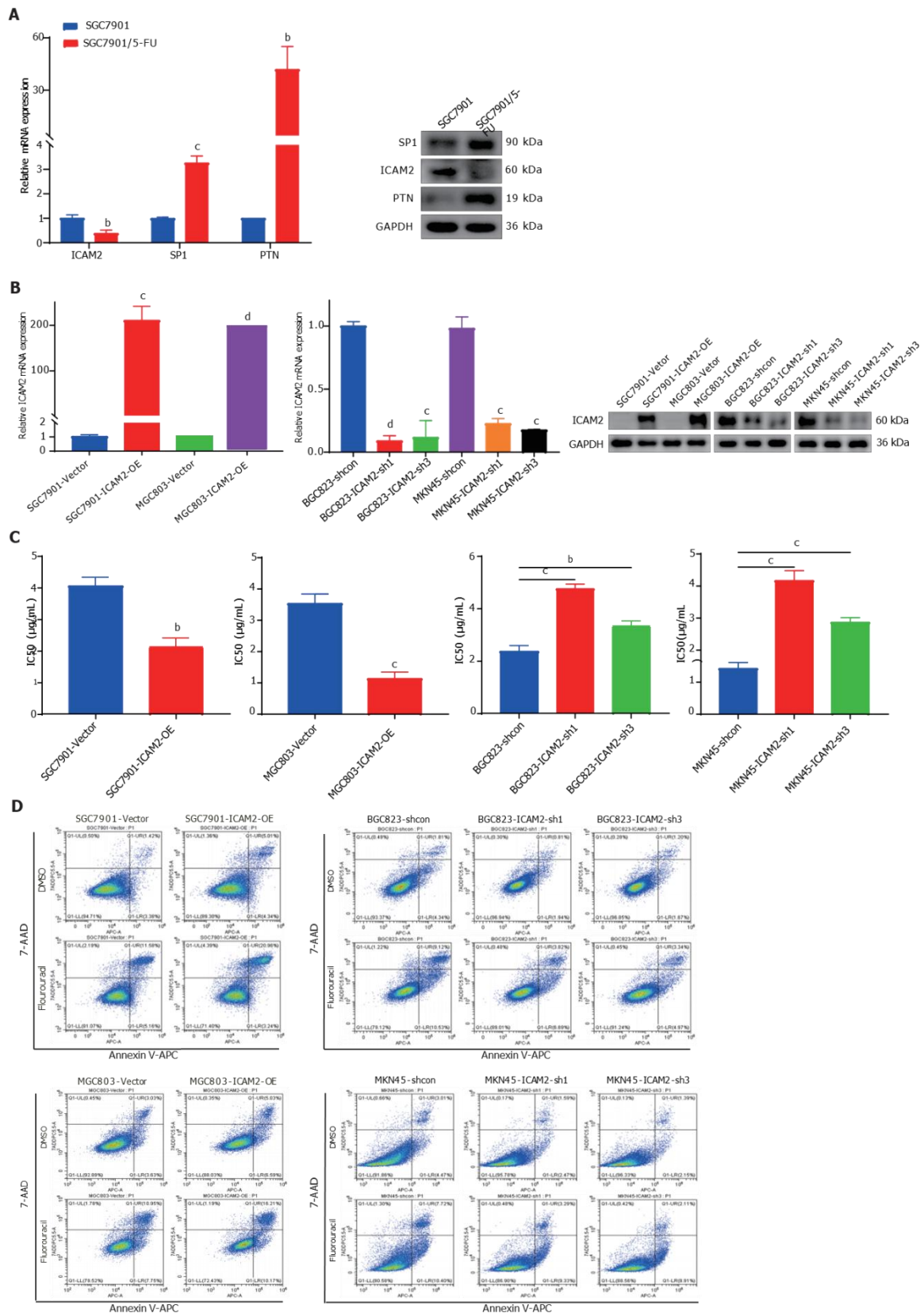
