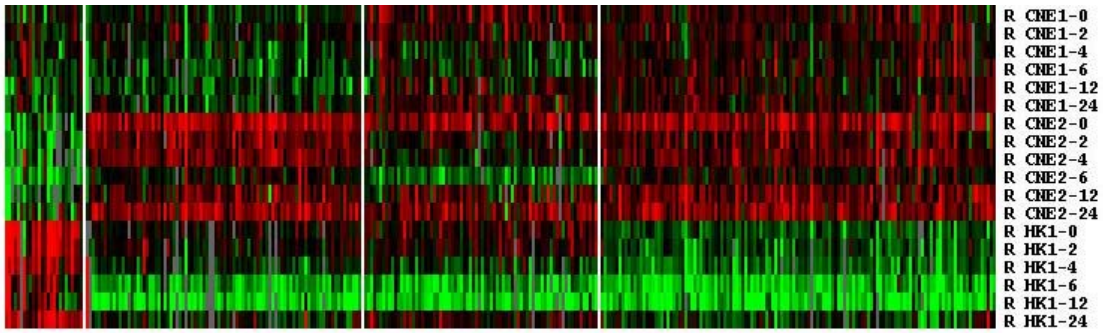
Supplementary Material

Part I: Sample Information

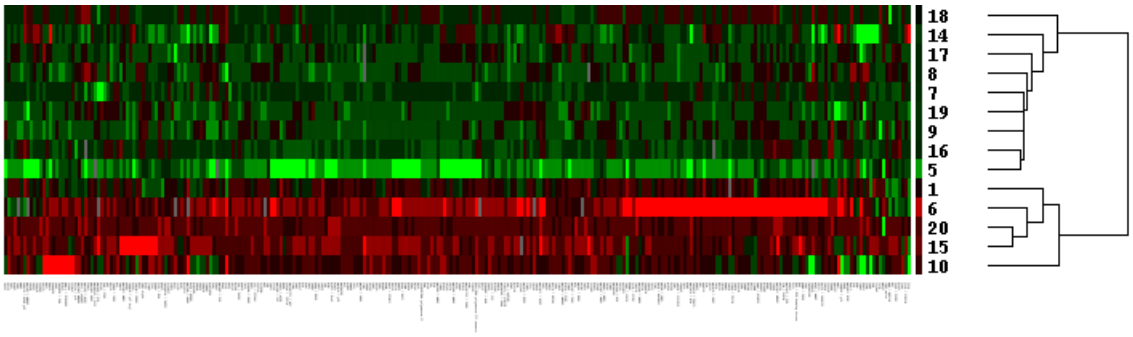
Three NPC cell lines, CNE1, CNE2, and HK1 were treated with CYC202. Gene expression of 380 selected genes were collected at 0, 2, 4, 6, 12 and 24 hours after treatment respectively. As a result, HK1 responsed the treatment; CNE2 partially responsed the treatment; CNE1 resisted the treatment. Figure Suppl_1 shows that unsupervised classification indicates genes were regulated differentially during the course of treatment among the three cell line.

Figure Suppl_1: Unsupervised classification of cell lines.



14 NPC patients were treated with CYC202. Gene expression were measured for these patients before and two weeks after the treatment, respectively. Figure Suppl_2 shows the unsupervised classification result on RE of these patients. According to the result, patients are classified into two molecular response group, responsive group (18, 14, 17, 8, 7, 19, 9, 16 and 5) and resistant group (1, 6, 20, 15, 10).

Figure Suppl_2: Unsupervised classification of patients.



Part II: Pathway Information

108 signaling pathways were collected from KEGG pathway database (September 14, 2008) [7] and 49 signaling pathways were collected from the Ingenuity Pathway database (July 12, 2008) [27]. All constructed pathways are organized in a particular XML format, which are available at the project

website.

