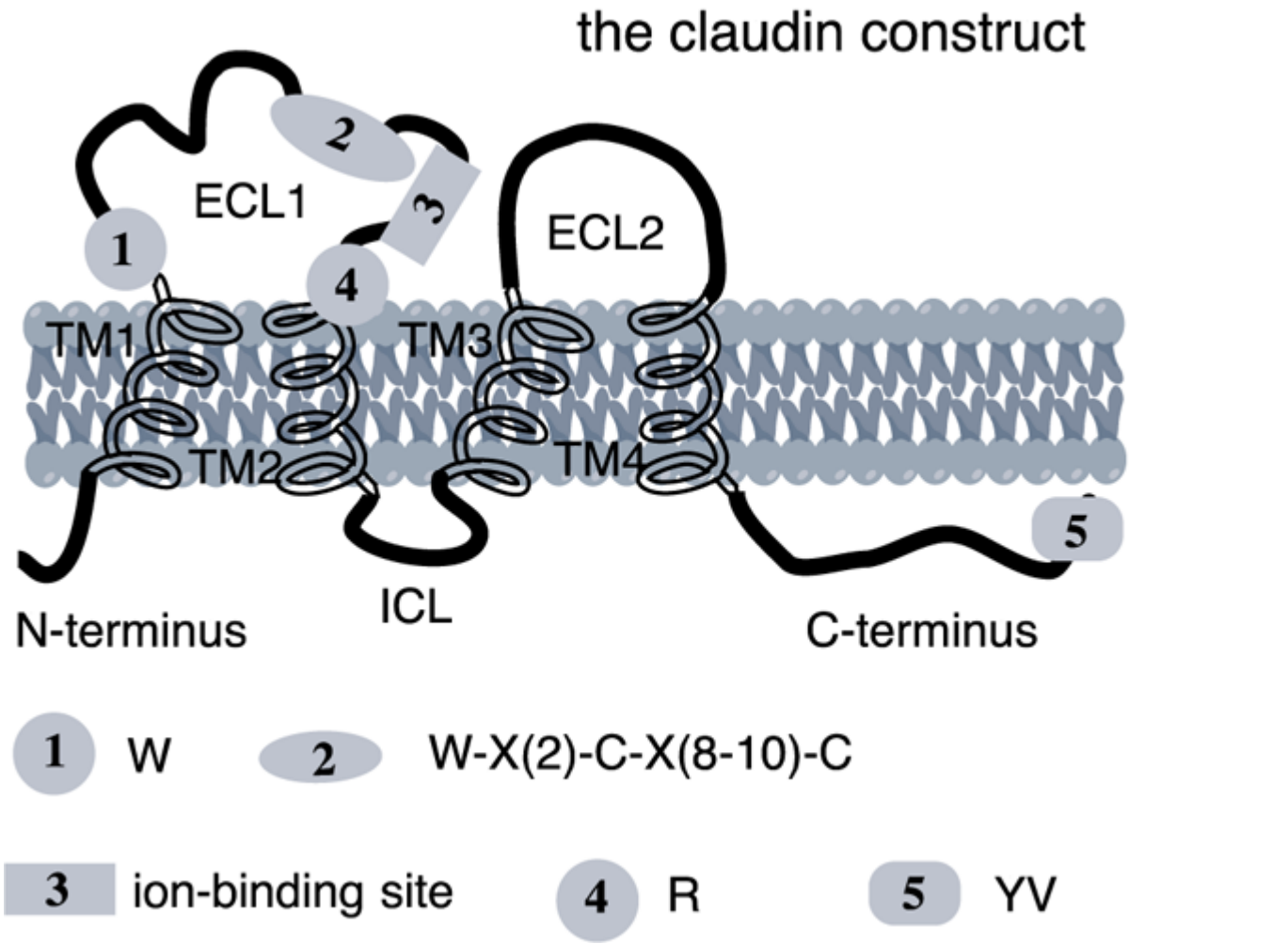

Fig.1 General scheme of the claudin protein structure

包括转录变体在内，已有27个哺乳动物Claudins基因被报道。至少有24个在人类中被发现，由HUGO基因命名委员会指定的Claudins的官方基因名称，如下表所示

