

Supplemental Table 1. Prioritization and selection of candidate biomarkers from CRC cell secretomes.

Category	Criteria*	Protein name	Gene symbol	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5
A	1+2 or 1+3	Tumor-associated calcium signal transducer 2/trophoblast cell surface antigen 2	TACSTD2/TR OP2**	Yes	No	Ref. 1~6		No
		Transmembrane 9 superfamily member 2	TM9SF2	Yes	Yes			No
B	1+4 or 2+3 or 2+4	Tetraspanin-6	TSPAN6	No	Yes		Ref. 7~9	No
		Bone marrow stromal antigen 2	BST2	No	Yes	Ref. 10~13		Yes
		Tumor necrosis factor receptor superfamily member 16	NGFR	No	Yes	Ref. 14~18		No
		Glia-activating factor	FGF9	No	Yes	Ref. 19~23		No
		Isoform 3 of Canalicular multispecific organic anion transporter 2	ABCC3***	Yes	No	Ref. 24~28		No
		Cell surface A33 antigen	GPA33	No	Yes	Ref. 29~33		No
		55 kDa erythrocyte membrane protein	MPP1	No	Yes		Ref. 34~37	No
		142 kDa protein	PCDH24	No	Yes	Ref. 38		No
		Isoform 2 of Ankyrin repeat-rich membrane spanning protein	KIDINS220	No	Yes	Ref. 39		No
		Flotillin 2	FLOT2	No	Yes	Ref. 40~43		No
		Trefoil factor 3	TFF3	No	Yes	Ref. 44~48		Yes
		Isoform long of Antigen KI-67	MKI67	No	Yes	Ref. 49~52		No
		22 kDa protein	TIMP2	No	Yes	Ref. 53~56		No
		Claudin-3	CLDN3	No	Yes	Ref. 57~62		No
		Metallothionein-3	MT3	No	Yes	Ref. 63~66		No
		EPHB6 protein	EPHB6	No	No	Ref. 67~71		No
		Rho-related BTB domain-containing protein 3	RHOBTB3	No	Yes			No
		Galactoside 3(4)-L-fucosyltransferase	FUT3	No	No	Ref. 72~74		No
		Protein VAC14 homolog	VAC14	No	Yes			No
		Isoform 1 of TRAF2 and NCK-interacting protein kinase	TNIK	No	Yes			No
		Isoform 3 of Misshapen-like kinase 1	MINK1	No	No		Ref. 75~77	No
		Protein-tyrosine kinase fyn isoform c	FYN	No	Yes			No
		Isoform 2 of protein phosphatase slingshot homolog 3	SSH3	No	Yes			No
		Xylosyltransferase 1	XYLT1****	Yes	Yes			No
		70 kDa protein	SLC6A6	No	Yes			No
		Protein APCDD1	APCDD1	No	Yes			No
		Isoform CSBP1 of Mitogen-activated protein kinase 14	MAPK14	No	Yes			No
Ephrin type-B receptor 3	EPHB3	No	Yes			No		
Ataxia telangiectasia mutated protein isoform 2	ATM	No	Yes			No		
Stromal cell-derived factor 2	SDF2	No	No	Ref. 78~79		No		
Perforin-1	PRF1	No	No	Ref. 80		No		
Inhibin beta B chain	INHBB	No	No	Ref. 81~84		No		
Coagulation factor XIII A chain	F13A1	No	No	Ref. 85~86		Yes		
Low-density lipoprotein receptor-related protein 4	LRP4	No	Yes			No		
CDC42 binding protein kinase alpha	CDC42BPA	No	No	Ref. 87		No		
Isoform long of Glycylpeptide N-tetradecanoyltransferase 1	NMT1	No	Yes			No		
Cell growth regulator with EF hand domain protein 1	CGREF1	No	Yes			Yes		
Isoform 1 of protein KIAA1199	KIAA1199	No	No	Ref. 88~90		No		
AP1B1 protein	AP1B1	No	No		Ref. 91~94	No		
Ladinin 1	LAD1	No	Yes			No		
Isoform 1 of von Willebrand factor A domain-containing protein 2	VWA2	No	No	Ref. 95		Yes		
Isoform 1 of Transmembrane protein 16A	TMEM16A	No	No	Ref. 96~98		No		
Isoform 2 of Condensin-2 complex subunit G2	NCAPG2	No	Yes			No		
Prostatic acid phosphatase	ACPP	No	Yes			No		
9 kDa protein	RPS27	No	No	Ref. 99~102		No		
Isoform 2 of General transcription factor 3C polypeptide 5	GTF3C5	No	No	Ref. 103~104		No		
Isoform 2 of Transmembrane and TPR repeat-containing protein 3	TMTC3	No	Yes			No		
Catenin, beta like 1	CTNNBL1	No	Yes			No		