Part III: Results of PathwayExpress

As a comparison to Decipherer, we evaluate CNE1 with PathwayExpress. However, we find 61 out 83 identified signaling pathways are more significant than 1E-4. See Figure Suppl_3 for the results of CNE1.

Figure Suppl_3: Result of Evaluating CNE1 by Pathway Express.

Pathway Details

Current Pathway Database Name : KEGG

Ra...	Datab...	Pathway Name	p-value	corrected p-value	gamma p-value	corrected gamma p-value
1	KEGG	Leukocyte transendothelial migration	3.65E-13	3.65E-13	3.3420791655608207E-14	3.3420791655608207E-14
2	KEGG	MAPK signaling pathway	1.012E-12	1.012E-12	4.86790388223406E-14	4.86790388223406E-14
3	KEGG	Toll-like receptor signaling pathway	2.26E-13	2.26E-13	6.892578684330755E-14	6.892578684330755E-14
4	KEGG	Regulation of actin cytoskeleton	3.396E-12	3.396E-12	1.3469819199528066E-13	1.3469819199528066E-13
5	KEGG	ErbB signaling pathway	1.1E-14	1.1E-14	2.919065414979744E-13	2.919065414979744E-13
6	KEGG	Small cell lung cancer	1.1E-14	1.1E-14	3.0939972431770117E-13	3.0939972431770117E-13
7	KEGG	Gap junction	6.8E-14	6.8E-14	1.503318678721295E-12	1.503318678721295E-12
8	KEGG	Melanogenesis	1.94E-13	1.94E-13	4.214279065444426E-12	4.214279065444426E-12
9	KEGG	Focal adhesion	2.079E-12	2.079E-12	4.350975257099812E-12	4.350975257099812E-12
10	KEGG	Prostate cancer	2.96E-13	2.96E-13	6.96813025205572E-12	6.96813025205572E-12
11	KEGG	Type II diabetes mellitus	7.89E-13	7.89E-13	1.886837053355796E-11	1.886837053355796E-11
12	KEGG	Cell cycle	1.204E-12	1.204E-12	2.120665278884745E-11	2.120665278884745E-11
13	KEGG	Natural killer cell mediated cytotoxicity	1.495E-12	1.495E-12	2.7020736794989198E-11	2.7020736794989198E-11
14	KEGG	Wnt signaling pathway	2.509E-12	2.509E-12	2.8274635002390064E-11	2.8274635002390064E-11
15	KEGG	Cytokine-cytokine receptor interaction	1.955E-12	1.955E-12	3.17766548281468E-11	3.17766548281468E-11
16	KEGG	Insulin signaling pathway	2.105E-12	2.105E-12	4.4582869477536574E-11	4.4582869477536574E-11
17	KEGG	Jak-STAT signaling pathway	2.291E-12	2.291E-12	4.976415333172364E-11	4.976415333172364E-11
18	KEGG	TGF-beta signaling pathway	8.625E-12	8.625E-12	1.871757049615259E-10	1.871757049615259E-10
19	KEGG	$hsa05131$	8.6923119E-8	8.6923119E-8	2.4114685386954475E-9	2.4114685386954475E-9
20	KEGG	Pathogenic Escherichia coli infection	8.6923119E-8	8.6923119E-8	2.4114685386954475E-9	2.4114685386954475E-9
21	KEGG	Basal cell carcinoma	7.67122E-10	7.67122E-10	1.4805134226985281E-8	1.4805134226985281E-8
22	KEGG	Nucleotide excision repair	9.42677E-10	9.42677E-10	1.758076066490001E-8	1.758076066490001E-8
23	KEGG	Long-term depression	2.275738E-9	2.275738E-9	3.3403393308571245E-8	3.3403393308571245E-8
24	KEGG	Dorso-ventral axis formation	7.874663E-9	7.874663E-9	1.284798477782979E-7	1.284798477782979E-7
25	KEGG	Axon guidance	1.4341456E-8	1.4341456E-8	2.189974319943979E-7	2.189974319943979E-7
26	KEGG	Huntington"s disease	1.4429549E-8	1.4429549E-8	2.2171349648285518E-7	2.2171349648285518E-7
27	KEGG	Amyotrophic lateral sclerosis (ALS)	1.5067409E-7	1.5067409E-7	1.986487866605333E-6	1.986487866605333E-6
28	KEGG	Phosphatidylinositol signaling system	3.222974871E-6	3.222974871E-6	3.0213962650443857E-6	3.0213962650443857E-6
29	KEGG	Calcium signaling pathway	7.22118038E-7	7.22118038E-7	8.827996708218528E-6	8.827996708218528E-6
30	KEGG	Hematopoietic cell lineage	4.64294089288E-4	4.64294089288E-4	6.020320675695191E-5	6.020320675695191E-5
31	KEGG	Ubiquitin mediated proteolysis	6.549183275E-6	6.549183275E-6	7.229343253999142E-5	7.229343253999142E-5
32	KEGG	Tight junction	9.407681636E-6	9.407681636E-6	9.766551116387484E-5	9.766551116387484E-5
33	KEGG	Hedgehog signaling pathway	2.9252349012E-5	2.9252349012E-5	3.1551472692511697E-4	3.1551472692511697E-4
34	KEGG	Long-term potentiation	-1.472E-12	-1.472E-12	5.838510679762472E-4	5.838510679762472E-4
35	KEGG	Dentatorubropallidoluysian atrophy	7.0175764041E-5	7.0175764041E-5	6.551392136720333E-4	6.551392136720333E-4
36	KEGG	Adherens junction	-2.9E-14	-2.9E-14	0.0011167014646890124	0.0011167014646890124
37	KEGG	Alzheimer"s disease	3.44866416576E-4	3.44866416576E-4	0.002586042397319618	0.002586042397319618

