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APPENDICES

APPENDIX A

REAGENTS

1. Reagents for cell culture

1.1 Complete RPMI 1640 medium

RPMI 1640 medium with glutamine	1	pack
$NaHCO_3$	2	g
1 HEPES	10	ml

Adjust pH to 7.3, add distilled water to final volume of 1 L and filter through 0.22 micro Millipore filter membrane.

Filtered RPMI 1640	80	ml
Fetal Bovine Serum	20	ml
Penicillin-Streptomycin	1	ml

Stored at 4 °C

1.2 Hank's buffered salt solution (HBSS)

10X HBSS	10	ml
Distilled water	90	ml
7.5 % $NaHCO_3$	460	µl
HEPES	1	ml
Penicillin-Streptomycin	2.5	ml

1.3 7.5 % $NaHCO_3$

$NaHCO_3$	7.5	g
Distilled water	100	ml

Steam Sterilization by using autoclave at 121 °C, 15 min.

2. Reagents for real-time PCR

2.1 Reagent for RNA extraction (70% Ethanol)

Trizol® reagent

Chloroform

Isopropanol

RNase free water

70% Ethanol

70% Ethanol preparation

Absolute Ethanol	70	ml
Distilled water	30	ml

Mix the solution then filter through 0.22 micro Millipore filter membrane and stored at 4 °C.

2.2 Reagents for reverse transcription (RT) reaction (first stand cDNA synthesis)

RT solution I (freshly prepared)

Total RNA	2.5	µg
Random hexamer (500 µg/ml)	1	ml

Add sterile water to final volume of 10 µl, mix solution then spin down and keep on ice.

RT solution II (freshly prepared)

5X RT buffer	4	µl
20 U RNase inhibitor	0.5	µl
5 mM dNTP mix	2	µl
200 U MMLV (reverse transcriptase)	1	µl
RNAse free water	2.5	µl

Mix solution, spin down and keep on ice.

2.3 Reagents for real-time PCR reaction

2x Taqman Universal PCR mastermix with AmpErase UNG	10 µl
20x Assay Mix (contains two target-specific primers and one TaqMan® MGB FAM™ dye-labeled probe)	1 µl
50 ng of cDNA sample	9 µl

APPENDIX B

DATA ANALYSIS

Table 3 Sensitivity of 5-FU (%I.I.) of CCA tissues

5-FU concentration (µg/ml) / Number of samples	Inhibition index (%)			
	100	**200**	**400**	**1000**
1	0	0	0	0
2	0	0	0	0
3	0	0	0	6
4	0	0	0	6
5	0	0	6	13
6	0	0	7	13
7	0	6	13	15
8	0	7	15	21
9	0	8	19	21
10	5	10	23	22
11	6	13	36	34
12	6	13	37	40
13	6	15	40	61
14	8	22	44	71
15	10	26	65	71
16	15	27	66	78
17	13	33	67	85
18	19	41	67	86
19	20	42	67	89
20	20	43	71	94
21	33	80	73	95
22	33	81	78	-
23	37	81	80	-
24	55	65	81	-
25	69	66	82	-
26	78	73	82	-
27	94	89	91	-
28	95	95	95	-

Table 4 Distribution levels of % cell viability on day 0 and day 4

Number of samples	%cell viability on day 0	%cell viability on day 4	% cell viability	
			day0(%)	day4(%)
1	50	30	100	60.0
2	56	56	100	100.0
3	50	40	100	80.0
4	100	70	100	70.0
5	27	24	100	88.9
6	45	36	100	80.0
7	50	40	100	80.0
8	26	26	100	100.0
9	50	50	100	100.0
10	50	33	100	66.0
11	50	43	100	86.0
12	19	19	100	100.0
13	40	36	100	90.0
14	90	86	100	95.6
15	90	65	100	72.2
16	90	63	100	70.0
17	60	52	100	86.7
18	40	37	100	92.5
18	55	36	100	65.5
20	90	90	100	100.0
21	58	58	100	100.0
22	45	27	100	60.0
23	65	54	100	83.1
24	75	52	100	69.3
25	59	59	100	100.0
26	30	20	100	66.7
27	50	50	100	100.0
28	26	18	100	69.2
		mean	**100**	**83.3**
		S.D.	**14.2**	