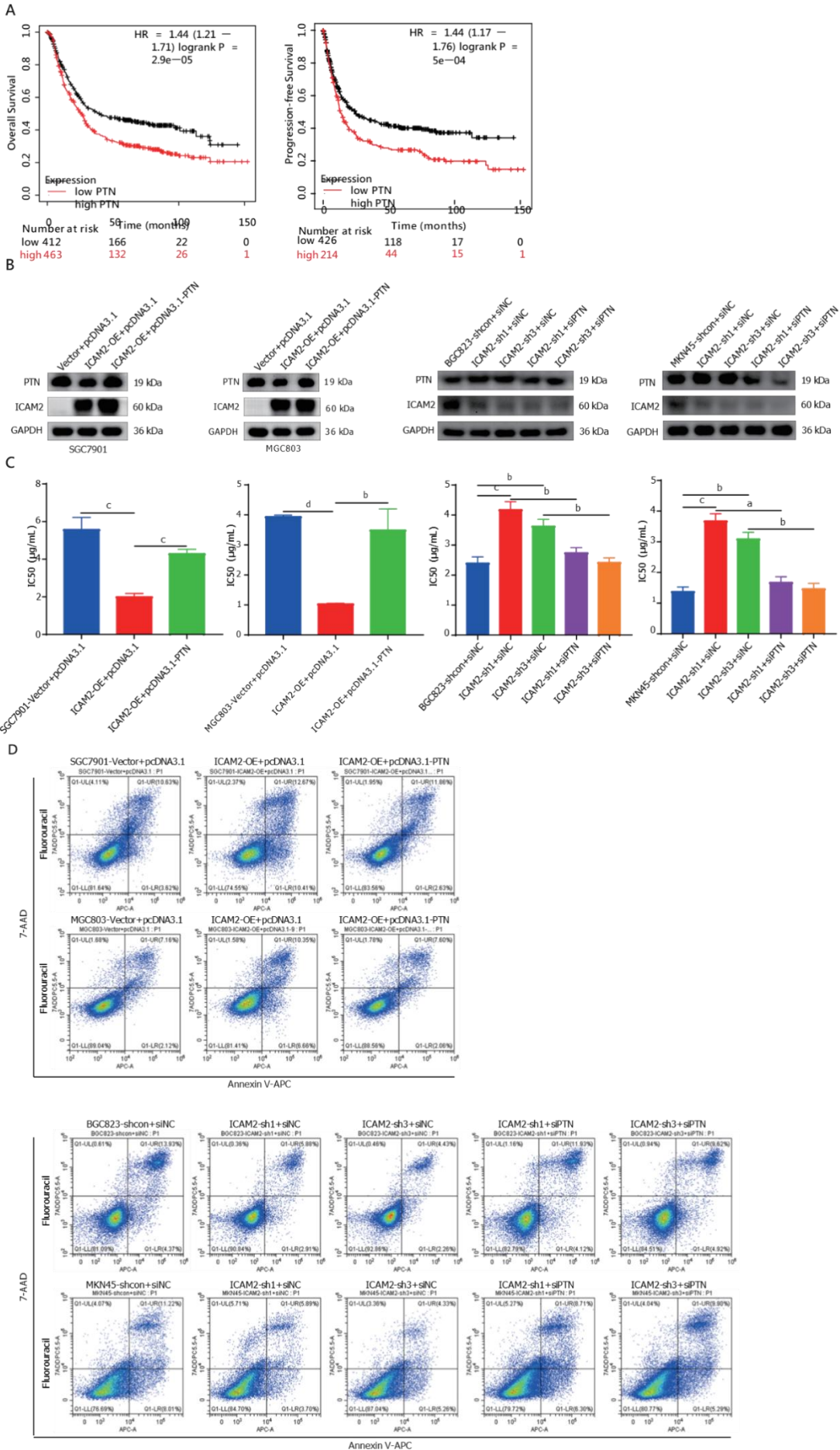