38	KEGG	Graft-versus-host disease	8.164	4.82173683006E-4	4.82173683006E-4	0.00260918534320871	0.00260918534320871
39	KEGG	Type I diabetes mellitus	7.946	6.00039239776E-4	6.00039239776E-4	0.0031675606606753467	0.0031675606606753467
40	KEGG	DNA replication	6.359	0.002103489389306	0.002103489389306	0.012739142407515785	0.012739142407515785
41	KEGG	Vibrio cholerae infection	6.201	0.002285186046046	0.002285186046046	0.014599323386483582	0.014599323386483582
42	KEGG	Taste transduction	4.806	0.00944363091651	0.00944363091651	0.04749607825524354	0.04749607825524354
43	KEGG	Base excision repair	4.394	0.014640812527532	0.014640812527532	0.0666225096849033	0.0666225096849033
44	KEGG	$hsa03450$	4.214	0.016985432045638	0.016985432045638	0.0770999471035711	0.0770999471035711
45	KEGG	Allograft rejection	3.858	0.02138184490894	0.02138184490894	0.10255324319951722	0.10255324319951722
46	KEGG	Antigen processing and presentation	3.669	0.049386248301122	0.049386248301122	0.1190686473138837	0.1190686473138837
47	KEGG	Notch signaling pathway	3.484	0.035135741512726	0.035135741512726	0.13758897299799536	0.13758897299799536
48	KEGG	Autoimmune thyroid disease	3.357	0.050107116679645	0.050107116679645	0.15179622951029498	0.15179622951029498
49	KEGG	Homologous recombination	2.753	0.066273195291285	0.066273195291285	0.2392025778862947	0.2392025778862947
50	KEGG	Basal transcription factors	2.515	0.098733891099674	0.098733891099674	0.2842331364065634	0.2842331364065634
51	KEGG	Regulation of autophagy	2.027	0.37703487972631	0.37703487972631	0.39874707116116864	0.39874707116116864
52	KEGG	Complement and coagulation cascades	2.005	0.293649589279483	0.293649589279483	0.4046541885649951	0.4046541885649951
53	KEGG	Biosynthesis of unsaturated fatty acids	1.992	0.304263007273265	0.304263007273265	0.40817554494751623	0.40817554494751623
54	KEGG	ECM-receptor interaction	1.937	0.155643399514495	0.155643399514495	0.4233265771625456	0.4233265771625456
55	KEGG	Mismatch repair	1.475	0.293196913043692	0.293196913043692	0.5662273494369255	0.5662273494369255
56	KEGG	PPAR signaling pathway	1.361	0.293649589279483	0.293649589279483	0.6053704211800345	0.6053704211800345
57	KEGG	RNA polymerase	1.349	0.325879463344753	0.325879463344753	0.6095646322086604	0.6095646322086604
58	KEGG	Renal cell carcinoma	1.278	-1.481E-12	-1.481E-12	0.6346369759560962	0.6346369759560962
