

Contents

Glossary	xiii
Acronyms	xiv
1 Introduction and Literature Review	1
1.1 Cancer Research in the Post-Genomic Era	1
1.1.1 Cancer is a Global Health Issue	2
1.1.1.1 The Genetics and Molecular Biology of Cancers	3
1.1.2 The Genomics Revolution in Cancer Research	4
1.1.2.1 High-Throughput Technologies	4
1.1.2.2 Bioinformatics and Genomics Data	6
1.1.3 Genomics Projects	6
1.1.3.1 The Cancer Genome Project	6
1.1.3.2 The Cancer Genome Atlas Project	7
1.1.4 Genomic Cancer Medicine	8
1.1.4.1 Cancer Genes and Driver Mutations	9
1.1.4.2 Precision Cancer Medicine	10
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine	10
1.1.4.4 Targeted Therapeutics and Pharmacogenomics	10
1.1.5 Systems and Network Biology	11
1.1.5.1 Network Medicine and Polypharmacology	13
1.2 A Synthetic Lethal Approach to Cancer Medicine	14
1.2.1 Synthetic Lethal Genetic Interactions	14
1.2.2 Synthetic Lethal Concepts in Genetics	15
1.2.3 Synthetic Lethality in Model Systems	16
1.2.3.1 Synthetic Lethal Pathways and Networks	16
1.2.3.2 Evolution of Synthetic Lethality	17
1.2.4 Synthetic Lethality in Cancer	18
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	19
1.2.6 High-throughput Screening for Synthetic Lethality	21
1.2.6.1 Synthetic Lethal Screens	22
1.2.7 Computational Prediction of Synthetic Lethality	25
1.2.7.1 Bioinformatics Approaches to Genetic Interactions	25
1.2.7.2 Comparative Genomics	26
1.2.7.3 Analysis and Modelling of Protein Data	29
1.2.7.4 Differential Gene Expression	31

1.2.7.5	Data Mining and Machine Learning	32
1.2.7.6	Mutually Exclusive Bimodality	35
1.2.7.7	Rationale for Further Development	35
1.3	E-cadherin as a Synthetic Lethal Target	36
1.3.1	The <i>CDH1</i> gene and its Biological Functions	36
1.3.1.1	Cytoskeleton	36
1.3.1.2	Extracellular and Tumour Micro-environment	37
1.3.1.3	Cell-Cell Adhesion and Signalling	37
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	37
1.3.2.1	Breast Cancers and Invasion	38
1.3.3	Hereditary Diffuse Gastric Cancer and Lobular Breast Cancer .	38
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations	39
1.4	Summary and Research Direction of Thesis	40
1.4.1	Thesis Aims	41
2	Methods and Resources	43
2.1	Bioinformatics Resources for Genomics Research	43
2.1.1	Public Data and Software Packages	43
2.1.1.1	Cancer Genome Atlas Data	44
2.1.1.2	Reactome and Annotation Data	45
2.2	Data Handling	45
2.2.1	Normalisation	45
2.2.2	Sample Triage	46
2.2.3	Metagenes and the Singular Value Decomposition	48
2.2.3.1	Candidate Triage and Integration with Screen Data .	48
2.3	Techniques	49
2.3.1	Statistical Procedures and Tests	49
2.3.2	Gene Set Over-representation Analysis	50
2.3.3	Clustering	50
2.3.4	Heatmap	51
2.3.5	Modeling and Simulations	51
2.3.5.1	Receiver Operating Characteristic (Performance) .	52
2.3.6	Resampling Analysis	52
2.4	Pathway Structure Methods	53
2.4.1	Network and Graph Analysis	53
2.4.2	Sourcing Graph Structure Data	54
2.4.3	Constructing Pathway Subgraphs	55
2.4.4	Network Analysis Metrics	55
2.5	Implementation	56
2.5.1	Computational Resources and Linux Utilities	56
2.5.2	R Language and Packages	57
2.5.3	High Performance and Parallel Computing	60

3 Methods Developed During Thesis	62
3.1 A Synthetic Lethal Detection Methodology	62
3.2 Synthetic Lethal Simulation and Modelling	65
3.2.1 A Model of Synthetic Lethality in Expression Data	65
3.2.2 Simulation Procedure	69
3.3 Detecting Simulated Synthetic Lethal Partners	72
3.3.1 Binomial Simulation of Synthetic lethality	72
3.3.2 Multivariate Normal Simulation of Synthetic lethality	74
3.3.2.1 Multivariate Normal Simulation with Correlated Genes	77
3.3.2.2 Specificity with Query-Correlated Pathways	84
3.3.2.3 Importance of Directional Testing	84
3.4 Graph Structure Methods	86
3.4.1 Upstream and Downstream Gene Detection	86
3.4.1.1 Permutation Analysis for Statistical Significance	87
3.4.1.2 Hierarchy Based on Biological Context	88
3.4.2 Simulating Gene Expression from Graph Structures	89
3.5 Customised Functions and Packages Developed	93
3.5.1 Synthetic Lethal Interaction Prediction Tool	93
3.5.2 Data Visualisation	94
3.5.3 Extensions to the iGraph Package	97
3.5.3.1 Sampling Simulated Data from Graph Structures	97
3.5.3.2 Plotting Directed Graph Structures	97
3.5.3.3 Computing Information Centrality	98
3.5.3.4 Testing Pathway Structure with Permutation Testing .	98
3.5.3.5 Metapackage to Install iGraph Functions	99
4 Synthetic Lethal Analysis of Gene Expression Data	100
4.1 Synthetic Lethal Genes in Breast Cancer	101
4.1.1 Synthetic Lethal Pathways in Breast Cancer	103
4.1.2 Expression Profiles of Synthetic Lethal Partners	104
4.1.2.1 Subgroup Pathway Analysis	107
4.2 Comparing Synthetic Lethal Gene Candidates	110
4.2.1 Primary siRNA Screen Candidates	110
4.2.2 Comparison with Correlation	111
4.2.3 Comparison with Primary Screen Viability	113
4.2.4 Comparison with Secondary siRNA Screen Validation	114
4.2.5 Comparison to Primary Screen at Pathway Level	116
4.2.5.1 Resampling Genes for Pathway Enrichment	118
4.2.6 Integrating Synthetic Lethal Pathways and Screens	121
4.3 Metagene Analysis	123
4.3.1 Pathway Expression	124
4.3.2 Somatic Mutation	126
4.3.3 Synthetic Lethal Pathway Metagenes	130
4.3.4 Synthetic Lethality in Breast Cancer	131
4.4 Replication in Stomach Cancer	132
4.5 Discussion	133

4.5.1	Strengths of the SLIPT Methodology	133
4.5.2	Synthetic Lethal Pathways for E-cadherin	134
4.5.3	Replication and Validation	136
4.5.3.1	Integration with siRNA Screening	136
4.5.3.2	Replication across Tissues	137
4.6	Summary	137
5	Synthetic Lethal Pathway Structure	139
5.1	Synthetic Lethal Genes in Reactome Pathways	139
5.1.1	The PI3K/AKT Pathway	140
5.1.2	The Extracellular Matrix	142
5.1.3	G Protein Coupled Receptors	145
5.1.4	Gene Regulation and Translation	145
5.2	Network Analysis of Synthetic Lethal Genes	146
5.2.1	Gene Connectivity and Vertex Degree	147
5.2.2	Gene Importance and Centrality	148
5.2.2.1	Information Centrality	148
5.2.2.2	PageRank Centrality	150
5.3	Relationships between Synthetic Lethal Genes	152
5.3.1	Hierarchical Pathway Structure	152
5.3.1.1	Contextual Hierarchy of PI3K	152
5.3.1.2	Testing Contextual Hierarchy of Synthetic Lethal Genes	152
5.3.2	Upstream or Downstream Synthetic Lethality	156
5.3.2.1	Measuring Structure of Candidates within PI3K . . .	156
5.3.2.2	Resampling for Synthetic Lethal Pathway Structure .	158
5.4	Discussion	160
5.5	Summary	162
6	Simulation and Modeling of Synthetic Lethal Pathways	164
6.1	Synthetic Lethal Detection Methods	165
6.1.1	Performance of SLIPT and χ^2 across Quantiles	165
6.1.1.1	Correlated Query Genes affects Specificity	169
6.1.2	Alternative Synthetic Lethal Detection Strategies	171
6.1.2.1	Correlation for Synthetic Lethal Detection	171
6.1.2.2	Testing for Bimodality with BiSEp	173
6.2	Simulations with Graph Structures	174
6.2.1	Performance over a Graph Structure	175
6.2.1.1	Simple Graph Structures	175
6.2.1.2	Constructed Graph Structures	177
6.2.2	Performance with Inhibitions	180
6.2.3	Synthetic Lethality across Graph Structures	185
6.2.4	Performance within a Simulated Human Genome	189
6.3	Simulations in More Complex Graph Structures	193
6.3.1	Simulations over Pathway-based Graphs	194
6.3.2	Pathway Structures in a Simulated Human Genome	197
6.4	Discussion	200