Table 1. Overview of the Human Claudin Family Members from Databases

gene	protein IDs (UniProt/ Ensembl[b])	synonyms (GeneCards)	chromosome localization[e]	tissue frequency with HPA evidence[f]	tissue-specific RNA FPKM[i] (max in nonspecific tissue)
CLDN1	O95832/163347	SEMP1, ILVASC	3q28	very common	– (skin: 224.1)
CLDN2	P57739/165376	SP82	Xq22	common[g]	– (kidney: 114.5)
CLDN3	O15551/165215	CPETR2	7q11	very common	– (colon: 94.8)
CLDN4	O14493/189143	CPER, CPETR1, WBSCR8	7q11	common[h]	– (colon: 160.9)
CLDN5	O00501/184113	AWAL, TMVCF	22q11	very common	adipose tissue: 110.8; lung: 32.1 (spleen: 10.4)
CLDN6	P56747/184697	UNQ757, PRO1488, Skullin	16p13	very common	– (placenta: 1.3)
CLDN7	O95471/181885	CEPTRL2, CPETRL2	17p13	very common	– (colon: 297.3)
CLDN8	P56748/156284	UNQ779, PRO1573	21q22	very common	– (kidney: 63.6)
CLDN9	O95484/213937		16p13	very common	– (pancreas: 2.0)
CLDN10	P78369/134873	CPETRL3, OSP-L	13q32	less common	– (salivary gland: 150.7)
CLDN11	O75508/013297	OSP, OTM	3q26	less common	– (testis: 167.0)
CLDN12	P56749/157224		7q21	very common	– (liver: 31.9)
CLDN14	O95500/159261	UNQ777, PRO1571, DFNB29	21q22	NA	kidney: 5.3; liver: 8.4 (appendix: 0.5)
CLDN15	P56746/106404		7q22	very common	duodenum: 184.0; small intestine: 140.1 (spleen: 12.6)
CLDN16	Q9Y5I7/113946	PCLN1, PCLN-1, HOMG3	3q28	rare	kidney: 39.0 (thyroid gland: 6.8)
CLDN17	P56750/156282	UNQ758 PRO1489	21q22	NA	esophagus: 6.4 (testis: 0.3)
CLDN18	P56856/066405	UNQ778 PRO1572, SFTA5, SFTPJ	3q22	rare	lung: 246.6; stomach: 556.1 (heart muscle: 7.3)
CLDN19	Q8N6F1/164007	HOMG5	1p34	NA	kidney: 21.9; placenta: 11.3 (adipose tissue: 0.2)
CLDN20	P56880/171217		6q25	NA	– (uterus: 0.3)
CLDN21[a]		see CLDN24			
CLDN22	Q8N7P3/177300		4q35	NA	– (adrenal gland: 0.1)
CLDN23	Q96B33/253958	2310014B08RikCLDNL, hCG1646163	8p23	NA	– (stomach: 17.6)
CLDN24	A6NM45/185758	also named CLDN21	4q35	NA	– (kidney: 0.7)
CLDN25	C9JDP6/228607		11q23	rare	– (adipose tissue: 0.0)
CLDN26	B3SHH9[c]	TMEM114[d]	16p13	NA	– (testis: 0.4)
CLDN27	A6NFC5[c]	TMEM235[d]	17q25	NA	– (testis: 0.1)

[a]Merged with CLDN24; see http://www.ncbi.nlm.nih.gov/gene/53843. [b]Ensemble code prefix: ENSG00000. [c]Not identified as claudin but as TMEM (transmembrane) proteins. [d]Tracked from GeneCards synonyms. [e]CLDN13 is absent in human. CLDN 6 and 9, as well as CLDN 8 and 17, may be considered as paralogs.[54] [f]HPA evidence was calculated based on the manual curation of western blot, tissue profiling, and subcellular location using a limited number of claudin antibodies that have been submitted to HPA and validated by HPA. Many other claudin antibodies are available but not included in the HPA list. Very common = high or medium levels in at least 20 tissues; common = high or medium levels in at least 10 tissues; less common = high or medium levels in more than 3 but less than 10 tissues; rare = high or medium levels in only 1−3 tissues; NA = no antibodies. [g]In nucleus but not nucleoli, cell junctions by immunofluorescence analysis. [h]In plasma membrane by immunofluorescence analysis. [i]FPKM value = number of fragments per kilobase gene model and million reads. The FPKM threshold value for detection is >1.[58] FPKM measurements reflect measured tissues represented in the database and are not necessarily representative of a complete mRNA expression profile.