Ras GTPase-activating-like protein IQGAP3	IQGAP3	No	No	Ref. 105~107	Yes
Isoform 1 of PDZ domain-containing protein 11	PDZD11	No	Yes		No
Lipocalin 2	LCN2	No	Yes		No
cDNA FLJ46245 fis, clone TESTI4020596, highly similar to Homo sapiens calpain 5	CAPN5	No	No	Ref. 108~109	No
Proliferating-cell nucleolar antigen p120	NOL1	No	No	Ref. 110~112	No
Isoform 1 of Pregnancy-specific beta-1-glycoprotein 11	PSG11	No	No	Ref. 113~115	No
Isoform 1 of Choline transporter-like protein 1	SLC44A1	No	No	Ref. 116	No
Phosphoglycerate mutase 2	PGAM2	No	No	Ref. 117~118	Yes
Isoform A of Nucleoporin SEH1-like	SEH1L	No	Yes		No
Fibroblast growth factor 19	FGF19	No	No	Ref. 119~120	No
Isoform 2 of Chloride intracellular channel protein 5	CLIC5	No	No	Ref. 121	No
36 kDa protein	MFNG	No	No		Ref. 122
Eukaryotic translation initiation factor 1A, Y-chromosomal	EIF1AY	No	Yes		Yes
Calcium and integrin-binding protein 1	CIB1	No	Yes		No
Neutral amino acid transporter A	SLC1A4	No	Yes		No
Receptor-type tyrosine-protein phosphatase epsilon precursor	PTPRE	No	Yes		No

* Criteria:

- (1) proteins detected in the high-confidence human plasma proteome reference set established in 2006 [States et al., 2006]
- (2) proteins overexpressed in CRC tissue specimens in the Human Protein Atlas (HPA) dataset [Bjorling et al., 2008]
- (3) proteins up-regulated in CRC in published references
- (4) functions as secreted proteins, or involving in apoptosis/signal transduction
- (5) proteins detected in the high-confidence human plasma proteome reference set established in 2011 [Farrah et al., 2011]
- (6) proteins overexpressed in CRC tissue specimens in the Human Protein Atlas (HPA) dataset, Protein Atlas version 13 - 2014.11.06

** TACSTD2(TROP2) was enrolled in Protein Atlas version 12 - 2013.12.05

*** ABCC3 was set in category B due to previous literature lacking positive association in CRC.

**** XYLT1 was set in category C because it is an enzyme which was not a favorable candidate for cancer biomarker.

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Criterion 6

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Supplemental Table 2. Characteristics of all study subjects used in this study.

Characteristics	Used for ELISA				Used for IHC analysis CRC case
	1 st phase		2 nd phase		
	CRC Case	Control	CRC Case	Control	
Age (yr, median ±SEM)	67.5 ± 12.3	43.1 ± 12.7	65.3 ± 12.7	45.3 ± 10.1	62.9 ± 12.8
Gender-Male [N, (%)]	22(68.8)	15(46.9)	73(60.8)	61(50.8)	74(56.1)
Female	10(31.2)	17(53.1)	47(39.2)	59(49.2)	58(43.9)
Location (Organ Code)					
Colon			62(51.7)		49(37.1)
Rectum			46(38.3)		70(53.0)
Others			12(10.0)		13(9.9)
Histological grade					
Well differentiation			10(8.3)		25(18.9)
Moderate differentiation			99(82.5)		96(72.7)
Poor differentiation			10(8.3)		9(6.8)
Unknown			1(0.8)		2(1.5)
Histological type					
Adenocarcinoma			115(95.8)		119(90.2)
Mucinous carcinoma			4(3.3)		10(7.6)
Others			1(0.8)		3(2.3)
TNM stage					
0/I/II			61(50.8)		67(60.8)
III/IV			59(49.2)		65(49.2)
CEA level					
< 5 ng/ml			93(77.5)		63(47.7)
≥ 5 ng/ml			27(22.5)		64(48.5)
Unknown			0(0)		5(3.8)
Total case No.	32	32	120	120	132

Supplemental Table 3. Association of BST2 plasma levels with different clinicopathologic characteristics of the 120 CRC patients.