6.4.1	Simulation Procedure	200
6.4.2	Comparing Methods with Simulated Data	201
6.4.3	Design and Performance of SLIPT	202
6.4.4	Simulations from Graph Structures	204
6.5	Summary	205
7	Discussion	207
7.1	Synthetic Lethality and <i>CDH1</i> Biology	207
7.1.1	Established Functions of <i>CDH1</i>	208
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer	208
7.2	Significance	209
7.2.1	Synthetic Lethality in the Genomic Era	209
7.2.2	Clinical Interventions based on Synthetic Lethality	211
7.3	Future Directions	212
7.4	Conclusions	214
References		216
A	Sample Quality	240
A.1	Sample Correlation	240
A.2	Replicate Samples in TCGA Breast	243
B	Software Used for Thesis	247
C	Mutation Analysis in Breast Cancer	256
C.1	Synthetic Lethal Genes and Pathways	256
C.2	Synthetic Lethal Expression Profiles	259
C.3	Comparison to Primary Screen	262
C.3.1	Resampling Analysis	264
C.4	Compare SLIPT genes	266
C.5	Metagene Analysis	268
C.6	Expression of Somatic Mutations	269
C.7	Metagene Expression Profiles	272
D	Intrinsic Subtyping	275
E	Stomach Expression Analysis	277
E.1	Synthetic Lethal Genes and Pathways	277
E.2	Comparison to Primary Screen	281
E.2.1	Resampling Analysis	283
E.3	Metagene Analysis	285
F	Synthetic Lethal Genes in Pathways	286
G	Pathway Connectivity for Mutation SLIPT	294
H	Information Centrality for Gene Essentiality	298

I Pathway Structure for Mutation SLIPT	301
J Performance of SLIPT and χ^2	304
J.1 Correlated Query Genes affects Specificity	310
K Graph Structures	316
K.1 Simulations from Simple Graph Structures	316
K.1.1 Simulations from Inhibiting Graph Structures	318
K.2 Simulation across Graph Structures	321
K.3 Simulations from Complex Graph Structures	325
K.3.1 Simulations from Complex Inhibiting Graphs	328
K.4 Simulations from Pathway Graph Structures	334

List of Figures

1.1	Synthetic genetic interactions	15
1.2	Synthetic lethality in cancer	19
2.1	Read count density	47
2.2	Read count sample mean	47
3.1	Framework for synthetic lethal prediction	63
3.2	Synthetic lethal prediction adapted for mutation	64
3.3	A model of synthetic lethal gene expression	66
3.4	Modeling synthetic lethal gene expression	67
3.5	Synthetic lethality with multiple genes	68
3.6	Simulating gene function	70
3.7	Simulating synthetic lethal gene function	70
3.8	Simulating synthetic lethal gene expression	71
3.9	Performance of binomial simulations	73
3.10	Comparison of statistical performance	73
3.11	Performance of multivariate normal simulations	75
3.12	Simulating expression with correlated gene blocks	78
3.13	Simulating expression with correlated gene blocks	79
3.14	Synthetic lethal prediction across simulations	80
3.15	Performance with correlations	81
3.16	Comparison of statistical performance with correlation structure	82
3.17	Performance with query correlations	83
3.18	Statistical evaluation of directional criteria	84
3.19	Performance of directional criteria	85
3.20	Simulated graph structures	89
3.21	Simulating expression from a graph structure	91
3.22	Simulating expression from graph structure with inhibitions	92
3.23	Demonstration of violin plots with custom features	95
3.24	Demonstration of annotated heatmap	95
3.25	Simulating graph structures	98
4.1	Synthetic lethal expression profiles of analysed samples	106
4.2	Comparison of SLIPT to siRNA	110
4.3	Compare SLIPT and siRNA genes with correlation	111
4.4	Compare SLIPT and siRNA genes with correlation	112
4.5	Compare SLIPT and siRNA genes with viability	113

4.6	Compare SLIPT genes with siRNA viability	114
4.7	Resampled intersection of SLIPT and siRNA candidates	118
4.8	Pathway metagene expression profiles	125
4.9	Expression profiles for constituent genes of PI3K	127
4.10	Expression profiles for estrogen receptor related genes	128
4.11	Somatic mutation against the PI3K metagene	129
5.1	Synthetic Lethality in the PI3K Cascade	141
5.2	Synthetic Lethality in the Elastic Fibre Formation Pathway	143
5.3	Synthetic Lethality in the Fibrin Clot Formation	144
5.4	Synthetic Lethality and Vertex Degree	147
5.5	Synthetic Lethality and Centrality	150
5.6	Synthetic Lethality and PageRank	151
5.7	Hierarchical Structure of PI3K	153
5.8	Hierarchy Score in PI3K against Synthetic Lethality in PI3K	154
5.9	Structure of Synthetic Lethality in PI3K	156
5.10	Structure of Synthetic Lethality Resampling in PI3K	157
6.1	Performance of χ^2 and SLIPT across quantiles	167
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	168
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	169
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	170
6.5	Performance of negative correlation and SLIPT	172
6.6	Simple graph structures	175
6.7	Performance of simulations on a simple graph	176
6.8	Performance of simulations is similar in simple graphs	178
6.9	Performance of simulations on a pathway	179
6.10	Performance of simulations on a simple graph with inhibition	181
6.11	Performance is higher on a simple inhibiting graph	182
6.12	Performance of simulations on a constructed graph with inhibition . . .	183
6.13	Performance is affected by inhibition in graphs	185
6.14	Detection of Synthetic Lethality within a Graph Structure with Inhibitions	187
6.15	Performance of simulations including a simple graph	190
6.16	Performance on a simple graph improves with more genes	191
6.17	Performance on an inhibiting graph improves with more genes	193
6.18	Performance of simulations on the PI3K cascade	196
6.19	Performance of simulations including the PI3K cascade	198
6.20	Performance on pathways improves with more genes	199
A.1	Correlation profiles of removed samples	241
A.2	Correlation analysis and sample removal	242
A.3	Replicate excluded samples	243
A.4	Replicate samples with all remaining	244
A.5	Replicate samples with some excluded	245
C.1	Synthetic lethal expression profiles of analysed samples	260

C.2	Comparison of mtSLIPT to siRNA	262
C.3	Compare mtSLIPT and siRNA genes with correlation	266
C.4	Compare mtSLIPT and siRNA genes with correlation	266
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	267
C.6	Somatic mutation against PIK3CA metagene	269
C.7	Somatic mutation against PI3K protein	270
C.8	Somatic mutation against AKT protein	271
C.9	Pathway metagene expression profiles	272
C.10	Expression profiles for p53 related genes	273
C.11	Expression profiles for BRCA related genes	274
E.1	Synthetic lethal expression profiles of stomach samples	279
E.2	Comparison of SLIPT in stomach to siRNA	281
F.1	Synthetic Lethality in the PI3K/AKT Pathway	286
F.2	Synthetic Lethality in the PI3K/AKT Pathway in Cancer	287
F.3	Synthetic Lethality in the Extracellular Matrix	288
F.4	Synthetic Lethality in the GPCRs	289
F.5	Synthetic Lethality in the GPCR Downstream	290
F.6	Synthetic Lethality in the Translation Elongation	291
F.7	Synthetic Lethality in the Nonsense-mediated Decay	292
F.8	Synthetic Lethality in the 3' UTR	293
G.1	Synthetic Lethality and Vertex Degree	294
G.2	Synthetic Lethality and Centrality	295
G.3	Synthetic Lethality and PageRank	296
H.1	Information centrality distribution	300
I.1	Synthetic Lethality and Heirarchy Score in PI3K	301
I.2	Heirarchy Score in PI3K against Synthetic Lethality in PI3K	302
I.3	Structure of Synthetic Lethality in PI3K	302
I.4	Structure of Synthetic Lethality Resampling	303
J.1	Performance of χ^2 and SLIPT across quantiles	304
J.2	Performance of χ^2 and SLIPT across quantiles	306
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	308
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation .	310
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation .	312
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	314
K.1	Performance of simulations on a simple graph	317
K.2	Performance of simulations on an inhibiting graph	318
K.3	Performance of simulations on a constructed graph with inhibition	319
K.4	Performance of simulations on a constructed graph with inhibition	320
K.5	Detection of Synthetic Lethality within a Graph Structure	321
K.6	Detection of Synthetic Lethality within an Inhibiting Graph Structure .	323