CLDN18.2

人类CLDN18基因有两个可选的第一外显子，产生了两个不同的蛋白异构体CLDN18.1和CLDN18.2(CLDN18.1和CLDN18.2胞外区1中仅存在8个氨基酸差别)。两个亚型具有不同的谱系功能，CLDN18.1主要表达于肺组织，而CLDN18.2则主要表现出胃特异性。

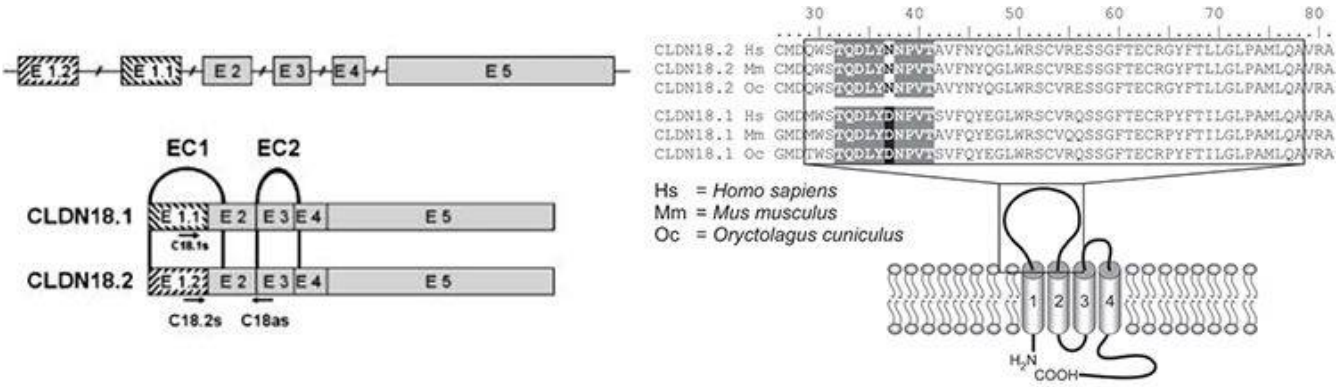

Fig. 2 Genomic structure of the CLDN18 locus

CLDN18.2蛋白作为一种高度选择性的胃谱系标记物，表达于短周期分化细胞，不表达于胃黏膜的干细胞区。但在多种肿瘤(胃癌、肺癌和胰腺癌等)中频繁异位激活和过表达，这种限制表达使其成为恶性肿瘤免疫治疗的理想靶点。