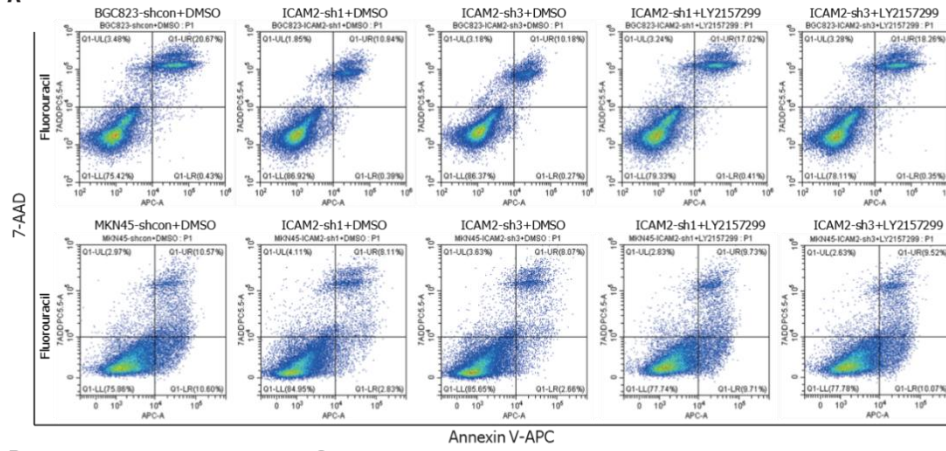


Supplementary Figure 1 Intercellular adhesion molecule 2 expression and its functional role in regulating 5-fluorouracil resistance in gastric cancer cells. A: RT-qPCR and Western blot analyses of intercellular adhesion molecule 2 (ICAM2), SP1 and PTN expression in parental and 5-fluorouracil (5-FU)-resistant SGC7901 cells; B: Verification of *ICAM2* overexpression and knockdown in SGC7901, MGC803, BGC823 and MKN45 cells at mRNA and protein levels; C: half-maximal inhibitory concentration values for 5-FU in GC cells with *ICAM2* overexpression or silencing; D: Flow-cytometric analysis of 5-FU-induced apoptosis in GC cells with *ICAM2* overexpression or knockdown. ICAM2: Intercellular adhesion molecule 2; PTN: Pleiotrophin; 5-FU: 5-fluorouracil; IC₅₀: Half-maximal inhibitory concentration.

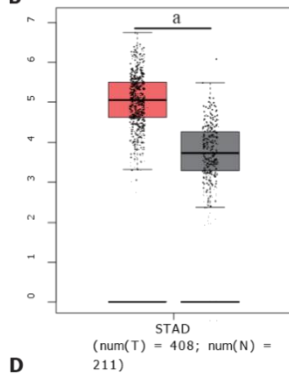


Supplementary Figure 2 Pleiotrophin mediates Intercellular adhesion molecule 2-driven 5-fluorouracil resistance in gastric cancer cells. A: Kaplan-Meier curves showing overall survival and progression-free survival in TCGA-STAD patients with high *vs* low PTN expression; B: Western blot confirmation of intercellular adhesion molecule 2 (ICAM2) and PTN expression in GC cells with *PTN* overexpression or knockdown in the context of *ICAM2* modulation; C: half-maximal inhibitory concentration values for 5-fluorouracil (5-FU) in GC cells with combined *ICAM2* and *PTN* overexpression or silencing; D: Flow-cytometric assessment of 5-FU-induced apoptosis in GC cells after *PTN* gain- or loss-of-function on the *ICAM2* background. ICAM2: Intercellular adhesion molecule 2; PTN: Pleiotrophin; 5-FU: 5-fluorouracil; IC₅₀: Half-maximal inhibitory concentration.