K.7	Detection of Synthetic Lethality within an Inhibiting Graph Structure	324
K.8	Performance of simulations on a branching graph	325
K.9	Performance of simulations on a complex graph	326
K.10	Performance of simulations on a large graph	327
K.11	Performance of simulations on a branching graph with inhibition	328
K.12	Performance of simulations on a branching graph with inhibition	329
K.13	Performance of simulations on a complex graph with inhibition	330
K.14	Performance of simulations on a complex graph with inhibition	331
K.15	Performance of simulations on a large constructed graph with inhibition	332
K.16	Performance of simulations on a large constructed graph with inhibition	333
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	334
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	335

List of Tables

1.1	Methods for Predicting Genetic Interactions	26
1.2	Methods for Predicting Synthetic Lethality in Cancer	27
1.3	Methods used by Wu <i>et al.</i> (2014)	28
2.1	Excluded Samples by Batch and Clinical Characteristics	46
2.2	Computers used during Thesis	57
2.3	Linux Utilities and Applications used during Thesis	57
2.4	R Installations used during Thesis	58
2.5	R Packages used during Thesis	58
2.6	R Packages Developed during Thesis	60
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	102
4.2	Pathways for <i>CDH1</i> partners from SLIPT	104
4.3	Pathway composition for clusters of <i>CDH1</i> partners from SLIPT	108
4.4	Analysis of variance (ANOVA) for Synthetic Lethality and Correlation with <i>CDH1</i>	112
4.5	Comparing SLIPT genes against secondary siRNA screen in breast cancer	115
4.6	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	117
4.7	Pathways for <i>CDH1</i> partners from SLIPT	120
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen	122
4.9	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT	131
5.1	ANOVA for Synthetic Lethality and Vertex Degree	148
5.2	ANOVA for Synthetic Lethality and Information Centrality	150
5.3	ANOVA for Synthetic Lethality and PageRank Centrality	152
5.4	ANOVA for Synthetic Lethality and PI3K Hierarchy	155
5.5	Resampling for pathway structure of synthetic lethal detection methods	159
B.1	R Packages used during Thesis	247
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT	257
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	258
C.3	Pathway composition for clusters of <i>CDH1</i> partners from mtSLIPT	261
C.4	Pathway composition for <i>CDH1</i> partners from mtSLIPT and siRNA	263
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	264
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	265
C.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT	268

D.1	Comparison of Intrinsic Subtypes	275
E.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	277
E.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	278
E.3	Pathway composition for clusters of <i>CDH1</i> partners in stomach SLIPT	280
E.4	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	282
E.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	283
E.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA screen	284
E.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT in stomach cancer	285
G.1	ANOVA for Synthetic Lethality and Vertex Degree	297
G.2	ANOVA for Synthetic Lethality and Information Centrality	297
G.3	ANOVA for Synthetic Lethality and PageRank Centrality	297
H.1	Information centrality for genes and molecules in the Reactome network	299
I.1	ANOVA for Synthetic Lethality and PI3K Hierarchy	301
I.2	Resampling for pathway structure of synthetic lethal detection methods	303

Glossary

synthetic lethal Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

Acronyms

ANOVA Analysis of Variance.

siRNA Short interfering ribonucleic acid.

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Appendix F

Synthetic Lethal Genes in Pathways

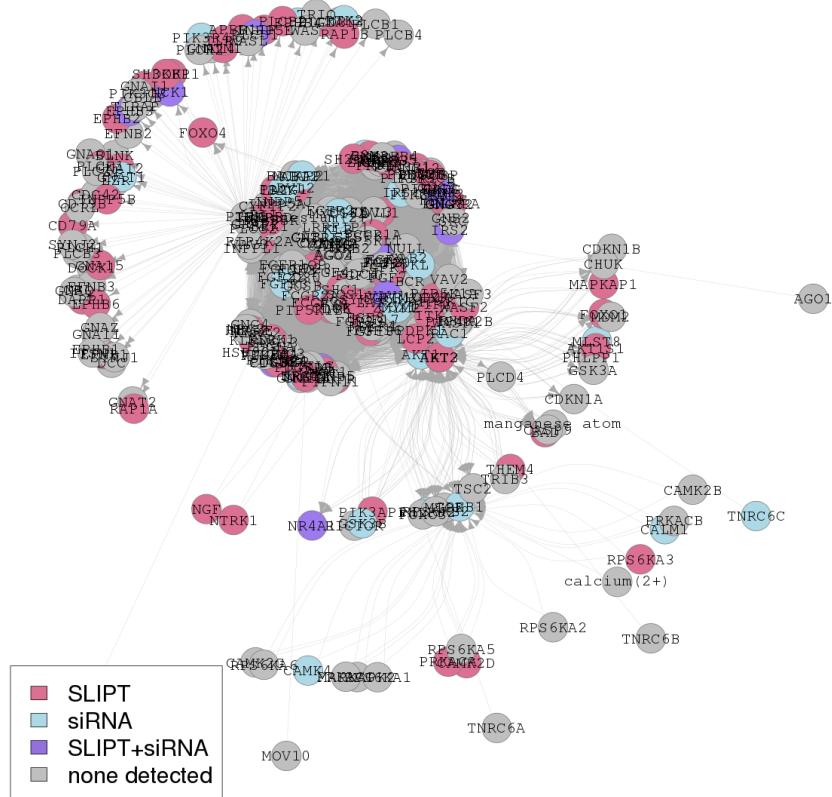


Figure F.1: **Synthetic Lethality in the PI3K/AKT Pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates coloured as shown in the legend.

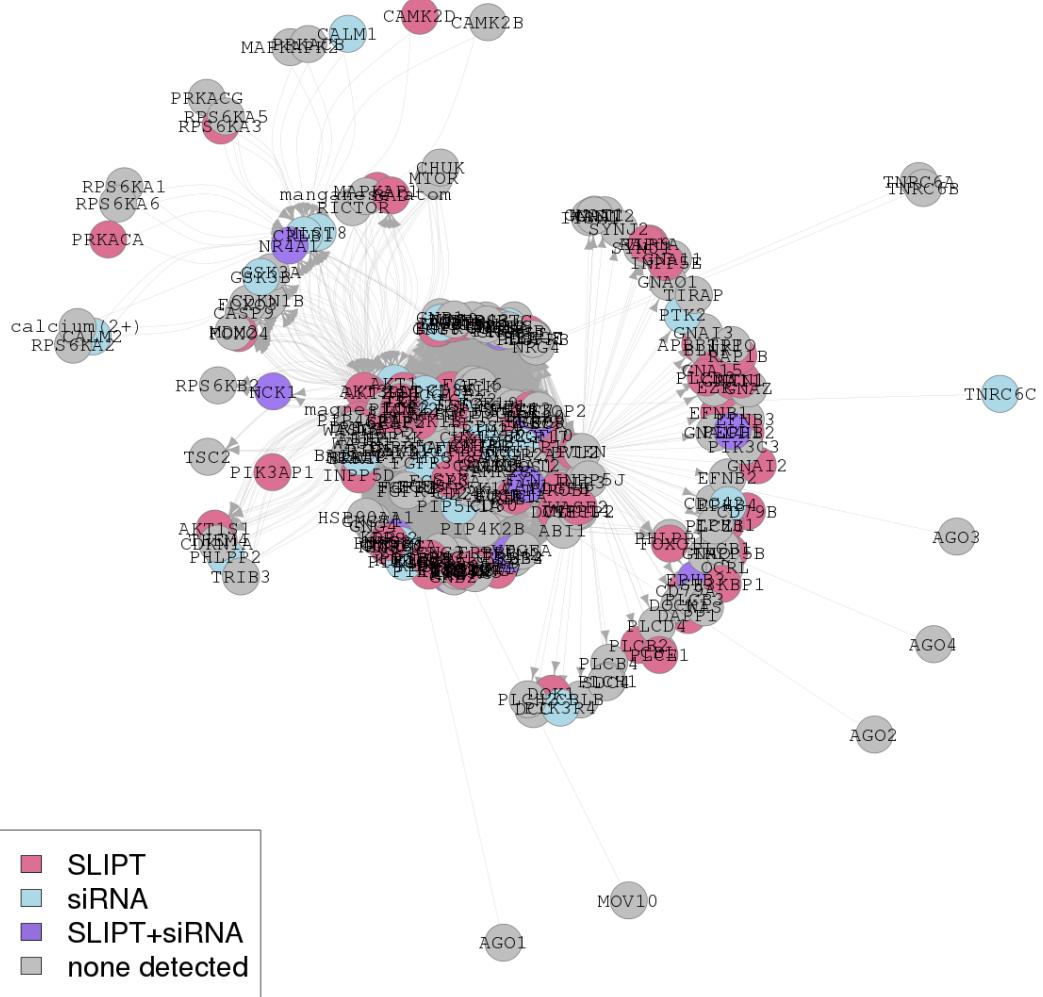


Figure F.2: Synthetic Lethality in the PI3K/AKT Pathway in Cancer. The Reactome PI3K/AKT Pathway in Cancer pathway with synthetic lethal candidates coloured as shown in the legend.