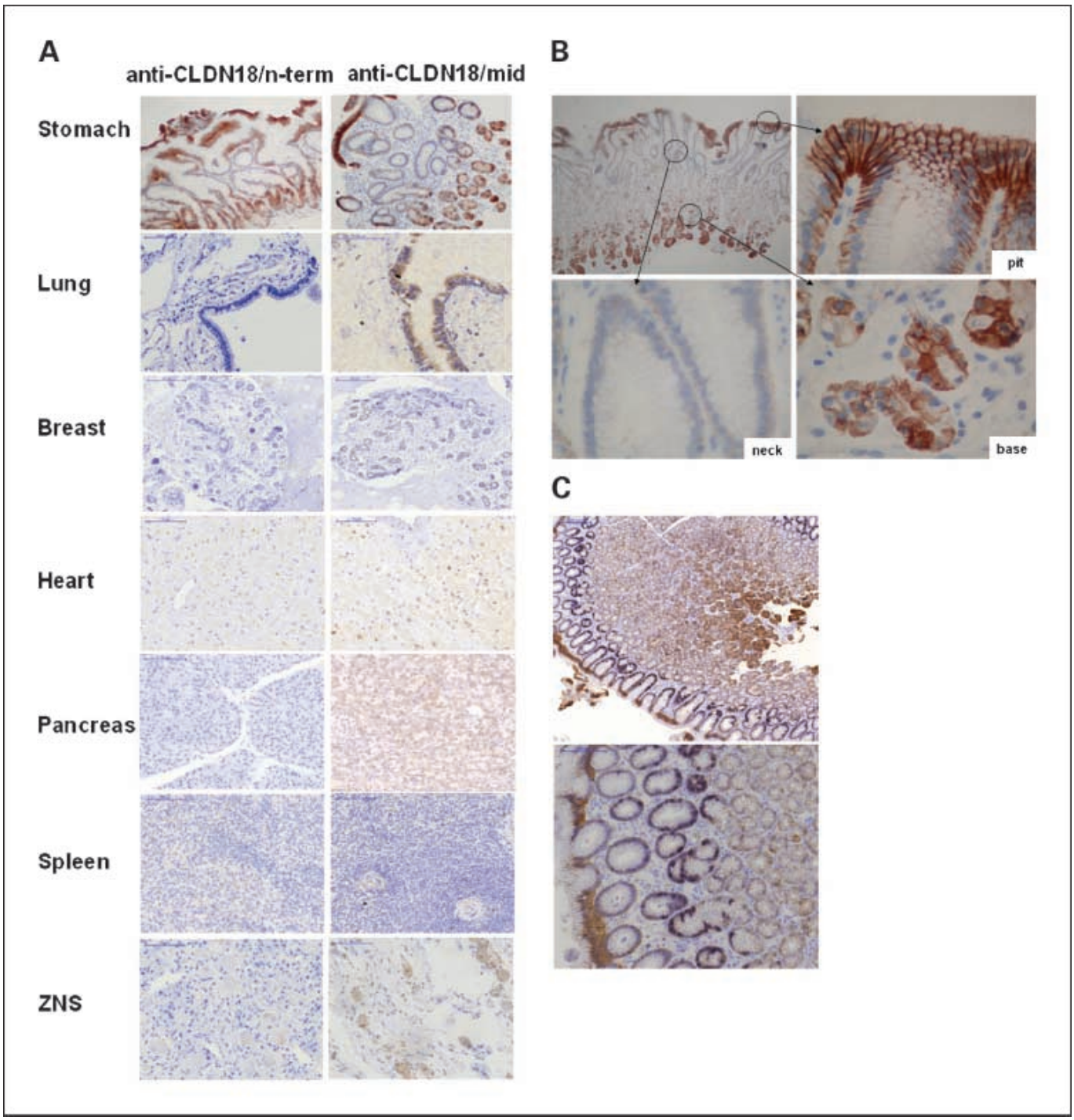

Fig. 3 Immunohistochemistry of normal human tissues with CLDN18.2 antibodies.