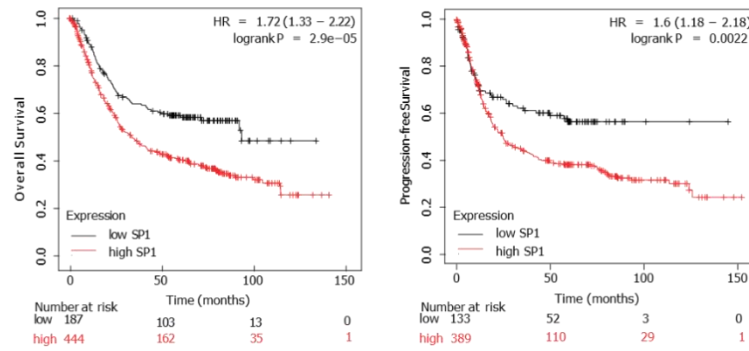
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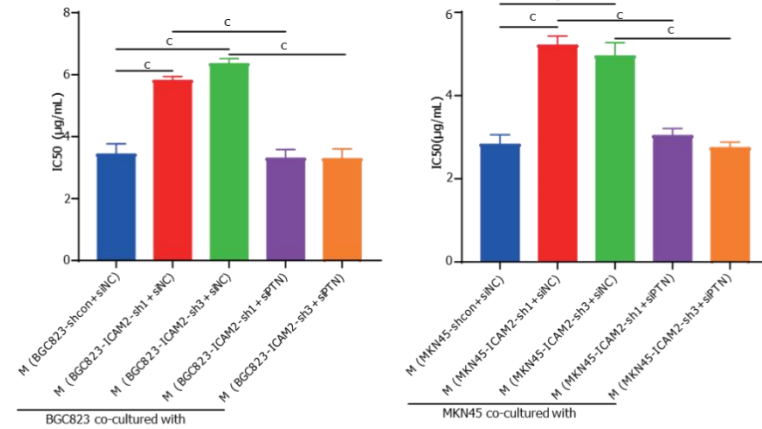
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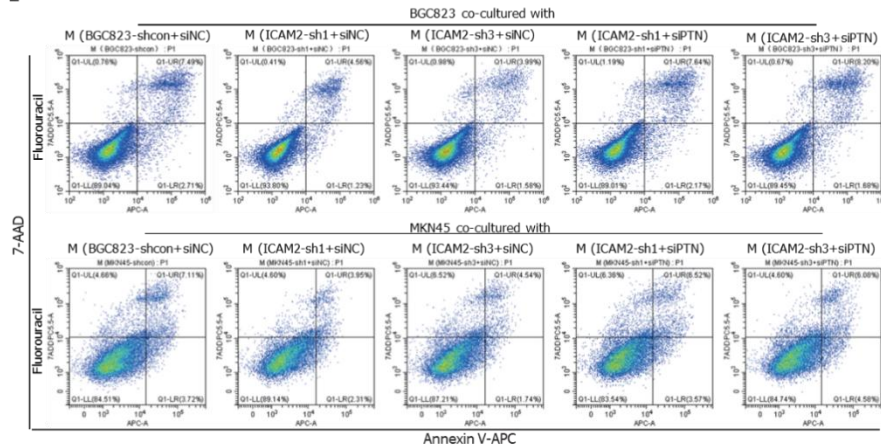
C



D



E



Supplementary Figure 3 TGF- β /Smad signaling and macrophage-derived pleiotrophin reinforce Intercellular adhesion molecule 2-related 5-fluorouracil resistance. A: Flow-cytometric analysis of apoptosis in *ICAM2*-silenced GC cells treated with DMSO or LY2157299 in the presence of 5-fluorouracil (5-FU); B-C: SP1 expression profile and survival curves for patients with high *vs* low SP1 expression in TCGA-STAD; D: half-maximal inhibitory concentration values for 5-FU in BGC823 and MKN45 cells co-cultured with tumor-associated macrophages conditioned by intercellular adhesion molecule 2-silenced GC cells with or without *PTN* knockdown; E: Flow-cytometric analysis of 5-FU-induced apoptosis in GC cells under the indicated macrophage co-culture conditions. ICAM2: Intercellular adhesion molecule 2; PTN: Pleiotrophin; 5-FU: 5-fluorouracil.