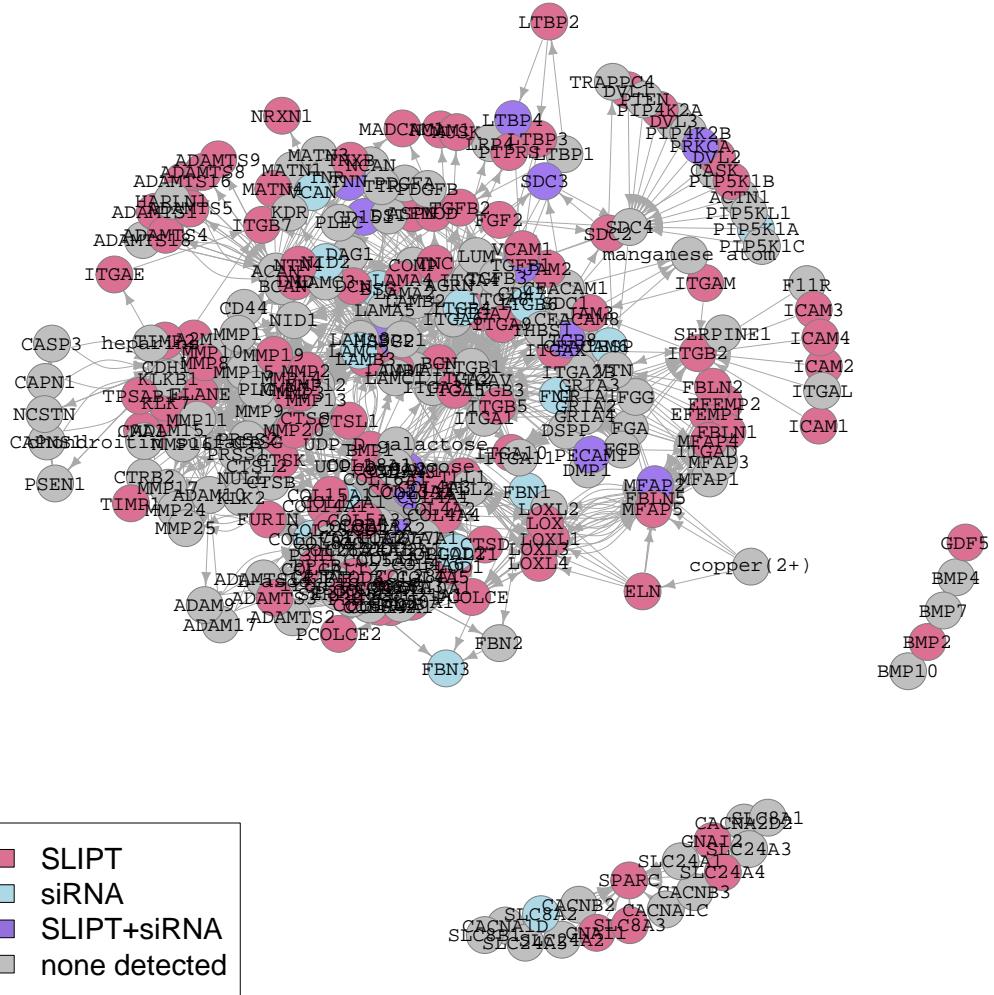


Figure F.3: Synthetic Lethality in the Extracellular Matrix. The Reactome Extracellular Matrix pathway with synthetic lethal candidates coloured as shown in the legend.

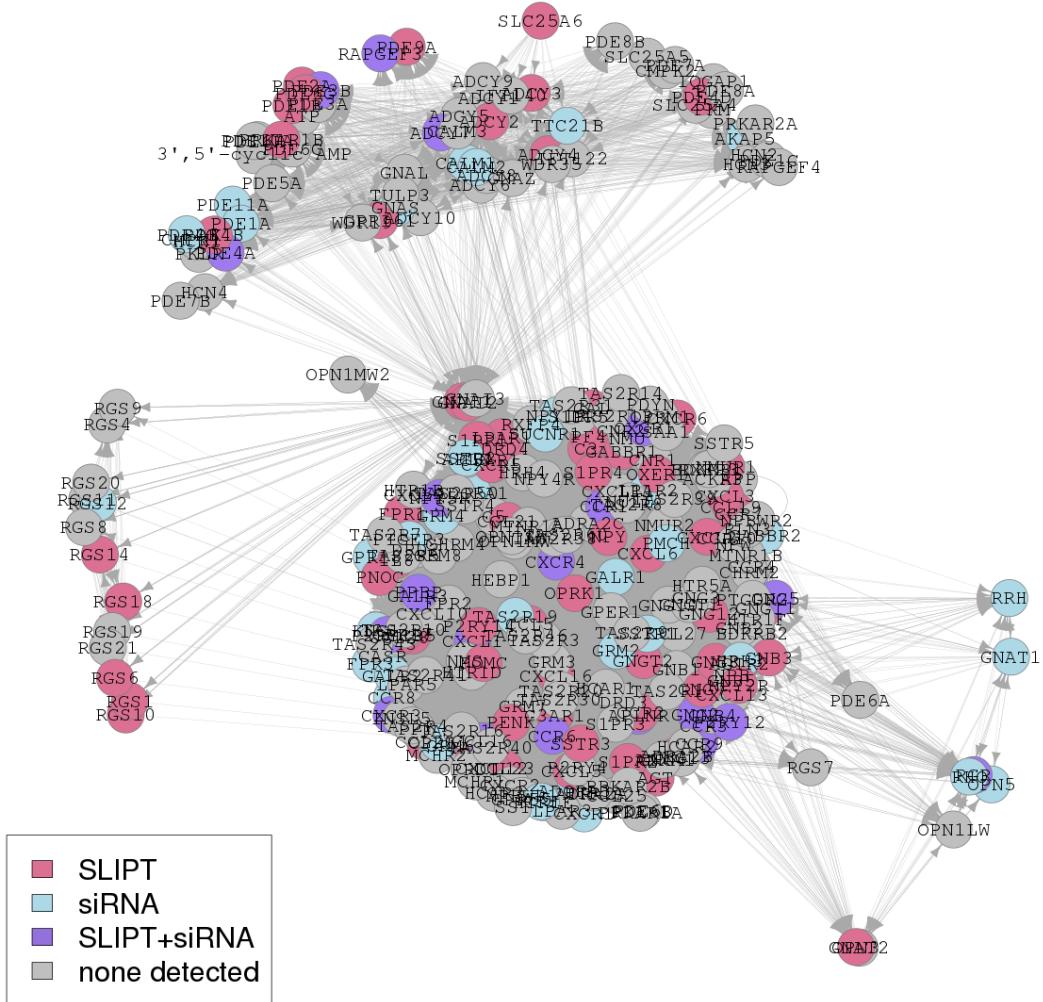


Figure F.4: Synthetic Lethality in the GPCRs. The Reactome $G_{\alpha i}$ pathway with synthetic lethal candidates coloured as shown in the legend.