Table 5 DPD, TP, TS and OPRT mRNA expression in CCA tissues

Number of samples	mRNA expression			
	DPD	**TP**	**TS**	**OPRT**
1	0.30	0.34	0.05	0.13
2	1.07	1.48	0.10	0.30
3	0.83	0.51	0.13	0.30
4	0.05	0.13	0.31	0.35
5	0.04	0.16	0.14	0.17
6	1.66	0.72	0.06	0.30
7	1.15	1.62	0.18	0.54
8	0.36	0.54	0.19	0.13
9	0.26	0.56	0.12	0.27
10	0.06	0.05	0.13	0.03
11	0.56	0.87	0.36	0.48
12	0.85	2.00	0.42	0.28
13	0.60	0.24	1.22	0.71
14	0.16	0.03	0.47	0.31
15	2.82	2.06	0.13	0.47
16	1.38	1.05	0.22	0.14
17	0.31	0.37	0.13	0.06
18	0.42	0.37	0.22	0.36
19	0.17	0.43	0.08	0.36
20	0.58	1.00	0.09	0.30
21	0.23	1.35	0.22	0.09
22	0.54	2.34	0.24	0.42
23	0.93	0.55	0.21	0.35
24	1.17	1.15	0.18	0.24
25	6.76	2.00	0.43	1.02
26	0.10	0.10	0.22	0.30
27	1.48	0.44	0.04	0.09
28	1.07	2.09	0.10	0.14
29	0.82	1.18	0.10	0.23
30	5.19	2.71	0.17	0.40
31	0.23	0.50	0.06	0.20
32	0.47	0.34	0.12	0.23
33	0.52	0.95	0.14	0.14
34	2.08	3.01	0.17	0.25
35	1.30	2.05	0.06	0.13
amount	**35**	**35**	**35**	**35**
Mean	**1.04**	**1.01**	**0.21**	**0.29**
Minimum	**0.04**	**0.03**	**0.04**	**0.03**
Maximum	**6.76**	**3.01**	**1.22**	**1.02**
fold-difference	**169**	**100**	**31**	**34**

Table 6 OPRT/TP, DPD/TS, DPD/OPRT, TS/OPRT, TP/TS and TP/DPD mRNA expression in CCA tissues

Number of samples	mRNA expression					
	OPRT/TP	DPD/TS	DPD/OPRT	TS/OPRT	TP/TS	TP/DPD
1	2.69	6.31	2.34	0.37	7.08	1.12
2	1.10	10.73	3.55	0.33	14.81	1.38
3	0.55	6.17	2.75	0.45	3.80	0.62
4	0.55	0.15	0.14	0.89	0.42	2.69
5	0.41	0.26	0.21	0.83	1.10	4.26
6	0.23	27.55	5.62	0.20	12.02	0.44
7	0.48	6.31	2.14	0.34	8.91	1.41
8	0.16	1.86	2.88	1.55	2.75	1.48
9	0.18	2.14	0.95	0.45	4.68	2.19
10	0.07	0.43	1.90	4.46	0.41	0.95
11	0.21	1.55	1.17	0.76	2.40	1.55
12	3.00	2.05	3.09	1.51	4.80	2.34
13	0.2	0.49	0.85	1.72	0.20	0.40
14	0.07	0.35	0.52	1.51	0.07	0.21
15	0.19	22.52	6.02	0.27	16.46	0.73
16	0.15	6.17	10.00	1.62	4.68	0.76
17	0.08	2.30	5.13	2.23	2.76	1.20
18	0.06	1.91	1.17	0.61	1.68	0.88
19	0.37	2.13	0.47	0.22	5.38	2.53
20	0.12	6.44	1.93	0.30	11.11	1.72
21	0.33	1.05	2.56	2.44	6.14	5.87
22	0.23	2.25	1.29	0.57	9.75	4.33
23	8.91	4.43	2.66	0.60	2.62	0.59
24	0.13	6.50	4.88	0.75	6.39	0.98
25	0.3	15.72	6.63	0.42	4.65	0.30
26	0.38	0.45	0.33	0.73	0.45	1.00
27	0.20	37.00	16.44	0.44	11.00	0.30
28	0.59	10.70	7.64	0.71	20.90	1.95
29	0.14	8.20	3.57	0.43	11.80	1.44
30	2.95	30.53	12.98	0.43	15.94	0.52
31	0.84	3.83	1.15	0.30	8.33	2.17
32	0.64	3.92	2.04	0.52	2.83	0.72
33	0.97	3.71	3.71	1.00	6.79	1.83
34	0.51	12.24	8.32	0.68	17.71	1.45
35	0.40	21.67	10.00	0.46	34.17	1.58