59	KEGG	Cell Communication	1.085	0.366620647228459	0.366620647228459	0.7045252235904766	0.7045252235904766
60	KEGG	Asthma	0.975	0.37703487972631	0.37703487972631	0.744954898287235	0.744954898287235
61	KEGG	Apoptosis	0.929	-1.34E-13	-1.34E-13	0.7618555820880597	0.7618555820880597
62	KEGG	Cell adhesion molecules (CAMs)	0.604	0.618305369740483	0.618305369740483	0.8767797218081347	0.8767797218081347
63	KEGG	Olfactory transduction	0.591	0.71796608587358	0.71796608587358	0.8810532161229907	0.8810532161229907
64	KEGG	p53 signaling pathway	0.521	-1.353E-12	-1.353E-12	0.9033619396914062	0.9033619396914062
65	KEGG	B cell receptor signaling pathway	0.396	-1.4E-13	-1.4E-13	0.9395173475285913	0.9395173475285913
66	KEGG	Epithelial cell signaling in Helicobacter	0.372	-1.481E-12	-1.481E-12	0.945794020743233	0.945794020743233
67	KEGG	Bladder cancer	0.333	-1.362E-12	-1.362E-12	0.9554546688095468	0.9554546688095468
68	KEGG	Melanoma	0.31	-4.91E-13	-4.91E-13	0.9608155126538189	0.9608155126538189
69	KEGG	Glioma	0.301	-1.115E-12	-1.115E-12	0.9628411823434665	0.9628411823434665
70	KEGG	Colorectal cancer	0.289	-1.34E-13	-1.34E-13	0.9654767327640407	0.9654767327640407
71	KEGG	Chronic myeloid leukemia	0.271	-9.25E-13	-9.25E-13	0.969285566930838	0.969285566930838
72	KEGG	Adipocytokine signaling pathway	0.243	-6.01E-13	-6.01E-13	0.9748494916180446	0.9748494916180446
73	KEGG	Thyroid cancer	0.236	-1.207E-12	-1.207E-12	0.9761689129809443	0.9761689129809443
74	KEGG	GnRH signaling pathway	0.233	-3.03E-13	-3.03E-13	0.9767253561554792	0.9767253561554792
75	KEGG	Neurodegenerative Diseases	0.229	-9.92E-13	-9.92E-13	0.9774587676777605	0.9774587676777605
76	KEGG	Non-small cell lung cancer	0.221	-3.97E-13	-3.97E-13	0.9788960666343285	0.9788960666343285
77	KEGG	Pancreatic cancer	0.217	-4.41E-13	-4.41E-13	0.9795997726441869	0.9795997726441869
78	KEGG	mTOR signaling pathway	0.193	-1.13E-13	-1.13E-13	0.9836069951479561	0.9836069951479561
79	KEGG	Fc epsilon RI signaling pathway	0.19	-1.182E-12	-1.182E-12	0.984081369392601	0.984081369392601
80	KEGG	T cell receptor signaling pathway	0.17	-1.68E-13	-1.68E-13	0.9870878354177689	0.9870878354177689
81	KEGG	Endometrial cancer	0.167	-2.78E-13	-2.78E-13	0.9875149464304988	0.9875149464304988
82	KEGG	Acute myeloid leukemia	0.141	-1.138E-12	-1.138E-12	0.9909463046470391	0.9909463046470391
83	KEGG	VEGF signaling pathway	0.141	-4.91E-13	-4.91E-13	0.9909463046470391	0.9909463046470391