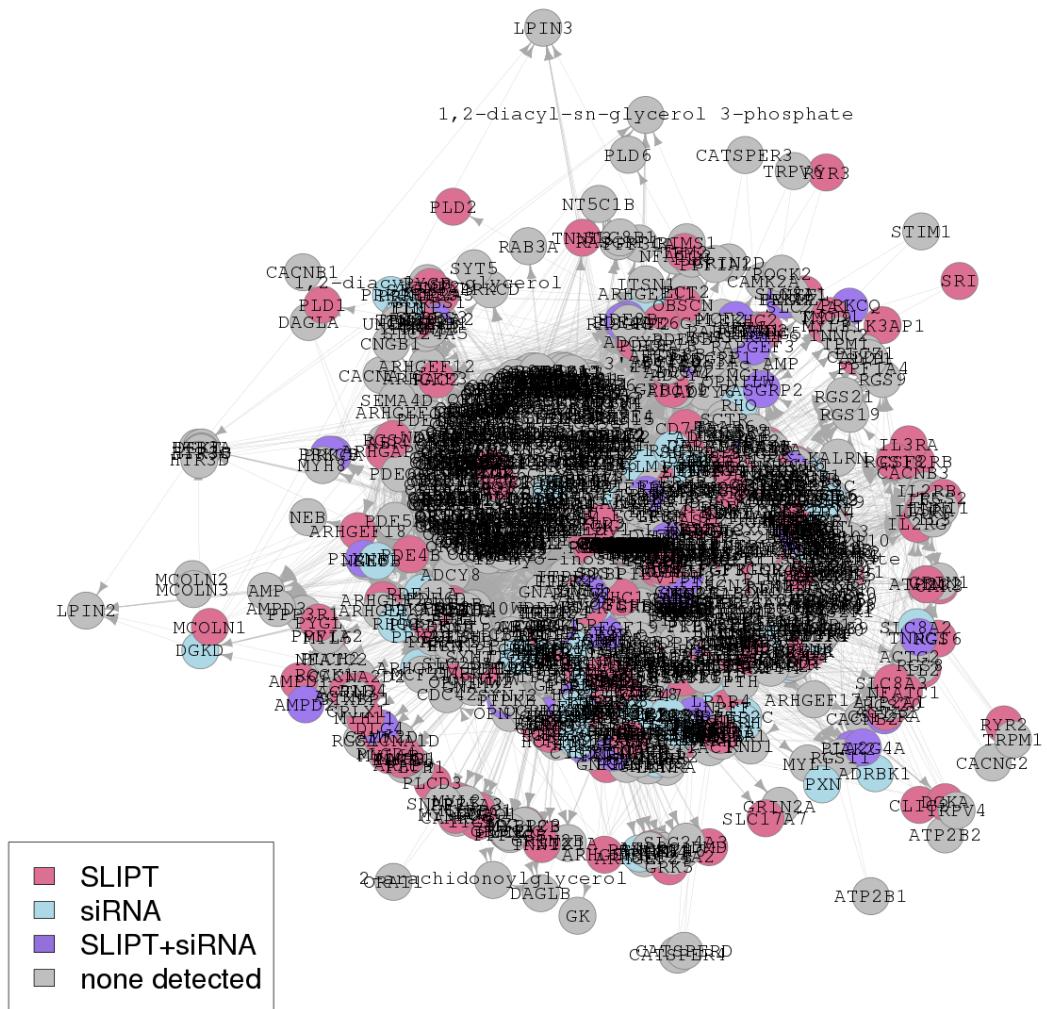


Figure F.5: **Synthetic Lethality in the GPCR Downstream.** The Reactome GPCR Downstream pathway with synthetic lethal candidates coloured as shown in the legend.

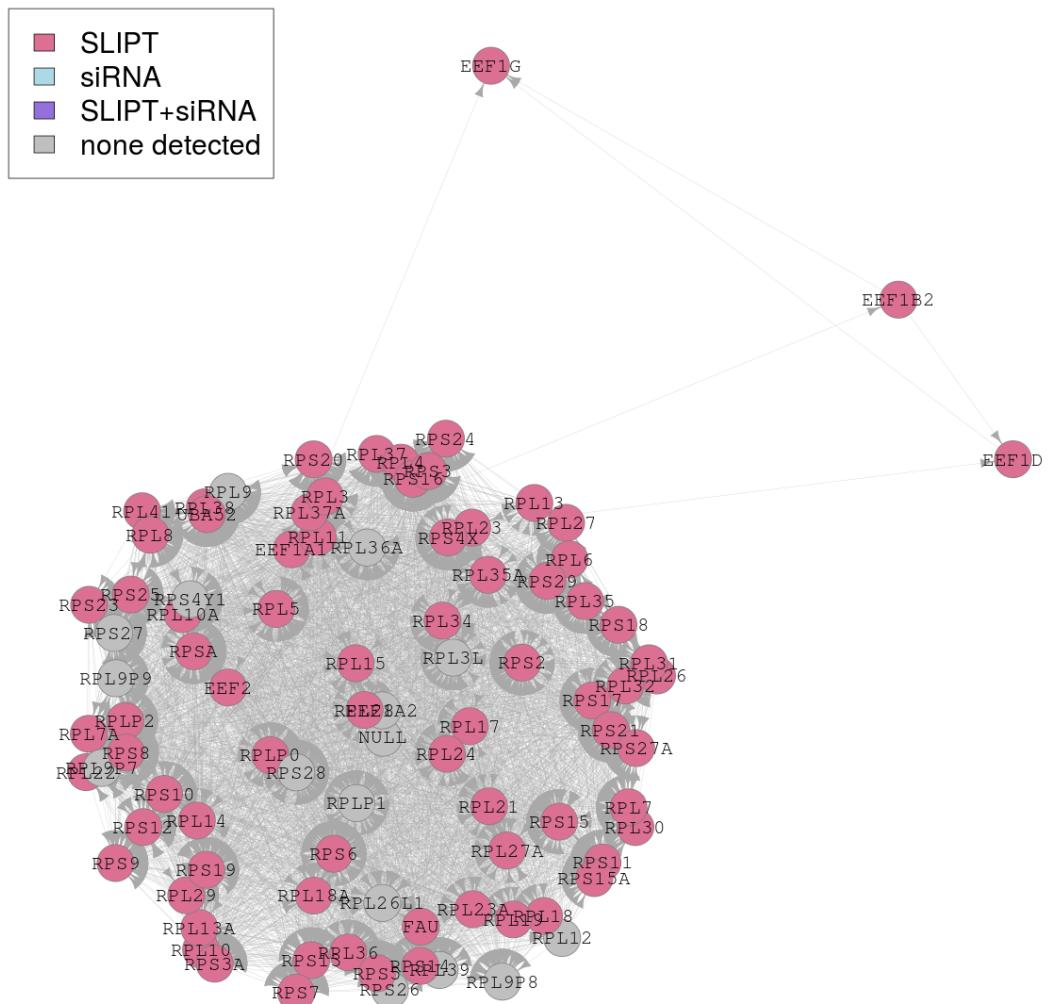


Figure F.6: **Synthetic Lethality in the Translation Elongation**. The Reactome Translation Elongation pathway with synthetic lethal candidates coloured as shown in the legend.

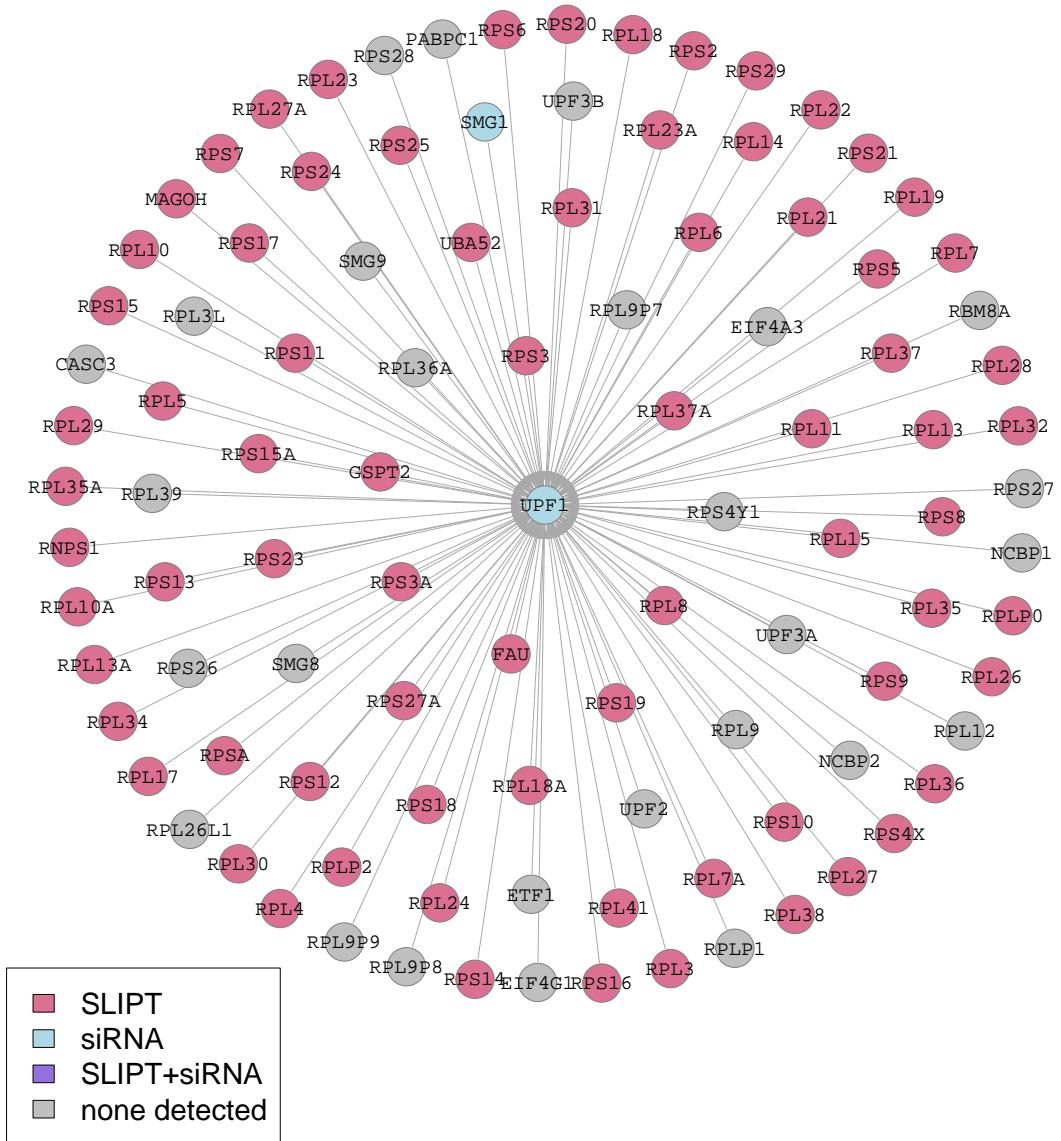


Figure F.7: Synthetic Lethality in the Nonsense-mediated Decay. The Reactome Nonsense-mediated Decay pathway with synthetic lethal candidates coloured as shown in the legend.