Characteristics	Number	BST2 (ng/ml)	<i>p</i>-value^a
Gender			
Male	73	2.40 ± 1.66	0.63
Female	47	2.26 ± 1.21	
Age (years)			
< 65	54	2.03 ± 1.63	0.03
≥ 65	66	2.61 ± 1.34	
Location (Organ Code)			
Colon	62	2.54 ± 1.67	0.70
Rectum	46	2.12 ± 1.30	
Histological grade			
Well differentiation	10	2.86 ± 1.69	
Moderate differentiation	99	2.25 ± 1.48	0.39
Poor differentiation	10	2.86 ± 1.46	
Histological type			
Adenocarcinoma	115	2.28 ± 1.48	0.05
Mucinous carcinoma	3	4.63 ± 0.45	
TNM stage			
I/II	61	2.42 ± 1.76	0.57
III/IV	59	2.27 ± 1.18	
Distant metastasis			
No	106	2.33 ± 1.55	0.83
Yes	14	2.42 ± 1.06	
CEA level			
< 5 ng/ml	93	2.18 ± 1.22	0.10
≥ 5 ng/ml	27	2.90 ± 2.13	
Albumin			
< 3.5 g/dL	14	4.14 ± 2.46	< 0.01
≥ 3.5 g/dL	105	2.12 ± 1.14	
Three years DFS^b			
< 3 years	86	2.50 ± 1.67	0.02
≥ 3 years	34	1.95 ± 0.81	
Chemotherapy			
No	56	2.41 ± 1.84	0.88
Yes	64	2.36 ± 1.17	

a: The *p*-values were determined by independent t test.

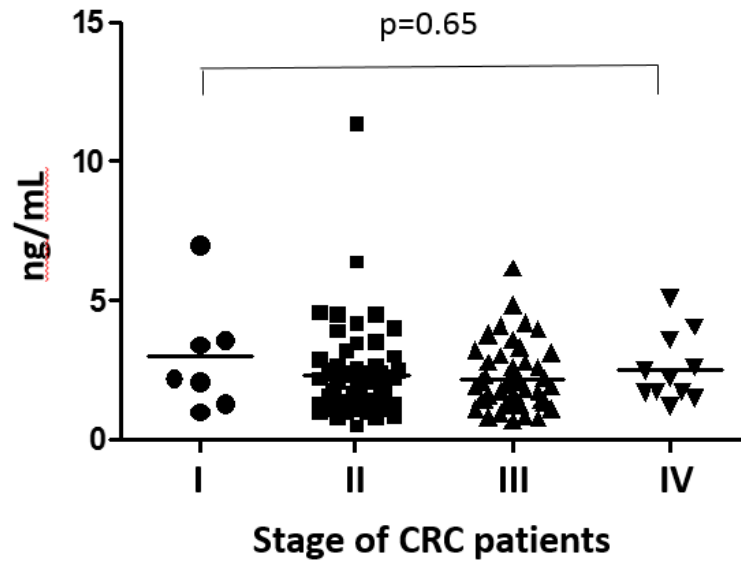
b: disease free survival

Supplemental Table 4. Association of BST2 IHC scores with different clinicopathologic characteristics of the 132 CRC patients.

Characteristics	Number	IHC score	<i>p</i>-value^a
Gender			
Male	74	144.5 ± 87.3	0.39
Female	58	137.7 ± 90.1	
Age (years)			
< 65	59	147.8 ± 85.2	0.15
≥ 65	73	136.5 ± 90.4	
Location (Organ Code)			
Colon	49	145.5 ± 98.6	0.47
Rectum	70	139.4 ± 83.1	
Histological grade			
Well differentiation	25	144.4 ± 99.7	0.60
Moderate differentiation	96	139.1 ± 88.2	
Poor differentiation	9	152.2 ± 56.1	
Histological type			
Adenocarcinoma	119	140.3 ± 89.9	0.92
Mucinous carcinoma	9	138.8 ± 68.2	
TNM stage			
I/II	67	133.7 ± 81.1	0.05
III/IV	62	149.1 ± 94.7	
Distant metastasis			
No	115	138.9 ± 88.9	0.11
Yes	16	158.1 ± 80.4	
CEA level			
< 5 ng/ml	63	135.1 ± 94.4	0.07
≥ 5 ng/ml	64	149.3 ± 82.7	
Five years survival			
< 5 years	59	155.9 ± 86.7	< 0.01
≥ 5 years	73	130.0 ± 83.7	
Chemotherapy			
No	47	151.1 ± 86.9	0.06
Yes	77	135.3 ± 89.1	

a: The *p*-values were determined by independent t test.

Fig. S1



Supplemental Figure 1. The ELISA analysis of BST2 according to stages in CRC patients' plasma was shown. The BST2 serum level were 2.20 ± 1.15 ng/mL (stage 1, n=7), 2.08 ± 0.74 ng/mL (stage 2, n=56), 1.90 ± 0.73 ng/mL (stage 3, n=46), and 2.20 ± 0.96 ng/mL (stage 4, n=11). There was no statistical difference among all stages for CRC patients ($p=0.65$, ANOVA).