Part IV: Genetic Pathway Hypotheses

Table Suppl_1 shows generated genetic hypotheses for each of the NPC patients.

Table Suppl_1: Genetic hypotheses for the NPC patients.

Source	Pathway	p-value	FDR
Pt1			
GNRH	GnRH-->GnRHR-->Gq/11-->PLC-Beta-->DAG-->PKC-->MEKK-->MK K3/6-->p38MAPK-->Gonadotropins gene expression and secretion	2.49E-3	0.157
MAPK	G-protein-->IP3-->Ca2+-->RasGRP-->Ras-->RafB-->MEK1-->ERK-->c-Myc-->c-fos-->DNA2---ERK-Pathway-->Proliferation, differentiation	9.30E-3	0.181
ADIPOCYTOKINE	TNF-Alpha-->TNFR2-->TRAF2-->JNK--|IRS-->Akt-->Insulin resistance	1.47E-2	0.181
MAPK	IL1-->IL1R-->TRAF2-->MEKK1-->MEK1-->ERK-->Elk-1-->SRF-->c-f	1.56E-2	0.181

	os-->Proliferation, differentiation 0.5130090559393918		
WNT	PS-1-->Beta-Catenin-->TCF/LEF-->cycD-->Cell cycle	2.23e-2	0.181
Pt5			
MAPK	IL1-->IL1R-->TRAF2-->MEKK1-->MEK1-->ERK-->c-Myc-->c-fos-->Proliferation, differentiation	1.00E-4	6.99E-3
MAPK	IL1-->IL1R-->TRAF2-->ASK1-->MKK6-->p38-->MAPKAPK-->CREB	1.80E-3	4.90E-2
JAK-STAT	STAM-->JAK-->SHP2-->GRB-->SOS-->MAPK signaling pathway-->CycD-->Cell cycle	2.10E-3	4.90E-2
MAPK	TGFB-->TGFBR-->DAXX-->ASK1-->MKK6-->p38-->p53-->p53 signaling pathway	5.80E-3	0.102
APOPTOSIS	TRAIL-->TRAIL-R-->FADD-->CASP8-->CASP7-->Cleavage of Caspase Substrate-->Apoptosis	1.75E-2	0.245
Pt6			
ERBB	EGF-->ErbB1-->Grb2-->GAB1-->PI3K-->PIP3-->PKB/Akt-->mTOR--|eIF-4EBP-->Protein synthesis	1.20E-3	7.32E-2
FOCAL-ADHESION	GF-->RTK-->FAK-->RhoGEF-->RhoA-->mDia1-->Actin-->Actin polymerization	6.20E-3	0.122
ERBB	EGF-->ErbB1-->Nck-->PAK-->JNKK-->JNK-->Elk-->Angiogenesis	7.90E-3	0.122
JAK-STAT	STAM-->JAK-->STAT-->Homo/hetero STAT dimers-->CBP-->Pim-1-->Growth, proliferation, fate determination, development, immunity	8.00E-3	0.122
FC-EPSILON	Lyn-->Syk-->PLC-Gamma-->DAG-->PKC-->Histamine, Heparin-->Toxic to parasites, Increase vascular permeability, Cause smooth muscle contraction	1.36E-2	0.139
Pt7			
APOPTOSIS	IL-1-->IL-1R-->MyD88-->IRAK-->NIK-->IKK--|IKB-Alpha--|NF-kB-->Bcl-XL-->Survival	2.00E-4	1.14E-2
MAPK	Heterotrimeric G-protein-->DAG-->PKC-->Raf1-->MEK1-->ERK-->MNK1/2-->CREB-->Proliferation, differentiation	6.00E-4	1.71E-2
MAPK	ASK2-->MKK6-->p38-->MAPKAPK-->CREB	1.50E-3	2.85E-2
MAPK	FGF-->FGFR-->GRB2-->SOS-->RAS-->RafB-->MEK2-->ERK-->Sap1a->SRF-->c-fos-->Proliferation, differentiation	5.10E-3	7.27E-2
APOPTOSIS	IL-1-->IL-1R-->TRADD-->FADD-->CASP8-->CASP3-->Cleavage of Caspase Substrate-->Apoptosis	2.24E-2	0.213
Pt8			
MAPK	ASK2-->MKK6-->p38-->PRAK-->CREB	2.10E-3	7.25E-2
MAPK	HGK-->MEKK1-->MKK4-->JNK-->ATF-2	2.50E-3	7.25E-2
APOPTOSIS	IL-1-->IL-1R-->MyD88-->IRAK-->NIK-->IKK--|IKB-Alpha--|NF-kB-->IAP-->Survival	5.30E-3	9.22E-2
JAK-STAT	STAM-->JAK-->STAT-->Homo/hetero STAT dimers-->CBP-->Pim-1-->Growth, proliferation, fate determination, development, immunity	1.30E-2	0.165