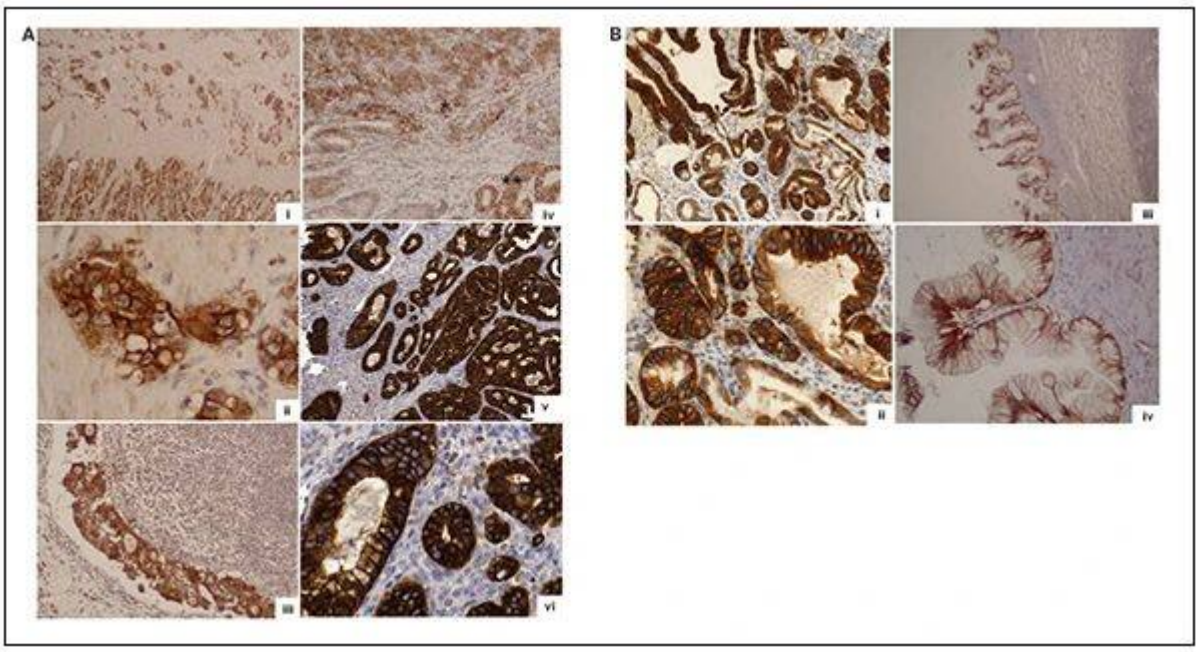

Fig.4 Immunohistochemistry of tumor tissues with CLDN18.2 antibodies

CLDN18.2靶向药物研发现状

2021年6 月 16 日，CDE 官网显示，石药集团巨石生物的 1 类新药SYSA1801 注射液（靶向Claudin18.2 的 ADC 产品）获批临床， 2021年6月11日，礼新医药Claudin 18.2抗体获批进行临床试验。根据 Insight 数据库，当前国内有 13 个靶向 Claudin 18.2 的生物药在研，详见下表。

药品名称	靶点	成分类别	企业名称	当前项目进度	适应症	当前进度进展时间
Zolbetuximab	CLDN-18.2	单抗	安斯泰来制药	III 期临床	CLDN18.2 阳性、HER2 阴性 晚期/转移性胃腺癌及胃食管交界处癌	2019-04-19
CT041	CLDN-18.2	CAR-T	上海科济制药	II 期临床	CLDN18.2 阳性、HER2 阴性 晚期转移性胃腺癌	2020-10-09
ASKB589	CLDN-18.2	ADC	江苏奥赛康药业	II 期临床	晚期/转移性实体瘤	2020-10-29
Q-1802	PD-L1,CLDN-18.2	双抗	启愈生物	I 期临床	晚期/转移性实体瘤	2021-04-14
M108	CLDN-18.2	单抗	明济生物	I 期临床	晚期/转移性实体瘤	2021-03-31
CMG901	CLDN-18.2	ADC	康诺亚生物	I 期临床	晚期/转移性实体瘤	2020-12-09
AB011	CLDN-18.2	单抗	恺兴生命科技	I 期临床	CLDN18.2 阳性实体瘤	2020-05-21
TST001	CLDN-18.2	单抗	迈博斯生物医药	I 期临床	晚期/转移性实体瘤	2020-08-03
MIL93	CLDN-18.2	单抗	北京天广实	I 期临床	晚期/转移性实体瘤	2020-12-02
QL1779	CLDN-18.2	单抗	齐鲁制药	批准临床	CLDN18.2 阳性实体瘤	2021-04-23
LM-102	CLDN-18.2	单抗	上海礼新医药	批准临床	CLDN18.2 阳性实体瘤	2021-06-11
SYSA1801	CLDN-18.2	ADC	石药集团巨石生物	批准临床	晚期/转移性实体瘤	2021-06-16
AMG 910	CLDN-18.2,CD3	双抗	百济神州	临床申请中		2020-07-01

Table 2 Claudin18.2 国内进入临床的项目（截至 6 月 16 日，来源：Insight数据库）

南模生物CLDN18.2人源化细胞系

CLAUDIN 18.2基因人源化的CT26结肠癌细胞系

CLAUDIN 18.2基因人源化的MC38结肠癌细胞系

Reference:

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