Table 7 DPD, TP, TS and OPRT mRNA expression according to %I.I. in CCA Tissues

mRNA expression							
DPD		TP		TS		OPRT	
poorly response	well response	poorly response	well response	poorly response	well response	poorly response	well response
0.05	0.30	0.13	0.34	0.31	0.05	0.35	0.13
0.56	1.07	0.87	1.48	0.36	0.10	0.48	0.30
1.66	0.85	0.72	2.00	0.06	0.42	0.30	0.28
0.36	0.60	0.54	0.24	0.19	1.22	0.13	0.71
0.26	0.93	0.56	0.55	0.12	0.21	0.27	0.35
0.31	0.42	0.37	0.37	0.13	0.22	0.06	0.36
0.54	6.76	2.34	2.00	0.24	0.43	0.42	1.02
0.23	0.23	1.35	0.50	0.22	0.06	0.09	0.20
1.17		1.15		0.18		0.24	
1.48		0.44		0.04		0.09	
1.07		2.09		0.10		0.14	
0.82		1.18		0.10		0.23	
0.52		0.95		0.14		0.14	
2.08		3.01		0.17		0.25	
1.30		2.05		0.06		0.13	
1.51		1.66		0.37		0.62	
4.57		4.27		0.14		0.50	
1.15		1.62		0.18		0.54	
1.38		1.05		0.22		0.14	
0.58		1.00		0.09		0.30	

Table 8 OPRT/TP, DPD/TS, DPD/OPRT, TS/OPRT, TP/TS and TP/DPD mRNA expression according to %I.I. in CCA tissues

mRNA expression					
OPRT/TP		**DPD/TS**		**DPD/OPRT**	
poorly response	**well response**	**poorly response**	**well response**	**poorly response**	**well response**
2.69	0.38	0.15	6.31	0.14	2.34
0.55	0.20	1.55	10.73	1.17	3.55
0.41	0.14	27.55	2.05	5.62	3.09
0.23	2.95	1.86	0.49	2.88	0.85
0.48	0.64	2.14	4.43	0.95	2.66
0.16	0.97	2.30	1.91	5.13	1.17
0.18	0.51	2.25	15.72	1.29	6.63
0.07	0.40	1.05	3.83	2.56	1.15
0.21		6.50		4.88	
0.2		37.00		16.44	
0.07		10.70		7.64	
0.19		8.20		3.57	
0.15		3.71		3.71	
0.08		12.24		8.32	
0.06		21.67		10.00	
0.37		4.07		2.45	
0.12		32.46		9.12	
0.33		6.31		2.14	
0.13		6.17		10.00	
0.30		6.44		1.93	
TS/OPRT		**TP/TS**		**TP/DPD**	
poorly response	**well response**	**poorly response**	**well response**	**poorly response**	**well response**
0.89	0.37	0.42	7.08	2.69	1.12
0.76	0.33	2.40	14.81	1.55	1.38
0.20	1.51	12.02	4.80	0.44	2.34
1.55	1.72	2.75	0.20	1.48	0.40
0.45	0.60	4.68	2.62	2.19	0.59
2.23	0.61	2.76	1.68	1.20	0.88
0.57	0.42	9.75	4.65	4.33	0.30
2.44	0.30	6.14	8.33	5.87	2.17
0.75		6.39		0.98	
0.44		11.00		0.30	
0.71		20.90		1.95	
0.43		11.80		1.44	
1.00		6.79		1.83	
0.68		17.71		1.45	
0.46		34.17		1.58	
0.60		4.47		1.10	
0.28		30.29		0.93	
0.34		8.91		1.41	
1.62		4.68		0.76	
0.30		11.11		1.72	