GNRH	GnRH-->GnRHR-->Gq/11-->PLC-Beta-->DAG-->PKC-->MEKK-->MKK3/6-->p38MAPK-->Gonadotropins gene expression and secretion	1.62E-2	0.165
Pt9			
MAPK	IL1-->IL1R-->CASP-->PAK1/2-->MEKK2/3	5.10E-3	0.123
APOPTOSIS	IL-1-->IL-1R-->MyD88-->IRAK-->NIK-->IKK--|IKB-Alpha--|NF-kB-->IAP-->Survival	6.70E-3	0.123
FOCAL-ADHESION	GF-->RTK-->FAK-->RhoGEF-->RhoA-->PIP5K-->PIP2-->Actin-->Actin polymerization	7.80E-3	0.123
MAPK	Heterotrimeric G-protein-->DAG-->PKC-->Raf1-->MEK1-->ERK-->c-Myc-->c-fos-->Proliferation, differentiation	8.30E-3	0.123
P53	Gamma-irradiation, UV, Genotoxic drugs-->DNA damage-->ATM-->CHK2-->p53-->DNA-->p48-->p53R2-->Gadd45-->Sestrins-->DNA repair and damage prevention	8.40E-3	0.123
Pt10			
MAPK	FGF-->FGFR-->GRB2-->SOS-->RAS-->Raf1-->MEK1-->ERK-->Elk-1-->SRF-->c-fos-->Proliferation, differentiation	1.00E-4	6.50E-3
FOCAL-ADHESION	PTEN--|FAK-->Grb2-->Sos-->Ha-Ras-->PI3K-->PIP3-->Vav-->Rac-->PAK--|MLCK-->MLC-->Actin-->Actin polymerization	7.00E-4	2.28E-2
GNRH	Ca2+-->CACN-->PKC-->MEKK-->MKK3/6-->p38MAPK-->Gonadotropins gene expression and secretion	2.20E-3	4.77E-2
JAK-STAT	STAM-->JAK-->SHP2-->GRB-->SOS-->MAPK signaling pathway-->BclXL-->Antiapoptosis	5.00E-3	8.13E-2
FC-EPSILON	Lyn-->Syk-->PI3K-->RAC-->MKK3/6-->p38-->DNA-->TNF-Alpha-->Promotes inflammation, Stimulates cytokine production by many cell types, Activates endothelium	8.40E-3	0.109
Pt14			
APOPTOSIS	IL-1-->IL-1R-->TRADD-->FADD-->CASP8-->Bid-->CytC-->Apaf-1-->CASP9-->CASP3-->Cleavage of Caspase Substrate-->Apoptosis	5.00E-4	3.40E-2
FOCAL-ADHESION	GF-->RTK-->FAK-->p130Cas-->Crk-->Paxillin-->Actin-->Actin polymerization	1.20E-3	4.08E-2
MAPK	Tpl2/Cot-->MEK2-->ERK-->c-Myc-->c-fos-->Proliferation, differentiation	3.50E-3	7.93E-2
CELL_CYCLE	TGF-Beta-->Smad2/3-->Smad4-->Kip1,2--|CycD-->CDK4,6--|Rb--|E2F-->DP1-->S-phase proteins	5.30E-3	8.02E-2
MAPK	IL1-->IL1R-->TRAF2-->MEKK1-->MEK2-->ERK-->MNK1/2-->CREB-->Proliferation, differentiation	5.90E-3	8.02E-2
Pt15			
ERBB	TGF-Alpha-->ErbB1-->Shc-->Grb2-->GAB1-->PI3K-->PIP3-->PKB/Akt-->mTOR--|eIF-4EBP-->Protein synthesis	2.00E-4	1.24E-2
APOPTOSIS	NGF-->TrkA-->PI3K-->Akt/PKB-->IKK--|IKB-Alpha--|NF-kB-->Bcl-XL-->Survival	3.60E-3	0.112
MTOR	INS/IGF-->Insulin signaling	5.90E-3	0.122