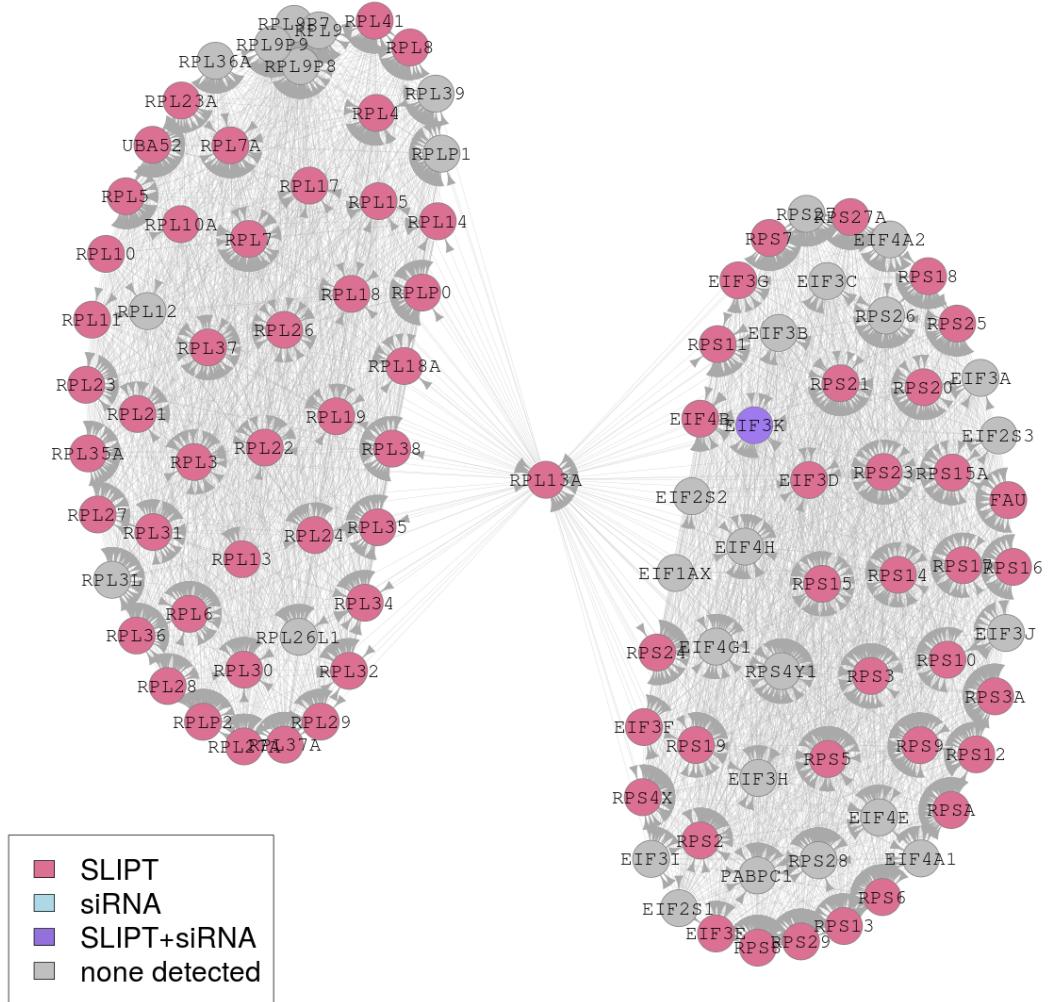


Figure F.8: **Synthetic Lethality in the 3' UTR.** The Reactome 3' UTR pathway with synthetic lethal candidates coloured as shown in the legend.

Appendix G

Pathway Connectivity for Mutation SLIPT

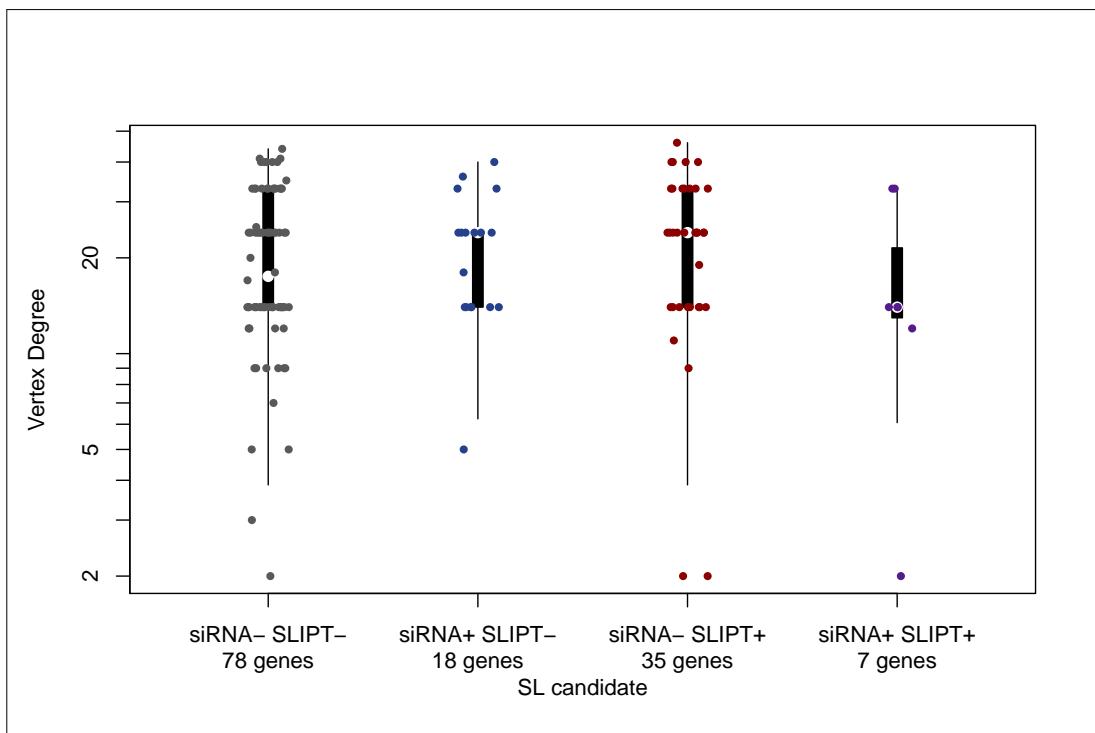


Figure G.1: **Synthetic Lethality and Vertex Degree.** The number of connected genes (vertex degree) was compared (on a log-scale across genes detected by mtSLIPT and short interfering RNA (siRNA) screening in the Reactome PI3K cascade pathway. There were very few differences in vertex degree between the groups, although genes detected by siRNA included those with the fewest connections.

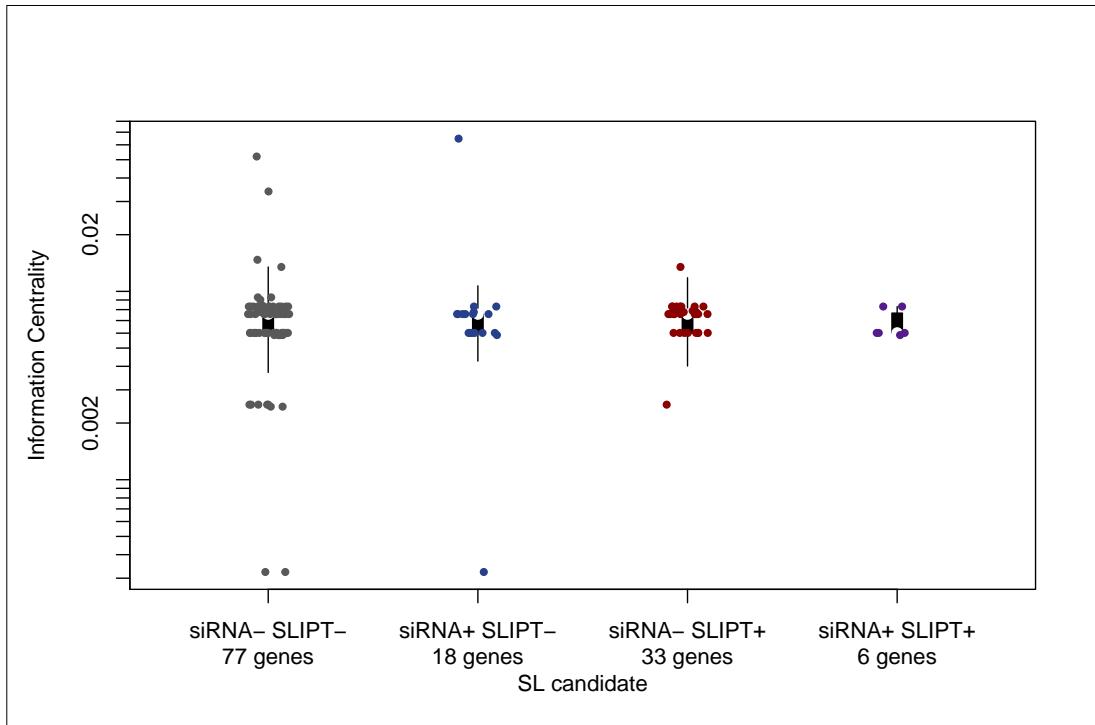


Figure G.2: Synthetic Lethality and Centrality. The information centrality was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by mtSLIPT or siRNA did not have higher connectivity than genes not detected by either approach. The gene with the highest centrality was detected by siRNA.