APPENDIX C

Standard curve of real-time PCR

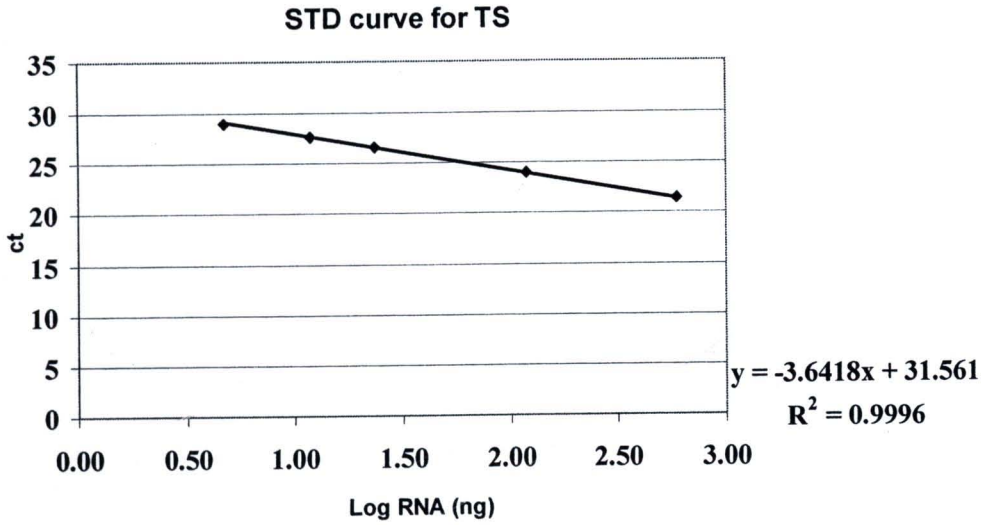

Figure 26 Standard curve for TS.

Efficacy rate (%) $= (10^{(-1/\text{slope})} - 1) \times 100$
$= (10^{(-1/-3.6418)} - 1) \times 100$
$= 0.8818 \times 100$
$= 88.18\ \%$

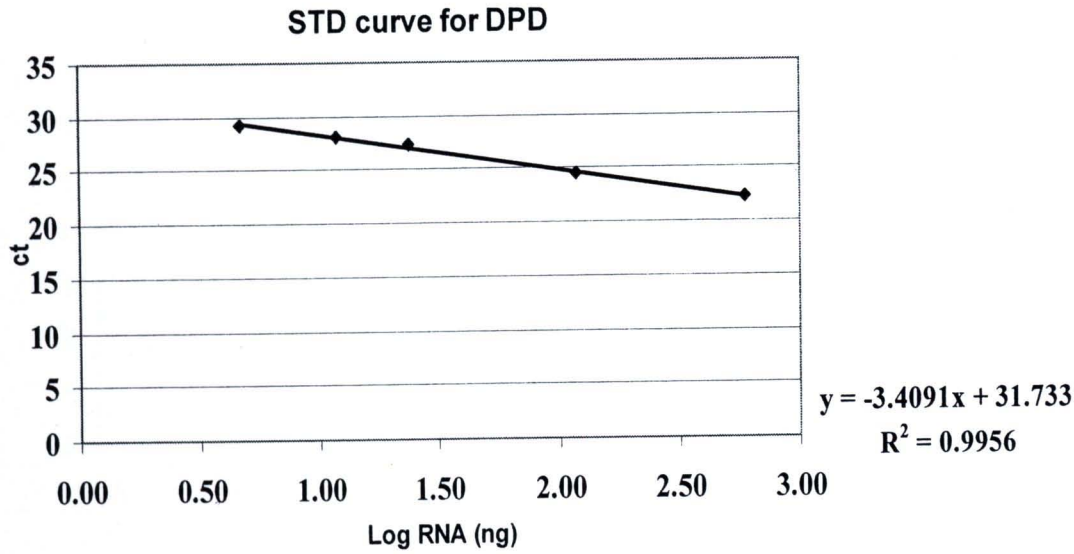

Figure 27 Standard curve for DPD.