Supplementary Table 1 The information of antibodies used in this study

Antibody	Manufacturer	Application
ICAM2	Cell Signaling Technology: #13355	1:100 for IHC, 1:1000 for WB
SP1	Proteintech: 21962-1-AP	1:2000 for WB, 1:100 for IP, 1:100 for CHIP
PTN	Proteintech: 27117-1-AP	1:100 for IHC, 1:1000 for WB
GAPDH	Proteintech: 60004-1-Ig	1:50000 for WB
Smad2	ZENBIO: R25742	1:500 for WB
Smad3	ZENBIO: R25743	1:2000 for WB
phospho-Smad2 (Ser465)	ZENBIO: 690444	1:500 for WB
phospho-Smad2 (Ser467)	ZENBIO: 310079	1:500 for WB
phospho-Smad3 (Ser423/425)	ZENBIO: R22919	1:500 for WB
Cleaved-PARP	ZENBIO: R23942	1:500 for WB
cleaved caspase-3 p17	ZENBIO: 341034	1:100 for IHC, 1:500 for WB

Bax	ZENBIO: R22708	1:500 for WB
Bad	ZENBIO: R23582	1:500 for WB
CD80	Proteintech: 66406-1-Ig	1:1000 for WB
CD86	Proteintech: 83523-4-RR	1:1000 for WB
Arginase-1	Proteintech: 16001-1-AP	1:5000 for WB
CD163	Abcam: ab182422	1:1000 for WB
CD206	Abcam: ab64693	1:100 for IHC, 1:1000 for WB
Ki67	Servicebio: GB111499-100	1:1000 for IHC
Histone H3	ZENBIO: R24572	1:500 for WB

Supplementary Table 2 Sequences of quantitative real-time PCR primers in this study

Gene name	Forward primer (5'→3')	Reverse primer (5'→3')
GAPDH	GACAGTCAGCCGCATCTTCTT	AATCCGTTGACTCCGACCTTC
ICAM2	GCCACAGCCACATTCAACAGCACG	ACAGGGACAGCAACACCGACACCAC
SP1	TGGCAGCAGTACCAATGGC	CCAGGTAGTCCTGTCAGAACTT
PTN	GGAGCTGAGTGCAAGCAAAC	CTCGCTTCAGACTTCCAGTTC

CES1	ACCCCTGAGGTTTACTCCACC	TGCACATAGGAGGGTACGAGG
CGA	TGCCCAGAATGCACGCTAC	TTGGACCTTAGTGGAGTGGGA
PRRX1	CAGGCGGATGAGAACGTGG	AAAAGCATCAGGATAGTGTGTCC
CD80	AAACTCGCATCTACTGGCAAA	GGTTCTTGTACTCGGGCCATA
CD86	CTGCTCATCTATACACGGTTACC	GGAAACGTCGTACAGTTCTGTG
TNF- α	CCTCTCTCTAATCAGCCCTCTG	GAGGACCTGGGAGTAGATGAG
CXCL9	CCAGTAGTGAGAAAGGGTCGC	AGGGCTTGGGGCAAATTGTT
iNOS	TTCAGTATCACAACCTCAGCAAG	TGGACCTGCAAGTTAAAATCCC
IL6	ACTCACCTCTTCAGAACGAATTG	CCATCTTTGGAAGGTTCAAGTTG
CD163	TTTGTCAACTTGAGTCCCTTCAC	TCCCGCTACACTTGTTTTAC
CD206	TCCGGGTGCTGTTCTCCTA	CCAGTCTGTTTTTGATGGCACT
Arg1	GTGGAAACTTGCATGGACAAC	AATCCTGGCACATCGGGAATC
IL10	TCAAGGCGCATGTGAACTCC	GATGTCAAACCTCACTCATGGCT
TGF- β	GGCCAGATCCTGTCCAAGC	GTGGGTTTCCACCATTAGCAC

Supplementary Table 3 Prediction of SP1 binding motifs and sites within the pleiotrophin promoter region using the JASPAR database

Matrix IDX	Model name	Score	Relative score	Sequence ID	Start	End	Strand	Predicted sequence
MA0079.3	SP1	12.241923	0.93515809	NC_000007.14:c13734573 #####	1965	1975	+	TCCCCGCCTTC
MA0079.3	SP1	11.445139	0.92513363	NC_000007.14:c13734573 #####	1848	1858	+	CTCCCTCCCTC
MA0079.3	SP1	9.028997	0.89473581	NC_000007.14:c13734573 #####	1892	1902	+	ATCCCTCCCAT
MA0079.3	SP1	8.751333	0.89124247	NC_000007.14:c13734573 #####	1920	1930	+	TTCCCTCCCTG