	pathway-->PI3K-->PIP3-->PDK1-->AKT-->Raptor-->G-BetaL-->mTOR-->HIF1-Alpha-->DNA-->VEGF-->VEGF signaling pathway		
MAPK	PP2CA--|MKK3-->p38-->ATF-2	9.70E-3	0.143
INSULIN	LAR--|SHC-->GRB2-->SOS-->Ras-->Raf-->MEK1/2-->ERK1/2-->MNK-->eIF4E-->Protein synthesis	1.15E-2	0.143
Pt16			
MAPK	IL1-->IL1R-->TAB1-->TAK1-->IKK-->NFkB-->Proliferation, inflammation, anti-apoptosis	1.70E-3	0.114
MAPK	Heterotrimeric G-protein-->DAG-->PKC-->Raf1-->MEK1-->ERK-->Sap1a-->SRF-->c-fos-->Proliferation, differentiation	4.80E-3	0.114
Pt17			
MAPK	IL1-->IL1R-->TAB1-->TAK1-->MKK6-->p38-->p53-->p53 signaling pathway	3.00E-4	1.89E-2
MAPK	MLTK-->MKK7-->JNK-->ATF-2	2.50E-3	7.87E-2
MAPK	PP5--|ASK1-->MKK6-->p38-->Sap1a-->Proliferation, differentiation, inflammation, apoptosis pathway, cell cycle pathway	7.60E-3	0.128
JAK-STAT	STAM-->JAK-->STAT-->Homo/hetero STAT dimers-->CBP-->Pim-1-->Growth, proliferation, fate determination, development, immunity	1.28E-2	0.128
ACTIN	GF-->RTK-->Sos-->Ras-->PI3K-->PIP3-->Vav/Tiam1-->Rac-->PAK-->MAPK signaling pathway-->Gene expression	1.40E-2	0.128
Pt18			
P53	Gamma-irradiation, UV, Genotoxic drugs-->DNA damage-->ATR-->CHK1-->p53-->DNA-->Fas-->PIDD-->DR5-->CASP8-->CASP3-->Apoptosis	5.00E-3	0.166
JAK-STAT	STAM-->JAK-->PI3K-->AKT-->Antiapoptosis	6.20E-3	0.166
APOPTOSIS	IL-1-->IL-1R-->TRADD-->FADD-->CASP8-->CASP7-->Cleavage of Caspase Substrate-->Apoptosis	6.90E-3	0.166
APOPTOSIS	TRAIL-->TRAIL-R-->FADD-->CASP8-->CASP3-->Cleavage of Caspase Substrate-->Apoptosis	1.23E-2	0.177
MAPK	IL1-->IL1R-->TRAF2-->MEKK1-->MEK1-->ERK-->c-Myc-->c-fos-->Proliferation, differentiation	2.04E-2	0.177
Pt19			
FOCAL-ADHESION	GF-->RTK-->Shc-->Grb2-->Sos-->Ha-Ras-->PI3K-->PIP3-->Vav-->Rac-->PAK--|MLCK-->MLC-->Actin-->Actin polymerization	1.70E-3	6.48E-2
MAPK	GLK-->MEKK1-->MKK4-->JNK-->ATF-2	1.80E-3	6.48E-2
MAPK	HGK-->MEKK1-->MKK4-->JNK-->p53-->p53 signaling pathway	3.90E-3	9.36E-2
MAPK	ASK2-->MKK3-->p38-->PRAK-->CREB---p38-Pathway	1.14E-2	0.204
CALCIUM	Growth factor-->PTK-->PLC-Gamma-->IP3-->IP3R-->Ca2+-->FAK2	1.42E-2	0.204
Pt20			
WNT	Wnt11-->Frizzled-->Dv1--|Daam1--|RhoA-->JNK-->Gene transcription	1.00E-3	6.12E-2
GNRH	GnRH-->GnRHR-->Gq/11-->PLC-Beta-->DAG-->PKC-->Src-->EGFR--	1.70E-3	6.12E-2