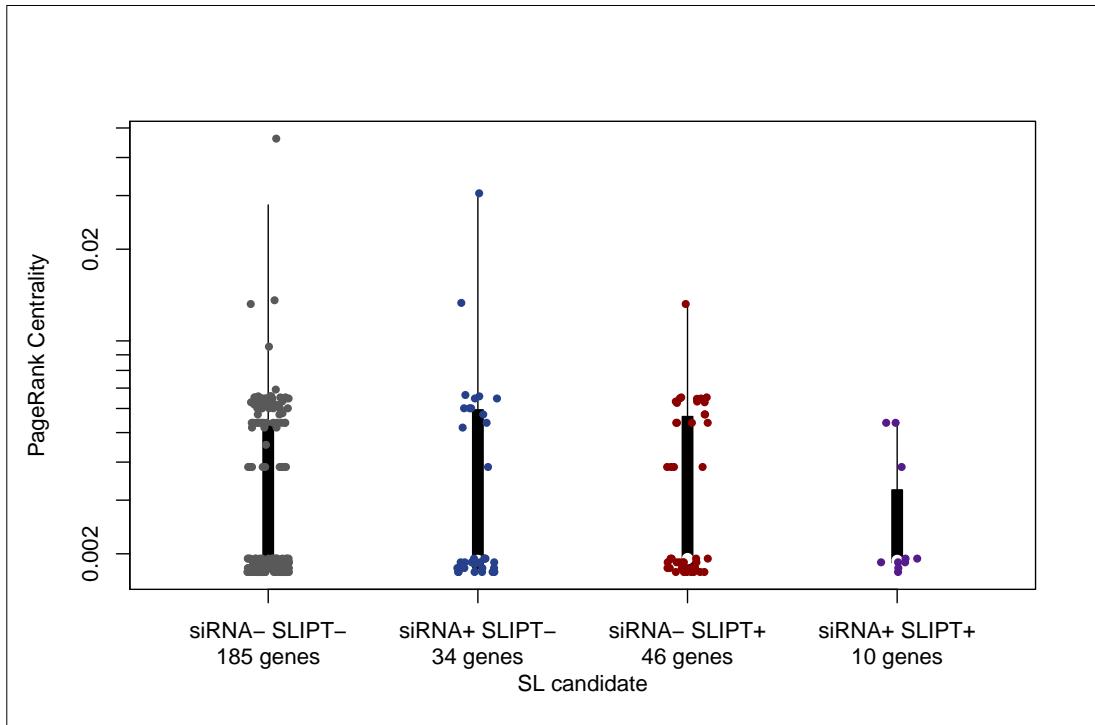


Figure G.3: Synthetic Lethality and PageRank. The PageRank centrality was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome PI3K cascade pathway. Genes detected by siRNA had a more restricted range of centrality values than other genes not detected by either approach, although these groups also had fewer genes.

Table G.1: ANOVA for Synthetic Lethality and Vertex Degree

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	15	15.50	0.0134	0.9084
mtSLIPT	1	196	195.94	0.1689	0.6825
siRNA×mtSLIPT	1	9	9.17	0.0079	0.9294

Analysis of variance for vertex degree against synthetic lethal detection approaches (with an interaction term)

Table G.2: ANOVA for Synthetic Lethality and Information Centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.000256	0.0002561	0.1851	0.6685
mtSLIPT	1	0.003225	0.0032247	2.3308	0.1318
siRNA×mtSLIPT	1	0.001238	0.0012385	0.8952	0.3476

Analysis of variance for information centrality against synthetic lethal detection approaches (with an interaction term)

Table G.3: ANOVA for Synthetic Lethality and PageRank Centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.0002038	2.0385×10^{-4}	1.1423	0.2892
mtSLIPT	1	0.0000208	2.0752×10^{-5}	0.1163	0.7342
siRNA×mtSLIPT	1	0.0000137	1.3743×10^{-5}	0.0770	0.7823

Analysis of variance for PageRank centrality against synthetic lethal detection approaches (with an interaction term)

Appendix H

Information Centrality for Gene Essentiality

Network structure is another useful strategy to analyse gene function and this has been used to investigate network properties of a network constructed from of Reactome pathways imported via Pathway Commons with Paxtools (Cerami *et al.*, 2011; Demir *et al.*, 2013). Most notably, information centrality which has been proposed as a measure of gene essentiality was calculated as performed by Kranthi *et al.* (2013) using the efficiency and shortest path between each pair of nodes in the network before and after a node of interest is removed to test the importance of a node to network connectivity. Reactome contains substrates and cofactors in addition to genes or proteins. In support of centrality as a measure of essentiality, a number nodes with the highest centrality (shown in Table H.1) were essential nutrients including Mg^{2+} , Ca^{2+} , Zn^{2+} , and Fe. In addition, there were genes important in development of epithelial tissues and breast cancer such as *IL8*, *GATA3*, and *CTNNB1* detected with relatively high information centrality.

Table H.1: Information centrality for genes and molecules in the Reactome network

Node	Centrality
<i>ZNF473</i>	0.0510
magnesium(2+)	0.0082
<i>XBP1</i>	0.0053
calcium(2+)	0.0050
zinc(2+)	0.0048
iron atom	0.0041
<i>FMN</i>	0.0040
<i>AGT</i>	0.0037
<i>HSP90AA1</i>	0.0029
phosphatidyl-L-serine	0.0029
<i>P2RX7</i>	0.0026
<i>PANX1</i>	0.0024
<i>NCAM1</i>	0.0022
<i>NUDT1</i>	0.0021
<i>PLAUR</i>	0.0020
<i>IL8</i>	0.0020
<i>HSPA8</i>	0.0019
<i>TYROBP</i>	0.0019
<i>CASP3</i>	0.0017
<i>GNAL</i>	0.0015
<i>CBLB</i>	0.0015
<i>HBB</i>	0.0014
<i>GATA4</i>	0.0013
<i>TGS1</i>	0.0013
<i>CTNNB1</i>	0.0012

Highest information centrality for genes (proteins), cofactors, and minerals in the Reactome network

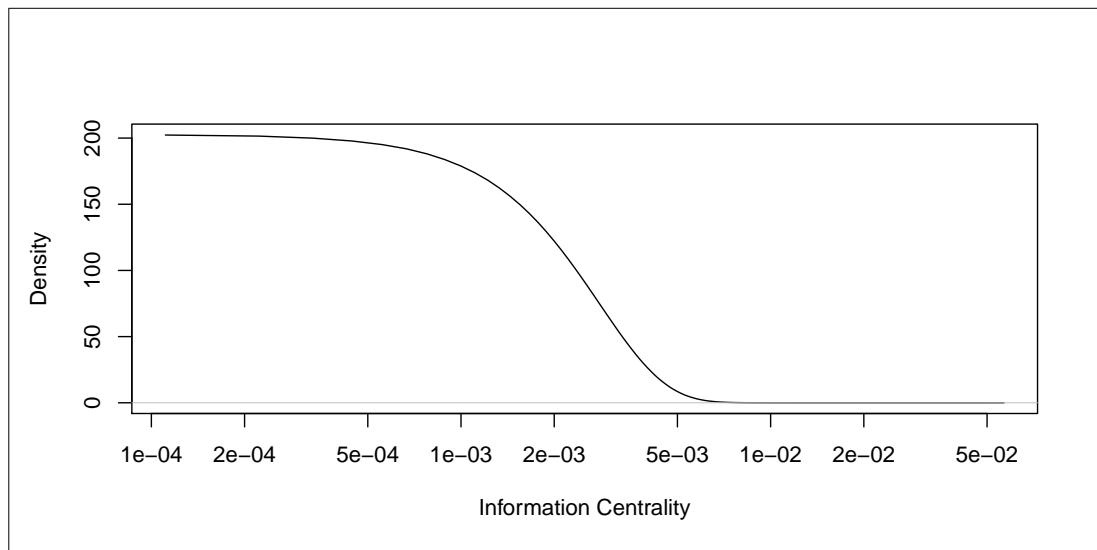


Figure H.1: **Information centrality distribution.** Information centrality in the Reactome network for nodes, including genes/proteins and other biomolecules.