Efficacy rate (%) $= (10^{(-1/\text{slope})} - 1) \times 100$
$= (10^{(-1/-3.4091)} - 1) \times 100$
$= 0.9648 \times 100$
$= 96.48\ \%$

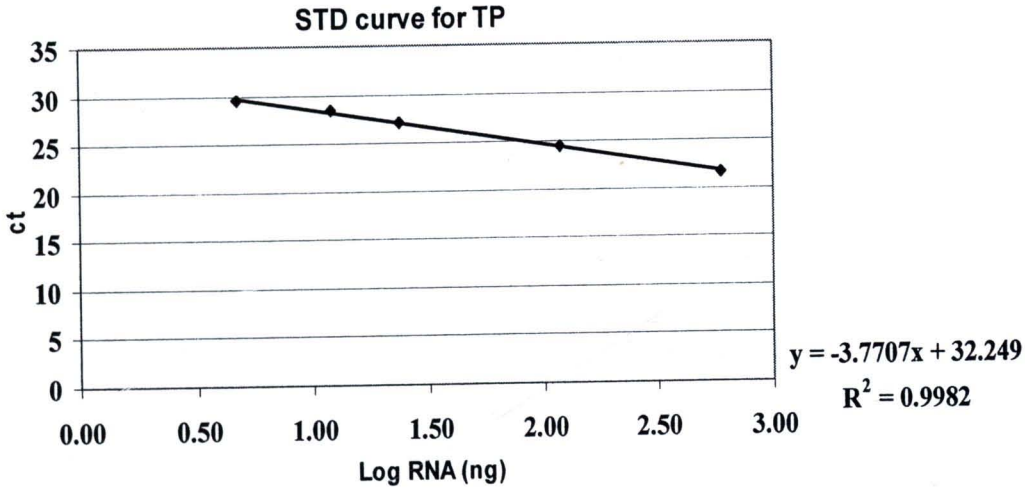

Figure 28 Standard curve for TP.

Efficacy rate (%) $= (10^{(-1/\text{slope})} - 1) \times 100$
$= (10^{(-1/-3.7707)} - 1) \times 100$
$= 0.8416 \times 100$
$= 84.16\ \%$

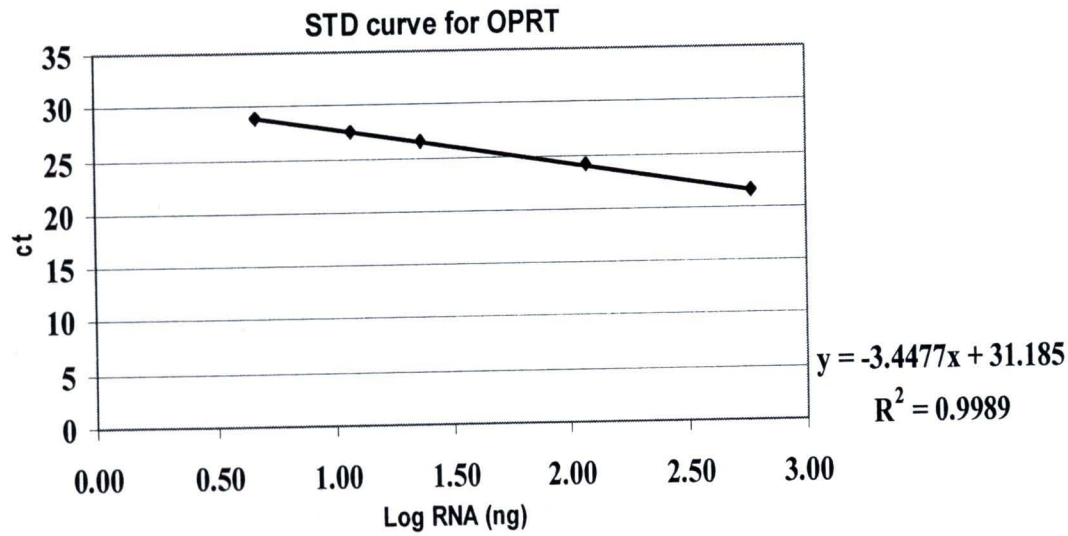

Figure 29 Standard curve for OPRT.