	>Grb2-->Sos-->Ras-->Raf-1-->MEK1/2-->ERK1/2-->Elk1-->LH-Beta--> Gonadotropins gene expression and secretion		
ERBB	TGF-Alpha-->ErbB1-->Shc-->Grb2-->GAB1-->PI3K-->PIP3-->PKB/Akt -->mTOR-->p70S6K-->Protein synthesis	5.20E-3	9.36E-2
FC-EPSILON	Lyn-->Syk-->PI3K-->PLC-Gamma-->DAG-->PKC-->Histamine, Heparin-->Toxic to parasites, Increase vascular permeability, Cause smooth muscle contraction	8.80E-3	0.111
P53	Hypoxia-->p53-->DNA-->Fas-->PIDD-->DR5-->CASP8-->CASP3-->Ap optosis	1.11E-2	0.111

Part V: Treatment Proposal

Table Suppl_2 shows some further treatment proposed to the CYC202 resistant patients.

Table Suppl_2: Proposed personal treatment.

Patient	Comments
Patient1	PI3K-NFκB-IAP pathway and G1/S progression are dysregulated. JNK/p38 pathway is activated only by the cytokinin regulation. Radiotherapy is suggested to be used together with CYC202 to further activate the stress regulated JNK/p38 pathway to promote the suppression of NFκB activity and the induction of caspase activity.
Patient7	No significant drug-resistant pathway pattern is identified for this patient. We suggest to increase the dose of CYC202 or to combine the treatment with other CDK inhibitors, such as Olomoucine and Staurosporine, to further suppress the cell cycle progression.
Patient10	The pathway regulation shows full resistance to the treatment of CYC202. Both ERK pathway and PI3K-NFκB-IAP anti-apoptotic pathway are dysregulated. It is suggested to use other therapy, such as radiotherapy, to replace the treatment of CYC202.
Patient15	This patient shows a significant resistant pattern to the drug treatment on both pro- and anti-apoptotic pathway. There is no identification for other signaling pathways. Radiotherapy is recommended to be used in stead of CYC202. An alternatively is to use drugs that regulate apoptosis via other pathways, such as p53 regulated pro-apoptotic pathway.
Patient20	PI3K-BAD anti-apoptotic pathway is identified rather than the NFκB regulated one. The function of NFκB is suspected to be dysregulated. Drugs regulating apoptosis via NFκB-independent pathway are recommended.