Appendix I

Pathway Structure for Mutation SLIPT

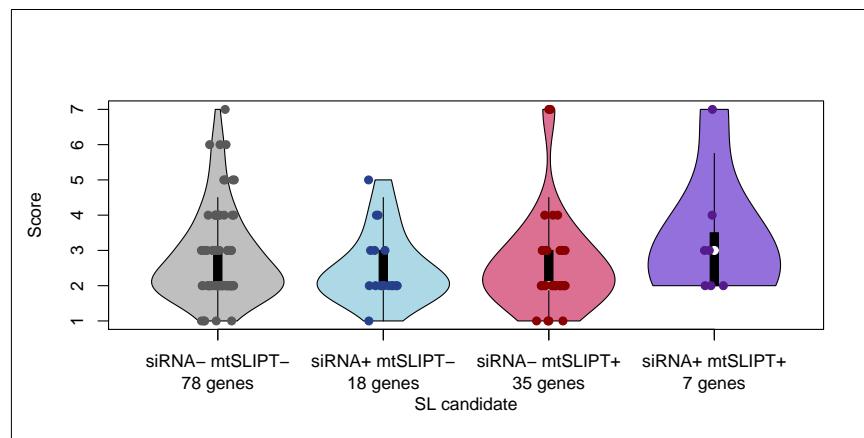


Figure I.1: **Synthetic Lethality and Heirarchy Score in PI3K.** The hierarchical distance scores were similarly distributed across mtSLIPT and siRNA genes. Genes detected by both methods had a higher (downstream) median than either group.

Table I.1: ANOVA for Synthetic Lethality and PI3K Hierarchy

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.001	0.00070	0.0004	0.9841
mtSLIPT	1	0.007	0.0066	0.0040	0.9496
siRNA×mtSLIPT	1	3.906	3.9056	2.3829	0.1250

Analysis of variance for PI3K hierarchy score against synthetic lethal detection approaches (with an interaction term)

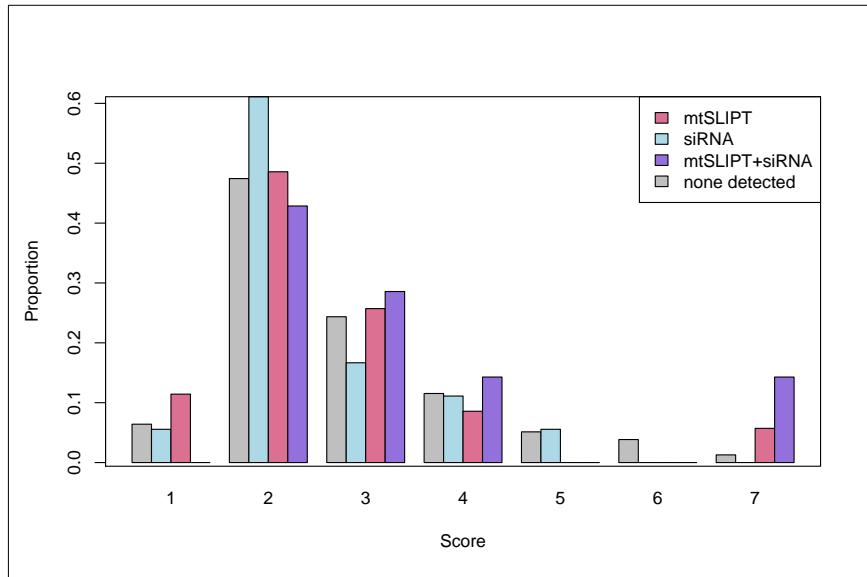


Figure I.2: **Heirarchy Score in PI3K against Synthetic Lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.

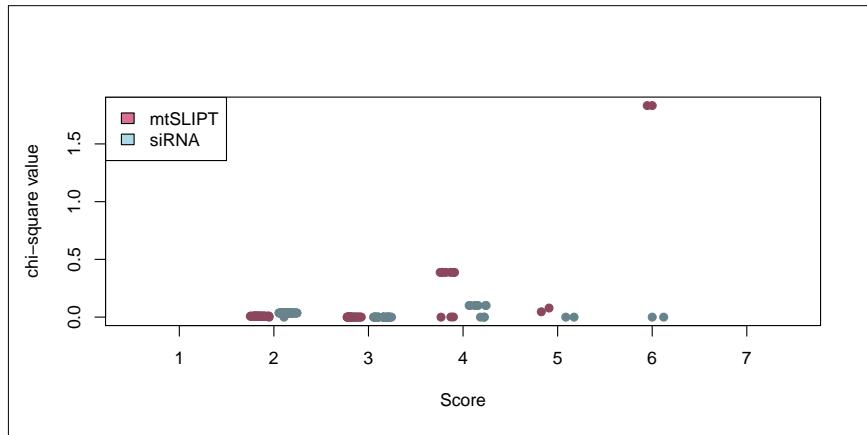


Figure I.3: **Structure of Synthetic Lethality in PI3K.** The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities. The number of mtSLIPT and siRNA genes upstream or downstream of each gene in the Reactome PI3K pathway were tested (by the χ^2 -test). These are plotted as a split jitter stripchart against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.

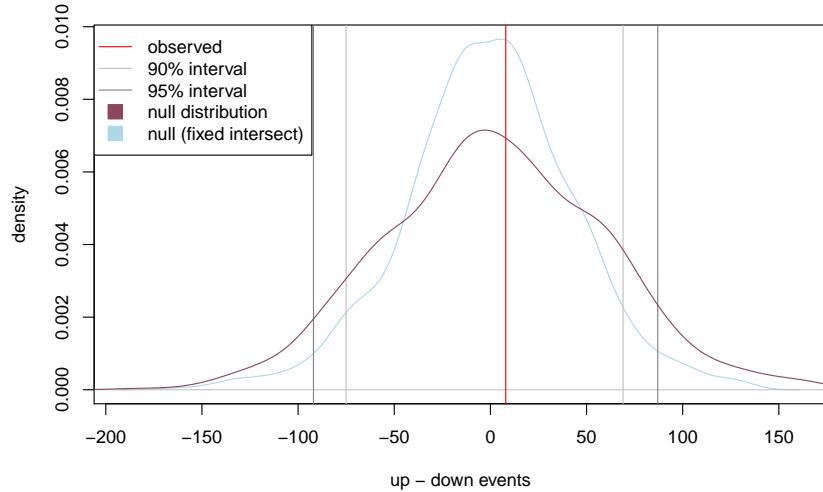


Figure I.4: Structure of Synthetic Lethality Resampling. A null distribution (10,000 iterations) of the siRNA genes upstream or downstream of mtSLIPT genes (shown by the difference) in the PI3K pathway. The observed events (red) were compared to the the distribution (violet) and were not significant. Genes detected by both methods were fixed for the distribution (blue). The genes detected by both approaches were used.

Table I.2: Resampling for pathway structure of synthetic lethal detection methods

Pathway	Graph		States		Observed				Permutation p-value	
	Nodes	Edges	mtSL	siRNA	Up	Down	Up-Down	Up/Down	Up-Down	Down-Up
PI3K Cascade	138	1495	42	25	131	123	8	1.065	0.4473	0.5466
PI3K/AKT Signalling in Cancer	275	12882	56	44	478	440	38	1.086	0.4163	0.5810
G_{αi} Signalling	292	22003	57	58	543	866	-323	0.627	0.9507	0.0488
GPCR downstream	1270	142071	218	160	7632	6500	1132	1.174	0.1707	0.8291
Elastic fibre formation	42	175	16	7	6	7	-1	0.857	0.5512	0.3681
Extracellular matrix	299	3677	81	29	313	347	-34	0.902	0.5762	0.4215
Formation of Fibrin	52	243	11	5	8	19	-11	0.421	0.7993	0.1800
Nonsense-Mediated Decay	103	102	56	2	0	0	0		0.197	0.1373
3'-UTR-mediated translational regulation	107	2860	56	1	52	1	51	52	0.1210	0.8751
Eukaryotic Translation Elongation	92	3746	57	0	0	0	0		0.4952	0.4892

Pathways in the Reactome network tested for structural relationships between mtSLIPT and siRNA genes by resampling. The raw p-value (computed without adjusting for multiple comparisons over pathways) is given for the difference in upstream and downstream paths from mtSLIPT to siRNA gene candidate partners of CDH1 with significant pathways highlighted in bold. Sampling was performed only in the target pathway and shortest paths were computed within it. Loops or paths in either direction that could not be resolved were excluded from the analysis. The gene detected by both mtSLIPT and siRNA (or resampling for them) were included in the analysis and the number of these were fixed to the number observed.