Efficacy rate (%) $= (10^{(-1/\text{slope})} - 1) \times 100$
$= (10^{(-1/-3.4477)} - 1) \times 100$
$= 0.9500 \times 100$
$= 95.00\ \%$

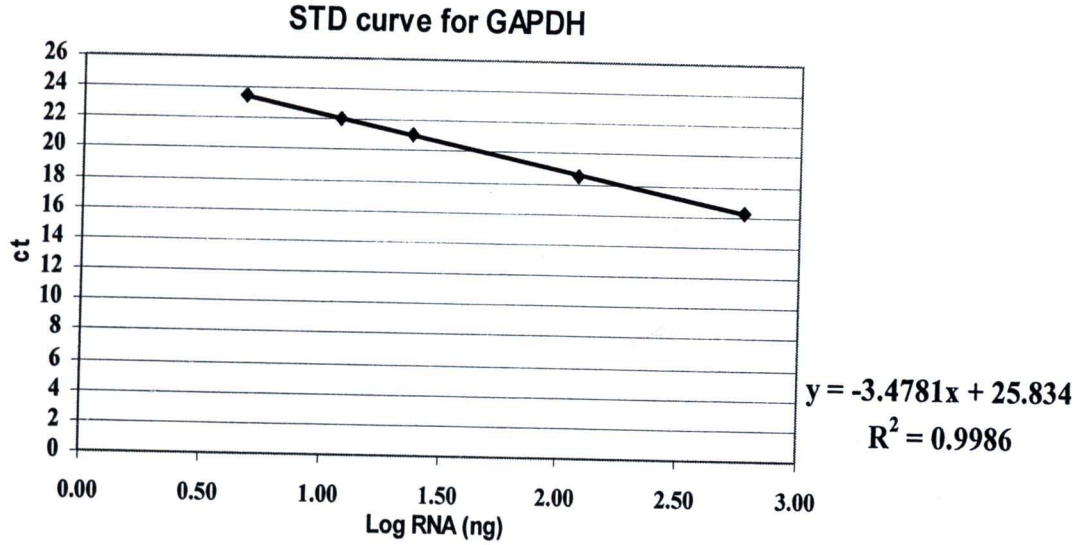

Figure 30 Standard curve for GAPDH.

Efficacy rate (%) $= (10^{(-1/\text{slope})} - 1) \times 100$

$= (10^{(-1/-3.4781)} - 1) \times 100$

$= 0.9387 \times 100$

$= 93.87\ \%$

RESEARCH PRESENTATIONS AND PUBLICATION

1. **Jariya. Chaiyagool,** Chariya. Hahnvajanawong, Banchob. Sripa, Vajarapong. Bhudhisawasdi, Narong. Khuntikeo, Ake. Pugkhem, Siri. Chau-in, Wichittra. Tassaneeyakul. (2009, 12-13 February). Dihydropyrimidine dehydrogenase (DPD) expression in cholangiocarcinoma predicts 5-FU sensitivity. ***The 12th National Graduate Research Conference***. Faculty of Engineering, Khon Kaen University, Thailand. (Poster presentation, proceeding publication).

2. **Jariya. Chaiyagool,** Chariya. Hahnvajanawong, Banchob. Sripa, Vajarapong. Bhudhisawasdi, Narong. Khuntikeo, Ake. Pugkhem, Siri. Chau-in, Wichittra. Tassaneeyakul. (2009, 10-12 May). Expression profile of genes involved in 5-fluorouracil metabolic pathway as predictive parameters for 5-fluorouracil response in cholangiocarcinoma. ***3rd Asian Pacific Regional Meeting: Understanding Xenobiotics for Better Drug Development and Therapy***. The Imperial Queen's Park Hotel, Bangkok, Thailand (Poster presentation).

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